JCMK

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

Recognised for exellence 5 star

Online ISSN 2313-1519
Print ISSN 1812-2892
www.clinmedkaz.org

№21 (6) 2024

Unraveling Vitiligo: From Immune Mechanisms to Promising Therapeutic Strategies

> See page 18 and 23

Clinical Value of NT-proBNP and Lactate Parameters in Infants with Congenital Heart Defects

> See page 41 and 47

Determination of Gynecologic Cancer Awareness and Attitudes Towards Screening in Women Aged 20–65

> See page 103 and 109

JCMK
JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

Online ISSN 2313-1519
Print ISSN 1812-2892
№21 (6) 2024.
Published since 2004.

EDITORIAL

AIMS AND SCOPE OF THE JOURNAL

Journal “Clinical Medicine of Kazakhstan” (ISSN 1812-2892) is a multi-field dedicated peer-reviewed medical journal. The main thematic scope – publication of materials on medical science and practice, education and healthcare organization. Joint Stock Company “National Scientific Medical Center” publishes the journal bimonthly in a year (in February, April, June, August, October, and December).

All articles sent to editors undergo double-blind review. Manuscripts are judged by two experts exclusively on the basis of their contribution to initial data, ideas and their presentations. Editors accept articles for consideration and publication at no cost. Detailed information is available in the section Information for authors at the end of this material.

The Journal of “Clinical Medicine of Kazakhstan” to the full extent is wedded to initiative of open access and ready to provide free access to full texts of articles, as soon as they will be published and available in the Internet (www.clinmedkaz.org).

Journal was registered in the Ministry of Information of the RK on 05.04.2004 and currently included to the list of Publications, approved by the Committee for Control of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan for publication of the main outcomes of scientific activity.

The journal is indexed in such international scientific-information bases as Index Copernicus International, Google Scholar, CrossRef. DOAJ.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN
Scientific and practical journal

JCMK
JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN
Editorial Office: Journal of Clinical Medicine of Kazakhstan
Ave Abylay-khan #42, 010009, Astana, Kazakhstan. Phone: +7(7172) 577411
Fax: +7(7172) 232927 E-mail: editor@clinmedkaz.org Web Adress: www.clinmedkaz.org

NATIONAL SCIENTIFIC MEDICAL CENTER JSC, ASTANA CITY,
REPUBLIC OF KAZAKHSTAN

CLINICAL - DIAGNOSTIC LABORATORY

All the brilliant achievements of mankind in the field of physics, chemistry, molecular biology, are embodied in the technologies used for the laboratory diagnosis of diseases at the molecular and cellular levels. The quality and accuracy of the analysis are guaranteed by the modern equipment, quality control, usage of the reagents of well-known world manufacturers, qualified personnel. The laboratory performs a wide range of well-known researches and a number of complex and rare analyzes for scientific purposes. The immediate goal of NSRMC, JSC is an establishment of PCR laboratory for the study of human genetic defects and tissue typing for organ transplants.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/15569

Ventricular-arterial Coupling: Advances and Current Perspectives in Cardiovascular Research

Bauyrzhan Toktarbay[1], Aizhan Zhankorazova[1], Zaukiya Khamitova[1], Dinara Jumadilova[1], Alessandro Salustri[1]

[1]Department of Medicine, Nazarbayev University School of Medicine, Astana, Kazakhstan

Received: 2024-10-15.
Accepted: 2024-10-30.

J Clin Med Kaz 2024; 21(6): 4–10

Corresponding author:
Alessandro Salustri.
E-mail: alessandro.salustri@nu.edu.kz.
ORCID: 0000-0002-4596-0887.

Abstract

The concept of ventricular-arterial coupling (VAC) was first introduced in the early 1980s to quantify the relationship between left ventricular contractility and arterial load. The mathematical formulation of VAC, expressed as the ratio of arterial elastance to ventricular elastance, has since then been refined with adjustments to allow for non-invasive assessment. By the early 2000s, advancements in echocardiography, cardiac magnetic resonance and arterial tonometry provided non-invasive alternatives to the traditional invasive method of cardiac catheterization, broadening the clinical application of VAC. Emerging technologies, such as machine learning and computational models, have further enhanced the precision and personalization of VAC, with potential applications in heart failure, hypertension and other clinical scenarios.

This review describes the physiological basis and the historical development of VAC, highlights the non-invasive assessment techniques, and discusses the potential for personalized treatment based on VAC insights. Machine learning models trained on large datasets from non-invasive imaging modalities may open new avenues in predicting individual patient responses to therapies. However, lack of standardized protocols across imaging modalities represents a challenge, making the call for standardization critical for consistent clinical application. This review underscores the need for harmonized methodologies to better utilize VAC in personalized medicine, aiming to improve cardiovascular outcomes through tailored therapies.

Keywords: Ventricular-arterial coupling; ventricular and aortic elastance; myocardial contractility; arterial compliance.

Introduction

The concept of ventricular-arterial coupling (VAC) and its mathematical formulation was first introduced by Sunagawa et al. in the early 1980s [1]. Their original work, published in 1983, laid the groundwork for understanding the interaction between the left ventricle and the arterial system in mechanical terms, using elastance-based parameters. The key formula included the arterial elastance (Ea), which represents the effective afterload of the arterial system, and the end-systolic elastance (Ees) which represents the left ventricular (LV) contractility. VAC was then defined as Ea/Ees. After the proposal of the original formula, researchers further refined the calculation of Ea and Ees to improve its clinical application. For instance, the method was applied in humans using non-invasive techniques (such as echocardiography) and systolic blood pressure (SBP) as a surrogate for end-systolic pressure. Kelly et al. introduced the concept of using 0.9 × SBP as a simplified estimate of end-systolic pressure for non-invasive VAC assessment in clinical settings [2]. This adjustment made the formula more feasible in clinical practice.

In this article we will review the physiological background, the different methods for assessment, and the directions of development of VAC.

Physiological background

The heart and the arterial system are fundamentally related, both anatomically and functionally, and VAC describes the relationship between the two systems [3]. VAC is estimated as the ratio of arterial and ventricular elastances. The ratio of the LV end-systolic pressure to the stroke volume is known as the effective arterial elastance (Ea), and it succinctly conveys the steady and pulsatile components of the arterial load.

Total peripheral resistance, as one of the properties of the steady component of the arterial load, mainly depends on microvasculature. Contrarily, the pulsatile arterial load is primarily determined by the properties of the macrovasculature, which include the impedance of the aorta (Zc), the total arterial compliance, and the wave reflections [4]. Ventricular elastance (Ees) represents the slope of the line connecting V0 to the LV end-systolic pressure-volume relation, which is unaffected by preload or afterload and is a measure of cardiac contractility. Combined with Ea, it has been used to assess heart-arterial coupling [5].

For a given beat-to-beat preload and afterload, the Ees may be obtained from the LV pressure-volume (PV) loop. The PV loop is predicted on the end-systolic pressure–volume relationship (ESPVR), which is a linear connection between the end-systolic ventricular pressure and the end-systolic LV volume. The Ees is the intracavitary pressure needed to expand its volume by one unit (mmHg ml−1; normal values 2.3 ± 1 mmHg ml−1), while Ea represents the slope of the line connecting the left ventricular end-diastolic volume to the ESPVR (normal values 2.2 ± 0.8 mmHg ml−1). Ventriculo-arterial coupling is the Ea/Ees ratio, and the normal values are 1 ± 0.36 mmHg ml−1 [4].

The Ea/Ees ratio is used to assess how well the heart and arterial system are matched. Under normal conditions, the ratio approximates 1. Increased Ea/Ees suggests higher arterial stiffness relative to ventricular function, commonly seen in heart failure and hypertension [6]. Decreased Ea/Ees indicates impaired contractility, as seen in cases of heart failure with reduced ejection fraction (HFrEF) [7]. Thus, VAC acts as a significant indicator of the mechanical function of the LV and regulation of the cardiovascular system.

Introduction of assessment methods

Since the early 2000s, there has been a growing interest in non-invasive methods for measuring VAC. Techniques such as arterial tonometry, echocardiography, and cardiac MRI, allowed for estimates of both Ea and Ees without the need for invasive PV loop recordings. This shift was critical for applying VAC in broader clinical settings, especially in patients with cardiovascular diseases such as heart failure and hypertension. More recent research has integrated advanced imaging techniques like MRI and echocardiography to assess VAC in greater detail. These developments allow for dynamic VAC assessment, considering how coupling changes under different physiological conditions (e.g., exercise or pharmacological stress) [8]. Additionally, some studies have refined how ventricular elastance is estimated non-invasively through models that incorporate ventricular strain and tissue Doppler imaging data, further enhancing the practical utility of the VAC formula [9]. The relative merits of invasive and non-invasive methods for VAC assessment are summarized in Table 1.

Table 1 Relative merits of invasive and non-invasive methods for VAC assessment

Parameter	Invasive method (cardiac catheterization)	Non-Invasive methods (echocardiography, MRI, arterial tonometry)
Accuracy	High accuracy for direct measurement of Ees and Ea [19].	Moderate to high accuracy; depends on the technique (MRI is highly accurate, echocardiography less precise) [20].
Data obtained	Direct real-time measurement of pressure-volume relationships and detailed hemodynamic parameters [21].	Estimation of Ees and Ea through indirect measurements; waveform analysis for arterial properties. [22]
Patient risk	High: involves catheter insertion, radiation exposure, and potential complications [23].	Low: non-invasive, generally safe with minimal patient discomfort [24].
Technical expertise	Requires advanced technical skills for both performance and interpretation [25].	Easier to perform but still requires training, especially in MRI and advanced echocardiography.
Cost	High: due to the need for specialized equipment and invasive procedures [26].	Moderate to high: MRI is expensive; echocardiography and tonometry are relatively cheaper [27].
Time required	Longer procedure: involves preparation, catheter insertion, and recovery.	Generally quicker (e.g., echocardiography), though MRI takes longer compared to others.
Patient comfort	Low: invasive procedures are uncomfortable and can be painful.	High: non-invasive techniques cause minimal discomfort.
Clinical Applicability	Limited to cases requiring highly accurate, direct measurements (e.g., severe heart failure, research) [28].	More widely applicable in routine clinical practice for screening, monitoring, and diagnosis [29].
Measurement of dynamic changes	Excellent: captures real-time changes in pressure and volume relationships.	Limited: non-invasive methods may not capture dynamic changes as accurately.
Reproducibility	High reproducibility in controlled settings.	Moderate reproducibility; can vary with operator skill and technique used.
Use in research vs clinical	Primarily used in research settings or complex clinical cases.	Common in both clinical and research settings, especially for regular monitoring.

Invasive method

- High fidelity conductance microcatheters

During cardiac catheterization, a PV loop can be generated, that is a graphical representation of the relationship between LV pressure and volume throughout the heartbeat. It provides valuable insights into both systolic and diastolic function, as well as the interaction between the heart and the arterial system. A catheter equipped with sensors is introduced into the left ventricle through a major artery (usually the femoral artery). The catheter records LV pressure and volume continuously. Volume changes can be measured using conductance technology or by integrating echocardiographic imaging with the catheter's data [3]. To determine the Ees and Ea, a brief occlusion of the inferior vena cava is performed to reduce venous return. This allows clinicians to generate multiple PV loops under different loading conditions and calculate the ESPVR (Figure 1) [10].

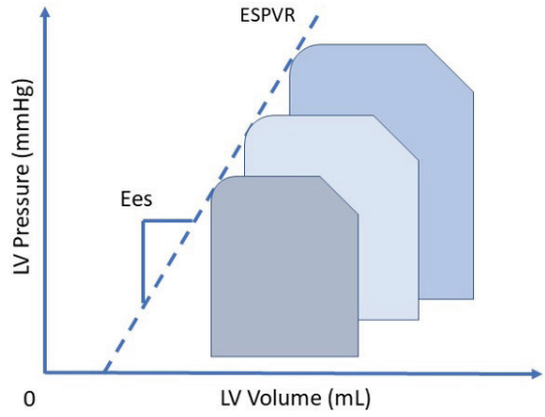


Figure 1 – SThis series of loops, that represent multiple cardiac cycles, allow us to observe how the heart's pressure-volume relationship changes over time under different loading conditions, contractility, or heart rates. By shifting the preload (end-diastolic volume), afterload (arterial pressure), or contractility, a family of loops can help assess cardiac function. The line connecting the end-systolic volumes represents the ventricular elastance. Ees: Ventricular elastance; ESPVR: End-systolic pressure-volume relationship.

An invasive simplified method is based on mathematical extrapolation of Ees from single-beat measures [11, 12]. Single PV loop measurement represents a single cardiac cycle with one contraction and relaxation phase. It can be used to examine detailed changes in pressure and volume during systole and diastole. From the PV loop, Ees is the slope of the line connecting V0 to the end-systolic pressure-volume relation, while Ea is the slope of the line connecting the LV end-diastolic volume to the end-systolic pressure-volume relation (Figure 2).

- Advantages and disadvantages of invasive approach

Since catheterization involves direct measurements of pressure and volume, it is by far more precise than non-invasive methods like echocardiography or MRI. For assessing complex cardiovascular dynamics like VAC, cardiac catheterization is considered the gold standard because it provides quantitative, real-time data that can be used to calculate indices of ventricular contractility and arterial load with unmatched accuracy. Furthermore, during catheterization, clinicians can also perform therapeutic procedures (e.g., coronary angioplasty or valvuloplasty) while assessing cardiac function, making it a diagnostic and therapeutic tool.

One of the disadvantages of the method is its invasiveness, requiring catheter insertion into the heart or arteries, which carries risks of complications like bleeding, infection, or vessel damage. Assessing VAC through catheterization requires expertise in both the procedure and the interpretation of data, including the calculation of Ees and Ea. Due to its invasiveness, cardiac catheterization is often reserved for patients with suspected or known significant cardiovascular disease, rather than being used for routine VAC assessment.

Non-invasive methods

- Echocardiographic estimation of Ees and Ea

Echocardiography is a non-invasive method used to estimate VAC through complex mathematical calculations, which allow to extrapolate Ees from the information obtained in a single cardiac cycle. The method developed by Chen et al. includes the calculation of stroke volume (from the velocity-time integral in the LV outflow tract and the LV outflow tract area), the LV ejection fraction, and the BP at two different moments of the heart cycle [13]. Doppler imaging are the key techniques for estimating these parameters. Arterial elastance is

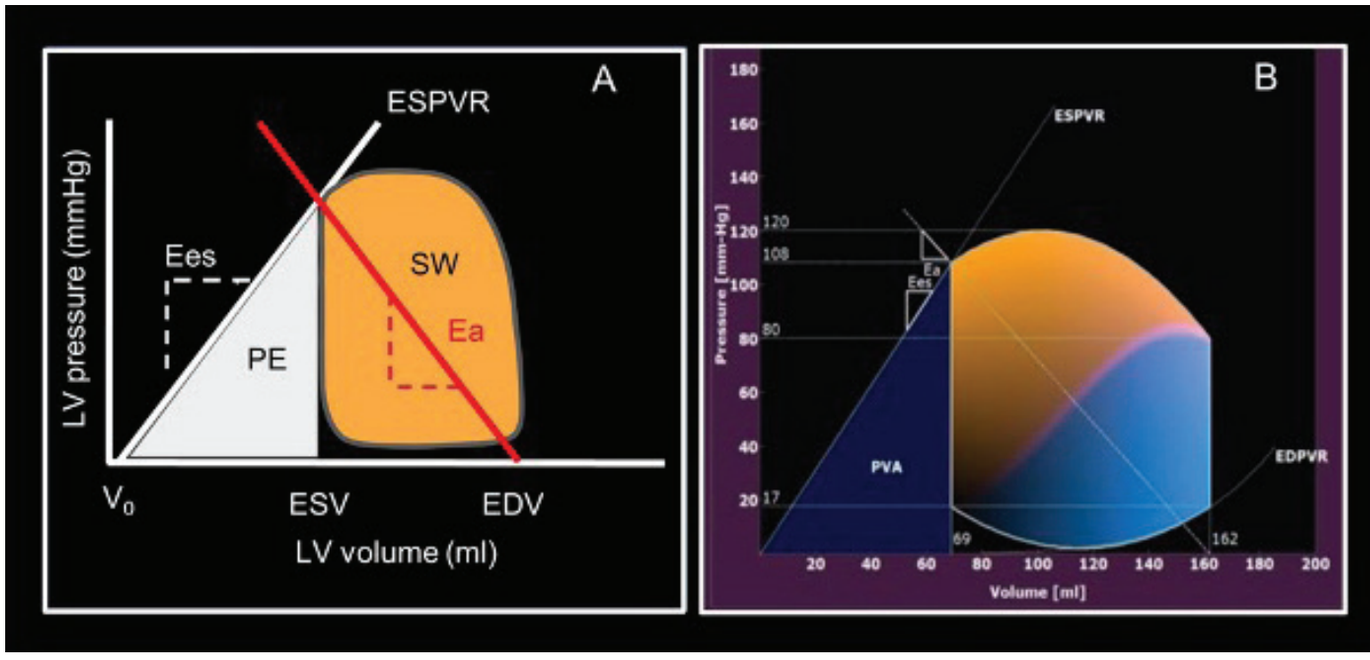


Figure 2 – Schematic drawing of the pressure-volume loop with lines identifying the arterial and ventricular elastance (panel A). Pressure-volume loop obtained in a normal subjects from feature-tracking cardiac magnetic resonance imaging. From the pressure-volume loop, arterial and ventricular elastance are derived (panel B). Ea: Arterial elastance; EDV: End-diastolic volume; Ees: Ventricular elastance; ESPVR: End-systolic pressure-volume relationship; ESV: End-systolic volume; PE: Potential energy; SW: Stroke work

calculated as the ratio of end-systolic pressure (often estimated as 0.9 x SBP) to stroke volume [2]. Echocardiography may be used to estimate end-systolic elastance, which is a measure of ventricular contractility, by monitoring end-systolic pressure and end-systolic volume [9].

- Advanced imaging to assess ventricular and arterial function

MRI offers precise measurements of both ventricular elastance and arterial elastance. Ea is calculated as the ratio of end-systolic pressure (ESP) to stroke volume (SV), which can be accurately measured through MRI's ability to quantify LV volumes and aortic blood flow during the cardiac cycle [14]. MRI provides high-resolution images to calculate ESV and assess myocardial strain, which is essential for evaluating ventricular function and contractility [8]. Recently, advanced software based on a mathematical model allows noninvasive analysis of PV loops from feature-tracking MRI or echocardiography [15]. This new method derives PV loops by combining CMR-derived volumes with brachial blood pressure measurements, providing insights into cardiac function without the need for invasive catheterization. This method has been validated against traditional invasive techniques, showing strong correlation for important hemodynamic parameters such as stroke work, ventricular efficiency, and potential energy [16].

- Arterial tonometry: pulse wave velocity and arterial compliance measurement.

Arterial tonometry is a non-invasive technique used to assess VAC by measuring pulse wave velocity (PWV) and arterial compliance. PWV reflects arterial stiffness, which is a key determinant of arterial elastance. PWV is calculated by measuring the speed of the pressure wave traveling through the arteries, with higher values indicating increased arterial stiffness and thus higher Ea [17].

PWV is measured by recording the pressure waveforms at two arterial sites (e.g., carotid and femoral arteries). The time it takes for the pressure wave to travel between these two points gives PWV, which correlates with arterial stiffness. Increased PWV indicates stiffer arteries, meaning higher arterial elastance. Arterial compliance is derived from the shape of the aortic pressure waveform, which is recorded through tonometry. Reduced compliance (stiffer arteries) increases Ea, thus increasing the afterload on the heart. Since tonometry focuses on arterial parameters, Ees is estimated using complementary data from imaging (e.g., echocardiography) or blood pressure-volume relationships.

Emerging technologies and computational models

The integration of computational models and machine learning algorithms is transforming how VAC is assessed. Computational models use mathematical representations of the heart and vasculature to simulate the interaction between ventricular and arterial function under various conditions. These models can incorporate real-time data from non-invasive imaging (e.g., echocardiography or MRI) and adjust to dynamic physiological changes. More recently, machine learning algorithms have been used to analyze large datasets from non-invasive imaging to predict VAC parameters, such as Ea and Ees, without the need for direct invasive measurements. Artificial neural networks and other machine learning models have been trained to recognize patterns in echocardiographic data that correlate with VAC, improving the speed and accuracy of VAC assessment [18]. These models have the potential to automate the analysis of large imaging datasets, providing personalized assessments of VAC for individual patients.

Comparative analysis of assessment methods

In the table provided below we compared invasive and noninvasive methods of the VAC assessment (Table 1).

Clinical application of VAC

VAC in heart failure with reduced ejection fraction (HFrEF)

Ees and Ea are mismatched in HFrEF due to a reduction in myocardial contractility. The mismatch between the heart's pumping ability and the arterial load exacerbates heart failure symptoms, resulting in decreased stroke volume and higher arterial pressures. In individuals with HFrEF, VAC evaluations can predict unfavorable outcomes including hospitalization and death [19].

VAC in heart failure with preserved ejection fraction (HFpEF)

Even though VAC responds dynamically in HFrEF (raised values with the lowered Ees and increased Ea), its relevance as a dimensionless number is less clear in HFpEF. In fact, in this case both Ees and Ea are elevated resulting in a "normal" VAC [6].

VAC in hypertension

Vascular artery stiffness and elastance are increased in hypertension, a common disorder that profoundly affects VAC. The long-term mismatch between artery and ventricular elastance deteriorates cardiovascular outcomes. Early-stage hypertension is compensated for by the LV enhanced contractility, which keeps VAC constant despite the increased afterload. But gradually, when arterial stiffness increases and VAC is affected, it leads to a decrease in cardiac output and the onset of HF symptoms [22]. Through VAC examination, this shift can be identified early and treated promptly. A greater risk of cardiovascular events, including myocardial infarction and stroke, is linked to significant VAC impairment in resistant or advanced hypertension. More potent antihypertensive methods or gadget-based treatments, like baroreceptor stimulation, may fall under this category [30].

VAC in aortic stenosis

Arterial elastance is increased with aortic stenosis because the left ventricle is challenged with a fixed outflow barrier. Ventricular geometry and contractility are eventually affected by this increased afterload. Thus, VAC might be a useful tool for monitoring patients with aortic stenosis to identify the best time to replace the valve [31]. Quantifying ventricular-arterial mismatch is often done using non-invasive techniques such as MRI and echocardiography [24].

VAC in coronary artery disease (CAD)

Ischemia in CAD impairs arterial function (increased Ea) and ventricular contractility (decreased Ees), which results in ineffective coupling. Clinicians can estimate the degree of ischemia and choose the best revascularization techniques with the use of VAC evaluation [20]. For long-term therapy and prognosis, routine VAC evaluation can be useful in patients with CAD.

VAC as a prognostic indicator

In patients with heart failure, the composite events of hospitalization for heart failure and cardiovascular mortality were substantially correlated with Ea/Ees [32]. VAC has a crucial role in forecasting long-term cardiovascular mortality in individuals with prior myocardial infarctions and is an independent echocardiographic correlate of B-type natriuretic peptide levels in these patients [33]. In patients admitted to the intensive care unit, VAC was a powerful and independent predictor of in-hospital clinical outcomes (acute heart failure, hypoperfusion, requirement for invasive ventilation, intra-aortic balloon pump, renal replacement therapy, and mortality) [34]. Furthermore, the researchers found that both very high and very low VAC values were associated with worse outcomes, including higher mortality and fewer ventilator-free days in patients with sepsis or septic shock [35]. This highlights VAC as a potential marker for patient prognosis in critical care settings.

Implications for therapeutic interventions

Clinicians can evaluate responses to therapy and modify treatment plans by assessing non-invasive evaluation of VAC [20]. Assessing VAC is critical for directing therapy methods, such as diuretics and vasodilators [29]. Reducing Ea by therapeutic procedures that target the arterial system (ACE inhibitors, angiotensin II receptor blockers, etc.) can improve cardiac output and restore a normal balance [21].

Future implications

Need for standardization of non-invasive techniques

Different non-invasive techniques provide different ways to estimate ventricular elastance and arterial elastance, leading to inconsistent results across studies and clinical settings. For example, echocardiography can measure Ees using either global longitudinal strain or TDI-derived myocardial velocities, which can yield different estimates of contractility [9]. The lack of standardized non-invasive techniques makes it difficult to establish clear clinical cut-offs for impaired VAC. Studies using different imaging modalities often report varying thresholds for pathological coupling [36]. The lack of standardized methods limits the use of non-invasive VAC assessment in routine care, where the ability to accurately monitor VAC could help optimize treatment for heart failure patients. Without standardized protocols, the variability in these measurements makes it difficult to compare findings between studies and ensure consistent clinical interpretation.

Potential for personalized treatment based on VAC

In order to provide individualized care, VAC evaluation provides a window into the degree of ventricular dysfunction and arterial stiffness. Based on VAC findings, tailored treatment is being further enhanced through the integration of big data and machine learning. AI algorithms are able to forecast individual patient responses to specific medicines by examining vast datasets from imaging, genetics, and electronic health records. For example, VAC parameters may be processed by machine learning algorithms to forecast outcomes in heart failure or hypertension, enabling more accurate drug and intervention modifications.

Conclusion

VAC provides a crucial framework for understanding the dynamic interplay between the heart and arterial system. VAC assessment has evolved significantly over time, integrating both invasive and non-invasive methods for assessing its arterial and ventricular components. Clinical applications of VAC span various cardiovascular conditions such as heart failure, hypertension, and coronary artery disease, offering valuable insights into disease prognosis and treatment optimization.

The transition from invasive methods like cardiac catheterization to non-invasive techniques such as echocardiography, MRI, and arterial tonometry has widened the clinical application of VAC assessment, making it more accessible in routine clinical practice. Each method comes with its own strengths and limitations, with MRI offering high precision and echocardiography providing widespread applicability.

Further advancements in computational models and machine learning algorithms have the potential to revolutionize VAC assessment by predicting patient-specific outcomes and tailoring therapeutic interventions. However, the variability in non-invasive measurement techniques underscores the need for standardized protocols to ensure consistency across clinical and research settings. Ultimately, VAC may serve as an essential diagnostic and prognostic tool in cardiovascular medicine, offering new avenues for personalized treatment strategies and improved patient outcomes. Ongoing research and technological developments are expected to refine VAC assessment and enhance its clinical utility.

Author Contributions: Writing – original draft preparation, BT; project administration, AZ; data curation, ZK; investigation, DJ; Conceptualization, writing – review and editing, funding acquisition, AS. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: None.

Funding: This study was funded by a grant of the Ministry of Education and Science of the Republic of Kazakhstan, № AP23490021.

References

1. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol.* 1983; 245 (5 Pt 1). https://doi.org/10.1152/ajpheart.1983.245.5.H773.
2. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, et al. Effective arterial elastance as index of arterial vascular load in humans. *Circulation*. 1992; 86 (2): 513–521. https://doi.org/10.1161/01.cir.86.2.513.
3. Sunagawa K, Sagawa K, Maughan WL. Ventricular interaction with the loading system. *Ann Biomed Eng.* 1984; 12(2): 163–189. https://doi.org/10.1007/BF02584229.

4. Ikonomidis I, Aboyans V, Blacher J, Brodmann M, Brutsaert DL, Chirinos JA, et al. The role of ventricular-arterial coupling in cardiac disease and heart failure: assessment, clinical implications and therapeutic interventions. *Eur J Heart Fail.* 2019; 21(4): 402–424. https://doi.org/10.1002/ejhf.1436.
5. Chantler PD. Arterial Ventricular Uncoupling With Age and Disease and Recoupling With Exercise. *Exerc Sport Sci Rev.* 2017; 45(2): 70–79. https://doi.org/10.1249/JES.0000000000000100.
6. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. *Heart Fail Clin.* 2008; 4(1): 23–36. https://doi.org/10.1016/j.hfc.2007.10.001.
7. Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. *J Appl Physiol*. 2008; 105(4): 1342–1351. https://doi.org/10.1152/japplphysiol.90600.2008.
8. Namasivayam M, Adji A, Lin L, Hayward CS, Feneley MP, O'Rourke MF, et al. Non-Invasive Quantification of Ventricular Contractility, Arterial Elastic Function and Ventriculo-Arterial Coupling from a Single Diagnostic Encounter Using Simultaneous Arterial Tonometry and Magnetic Resonance Imaging. *Cardiovasc Eng Technol.* 2020; 11(3): 283–294. https://doi.org/10.1007/s13239-020-00462-2.
9. Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: part 1: pressure and flow measurements and basic principles of wave conduction and reflection. *Hypertension.* 2010; 56(4): 555–562. https://doi.org/10.1161/HYPERTENSIONAHA.110.157321.
10. Starling MR. Left ventricular-arterial coupling relations in the normal human heart. *Am Heart J.* 1993; 125(6): 1659–1666. https://doi.org/10.1016/0002-8703(93)90756-y.
11. Senzaki H, Chen CH, Kass DA. Single-beat estimation of end-systolic pressure-volume relation in humans. A new method with the potential for noninvasive application. *Circulation*. 1996; 94(10): 2497–2506. https://doi.org/10.1161/01.cir.94.10.2497.
12. Shishido T, Hayashi K, Shigemi K, Sato T, Sugimachi M, Sunagawa K. Single-beat estimation of end-systolic elastance using bilinearly approximated time-varying elastance curve. *Circulation.* 2000; 102(16): 1983–1989. https://doi.org/10.1161/01.cir.102.16.1983.
13. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol.* 2001; 38(7): 2028–2034. https://doi.org/10.1016/s0735-1097(01)01651-5.
14. Bastos MB, Burkhoff D, Maly J, Daemen J, den Uil CA, Ameloot K, et al. Invasive left ventricle pressure-volume analysis: overview and practical clinical implications. *Eur Heart J.* 2020; 41(12): 1286–1297. https://doi.org/10.1093/eurheartj/ehz552.
15. Pedrizzetti G, Claus P, Kilner PJ, Nagel E. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. *J Cardiovasc Magn Reson.* 2016; 18(1): 51. https://doi.org/10.1186/s12968-016-0269-7.
16. Arvidsson PM, Green PG, Watson WD, Shanmuganathan M, Heiberg E, De Maria GL, et al. Non-invasive left ventricular pressure-volume loops from cardiovascular magnetic resonance imaging and brachial blood pressure: validation using pressure catheter measurements. *Eur Heart J Imaging Methods Pract.* 2023; 1(2): qyad035. https://doi.org/10.1093/ehjimp/qyad035.
17. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J.* 2006; 27(21): 2588–2605. https://doi.org/10.1093/eurheartj/ehl254.
18. Zhou J, Du M, Chang S, Chen Z. Artificial intelligence in echocardiography: detection, functional evaluation, and disease diagnosis. *Cardiovasc Ultrasound.* 2021;19(1): 29. https://doi.org/10.1186/s12947-021-00261-2.
19. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res.* 1974; 35(1): 117–126. https://doi.org/10.1161/01.res.35.1.117.
20. Walsh TF, Hundley WG. Assessment of ventricular function with cardiovascular magnetic resonance. *Cardiol Clin.* 2007; 25(1): 15–33. https://doi.org/10.1016/j.ccl.2007.01.002.
21. Kass DA, Maughan WL. From 'Emax' to pressure-volume relations: a broader view. *Circulation.* 1988; 77(6): 1203-1212. https://doi.org/10.1161/01.cir.77.6.1203.
22. Kelly R, Hayward C, Ganis J, Daley J, Avolio A, O'Rourke M. Noninvasive registration of the arterial pressure pulse waveform using high-fidelity applanation tonometry. *J Vasc Med Biol.* 1989; 1: 142–149.
23. West R, Ellis G, Brooks N; Joint Audit Committee of the British Cardiac Society and Royal College of Physicians of London. Complications of diagnostic cardiac catheterisation: results from a confidential inquiry into cardiac catheter complications. *Heart.* 2006; 92(6): 810–814. https://doi.org/10.1136/hrt.2005.073890.
24. Marcu CB, Beek AM, van Rossum AC. Clinical applications of cardiovascular magnetic resonance imaging. *CMAJ*. 2006; 175(8): 911–917. https://doi.org/10.1503/cmaj.060566.
25. Muller JC, Kennard JW, Browne JS, Fecher AM, Hayward TZ. Hemodynamic monitoring in the intensive care unit. *Nutr Clin Pract.* 2012; 27(3): 340–351. https://doi.org/10.1177/0884533612443562.
26. Otero HJ, Rybicki FJ, Greenberg D, Mitsouras D, Mendoza JA, Neumann PJ. Cost-effective diagnostic cardiovascular imaging: when does it provide good value for the money? *Int J Cardiovasc Imaging.* 2010; 26(6): 605–12. https://doi.org/10.1007/s10554-010-9634-z.
27. Klaeboe LG, Edvardsen T. Echocardiographic assessment of left ventricular systolic function. J Echocardiogr. 2019;17(1):10-16. https://doi.org/10.1007/s12574-018-0405-5.
28. Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. *Am J Physiol.* 1986;250(6 Pt 2). https://doi.org/10.1152/ajpregu.1986.250.6.R1021.
29. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28(1):1-39.e14. https://doi.org/10.1016/j.echo.2014.10.003.

30. Howard LS, Grapsa J, Dawson D, Bellamy M, Chambers JB, Masani ND, et al. Echocardiographic assessment of pulmonary hypertension: standard operating procedure. Eur Respir Rev. 2012;21(125):239-48. https://doi.org/10.1183/09059180.00003912.
31. Sevilla T, Revilla-Orodea A, San Román JA. Timing of Intervention in Asymptomatic Patients with Aortic Stenosis. *Eur Cardiol.* 2021;16. https://doi.org/10.15420/ecr.2021.11.
32. Yokoyama H, Yamanaka F, Shishido K, Ochiai T, Yokota S, Moriyama N, et al. Prognostic Value of Ventricular-Arterial Coupling After Transcatheter Aortic Valve Replacement on Midterm Clinical Outcomes. *J Am Heart Assoc.* 2021;10(18). https://doi.org/10.1161/JAHA.120.019267.
33. Antonini-Canterin F, Enache R, Popescu BA, Popescu AC, Ginghina C, Leiballi E, et al. Prognostic value of ventricular-arterial coupling and B-type natriuretic peptide in patients after myocardial infarction: a five-year follow-up study. *J Am Soc Echocardiogr.* 2009 Nov;22(11):1239-45. https://doi.org/10.1016/j.echo.2009.08.009. Epub 2009 Sep 26
34. Trambaiolo P, Figliuzzi I, Salvati M, Bertini P, Brizzi G, Tocci G, et al. Ventriculo-arterial coupling in the intensive cardiac care unit: A non-invasive prognostic parameter. *Int J Cardiol.* 2022;348:85-89. https://doi.org/10.1016/j.ijcard.2021.12.026.
35. Lian H, Li S, Zhang Q, Wang X, Zhang H. U-shaped prognostic value of left ventricular-arterial coupling in septic patients: a prospective study. *Eur J Med Res*. 2024 Aug 29;29(1):435. https://doi.org/10.1186/s40001-024-02037-6.
36. Johannesen J, Fukuda R, Zhang DT, Tak K, Meier R, Agoglia H, et al. Direct comparison of echocardiography speckle tracking and cardiac magnetic resonance feature tracking for quantification of right ventricular strain: a prospective intermodality study in functional mitral regurgitation. *Echo Res Pract.* 2022;9(1):11. https://doi.org/10.1186/s44156-022-00011-8.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/15571

Metabolomics in Search of Noninvasive Biomarkers for Allograft Rejection in Pediatric Kidney Transplantation

Vitaliy Sazonov[1],[2], Azhar Zhailauova[1],[2], Sholpan Altynova[3], Mirgul Bayanova[4] Gulnur Daniyarova[5], Aidos Bolatov[6], Yuriy Pya[7]

[1]Department of Surgery, School of Medicine, Nazarbayev University, Astana, Kazakhstan
[2]Research Department, Corporate Fund "University Medical Center", Astana, Kazakhstan
[3]Medical and Regulatory Affairs Department, Corporate Fund "University Medical Center", Astana, Kazakhstan
[4]Department of Clinical and Genetic Diagnostics, CAD of Laboratory Medicine, Pathology and Genetics, Corporate Fund "University Medical Center", Astana, Kazakhstan
[5]Academic secretary, Corporate Fund "University Medical Center", Astana, Kazakhstan
[4]Doctoral program, Shenzhen University, Shenzhen, China
[5]Chairman of the Board, Corporate Fund "University Medical Center", Astana, Kazakhstan

Received: 2024-08-30.
Accepted: 2024-10-31.

J Clin Med Kaz 2024; 21(6): 11–17

Corresponding author:
Vitaliy Sazonov.
E-mail: vitaliy.sazonov@nu.edu.kz.
ORCID: 0000-0003-0437-4694.

Abstract

Introduction: Kidney transplantation is recognized as the most effective treatment for children with end-stage renal disease (ESRD), providing significant improvements in quality of life and long-term survival. Traditional methods to detect involve after allograft rejection AR primarily invasive biopsy procedures that, while diagnostic, carry significant risks, especially in pediatric patients. Therefore, there is an urgent need for safer, less invasive, and more patient-friendly methods to monitor graft health. Metabolomics, the comprehensive analysis of small-molecule metabolites within a biological sample, offers a promising solution.

Materials and Methods: This paper is a non-systematic review. PubMed and Scopus-indexed journals were used to collect articles for research. In general, 6 papers were included.

Results: Our findings indicate that specific urinary metabolites can serve as sensitive and specific indicators of AR, offering a safer alternative to biopsies. Metabolomic profiling not only provides real-time insights into graft health, but also supports personalized management strategies to improve patient outcomes. This study contributes to the evolving field of transplant diagnostics, demonstrating how non-invasive methods such as metabolomics could revolutionize the monitoring and treatment of pediatric kidney transplant recipients.

Keywords: Metabolomics, pediatrics, kidney transplantation, rejection, biomarkers.

Introduction

Kidney transplantation is recognized as the most effective treatment for children with end-stage renal disease (ESRD), offering significant improvements in quality of life and long-term survival [1, 2].

Additionally, pediatric kidney transplantation can improve growth and development outcomes, neurocognitive function, learning ability, and quality of life compared to young patients on chronic hemodialysis or peritoneal dialysis [3, 4].

Despite advances in posttransplant management, including immunosuppressive therapy, long-term success is still limited by complications of immunosuppression, rejection, and disease recurrence [5].

In Figure 1, we have plotted some of the possible complications according to their time of onset. It is important to note that some of these are unique to the pediatric population. And the risk of acute graft rejection (AR) remains high in both adults and children and can lead to graft dysfunction and loss if not promptly recognized and treated [6].

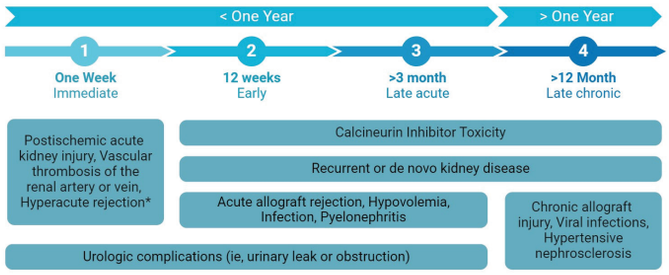


Figure 1 – Possible complications according to their time of onset

Traditional methods of detecting AR mainly involve invasive biopsy procedures that, while diagnostic, carry significant risks, especially in pediatric patients. These risks include bleeding, infection, and the psychological distress associated with invasive testing [7]. Therefore, there is an urgent need for safer, less invasive, and more patient-friendly methods to monitor graft health.

In recent years, attention has focused on identifying noninvasive biomarkers that can reliably predict acute rejection episodes. Non-invasive biomarkers detectable in biological fluids such as blood, urine, or saliva are a promising alternative to biopsy [8]. They have the potential to transform post-transplant care by allowing earlier and more frequent monitoring of graft status without the discomfort and risks associated with tissue biopsy.

Metabolomics, the comprehensive analysis of small molecule metabolites within a biological sample, offers a promising solution [9]. By reflecting the body's dynamic response to biological conditions or disease states, metabolomic profiling has the potential to serve as a sensitive and specific biomarker for the early detection of graft rejection.

The aim of our paper is to explore the use of metabolomics as a noninvasive biomarker of metabolomics profile in children with diverse graft conditions, including non-specified chronic injury after kidney transplantation. By analyzing changes in metabolic pathways and identifying signature metabolites associated with rejection, this study aims to contribute to the development of a safer and more effective approach to posttransplant monitoring that may significantly improve patient management and outcomes.

Methods

This review was conducted using peer-reviewed journals indexed in PubMed, Google Scholar, Scopus, and EMBASE. The literature search spanned from inception to 2024, focusing on articles related to metabolomics in pediatric kidney transplantation. The search strategy was designed to identify relevant studies, and the screening process included several steps.

First, all references identified by the database searches were independently reviewed at the abstract level by the lead author. Studies considered potentially relevant were selected for full-text retrieval and further assessment. To be eligible for inclusion, studies had to meet the following criteria 1) Population: Pediatric patients, regardless of body mass, who had undergone renal transplantation; 2) Intervention: Use of metabolomic analysis of urine samples; 3) Outcome: Any reported clinical outcome related to kidney transplantation or rejection; 4) Study design: Case reports, case series, retrospective or prospective studies; 5) General: Studies without identified conflicts of interest and those considered unbiased.

The following medical subject headings (MeSH) were used: 'metabolites'/exp OR metabolites AND 'kidney graft rejection'/exp OR 'kidney graft rejection' AND 'acute graft rejection'/exp OR 'acute graft rejection' AND 'child'/exp OR child; 'metabolites'/exp OR metabolites AND 'kidney graft rejection'/exp OR 'kidney graft rejection' AND ('child'/exp OR child; 'metabolites'/exp OR metabolites AND 'kidney transplantation'/exp OR 'kidney transplantation' AND 'child'/exp OR child AND 'kidney injury'/exp OR 'kidney injury'; 'metabolites'/exp OR metabolites AND 'kidney allograft rejection'/exp OR 'kidney allograft rejection' AND 'child'/exp OR child.

Studies were excluded if their populations overlapped with those of previously included articles or if they focused on adult populations. Following the screening and selection process, data were extracted and analyzed for inclusion in the final review. Only English language publications were included.

The flowchart of this literature search according to the PRISMA guidelines is shown in Figure 2.

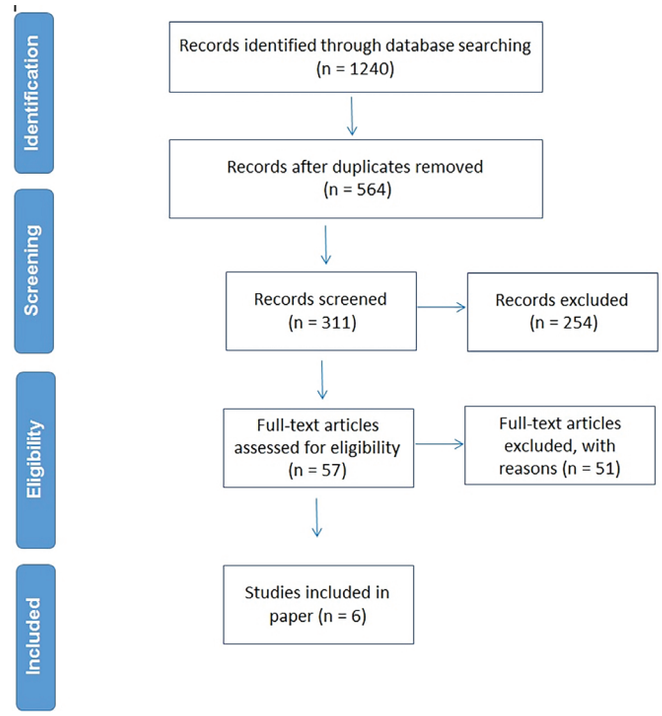


Figure 2 – Flowchart of Study Selection

Results

A total of six clinical research articles were included in the final analysis. These studies primarily presented aggregated clinical and laboratory data from pediatric patients who had undergone renal transplantation. A total of 716 samples were reported, with the number of metabolites reported ranging from 10 to 20 in each study.

All included studies focused on posttransplant patients; however, the objectives of the studies varied. Two studies specifically investigated the metabolite profiles associated with T-cell-mediated rejection, while one study focused on antibody-mediated rejection. In addition, one study each investigated acute rejection, chronic rejection and nonrejection renal injury. A detailed summary of the metabolite data and the study objectives is provided in Table 1.

Table 1 Summary of the studies from 1999-2024 on metabolites as non-invasive biomarkers of allograft injury/ rejection in kidney pediatric transplantation

	Author, year	Sample, n	Goal of the study	Result
1.	Blydt-Hansen et al. 2014 [10]	Urine, n = 57 Pts	T cell–mediated rejection (TCMR) metabolites	10 metabolites classifier, AUC = 0.88
2.	Blydt-Hansen et al. 2017 [11]	Urine, n = 59 Pts	Antibody-mediated rejection metabolites	10 metabolites classifier AUC = 0.806
3.	Mincham et al. 2018 [12]	Urine, n = 40 Pts.	Association b/w TCMR acuity and urine biomarkers	Urine metabolites + CXCL10 are better in assessing TCMR acuity than GFR
4.	Landsberg et al. 2018 [13]	Urine, n = 51 Pts.	Chronic injury metabolites after KTx	20 metabolites classifier, IFTA (AUC = 0.71), percent GS (AUC = 0.81)
5	Archdekin et al. 2019 [14]	Urine, n =199 samples	Non-rejection kidney injury metabolites	20 metabolites classifier, AUC = 0.79
6.	Sigdel et al. 2020 [15]	Urine, n = 310 Pts	Acute rejection, and kidney injury metabolites in KTx	11 metabolites and 9 metabolites

Pts, Participants; KTx kidney transplantation.

This variation in the focus of the study highlights the diversity of metabolic alterations associated with different forms of graft injury in pediatric renal transplantation. Despite differences in the type of rejection studied, all reports provided valuable insight into the potential utility of metabolomics as a biomarker of graft health and injury.

T cell-mediated rejection (TCMR)

Blydt-Hansen et al. established one of the first reports on metabolites associated with T-cell-mediated rejection (TCMR) in the pediatric cohort [10]. The availability of urine samples provided an opportunity to investigate the metabolic signature that directly reflects the catabolic and anabolic pathways inside transplanted kidney tissue. Urine samples of 57 patients were collected and cases with biopsy confirmed TCMR and non-TCMR were analyzed. Metabolics was run in accordance with the provided list of urine metabolites through liquid chromatography and then mass spectrometry [16]. 134 metabolites were identified in each sample. Urine samples were selected only in the presence of biopsy material collected for surveillance in a two-year period. The quantitative amount of metabolites was normilized to urine creatinine. The partial least squares discriminant analysis (PLS-DA) model suggested a threshold for a discriminant score of -0.4 to predict the presence of TCMR in comparison to non TCMR samples. The predictive accuracy of this discriminant score (AUC = 0.892) was shown to be higher compared to the prediction based on creatinine value (AUC = 0.756). Metabolites that were run in this PLS-DA model retained more than 50% significance of the TCMR discriminant value and were shown to be significantly different from the non TCMR group. The metabolites were: proline, PC: aa: C34: 4, kynurenine, sarcosine, methionine.SO, PC: ae: C38: 6, sulfoxide, threonine, glutamine, phenylalanine, alanine. The prediction model based on the selected 10 metabolites comprised AUC = 0.88 which is still higher than AUC = 0.756 based on GFR. Furthermore, the discriminant score for the condition of borderline tubulitis that reflects the extent of kidney injury was placed in the range between non-TCMR and TCMR cases. This supports the notion that tubulitis is in the continuity towards development of TCMR phenotype [10]. This study investigated metabolites that could reflect the state of T cell–mediated rejection in a period of 2 years after transplantation.

Mincham et al. assessed the association between the severity of kidney rejection histology and urinary biomarkers [12]. The study examined a sequential pair of biopsy samples along with urine metabolites and CXCL10. CXCL10 chemokine was selected as a marker of T cell cytotoxicity. The first tissue sample was performed > 2.5 months after kidney transplantation. The second kidney sampling was carried out in a period of 1-3 months after the first biopsy. The urine metabolites and CXCL10 was taken before biopsy. At the same time, GFR measurements were performed at the beginning of the study, every time prior to biopsy, and at a 12-month interval. The material of 40 patients was collected. Metabolite discriminant score (MDS), was obtained according to the same pattern as in the previous studies conducted by Blydt-Hansen et al. following the PLS analysis. The results showed that the change in GFR taken to assess severity between two consequential biopsies did not reflect any significance in TCMR acuity. On the contrary, changes as well as the change in metabolite discriminant scores of two tissue samples, were shown to contain significant association with the severity of T-cell-mediated kidney rejection [12]. This was the first study to implement an assessment of the metabolic change in combination with chemokine CXCL10 to assess the acuity of TCMR in two consecutive histological samples.

Antibody-mediated rejection

Blydt-Hansen et al. team also investigated the urine metabolomic signature in the antibody mediated rejection (AMR) after kidney transplantation [11]. The study included 59 patients. AMR was selected in comparison to the non-AMR group on histopathological presence of antibodies that interact with kidney endothelium and presence of donor-specific HLA antibodies (DSA) in plasma. Biopsies were collected in the first month and then every 3-6-12 months after transplantation. Liquid chromatography along with mass spectrometry analysis identified 133 metabolites in each urine sample. Partial least squares (PLS) analysis was applied to determine AMR discriminant score. The mean AMR score was 0.28 ± 0.14 with the threshold level for AMR prediction 0.23, while the mean score for non-AMR was 0.10 ± 0.13. Interestingly, it was shown that other inflammatory conditions such as UTI have an AMR score of 0.07 ± 0.08 which is similar to the non-AMR group. It shows that AMR differentiates between rejection and inflammation. The AMR model highlighted the contribution of 10 metabolites with AUC = 0.806: proline, citrulline, phosphatidylcholine aa.C34.4, C10.2, tetradecanoylcarnitine, lysine, methionine sulfoxide, hexose, threonine, acetylornithine. It is noteworthy that the first five metabolites were statistically significant compared to the AMR and non-AMR groups. Interestingly, the AMR group also demonstrated some clinical differences. Posttransplantation time in the AMR group was almost two times higher versus non-AMR group. Although proteinuria was the same in both groups, the AMR group showed a 25% decrease in eGFR compared to non-AMR samples. When the AMR classifier model was compared to the previous TCMR model, common metabolites such as PC.aa.C34.4, proline, citrulline, methionine sulfoxide and threonine. were noticed [11].

This supports the common pathophysiology in the mechanism of allograft rejection. Therefore, the study demonstrated the development of an antibody-mediated rejection classifier with 10 distinct metabolites that share common composition with T-cell-mediated kidney allograft rejection.

Chronic injury metabolites after KTx

The next study highlighted the search of metabolites specificity for post transplantation chronic kidney injury [13]. The study model was based on the previously elaborated PLS discriminant analysis, resulting in the elucidation of the discriminant score, i.e., Dscore. The Dscore was obtained as a solution to the discriminant equation, where the relative weight of the 133 urine metabolites was considered during model training towards a specific clinical condition. In this study, the dscore was calculated for glomerulosclerosis (GS) and interstitial fibrosis and tubular atrophy (IFTA) that were assumed to be chronic damage processes that accumulate after allograft transplantation [13]. 51 participants were included and sampling time was 28.9 ± 30.3 months after allograft transplantation. As a result, 20 most important metabolites for IFTA (AUC = 0.71), percent GS (AUC = 0.81) were identified. IFTA metabolites consisted of hexose, ornithine, leucine, c8, arginine, SM.OH.C22.2, histamine, C5.1, PC.aa.C30.2, histidine, lysine, C4.1, SM.C16.0, C6.1, C5.OH. C3.DC.M, SM.C20.2, PC.aa.C32.3, C5.M.DC, C3.DC.C4.OH, PC.ae.C38.2. While GS metabolites were arginine, C8, Met. SO, C5.OH.C3.DC.M, histidine, threonine, C10.2, kynurenine, glutamine, SM.OH.C22.2, proline, SM.C16.0, PC.aa.C30.2, ornithine, SM.C26.1, C4.1, leucine, SDMA, SM.C20.2, histamine. The classifiers share 12 metabolites in common, representing the intertwined nature of two processes in the formation of a chronic kidney injury condition. Therefore, the study was the first to define the metabolome composition of urea for such chronic processes such as IFTA and GS.

Non-rejection kidney injury after KTx

Another study searched for metabolites during nonrejection kidney injury (NRKI) emerged [14]. The authors assumed that NRKI may be one of the pathophysiological mechanisms as a result of adult kidney transplantation to a child that cannot meet the perfusion demands of an organ. During selection, all tissue that contained signs or rejection such as TCMR, AMR were excluded from NRKI group, thus reflecting the cohort with the clinical and histological traits of kidney injury phenotype. The study applied the PLS-DA method to measure the contribution of the 133 metabolites found in each urine sample that best describes the clinical condition of interest [14]. 199 urine samples were run through the machine learning protocol to identify NRKI and non-NRKI metabolites. Thus, 20 most significantly contributing the the phenotype were selected (AUC = 0.79): Orn, Met.SO, Leu, Hexose, Ac.Orn, PC.aa.C34.4, Pro, C5.1, C4, C3.OH, PC.ae.C44.5, PC.aa.C30.2, ADMA, Histamine, C9, Met, C2, C5.M.DC, C5.OH.C3.DC.M. Furthermore, the model was able to distinguish NRKI from clinical rejection with AUC = 0.81. The current investigation was the first in the direction of metabolite identification to differentiate between patterns of kidney injury and kidney rejection.

Acute rejection and kidney injury in KTx

One of the recent studies identified the panel of metabolites that differentiate kidney injury and rejection based on the larger number of participants (n=310) compared to previous studies [15]. Gas chromatography-mass spectrometry analysis identified 266 metabolites present in the urine samples of participants. After applying VSURF methodology, the team identified 9 metabolites (Glycine, N-methylalanine, Adipic acid, Glutaric acid, Inulobiose, Threitol, Isothreitol, Taurine, Sorbitol, Isothreonic acid) that characterized acute and chronic injury after transplantation in comparison to stable allograft phenotype (AUC = 0.950). Applying the same method, they identified 11 metabolites (Glycine, Glutaric acid, Adipic acid, Inulobiose, Threose, Sulfuric. Taurine, acid N-methylalanine, Asparagine, 5-aminovaleric acid lactam, Myo-inositol) differentiating the acute rejection phenotype from the stable allograft (AUC = 0.985). Thus, the study investigated a panel for the the metabolic signature for phenotypes of kidney injury and acute rejection compared to stable kidney transplant [15].

Discussion

Although a few studies were conducted in search of metabolomic profile for detection of allograft rejection, some conclusions could be drawn. Notably, five out six studies described in this review were conducted by the Blydt-Hansen et al. team. The team applied the partial least squares discriminant analysis (PLS-DA) model, highlighting the most frequent metabolites that are converted into a classifier. In every study, gas chromatography and mass spectrometry analysis detected only 133-134 metabolites, in comparison with the last study conducted by Sigdel TK et al., where the team detected 266 metabolites. Although the spectrum of urine metabolites includes 2651 identified compounds [16], only 5 % of the total identified urine metabolites was mentioned in the first five studies and 10 % in the last study. Both teams applied different bioinformatics methodologies to identify the most frequently attractive metabolites. It is interesting to know whether the classifiers composition changes if the number of detected metabolites increases and the bioinformatics methodology is unified. It should also be mentioned that only last study elaborated on the metabolic pathways that were involved based on the metabolite composition. Separation between acute and chronic rejection would also be beneficial for unifying common metabolic panels for acute and chronic states. However, in order to elucidate similar patterns of metabolites as biomarkers predicting allograft rejection, the ideal scenario includes patients with the same meal plan, drug consumption, enzyme liver activity and similar microbiome patterns, since urine contains the waste products of all reactions in the body. Therefore, to generalize the metabolic panel predicting kidney allograft rejection, further studies should be implemented, starting with the description of the metabolic pathways involved and stratification of the patient with respect to the drugs consumed, food preferences, and microbiome characterization.

Traditional methods and their limitations

Traditional methods for detecting renal allograft rejection in pediatric patients include serum creatinine, proteinuria measurement, and renal biopsy. Although these methods are fundamental to transplant monitoring, they have significant limitations that can affect clinical decision-making and patient outcomes.

The measurement of creatinine and its derivatives, although inexpensive and accessible, has low specificity and sensitivity. In pediatric practice, subclinical rejection confirmed histologically by biopsy is often found in the absence of any change in creatinine levels [17].

The study by Naesens and colleagues shown that, despite its relatively high specificity for transplant glomerulopathy, microcirculatory inflammation, and glomerular disease, proteinuria has a low sensitivity for intragraft injury [18]. Thus, proteinuria can be >1.0 g/24 h, and significant injury also confirmed histologically.

Although tissue biopsy is the gold standard for assessing graft status in transplantation [19], its use, especially in pediatric patients, is associated with complications, including the risk of adverse events such as bleeding and arteriovenous fistula, variability in interpretation, and is usually limited to the early post-transplant period [7, 20].

There continues to be a debate about the role of protocol biopsies in altering long-term allograft survival due to variability in immunosuppressive regimens and treatment of subclinical rejection. Studies suggest that pre-emptive treatment based on subclinical signs may improve graft survival, but stable patients sometimes show no adverse effects due to lack of treatment despite biopsies indicating potential problems [21, 22]. Another challenge in the routine use of biopsies is the variability in interpretation. Interpretation of biopsy results can vary widely depending on the pathologist's experience and the quality of the specimen [23]. This variability can lead to inconsistent diagnoses that affect treatment decisions. However, biopsy is currently the validation method for the development of new noninvasive markers.

Search for noninvasive biomarkers

The need for non-invasive monitoring is underscored by the results of studies such as the Canadian PROBE study, which suggest that traditional functional monitoring cannot adequately resolve or accurately assess the treatment of rejection episodes [24]. This underscores the growing interest in the need for improved non-invasive monitoring techniques that can provide a continuous and reliable assessment of graft status and help to better tailor personalized treatment strategies.

Urine biomarkers are the most promising way to noninvasively monitor graft status in pediatric kidney transplant patients. Unlike tissue biopsy, urine biomarkers offer a safe, reproducible, and stress-free alternative for ongoing assessment [25]. This is particularly important in children, where avoiding invasive procedures is a priority due to their smaller anatomical size, higher risk of procedural complications and the psychological impact of repeated procedures. Biomarkers in urine can be collected non-invasively and frequently, allowing real-time monitoring of graft function and detection of early rejection without the need for hospital visits or anesthesia [26].

The studies presented in this review offer significant potential for noninvasive monitoring of kidney transplant status in the pediatric population using urinary metabolomic biomarkers. These results highlight the potential of these biomarkers to improve the detection, differentiation, and management of renal allograft injury and rejection, thus improving patient care and reducing the reliance on invasive biopsy procedures.

Metabolomics play an important role in the early detection of AKI in kidney transplant recipients and in the differentiation between NRKI and rejection in children. Thus, the Archdekin study highlights the potential of metabolomics as a powerful tool for the noninvasive diagnosis and differentiation of NRKI from acute graft rejection (AR) in pediatric kidney transplant recipients [15]. The development of a urinary metabolite signature to accurately differentiate NRKI from AR represents a significant step forward in the post-transplant management of pediatric patients. The results of this study are particularly relevant in clinical settings where the distinction between NRKI and rejection is critical to determine the appropriate intervention. Current methods, based primarily on invasive biopsies and serum creatinine measurement, do not adequately detect NRKI at an early stage, often resulting in delayed or inadequate treatment. The introduction of a metabolomic approach could significantly change the approach by providing a rapid, non-invasive, and reliable method to assess renal function and identify lesion types.

Our analysis also highlights the potential of metabolomics to generate highly sensitive and specific biomarkers of acute rejection and BK-viral nephritis (BKVN) [16]. Additionally, the ability to differentiate BKVN from acute rejection using a separate set of four metabolites underscores the individualized approach to metabolomics. BKVN, which is often difficult to diagnose and treat, can have a significant impact on patient management. The ability to distinguish between different types of kidney damage using noninvasive urine tests represents a significant advance in transplantation, especially in pediatric populations who are often more susceptible to the risks associated with invasive procedures.

Advantages of Metabolomics

The use of metabolomics has the distinct advantage of providing a real-time metabolic snapshot of the organ. This is very important in transplantation, where early intervention can dramatically affect patient outcome. The ability to detect acute and borderline TCMR with high accuracy may help physicians more effectively tailor immunosuppressive therapy, potentially prolonging graft survival and improving patient quality of life [10, 13]. The incorporation of urine metabolomics into routine posttransplant monitoring may change current practice by reducing the frequency and need for invasive biopsies, which carry a risk of complications and are particularly challenging in the pediatric population.

Studies have shown that certain metabolomic profiles can predict long-term renal function and graft survival. For example, the Metabolite Discriminant Score (MDS) correlates with changes in kidney graft health over time and has been shown to predict mid- to long-term functional outcomes [13, 22]. This predictive ability allows the development of more personalized management strategies and the adjustment of immunosuppressive therapy prior to the onset of clinical symptoms or irreversible damage.

Considering the potential of urinary metabolomics as the least invasive, other studies are noteworthy. For example, Wang et al. conducted a study in adults showing that the intestinal metabolic profile of patients with AMR was significantly different from that of patients with ESRD, while it was not clearly different from that of recipients with stable renal function [27].

Additionally, metabolomic studies can be performed in different biological media from the same patient, potentially increasing the diagnostic relevance. Iwamoto and colleagues used CE-MS to analyze the metabolomic profiles of saliva, plasma, and urine collected from kidney transplant recipients and donors. Clear differences in metabolomic profiles were demonstrated between recipients with impaired and stable renal function [28].

Challenges and barriers to metabolomics implementation

At the same time, we should understand some challenges and barriers to the implementation of metabolomics [29]. One of the major challenges in using metabolomics for clinical diagnosis, such as the detection of acute transplant rejection, is achieving high sensitivity and specificity. Metabolic changes associated with rejection can be subtle and masked by metabolic fluctuations caused by other physiological or pathological conditions. The identification of metabolites that are consistently and uniquely altered during graft rejection requires comprehensive and controlled studies [30]. The reproducibility of metabolomic analyzes can be affected by variations in sample

collection, processing, and storage, as well as differences in analytical techniques and equipment. Standardizing these aspects is crucial to ensure that metabolomic profiles are reliable and comparable across different settings and time points [31]. For metabolomics to be applicable in clinical settings, the methods used must be compatible with the routine workflow of medical laboratories. This includes aspects such as cost, analysis time, and the need for specialized equipment and trained personnel [32]. Collaboration between researchers, clinicians, and industry is needed to overcome these challenges. The development of robust, standardized, and validated protocols and advanced computational tools for data analysis will increase the reliability and clinical utility of metabolomics.

The limitations of our study are that we only considered urinary metabolomics and only in pediatric practice in the post-transplant period. However, other omics can be considered as potential and diagnostically relevant. For example, consider metabolomics in the diagnosis of other acute and chronic diseases.

Conclusion

Our study highlights the promising potential of metabolomics as a noninvasive biomarker for the detection of graft rejection in pediatric kidney transplant recipients. By identifying specific metabolic signatures in urine, our study provides an important tool that can significantly improve post-transplant monitoring by offering a reliable, safe, and patient-friendly alternative to invasive biopsies. The results highlight the sensitivity and specificity of urinary metabolites in reflecting the status of the graft, which can allow earlier and more accurate interventions to prevent graft loss and improve long-term results.

Furthermore, the use of metabolomics represents a shift toward more personalized medicine, where treatments can be tailored based on individual metabolic changes. This may lead to a more nuanced and effective management of immunosuppression, reducing the incidence of rejection and other complications associated with pediatric kidney transplantation. Future research should focus on large-scale multicenter studies to validate these findings and facilitate the development of standardized guidelines for the use of urinary biomarkers and metabolomics in clinical practice. In addition, the combination of metabolomics with other "omics" technologies, such as genomics and proteomics, may lead to a more comprehensive understanding of graft health and rejection mechanisms. This integrated approach may pave the way for truly personalized medicine in kidney transplantation.

Author Contributions: Conceptualization and methodology, V.S and A.Z.; resources, G.D. and M.B.; writing – original draft preparation, V.S. and A. Z.; writing – review and editing, A.B. and S.A.; supervision, Y. P. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: This research has been funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. BR21882206).

References

1. Medynska A, Kilis-Pstrusinska K, Makulska I, Zwolinska D. Kidney transplantation and other methods of renal replacement therapy in children: 30 years of observations in one center. Adv Clin Exp Med. 2020; 29(5): 611–613. https://doi.org/10.17219/acem/121928.
2. Voora S, Adey DB. Management of Kidney Transplant Recipients by General Nephrologists: Core Curriculum 2019. *Am J Kidney Dis.* 2019; 73(6): 866–879. https://doi.org/10.1053/j.ajkd.2019.01.031.
3. Ingelfinger JR, Kalantar-Zadeh K, Schaefer F, World Kidney Day Steering C. Averting the legacy of kidney disease–focus on childhood. *Kidney Int.* 2016; 89(3): 512–518. https://doi.org/10.1016/j.kint.2015.10.014.
4. Bonthuis M, Groothoff JW, Ariceta G, Baiko S, Battelino N, Bjerre A, et al. Growth Patterns After Kidney Transplantation in European Children Over the Past 25 Years: An ESPN/ERA-EDTA Registry Study. *Transplantation*. 2020; 104(1): 137–144. https://doi.org/10.1097/TP.0000000000002726.
5. Marcou M, Galiano M, Tzschoppe A, Sauerstein K, Wach S, Taubert H, et al. Risk Factor Analysis for Long-Term Graft Survival Following Pediatric Kidney Transplantation: The Importance of Pretransplantation Time on Dialysis and Donor/Recipient Age Difference. *J Clin Med.* 2023; 12(22). https://doi.org/10.3390/jcm12227014.
6. Bertacchi M, Parvex P, Villard J. Antibody-mediated rejection after kidney transplantation in children; therapy challenges and future potential treatments. *Clin Transplant.* 2022; 36(4): e14608. https://doi.org/10.1111/ctr.14608.
7. Gordillo R, Munshi R, Monroe EJ, Shivaram GM, Smith JM. Benefits and risks of protocol biopsies in pediatric renal transplantation. Pediatr Nephrol. 2019; 34(4): 593–598. https://doi.org/10.1007/s00467-018-3959-6.
8. Peruzzi L, Deaglio S. Rejection markers in kidney transplantation: do new technologies help children? Pediatr *Nephrol*. 2023; 38(9): 2939–2955. https://doi.org/10.1007/s00467-022-05872-z.
9. Pan X, Peng J, Zhu R, An N, Pei J. Non-invasive biomarkers of acute rejection in pediatric kidney transplantation: New targets and strategies. *Life Sci.* 2024; 348: 122698. https://doi.org/10.1016/j.lfs.2024.122698.
10. Blydt-Hansen TD, Sharma A, Gibson IW, Mandal R, Wishart DS. Urinary metabolomics for noninvasive detection of borderline and acute T cell-mediated rejection in children after kidney transplantation. *Am J Transplant.* 2014; 14(10): 2339–2349. https://doi.org/10.1111/ajt.12837.
11. Blydt-Hansen TD, Sharma A, Gibson IW, Wishart DS, Mandal R, Ho J, et al. Urinary Metabolomics for Noninvasive Detection of Antibody-Mediated Rejection in Children After Kidney Transplantation. *Transplantation*. 2017; 101(10): 2553–2561. https://doi.org/10.1097/TP.0000000000001662.
12. Mincham CM, Gibson IW, Sharma A, Wiebe C, Mandal R, Rush D, et al. Evolution of renal function and urinary biomarker indicators of inflammation on serial kidney biopsies in pediatric kidney transplant recipients with and without rejection. *Pediatr Transplant.* 2018; 22(5): e13202. https://doi.org/10.1111/petr.13202.
13. Landsberg A, Sharma A, Gibson IW, Rush D, Wishart DS, Blydt-Hansen TD. Non-invasive staging of chronic kidney allograft damage using urine metabolomic profiling. *Pediatr Transplant.* 2018; 22(5): e13226. https://doi.org/10.1111/petr.13226.

14. Archdekin B, Sharma A, Gibson IW, Rush D, Wishart DS, Blydt-Hansen TD. Non-invasive differentiation of non-rejection kidney injury from acute rejection in pediatric renal transplant recipients. *Pediatr Transplant.* 2019; 23(3): e13364. https://doi.org/10.1111/petr.13364.
15. Sigdel TK, Schroeder AW, Yang JYC, Sarwal RD, Liberto JM, Sarwal MM. Targeted Urine Metabolomics for Monitoring Renal Allograft Injury and Immunosuppression in Pediatric Patients. *J Clin Med*. 2020; 9(8). https://doi.org/10.3390/jcm9082341.
16. Bouatra S, Aziat F, Mandal R, Guo AC, Wilson MR, Knox C, et al. The human urine metabolome. *PLoS One.* 2013; 8(9): e73076. https://doi.org/10.1371/journal.pone.0073076.
17. Moudgil A, Martz K, Stablein DM, Puliyanda DP. Variables affecting estimated glomerular filtration rate after renal transplantation in children: a NAPRTCS data analysis. *Pediatr Transplant.* 2010; 14(2): 288–294. https://doi.org/10.1111/j.1399-3046.2009.01222.x.
18. Naesens M, Lerut E, Emonds MP, Herelixka A, Evenepoel P, Claes K, et al. Proteinuria as a Noninvasive Marker for Renal Allograft Histology and Failure: An Observational Cohort Study. *J Am Soc Nephrol.* 2016; 27(1): 281–292. https://doi.org/10.1681/ASN.2015010062.
19. Williams WW, Taheri D, Tolkoff-Rubin N, Colvin RB. Clinical role of the renal transplant biopsy. *Nat Rev Nephrol.* 2012; 8(2): 110–121. https://doi.org/10.1038/nrneph.2011.213.
20. Kanzelmeyer NK, Lerch C, Ahlenstiel-Grunow T, Brasen JH, Haffner D, Pape L. The role of protocol biopsies after pediatric kidney transplantation. *Medicine (Baltimore).* 2020; 99(23): e20522. https://doi.org/10.1097/MD.0000000000020522.
21. Kanzelmeyer NK, Ahlenstiel T, Drube J, Froede K, Kreuzer M, Broecker V, et al. Protocol biopsy-driven interventions after pediatric renal transplantation. *Pediatr Transplant*. 2010; 14(8): 1012–1018. https://doi.org/10.1111/j.1399-3046.2010.01399.x.
22. Zotta F, Guzzo I, Morolli F, Diomedi-Camassei F, Dello Strologo L. Protocol biopsies in pediatric renal transplantation: a precious tool for clinical management. *Pediatr Nephrol.* 2018; 33(11): 2167–2175. https://doi.org/10.1007/s00467-018-4007-2.
23. Furness PN, Taub N, Convergence of European Renal Transplant Pathology Assessment Procedures P. International variation in the interpretation of renal transplant biopsies: report of the CERTPAP Project. *Kidney Int.* 2001; 60(5): 1998–2012. https://doi.org/10.1046/j.1523-1755.2001.00030.x.
24. Hoffmann AJ, Gibson IW, Ho J, Nickerson P, Rush D, Sharma A, et al. Early surveillance biopsy utilization and management of pediatric renal allograft acute T cell-mediated rejection in Canadian centers: Observations from the PROBE multicenter cohort study. *Pediatr Transplant.* 2021; 25(2): e13870. https://doi.org/10.1111/petr.13870.
25. Sequeira-Antunes B, Ferreira HA. Urinary Biomarkers and Point-of-Care Urinalysis Devices for Early Diagnosis and Management of Disease: A Review. *Biomedicines*. 2023; 11(4). https://doi.org/10.3390/biomedicines11041051.
26. Pierce JD, McCabe S, White N, Clancy RL. Biomarkers: an important clinical assessment tool. *Am J Nurs*. 2012; 112(9): 52–58. https://doi.org/10.1097/01.NAJ.0000418926.83718.28.
27. Wang J, Zhang X, Li M, Li R, Zhao M. Shifts in Intestinal Metabolic Profile Among Kidney Transplantation Recipients with Antibody-Mediated Rejection. *Ther Clin Risk Manag.* 2023; 19: 207–217. https://doi.org/10.2147/TCRM.S401414.
28. Iwamoto H, Okihara M, Akashi I, Kihara Y, Konno O, Kawachi S, et al. Metabolomic Profiling of Plasma, Urine, and Saliva of Kidney Transplantation Recipients. *Int J Mol Sci.* 2022; 23(22). https://doi.org/10.3390/ijms232213938.
29. Li S, Looby N, Chandran V, Kulasingam V. Challenges in the Metabolomics-Based Biomarker Validation Pipeline. *Metabolites*. 2024; 14(4). https://doi.org/10.3390/metabo14040200.
30. Alseekh S, Aharoni A, Brotman Y, Contrepois K, D'Auria J, Ewald J, et al. Mass spectrometry-based metabolomics: a guide for annotation, quantification and best reporting practices. *Nat Methods.* 2021; 18(7): 747–756. https://doi.org/10.1038/s41592-021-01197-1.
31. Dalamaga M. Clinical metabolomics: Useful insights, perspectives and challenges. *Metabol Open.* 2024; 22: 100290. https://doi.org/10.1016/j.metop.2024.100290.
32. Taunk K, Jajula S, Bhavsar PP, Choudhari M, Bhanuse S, Tamhankar A, Naiya T, Kalita Bh, Rapole S. The prowess of metabolomics in cancer research: current trends, challenges and future perspectives. *Mol Cell Biochem.* 2024. https://doi.org/10.1007/s11010-024-05041-w.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/15715

Unraveling Vitiligo: From Immune Mechanisms to Promising Therapeutic Strategies

Artur Kovenskiy[1], Nurlubek Katkenov[1], Zhussipbek Mukatayev[1], Almagul Kushugulova[1]

[1]*National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan*

Received: 2024-10-04.
Accepted: 2024-12-12

J Clin Med Kaz 2024; 21(6): 18–23

Corresponding author:
Almagul Kushugulova.
E-mail: akushugulova@nu.edu.kz
ORCID: 0000-0001-9479-0899

Abstract

Vitiligo is a dermatological condition affecting 1% of the global population, characterized by the loss of skin pigmentation. It appears in two main forms: nonsegmental (symmetrical depig-mentation) and segmental (localized depigmentation). Oxidative stress and mitochondrial dysfunc-tion in melanocytes cause vitiligo, while immune privilege protects hair follicle melanocytes, allow-ing for possible repigmentation. Genetic factors and associations with other autoimmune diseases, such as type 1 diabetes and thyroiditis, suggest a heritable autoimmune component. CD8+ T cells play a crucial role in vitiligo, targeting melanocytes and promoting apoptosis. These cells, along with IFN-γ signaling, contribute to disease progression. Therapies targeting these pathways, such as JAK inhibitors, have shown promise in repigmentation, particularly when combined with nar-rowband UVB phototherapy, a gold standard treatment. Surgical interventions, including punch grafting and suction blister grafting, show high efficiency but bring high risks of skin damage and hyperpigmentation. Vitiligo patients experience significant emotional suffering, requiring both a psychological and medical treatment approach. Dietary interventions, specifically those rich in anti-oxidants, may support disease treatment. Vitamin D, in particular, is a promising therapeutic agent by protecting melanocytes from oxidative stress via the WNT/β-catenin pathway. This review points out the need for more research on targeted therapies that combine immune regulation, photo-therapy, and dietary strategies for effective vitiligo treatment.

Keywords: vitiligo, interferon gamma, melanocyte, janus kinases.

Introduction

Vitiligo is a distinctive dermatological condition characterized by the loss of pigmentation in patch-es of skin. It affects approximately 1% of the global population regardless of sex, ethnicity, or geo-graphic region [1]. As illustrated in Figure 1, vitiligo can present in two main forms: nonsegmental and segmental.

Nonsegmental vitiligo, the more prevalent form, usually manifests symmetrically in acral areas. In contrast, segmental vitiligo is affects one region of the skin and often progresses more quickly, sometimes leading to early hair whitening [2, 3]. The entire epithelium of vitiligo patients is sub-jected to increased oxidative stress, which leads to significant metabolic disruptions, particularly within the mitochondria [2].

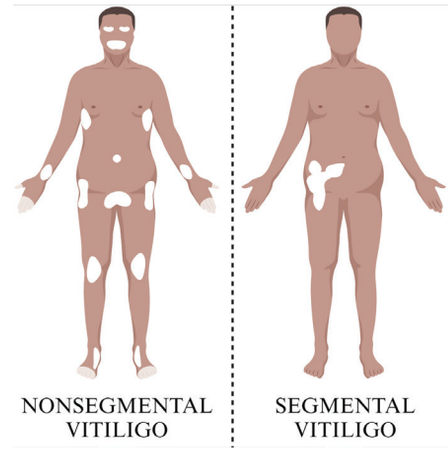


Figure 1 – Vitiligo types

Created in BioRender.com

The disease is marked by its ability to reverse, distinguishing it from many other autoimmune disorders.

The primary targets of vitiligo are melanocytes, the cells re-sponsible for pigment production located in the interfollicular epidermis. However, melanocytes residing within the hair follicles often remain unaffected due to immune privilege at these sites. This immune protection is similar to the privileged melanocytes located in the brain, eyes, and inner ear [4]. Hair follicles contain melanocyte stem cells capable of repopulating the epidermis in vitili-go-affected areas. This process allows new, functional melanocytes to restore pigmentation in the skin. As a result, repigmentation typically occurs as small spots around hair follicles. Nonetheless, areas lacking hair or containing white hairs, where follicular melanocytes have not been protected from autoimmunity, do not repigment [4]. The statement that genetic factors play a significant role in vitiligo appears from observing a high incidence in certain families and an increased risk among individuals with first-degree relatives affected by the condition [5]. Moreover, the association of vitiligo with other autoimmune diseases, such as type 1 diabetes, autoimmune thyroiditis, and rheumatoid arthritis, points to a shared heritable risk for autoimmunity [5-7].

While a variety of treatment strategies are currently available for vitiligo, including topical agents, phototherapy, and surgical approaches, achieving consistent and sustained repigmentation remains a significant challenge [3]. This study aims to explore which existing therapies may dis-play synergy when combined, with a particular focus on enhancing repigmentation outcomes in treatment-resistant cases. Also underlining the gap in the knowledge about environmental factors of the vitiligo patients, such as psychological impact and vitamin D deficiency [8, 9], as it is important but rare discussed in traditional treatment strategies.

Vitiligo Pathogenesis

Patients with vitiligo have been found to have elevated serum levels of melanocyte-reactive anti-bodies, which have shown the capacity to damage melanocytes in vitro and in vivo models [10-12]. However, the role of these autoantibodies in disease pathogenesis is questionable, as the antibody-induced damage is relatively weak, and their titers do not correlate with disease activity [13, 14]. Histological examination of vitiligo lesions has revealed lymphocytic infiltrates, predominantly composed of CD8+ T cells, at the borders of depigmented areas, indicating active disease [15]. These CD8+ T cells have been found in increased numbers in both the skin of active lesions and in the peripheral blood of vitiligo patients, compared to healthy individuals [16-18]. CD8+ T cells specifically target melanocyte antigens, such as tyrosinase and Melan-A/MART-1 [19]. Remarka-bly, CD8+ T cells isolated from peri-lesional skin can induce melanocyte apoptosis in vitro, facili-tating the appearance of new depigmented patches. While the presence of antimelanocyte antibodies in vitiligo patients suggests an autoimmune component, the primary drivers of the disease appear to be CD8+ T cells. As shown in Figure 2 CD8+ T cells and their production of interferon-gamma (IFN-γ) orchestrates the disease's pathogenesis [1].

The recruitment of these pathogenic CD8+ T cells to the skin is mediated by a network of cyto-kines and chemokines, which are upregulated in the lesional skin of vitiligo patients. Gene expres-sion analyses have demonstrated an increased presence of IFN-γ and IFN-γ–dependent genes, such as the chemokine receptor CXCR3 and its ligands CXCL9, CXCL10,

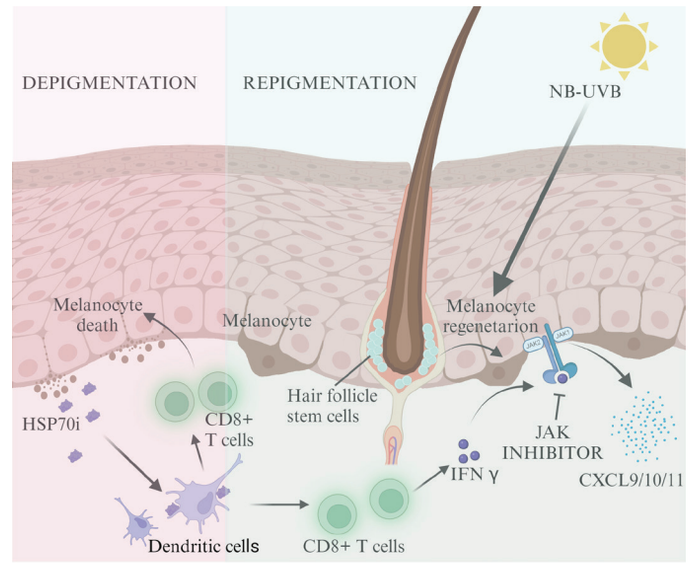


Figure 2 – Vitiligo pathogenesis and treatment approaches

Depigmentation is caused by stress-induced HSP70i, which recruits CD8+ T cells by activation of dendritic cells. CD8+ T cells produce IFN-γ, which induces release of chemokines CXCL9, CXCL10, CXCL11, further recruiting T cells to the affected area. JAK inhibitor therapy blocks the IFN-γ signaling pathway, thereby reducing chemokine production. At the same time NB-UVB therapy facilitates melanocyte regeneration from melanocyte stem cells preserved among hair fol-licle stem cells. IFN-γ: Interferon-gamma, NB-UVB: Narrowband ultraviolet B, JAK: Janus ki-nase, CXCL 9-11: C-X-C motif ligand 9-11. Created in BioRender.com

and CXCL11, which facili-tate the chemotaxis of T cells to the affected areas [20]. Recent research has shifted interest to keratinocytes as the primary producers of these chemokines. Disruption of IFN-γ signaling specifi-cally in keratinocytes has been shown to reduce depigmentation in mouse models. This suggests that topical targeting of IFN-γ signaling in these cells might offer a novel and effective treatment strategy for vitiligo [21]. This is supported by clinical evidence where blockade of the IFN-γ path-way using JAK inhibitors, such as tofacitinib or ruxolitinib, has led to rapid repigmentation in pa-tients with vitiligo. The decrease in serum CXCL10 levels post-treatment with JAK inhibitors fur-ther validates the mechanistic role of IFN-γ signaling in the disease [22-24]. Despite the effective-ness of treatments, vitiligo lesions frequently relapse after the cessation of therapy, with a 40% re-currence rate within the first year. This high relapse rate can be attenuated through periodic applica-tion of topical calcineurin inhibitors, indicating the presence of a long-lasting autoimmune memory within the lesional skin [25]. CD8+ resident memory T (Trm) cells are involved in the persistence of this memory. These cells are known for their key role in providing immunity against viral rein-fections. The potential targeting of Trm cells in vitiligo could lead to more long-lasting treatment outcomes, possibly even after discontinued treatment [26].

The innate immune response also contributes to the pathogenesis of vitiligo. Stress-induced heat shock protein 70 (HSP70i) is released from the epidermis. It is capable of initiating autoimmunity by activating dermal dendritic cells (DCs), which in turn recruit T cells to propagate an autoimmune attack on melanocytes [27]. Additionally, a lowered regulatory T cells (Tregs) in the skin of vitiligo patients was observed [28].

Tregs, identified by the expression of the FOXP3 transcription factor, are essential in suppressing effector T cell activity and preventing autoimmunity. IPEX syndrome shows the critical role of Tregs, where patients lacking functional Tregs due to mutations in the FOXP3 gene suffer from a range of autoimmune disorders, including vitiligo [4]. Multifaceted mechanisms involving CD8+ T cells, IFN-γ signaling, Trm cells, and innate immune responses provide a complex picture of vitiligo pathogenesis. These findings give new directions for targeted therapies that may provide more effective and lasting treatments for patients suffering from vitiligo.

Current Therapeutic Approaches to Vitiligo

Treating vitiligo is often difficult. Various therapies are available for vitiligo, but they usually fail to meet patient expectations. General reasons for that are complicated methodology, time-consuming therapy strategy, and, most importantly, low efficacy and need for periodically repeated therapies [2].

Narrowband UVB (NB-UVB) is a gold standard therapy, largely due to its effectiveness and fa-vorable safety profile. Administered typically at a discrete erythematogenic dose, NB-UVB therapy is recommended 2 to 3 times weekly, which is more effective than its predecessor, PUVA therapy [29]. The advantages of NB-UVB include simplicity of administration and a reduced risk of side effects, leading to its classification as the preferred phototherapy option in vitiligo treatment guide-lines [30]. NB-UVB therapy is recommended for patients with both generalized vitiligo and those experiencing active, progressive disease, intending to stop disease activity and promote repigmenta-tion [31]. This form of phototherapy has been efficient in the repigmentation process, mainly when other therapies have not worked.

Recent findings have introduced the use of Janus kinase (JAK) inhibitors in treating vitiligo, providing a novel therapeutic approach. Early attempts to combine NB-UVB therapy with JAK inhibitors, such as tofacitinib and ruxolitinib, have shown promising results. The combination ther-apy has outperformed monotherapy with JAK inhibitors, especially in cases of facial vitiligo, sug-gesting a synergistic effect that enhances repigmentation outcomes [32]. JAK inhibitors have shown potential in interrupting the pathogenic mechanisms of vitiligo. In mouse models, the neu-tralization of IFN-γ antibodies has been demonstrated to prevent CD8+ T cell accumulation and subsequent lesion depigmentation [33]. By blocking IFN-γ signaling, JAK inhibitors, currently under clinical trials, such as tofacitinib, ruxolitinib, and baricitinib contribute to the repigmentation process, offering hope for patients with vitiligo [34-36]. However, the use of the top three market-ed JAK inhibitors—ruxolitinib, tofacitinib, and baricitinib—has been associated with an increasing number of reported adverse effects. These adverse events are primarily linked to overdosage and may include infectious complications, embolism, and thrombosis [37]. To effectively manage vitili-go, repeated and continuous therapeutic interventions are often necessary. This makes it crucial to explore combination treatment strategies that minimize side effects while maximizing efficacy. Alt-hough NB-UVB remains the gold standard for vitiligo therapy, the addition of JAK inhibitors into treatment strategy represents a significant advancement in the field.

Surgical Approaches to Vitiligo

Surgery is a practical option for patients with vitiligo, particularly those with stable disease. A cru-cial consideration for patient selection is the absence of the Koebner phenomenon, which could worsen the condition postoperatively [38]. The Koebner phenomenon is characterized by the ap-pearance of new vitiligo lesions at sites of skin depigmentation, which is particularly concerning in surgical intervention due to the potential for relapse or worsening of the disease. Before consider-ing surgical treatments, patients need to be fully informed about the risks, especially the possibility of relapse. Disease stability should be confirmed through detailed clinical follow-up to ensure the appropriateness of surgical intervention [39]. Several surgical techniques have been developed to treat vitiligo, each with its methodology and potential benefits. Punch grafting is a straightforward technique that involves transferring small biopsies of pigmented skin into depigmented lesions [38]. Suction blister grafting is another method that uses epidermal blisters created on pigmented skin, which are then transplanted onto areas lacking pigmentation. Non-cultured epidermal cellular grafting involves the application of epidermal cells, harvested from the skin, directly onto the depigmented dermis. Cultured epidermal cellular grafting grows cells in vitro before transplanta-tion, allowing for coverage of larger areas [40]. In addition to these surgical options, adjunctive treatments such as microneedling or ablative laser therapy, combined with NB-UVB phototherapy, enhanced repigmentation outcomes while minimizing adverse effects [41]. Nonetheless, it is essen-tial to note that while suction blister grafting and punch grafting may give the most promising re-sults regarding repigmentation, they also carry risks, such as scarring and hyperpigmentation that must be carefully weighed against the potential benefits [38]. The surgical management of vitiligo requires a personalized approach, considering the stability of the disease, the absence of the Koeb-ner phenomenon, and the patient's informed consent regarding the risks and benefits. With a range of techniques available, careful selection and use of the appropriate method can offer hope for sig-nificant repigmentation and improvement in the quality of life for vitiligo patients.

Psychological Impact and Dietary Considerations in Vitiligo Treatment.

Although the physical symptoms may seem straightforward, the condition often carries a signifi-cant psychological burden. Patients with vitiligo experience anxiety at rates comparable to those with other severe dermatological conditions, such as psoriasis or eczema [41]. Vitiligo patients per-ceive higher psychological stress, primarily related to the visibility of lesions, further leading to lowered self-confidence and social stigma [8, 42]. The psychosocial implications of vitiligo require a complete treatment approach that goes beyond skin depigmentation. Although the number of studies is limited, evidence supports the benefits of adjuvant care through group therapy, cognitive-behavioral therapy, and self-help programs [43].

Dietary factors, while not directly implicated in the etiology of vitiligo, have been considered in the context of disease treatment. The role of diet is primarily focused on the antioxidant properties of foods, their vitamin content, and the presence of micronutrients that may influence the pathophysi-ology of the condition. Specific dietary components, such as vegetable oils rich in omega-6 fatty acids, are thought to inflame vitiligo by promoting the production of reactive oxygen species (ROS) and pro-inflammatory cytokines [44]. Additionally, avoiding allergenic foods that could potentially trigger or develop vitiligo is recommended, as allergic reactions or irritation may worsen

the condition [45]. Recent advancements have shed light on the therapeutic potential of vitamin D in vitiligo treatment. Vitamin D analogs, mainly when used with UV light or corticosteroids, have been shown to enhance the repigmentation process [46]. The basic mechanisms of vitamin D's ac-tion in vitiligo, however, have mostly stayed unclear until recent studies started to reveal these complexities. Vitamin D was found to protect melanocytes from oxidative damage by activating the WNT/β-catenin signaling pathway. This pathway is key for vitamin D to control other important targets, such as Nrf2/ARE, MITF, and processes related to cell death, which are necessary for cell survival and pigmentation [47]. Furthermore, vitamin D insufficiency has been closely linked to the severity of oxidative stress in vitiligo patients, highlighting the importance of having normal vita-min D levels in disease treatment. Vitamin D positively influences β-catenin signaling at both the translational and posttranslational levels in melanocytes subjected to oxidative stress [47]. This is similar to the effects observed with WNT agonists, where vitamin D significantly reduced ROS accumulation and cell apoptosis in H2O2-treated melanocytes while promoting their proliferative and migratory activities. Notably, these protective effects were negated when β-catenin was si-lenced, further emphasizing the central role of β-catenin in the protective actions of vitamin D [46, 47]. Deficiency in β-catenin also inhibited the activation of Nrf2, MITF, and apoptosis, which are critical processes modulated by vitamin D in the context of vitiligo [47]. Dietary interventions, par-ticularly those emphasizing antioxidant-rich foods, may play a supportive role in managing the condition. Moreover, vitamin D is a promising agent in vitiligo therapy, with a newly explained mechanism involving the WNT/β-catenin pathway, providing a potential option for targeted treatment strategies. Future research should continue to examine the molecular interactions between vit-amin D and melanocyte biology to optimize therapeutic outcomes for vitiligo patients.

Conclusions

In conclusion, vitiligo is a complex autoimmune condition characterized by the loss of skin pig-mentation due to the destruction of melanocytes. While its pathogenesis involves a range of genetic, immunological, and environmental factors, CD8+ T cells, IFN-γ signaling, and oxidative stress play critical roles in disease progression. Advances in therapeutic approaches, including using JAK inhibitors, NB-UVB phototherapy, and surgical interventions, offer hope for improved outcomes, especially when tailored to individual patient needs. Despite these advancements, challenges re-main, such as the high relapse rate and the psychological impact of the disease. Addressing these issues requires a comprehensive approach, combining medical, psychological, and lifestyle inter-ventions, including dietary considerations and the potential role of vitamin D in promoting melano-cyte survival. Long-term efficacy studies are essential to determine the most effective combinations of therapies, especially in treatment-resistant cases. These studies should focus on evaluating the durability of repigmentation, minimizing adverse effects, and optimizing treatment protocols for sustained results. Continued research into the underlying mechanisms of vitiligo will be essential to develop more effective, long-lasting treatment options and to enhance the quality of life for those affected by this condition.

Author Contributions: Conceptualization, A.K., N.K., Z.M. and A.K.; methodology – A.K., Z.M, and A.K.; validation – not applicable; formal analysis – not applicable; investigation, A.K. and N.K.; resources, A.K.; data curation, Z.M.; writing – original draft preparation A.K. and N.K.; writing – review and editing, Z.M. and A.K.; visualization, A.K.; supervision, A.K.; project admin-istration – not applicable.; funding acquisition – Z.M. All authors have read and agreed to the pub-lished version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: This research has been funded by the Science Committee of the Ministry of Sci-ence and Higher Education of the Republic of Kazakhstan (Grant No. AP13068072).

References

1. Frisoli ML, Essien K, Harris JE. Vitiligo: Mechanisms of Pathogenesis and Treatment. *Annu Rev Immunol*. 2020; 38: 621–648. https://doi.org/10.1146/annurev-immunol-100919-023531.
2. Vitiligo. Nat Rev Dis Primers. 2015; 1: 15046. https://doi.org/10.1038/nrdp.2015.46.
3. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet*. 2015; 386(9988): 74–84. https://doi.org/10.1016/s0140-6736(14)60763-7.
4. Frisoli ML, Harris JE. Vitiligo: Mechanistic insights lead to novel treatments. *J Allergy Clin Immunol.* 2017; 140(3): 654–662. https://doi.org/10.1016/j.jaci.2017.07.011.
5. Spritz RA, Andersen GH. Genetics of Vitiligo. *Dermatol Clin.* 2017; 35(2): 245–255. https://doi.org/10.1016/j.det.2016.11.013.
6. Hadi A, Wang JF, Uppal P, Penn LA, Elbuluk N. Comorbid diseases of vitiligo: A 10-year cross-sectional retrospective study of an urban US population. *J Am Acad Dermatol.* 2020; 82(3): 628–633. https://doi.org/10.1016/j.jaad.2019.07.036.
7. Gill L, Zarbo A, Isedeh P, Jacobsen G, Lim HW, Hamzavi I. Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study. *J Am Acad Dermatol.* 2016; 74(2): 295–302. https://doi.org/10.1016/j.jaad.2015.08.063.
8. Bibeau K, Pandya AG, Ezzedine K, Jones H, Gao J, Lindley A, et al. Vitiligo prevalence and quality of life among adults in Europe, Japan and the USA. *J Eur Acad Dermatol Venereol.* 2022; 36(10): 1831–1844. https://doi.org/10.1111/jdv.18257.
9. Piotrowska A, Wierzbicka J, Żmijewski MA. Vitamin D in the skin physiology and pathology. *Acta Biochim Pol*. 2016; 63(1): 17–29. https://doi.org/10.18388/abp.2015_1104.
10. Naughton GK, Eisinger M, Bystryn JC. Antibodies to normal human melanocytes in vitiligo. *J Exp Med.* 1983; 158(1): 246–251. https://doi.org/10.1084/jem.158.1.246.
11. Cui J, Arita Y, Bystryn JC. Cytolytic antibodies to melanocytes in vitiligo. *J Invest Dermatol.* 1993; 100(6): 812–815. https://doi.org/10.1111/1523-1747.ep12476636.

12. Gilhar A, Zelickson B, Ulman Y, Etzioni A. In vivo destruction of melanocytes by the IgG fraction of serum from patients with vitiligo. *J Invest Dermatol.* 1995; 105(5): 683–686. https://doi.org/10.1111/1523-1747.ep12324456.
13. Merimsky O, Shoenfeld Y, Baharav E, Altomonte M, Chaitchik S, Maio M, et al. Melanoma-associated hypopigmentation: where are the antibodies? Am J Clin Oncol. 1996; 19(6): 613–618. https://doi.org/10.1097/00000421-199612000-00017.
14. Kroon MW, Kemp EH, Wind BS, Krebbers G, Bos JD, Gawkrodger DJ, et al. Melanocyte antigen-specific antibodies cannot be used as markers for recent disease activity in patients with vitiligo. *J Eur Acad Dermatol Venereol.* 2013; 27(9): 1172–1175. https://doi.org/10.1111/j.1468-3083.2012.04501.x.
15. Le Poole IC, van den Wijngaard RM, Westerhof W, Das PK. Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. *Am J Pathol.* 1996; 148(4): 1219–1228.
16. Strassner JP, Rashighi M, Ahmed Refat M, Richmond JM, Harris JE. Suction blistering the lesional skin of vitiligo patients reveals useful biomarkers of disease activity. *J Am Acad Dermatol.* 2017; 76(5): 847-55.e5. https://doi.org/10.1016/j.jaad.2016.12.021.
17. Ogg GS, Rod Dunbar P, Romero P, Chen JL, Cerundolo V. High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitiligo. *J Exp Med.* 1998; 188(6): 1203–1208. https://doi.org/10.1084/jem.188.6.1203.
18. Palermo B, Campanelli R, Garbelli S, Mantovani S, Lantelme E, Brazzelli V, et al. Specific cytotoxic T lymphocyte responses against Melan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major histocompatibility complex/peptide tetramers: the role of cellular immunity in the etiopathogenesis of vitiligo. *J Invest Dermatol.* 2001 Aug; 117(2): 326–332. https://doi.org/10.1046/j.1523-1747.2001.01408.x.
19. Kirkin AF, Dzhandzhugazyan K, Zeuthen J. Melanoma-associated antigens recognized by cytotoxic T lymphocytes. *Apmis*. 1998 Jul; 106(7): 665–679. https://doi.org/10.1111/j.1699-0463.1998.tb00210.x.
20. Rashighi M, Agarwal P, Richmond JM, Harris TH, Dresser K, Su MW, et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. Sci Transl Med. 2014; 6(223): 223ra23. https://doi.org/10.1126/scitranslmed.3007811.
21. Richmond JM, Bangari DS, Essien KI, Currimbhoy SD, Groom JR, Pandya AG, et al. Keratinocyte-Derived Chemokines Orchestrate T-Cell Positioning in the Epidermis during Vitiligo and May Serve as Biomarkers of Disease. *J Invest Dermatol*. 2017 Feb; 137(2): 350–358. https://doi.org/10.1016/j.jid.2016.09.016.
22. Harris JE, Rashighi M, Nguyen N, Jabbari A, Ulerio G, Clynes R, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). *J Am Acad Dermatol.* 2016; 74(2): 370–371. https://doi.org/10.1016/j.jaad.2015.09.073.
23. Craiglow BG, King BA. Tofacitinib Citrate for the Treatment of Vitiligo: A Pathogenesis-Directed Therapy. *JAMA Dermatol.* 2015 Oct; 151(10): 1110–1112. https://doi.org/10.1001/jamadermatol.2015.1520.
24. Damsky W, King BA. JAK inhibitors in dermatology: The promise of a new drug class. *J Am Acad Dermatol.* 2017 Apr; 76(4): 736–744. https://doi.org/10.1016/j.jaad.2016.12.005.
25. Cavalié M, Ezzedine K, Fontas E, Montaudié H, Castela E, Bahadoran P, et al. Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double blind, placebo-controlled study. *J Invest Dermatol.* 2015; 135(4): 970–974. https://doi.org/10.1038/jid.2014.527.
26. Mueller SN, Mackay LK. Tissue-resident memory T cells: local specialists in immune defence. *Nat Rev Immunol.* 2016; 16(2): 79–89. https://doi.org/10.1038/nri.2015.3.
27. Mosenson JA, Zloza A, Klarquist J, Barfuss AJ, Guevara-Patino JA, Poole IC. HSP70i is a critical component of the immune response leading to vitiligo. *Pigment Cell Melanoma Res.* 2012; 25(1): 88–98. https://doi.org/10.1111/j.1755-148X.2011.00916.x.
28. Klarquist J, Denman CJ, Hernandez C, Wainwright DA, Strickland FM, Overbeck A, et al. Reduced skin homing by functional Treg in vitiligo. *Pigment Cell Melanoma Res.* 2010; 23(2): 276–286. https://doi.org/10.1111/j.1755-148X.2010.00688.x.
29. Trovato E, Pellegrino M, Filippi F, Mancini V, Pimpinelli N, Fimiani M. Clinical and histological evaluation in patients with mycosis fungoides treated with UVA1. *G Ital Dermatol Venereol.* 2020; 155(3): 306–311. https://doi.org/10.23736/s0392-0488.18.05867-4.
30. Böhm M, Schunter JA, Fritz K, Salavastru C, Dargatz S, Augustin M, et al. S1 Guideline: Diagnosis and therapy of vitiligo. *J Dtsch Dermatol Ges.* 2022; 20(3): 365–378. https://doi.org/10.1111/ddg.14713.
31. Bae JM, Jung HM, Hong BY, Lee JH, Choi WJ, Kim GM. Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. *JAMA Dermatol.* 2017; 153(7): 666–674. https://doi.org/10.1001/jamadermatol.2017.0002.
32. Phan K, Phan S, Shumack S, Gupta M. Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and Meta-analysis. *J Dermatolog Treat.* 2022; 33(1): 173–177. https://doi.org/10.1080/09546634.2020.1735615.
33. Qi F, Liu F, Gao L. Janus Kinase Inhibitors in the Treatment of Vitiligo: A Review. *Front Immunol.* 2021; 12: 790125. https://doi.org/10.3389/fimmu.2021.790125.
34. Harris JE, Harris TH, Weninger W, Wherry EJ, Hunter CA, Turka LA. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-γ for autoreactive $CD8^+$ T-cell accumulation in the skin. *J Invest Dermatol.* 2012; 132(7): 1869–1876. https://doi.org/10.1038/jid.2011.463.
35. Mobasher P, Guerra R, Li SJ, Frangos J, Ganesan AK, Huang V. Open-label pilot study of tofacitinib 2% for the treatment of refractory vitiligo. *Br J Dermatol.* 2020; 182(4): 1047–1049. https://doi.org/10.1111/bjd.18606.
36. Mumford BP, Gibson A, Chong AH. Repigmentation of vitiligo with oral baricitinib. *Australas J Dermatol.* 2020; 61(4): 374–376. https://doi.org/10.1111/ajd.13348.
37. Hoisnard L, Lebrun-Vignes B, Maury S, Mahevas M, El Karoui K, Roy L, et al. Adverse events associated with JAK inhibitors in 126,815 reports from the WHO pharmacovigilance database. *Scientific Reports*. 2022; 12(1): 7140. https://doi.org/10.1038/s41598-022-10777-w.
38. McCrary MR, Gibbs DC, Alharthi M, Krueger LD. Utilization of Our Toolkit: A Systematic Review and Meta-analysis of Surgical Therapies in Vitiligo Treatment. *Dermatol Surg.* 2022; 48(8): 815–821. https://doi.org/10.1097/dss.0000000000003503.
39. Post NF, Narayan VS, Bekkenk MW, Wolkerstorfer A. Meek micrografting, a novel surgical technique for the treatment of vitiligo and piebaldism: A case series. J Eur Acad Dermatol Venereol. 2023; 37(4): e460-e2. https://doi.org/10.1111/jdv.18829.
40. Dev A, Vinay K, Bishnoi A, Kumaran MS, Dogra S, Parsad D. Dermatoscopic assessment of treatment response in patients undergoing autologous non-cultured epidermal cell suspension for the treatment of stable vitiligo: A prospective study. *Dermatol Ther.* 2021; 34(5): e15099. https://doi.org/10.1111/dth.15099.

41. Kussainova A, Kassym L, Akhmetova A, Glushkova N, Sabirov U, Adilgozhina S, et al. Vitiligo and anxiety: A systematic review and meta-analysis. *PLoS One.* 2020; 15(11): e0241445. https://doi.org/10.1371/journal.pone.0241445.
42. Henning SW, Jaishankar D, Barse LW, Dellacecca ER, Lancki N, Webb K, et al. The relationship between stress and vitiligo: Evaluating perceived stress and electronic medical record data. *PLoS One.* 2020; 15(1): e0227909. https://doi.org/10.1371/journal.pone.0227909.
43. Rzepecki AK, McLellan BN, Elbuluk N. Beyond Traditional Treatment: The Importance of Psychosocial Therapy in Vitiligo. *J Drugs Dermatol*. 2018; 17: 688–691.
44. Namazi MR, Chee Leok GO. Vitiligo and diet: a theoretical molecular approach with practical implications. Indian *J Dermatol Venereol Leprol.* 2009; 75(2): 116–118. https://doi.org/10.4103/0378-6323.48654.
45. imi Y, Young-Woo S, Tae-Heung K. Complementary and Alternative Medicine for Vitiligo. In: Kelly KyungHwa P, Jenny Eileen M, editors. Vitiligo. Rijeka: *IntechOpen*; 2011. p. Ch. 10.
46. Birlea SA, Costin GE, Norris DA. New insights on therapy with vitamin D analogs targeting the intracellular pathways that control repigmentation in human vitiligo. *Med Res Rev.* 2009; 29(3): 514–546. https://doi.org/10.1002/med.20146.
47. Tang L, Fang W, Lin J, Li J, Wu W, Xu J. Vitamin D protects human melanocytes against oxidative damage by activation of Wnt/β-catenin signaling. *Lab Invest.* 2018; 98(12): 1527–1537. https://doi.org/10.1038/s41374-018-0126-4.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/15716

Artificial Intelligence as a Tool to Prevent Autoaggressive Destructive Behavior Among Children and Adolescents: a Brief Overview

Korlan Saduakassova[1], Mukhit Zhanuzakov[2], Gulzhan Kassenova[1], Vassiliy Serbin[3]

[1]*Higher school of medicine, Faculty of medicine and healthcare, Al-Farabi Kazakh National University, Almaty, Kazakhstan*
[2]*Department of computer science, Al-Farabi Kazakh National University, Almaty, Kazakhstan*
[3]*Department of Cybersecurity, information processing and storage, Kazakh National Research Technical University, Almaty, Kazakhstan*

Received: 2024-11-08.
Accepted: 2024-12-12.

J Clin Med Kaz 2024; 21(6): 24–29

Corresponding author:
Gulzhan Kassenova.
E-mail: gulzhanerdanai@gmail.com.
ORCID: 0000-0003-0815-279.

Abstract

Suicides and suicidal behaviors are complex disorders with diverse symptoms, often lacking clear etiology, especially in spontaneous or childhood cases. This complicates timely diagnosis, therapy, and treatment. As a result, research into markers for depression and suicidal behavior continues. The use of artificial intelligence represents a significant advancement in suicide prevention, offering new tools for early detection and intervention to improve outcomes for at-risk individuals. According to the World Health Organization (WHO), 726,000 people commit suicide, not counting the much larger number of people who attempt suicide each year. Suicides occur throughout life, but in 2021 they became one of the leading causes of death among 15-29 year-olds worldwide. This problem is also relevant in Kazakhstan, and this article is the first to reflect an interdisciplinary approach to suicide prevention among minors using AI methods in application to scientific data obtained in the study of respondents with suicidal behavior. Suicide is a significant public health issue with profound societal impacts. Its effects extend beyond the loss of life, leading to emotional suffering for families and loved ones, and economic losses from reduced productivity and increased healthcare costs. For each suicide, there are over 30 attempted suicides, compounding the social and economic burden. The repercussions affect countless individuals, both directly and indirectly, leaving long-lasting emotional and financial strain. Additionally, the economic impact includes treatment costs for psychosomatic and mental disorders in those left behind, highlighting the extensive and multifaceted consequences of suicidal behavior.

Keywords: suicide prevention, risk factors, age-related ontogenesis, children and adolescents, young people, artificial intelligence, machine learning, neural networks.

Introduction

The problem of the autodestructive behavior of minors is one of the main medical and socio-psychological problems of modern science, since destructions are most clearly manifested precisely in adolescence – one of the most difficult periods in the development of each person. A destructive behavior model can develop as a result of the action of many factors – a genetic predisposition (with a burdened heredity with mental diseases with a debut in age-related crises of ontogenetic development); increased susceptibility of characterological reactions to external psychogenic factors with transformation into pathocharacterological reactions and development (reactions of protest, emancipation, hypercompensation, opposition, grouping, imitation, hobby-reactions, reactions caused by the formation of sexual desire – masturbation, petting, etc.).

In the last decade, self–harm without suicidal intentions has become widespread – this is also one

of the forms of destruction characteristic of adolescence. For a growing child's body, when every year of life is associated with the need to meet new requirements of society, the need to adapt to new constantly changing requirements of the surrounding reality, due to small life experience, this is a rather serious problem – a teenager cannot always use the protective mechanisms of the psyche, build a psychological strategy. The experience of family education will play an important role in overcoming emerging conflicts. One of the most dangerous in adolescence is primarily destructive intrapersonal behavior, manifested by self-destruction (suicide), self-harm (risky behavior), self-modification (body modifications, tattoos, piercings, excessive use of alcohol and drugs, involvement in destructive games). With the growing number of suicides in adolescence, there is an urgent need for a systematic approach to both early diagnosis and timely psychological and psychotherapeutic correction of these adolescent perturbations and timely initiation of psychopharmacotherapy in the presence of mental disorders, as well as the search for new methods of identifying the risk group using new technologies, for example, artificial intelligence.

The purpose of this article is to study research papers in order to find possible solutions for the early detection of suicidal ideation among children and adolescents, youth using artificial intelligence (AI) technologies, which describe the prediction of possible suicidal attempts at an early stage and can serve as one of the tools to prevent suicide attempts.

Materials and Methods

To find relevant scientific papers, we conducted a search on popular scientific platforms (Science Direct, Research Gate) for the following keywords: suicide prevention, artificial intelligence, machine learning, neural networks, children, adolescents, youth. During the search, 367 articles were found, 10 of which met the search criteria and were analyzed and compared.

Many researchers use artificial intelligence to predict suicide attempts as accurately as possible. For this reason, from 2018 to 2024, many studies were conducted around the world using machine learning and neural networks to predict the risk of suicide. Accordingly, we have established selection criteria – a deep search for scientific sources in the period 2018-2024 devoted to the use of AI to predict suicide risks among young people.

Problem

The situation with the early identification of a risk group among minors with autodestructive behavior is complicated by the presence of age-related ontogenesis of understanding death and crisis periods of development, which have their own difference in almost every year of a child's or teenager's life. Thanatopsychological education has studied the formation of the concept of death in children according to age, where the family factor plays the most important role, religion, education, cognitive and intellectual functions, somatic and mental health status have also been noted [2-4]. The age from 12 to 15 years and older deserves special attention in the context of studying this problem.

At this age, there is a transition from childhood to the so-called "growing up", and against the background of increasing social influences and the presentation of new "adult" requirements to the child, respectively, the child experiences a number of events such as the loss of "ideal parents", the loss of naive ways of knowing the world around him, which can violate child-parent attachment. Also in this age period (and this is an active prepubertal), children experience such an ontogenetically phenomenon of personality formation as the so-called "social death" (a term in adolescent psychology) – it is at this age that children feel lonely, experience isolation from a group of peers, a feeling of loneliness is formed, the level of anxiety increases, which can lead to the so-called "normal teenage mourning" (a term of adolescent psychology). And another important point is that all of the above is one end of the so-called "scissors", at the other end of which the phenomenon of "personal myth" peculiar to this age is optimism, vivacity of reactions, the child's faith in his uniqueness, immortality, the belief that other people are mortal, but this will not affect the child himself, which, as it increases the external adverse factors are gradually weakening. And it is precisely such contradictions – between the seemingly optimistic features of adolescence and its losses – that create a special attraction to the topic of death, the need to understand it, and at the same time an increased fear caused by these experiences. It can be said that suicidality in adolescence is associated with a poor understanding of death and suicidal ideas for a child or teenager are a tool of avoidance and death is seen as a way out of a situation of deprivation (if the child is experiencing distress).

Also we should not forget that behind the facade of psychological ontogenetic "growing up" there is the main ontogenetic period of reproductive system formation (average age from 12-16 years), when the activity of sex hormones (estradiol, testosterone, progesterone) leads to thickening of bones, increasing their density – children and adolescents feel that the body has become "dense", "heavy", feel the heaviness of the body, a kind of adolescent "clumsiness". Physiological emotional instability, irritability, and the manifestation of active forms of characterological reactions caused by the activity of sex hormones form undesirable behavior of adolescents, familiar to everyone as the difficult "puberty" [5]. All this complicates the early diagnosis of suicidal ideation among minors and the use of AI methods can serve the purpose of early identification of a risk group for suicide. The above is only part of the changes in the psyche of children and adolescents who, throughout their lives, before moving into the so-called "adult state", experience a number of age-related crises.

Results and discussions

In recent decades, AI has been widely used by many experts from various fields of human activity. This is due to its effectiveness in finding various patterns and its ability to predict results based on available data. Machine learning (ML) is a branch of AI that is designed to allow computers to learn from data and improve their performance when performing a specific task without explicitly programming for that task [6]. Neural networks (NW) are another approach to function approximation, inspired by how the human brain works [7]. These methods are designed to predict possible suicide attempts, mainly based on data collected by experts in the field of child mental health. However, there are cases when researchers use NLP (natural language processing) and NW to analyze text data obtained from the Internet.

The number of studies conducted in this direction increases over time. This can be seen in Figure 1, which shows the distribution of the found articles by year from ScienceDirect. According to him, the number of research papers has increased from 10 in 2018 to more than 90 in 2024. This shows that interest in using AI to combat suicide is growing.

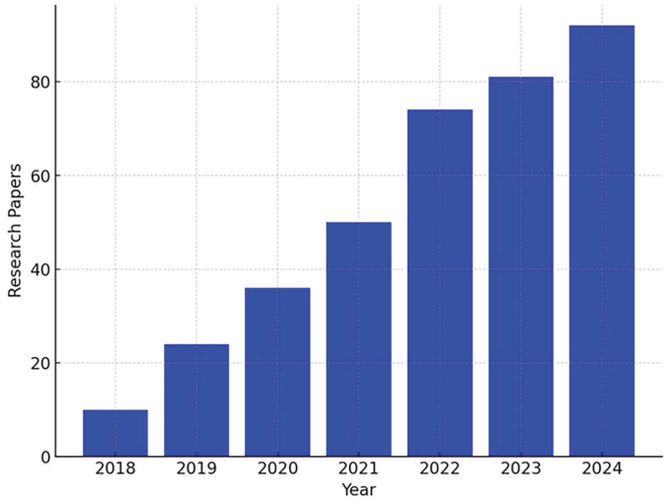


Figure 1 – Annual distribution of research papers found using the ScienceDirect platform

Many studies have reviewed various approaches to suicide prevention using AI. Similar work [8] was carried out by Alban Lejeune et al., where the authors compared studies published between 2014 and 2020 aimed at predicting suicide risks. The authors concluded that AI performance was good, although it varied depending on different algorithms and application settings. The studies reviewed in this paper show that various machine learning algorithms, including ridge regression, classification trees, and random forests, provide promising predictive capabilities for determining suicide risk in adolescents and young adults, reaching AUC values from 0.8 to 0.9.

In another work by Rebecca A. Bernert et al. [9] considers AI and ML in predicting suicidal behavior. The results demonstrated a high level of accuracy (over 90%) and strong predictive efficacy (AUC) in the studies. The authors conclude that AI and ML applications may be crucial for early detection of suicide risk, with important methodological and statistical caveats.

In the work of Lin et al. [10], the authors collected data on psychiatric hospital patients diagnosed with suicide in the National Database of Health Insurance Research. Machine learning methods were used to develop models for predicting the risk of future multiple suicide attempts. The authors' experimental results showed that Adaboost+DT is best suited for predicting the behavior of multiple suicide attempts among psychiatric patients.

The authors Kharrat et al. [11] developed gender-sensitive machine learning models to predict suicide risk using data from the Integrated Monitoring System for Chronic Diseases of Patients from Québec, which included more than 20,000 cases of suicide from 2002 to 2019. The study demonstrated the potential of explicable AI in improving suicide prevention efforts, while emphasizing the need for caution in interpreting predictive associations.

An observational study conducted by the authors Servi et al. [12] was aimed at identifying early predictors of suicidal risk among 237 inpatient patients with suicidal behavior and thoughts in the emergency department of child and adolescent psychiatry at the Meyer Children's Hospital in Florence (Italy). The researchers collected epidemiological and psychopathological data and stratified patients into two groups: "patients with suicidal will" and "patients with suicidal motivation", finding that factors such as age under 12, diagnosis of destructive disorders, previous suicide attempts and intoxication are statistically correlated with increased risk.

Artificial intelligence analysis confirmed these risk factors with 86.7% accuracy, which highlights the potential of AI to help doctors assess suicidal risk, while recognizing the limitations of the study due to its retrospective design.

The study by authors Su et al. [13] was aimed at developing machine learning models for predicting suicidal behavior in children and adolescents using longitudinal clinical records from the Connecticut Children's Medical Center. The authors analyzed data from 41721 patients aged 10 to 18 years from October 2011 to September 2016. The obtained models achieved areas under the curve (AUC) in the range from 0.81 to 0.86, accurately identifying 53-62% of subjects with positive suicidal status with 90% specificity, thereby demonstrating that regularly collected electronic medical records can be effectively used to predict suicide risk in the pediatric population.

A study by Tan et al. [14] examines the effectiveness of explicable artificial intelligence (EAI) in predicting suicide risk based on medical tabular data, solving the problem of limited datasets in health-related machine learning applications through data augmentation. The researchers used Shapley Additive explanations (SHAP) along with traditional correlation analysis to rank the importance of traits, identifying key factors such as anger problems, depression, and social isolation as significant predictors of suicide risk, while it was found that people with high incomes, respected professions, and higher education have lower the risk.

The study done by the authors Walsh et al. [15] was aimed at improving the prediction of suicide risk among adolescents by using machine learning algorithms applied to regularly collected clinical data from a synthetic Vanderbilt derivative, including 974 adolescents with nonfatal suicide attempts and various control groups. The results show that machine learning approaches using longitudinal clinical data can improve screening of nonfatal suicide risk in adolescents by providing a scalable solution that bypasses the limitations of traditional face-to-face screening methods.

Navarro et al. [16] used data from the Québec Longitudinal Study of Child Development to assess the predictive power of early life factors for suicide attempts in adolescents and young adults from the general population, tracking participants from birth to 20 years of age. Using random forest classification algorithms, the researchers evaluated 150 variables in various areas of early life, revealing moderate prediction efficiency with areas under the curve of 0.72 for women and 0.62 for men, as well as low sensitivity, but good specificity and negative predictive values.

The study by Nobles et al. [17] solves an important problem of suicide prevention among young people by focusing on the development of a predictive model using text messages from people with a history of suicidal thoughts and behavior. The researchers used a promising study design, reconstructing the chronology of recent suicidal behavior through retrospective clinical interviews, to analyze whether text messages can effectively predict periods of suicidality, including suicidal thoughts and nonfatal suicide attempts, as opposed to simple depressive episodes.

Another study done by Bhandarkar et al. [18] was the development of an artificial intelligence model for natural language processing trained on patient portal messages to predict 30-day suicide-related events (SRE).

The aim of the study by Xu et al. [19] was to improve suicide detection in online counseling systems by developing

a risk assessment model based on knowledge in a subject area called KARA, using a substantial dataset of conversations in Cantonese between help seekers and counselors. The data set included 5,682 conversations, of which 682 disclosed suicide intentions, and a suicide knowledge graph was built to embed relevant domain knowledge into a deep learning model. The results of the review are presented in Table 1.

Table 1 Review of selected articles

Author	Year	Country (Countries)	Size and type of training data	The best algorithm/ model	Peak performance (with metric)
Lin et al. [10]	2022	Taiwan	523 (tabular)	Adaboost+DT	0.971 (accuracy)
Kharrat et al. [11]	2018	Canada	9440 (tabular)	RF	0.87 (AUC)
Servi et al. [12]	2023	Italy	237 (tabular)	NN	0.89 (accuracy)
Su et al. [13]	2020	USA	641708 (tabular)	LR	0.80 > (AUC)
Tan et al. [14]	2024	Australia	1000 (tabular)	RF	0.97 (AUC)
Walsh et al. [15]	2018	USA	2247 (tabular)	RF	0.83 (AUC)
Navarro et al. [16]	2021	France, Canada	1623 (tabular)	RF	0.72 (AUC)
Nobles et al. [17]	2018	USA	136347 (text)	NN (DNN)	0.75 (F1)
Bhandarkar et al. [18]	2023	USA	840 (text)	NN	0.710 (AUC-ROC)
Xu et al. [19]	2021	China	5682 (text)	KARA	0.815 (AUC-ROC)

The models developed by the authors show peak performance results starting from 70%. For convenience, some comparisons are displayed in the form of diagrams (Figure 2 – Figure 4).

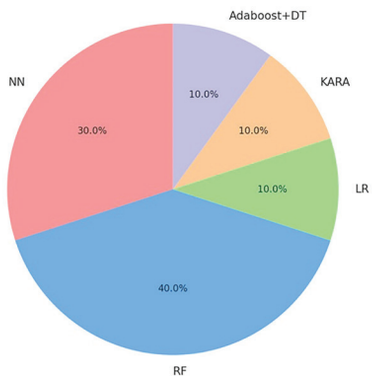


Figure 2 – Distribution of the most efficient algorithms/models

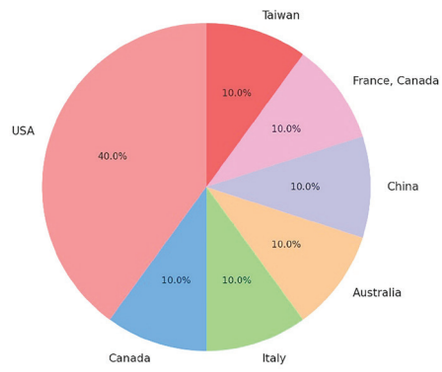


Figure 3 – Distribution by country

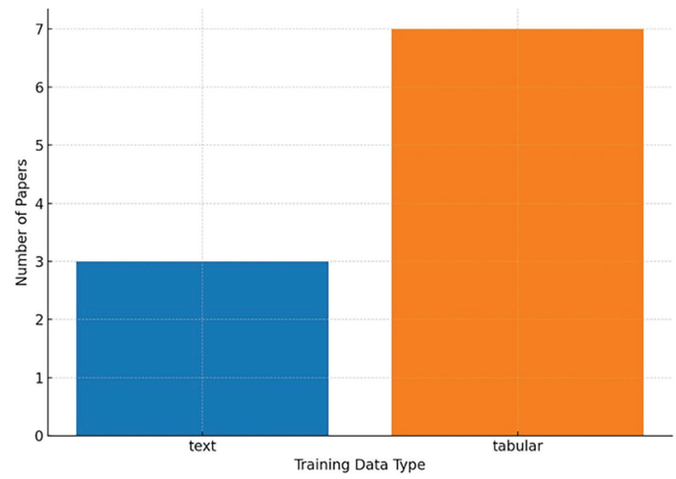


Figure 4 – Distribution by type of training data

Figure 2 illustrates the distribution of the most effective models according to the articles considered. NN and RF (Random Forest) models turned out to be the most popular algorithms used in the articles (30% and 40%, respectively).

Researchers from Taiwan [10] have shown that the combined model (Adaboost + Decision Trees) returns the highest accuracy of peak performance: 0.971. On the contrary, RF models often showed good results with AUC values of 0.97 [14] and 0.87 [11]. This indicates that RF and ensemble methods are well suited for such a forecasting task.

The geographical distribution shown in Figure 3 showed that the majority of the selected articles were written by researchers from the USA – 40% [13, 15, 17, 18]. Other countries have the same percentage distribution – 10% [10, 11, 12, 14, 16, 19].

Table 1 and Figure 4 show the different sizes and types of training data. This shows that most researchers used the tabular type [10-16]. Textual information is used less frequently [17-

19], but one study by Nobles et al. [17] effectively applied it with NN. The preference for tabular data may be due to their structured nature, which leads to easier processing and analysis [11].

The training data varies significantly in size, ranging from small datasets such as the 237 data used by Servi et al. [12], up to much larger ones, such as 641,708 samples in the study by Su et al. [13]. This range shows that models can be adapted to handle different scales of data.

Conclusion

The results we have obtained show that research on the use of AI models to predict and prevent suicide rates among young people is growing.

We concluded that the reviewed research articles show good effectiveness (more than 0.70%) in predicting suicide attempts.

Overall, although it is difficult to single out a universally superior model due to the variety of data and contexts, RF and NN seem to be the most reliable choices among the various datasets. In the future, the authors of the article plan to use various AI methods to predict possible suicide cases using both text and tabular data.

It is relevant to early identify possible clinical and psychological markers of deviant behavior using text materials of suicides (suicide notes, correspondence, messages about an impending act of attempt on life, etc.), which can be the basis for the development of an information system using machine learning methods and models to predict suicidal tendencies in children in order to increase the effectiveness of early identification and prevention of suicidal actions in educational and medical practices.

Further research and development of AI suggests the creation and adaptation of specific algorithms focused on the analysis of biopsychosocial risk factors combining knowledge of medicine, age, crisis psychology, pedagogy, sociology and information technology, which will contribute to the development of a comprehensive view of the problem and will allow more accurately predicting the likelihood of suicidal intentions.

Author Contributions: Conceptualization K.S.; methodology K.S. and M.Zh.; formal analysis M.Zh.; investigation K.S. and M.Zh.; resources M.Zh. and G.K.; data curation M.Zh.; writing – original draft preparation K.S. and M.Zh.; writing – review and editing K.S., M.Zh., G.K. and V.S.; visualization M.Zh.; supervision K.S.; project administration K.S.; funding acquisition K.S. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: This study was supported by grants from the Ministry of Education and Science of the Republic of Kazakhstan Grant Funding 2024–2026 (Funder Project Reference: AP23490290 "Development of a comprehensive system for the prevention of autodestructive and destructive behavior among the children's population of the Republic of Kazakhstan"). K.S. is a principal investigator of the projects.

Ethical Considerations: This study received approval from the Al-Farabi Kazakh National university's Ethics Committee on 11/20/2023, Protocol No. IRB-A705 dated 11/20/2023 (IRB00010790 al-Farabi Kazakh National University IRB№1). All study participants were informed about the study aims, methods, and potential risks and benefits.

References

1. World Health Organization. Suicide: key facts. Geneva: *World Health Organization*; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide. Accessed 23 October 2024.
2. Nagy M. The Child's Theories concerning Death [In Russian]. *Journal of Genetic Psychology*. 1948; 73: 3–27.
3. Elkind D. Egocentrism in Adolescence. *Child Development.* 1967; 38(4): 1025–1034. https://doi.org/10.2307/1127100.
4. Rostovtseva ME. Children's understanding of death: formation of the concept of death and its main characteristics [In Russian]. Russian Psychological Journal. 2024; 21(1): 87–106.
5. Fedorov GN. Hormonal indicators in adolescents 12-16 years old [In Russian]. *Pediatrics*. 2004; (4): 87–90.
6. Mitchell TM. Machine learning. McGraw-Hill, 1997. 491 p.
7. LeCun, Y, Bengio Y, Hinton G. Deep learning. *Nature*. 2015; 521(7553): 436–444. https://doi.org/10.1038/nature14539.
8. Lejeune A, Le Glaz A, Perron P-A, Sebti J, Baca-Garcia E, Walter M, Lemey C, Berrouiguet S. Artificial intelligence and suicide prevention: A systematic review. *European Psychiatry.* 2022; 65(1): e19:1–8 https://doi.org/10.1192/j.eurpsy.2022.8.
9. Bernert RA, Hilberg AM, Melia R, Kim JP, Shah NH, Abnousi F. Artificial Intelligence and Suicide Prevention: A Systematic Review of Machine Learning Investigations. *International Journal of Environmental Research and Public Health.* 2020; 17(16): 5929. https://doi.org/10.3390/ijerph17165929.
10. Lin I-L, Tseng JY-C, Tung H-T, Hu Y-H, You Z-H. Predicting the Risk of Future Multiple Suicide Attempt among First-Time Suicide Attempters: Implications for Suicide Prevention Policy. *Healthcare*. 2022; 10(4): 667. https://doi.org/10.3390/healthcare10040667.
11. Kharrat F, Gagne C, Lesage A, Gariépy G, Pelletier J-F, Brousseau-Paradis C, Rochette L, Pelletier E, Lévesque P, Mohammed M, Wang J. Explainable artificial intelligence models for predicting risk of suicide using health administrative data in Quebec. *PLoS ONE*. 2024; 19(4): e0301117. https://doi.org/10.1371/journal.pone.0301117.
12. Servi M, Chiaro S, Mussi E, Castellini G, Mereu A, Volpe Yary, Tiziana P. Statistical and artificial intelligence techniques to identify risk factors for suicide in children and adolescents. *Science Progress.* 2023; 106(4). https://doi.org/10.1177/00368504231199663.
13. Su, C. Aseltine R., Doshi R. Chen K, Rogers S-C, Wang F. Machine learning for suicide risk prediction in children and adolescents with electronic health records. *Transl Psychiatry* 2020; 10: 413. https://doi.org/10.1038/s41398-020-01100-0.
14. Tang H, Rekavandi AR, Dharjinder D, Girish D, Frank MS, Farid B, Mohammed B. Analysis and evaluation of explainable artificial intelligence on suicide risk assessment. *Scientific Reports.* 2024; 14/6263. https://doi.org/10.1038/s41598-024-53426-0.
15. Walsh CG, Ribeiro JD, Franklin JC. Predicting suicide attempts in adolescents with longitudinal clinical data and machine learning. *J Child Psychol Psychiatr.* 2018; 59: 1261–1270. https://doi.org/10.1111/jcpp.12916.

16. Navarro MC, Ouellet-Morin I, Geoffroy M, Boivin M, Trembley RE, Cote S, Orri M. Machine Learning Assessment of Early Life Factors Predicting Suicide Attempt in Adolescence or Young Adulthood. *JAMA Netw Open.* 2021; 4(3):e211450. https://doi.org/10.1001/jamanetworkopen.2021.1450.
17. Nobles AL, Glenn JJ, Kowsari K, Teachman B.A, Barnes LE. Identification of imminent suicide risk among young adults using text messages. In: Proceedings of the 2018 CHI Conference on Human Factors in Computing Systems. New York: *Association for Computing Machinery*, 2018; paper 413: 1–11. https://doi.org/10.1145/3173574.3173987.
18. Bhandarkar AR, Arya N, Lin KK, North F, Duvall MJ, Miller NE, Pecina JL. Building a natural language processing artificial intelligence to predict suicide-related events based on patient portal message data. Mayo Clinic Proceedings: *Digital Health.* 2023; 1(4): 510–518. https://doi.org/10.1016/j.mcpdig.2023.09.001.
19. Xu Z, Xu Y, Cheung F, Cheng M, Lung D, Law YW, Chiang B, Zhang Q, Yip PSF. Detecting suicide risk using knowledge-aware natural language processing and counseling service data. *Social Science & Medicine.* 2021; 283: 114176. https://doi.org/10.1016/j.socscimed.2021.114176.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15667

Outcomes of Valve-Sparing Aortic Root Replacement (David I Procedure) at a Single Center in Kazakhstan.

Almas Tolegenuly[1], Aidos Yerpashov[1], Adilzhan Albazarov[2], Erkebulan Shirinbekuly[1], Alimzhan Yelzhasov[1], Abay Baigenzhin[3]

[1]Department of Cardiac Surgery, National Scientific Medical Center JSC, Astana, Republic of Kazakhstan
[2] Department of Cardiac Surgery, Pavlodar Regional Cardiology Center, Pavlodar. Kazakhstan
[3]Chairman of the Board, National Scientific Medical Center, Astana, Kazakhstan

Received: 2024-10-30.
Accepted: 2024-12-01.

J Clin Med Kaz 2024; 21(6): 30–34

Corresponding author:
Almas Tolegenuly.
Email: almas.tolegenuly@gmail.com.
ORCID: 0000-0002-0197-6916.

Abstract

Valve-sparing aortic root replacement, commonly known as the David procedure, stands as a pioneering surgical technique aimed at addressing aortic root aneurysms while retaining the patient's native aortic valve. This procedure signifies a significant advancement in cardiac surgery, offering patients the potential for improved outcomes both in the short and long term.

Aims. The aim of the study was to analyze short- and long-term outcomes after valve sparing aortic root replacement operation using David I technique.

Methods. From January 2013 to November 2020 a total 124 David I procedures were performed. We analyzed survival and freedom from reoperation. Follow-up was performed 8 years postoperatively.

Results. Early mortality was 0.8% (n = 1). Mean age was 48.25 ± 17.42. The left ventricular ejection fraction (%) before discharge was significantly increased (p = 0.038) after surgery. The 1, 3, 6, 8 –year survival and freedom from reoperation rates were 99%, 99%, 98%, 87% and 99%, 98%, 95%, 91% retrospectively.

Conclusion. David procedure is a valuable option for treating aortic root aneurysms offering the potential for excellent long-term outcomes, especially when the native aortic valve can be preserved. The decision should be made on a case-by-case basis, considering the patient's individual factors and the expertise of the surgical team.

Keywords: Aortic root aneurysm, David procedure, valve-sparing aortic root replacement, aortic surgery.

Introduction

The valve-sparing aortic root replacement, commonly known as the David procedure, is a surgical technique used to treat aortic root aneurysms or conditions affecting the aortic valve. This procedure is named after its pioneer, Dr. Tirone David, who introduced it in the 1990s as an alternative to traditional aortic valve replacement (AVR) with a mechanical or biological valve [1]. The aortic root, comprising the aortic valve and the beginning portion of the aorta, can sometimes become enlarged due to various reasons, such as genetic predisposition, connective tissue disorders like Marfan syndrome, or age-related degeneration [2]. This enlargement, known as an aortic root aneurysm, can lead to life-threatening complications like aortic dissection or rupture.

The David procedure was developed to address these issues while preserving the patient's native aortic valve whenever possible. Unlike traditional AVR, where the aortic valve is replaced along with the diseased aortic root, the David procedure aims to conserve the patient's own valve, thus potentially avoiding the need for long-term anticoagulation therapy and the risk of prosthetic valve-related complications [3].

In essence, the Valve-sparing aortic root replacement or David procedure represents a significant advancement in aortic root surgery, offering patients the possibility of preserving their native valve while effectively treating aortic root aneurysms, thereby enhancing their long-term prognosis and quality of life.

The aim of the study was to analyze both short- and long-term outcomes of patients who underwent valve-sparing aortic root replacement (David I procedure) at a single center in Kazakhstan. Specifically, the study focused on evaluating the survival rates and freedom from reoperation after this surgical technique was performed. The follow-up period for these patients extended up to eight years postoperatively to assess the effectiveness and durability of the procedure over time

Materials and Methods

Ethics

This study was conducted in accordance with the ethical standards of our institution and adheres to the principles outlined in the Declaration of Helsinki. As a retrospective study, it did not require institutional review board approval according to our institution's policies.

Study design

Between January 2013 and November 2020, 124 patients underwent the David procedure using the classical reimplantation method, known as the David I technique. We conducted a retrospective analysis of the outcomes for these 124 patients. The procedures included isolated David procedures as well as those involving aneurysms or aortic dissections. Additionally, some patients required coronary artery bypass grafting (CABG), as well as repair or replacement of the mitral or tricuspid valves.

Preoperatively, all patients routinely underwent transthoracic echocardiography (TTE) and computed tomography (CT) for lesion assessment. Coronary angiography was performed as indicated. Intraoperatively, transesophageal echocardiography (TEE) was utilized before surgery and again postoperatively to assess myocardial contractility, the degree of heart valves insufficiency and the nature of the lesion, the size of the heart chambers and aorta, and so on.

This retrospective study included follow-up data collected over an average of 8 years. We evaluated survival rates, freedom from reoperation, and various postoperative outcomes.

Operative procedures

We used standard David 1 technique for all patients, with vascular (Woven Polyester) graft (Figure 1). The procedure were performed through a standard full sternotomy approach. Patients received total anesthesia with endotracheal intubation. Aortic cannulation was executed higher than usual, closer to the aortic arch, and a two-stage cannula was used for venous return through the right atrium. Patient cooling was required during aortic arch replacement, followed by selective cerebral perfusion and circulatory arrest.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics and perioperative data. Continuous variables were compared using Student's t-test or Mann-Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Kaplan-Meier survival analysis was used to estimate overall survival and freedom from reoperation, with differences between subgroups assessed using the log-rank test. All data are presented as mean ± standard deviation with or without ranges, or the numbers and percentages were appropriate. A p-value <0.05 was considered statistically significant.

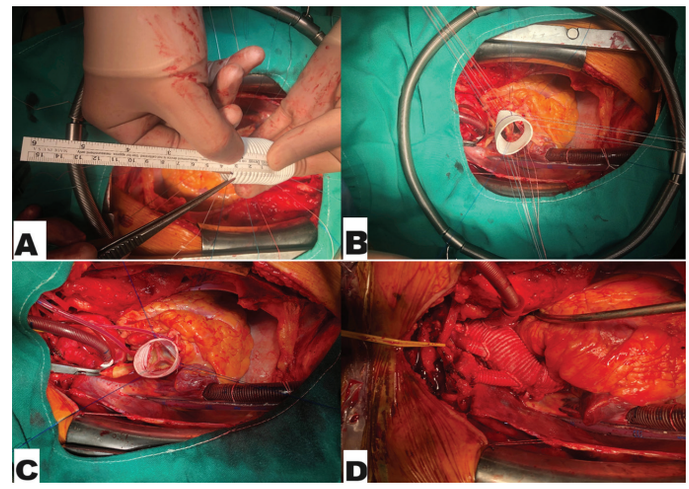


Figure 1 – Reimplantation (David) procedure for the patient with acute aortic dissection. (A) Measuring the height of the neo-aortic root. (B) Aortic valve reimplanted into a vascular graft. (C) Aortic valve cusps assessment. (D) Final view of operation

Results

The study cohort (Table 1) had a mean age of 48.25 years, with a notable male predominance (57.2%). The high prevalence of arterial hypertension (76.6%) and ischemic heart disease (20.1%) indicates that these patients had significant cardiovascular risk factors.

Table 1 Patient Characteristics

Valuables	**n = 124**
Age, years	48.25 ± 17.42
Male sex	71 (57.2)
Body mass index (kg/m^2)	28.00 ± 5.86
Body surface area (m^2)	1.96 ± 0.22
Height (cm)	172.08 ± 11.07
Weight, (kg)	82.58 ± 17.35
Arterial hypertension	95 (76.6)
Diabetes	10 (8)
Ischemic heart disease	25 (20.1)
Atrial fibrillation	7 (5.6)
Bundle branch block	3 (2.4)
Chronic renal failure	5 (4.03)
Multifocal atherosclerosis	11 (8.87)
Pulmonary hypertension	8 (6.4)
Aortic dissection	17 (13.7)
LVEF (%)	56.6 ± 7.0
NYHA III–IV	46 (37.0)
Mitral insufficiency	22 (17.7)
Bicuspid AV	37 (29.8)
Diameter of the aorta ascending (mm)	50.6 ± 5.8
Diameter of the aortic root (mm)	44.8 ± 7.7
Aortic valve insufficiency	
grade 0	7 (5.6)
grade I	15 (12.0)
grade II	28 (22.5)
grade III	52 (41.9)
grade IV	22 (17.7)

Data presented as mean and standard deviation with or without ranges, or the numbers and percentages. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

The average cardiopulmonary bypass (CPB) time was 159.7 minutes, and the aortic cross-clamp time was 121.1 minutes (Table 2).

Table 2 Intraoperative characteristics

Type of operation	Total n = 124
Combined operation	56 (45.1)
Re-operation (redo)	0 (0,0)
Isolated David pr. and aorta ascending replacement	68 (54)
Combined surgeries David pr. and partial or total aortic arch replacement	20 (16)
David pr. and CABG	19 (15)
David pr. and MV reconstruction	10 (8)
David pr. and CABG + MV reconstruction	4 (3.2)
David pr. and MV+TV reconstruction	3 (2.4)
Size of prosthesis (mm)	28.9 ± 2.3
AV cusps intervention	45 (36.2)
CPB Time (min)	159.7 ± 37.1
Cross clamp time (min)	121.1 ± 25.3

Data presented as mean and standard deviation with or without ranges, or the numbers and percentages. CABG, Coronary artery bypass grafting; MV, Mitral valve; TV, Tricuspid valve; AV, Aortic valve; CBP, Cardiopulmonary bypass.

Low Cardiac Output Syndrome was in 3 (2.4%) cases. Arrhythmias requiring therapy was in 33 (26.6%) patients and pacemaker implantation was in 3 (2.4%) of patients. Reoperation for bleeding was 11 (8.8%) cases and cerebrovascular accidents/stroke was in 1 (0.8%) patient. The 30-day mortality rate was 0.8% (Table 3).

Table 3 Postoperative characteristics

Complications	n = 124
Low cardiac output syndrome	3 (2.4)
Arrhythmias (requiring medical therapy/ cardioversion)	33 (26.6)
Pacemaker implantation	3 (2.4)
Reoperation for bleeding	11 (8.8)
Cerbrovascular accidents/Stroke	1 (0.8)
Renal failure	1 (0.8)
Gastrointestinal complications	3 (2.4)
30-day mortality	1 (0.8)
Number of days after surgery before discharge	8.60 ± 4.93
Aortic valve insufficiency	
grade I	19 (15.3)
grade II	0 (0)
Aortic valve stenosis	0 (0)

Data presented as numbers and percentages and mean and standard deviation with ranges.

The echocardiographic data (Table 4) before discharge and at follow-up provide critical insights into the procedure's effectiveness: gradient on aortic valve: the stability of the mean gradient was 6.45 mmHg before discharge to 6.88 mmHg at follow-up. Left Ventricular Ejection Fraction (LVEF%): significant improvement from 49.85% before discharge to 55.47% at follow-up (p = 0.038).

Table 4 Echocardiographic data

Echocardiagraphic data	before discharge (n = 123)	follow-up (n = 95)	P value
Gradient on the aortic valve (mmHg)	6.45 ± 2.58	6.88 ± 3.72	0,1143
Left ventricular ejection fraction (%)	49.85 ± 9.60	55.47 ± 12.96	0,0384
Left ventricular end-diastolic volume (ml)	134.00 ± 33.57	146.36 ± 61.39	0,5516

Data presented as mean and standard deviation with or without ranges, or the numbers and percentages.

The long-term survival rates (99% at 1 and 3 years, 98% at 6 years, and 87% at 8 years) and freedom from reoperation (99% at 1 year, 98% at 3 years, 95% at 6 years, and 91% at 8 years) are indicative (Figure 2).

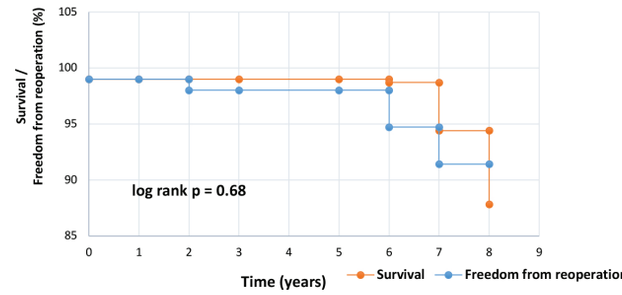


Figure 2 – Kaplan-Meier curves for the entire cohort patients. Survival curve and freedom from aortic valve-related reoperation

Discussion

The outcomes of the David procedure at the National Scientific Medical Center in Astana, Kazakhstan, affirm its efficacy and safety for treating aortic root aneurysms in our center. This discussion analyze the implications of these findings, compares them with existing literature, and addresses the limitations and future directions for this surgical technique.

The primary objective behind the David procedure is to maintain the functionality of the patient's natural valve while correcting the aneurysmal dilation of the aortic root. This technique involves replacing the dilated portion of the aorta while preserving the native aortic valve and reimplanting it into a Dacron graft, which acts as a support structure for the repaired aortic root.

The enduring success of the David procedure manifests over the long term, offering several advantageous outcomes. Previous studies showcase the sustained durability of the preserved aortic valve over an extended period, often circumventing the necessity for additional interventions due to valve dysfunction [4].

The relatively young age of patients in our study suggests that the David procedure is often chosen for younger individuals who may benefit from valve preservation over the long term, avoiding the complications associated with prosthetic valves. The David procedure success hinges on meticulous surgical technique and intraoperative management. These durations of procedure are comparable to other complex cardiac surgeries in our department and reflect the technical demands of the procedure (Table 2). Despite these challenges, the absence of redo surgeries within the cohort suggests that the initial surgeries were performed with high precision and effectiveness.

The long-term survival rates (Figure 2) are acceptable for us in this study. These outcomes affirm the procedure's durability

and ability to provide sustained benefits without additional interventions. This aligns with other studies demonstrating similar long-term success rates for the David procedure [5, 6]. Long-term observations indicate lower occurrences of complications typically associated with neo-root (prosthetic), such as infections, thrombotic events, or structural valve deterioration [7].

Patients undergoing successful valve-sparing procedures typically enjoy an improved quality of life compared to those necessitating mechanical valve replacements. This is attributed to avoiding lifelong anticoagulation and retaining the functionality of their native valve [8-12].

These outcomes underscore the clinical efficacy and promise of the David procedure in mitigating complications, enhancing patient well-being, and extending longevity by preserving the native aortic valve. However, individual variations, surgical techniques, and post-operative care profoundly impact these outcomes, emphasizing the necessity for diligent patient monitoring and adherence to medical guidance for optimal results.

Retaining the native aortic valve offers significant benefits, such as a lower risk of thromboembolic events, which are more common with mechanical valve replacements. This can lead to better hemodynamics and potentially improved long-term quality of life compared to those receiving prosthetic valves [13-17].

The rate of postoperative arrhythmias (26.6%) is in line with other cardiac surgeries in our clinic. Arrhythmias are common after heart surgery and often manageable with medication or intervention. Pacemaker implantation (2.4%): This low rate suggests that the procedure does not significantly disrupt the heart's electrical conduction system in this study. This is also a procedure demonstrated low rates of postoperative complications such as low cardiac output syndrome (2.4%), cerebrovascular accidents (0.8%) and low incidence of reoperation for bleeding (8.8%)

These rates are consistent with reported in other studies, indicating that this procedure is not only effective but also safe for most patients [18-23].

The echocardiographic data (Table 4) indicates that the valve function is well-maintained postoperatively and left ventricle function demonstrates enhanced cardiac function, likely due to the relief of aortic valve regurgitation and improved ventricular mechanics in the long term. Similar studies have reported comparable improvements in LVEF, reinforcing the benefit of valve preservation over replacement [17].

One of the significant findings of this study is the improvement in left ventricular ejection fraction (LVEF) postoperatively, from 49.85% before discharge to 55.47% at follow-up, comparable to preoperative data. Here we can assume that despite the decrease in ejection fraction after surgery, taking into account myocardial ischemia and traumatism of the operation, myocardial function is restored in the long term.

The continual advancement of cardiac surgical techniques holds promise for further refining outcomes and expanding the horizons of patient care in the realm of aortic root aneurysm management.

It's important to note that the decision to perform the David procedure depends on the specific characteristics of the patient's condition, and not all patients may be suitable candidates. The choice between the David procedure and other aortic surgery techniques is made based on individual factors and the surgeon's expertise.

The outcomes of this study are comparable with those reported in other centers performing the David procedure. For instance, a study by Kvitting et al. reported 5 years, the survival rate was 98.7% ± 0.7%, and at 10 years, it was 93.5% ± 5.1%. The freedom from reoperation on the aortic root for any cause at 10 years was 92.2% ± 3.6%, with three reoperations due to structural valve deterioration. The freedom from structural valve deterioration at 10 years stood at 96.1% ± 2.1% [12], which is consistent with the results observed in our study.

The survival rates of 99% at 1 and 3 years, 98% at 6 years, and 87% at 8 years are impressive and align with findings from other centers performing this procedure. The freedom from reoperation rates also remained high, with 99% at 1 year, 98% at 3 years, 95% at 6 years, and 91% at 8 years. These results affirm the procedure's long-term efficacy and its potential to provide sustained benefits without the need for further surgical interventions.

The success of the David procedure heavily relies on careful patient selection and the expertise of the surgical team. Patients with a structurally intact aortic valve, free from significant sclerosis or calcification, are ideal candidates. The decision to proceed with the David procedure should be individualized, considering the patient's specific anatomical and clinical characteristics. Furthermore, the proficiency of the surgical team in performing this technically demanding procedure is crucial for achieving optimal outcomes.

Limitations

This study has several limitations that should be acknowledged. Firstly, it is a retrospective study, which limits the collection of additional data. Secondly, the follow-up period, although averaging 4.6 years, may not be sufficient to capture all long-term complications or reoperations.

Considering that the operations were performed on patients from all over the region of Kazakhstan, follow-up examinations in our clinic were limited due to the time and financial burden. It would also be useful to assess the quality of life.

Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to other populations or healthcare settings.

Conclusion

The outcomes of the David procedure have shown promising results. Studies indicate favorable survival rates and reduced incidences of valve-related complications, making it an attractive option for eligible patients with aortic root pathology.

By preserving the native aortic valve, this procedure reduces the need for lifelong anticoagulation therapy and enhances patient quality of life. Considering our relatively limited experience careful patient selection are essential for achieving the best possible outcomes, and ongoing research is needed to continue improving and expanding the use of this valuable technique in Kazakhstan.

Author Contributions: Conceptualization, A.T., A.Y.; methodology, A.A., E.S.; validation, A.E.; formal analysis, A.T., A.E.; investigation, A.Y., A.A.; resources, A.B.; data curation, A.T.; writing – original draft preparation, A.T.; writing – review and editing, A.B., A.A.; visualization, A.Y., A.E., E.S.; supervision, A.B.; project administration, A.T. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. David, Tirone E., and Christopher M. Feindel. "An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta." *The Journal of thoracic and cardiovascular surgery* 103.4 (1992): 617-622.
2. Schneider, U., Ehrlich, T., Karliova, I., Giebels, C., & Schäfers, H. J. (2017). Valve-sparing aortic root replacement in patients with Marfan syndrome—the Homburg experience. *Annals of cardiothoracic surgery,* 6(6), 697.
3. Norton, E. L., Patel, P. M., Levine, D., Wei, J. W., Binongo, J. N., Leshnower, B. G., ... & Chen, E. P. (2023). Bentall versus valve-sparing aortic root replacement for root pathology with moderate-to-severe aortic insufficiency: a propensity-matched analysis. *European Journal of Cardio-Thoracic Surgery,* 64(2), ezad231.
4. Arabkhani, B., Mookhoek, A., Di Centa, I., Lansac, E., Bekkers, J. A., Van Wijngaarden, R. D. L., ... & Takkenberg, J. J. (2015). Reported outcome after valve-sparing aortic root replacement for aortic root aneurysm: a systematic review and meta-analysis. *The Annals of thoracic surgery,* 100(3), 1126-1131.
5. Beckmann, E., Martens, A., Krüger, H., Korte, W., Kaufeld, T., Stettinger, A., ... & Shrestha, M. L. (2021). Aortic valve-sparing root replacement with Tirone E. David's reimplantation technique: single-centre 25-year experience. *European Journal of Cardio-Thoracic Surgery,* 60(3), 642-648.
6. Mastrobuoni, S., Govers, P. J., Veen, K. M., Jahanyar, J., van Saane, S., Segreto, A., ... & Arabkhani, B. (2023). Valve-sparing aortic root replacement using the reimplantation (David) technique: a systematic review and meta-analysis on survival and clinical outcome. *Annals of cardiothoracic surgery,* 12(3), 149.
7. Deng, J., & Zhong, Q. (2021). Clinical analysis of redo aortic root replacement after cardiac surgery: a retrospective study. *Journal of Cardiothoracic Surgery,* 16, 1-10.
8. Hamandi, M., Nwafor, C. I., Baxter, R., Shinn, K., Wooley, J., Vasudevan, A., ... & Brinkman, W. T. (2020, October). Comparison of the Bentall procedure versus valve-sparing aortic root replacement. *In Baylor University Medical Center Proceedings* (Vol. 33, No. 4, pp. 524-528). Taylor & Francis.
9. Bethancourt, C. N., Blitzer, D., Yamabe, T., Zhao, Y., Nguyen, S., Nitta, S., ... & Takayama, H. (2022). Valve-sparing root replacement versus bio-bentall: inverse propensity weighting of 796 patients. *The Annals of Thoracic Surgery,* 113(5), 1529-1535.
10. Greason, K. L., Pochettino, A., Sandhu, G. S., King, K. S., & Holmes, D. R. (2016). Transfemoral transcatheter aortic valve insertion-related intraoperative morbidity: Implications of the minimalist approach. *The Journal of Thoracic and Cardiovascular Surgery,* 151(4), 1026-1029.
11. Salmasi MY, Theodoulou I, Iyer P, Al-Zubaidy M, Naqvi D, Snober M, Oo A, Athanasiou T. Comparing outcomes between valve-sparing root replacement and the Bentall procedure in proximal aortic aneurysms: systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg.* 2019; 29(6): 911–922. https://doi.org/10.1093/icvts/ivz211.
12. De Paulis R, Scaffa R, Salica A, Weltert L, Chirichilli I. Biological solutions to aortic root replacement: valve-sparing versus bioprosthetic conduit. *Journal of Visualized Surgery*. 2018; 4. https://doi.org/10.21037/jovs.2018.04.12.
13. Patel ND, Weiss ES, Alejo DE, Nwakanma LU, Williams JA, Dietz HC, Spevak PJ, Gott VL, Vricella LA, Cameron DE. Aortic root operations for Marfan syndrome: a comparison of the Bentall and valve-sparing procedures. *The Annals of Thoracic Surgery*. 2008; 85(6): 2003-2011. https://doi.org/10.1016/j.athoracsur.2008.01.032.
14. Skripochnik E, Michler RE, Hentschel V; Neragi-Miandoab S. Repair of aortic root in patients with aneurysm or dissection: comparing the outcomes of valve sparing root replacement with those from the Bentall procedure. *Brazilian Journal of Cardiovascular Surgery.* 2013; 28(4): 435–441. https://doi.org/10.5935/1678-9741.20130064.
15. Kvitting JPE, Kari FA, Fischbein MP, Liang DH, Beraud AS, Stephens EH. David valve-sparing aortic root replacement: equivalent mid-term outcome for different valve types with or without connective tissue disorder. *The Journal of Thoracic and Cardiovascular Surgery.* 2013; 145(1): 117–127.e5. https://doi.org/10.1016/j.jtcvs.2012.06.028.
16. Levine D, Patel P, Wang C, Pan C, Dong A, Leshnower B, Kurlansky P, Smith CR, Chen E, Takayama H. Valve-sparing root replacement versus composite valve graft root replacement: Analysis of more than 1500 patients from 2 aortic centers. *J Thorac Cardiovasc Surg.* 2023; 168(3): 770–780.e6. https://doi.org/10.1016/j.jtcvs.2023.05.022.
17. Zhou T, Lv Ch-H, Huang W-F, LiY-G, Zeng X-Ch, Chen M-H. A retrospective study: do patients with left ventricular ejection fraction ≤50% benefit from heart valve surgery? Journal of Thoracic Disease. 2022; 14(12): 4803. https://doi.org/10.21037/jtd-22-1345.
18. McIntyre WF. Post-operative atrial fibrillation after cardiac surgery: Challenges throughout the patient journey. *Front. Cardiovasc. Med.* 2023; 10: 1156626. https://doi.org/10.3389/fcvm.2023.1156626.
19. Stefanelli G, Pirro F, Chiurlia E, Bellisario A, Weltert L. Mid-term outcomes of stentless Bio-Bentall vs. David Reimplantation for aortic root replacement. *J Card Surg*. 2022; 37(4): 781–788. https://doi.org/10.1111/jocs.16271.
20. Tsaroev B, Sharifulin R, Karadzha A, Pivkin A, Afanasyev A, Zalesov A, Mustaev M, Bogachev-Prokophiev A. Multimed Man *Cardiothorac Surg.* 2023; 2023. https://doi.org/10.1510/mmcts.2023.024.
21. Liu Y, Benzha MY, Hubert M, Perin B, Lauria G, Dan P, Phamisith E, Scadi S, Dong N, Villemot JP, Maureira JP. *Heart Lung Circ*. 2022; 1: 144–152. https://doi.org/10.1016/j.hlc.2021.07.013.
22. Salehi Omran A, Aeen A, Nayebirad S, Vakili-Basir A, Najafi MS, Mohseni-Badalabadi R, Shirani S, Zoroufian A, Jalali A, Mostafanejad FA, Sahebjam M. *J Cardiothorac Surg.* 2024;19: 1;36. https://doi.org/10.1186/s13019-024-02546-9.
23. Bori Bata AK, D'Ostrevy N, Pereira B, Geoffroy E, Dauphin N, Eljezi V, Azarnoush K, Ulman L, Camilleri L. *Cardiovasc Diagn Ther.* 2017; 6: 572–580. https://doi.org/10.21037/cdt.2017.08.02.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15570

About Fertility: Fertile and Infertile Women's Views on Fertility Awareness and Lifestyles

Betul Uncu[1], Rukiye Duman[2], Elif Dogan[1], Aysenur Yaman[2]

[1]Institute of Graduate Studies, Istanbul University-Cerrahpasa, Istanbul, Turkey
[2]Department of Midwifery, Istanbul University-Cerrahpasa, Istanbul, Turkey

Received: 2024-08-02.
Accepted: 2024-11-04.

J Clin Med Kaz 2024; 21(6): 35–40

Corresponding author:
Rukiye Duman
E-mail: rukiye.duman@iuc.edu.tr.
ORCID: 0000-0002-7007-7922.

Abstract

Background: Infertility is a widespread problem that has significant impacts on individuals, families, and society. It's known that low fertility awareness and lack of knowledge about lifestyle factors affect fertility.

Aim: To compare fertility awareness and healthy lifestyle practices among women with and without infertility.

Methods: Data were collected from 172 infertile and fertile women who received care at the Infertility Unit and the Antenatal Care Unit of a hospital in Turkey between November 2022 and January 2023. The study data were obtained using the Healthy Lifestyle Behavior Scale and Fertility Awareness Scale.

Results: Although there were variations between infertile and fertile women in characteristics such as marriage duration, frequency of exercise, smoking habits, history of depression and caffeine intake, these differences were not statistically significant. But, fertile women had a more positive lifestyle in terms of nutrition ($p<0.001$). Additionally, fertile women had a higher fertility awareness than the infertile women. The main factor affecting fertility awareness in these women was cognitive and somatic awareness ($p<0.001$).

Conclusions: There are distinct differences in healthy lifestyle behaviors and fertility awareness between fertile and infertile women.

Keywords: fertility; fertility awareness; healthy lifestyle; infertility.

Introduction

According to the World Health Organization (WHO), infertility is defined as "a reproductive system disorder characterized by the inability to achieve a clinical pregnancy after 12 months or more of regular, unprotected sexual intercourse." It is estimated that around 48 million couples and 186 million individuals globally are affected by infertility [1]. In Turkey, approximately 1.5 to 2 million couples are reported to experience fertility issues [2]. Infertility is a widespread problem that has significant impacts on individuals, families, and society. Achieving the necessary conditions for fertility is crucial for a healthy pregnancy, and these conditions encompass various factors such as nutrition, physical activity, sleep, alcohol and tobacco use, work conditions, and medication use [3,4]. It is hypothesized that making lifestyle adjustments and increasing fertility awareness could potentially enhance fertility outcomes. The female reproductive system and fertility are influenced by various factors, including a woman's age and lifestyle choices. Among these lifestyle factors, aspects like nutrition, exercise, body weight, obesity, eating disorders, psychological health, substance use (such as smoking, alcohol, and drugs), caffeine intake, environmental and occupational exposures, and sexually transmitted infections can impact female fertility. While age is an unchangeable factor, lifestyle behaviors and habits are modifiable and

within an individual's control [5].

Research indicates that women experiencing infertility often have low fertility awareness and lack knowledge about how lifestyle factors affect fertility [6]. Lifestyle choices are crucial not only for fertility but also for overall health, reproductive health, and sexual health. These behaviors, which individuals can control and improve, can either positively or negatively influence reproductive health. Those who understand the impact of lifestyle on fertility are more likely to adopt healthy habits to preserve their fertility. To protect fertility and enhance fertility awareness, individuals should be encouraged to make healthy changes to risky lifestyle behaviors, such as quitting smoking, improving eating habits, and exercising regularly. Increasing fertility awareness among women, preventing infertility, and promoting healthy behaviors require a collaborative approach involving multidisciplinary teamwork [7,8]. In consequence, while research in the literature generally focuses on general fertility awareness, the differences between these two groups have not been sufficiently examined. In particular, determining the differences between infertile women's lack of knowledge and fertile women's awareness levels may help us better understand the impact of socio-cultural and economic factors. It is also important to consider the relationship between fertility awareness and healthy life behaviors. Individuals with fertility awareness are more likely to adopt healthy living habits such as healthy eating, regular exercise and stress management. In this context, developing an understanding of the factors that increase or inhibit fertility awareness in women experiencing infertility may both improve individuals' healthy living behaviors and increase the effectiveness of support and treatment processes.

This research aims to compare fertility awareness and healthy lifestyle practices among women with and without infertility. Given the lack of comparative studies in this area, the findings from this research are anticipated to provide valuable insights and contribute to the existing literature.

Material and methods

This study, which was descriptive, cross-sectional, and comparative in design, was conducted between November 2022 and June 2023. The research adhered to the guidelines set forth by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Sample

The study population included both infertile and fertile women who received care at the Infertility Unit and the Antenatal Care Unit of a hospital in Turkey between November 2022 and January 2023. Sample size calculations were conducted using the G*Power (3.1.9.2) software, with a 0.05 significance level and 90% power. Based on an assumed medium effect size (d=0.5) for comparisons in independent groups, the calculations indicated that each group should include 86 participants, as determined using the chi-square test (Figure 1).

Inclusion criteria: The sample included infertile women, which consisted of primary infertile women receiving infertility treatment without any previous successful live births or pregnancies, and fertile women, which consisted of primiparous women between 32 and 40 weeks of gestation. The study included women aged 18 to 49 years who had at least a primary school education.

Exclusion criteria: Women with chronic disorders, diagnosed with obstetric or gynecological diseases.

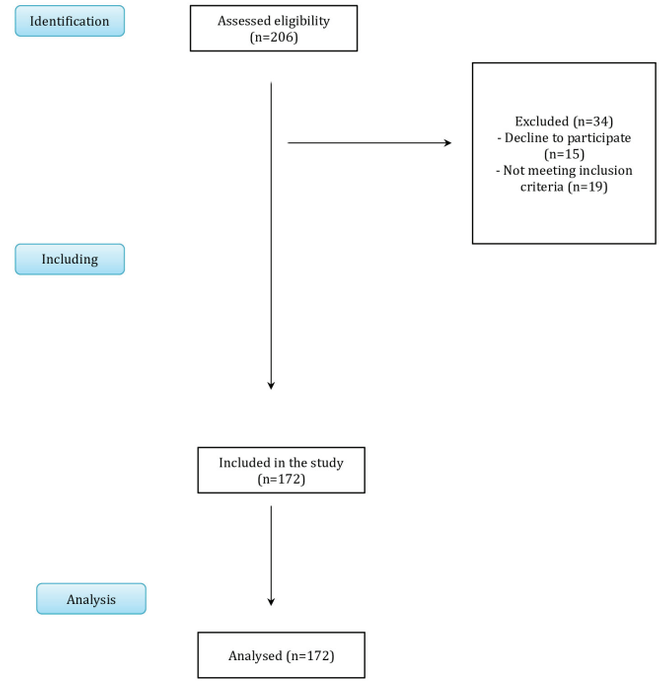


Figure 1 – Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow diagram

Measurement tools

Measurement tools are given below.

Descriptive Information Form: The researchers developed this form following an extensive review of existing literature [9,10]. It comprised 13 questions designed to gather information about the characteristics of women experiencing infertility, including details such as age, level of education, spouse's age, length of marriage, duration of infertility treatment, types of treatments received, smoking habits, and other relevant factors.

Healthy Life Style Behaviour Scale II (HLSBS-II): The scale, initially developed by Walker et al. in 1987, is based on Pender's Health Promotion Model and was designed to assess health promotion behaviors [11]. It underwent revisions in 1996 and was subsequently renamed the Healthy Lifestyle Behavior Scale II (HLSBS-II) [12]. The Turkish version's validity and reliability were established by Bahar et al. in 2008. This scale comprises 52 items across six subscales: spiritual growth, interpersonal relations, nutrition, physical activity, health responsibility, and stress management. Higher scores on the scale reflect increased positive health behaviors. The original Cronbach's alpha coefficient was reported as 0.92 [13], while in this study, the coefficient was found to be 0.91.

Fertility Awareness Scale (FAS): Özşahin and Derya (2022) conducted the Turkish validity and reliability study of the scale. The scale consists of 19 items and two subscales, which are “Bodily Awareness” (consisting of 10 items) and “Cognitive Awareness” (consisting of 9 items). As the total score on the scale increases, the level of awareness also increases. When evaluating the total score on the scale, a score between 19 and 43 indicates low awareness, a score between 44 and 69 indicates moderate awareness, and a score between 70 and 95 indicates high awareness. The Cronbach's alpha coefficient for internal consistency of the total scale score is 0.887 [14]. In this study, the Cronbach's alpha coefficient was found to be 0.713.

Research Process

This study was conducted in an in vitro fertilization center in Turkey. The hospital provides important services in the field of reproductive health with its laboratories and specialized physician staff. In addition, the pregnancy outpatient clinic of the same hospital provides comprehensive support and follow-up services for women during pregnancy. These two units work in an integrated manner to meet the needs of patients in fertility treatment and pregnancy monitoring.

The fertility clinic of the hospital conducts new patient admissions on Mondays and Tuesdays. On these days, face-to-face interviews were held with women who were seeking services for the first time and had been diagnosed with primary infertility. During these interviews, the purpose of the study was explained in detail. Forms were filled out by researchers for infertile women who agreed to participate and met the inclusion criteria (BU, AY). Additionally, the hospital has an antenatal clinic on Thursdays and Fridays for pregnant women. In this clinic, face-to-face interviews were conducted with primiparous women between 32 and 40 weeks of gestation. During these meetings, the purpose of the study was explained to these women as well, and forms were filled out by researchers for fertile women who agreed to participate and met the inclusion criteria (RD, ED). The study is anonymous; therefore, the identities of the participants were kept strictly confidential. Participants were given detailed information about the process before participating in the study and their written informed consent was obtained. All data were recorded free of personal identifying information and was used for research purposes only.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 25.0. Continuous variables were reported as means ($\bar{x}$) and standard deviations (SD), whereas categorical variables were reported as frequencies (n) and percentages (%). The Shapiro-Wilk test was employed to evaluate the normality of continuous variables. To compare continuous variables between groups, both the Student's t-test and Mann-Whitney U test were utilized. The Chi-square test was used for categorical variables. Additionally, Pearson correlation analysis was performed to examine relationships between different scales.

Ethics Approval

The study received ethical approval from Istanbul University-Cerrahpaşa Social and Humanities Ethics Committee (Ethics Committee Date: 11.08.2022, No: 347). All phases of the research adhered to the principles outlined in the Helsinki Declaration. Authorization was secured from the relevant institution for data collection, as well as from the owners of the measurement scales and the participating women.

Results

Table 1 displays the descriptive characteristics and comparative data for infertile and fertile women. The average age of women with infertility was found to be 32.5±5.18 years, while the average age of their husbands was 35±6.05 years. The average duration of marriage was 5.00±3.92 years, the average duration of infertility was 2.50±3.27 years, and the average sleep duration was 7.5±1.26 hours. In contrast, fertile women had an average age of 28.5±4.69 years, with their husbands averaging 32±5.29 years. The duration of marriage for fertile women was also 5.00±4.06 years, and their average sleep duration was 8.00±1.66 hours. Statistically significant differences were observed between the groups: infertile women were older ($p<0.001$), their spouses were older ($p=0.001$), and they had a shorter sleep duration ($p=0.031$). However, there were no significant differences between the groups concerning the duration of marriage, regular physical activity, smoking status, history of depression, or caffeine intake ($p>0.05$).

Table 1 Comparison of descriptive characteristics between groups

	Infertile Women (n=86)		**Fertile Women (n=86)**			
	x̄	**SD**	**x̄**	**SD**	**Test**	**p**
Age	32.50	5.18	28.5	4.69	t=4.639	<0.001*
Husband Age	35	6.05	32.0	5.29	Z=-3.432	0.001*
Duration of Marriage (year)	5	3.92	5	4.06	Z=-1.680	0.093
Duration of Infertility (year)	2.50	3.27	---	---		
Sleep Duration (hour)	7.50	1.26	8	1.66	Z=-2.151	0.031*
	N	**%**	**N**	**%**		
Regular Exercise						
Yes	17	19.8	22	25.6	χ2=0.829	0.363
No	69	80.2	64	74.4		
History of Depression						
Yes	15	17.4	15	17.4	χ2=0.000	1.000
No	71	82.6	71	82.6		
Smoking Status (per day)						
1-20	13	15.2	7	8.1	χ2=4.487	0.106
Never	73	84.8	79	91.9		
Caffeine Consumption						
Rarely	19	22.1	28	32.6	χ2=5.301	0.258
Sometimes	24	27.9	26	30.2		
Frequently	15	17.4	11	12.8		
Always	12	14.0	5	5.8		
Never	16	18.6	16	18.6		
Duration of Infertility Treatment (years)						
1-3	54	62.8	-----	-----		
4-6	20	23.3				
7-+	12	14.0				
Infertility Treatment						
Intrauterine Insemination (IUI)	18	20.9	-----	-----		
In Vitro Fertilization (IVF)	68	79.1				
Cause of Infertility						
Female factors	32	37.2				
Both factors	26	30.2				
Unexplained	28	32.6				
Pregnancy						
Planned	-----	-----	66	76.7		
Unplanned			20	23.3		

X: Mean, SS: Standard deviation, t: Student-t Test, Z:Mann- Whitney U Test , χ2: Chi-square test

The data regarding the comparison of mean scores obtained from HLSBS-II for infertile and fertile women are shown in Table 2. According to our findings, the mean score of the Nutrition subscale was significantly higher in fertile women compared to infertile women, indicating a high and very significant statistical difference (p<0.001). There were no significant differences between the groups in terms of total scale score and other subscales (p>0.05).

Table 2 Mean scores of infertile and fertile women on the HLSBS-II Scale and its subscales

Parameters	Infertile Women (n=86)	Fertile Women (n=86)		
	x̄±SD	x̄±SD	Test	p
HLSBS-II Subscales				
Physical Activity	11.50±5.24	14.00±4.86	Z=-1.589	0.112
Nutrition	22.00±4.55	26.00±4.31	Z=-4.345	<0.001*
Health Responsibility	24.00±4.63	24.00±4.44	Z=-0.286	0.775
Spiritual Growth	31.00±4.41	31.00±4.91	Z=-0.405	0.686
Interpersonal Relations	29.50±4.04	30.00±4.23	Z=-0.214	0.831
Stress Management	21.00±4.10	22.00±4.35	Z=-0.087	0.930
Total Score	140.00±19.96	150.00±20.22	t=-1.188	0.237

t=Student-t test, Z=Mann Whitney-U test, p<0.05

The data regarding the comparison of mean scores obtained from FAS for infertile and fertile women are presented in Table 3. According to our findings, infertile women showed a moderate level of mindfulness, while fertile women demonstrated a high level of mindfulness (total scale score: infertile women: 64.50; fertile women: 71.00). The mean score of FAS was significantly higher in fertile women compared to infertile women, indicating a high and very significant statistical difference (p<0.001). In the subscales of the scale, Cognitive Awareness total score (p<0.001) and Somatic Awareness total score (p=0.005) were higher in fertile women, and there was a significant difference between the groups.

Table 3 Mean Scores of infertile and fertile women on the FAS and its subscales

Parameters	Infertile Women (n=86)	Fertile Women (n=86)		
	x̄±SD	x̄±SD	Test	p
FAS Subscales				
Cognitive Awareness	26.50±5.49	30.00±6.03	t=-4.122	<0.001*
Bodily Awareness	39.00±6.51	42.00±5.54	Z=-2.800	0.005*
Total Score	64.50±10.07	71.00±9.68	t=-4.353	<0.001*

t=Student-t test, Z=Mann Whitney-U test, p<0.05.

A weak positive correlation was observed between the average scale scores for infertile women (P=0.445; p<0.001), while a moderate positive correlation was found for fertile women (P=0.591; p<0.001) (Table 4).

Table 4 Relationship between HLSBS-II Scale and FAS scores

Category	Results	
	P	p
Infertile Women	0.445	<0.001
Fertile Women	0.591	<0.001

P=Pearson, p<0.05

Discussion

This study was conducted to compare fertility awareness and healthy lifestyle practices between women with and without infertility. According to the findings of the current study, it was determined that fertile women had healthier eating behaviors and had higher fertility awareness in general. It was determined that the main factor affecting fertility awareness in these women was cognitive and somatic awareness. Current studies often evaluate fertility awareness of infertile and fertile women separately. However, studies comparing fertility awareness of infertile and fertile women are limited in the literature.

The findings reveal differences in descriptive characteristics between the two groups, with fertile women and their partners being younger on average. It is well-documented that advanced maternal age can lead to a reduced ovarian reserve, while older paternal age is linked to diminished sperm quality and testicular function, both of which can contribute to infertility [15,16]. The elevated ages observed in the infertile group of this study align with existing literature on this issue. When examining sleep duration, it is observed that infertile women had shorter sleep durations, which was statistically significant. The literature suggests that healthy sleep has positive effects on fertility, while negative sleep habits are often found in infertile women. Additionally, infertility is known to have a negative impact on sleep [17]. Although caffeine consumption was similar between infertile and fertile women in the current study, studies in the literature have reported conflicting results regarding the effects of caffeine on fertility [18,19]. The uncertainty of caffeine's effects on fertility was also reflected in the data of this study. While physical activity and exercise are known to positively support fertility, a meta-analysis has indicated contradictory results [20]. The present study showed similar rates of regular exercise between the groups, which is in line with the literature.

Studies emphasize that diet may have an effect on fertility [21]. Yang et al. (2023) reported that the Mediterranean diet may have a positive effect on fertility [22]. Poor dietary habits are known to affect fertility adversely by contributing to metabolic disorders like obesity, diabetes, hyperlipidemia, and negatively impacting oocyte quality [23]. Nevertheless, studies report that the consequences of diet for fertility are unclear. In a study of women's reproductive awareness, it was reported that the majority thought there was an association between obesity and infertility [24]. In the present study, fertile women were found to have healthier eating behaviors. However, no study was found in the literature directly evaluating the nutritional habits of women according to their fertility status. A systematic review indicates that individuals experiencing difficulty in conceiving and those planning their pregnancies have higher fertility awareness [25]. In a study involving women admitted to hospital for infertility, it was determined that women had a high level of knowledge about

the causes of infertility. However, they were still reported to have low awareness about reproductive health [24]. Similarly, the current study showed that infertile women had lower awareness. It is believed that this lack of fertility awareness contributes to the development of infertility. However, in a study including fertile women and men, fertility awareness was again found to be low. In the study, it was reported that higher education levels positively affected fertility awareness [26]. As can be seen, there are studies on fertility awareness conducted with different populations in the literature. However, the findings on the level of fertility awareness of fertile or infertile women are controversial.

Conclusion

Infertility stands out as a significant public health problem. Many infertile women do not have sufficient information about reproductive health, fertility processes and treatment options. This lack of information leads to misunderstandings and disregard for healthy lifestyle choices. The findings of the study show that women experiencing infertility generally exhibit lower levels of healthy lifestyle behaviors and fertility awareness. This situation reveals that infertile women face problems such as lack of information affecting their health decisions and not adopting healthy lifestyle habits. At the same time, the difficulties brought by the infertility treatment process also negatively affect women's mental health. Uncertainty and anxiety during the treatment process make it difficult for them to adopt habits such as healthy nutrition, regular exercise and stress management. Women under stress may disregard healthy choices and this situation negatively affects their general health status and creates a vicious cycle regarding reproductive health. Therefore, addressing the lack of information and encouraging healthy lifestyle habits is of critical importance in the fight against infertility. In light of these results, it is recommended that midwives systematically collect information about women's pre-pregnancy lifestyle habits and fertility awareness. In addition, implementation of educational programs aimed at raising awareness of effective fertility management may be beneficial in addressing and improving these issues within the community. It is recommended that future research include longitudinal studies to monitor the long-term effects of lifestyle changes on fertility outcomes. Such studies should focus on the development and implementation of interventions aimed at promoting healthy lifestyle behaviors among infertile women. Thus, with the fertility awareness gained, women can adopt healthy lifestyle behaviors and improve their reproductive health.

Strengths and Limitations

One of the strengths of this study is that it conducts a comparative analysis among women in both the in vitro fertilization clinic and the antenatal care unit. This approach allows for a more comprehensive understanding of the effects of healthy lifestyle behaviors on fertility awareness. By focusing on women's healthy lifestyle behaviors and health literacy, the study identifies potential intervention areas to enhance women's knowledge regarding reproductive health. However, there are some limitations to this study. The research is confined to women receiving care at a hospital's in vitro fertilization and antenatal clinics in Turkey, which may restrict the generalizability of the findings to other settings or populations. Additionally, the data were collected through self-reported questionnaires; this reliance on participants' self-disclosure may introduce response biases or inaccuracies. These factors should be considered when interpreting the results and applying them to broader contexts.

Author Contributions: Conceptualization, B.U., R.D., E.D. and A.Y.; methodology, B.U., R.D. and E.D.; validation, B.U., R.D. and E.D.; formal analysis, E.D. and A.Y; investigation, B.U. and R.D.; resources, B.U., E.D. and A.Y.; data curation, B.U. and E.D.; writing – original draft preparation, B.U., R.D., E.D. and A.Y.; writing – review and editing, B.U., R.D. and E.D.; visualization, R.D. and E.D.; supervision, B.U.; project administration, B.U., R.D. and E.D.; funding acquisition, B.U., R.D., E.D. and A.Y.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: The authors extend their sincere gratitude to all the women who generously participated in this study. We especially appreciate the willingness of the women experiencing infertility to contribute their time and insights, despite the considerable stress and personal challenges they face. Engaging with individuals under such circumstances is not only demanding but also deeply rewarding. Their cooperation and openness have been invaluable to the success of this research. We are profoundly grateful for their dedication and the opportunity to learn from their experiences.

Funding: None.

Ethics approval: The study obtained approval from the Istanbul University Cerrahpaşa Social and Human Sciences Ethics Committee (Ethics Committee Date: 08.11.2022 No: 2022/347). All stages of the study were conducted in accordance with the Helsinki Declaration. Permission was obtained from the institution where the study data would be collected, the owners of the scales used, and the women participating in the study.

References

1. World Health Organization. Available at: https://www.who.int/news-room/fact-sheets/detail/infertility. Access Date: May, 2023
2. Fırat BÖ, Şahin NH. Infertility and stigmatization within the context of gender roles: A systematic review. *Ordu University J Nurs Stud.* 2022; 5(1): 93–103. https://doi.org/10.38108/ouhcd.933034.
3. Boedt T, Vanhove AC, Vercoe MA, Matthys C, Dancet E, Lie Fong S. Preconception lifestyle advice for people with infertility. Cochrane Database Syst Rev. 2021; 4(4): CD008189. *Published* 2021 Apr 29. https://doi.org/10.1002/14651858.CD008189.pub3.
4. Carson SA, Kallen AN. Diagnosis and management of infertility: A Review. JAMA. 2021; 326(1): 65–76. https://doi.org/10.1001/jama.2021.4788.
5. Emokpae MA, Brown SI. Effects of lifestyle factors on fertility: Practical recommendations for modification. *Reproduction and Fertility.* 2021; 2(1): R13-R26. https://doi.org/10.1530/RAF-20-0046.

6. Verulava T, Pirtskhalava M. Fertility Awareness and Knowledge among Infertile Women in Georgia: A Cross-sectional Study. *International Journal of Infertility & Fetal Medicine.* 2022; 13(2): 70–75. https://doi.org/10.5005/jp-journals-10016-1284.
7. Lino K, Fukuhara R, Yokota M, Yokoyama, Y. Fertility awareness and subclinical infertility among women trying to get pregnant at home. *BMC Women's Health,* 2022; 22(1), 43. https://doi.org/10.1186/s12905-022-01626-z.
8. Ozsahin Z, Altıparmak S. Determining the effects of women's fertility awareness levels on obstetric history. *Middle Black Sea J Health Sci.* 2021; 7(1), 132–142. https://doi.org/10.19127/mbsjohs.892012.
9. Vahedian Shahroodi M, Tavakoly Sany SB, Hosseini Khaboshan Z, Esmaeily H, Jafari A, Tajfard M. Effect of a theory-based educational intervention for enhancing nutrition and physical activity among Iranian women: a randomised control trial. *Public Health Nutr.* 2021; 24(18): 6046–6057. https://doi.org/10.1017/S1368980021002664.
10. Wdowiak A, Anusiewicz A, Bakalczuk G, Raczkiewicz D, Janczyk P, Makara-Studzińska M. Assessment of Quality of Life in Infertility Treated Women in Poland. *Int J Environ Res Public Health.* 2021; 18(8): 4275. https://doi.org/10.3390/ijerph18084275.
11. Walker SN, Sechrist KR, Pender NJ. The Health-promoting lifestyle profile: Development and psychometric characteristics. *Nurs Res.* 1987; 36(2): 76–81.
12. Walker SN, Hill-Polerecky DM. Psychometric evaluation of the Health Promoting Lifestyle Profile II. Unpublished manuscript, University of Nebraska Medical Center. 1996.
13. Bahar Z, Beşer A, Gördes N, Ersin F, Kıssal A. Healthy life style behavior scale II: A reliability and validity study. *C.U.Hemsirelik Yuksekokulu Dergisi.* 2008; 12(1): 1–13.
14. Ozsahin Z, Derya YA. Fertility awareness scale development study in Turkish women. *European Journal of Integrative Medicine.* 2022; 49: 102101.
15. Secomandi L, Borghesan M, Velarde M, Demaria M. The role of cellular senescence in female reproductive aging and the potential for senotherapeutic interventions. *Hum Reprod Update.* 2022; 28(2): 172–189. https://doi.org/10.1093/humupd/dmab038.
16. Sharma R, Agarwal A, Rohra VK, Assidi M, Abu-Elmagd M, Turki RF. Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. *Reprod Biol Endocrinol.* 2015; 13: 35. https://doi.org/10.1186/s12958-015-0028-x.
17. Reschini M, Buoli M, Facchin F, Limena A, Dallagiovanna C, Bollati V, Somigliana E. Women's quality of sleep and in vitro fertilization success. *Sci Rep.* 2022; 12(1): 17477. https://doi.org/10.1038/s41598-022-22534-0.
18. Ricci E, Viganò P, Cipriani S, Somigliana E, Chiaffarino F, Bulfoni A, Parazzini F. Coffee and caffeine intake and male infertility: a systematic review. *Nutr J*. 2017; 16(1): 37. https://doi.org/10.1186/s12937-017-0257-2.
19. Gaskins AJ, Chavarro JE. Diet and fertility: a review. *Am J Obstet Gynecol.* 2018; 218(4): 379–389. https://doi.org/10.1016/j.ajog.2017.08.010.
20. Zhao F, Hong X, Wang W, Wu J, Wang B. Effects of physical activity and sleep duration on fertility: A systematic review and meta-analysis based on prospective cohort studies. *Front Public Health.* 2022; 10: 1029469. https://doi.org/10.3389/fpubh.2022.1029469.
21. Winter HG, Rolnik DL, Mol BWJ, et al. Can Dietary Patterns Impact Fertility Outcomes? A Systematic Review and Meta-Analysis. Nutrients. 2023; 15(11): 2589. *Published* 2023 May 31. https://doi.org/10.3390/nu15112589.
22. Yang J, Song Y, Gaskins AJ, et al. Mediterranean diet and female reproductive health over lifespan: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2023; 229(6): 617–631. https://doi.org/10.1016/j.ajog.2023.05.030.
23. Silvestris E, Lovero D, Palmirotta R. Nutrition and female fertility: An interdependent Correlation. *Front Endocrinol (Lausanne).* 2019; 10: 346. https://doi.org/10.3389/fendo.2019.00346.
24. Zalewska O, Wszołek K, Pięt M, Wilczak M, Chmaj-Wierzchowska K. Women's Awareness of Reproductive Health. *Medicina (Kaunas).* 2024; 60(1): 158. Published 2024 Jan 15. https://doi.org/10.3390/medicina60010158.
25. Pedro J, Brandão T, Schmidt L, Costa ME, Martins MV. What do people know about fertility? A systematic review on fertility awareness and its associated factors. *Ups J Med Sci.* 2018; 123(2): 71–81. https://doi.org/10.1080/03009734.2018.14801866.
26. Ahmed HM, Khan M, Yasmin F, et al. Awareness Regarding Causes of Infertility Among Out-patients at a Tertiary Care Hospital in Karachi, Pakistan. *Cureus*. 2020; 12(4): e7685. *Published* 2020 Apr 16. https://doi.org/10.7759/cureus.7685.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/15603.

Clinical Value of NT-proBNP and Lactate Parameters in Infants with Congenital Heart Defects

Narmin Akif Azizova[1]

[1]*Neonatal intensive care unit, Scientific Research Institute of Pediatrics named after K.Farajova, Baku, Azerbaijan*

Received: 2024-08-05.
Accepted: 2024-11-11.

J Clin Med Kaz 2024; 21(6): 41–47

Corresponding author:
Narmin Azizova Akif
E-mail: dr.narmin.azizova@gmail.com.
ORCID: 0000-0002-4512-4790.

Abstract

Aim: Congenital heart disease (CHD), defined as anatomic abnormalities of the heart and/or great vessels, is considered one of the most common anomalies worldwide. The aim of the study was to determine whether the NT-proBNP indicator has a diagnostic value in identifying and determining the severity of the disease, based on the analysis of this marker in patients admitted with congenital heart defects at the age of up to 1 year, and also to check whether there is a correlation between lactate and NT-proBNP among patients with congenital heart defects.

Methods: NT-proBNP values in 81 critical condition congenital anomaly patients averaged 12811.6±810.7 (445-40163), control group averaged 135.6±14.0 (78-320) among 20 patients, Pf< 0.001 which was reported to be statistically significant.

Results: In our study, NT-proBNP indicators of patients diagnosed with CHD were found to be higher in the first 28 days compared to other infant groups (1-6 months and 6-12 months). The results revealed that the difference between the CHD lactate level between the surviving and lethal groups was statistically significant (Pf< 0.001; Pu 0.017).

Conclusion: We should state that in our study, blood NT-ProBNP levels in critically ill infants with congenital heart anomalies were found to be approximately 10 times higher than in healthy infants (Pf < 0.001). At the same time, a correlation was established between the blood lactate index and the blood NT-ProBNP level.

Keywords: Congenital heart anomalies, NT-proBNP level, lactate level, mortality predictor.

Introduction

CHD is defined as an anatomical abnormality of the heart and/or great vessels resulting from intrauterine development [1]. Diagnosis of innate defects during the antenatal period or immediately after birth remains one of the current problems of medicine. Despite advances in diagnostic evolution, in modern times a large proportion of children with congenital heart defects remain undiagnosed until serious complications develop.

Congenital heart disease (CHD) is one of the most common anomalies worldwide, affecting approximately 0.8%–1.2% of live births [2, 3]. The prevalence of congenital heart defects has been extensively studied and is reported to be approximately 9.5/1000 [4].

CHD incidence and mortality rates have been found to be significantly heterogeneous across geographic regions and countries [5, 6]. Thus, it was determined that the incidence of CHD varied by region, and the results presented the frequency as varying between 1.2 and 17 per 1000 live births [7]. Although the field of cardiology and cardiovascular surgery has advanced in recent years, with mortality rates decreasing dramatically, allowing most patients to reach adulthood, congenital anomalies remain the leading cause of death and result in a reduced quality of life associated with the disease [8]. Congenital heart defects account for 3% of infant deaths. Studies have shown that with timely detection of congenital heart defects and early intervention, neonatal mortality rate

can decrease from 2–3/1000 to 0.6–0.8/1000 live births [9].

Various tests have been tested to improve the diagnosis of CHD and reduce mortality. Screening tests using pulse oximetry are used to detect critical CHD, allowing early diagnosis in infants who have not been diagnosed with the disease before birth. Meta-analyses have shown that this screening test has a specificity of 99.9%, a sensitivity of approximately 76%, and a false-positive rate of 0.14% for critical CHD [10]. Although screening is now mandatory in many high-income countries, challenges remain in implementing screening in low- and middle-income countries (LMIC) [11, 12].

CHD is classified into two main groups: 1. Asianotic CHD: Left to right shunt- VSD; ASD; PDA and Outflow obstruction - Pulmonary stenosis; aortic stenosis; aortic coarctation. 2. Cyanotic CHD: Tetrada of Fallot; Tricuspid atresia; transposition of trunk vessels; truncus arteriosus; total pulmonary venous return anomaly (TAPVR); Ebstein anomaly.

Guidelines prepared by the European Society of Cardiology (2016) recommend the use of brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as clinical biomarkers for the diagnosis and prognosis of heart failure [13]. Compared to BNP, NT-proBNP is a more stable protein and its serum half-life is longer than that of BNP [14].

Cantinotti et al. in 2015, BNP/NT-proBNP was found to be informative as an additional marker in the course of screening, diagnosis, and surgical treatment, indicating specific haemodynamics associated with congenital heart defects. The authors advocate widespread clinical use of peptides, particularly NT-proBNP (BNP as the active moiety and NT-proBNP as the inactive moiety) as substantial biomarkers in congenital heart disease [15]. The plasma half-life of NT-proBNP is 1-2 hours [16]. Cardiomyocytes located in the ventricles of the heart secrete pro-BNP, an inactive prohormone, which is converted to biologically active NT-proBNP in a 1: 1 ratio. Because proBNP is a more stable peptide, it appears in higher plasma concentrations than the actual hormone BNP [17].

Serum NT-proBNP levels have been shown to correlate with the severity of left ventricular (LV) dysfunction and functional status and can be used to help differentiate between dyspnea due to respiratory problems and heart failure [18]. The importance of NT-proBNP level in the diagnosis and assessment of heart failure has been proven. Many studies have demonstrated the important role of natriuretic peptide testing, including NT-proBNP, in heart failure management from diagnosis to monitoring, leading to recommendations for the use of these tests in clinical practice, with a high level of evidence and recommendation in most cases [13].

Lactate is a classic marker in critically patients and has been shown to be more elevated in cases of severe illness and death [19]. Hyperlactatemia is one of the main parameters in shock states due to lactate synthesis in anaerobic metabolism and is an indicator of inadequate oxygen supply [20].

In our study, we investigated and compared NT-proBNP and lactate parameters in critically infant CHD patients.

Material and metods

The purpose of our study is to find out whether this marker is diagnostically important in detecting and determining the severity of the disease, based on the analysis of NT-proBNP indicators of patients admitted with congenital heart defects under the age of 1 year, and also to check whether there is a correlation between lactate and NT-proBNP among patients with congenital heart defects. Congenital heart defects were not specified, patients with renal failure, sepsis, and children who stayed in the intensive care unit for less than 24 hours were excluded.In a study of 101 infants, children were divided into two groups: patients diagnosed with CHD (n=81) and healthy children (n=20).

Blood samples taken from arterial, central and peripheral vessels of patients were tested for NT-proBNP with Cobas E601 and Cobas E602 analyzers. NTproBNP measurement range is 10-35000 pg/ml. The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

Ethical Considerations

The principles of the Declaration of Helsinki were considered at all stages of the study. In order to carry out the research, permission was obtained from the Ethics Committee of Azerbaijan Medical University to take additional blood analysis from patients diagnosed with congenital heart defects (18.10.2024/36). Written and verbal consent was obtained from the parents of the patients participating in the study.

Statistical analyses

Statistical studies were performed using variation (t-Student-Bonferroni, U-Mann-Whitney, H- Kruskal-Wallis), discriminant (Chi-square Pearson), variance (F-Fisher) and correlation (Rho-Spearman) methods" IBM Statistics SPSS-26 programs were performed. The "0" hypothesis was rejected when $p<0.050$ [21].

Results

In our study, NT-proBNP test was performed in 55 (67.9%) of 81 infants with critical congenital heart disease in the first 28 days; 21 (25.9%) in 1-6 months; and 5 (6.2%) in 7-12 months. 69.1% of the patients were male (56) and 30.9% (25) were female (Table 1).

Table 1 Characteristics of patients

			Mean	Std error
Gestasional week	Preterm	22 (27.2%)	37.3	0.2
	Term	59 (72.8%)		
Age range	1-28 days	55 (67.9%)	38.6	7.1
	1-6 month	21 (25.9%)		
	7-12 month	5 (6.2%)		
Gender	Male	56 (69.1%)		
	Female	25 (30.9%)		
Weight			2933,1	61,9
Delivery	Physiological	29 (35,8%)		
	Caesarean section	52 (64,2%)		
Abqar scale 1 st min	< 7 score ≥ 7 score	40 (49,4%) 41 (50,6%)	6,3	0.1
5 st min	< 7 score ≥ 7 score	19 (23,5%) 62 (76,5%)	6,8	0,1

In the healthy group, 10 out of 20 babies (50%) were born in the first 28 days; 3 (15%) between 1-6 months; and 7-12 months (35%). Of these, 5 (25%) were preterm and 15 (75%) were term babies. Of the healthy group, 17 (85%) were male and 3 (15%) were female. Mean birth weight was 2957.5 ± 107.7. Nine (45%) of the healthy children were born physiologically and 11 (55%) were born by cesarean section. The mean Abqar 1 score was 7.7±0.2 and the mean Abqar 5 score was 8±0.1.

When the reasons for these patients being admitted to intensive care were examined, it was seen that 33 (40.7%) patients were not associated with anomaly, 32 (39.5%) patients

were associated with anomaly, and 16 (19.8%) patients were suspected of anomaly. Multiple anomalies were detected in 12 (14.8%) of these patients; 4 (4.9%) of them simultaneously had gastrointestinal system anomalies, 2 (5%) had nervous system anomalies, 1 (1.2%) had metabolic diseases, and 8 (9.9%) had other anomalies (Table 2).

Table 2 Evaluation of patients according to anomaly and clinical condition

Reason for admission to intensive care	not due to anomaly	33 (40,7%)	
	related to the anomaly	32 (39,5%)	
	Suspected anomaly	16 (19,8%)	
A congenital anomaly has been identified	In the birth house	34 (42%)	
	In intensive care	47 (58%)	
According to the type of anomaly	Structural	80 (98,8%) .	
	Structural+functional	1 (1,2%)	
According to the damage number of the anomaly	Single	69 (85.2%)	
	Multipl	12 (14.8%)	
Mechanical ventilation	None	34 (42%)	4.5± 0.6 days
	Yes	47 (58%)	
Duration of parenteral nutrition			1.9±0.3 days
Surgical intervention	None	72 (88,9%)	
	Yes	9 (11,1%)	
Length of stay in intensive care		10.8± 0.9	
Conclusion	Survived	65 (80.2%)	
	Lethal	16 (19.8%)	

NT-proBNP values in 81 critical condition congenital anomaly patients averaged 12811.6±810.7 (445-40163), control group averaged 135.6±14.0 (78-320) among 20 patients, Pf < 0.001 which was reported to be statistically significant (Table 3).

Table 3 Comparison of NTproBNP patient group and control group.

Groups	Patient №	Mean	St error	Min	Max	
Control	20	135,6	14,0	78	320	Pf < 0.001
Main	81	12811,6	810,7	445	40163	

When we analyzed NT-proBNP values separately for congenital heart defect anomalies, we obtained the results shown in Table 4.

Table 4 Analysis of NT-proBNP values of congenital heart defect anomalies.

CHD	Patient №	NT-proBNP average value pg/ml	Pf	Pu
Coarctation of the aorta	7	11651,7±1705,1	< 0.001	< 0.001
Aortic stenosis	4	13295,0±1454,3	< 0.001	0.002
Aortic hypoplasia	3	10233,3±2316,8	< 0.001	0.006
ASD	48	12228,2±1056,7	< 0.001	< 0.001
AVSD	14	15816,6±2952,4	< 0.001	< 0.001
Dextrocardia	2	12136,0±7624,0	< 0.001	0.022
Ebstein anomaly	3	19643,3±5652,5	< 0.001	0.006
Fallot tetrada	10	15163,2±1368,0	< 0.001	< 0.001
Magistral damar transpozisya	8	11993,8±2147,8	< 0.001	< 0.001
PDA	14	16413,4±2497,9	< 0.001	< 0.001
Pulmonar stenoz	24	12799,8±1617,6	< 0.001	< 0.001
Taussig Big	1	40163,0	< 0.001	0.098
Single ventricle	4	15782,5±1485,5	< 0.001	0.002
VSD	42	11290,7±837,8	< 0.001	< 0.001

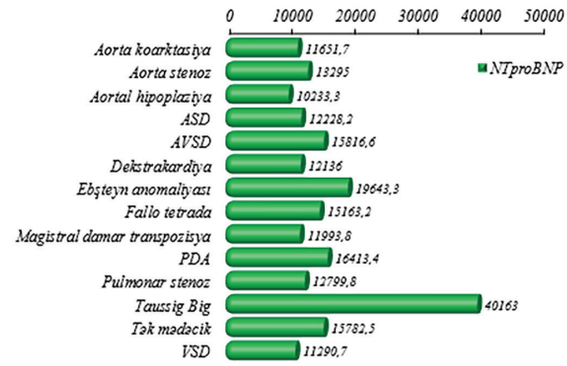


Figure 1 – text

When conducting a comparative analysis of the indicators lactat and NT-proBNP, according to the age range, the following results were noted. Also, in our study, a comparative analysis was conducted according to the age range (Table 5).

Table 5 Blood levels of lactat and NT-proBNP depending of age of infants.

	Age range	Patient №	Means	St error	Min	Max	Pf
Lactate	1-28 day	253	6,0	0,2	1	22	0,943
	1-6 month	68	5,9	0,5	1	20	
	7-12 month	11	6,3	1,1	2	14	
NT-proBNP	1-28 day	55	13398,2	1095,5	445	40163	0,442
	1-6 month	21	10951,9	1082,4	3000	18500	
	7-12 month	5	12060,0	3438,4	1000	19800	

Also, in our study conducted by Spearman's rho method, it was found that there is a correlation between lactate and NT-proBNP (rho=0.333; p=0.003) (Table 6).

Table 6 Correlation between lactate and NT-proBNP

Lactate	Correlation Coefficient	1,000	0,333
	Sig. (2-tailed)		0,003
NT-proBNP	Correlation Coefficient	0,333	1,000
	Sig. (2-tailed)	0,003	

In the patients examined in our study, the average value of the lactate index in the survived group was 5.6±0.2, and NT-proBNP was determined as 12894.9±853.3. In the lethal infant group, lactate index was 7.9 ±0.8 and NT-proBNP was 11903.8 ±2371.2. The results revealed that the difference between the CHD lactate level between the surviving and lethal groups was statistically significant (Pf< 0.001; Pu 0.017) (Table 7).

Table 7 Comparative analysis of lactate and NTproBNP values between surviving and lethal groups

Patient groups	Lactate mg/l	NT-proBNP pg/ml
Survived 65 (80.2%)	5.6 ± 0.2	12894,9 ± 853,3
Lethal 16 (19.8%)	7,9 ± 0,8 (Pf< 0.001; Pu 0,017)	11903,8 ± 2371,2 (Pf= 0,633; Pu= 0,239)

Discussion

Although it is known that the NT-proBNP test in patients with severe cardiac pathology is informative in terms of identifying the degree of heart failure, we studied the effect of this indicator on the occurrence of complications and mortality in children admitted to the intensive care unit with a diagnosis of congenital heart disease, as well as the level of lactate, reflecting tissue hypoxemia, and the correlation of its level with NT-proBNP in hypoxia caused by heart defects, and analyzed its prognostic value.

Improvements in diagnosis now estimate that 1.35 million children are diagnosed with CHD each year [22]. CHD is clinically classified into three main categories: 1) Life-threatening CHD - structural heart defects in which cardiovascular collapse is possible and is at risk if not treated early. Critical CHD is divided into 3 parts according to the injury: 1.Obstructive lesions of the right heart (dependent pulmonary circulation): pulmonary athesia complete ventricular wall; Critical pulmonary stenosis; combined with pulmonary atresia in tetrada of fallot; tricuspid atresia; severe Ebstein anomaly. 2. Obstructive damage of the left heart (depending on the flow-systemic circulation): Hypoplastic left heart syndrome; Critical aortic stenosis; Coarctation of the aorta; Interrupted aortic arch. 3. Mixed injuries: Truncus transposition; Total pulmonary venous return anomaly; Truncus arteriosus.

2. Clinically significant CHD - early intervention is needed in the case of structural heart defects due to the impact on heart function and the development of heart failure as a result. This group includes large ventricular septal defect (VSD), complete atrioventricular septal defect (AVSD), large atrial septal defect (ASD), and tetralogy of Fallot with good pulmonary artery anatomy (TOF).

3. Clinically insignificant CHD - anatomically defined heart defects, but functionally and clinically insignificant. These include small ventral septal defect (VSD), atrial septal defect (ASD), mild pulmonary artery stenosis (PS), diseases that can be detected only by echocardiography and require no treatment [9, 23]. We did not include patients with clinically insignificant CHD in our study.

Etiological studies reveal the cause of CHD in approximately 15% of infants with congenital heart defects [24]. In 2017, CHD caused at least 260,000 deaths, 180,000 of which were among infants [25].

BNP level may be a prognostic criterion in patients admitted to cardiac intensive care units and may indicate the presence of LV volume and pressure overload in the presence of shunts and ay identify overt cardiac disease in acute care settings [26]. Harris SL et al. study, NT-proBNP was determined as an informative biomarker in predicting HsPDA and it was found that ventilation, hypoxia and hemoglobin levels did not affect NT-proBNP, but creatinine level showed a positive correlation [27]. Jourdain P. et al. study revealed that serum NT-proBNP levels predict mortality risk and that monitoring the level of this peptide in treated CHF patients reduces the risk of CHF-related death and length of hospital stay [28].

High end-diastolic pressure and increased ventricular wall stress are the main triggers that stimulate BNP synthesis [29]. BNP is a peptide hormone that regulates circulating blood volume and arterial pressure by stimulating diuresis and natriuresis, inhibiting renin and aldosterone synthesis, and causing vasodilatation [30]. BNP acts on many organs and increases sodium excretion, stimulates urine output, causes vasodilation, and inhibits the renin-angiotensin-aldosterone system and sympathetic nerves. NT-proBNP levels increase due to abnormally high intraventricular pressure during heart failure and this level is positively correlated with the degree of heart failure [31].

In newborns, the concentration of NT-proBNP has a maximum value at birth and decreases almost 2 times in the first week of life. Measurement of NT-proBNP concentration can be used in neonates at risk of CHD and HF in the neonatal period [32].

NT-proBNP values decrease from 400 ng/L in the first 3 months of childhood to 138 ng/L in girls and 65 ng/L in boys by the age of 18. Values decrease rapidly, especially during adolescence [33]. In our study, NT-proBNP indicators of patients diagnosed with CHD were found to be higher in the first 28 days compared to other infant groups (1-6 months and 6-12 months).

In pediatric age, BNP/NT-proBNP plasma concentration values may be influenced by many factors [15]. Higher BNP/NT-proBNP values have been reported in infants with the following characteristics: maternal type 1 diabetes, premature birth, intrauterine growth retardation, cesarean delivery after uterine contraction, twins, and mothers with prenatal stress conditions, etc. [34].

Serum NT-proBNP levels can be used to help distinguish between dyspnea due to respiratory failure and heart failure and have been found to increase with the severity of left ventricular (LV) dysfunction [35]. On average, plasma BNP/NT-proBNP concentrations are highest during the first 4 days of life and then decline rapidly during the first week with a slower, progressive decline during the first month of life [36]. High NT-proBNP and BNP values are observed in infants with hemodynamically significant patent ductus arteriosus (hsPDA) and other CHD, in patients with pulmonary hypertension [37], bronchopulmonary dysplasia [38], retinopathy [39], inflammation or sepsis [40], and in premature infants [41].

In our study, the number of patients born prematurely was 22 (27.2%) (17 of these patients in the first 28 days, 5 patients among between 1 and 6 months and 7 of them died.

Among infants diagnosed with CHD, NT-proBNP has the highest value in Taussig BIG, followed by Ebstein's anomaly and AVSD. In our study, in patients marked as PDA, along with PDA, anomalies such as trunk vessel transposition, coarctation of the aorta, ASD, VSD, etc. were found. 12 of the patients were born on time ≥ 37 weeks, the other two were born at 36 gestational weeks, and other heart defects were found along with PDA.

NT-proBNP levels <400 ng/l have a low probability of heart failure, with a negative predictive value of ~90%. However, with heart failure levels >450 ng/l, a positive predictive value of ~90% is possible [42].

In the study conducted by Ayşe Sulu and her colleagues, unlike the studies conducted in adults, the benefit of using NT-ProBNP levels in the diagnosis of heart disease in children could not be demonstrated. Therefore, randomized prospective studies are recommended to demonstrate the value of Pro-BNP in distinguishing cardiac disorders from non-cardiac diseases in children [43].

Walsh et al. found that preoperative N-terminal-pro-brain natriuretic was a predictor of mean PICU days, but they did not consider any other biochemical markers such as troponin or lactate. In a study conducted by Xiao-Jun Deng et al., blood lactate and NT-proBNP were shown to be suitable for use as a prognostic device for ventilatory support [44]. In our study, NT-proBNP was checked in 47 (58%) MVs, and it was observed that the average ventilation was 4.5 ± 0.6 days.

In our study, when we compared the blood lactate level indicators between the surviving and deceased patients, we found that the lactate level increased statistically significantly in the second group (Pf< 0.001; Pu 0.017). This result makes it suitable to use the blood lactate level as a predictor in critically patients with congenital heart anomalies. At the same time in our study, it was found that there is a correlation between NT-proBNP values and lactate values.

Studies have shown that higher NT-proBNP values prolong ICU stay [45]. In our practice, the length of stay in the intensive care unit of patients whose blood NT-proBNP levels were controlled was 10.8 ± 0.9 days.

Our study did not reveal a statistically significant difference in blood NT-proBNP levels between the group of patients with fatal heart defects and those with surviving heart defects. On the one hand, this raises the question whether blood NT-proBNP levels can be a predictor of mortality in a group of critically patients with congenital anomalies, and requires randomized studies in a larger group of patients to have a final opinion in this group of critically patients. A striking result in our study is that the statistical deviation index in the group of patients who died was 2.8 times higher than the index in the group of patients who survived. This also shows that the blood NT-proBNP level in some patients in the group of dead patients is slightly elevated, which can be explained by the limited compensatory capacity in those patients in a critical situation. Thus, it is known that BNP is synthesized by cardiomyocytes due to increased pressure in the heart cavity. More than 16 patients who died in our study group had a critical decrease in arterial pressure during the initial examination, and these patients received inotropic support to normalize blood pressure.

Conclusion

In conclusion, we should state that in our study, blood NT-proBNP levels in critically ill infants with congenital heart anomalies were found to be approximately 10 times higher than in healthy infants (Pf < 0.001). However, the difference of this indicator between the group of patients who survived and the group of patients who died is not statistically significant and has a significant high deviation in the second group. This result requires larger-scale randomized studies to investigate the possibility of using NT-proBNP level in blood as a mortality indicator in critically ill infants with heart defects. On the other hand, in our study, it was confirmed that the blood lactate index increased statistically significantly in patients who died compared to the group of patients who survived. At the same time, a positive correlation was established between the blood lactate index and the blood NT-proBNP level.

Author Contributions: The author contributed to all aspects of the paper: literature search, interpretation, writing, editing. The author has read and agreed to the published version of the manuscript.

Disclosures: The author has no conflicts of interest.

Acknowledgments: None.

Funding: None.

References

1. Liu Y, Chen S, Zuhlke L, Black GC, Choy M-K, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* 2019; 48: 455–463. https://doi.org/10.1093/ije/dyz009.
2. Bouma BJ, Mulder BJ. Changing landscape of congenital heart disease. *Circ Res.* 2017; 120: 908–922. https://doi.org/10.1161/circresaha.116.309302.
3. Van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011; 58: 2241–2247. https://doi.org/10.1016/j.jacc.2011.08.025.
4. Liu Y, Chen S, Zühlke L, Black GC, Choy M-K, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* 2019; 48: 455–463. https://doi.org/10.1093/ije/dyz009.
5. Srisawasdi P, Vanavanan S, Charoenpanichkit C, Kroll MH. The efect of renal dysfunction on BNP, NT-proBNP, and their ratio. *Am J Clin Pathol.* 2010; 133: 14–23. https://doi.org/10.1309/AJCP60HTPGIGFCNK.
6. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study. *Lancet*. 2018; 392: 1736–1788. https://doi.org/10.1016/S0140-6736(18)32203-7.
7. Bernier P-L, Stefanescu A, Samoukovic G, Tchervenkov CI. The challenge of congenital heart disease worldwide: epidemiologic and demographic facts. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2010; 13: 26–34. https://doi.org/10.1053/j.pcsu.2010.02.005.
8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai Sh, Ford ES, Fox CS, Franco Sh, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB.. Executive summary: heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation*. 2014; 129: 399–410. https://doi.org/10.1161/01.cir.0000442015.53336.12.
9. Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C. Newborn screening for congenital heart defects: a systematic review and costeffectiveness analysis. *Health Technol Assess.* 2005; 9: 1–152, iii–iv. https://doi.org/10.3310/hta9440.
10. Plana MN, Zamora J, Suresh G, Fernandez-Pineda L, Thangaratinam S, Ewer AK. Pulse oximetry screening for critical congenital heart defects. *Cochrane Database Syst Rev.* 2018; 3(3): CD011912. https://doi.org/10.1002/14651858.CD011912.
11. Abbas A, Ewer AK. New born pulse oximetry screening: a global perspective. *Early Hum Dev.* 2021; 162: 105457. https://doi.org/10.1016/j.earlhumdev.2021.105457.
12. Martin GR, Ewer AK, Gaviglio A, Hom LA, Saarinen A, Sontag M, Burns KM, Kemper AR, Oster ME. Updated strategies for pulse oximetry screening for critical congenital heart disease. *Pediatrics*. 2020; 146: e20191650. https://doi.org/10.1542/peds.2019-1650.

13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. European Journal of Heart Failure. 2016; 37(27): 2129–2200. https://doi.org/10.1093/eurheartj/ehw128.
14. Mir TS, Haun C, Lilje C, Laer S, Weil J. Utility of N-terminal brain natriuretic peptide plasma concentrations in comparison to lactate and troponin in children with congenital heart disease following open-heart surgery. *Pediatr Cardiol.* 2006; 27(2): 209–216. https://doi.org/10.1007/s00246-005-1152-8.
15. Cantinotti M, Walters HL, Crocetti M, Marotta M, Murzi B, Clerico A. BNP in children with congenital cardiac disease: Is there now sufficient evidence for its routine use? *Cardiol. Young.* 2015; 25: 424–437. https://doi.org/10.1017/s1047951114002133.
16. Clerico A, Zucchelli GC, Pilo A, Passino C, Emdin, M. Clinical relevance of biological variation: The lesson of brain natriuretic peptide (BNP) and NT-proBNP assay. *Clin. Chem. Lab. Med.* 2006; 44: 366–378. https://doi.org/10.1515/cclm.2006.063.
17. Jungbauer CG, Buchner S, Birner C, Resch M, Heinicke N, Debl K, Buesing M, Biermeier D, Schmitz G, Riegger G, Luchner A. N-terminal pro-brain natriuretic peptide from fresh urine for the biochemical detection of heart failure and left ventricular dysfunction. *European Journal of Heart Failure.* 2010; 12: 331–337. https://doi.org/10.1093/eurjhf/hfq016.
18. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003; 107: 2786–2792. https://doi.org/10.1161/01.cir.0000070953.76250.b9.
19. Bakker J, Postelnicu R, Mukherjee V. Lactate: Where Are We Now? *Crit. Care Clin.* 2020; 36: 115–124. https://doi.org/10.1016/j.ccc.2019.08.009.
20. Levy B. Lactate and shock state: The metabolic view. *Curr. Opin. Crit. Care.* 2006; 12: 315–321. https://doi.org/10.1097/01.ccx.0000235208.77450.15.
21. Qafarov İ.A. Biostatistika. Bakı, Təbib, 2022, 240 s. ISBN: 978-9952-37-813-9.
22. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011; 58: 2241–2247. https://doi.org/10.1016/j.jacc.2011.08.025.
23. Yun SW. Congenital heart disease in the newborn requiring early intervention. *Korean J Pediatr.* 2011; 54(5): 183–191. https://doi.org/10.3345/kjp.2011.54.5.183.
24. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJM. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol.* 2011; 8: 50–60. https://doi.org/10.1038/nrcardio.2010.166.
25. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet Child Adolesc Health.* 2020; 4(3): 185–200. https://doi.org/10.1016/S2352-4642(19)30402-X.
26. Maher KO, Reed H, Cuadrado A, Simsic J, Mahle WT, DeGuzman M, Leong T, Bandyopadhyay S. B-type natriuretic peptide in the emergency diagnosis of critical heart disease in children. *Pediatrics*. 2008; 121(6): e1484-8. https://doi.org/10.1542/peds.2007-1856.
27. Harris SL, More K, Dixon B, Troughton R, Pemberton C, Horwood, J, Ellis N, Austin N. Factors afecting N-terminal pro-B-typenatriuretic peptide levels in preterm infants and use in determinationof haemodynamic signifcance of patent ductus arteriosus. *Eur JPediatr.* 2018; 177: 521–532. https://doi.org/10.1007/s00431-018-3089-y.
28. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juillière Y. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol.* 2007; 49: 1733–1739. https://doi.org/10.1016/j.jacc.2006.10.081.
29. Hauser JA, Demyanets S, Rusai K, Goritschan C, Weber M, Panesar D, Rindler L, Taylor AM, Marculescu R, Burch M, Wojta J, Michel-Behnke I. Diagnostic performance andreference values of novel biomarkers of pediatric heart failure. *Heart*. 2016; 102(20): 1633–1639. https://doi.org/10.1136/heartjnl-2016-309460.
30. Magga J, Marttila M, Mantymaa P, Vuolteenaho O, Ruskoaho H. Brain natriuretic peptide in plasma, atria, and ventricles of vasopressin- and phenylephrine-infused conscious rats. *Endocrinology*. 1994; 134: 2505–2515. https://doi.org/10.1210/endo.134.6.8194476.
31. 31. Rusconi P, Ludwig DA, Ratnasamy C, Mas R, Harmon WG, Colan SD, Lipshultz SE. Serial measurements of serum NT-proBNP as markers of left ventricular systolic function and remodeling in children with heart failure. *Am Heart J.* 2010; 160: 776–783. https://doi.org/10.1016/j.ahj.2010.07.012.
32. Maslennikova I, Bockeriya E, Ivanetc T, Kazantseva I, Degtyarev D. Experience of the natriuretic peptide use in the complex diagnosis and treatment of newborns with heart failure [In Russian]. *Pediatriya.* 2020; 99(3): 16–22. https://doi.org/10.24110/0031-403X-2020-99-3-16-22.
33. Kiess A, Green J, Willenberg A, Ceglarek U, Dähnert I, Jurkutat A, Körner A, Hiemisch A, Kiess W, Vogel M. Age-Dependent Reference Values forhs-Troponin T and NT-proBNP and determining Factors in a Cohort of Healthy Children (The LIFE Child Study). *Pediatric Cardiology*. 2022; 43: 1071–1083 https://doi.org/10.1007/s00246-022-02827-x.
34. Kanbe T, Maeno Y, Fujino H, Kanda H, Hirose A, Okada J, Morikawa T, Iwata S, Iwata O, Matsuishi T. Brain-type natriuretic peptide at birth reflects foetal maturation and antenatal stress. *Acta Paediatr.* 2009; 98(9): 1421–1425. https://doi.org/10.1111/j.1651-2227.2009.01357.x.
35. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton Ch, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003; 107: 2786–2792. https://doi.org/10.1161/01.cir.0000070953.76250.b9.
36. Clerico A, Giannoni A, Vittorini S, Passino C. Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones. *Am J Physiol Heart Circ Physiol.* 2011; 301(1): H12–H20. https://doi.org/10.1152/ajpheart.00226.2011.
37. 37. Ten Kate CA, Tibboel D, Kraemer US. B-type natriureticpeptide as a parameter for pulmonary hypertension in children. Asystematic review Eur J Pediatr. 2015; 174: 1267–1275. https://doi.org/10.1007/s00431-015-2619-0.
38. 38. Mendez-Abad P, Zafra-Rodriguez P, Lubian-Lopez S, BenaventeFernandez I. NTproBNP is a useful early biomarkerof bronchopulmonary dysplasia in very low birth weightinfants. *Eur J Pediatr.* 2019; 178: 755–761. https://doi.org/10.1007/s00431-019-03347-2.
39. Buhrer C, Erdeve O, van Kaam A, Berger A, Lechner E, Bar-Oz B, Allegaert K, Stiris T, Celik IH, Berrington J. N-terminalB-type natriuretic peptide urinary concentrations and retinopathyof prematurity. *Pediatr Res.* 2017; 82: 958–963. https://doi.org/10.1038/pr.2017.179.

40. Ogawa T, de Bold AJ. Brain natriuretic Peptide productionand secretion in infammation. *J Transplant*. 2012: 962347. https://doi.org/10.1155/2012/962347.
41. Cantinotti M, Giovannini S, Murzi B, Clerico A. Diagnostic, prognostic and therapeutic relevance of B-type natriuretichormone and related peptides in children with congenital heartdiseases. *Clin Chem Lab Med.* 2011; 49: 567–580. https://doi.org/10.1515/CCLM.2011.106.
42. Pérez-Piaya MR, Abarca E, Soler V, Coca A, Cruz M, Villagrá F, Giannivelli S, Asensio A. Levels of N-terminal-pro-brain natriuretic peptide in congenital heart disease surgery and its value as a predictive biomarker . *Interactive CardioVascular and Thoracic Surgery.* 2011; 12: 461–466. https://doi.org/10.1510/icvts.2010.245803.
43. Sülü A, Kıztanır H, Kosger P, Ucar B. Relationship of Pro-BNP Levels with Cardiovascular Events in Pediatric Cardiac and Non-cardiac Diseases. J Contemp Med. 2023; 13(3): 549–554 . https://doi.org/10.16899/jcm.1279791.
44. Lin Z, Chen Y, Zhou L, Chen S and Xia H. Serum N-Terminal Pro-B-Type Natriuretic Peptide as a Biomarker of Critical Pulmonary Stenosis in Neonates. *Front. Pediatr.* 2022; 9: 788715. https://doi.org/10.3389/fped.2021.788715.
45. Walsh R, Boyer C, LaCorte J, Parnell V, Sison C, Chowdhury D, Ojamaa K. N-terminal B-type natriuretic peptide levels in pediatric patients with congestive heart failure undergoing cardiac surgery. *J Thorac Cardiovasc Surg*. 2008; 135(1): 98–105. https://doi.org/10.1016/j.jtcvs.2007.08.012.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Short Communication DOI: https://doi.org/10.23950/jcmk/15573

Understanding Psychological Distressing Symptoms and Adult Cancer Survivors

Fariza Saidin[1], Suantak Demkhosei Vaiphei[2]

[1]Department of Psychology, The Assam Royal Royal Global University, Guwahati, India
[2]School of Liberal Arts and Humanities, Woxsen University, Hyderabad, India

Received: 2024-07-10.
Accepted: 2024-10-30.

J Clin Med Kaz 2024; 21(6): 48–53

Corresponding author:
Fariza Saidin.
Email: farizasaidin@gmail.com.
ORCID: 0000-0002-9920-6126.

Corresponding author:
Suantak Demkhosei Vaiphei.
Email: georgedsuantak@gmail.com.
ORCID: 0000-0002-4134-2926.

Abstract

Aim: The objective of this research was to assess mental disorders that frequently coexist with typical cancer diseases in what is referred to as comorbidity, which is crucial for addressing the mental well-being of cancer survivors. The research aims to determine the underlying factors for the failure of mental health-related quality of life and well-being among cancer survivors.

Material and Method: The present qualitative study aims to understand the factors contributing to the prevailing mental health challenges among adult (16-68 years) cancer survivors through questionnaires and semi-structured interviews. The Patient Health Questionnaire depression scale and the 7-item Generalized Anxiety Disorder questionnaire were used to gauge the severity of mental health symptoms. The Data from the National Cancer Registry and Regional Cancer Centers were all sources of information and reports used in the current study.

Results: The research indicates that Indian cancer patients and survivors faced challenges in accessing mental health services due to the stigma surrounding mental illness, the scarcity of mental health professionals, obstacles related to affordability and awareness, and lower incomes. This resulted in individuals being unable to afford necessary mental health evaluations: psychosocial issues – 53% to 70%, psychological discomfort – 45% to 73%, accessed mental health assessment – 9.1%, not able to access mental health assessment – 33.4%, not aware of mental health assessment – 19%.

Conclusion: There is no universally accepted set of coping mechanisms or cognitive and behavioral techniques that people may use to control their emotions and deal with stressful events. Given that people's reactions to stress are frequently complicated and multifaceted, several recent studies involving cancer patients and survivors have questioned the psychometric validity of the classification of coping techniques. Both cancer patients and survivors who adopted problem-focused strategies or maladaptive coping were reported with higher levels of symptom burden, anxiety, and depression. Acceptance, religion, and emotional support are the most common effective and implemented coping strategies among adult cancer survivors.

Keywords: Cancer Survivors, Mental Health, mental Health Disorder, Stress, Depression, and Anxiety.

Introduction

Due to the progress of modern medical technology and pharmaceutical drugs, the survival rates of cancer patients have consistently risen over four decades. An increasing number of cancer survivors deal with long-term challenges including maintaining a healthy lifestyle, family dynamics, and physical and emotional health. The two main things impeding cancer therapy and recovery, as well as survival and quality of life, are depression and anxiety.[1] Psychosocial requirements—such as anxiety about a cancer recurrence, uncertainty about the future, support in managing stress, and changes in one's sexual orientation—remain the most mentioned unmet needs among cancer survivors. Poor mental health is the current leading cause of patient disability during and after treatment. Physical symptoms are typically more readily identified and assessed clinically, while psychosocial symptoms in end-of-life care are often overlooked. Lack of awareness, education, lower income, and early cancer

diagnosis in young patients are key risk factors for poor mental health-related quality of life and well-being in cancer survivors. [2] Modern scientific research study demonstrates that prevalent oncological illnesses frequently coexist with cognitive problems, a phenomenon known as comorbidity. Anxiety and depression are often mental health problems that are closely associated with a patient's disability, the progression of their disease, the presence of pain, and the adverse effects of certain chemotherapy drugs. Despite the differences in course, stage, and outlook of oncological diseases and mental disorders, it is still true that oncological illnesses are more closely linked to depression and anxiety than any other type of illness.[3] In addition to mental illnesses, oncological conditions can exacerbate the condition by impairing adherence to recommended treatment plans.

Prevailing Mental Health Challenges Among Adult Cancer Survivors

Looking at the present cancer diagnosis scenario in India, the survival rates of cancer patients are visible at a minimal rate compared to developed countries. Although various studies have looked at the trajectories of mental health following therapy from 8 to 55 months after diagnosis, the first three years after treatment are a crucial time to track the mental health of cancer survivors. Numerous significant stresses related to the body, mind, social life, job, and finances accompany it, exacerbating symptoms of depression and anxiety [1, 2].

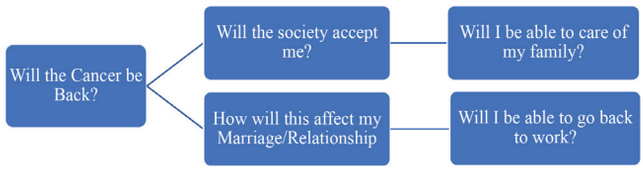


Figure 1 – Common Distressing Symptoms among Cancer Survivors
Source: [3].

In the early post-treatment period, cancer survivors face a change in the focus of medical care from curing the disease to monitoring, healing, or wellness; they also face the dread of recurrence and the long-term, late consequences of therapy, which can include psychological and physical side effects [1, 4]. Population-based cancer survival is the core indicator for assessing the effectiveness of cancer control by a healthcare system in a specific geographic area. At present 70% of cancer survivors experience psychosocial distressing symptoms that decrease the patient's quality of life and wellbeing. Symptoms like Anxiety (45%), depression (54%), and mood disorder (37.5%) are common factors leading to mental health issues among cancer survivors [5, 6]. The heightened psychological distressing symptoms are due to a lack of clinical consultations and support follow-up treatment. Fear of Cancer Recurrence (FCR) and the potential risk of cancer relapse become the source of distressing symptoms that reduce patient Quality of Life (QoL) [3].

Stomach Cancer	*Colon Cancer*	*Breast And Prostate Cancers*	*Liver Cancer*	*Cervical Cancer*
19%	37%	60%	4%	51.7%

Figure 2 – Cancer Survivor Statistics. Adapted from Population-Based Cancer Registries (PBCRs) in India

Source: [2, 6].

The study found depressive symptoms are more common and at a higher level (with more than 50%) among younger and more socially disadvantaged individuals. At present, 73% of cancer patients in India having depressive symptoms fail to undergo mental health treatment. Anxiety and depression in cancer survivors are associated with diagnostic and treatment delay, non-adherence to therapy, diminished efficacy of chemotherapy, increased symptom burden and diminished function, rising rates of suicide among survivors, greater burden on families, increased cost of care, and shortened survivor rates. [7] It is also visible that psychological depressive symptoms and anxiety disorders are at higher rates among those experiencing breast cancer, cervical cancer, ovarian cancer, endometrial cancer, and testicular cancer survivors. Leaving these psychosocial depressive symptoms resulted in patients associating with risky behaviors and complicated psycho-emotional issues [6].

Risky Drinking Behaviors	*Demoralization*	*Loneliness*	*Meaninglessness*	*Death Anxiety*
33.8%	48.2%	37%	19.7%	67%

Figure 3 – Complicating Psychosocial Concerns and Emotional Issues
Source: [7,8].

Across the cancer types, younger age is a risk factor for higher levels of poorer mental health outcomes and challenges compared to those receiving terminal ill diagnoses at older ages (50 and above). Risky drinking behaviors in cancer survivors are associated with a higher risk of cancer recurrence, development of new primary tumors, and increased mortality. Demoralization is the most common syndrome experienced by both cancer patients and survivors.[8] The prevalence of demoralization syndrome like feelings of hopelessness, helplessness, and loss of purpose ranges from 19.7% to 48.2%, including poor management of physical pain symptoms in Indian clinical practices. Higher levels of loneliness and meaninglessness were reported as common experiences among cancer survivors and had higher mortality risks.[3] Death anxiety is another common phenomenon and a natural, normal experience among cancer patients and survivors. 67% of patients with advanced cancer and survivors reported death anxiety experiences. Women cancer survivors have higher levels of death anxiety compared to male cancer survivors. Type of cancer, gender, and marital and financial status are identified as the contributing factors to death anxiety. Individual beliefs, attitudes, and sociocultural context are also visible as the significant contributor to death anxiety. [7] Fear of death results in a decreased awareness of intense neurotic fears related to losing oneself, and is accompanied by emotions of powerlessness, lack of autonomy, and absence of significance. Religious and cultural beliefs and confidence in oneself can help alleviate feelings of loneliness, insignificance, and mortality. Terror management theory (TMT) is the primary and most impactful theoretical perspective on fear of death. Dealing with one's mortality has also increased a personal sense of purpose and living in alignment with authentic personal aspirations and values [8].

Coping Strategies Towards Psychological Distressing Symptoms

The existing evidence for treating psychologically distressing symptoms among cancer patients and survivors is limited and of varying quality. The most significant tool in assessing psychological distressing syndrome among cancer patients and survivors is to identify the symptoms. Addressing

social stigma and clinical barriers has been reported as an effective symptom management technique.[9] Approach-focused and problem-solving coping strategies are found to be significantly effective in dealing with patients' anxiety and depression-like self-blame, negative body image, social stigma fatalism, and lower positive reframing. Positive psychological attributes, adjudgment, and adaptive coping strategies like the optimistic aspects of cancer are also visible in enhancing the individual quality of life and positive aspects of cancer.[6] Religion and spiritual coping mechanisms not only reduce depression but also significantly influence post-treatment outcomes and survival rates. Integrating emotional focus against self-destruction among cancer survivors had higher levels of pain symptom management, building relationships, and functional status of quality of life.[7]

Self-management and self-administered stress management techniques instilled the ability to manage physical symptoms, psychosocial consequences, and lifestyle changes along the cancer continuum. Self-management and self-administered intervention were evidence of improving patient outcomes during and after treatment, even in end-of-life assessment. However, these interventions required facilitation and resources for delivery.[10] Psychosocial adjustment/adaptation acquires mastery and control over occurrences in life connected to cancer, resolves specific cancer-related difficulties, and regulates emotional suffering. Non-pharmacological interventions, which include a range of common elements like cognitive and behavioral coping strategies, cancer education/information sessions, relaxation techniques, existential therapy, and group social support in both individual and group settings, are not the same as psychosocial interventions [11]. Individuals with cancer have a unique need, as the effect of cancer during and after the treatment interrupted lives with rapid emotional and psychological growth. Over thirty percent of cancer patients and survivors recognize the benefits of mindfulness-based stress management and acceptance and commitment therapy (ACT), a more recent type of cognitive behavioral therapy, in coping with stressful situations.

The efficacy of the coping strategies differs from individual to individual, yet the underlying focus is to deliver the quality of life, which is threatened and disrupted by terminal illness. Coping strategies are being adopted to pursue life goals, and deal with personal challenges that promote total recovery, and are emotionally intact. The existing challenges are mainly medical, physical, emotional, interpersonal, and spiritual components [9].

Effective Coping Strategies for Emotional Well-being

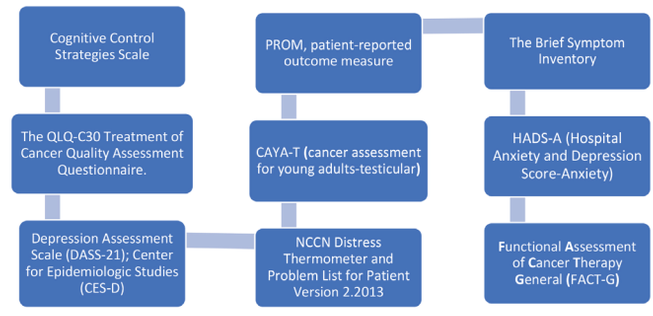
Confronting the Reality of Your Illness	Positive Outlook and Confidence
Emotions Expression	Seeking Assistance
Finding a Positive Meaning	Spirituality, Faith, and Prayer
Proportion and Balance	Adopting a Participatory Stance
Upholding Self-Esteem	Coming To Terms with Death and Dying

Figure 4 – Coping Skills and Strategies

Source: [10, 11].

Problem- and emotion-focused coping techniques, such as accepting reality, self-esteem, and social-spiritual and emotional support, have been proven to be strongly linked to improving physical and mental health as well as quality of life in cancer survivors. Two-thirds of cancer patients experience psychologically uncomfortable symptoms, primarily anxiety and sadness. The patient's psychological distress hugely contributed to the impairment of individual physical capacity, and ability to adhere to therapy, decreasing quality of life and leading to mortality rates [12]. The arousals interfere with the daily of the patient by limiting their social activities, developing negative feelings and self-image, and minimizing the patient's self-esteem. On the other hand, due to the lack of awareness and education among terminally ill patients in rural India, they are mostly unaware of the common warning signs leading to worsening the terminal condition. Another problem in the nation's healthcare procedures that significantly lowers patient quality of life and raises death rates is misdiagnosis of symptoms [10].

Measuring Instruments/Tools for Psychological Distressing Symptoms [5,6,8]



Psychological distressing symptoms require proper assessment as they can affect individual thought processes and make it harder to cope with the terminal ill diagnosis, its symptoms, and the aftermath treatment process among cancer survivors. A useful tool for measuring unpleasant experiences of a mental, physical, social, or spiritual nature is the National Comprehensive Cancer Network. Cancer patients' health-related quality of life is evaluated using the European Organization for Research and Treatment for Cancer Quality Assessment Questionnaire (EORTC QLQ-C30).[13] The EORTC QLQ-C305 includes three symptom scales (pain, fatigue, and nausea/vomiting), five functional scales (physical, social, emotional, cognitive, and role functioning), and an overall health and quality of life scale. It includes six single-item scales measuring dyspnea, insomnia, appetite, constipation, diarrhea, and financial difficulties, along with thirty 30-question questionnaires. Numerous international studies, each concentrating on a particular tumor site, have validated the EORTC QLQ-C30.[12] A self-report tool called the COPE (Coping Orientation to Problems Experienced) Inventory was created to evaluate a wide range of coping strategies. The fourteen subscales that make up the COPE include behavioral disengagement, denial, self-distraction, self-blaming, substance use, humor, positive reframing, religion, acceptance, emotional support, planning, active coping, instrumental support, and venting to let unpleasant feelings escape/expressing negative feelings [13].

Cancer patients' quality of life about their health is evaluated using the Functional Assessment of Cancer Therapy General (FACT-G) questionnaire. The 27-item survey measures the burden of symptoms and physical well-being of patients using a five-point answer scale, evaluated by the questionnaire containing: functional, emotional, social/family, and physical well-being. The ninety-odd-item CAYA-T (Cancer Assessment for Young Adults-Testicular) questionnaire covers the seven biopsychosocial domains: emotional functioning (fear, obsession with illness, anxiety, and depressive symptoms), social functioning, education and work, memory and concentration, and sexual relationships. The Epidemiologic Studies Center A 20-item self-report questionnaire on depressed symptoms is called the Depression Scale (CES-D) [14]. The Depression

Anxiety Stress Scales 21, which measures psychological discomfort in three multi-item domains—anxiety, depression, and stress/tension—is a condensed version of the 42-item Depression Anxiety Stress Scales (DASS) questionnaire. Self-reported despair, self-deprecation, interest, anhedonia, inertia, and dysphoria were evaluated in the depression domain. The experience of anxiety and any associated bodily consequences were assessed in the anxiety domain. Measurements of agitation, irritation, impatience, and difficulties relaxing were made in the stress/tension domain [15, 14].

Both recently created and well-known distress screening instruments that have been verified in cancer patients are included in the current investigation. According to the study, distress is characterized as a depressive condition that may be indicative of adjustment, anxiety, or affective disorders. The unique type of adaptation that normal people experience in response to exceptionally stressful situations is called coping. Coping is the dynamic process by which an individual adjusts their cognitive and behavioral strategies to meet demands that are particularly difficult and likely beyond their current abilities and resources.[16] The three primary components of the coping process are the stressor, or the source of the stress, cognitive assessment, and coping methods. Many conventional coping techniques have been divided into primary and secondary control coping, problem-versus-emotion-focused, functional-versus-dysfunctional, approach-versus-avoidance, and engagement-versus-disengagement. The most well-known and often applied technique in the research of coping is the division of coping actions into problem- and emotion-focused categories [17].

The secondary Control Coping technique involves increasing an individual’s coping based on the current situation and the use of adaptive coping strategies is a significant predictor of decreased emotional distress. In post-cancer diagnosis, secondary control strategies techniques of acceptance and cognitive appraisal help in minimizing anxiety and depressive symptoms. Mostly among adult cancer survivors the use of secondary control coping strategies helped to mediate negative thoughts about cancer treatment, promoted a higher concordance to medical regimens, and assisted in the management of stress. In common experiences, cancer survivors felt that their diagnosis had a greater impact on their psychological distress than did their demographic or clinical characteristics [14]. Coping strategies explained 38% of the variance in psychological distress, whereas demographic factors, such as gender, relationship status, and late medical effects, accounted for only 12%. Similarly, using a multiple regression analysis, social support and coping strategies explained about 30% of the psychosocial distress outcome model [8, 9]. The study shows that cancer patients from rural backgrounds had higher coping scores than urban patients, which was statistically significant. On the other hand, the male cancer population has a higher level of coping strategies compared with females. The finding also shows that patients of joined-family age have higher coping abilities compared to single or nuclear families [15].

Discussion

As more and more modern scientific medical success stories transform cancer into a treatable illness that can be effectively managed, the number of cancer survivors rises, and by 2030, that number is expected to reach roughly 75 million. In developing nations, between 30% and 65% of all cancer patients are long-term survivors due to cancer screening and early detection. Nonetheless, the survivorship experience also influences the survivor's experiences as family members, friends, and caregivers while they are coping with and beyond cancer [6]. The present models of terminal ill assessment in India have failed to acknowledge the existing psychologically distressing symptoms as the treatment focus is largely on cure, disease failure, and survival rates. The majority of the clinicians (oncologists and nurses) have little formal training in the survivorship care plan and addressing the psychological non-pain symptoms. The patients on the other hand are not comfortable sharing their psychosocial-emotional distressing symptoms to their clinicians [9]. Poor identification of psychologically distressing symptoms both by patients and clinicians becomes the underlying barrier to not engaging with psychological assessment in Indian clinical practices.

Socio-cultural stigma is another significant barrier for patients to avoid psychological support or refuse referral if offered, and preference for managing their emotional and psychological difficulties on their own. The results of the current study indicate that cancer survivors generally had higher hospitalization rates, poor self-rated health, depressive symptoms, functional limitations, and sleep issues. Because urban residents have better access to healthcare, including cancer screening and treatment, which increases survival rates, cancers linked to lifestyle factors are more common in higher socioeconomic groups and urban areas. A person's experience of psychosocial distress among cancer survivors varies based on their culture and how they view their illness. In addition to anxiety and depression, there is a higher chance of suicidal behavior, which can cause intense emotional suffering and mental discord that can hurt an individual's quality of life in several ways. Only 9.1% of the long-term cancer survivors accessed proper mental health support, while 33.4% reported being unable to afford professional mental health services due to socio-economic conditions [17]. Sadly, 19% of the cancer survivors were not aware of the existing mental services, mainly in rural India. Indigenous tribal communities experience poor access to both health care systems and mental health services. Sleep disturbance, fatigue, loss of appetite, and fear of cancer recurrence (45.5%) were also seen as contributing factors for mental health issues among cancer survivors. Social anxiety, change in personal and social relationships after cancer diagnosis, and its treatment procedure were also observed as the common contributing factors mainly in rural India. Another 19.2% of the cancer survivors were seen experiencing Post-Traumatic Stress Disorder (PTSD) [16].

The cognitive and social functioning are significantly different between the general population and cancer-affected survivors. Apart from its physical and mental negative health outcomes, individuals have experienced limited social functioning resulting in relying less on their social network for support. Compared with the general population, adult cancer survivors reported greater severity of anxiety and depression symptoms than those without a history of cancer. Cancer survivorship can live a normal life for 50 to 60 years, in which one-third of the population failed to access regular follow-up cancer care and regular symptom screening with validated tools resulting in living with high prevailing depressive symptoms [10, 11]. Individuals who had financial difficulties and stigmatization were more likely to have higher levels of worry, stress, and sadness. Patients who used problem-focused or maladaptive coping methods were shown to have greater levels of symptoms in most cases. Conversely, patients who utilized emotion-focused coping strategies showed lower levels of anxiety, sadness, hazardous undesired behaviors, and fear of cancer recurrence. To deal with stress and uncomfortable symptoms,

cancer survivors who use unhealthy coping mechanisms are strongly linked to receiving direct psychological help as well as encouragement to utilize alternative, approach- or emotion-focused coping mechanisms.

Limitations and Strengths of the Study

The present study results have certain limitations and strengths.

- Since the study was a cross-sectional study, the temporal relationship between cause and effect could not be ascertained.
- Some measurement tools used were self-rating questionnaires. This may have led to some bias.
- It provides insights for healthcare professionals and policymakers to better understand and cater to the mental health needs of this population.
- Long-term survivors often experience depression, anxiety, stress, and body image concerns. Follow-up management strategies for cancer survivors should involve assessing and treating psychological distress, as well as addressing body image issues and social prejudice in patients having mastectomies.

Author Contributions: Conceptualization, S.D.V; methodology, F.S; validation, S.D.V; formal analysis, F.S; investigation, F.S, and S.D.V; resources, S.D.V; data curation, S.D.V; writing – original draft preparation, F.S. and S.D.V; writing – review and editing, S.D.V. and F.S; visualization, S.D.V; supervision, S.D.V; project administration, S.D.V.

All authors have read and agreed to the published version of the manuscript.

Author Contributions: Conceptualization, F. S., S. D. V.; methodology, F. S., S. D. V.; validation, F. S., S. D. V.; formal analysis, F. S., S. D. V.; investigation, F. S., S. D. V.; resources, F. S., S. D. V.; data curation, F. S., S. D. V.; writing – original draft preparation, F. S., S. D. V.; writing – review and editing, F. S., S. D. V.; visualization, F. S., S. D. V.; supervision, F. S., S. D. V.; project administration, F. S., S. D. V.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: None.

Funding: None.

Informed Consent: Informed consent was obtained from all individual adult participants included in the study.

References

1. Walker J, Holm Hansen C, Martin P, Sawhney A, Thekkumpurath P, Beale C, Symeonides S, Wall L, Murray G, Sharpe M. Prevalence of depression in adults with cancer: a systematic review. *Ann Oncol.* 2013; 24(4): 895–900. https://doi.org/10.1093/annonc/mds575.
2. Carlson LE, Ismaila N, Addington EL, Asher GN, Balneaves LG, Bradt J, Fuller-Shavel N, Goodman J, Hoffman CJ, Huston A, Mehta A, Paller ChJ, Richardson K, Seely D, Siwik ChJ, Temel JS, Rowland JH. Integrative oncology care of symptoms of anxiety and depression in adults with cancer: Society for Integrative Oncology-ASCO Guideline. *J Clin Oncol.* 2023; 41(28): 4562–4591. https://doi.org/10.1200/JCO.23.00857.
3. Neel C, Lo C, Rydall A, Hales S, Rodin G. Determinants of death anxiety in patients with advanced cancer. *BMJ Support Palliat Care.* 2015; 5(4): 373–380. https://doi.org/10.1136/bmjspcare-2012-000420.
4. Greenberg J, Greenberg J, Martens A, Jonas E, Eisenstadt D, Pyszczynski T, Solomon S. Psychological defense in anticipation of anxiety: eliminating the potential for anxiety eliminates the effect of mortality salience on worldview defense. *Psychol Sci.* 2003; 14(5): 516–519. https://doi.org/10.1111/1467-9280.03454.
5. Chen F, Ou M, Xiao Z, Xu X. The relationship between fear of cancer recurrence and death anxiety among Chinese cancer patients: the serial mediation model. *BMC Psychiatry*. 2024; 24(1): 416-420. https://doi.org/10.1186/s12888-024-05819-8.
6. Sharp L, Carsin AE, Timmons A. Associations between cancer-related financial stress and strain and psychological well-being among individuals living with cancer. *Psychooncology*. 2013; 22(4): 745–755. https://doi.org/10.1002/pon.3055
7. Krause N, Hayward RD. Religious involvement and death anxiety. *Omega (Westport).* 2014; 69(1): 59–78. https://doi.org/10.2190/OM.69.1.d
8. Stanton AL. What happens now? Psychosocial care for cancer survivors after medical treatment completion. *J Clin Oncol.* 2012; 30(11): 1215–1220. https://doi.org/10.1200/JCO.2011.39.7406
9. Manning-Walsh J. Social support as a mediator between symptom distress and quality of life in women with breast cancer. *J Obstet Gynecol Neonatal Nurs.* 2005; 34(4): 482–493. https://doi.org/10.1177/0884217505278310
10. Andersen BL. Biobehavioral outcomes following psychological interventions for cancer patients. *J Consult Clin Psychol.* 2022; 70(3): 590–610. https://doi.org/10.1037//0022-006x.70.3.590
11. Hong YJ, Han S, Lim JU,· Kang HS, Kim SK, Kim JW, Lee SH, Kim SJ, Yeo ChD. Association Between Quality of Life Questionnaire at Diagnosis and Survival in Patients With Lung Cancer. *Clinical Lung Cancer.* 2023; 24(5): 459-466. https://doi.org/10.1016/j.cllc.2023.03.007.
12. Arraras JI, Arias F, Tejedor M, Pruja E, Marcos M, Martínez E, Valerdi J. The EORTC QLQ-C30 (version 3.0) Quality of Life Questionnaire: Validation study for Spain with head and neck cancer patients. *Psycho-Oncology.* 2022; 11(3): 249–256. https://doi.org/10.1002/pon.555
13. García FE, Barraza-Peña CG, Wlodarczyk A, Alvear-Carrasco M, Reyes-Reyes A. Psychometric properties of the Brief-COPE for the evaluation of coping strategies in the Chilean population. Psicologia: *Reflexão e Crítica.* 2018; 31(22): 1-11. https://doi.org/10.1186/s41155-018-0102-3.
14. Dincer AN, Brunckhorst O, Genel O, Dasgupta P, Muneer A, Ahmed K. Quality of life, anxiety and depression patient-reported outcome measures in testicular cancer: *A systematic review. Psycho-Oncology.* 2021; 30(9): 1420–1429. https://doi.org/10.1002/pon.5700.
15. Lazarus RS. Emotions and interpersonal relationships: toward a person-centered conceptualization of emotions and coping. Journal of Personality. 2006; 74(1): 9–46. https://doi.org/10.1111/j.1467-6494.2005.00368.x.

16. Hoffman KE, McCarthy EP, Recklitis CJ, Ng AK. Psychological Distress in Long-term Survivors of Adult-Onset Cancer: Results From a National Survey. *Arch Intern Med.* 2009; 169(14): 1274–1281. https://doi.org/10.1001/archinternmed.2009.179.
17. Anthony NK, Baaba B. Coping, health anxiety, and stress among health professionals during Covid-19, Cape Coast, Ghana. *PLoS One.* 2024; 19(1): e0296720. https://doi.org/10.1371%2Fjournal.pone.0296720.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Short Communication DOI: https://doi.org/10.23950/jcmk/15572

Retrospective Analysis of Ankle Osteoarthritis: Evaluation of Clinical and Epidemiologic Data at the Kazakh National Scientific Center of Traumatology and Orthopedics

Meruyert Makhmetova[1,4], Birzhan Suiindik[1], Yerik Raimagambetov[3], Bagdat Balbossynov[4], Marat Urazayev[4], Dina Saginova[5]

[1]Research School, Astana Medical University, Astana, Kazakhstan
[2]Institute of Life Sciences, Karaganda Medical University, Karaganda, Kazakhstan
[3]Orthopedics Department No. 5, National scientific center of traumatology and orthopedics named after academician N.D. Batpenov, Astana, Kazakhstan
[4]Department of the Arthroscopy and Sports Trauma, National scientific center of traumatology and orthopedics named after academician N.D.Batpenov, Astana, Kazakhstan
[5]Centre for Science and Education, National scientific center of traumatology and orthopedics named after academician N.D.Batpenov, Astana, Kazakhstan

Received: 2024-06-27.
Accepted: 2024-10-31.

J Clin Med Kaz 2024; 21(6): 54–58

Corresponding author:
Meruyert Makhmetova.
Email: meruert1995@mail.ru.
ORCID: https://orcid.org/0009-0004-3044-7724.

Abstract

Introduction: Ankle osteoarthritis is a prevalent condition that significantly impacts patient mobility and quality of life. Surgical interventions, such as arthroscopic debridement and arthrodesis, are commonly employed to alleviate symptoms and restore function. However, the optimal choice between these procedures remains a subject of debate.

Objective: This retrospective study aims to evaluate the clinical and epidemiologic data of patients with ankle osteoarthritis treated at the hospital. We compared the outcomes of arthroscopic debridement and arthrodesis, focusing on pain relief and functional improvements based on the severity of osteoarthritis.

Design: Cross-sectional, retrospective case series.

Results: Group I had a significantly younger median age (41 years) compared to Group II (59 years, p = 0.0021). Group II also presented a higher mean BMI (26.2 vs. 23.9; p = 0.0391). Preoperatively, Group I demonstrated a mean VAS score of 4.63, improving to 1.52 postoperatively (p = 0.0000) and 3.63 after 12 months (p = 0.0003). In Group II, the VAS score improved from 6.92 to 3.85 postoperatively (p = 0.0000), but increased to 5.08 after 12 months (p = 0.0001). Functional outcomes as measured by the AOFAS score significantly improved in both groups, although Group I showed better long-term functional outcomes.

Conclusion: Arthroscopic debridement provided better short-term functional improvement and pain relief, particularly in younger patients with early-stage osteoarthritis. Arthrodesis, while effective for advanced disease, was associated with a higher risk of recurrent pain and reduced functionality over time. The choice of treatment should be individualized, considering patient age, BMI, arthritis severity, and comorbidities.

Keywords: Ankle Joint, Retrospective Studies, Osteoarthritis, Arthrodesis, Arthroscopy.

Introduction

Arthritis is one of the most common chronic diseases and takes a leading role as a cause of disability among adults [1]. Globally, around 15% of people experience joint pain and disability due to osteoarthritis, with approximately 1-4% specifically suffering from ankle osteoarthritis [2]. Ankle joint problems are quite common but still have received lack of attention. Post-traumatic arthritis (PTA) of the ankle joint is the most frequent, accounting for 80% of cases, compared to other

major joints of the lower extremities, such as the knee (10%) and hip (2%) [3]. PTA occurs at a younger age (about 10 years earlier than primary osteoarthritis), which leads to increased disability of the able-bodied population and creates additional difficulties for the choice of treatment method for patients [4]. Moreover, it is also important to consider the substantial financial burden associated with the necessary of therapy. Nowadays, the existing methods of treatment are symptomatic and do not provide restoration of the joint. The applied surgical treatment methods are aimed only at debridement of the joint without restoration of cartilage tissue. For the treatment of osteochondral defects of the ankle joint, methods aimed at stimulating cartilage regeneration in the damaged joint such as multiple microperforations of the articular surface, mosaic chondroplasty, abrasion and microfracturing are used. One example is microfracturing, which involves drilling through bone to release fat and blood while simultaneously releasing resident reparative bone marrow cells to create cartilage. Other alternatives include autologous bone and cartilage transplantation (AOT) or methods involving joint distraction. Each of these treatments is based on the use of endogenous cells to remodel the surrounding area. However, clinical practice has shown that they cannot provide complete and sustained restoration of articular hyaline cartilage and often result in fibrotic cartilage formation, ultimately leading to treatment ineffectiveness [5]. The current treatment with the best clinical outcome is ankle arthrodesis, which is usually provided at age 68 years, approximately 16 years after disease onset. But at the same time there are some disadvantages of this method: loss of joint mobility, change in gait, increased stress on adjacent joints, failure to fuse or delayed fusion, risk of infection, hardware complications, long recovery period, poor pain relief. Total endoprosthetics (total joint replacement) is another surgical treatment option that provides a higher degree of patient satisfaction. Ankle endoprosthetics can be complicated by the development of infection, instability, or periprosthetic fractures. Due to the high wear rate of the prosthesis, revision endoprosthetics is necessary every 7 years [6]. In addition, this operation is expensive and the number of endoprostheses in Kazakhstan is limited. In view of the above, the development of etiotropic, safe and long-term regenerative method of treatment of osteoarthritis of the ankle joint is in demand.

The aim of the study was to evaluate the differential treatment of patients with degenerative ankle joint disease depending on the stage of osteoarthritis.

Materials and methods

This study was conducted with patients' informed consent and according to a protocol approved by the local institutional review board, adhering to the ethical standards outlined in the 1964 Declaration of Helsinki. We collected 40 patients who underwent surgical treatment regarding pain of ankle joint in National scientific center of traumatology and orthopedics named after academician N. D. Batpenov (Astana, Kazakhstan). Surgical procedures were determined based on the severity of ankle joint osteoarthritis, patient complaints, age, and concurrent medical conditions. Exclusion criteria: acute trauma, lower limb axial deformities, limb shortening, and patients with psychiatric disorders.

Radiography was performed for all patients to assess joint space narrowing, presence of osteophytes, and subchondral bone sclerosis and to determine the stage of osteoarthritis (Figures 1). MRI was utilized to detect subchondral cysts, tissue inflammation and edema around the joint, and evaluate blood supply (Figures 2).

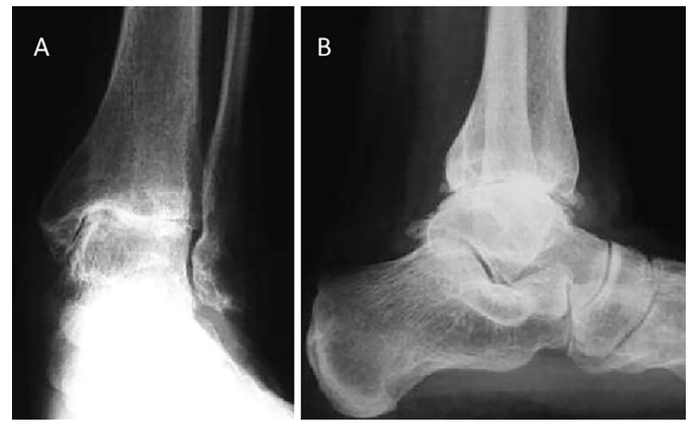


Figure 1 – X-Ray Scan of the patient's 2 left ankle joint with grade IV osteoarthritis in frontal (A) and sagital (B) side

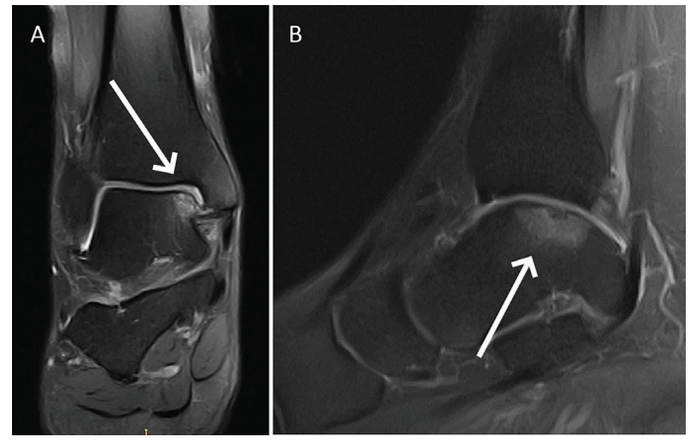


Figure 2 – MRI of the patient's 4 right ankle with osteochondral defect of the talus bone (white arrow), frontal (A) and sagital (B) side

All 40 patients were divided into two groups based on the type of surgical treatment they received. Group I, consisting of 27 patients, underwent arthroscopic debridement, while Group II, comprising 13 patients, underwent ankle arthrodesis using screws and plates. Arthroscopic vaporization of the capsule-ligamentous structures of the ankle joint was the most frequently performed operation in these cases. In addition to vaporization of capsule-ligamentous structures, arthroscopic decompression and debridement were also performed for anterior and posterior impingement of the ankle joint. This method of surgical intervention in the treatment of degenerative joint disease reflects the trend toward minimally invasive surgical treatment methods in the early stages of osteoarthritis, which can prevent the progression of cruzarthrosis. Ankle arthrodesis is a method of tibial and talus fusion that has been most commonly performed in patients with 3-4 stage of osteoarthritis. Athrodesis completely blocks movements in the ankle joint, but at the same time it releave pain syndrome.

The clinical efficacy of surgical treatment was evaluated by the regression of pain syndrome and improvement of ankle joint function. Ankle joint function was assessed using the American Orthopaedic Foot and Ankle Society (AOFAS) scale, and pain syndrome was assessed using the VAS pain rating scale.

Statistical analysis

All statistical analyses were conducted using Stata software (version 18), StataCorp, College Station, TX, USA). Statistical significance was set at $p < 0.05$ for all tests. Quantitative measures were assessed for conformity to a normal distribution using the Shapiro-Wilk criterion. Continuous variables, including the

Visual Analog Scale (VAS), the American Orthopaedic Foot and Ankle Society (AOFAS) score, gait abnormality, and range of motion, were expressed as mean ± standard deviation (SD)with the corresponding range.

Paired t-tests were employed to compare preoperative and postoperative values within each treatment group (arthroscopic debridement or arthrodesis) at different time points (preoperative, postoperative, 6 months, and 12 months). Statistical significance between these time points was determined by calculating p-values, with significance set at $p < 0.05$. For comparing the outcomes between the two independent treatment groups (arthroscopic debridement and arthrodesis), independent t-tests were used. In cases where the normality assumption was not met, the Mann-Whitney U-test was applied as a non-parametric alternative to assess differences between groups.

Results

A total of 40 patients were included in the study, divided into two groups based on the surgical treatment they received. Evaluation criteria included age, gender, weight, BMI, side of lesion, stage of osteoarthritis, and presence of comorbidities. The demographic and clinical characteristics of the patients were compared between the groups (Table 1).

Patients in Group II were significantly older, with a median age of 59 years (range 46–64), compared to 41 years (range 31–47) in Group I (p = 0.0021). There were no statistically significant differences in gender distribution, with males representing 67% in Group I and 46% in Group II (p = 0.3704). Group II had a significantly higher mean BMI (26.2 vs. 23.9; p = 0.0391). In terms of arthritis staging, the majority of Group I patients had early-stage arthritis (I and II), while Group II predominantly consisted of patients with more advanced arthritis (IIIb and IV). Comorbidities were present more frequently in Group II, including diabetes mellitus, rheumatoid arthritis, and cardiovascular conditions.

Table 1 Demographic and clinical data of patients

Indicator	Group I Arthroscopic debridement	Group II Arthrodesis	p-value
Total	n = 27	n = 13	
Age	41 (31,5-47,5)	59 (46-64)	p = 0.0021
Gender Male Female	 18 (66,7 %) 9 (33,6 %)	 6 (46,2 %) 7 (53,8 %)	p = 0.3704
Weight	70 (61,5-75,5)	75 (70-84)	p = 0.0773
Body mass index (BMI)	23,9 (22,6-25,15)	26.2 (24,6-27,6)	p = 0.0391
Side Right Left	 13 (48,1 %) 14 (51,9 %)	 9 (69,2 %) 4 (30,8 %)	
Stage of arthritis I II IIIa IIIb IV	 19 (70,4 %) 8 (29,6 %)	 - - 1 (7,7 %) 5 (38,5 %) 7 (53,8 %)	
Comorbidities No Diabetes mellitus Rheumatoid arthritis Cardiovascular Other More than 2	 19 - - 4 3 1	 5 2 3 1 - 2	

Functional Outcomes

Pre-operatively, In Group I the mean VAS score was 4.63 ± 0.63, which improved to 1.52 ± 0.51 post-operatively (p = 0.0000) (Table2, Figure 3). After 6 months, the VAS score was maintained at 1.70 ± 0.47, and after 12 months, a slight increase to 3.63 ± 0.56 was noted, though this still represented a significant improvement from baseline (p = 0.0003).

Table 2 Pre- and post-operative functional scores

	Group I		Group II	
	VAS (Mean ± SD, Range)	AOFAS (Mean ± SD, Range)	VAS (Mean ± SD, Range)	AOFAS (Mean ± SD, Range)
Pre-operative	4.63 ± 0.63 (4-6)	84.1 ± 1.58 (83-85)	6.92 ± 0.76 (6-8)	43.2 ± 8.88 (25-56)
Post-operative	1.52 ± 0.51 (1-2)	93.4 ± 3.00 (92-95)	3.85 ± 0.69 (3-5)	56.16 ± 7.47 (38-65)
p-value	0.0000	0.0000	0.0000	0.0000
After 6 months	1.70 ± 0.47 (1-2)	81.3 ± 4.78 (79-83)	4.15 ± 1.07 (2-6)	58 ± 8.82 (42-73)
p-value	0.0000	0.0018	0.0000	0.0000
After 12 months	3.63 ± 0.56 (3-4)	79.6 ± 4.72 (77-81)	5.08 ± 1.19 (3-7)	52.38 ± 7.15 (40-60)
p-value	0.0003	0.0000	0.0001	0.0000

The AOFAS score improved from a pre-operative mean of 84.1 ± 1.58 (range: 83-85) to 93.4 ± 3.00 post-operatively (p = 0.0000) (Figure 4). At the 6-month follow-up, the AOFAS score decreased slightly to 81.3 ± 4.78 but remained significantly better than the pre-operative score (p = 0.0018). After 12 months, the score further declined to 79.6 ± 4.72 (p = 0.0000).

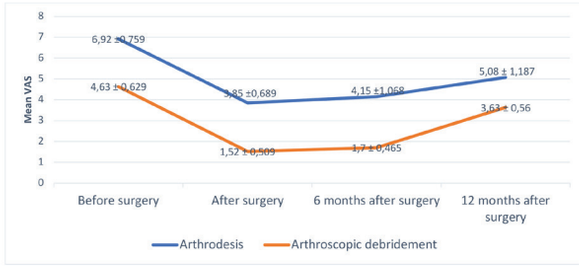


Figure 3 – Comparative analysis of pain level changes in patients of both groups

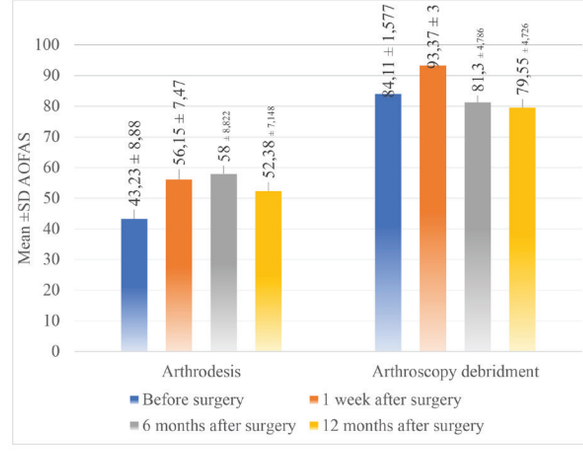


Figure 4 – Comparative analysis of ankle joint function changes in patients of both groups

In Group II, the mean pre-operative VAS score was 6.92 ± 0.76, which decreased to 3.85 ± 0.69 post-operatively (p = 0.0000). However, after 6 months, the VAS score increased to 4.15 ± 1.07, and by 12 months, it reached 5.08 ± 1.19 (p = 0.0001).

The AOFAS score in Group II also demonstrated improvement, from a pre-operative mean of 43.2 ± 8.88 to 56.16 ± 7.47 post-operatively (p = 0.0000). At the 6-month mark, the score increased to 58 ± 8.82 and remained stable at 52.38 ± 7.15 after 12 months (p = 0.0000).

Discussion

The literature provides a rather large list of indications for ankle arthroscopy [7]. In addition to free intraarticular bodies, osteochondral fractures, rheumatoid polyarthritis, and anterior impingement syndrome, arthroscopic interventions on the ankle joint are often used for ligamentous apparatus pathology and infectious arthritis as sanitizing measures. The list of indications is still expanding, and the number of ankle arthroscopies performed is increasing due to development of surgical techniques. The data obtained from other sources indicate that treatment of patients with osteochondropathy of the talus, anterior impingement syndrome, synovitis allow us to recommend ankle arthroscopy as the operation of choice for this pathology, thanks to which minimally invasive and highly effective treatment of this category of patients can be performed [8]. In patients with ankle osteoarthritis, the prognosis depends on such factors as the degree and size of cartilage damage and the presence of adjacent joint pathologies. According to the data of our study, the majority of patients in the early postoperative period showed pain reduction and improvement of joint mobility. However, within 12 months, almost all patients experienced a recurrence of pain and a decrease in ankle joint function to the preoperative level. Data on complications vary widely in the literature, with neurologic, vascular, and infectious complications reported. Researchers have noted a higher risk of neurologic complications with ankle arthroscopy compared with knee and shoulder procedures. For example, Sprague N.F. reports 24% complications [9], while Small N.C. reports only 0.7% [10]. These data, as well as our own experience, emphasize the need for careful surgical preparation, careful handling during procedures, and careful patient education about the potential risks and complications associated with arthroscopic interventions.

Ankle arthrodesis remains the "gold standard" in the treatment of late-stage osteoarthritis [11]. However, the patient's ankle joint function is limited, which causes a compensatory increase in the range of motion of the adjacent joints of the foot, leads to overloading and possible degenerative changes in joints such as the subtalar and talus and calcaneo-cuboid joints later on [12]. In addition, there are observations that the movement of the small joints of the healthy foot mimics the affected side so that the patient develops a symmetrical altered gait on both sides. As a result, a number of patients develop symmetrical limb pathology after arthrodesis [13]. Some patients require repeat arthrodesis after intervention [14], moreover stress fractures of the tibia and fibula may occur [15]. In avascular necrosis of the talus, there is insufficient blood supply, and long-term use of various medications and systemic disorders in patients with rheumatoid arthritis increase the risk of arthrodesis failure [16]. Adequate compression is a prerequisite for successful arthrodesis [17, 18]. The clinical results with endoprosthesis, arthrodesis and arthroscopy were similar. However, patients with endoprosthesis were significantly more likely to have reoperations [19]. According to other data, endoprosthesis and arthrodesis were equally effective in osteoarthritis [20].

Retrospective analysis of data on surgical treatment of ankle osteoarthritis revealed differences in outcomes between the two main methods of intervention: arthroscopic debridement and ankle arthrodesis. Of the 40 patients included in the study, 67.5% underwent arthroscopic debridement, while 32.5% underwent arthrodesis. The arthroscopic debridement group was predominantly male (66.7%) and the age of the patients was younger. The cause of osteoarthritis in this group was most often trauma. In the arthrodesis group, women accounted for 53.8%. These patients tended to present with a later degree of osteoarthritis, often having comorbidities, and their age was significantly older. Arthroscopic debridement has shown good results in the short term, especially in patients with early stages of osteoarthritis. This method is characterized by less invasiveness and faster recovery. The arthrodesis group, which had more advanced disease, demonstrated significant post-operative benefits. The increase in pain syndrome in the arthrodesis group is evidently associated with the increased load on the adjacent joints of the foot.

A key finding of our study is the significant difference in patient demographics between the two groups. Patients in the arthrodesis group were older and had a higher body mass index (BMI), which could have influenced the clinical outcomes. Additionally, the prevalence of comorbidities was higher in the arthrodesis group, particularly cardiovascular diseases and diabetes mellitus, which may have impacted their recovery and rehabilitation. These factors underscore the importance of individualized treatment plans based on patient characteristics, comorbidities, and disease severity.

The differences in outcomes between the two groups are consistent with previous studies that have shown that arthroscopic debridement is more suitable for patients with early-stage osteoarthritis, while arthrodesis is more appropriate for patients with severe joint destruction. However, it is important to note that the retrospective nature of our study and the relatively small sample size limit the generalizability of our findings. Future prospective studies with larger sample sizes and longer follow-up periods are needed to confirm these results and to further refine treatment criteria.

Our study also highlights the need for a multidisciplinary approach in the management of ankle osteoarthritis. In addition to surgical interventions, conservative measures such as weight management, physical therapy, and pharmacological treatments should be considered, especially for patients with multiple comorbidities. Moreover, the development of innovative surgical techniques and biologic treatments aimed at cartilage restoration may offer promising alternatives to traditional procedures in the future.

Conclusion

It is important to emphasize that early intervention to prevent the progression of osteoarthritis is the most important aspect of the treatment of this disease. This implies a deep understanding of the mechanisms of osteoarthritis development and the development of new, more effective methods of prevention and treatment. Further prospective studies with a large number of participants are needed to confirm our findings and to determine the optimal criteria for selecting treatment approaches.

The introduction of preventive measures and innovative strategies can significantly improve the prognosis and quality of life of patients with ankle osteoarthritis. These findings emphasize the importance of early intervention and the use of innovative methods in the treatment of osteoarthritis, which may stimulate additional research in this area.

Author Contributions: Conceptualization, Y.R., B.B. and D.S.; methodology, M.M., B.S. and D.S.; validation, M.M., M.U. and B.S.; formal analysis, Y.R., B.B., and M.U.; investigation, B.S., M.M., D.S. and Y.R.; resources, Y.R. and B.B.; data curation, S.B. and M.M.; writing – original draft preparation, S.B., M.M. and D.S.; writing – review and editing, S.B., M.M., M.U. and D.S.; visualization, M.M. and U.M.; supervision, Y.R., B.B. and D.S.; project administration, D.S. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: This research is funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP19679620).

References

1. Valderrabano V, Horisberger M, Russell I, Dougall H, Hintermann B. Etiology of ankle osteoarthritis. *Clin Orthop Relat Res*. 2009; 467(7): 1800–1806. https://doi.org/10.1007/s11999-008-0543-6.
2. Saltzman CL, Salamon ML, Blanchard GM, Huff T, Hayes A, Buckwalter JA, Amendola A. Epidemiology of ankle arthritis: report of a consecutive series of 639 patients from a tertiary orthopaedic center. *Iowa Orthop J.* 2005; 25: 44–46.
3. Stufkens SA, Knupp M, Horisberger M, Lampert C, Hintermann B. Cartilage lesions and the development of osteoarthritis after internal fixation of ankle fractures: a prospective study. *J Bone Joint Surg Am.* 2010; 92(2): 279–286. https://doi.org/10.2106/JBJS.H.01635.
4. Glazebrook M, Daniels T, Younger A, Foote CJ, Penner M, Wing K, Lau J, Leighton R, Dunbar M. Comparison of health-related quality of life between patients with end-stage ankle and hip arthrosis. *J Bone Joint Surg Am.* 2008; 90(3): 499–505. https://doi.org/10.2106/JBJS.F.01299. PMID: 18310699.
5. Weigelt L, Laux CJ, Urbanschitz L, Espinosa N, Klammer G, Götschi T, Wirth SH. Long-term Prognosis After Successful Nonoperative Treatment of Osteochondral Lesions of the Talus: An Observational 14-Year Follow-up Study. *Orthop J Sports Med.* 2020; 8(6): 2325967120924183. https://doi.org/10.1177/2325967120924183.
6. Lindsjö U. Operative treatment of ankle fractures. *Acta Orthop Scand Suppl.* 1981; 189: 1–131. https://doi.org/10.3109/ort.1981.52.suppl-189.01.
7. Barber FA, Britt BT, Ratliff HW, Sutker AN. Arthroscopic surgery of the ankle. *Orthop. Rev*. 1988; 17: 446-451.
8. Ferkel RD, Fischer SP. Progress in ankle arthroscopy. *Clin. Orthop*. 1989; 240: 210–220
9. Sprague NF. Complications in arthroscopy. *New York: Raven Press,* 1989. P. 21–223.
10. Small NC. Complications in arthroscopic surgery. *Arthroscopy*. 1988; 4: 215–221.
11. Khominets VV, Mikhailov SV, Shakun DA, Shumagaziev SE, Komarov AV. Ankle arthrodesis with three cancellous screws. *Traumatology and Orthopedics of Russia*. 2018; 24(2): 117–126. https://doi.org/10.21823/2311-2905-2018-24-2-117-126.
12. Coester LM, Saltzman CL, Leupold J, Pontarelli W. Long-term results following ankle arthrodesis for post-traumatic arthritis. J Bone Joint Surg Am. 2001; 83(2): 219–228. https://doi.org/10.2106/00004623-200102000-00009.
13. Mazur JM, Schwartz E, Simon SR. Ankle arthrodesis. Long-term follow-up with gait analysis. *J Bone Joint Surg Am.* 1979; 61(7): 964–975.
14. Henricson A, Jehpsson L, Carlsson A, Rosengren BE. Re-arthrodesis after primary ankle fusion: 134/1,716 cases from the Swedish Ankle Registry. *Acta Orthop.* 2018; 89(5): 560–564. https://doi.org/10.1080/17453674.2018.1488208.
15. Lidor C, Ferris LR, Hall R, Alexander IJ, Nunley JA. Stress fracture of the tibia after arthrodesis of the ankle or the hindfoot. *J Bone Joint Surg Am.* 1997; 79(4): 558–564.
16. Fedorov VG. Ankle arthrodesis in rheumatoid arthritis. Rheumatology Science and Practice. 2011; 49(1): 75–77. https://doi.org/10.14412/1995-4484-2011-872.
17. Jeng CL, Baumbach SF, Campbell J, Kalesan B, Myerson MS. Comparison of initial compression of the medial, lateral, and posterior screws in an ankle fusion construct. *Foot Ankle Int.* 2011; 32: 71–76. https://doi.org/10.3113/FAI.2011.0071.
18. Veljkovic AN, Daniels TR, Glazebrook MA, Dryden PJ, Penner MJ, Wing KJ, Younger ASE. Outcomes of total ankle replacement, arthroscopic ankle arthrodesis, and open ankle arthrodesis for isolated non-deformed end-stage ankle arthritis. *J Bone Joint Surg Am.* 2019; 101(17): 1523–1529. https://doi.org/10.2106/JBJS.18.01012.
19. Norvell DC, Ledoux WR, Shofer JB, Hansen ST, Davitt J, Anderson JG, Bohay D, Coetzee JC, Maskill J, Brage M, Houghton M, Sangeorzan BJ. Effectiveness and safety of ankle arthrodesis versus arthroplasty: A prospective multicenter study. *J Bone Joint Surg Am.* 2019; 101(16): 1485–1494. https://doi.org/10.2106/JBJS.18.01257.
20. Brodsky JW, Kane JM, Coleman S, Bariteau J, Tenenbaum S. Abnormalities of gait caused by ankle arthritis are improved by ankle arthrodesis. *Bone Joint J.* 2016; 98-B(10): 1369–1375. https://doi.org/10.1302/0301-620X.98B10.37614.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15720

Comparative Study of Urinary Calcium Levels in Women With Preeclampsia Compared to Normotensive Pregnant Women in Lagos, Nigeria

Nwabueze Gabriel Osuji[1], Christian C Makwe[1,2], Kehinde S Okunade[1,2], Aloy O. Ugwu1, Sunday Isaac Omisakin[1,2], Achonu Chinemeri U[1], Odoh Elizabeth Uchechukwu[1], Daniel Bukunmi Fadeyi[3]

[1]Department of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, Lagos University Teaching Hospital, Lagos, Nigeria
[2]Department of Obstetrics and Gynaecology, College of Medicine University of Lagos, Lagos, Nigeria
[3]Department of Obstetrics and Gynaecology, 68 Nigerian Army Reference Hospital Yaba, Lagos, Nigeria

Received: 2024-11-13.
Accepted: 2024-12-12.

J Clin Med Kaz 2024; 21(6): 59–65

Corresponding author:
Aloy Okechukwu Ugwu.
Email: Okeyugwu92@gmail.com.
ORCID: 0000-0003-2405-9720.

Abstract

Background: Preeclampsia is currently defined as multisystem progressive disorder characterized by the new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria, typically presenting in the second half of pregnancy (after twenty weeks) or postpartum in a previously normotensive woman without proteinuria and resolves within six weeks postpartum

Despite numerous theories, the aetiology of preeclampsia has not been fully elucidated. It is postulated that the rise in blood pressure is a manifestation of more than one patho-physiological condition. One of these conditions is related to abnormal renal function and probably impairment of urinary calcium excretion.

Objective: This study compared urinary calcium levels in women diagnosed with pre-eclampsia and normotensive pregnant women at the Lagos University Teaching Hospital, Lagos, Nigeria.

Methods: This was an analytical cross-sectional study that enrolled 100 preeclamptic pregnant women and their matched normotensive counterparts carried out at the antenatal clinic and the labour ward of the Lagos University Teaching Hospital. The urinary calcium level was analysed with spot urine using Orthocresolphthaleincomplexone (CPC) method (Fortress Diagnostics Limited United Kingdom, Product code BXC0291A).

Results: The mean urinary calcium levels in women with preeclampsia (2.44±1.45mmol/L) was significantly lower than that of normotensive pregnant women (4.43±1.84mmol/L) ($p < 0.001$). However, there was no significant difference in the mean urinary calcium levels in participants with mild preeclampsia (2.49±1.54mmol/l) compared to those with severe preeclampsia (2.42±1.42mmol/L), ($p = 1.000$). Conclusion: The study revealed a significantly lower level of urinary calcium in women with preeclampsia compared with that of their healthy normotensive counterparts. However, the study did not reveal any significant difference in the urinary calcium level in participants with mild and severe preeclampsia.

Keywords: Hypertension, Preeclampsia, Normotensives, Urinary calcium, proteinuria.

Introduction

Hypertensive disorders commonly complicate pregnancies worldwide [1–4]. It is found in 5-10% of pregnancies worldwide and contributes a significant proportion to both maternal and perinatal morbidity and mortality [4–6].

It has been argued to be the commonest medical disorder seen in

pregnancy [1]. Therefore, it is characterized by elevated systolic or diastolic blood pressure recorded at least twice 4-6 hours apart in pregnancy [1, 2] With subtle variations, most international societies/

guidelinesclassify hypertension during pregnancy as chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia [7–9]. Just as important, preeclampsia is a multi-systemic disease with poorly understood aetiology. Its prominent features include a rise in blood pressure (BP) of greater than or equal to 140/90 mmHg with evidence of significant proteinuria in the second half of pregnancy in a previously normotensive pregnant woman without prior history of proteinuria [1, 2]. However, contrary to popular belief, recent evidence has shown that the diagnosis of preeclampsia can be made when there is hypertension with associated end-organ damage irrespective of the woman's proteinuric status [1, 7–10].

Even more important, pre-eclampsia has consistently remained one of the major causes of maternal and perinatal mortality and morbidity in both technologically advanced and developing nations [11–13]. In Nigeria, it has a prevalence of 5.5-7.6% and in terms of maternal mortality it has been speculated to be among the first three causesaccounting for about 30% of all maternal deaths [13–16]. There is a five-fold increase in perinatal mortality in pre-eclampsia with iatrogenic prematurity being the main culprit [17-19]. For this reason, it is believed that approximately 70,000 women per annum and more than 500,000 of their fetuses and newborns die as a result of preeclampsia or it's complications. This is a significant proportion and is equivalent to the loss of 1600 lives per day [10, 20, 21]. Expectedly, greater than 99% of these preventable deaths occur in maternities spread across low- and middle-income countries, especially South-east Asia and sub-Saharan Africa [1, 11, 18, 19, 22].

The aetiology of pre-eclampsia as of today is still largely unknown and is still been explored. That is why many authors has postulated that the elevated BP, may be a manifestation of several pathophysiological conditions [2, 23, 24]. Some of these conditions include abnormal renal function, changes in the metabolism of certain ions such as calcium, and probably impairment of urinary calcium excretion [20, 25, 26]. The widely accepted patho-physiology is that of dysfunction in the endothelium [3]. This widespread endothelial dysfunction is believed to be as early as 8th weeks of gestation. However, the manifestation of the disease may appear in the late second or early third trimester weeks after the patho-physiological process had started [20, 21, 27, 28].

Additionally, it is well known that intracellular calcium regulation plays a vital role in hypertension and literature abounds on studies of blood calcium levels during pregnancy with significant variations in total and mean serum calcium levels as pregnancy progresses [5, 6, 20, 29–32]. Conversely, not so much robust literature exists especially from a homogenous pregnant population of black women on the possible relationship between urinary calcium levels and preeclampsia. This study, therefore, compared the levels of urinary calcium excreted in preeclamptics to that of normotensive pregnant women in Lagos, Southwest Nigeria.

Materials and methods

Setting

It was an analytical cross-sectional study done at the outpatient antenatal clinic and the delivery suite Lagos University Teaching Hospital (LUTH), Lagos, Nigeria. LUTH, located on the mainland of Lagos.

Study population

A total of 200 eligible pregnant women were recruited for the study between January 2021 and August 2021. They were accessed for inclusion criteria which include pregnant women with singleton pregnancy at 20 weeks' gestation and above with preeclampsia (cases) and their matched normotensive pregnant counterparts (comparators) who gave written informed consent. Those with a history of chronic medical or surgical conditions like hypertension, diabetes mellitus, renal failure, heart disease, chronic hypertension, urolithiasis, thyroidectomy, women with twin or high order multiples, those on over the counter medication containing calcium or those already prescribed calcium supplementation were excluded from this cross sectional study. The study population consisted of two groups matched for maternal age and gestational age. After obtaining a written informed consent, a unique identification number was assigned to each participant.

Sample size estimation

Using the findings from the study by Taufield et al, a minimum sample size of 100 participants was required in each group based on an intergroup mean difference of 40mg/ml to achieve a power of 80%, a type I error rate of 5% and a non-response rate of 20%.

Study procedures

Women who consented to be enrolled into the study were recruited. They include all pre-diagnosed women who met the inclusion criteria their age and gestational age matched healthy, normotensive counterparts as the comparator.

Group

An interviewer-administered questionnaire was used to obtain participants' information. Blood pressures were measured by the midwives using mercury sphygmomanometer according to standard protocols. Thereafter, ten milliliters of clean catch, mid-stream urine or catheter urine specimen (if catheterized) was collected from the participants into a clean universal bottle and the urine was tested for protein using urine dipstick. Based on the blood pressure, result of the urine dipstick and associated symptoms/signs, the participants were grouped into the study or comparative group and the remaining urine sample was labeled and sent immediately to LUTH Central Research Laboratory for storage and subsequent urinary calcium estimation.

Laboratory Method

The urine samples were aliquoted and transferred into cryogenic vials then stored in cryogenic box at ultra-low temperature of -80OC until laboratory analysis. The reagents with product code BXC0291A, LOT 202220, manufactured date 2020/11 and expiry date 2022/09 were all supplied ready to use by the manufacturer, Fortress Diagnostics Limited, United Kingdom. The reagents were stable until the expiry date stated by the manufacturer. A working reagent was prepared by mixing equal volumes of the buffer and chromagen and this mix was stable for 3 days at room temperature up to 25oC, or 7 days at 2-8oC. The urine samples were then diluted using 100µl of samples and 100µl of normal saline. The standard solution was prepared by mixing 25µl of the standard solution with 1000µl of the working reagent. The reagent blank was also prepared by mixing 25µl of distilled water with 1000µl of the working reagent. 25µl of the diluted urine samples was then added to 1000µl of the working reagent. This was mixed and the absorbance was then read against the prepared reagent blank after 5 to 50 minutes at a wavelength of 578nm and temperature 20-25oC.

The calcium concentration was calculated as shown below:

Calcium concentration= ($\frac{absorbance\ of\ sample}{absorbance\ of\ standard}$) x standard concentration

The kit's inter-assay imprecisions were 4.4% and 4.1% for the low control (2.20mmol/l) and high control (3.40mmol/l). The intra-assay coefficients of variation were 3.5% and 2.8% respectively for the low and high control levels, respectively. The low calcium detection limit of the assay was 0.12mmol/l and no limit to the highest detectable level was stated by the manufacturers.

Statistical analysis

Data was entered into an excel spreadsheet initially, it was later imported and analyzed using statistical package for the social sciences version 29; (SPSS) Armonk, NY: IBM Corp. The categorical variables were presented as percentage and frequency tables. With regards to continuous variables, test of normality was also done Kolmogorov-Smirnov test. Those that were normally distributed were presented as mean (± standard deviation), while others presented as median and interquartile range. The student's independent t- test was used to compare mean of normally distributed continuous variables, while Mann Whitney U test was used to compare the median of non-normally distributed variables between the preeclamptic and normotensive participants. One Way Analysis of Variance (ANOVA) and the Kruskal Wallis test were used to assess the differences in the mean and median urinary calcium levels respectively across the study groups of normotensives, mild and severe preeclamptic participants. Furthermore, a Post hoc Bonferroni test was done to determine the pairwise difference between severity of pre-eclampsia. A two-tailed test of hypothesis was assumed, and the level of statistical significance was set at $p < 0.05$.

Ethical Consideration

The ethical principle of Helsinki was obeyed throughout the study. The approval of this study was given by the Health Research Ethics Committee in our facility. The approval number is ADM/DCST/HREC/APP/3518.

Results

All in all, two hundred women will enrolled in this study, 100 (50%) were diagnosed with preeclampsia and 100 (50%) were healthy pregnant women matched for age and gestational age.

The mean participants' ageand gestational age of the preeclamptic study participants was not significantly different to that of the normotensive comparative participants (Table 1).

From Table 2, it is evident that the mean urinary calcium levels were significantly lower in preeclamptic (2.44± 1.45 mmol/l) than in than in normotensive pregnancy (4.43± 1.84 mmol/l).

Table 3 shows that there was a statistically significant difference in the urinary calcium levels amongst the normotensive, mild and severe preeclamptic participants ($p < 0.001$).

In Table 4, a pairwise comparison of urinary calcium levels among preeclamptic subgroups and normotensives by post hoc Bonferroni test revealed that there were statistically significant differences in the mean urinary calcium levels between women with mild preeclampsia and that of normotensive pregnant women (2.49 ± 1.54 mmol/L vs 4.43 ± 1.85 mmol/L, $p < 0.001$) and also that of women with preeclampsia with severe features and normotensive pregnant women (2.42 ± 1.42 mmol/L vs 4.43

Table 1 Socio Demographics and Obstetrics Characteristics of the Respondents

Characteristics	**Preeclampsia N=100**	**Normotensive N=100**	**Total (%) N=200**	**Statistics**
	Frequency n (%)	**Frequency n (%)**		**P-value**
Age (years)				
20-25	7(7.0)	9(9.0)	16(8.0)	0.927^
26-30	26(26.0)	25(25.0)	51(25.5)	
31-35	32(32.0)	34(34.0)	66(33.0)	
>35	35(35.0)	32(32.0)	67(33.5)	
Mean Age ±SD	32.2±5.5	31.7±5.6	32.0±5.5	0.531#
Booking Status				
Booked	32(32.0)	100(100.0)	132(66.0)	<0.001Δ
Unbooted	68(68.0)	0(0.0)	68(34.0)	
Parity (median, range)	1(0-7)	1(0-5)		0.804*
0	26(26.0)	25(25.0)	51(25.5)	0.599^
1	26(26.0)	29(29.0)	55(27.5)	
2	26(26.0)	27(27.0)	53(26.5)	
>3	22(22.0)	19(19.0)	41(20.5)	
Gestational age (weeks)				
<34	55(55.0)	51(51.0)	106(53.0)	0.389^
34-37	28(28.0)	24(24.0)	52(26.0)	
>37	17(17.0)	25(25.0)	42(21.0)	
Mean Gestational age ± SD	32.9±4.5	33.2±4.6	33.0±4.5	0.628#
Educational Qualification				
None	0(0.0)	1(1.0)	1(0.5)	0.016 Δ
Primary	6(6.0)	1(1.0)	7(3.5)	
Secondary	46(46.0)	33(33.0)	79(39.5)	
>secondary/ Tertiary	48(48.0)	65(65.0)	113(56.5)	
Marital Status				
Married	99(99.0)	99(99.0)	198(99.0)	1.000 Δ
Single	1(1.0)	1(1.0)	2(1.0)	
Occupational status				
Professional	4(4.0)	12(12.0)	16(8.0)	0.147 Δ
Semi-skilled	20(20.0)	22(22.0)	42(21.0)	
Skilled	18(18.0)	12(12.0)	30(15.0)	
Housewife/ unskilled	58(58.0)	54(54.0)	112(56.0)	
Symptoms at Presentation				
Yes	62(62.0)	0(0.0)	62(31.0)	<0.001 Δ
No	38(38.0)	100(100.0)	138(69.0)	
Proteinuria				
Nil	0(0.0)	100(100.0)	100(50.0)	<0.001 Δ
1+	0(0.0)	0(0.0)	0(0.0)	
2+	80(80.0)	0(0.0)	80(40.0)	
3+	18(18.0)	0(0.0)	18(9.0)	
4+	2(2.0)	0(0.0)	2(1.0)	
SBP (mmHg) (mean ± SD)	162.0 ± 15.8	115.8 ± 8.2	138.9 ± 26.3	<0.001#
DBP (mmHg) (mean ± SD)	102.8 ± 10.9	69.8 ± 6.2	86.3 ± 18.8	p<0.001#

 # Student's t-test; Δ Fischer's test; ^ Pearson's Chi-square,
**Mann Whitney U test,*
SBP- systolic BP, DBP- Diastolic BP.

Table 2 Comparison of Urinary Calcium Levels between Respondents

Variable	Measure of central tendency	Preeclampsia N=100	Normotensive N=100	Total N=200	P-value
Urinary Calcium (mmol/L)	Mean (SD)	2.44 (1.45)	4.43 (1.84)	3.44 (1.93)	<0.001#
	Median (IQR)	2.26 (2.06-2.46)	3.91 (3.19-5.31)	2.71 (2.22-4.17)	<0.001*

*SD: Standard deviation. *Mann Whitney U test. # Student's t-test*

Table 3 One-way analysis of variance in mean Urinary calcium levels across the study groups

Variable	Measure of central tendency	Normotensives N=100	Preeclampsia (mild) N=30	Preeclampsia (severe) N=70	Statistics	P-value
Urinary Calcium (mmol/l)	Mean (SD)	4.43 (1.85)	2.49 (1.54)	2.42 (1.42)	◊=35.836	p<0.001
	Median (IQR)	3.91 (3.19-5.31)	2.28 (2.11-2.48)	2.24 (2.02-2.45)	ŏ=108.862	p<0.001

ŏKruskal Wallis test ◊ANOVA

Table 4 Pairwise Comparison of Urinary Calcium Levels among Preeclamptics and Normotensives by Post hoc Bonferroni Test

Preeclampsia status	Normotensive (N=100)	Mild preeclampsia (N=30)
Mild preeclampsia (N=30)	< 0.001$	
Preeclampsia with severe features (N=70)	< 0.001$	1.000$

$ p-value for Bonferroni pear wise comparison

± 1.85 mmol/L, p < 0.001). However, there was no observed statistical difference between the urinary calcium levels in pre-diagnosed women with either mild or severe preeclampsia (2.49 ± 1.54 mmol/L vs 2.42 ± 1.42 mmol/L), respectively. (P-value =1.0).

Discussion

This study compared the levels of urinary calcium excreted in women diagnosed with preeclampsia and normotensive pregnant women using Orthocresolphthaleincomplexone (CPC) method which is an accurate, inexpensive, less time-consuming and the recommended field method of calcium estimation. We found that the mean urinary calcium level among preeclamptic women was significantly lower than that of normotensive pregnant women. However, further sub analysis showed that there is so significant difference in urinary calcium level in women with mild or severe preeclampsia.

The finding of significantly lower levels of mean urinary calcium levels in preeclamptic women than in normotensive pregnant women is in agreement with the findings by Pal and colleagues who also reported in their study that pregnant women diagnosed with preeclampsia excrete lesser amount of calcium in urine when compared with healthy normotensive pregnant women at the same gestational age at diagnosis [32]. Although they suggested different mechanisms to explain the reason behind the hypocalciuria in women with preeclampsia, the most plausible in their explanation was that of changes in glomerular filtration rate in preeclampsia, increased requirement of calcium by the pregnant hypertensive women resulting in increased intestinal absorption and increased calcium uptake by the developing fetus with or without changes in calcium reabsorption in the renal tubules.

Furthermore, although Agarwal and co-workers in their study were able to establish that there is an association between low urinary calcium levels and urinary calcium to creatinine ratio in preeclampsia, there sample size was not sufficient to draw a definitive conclusion. Currently, not so much studies exist in literature that evaluated the relationship between urinary calcium and preeclampsia [33]. Other possible explanation for these findings in our study may be related to the decreased dietary intake of calcium, decreased intestinal absorption of calcium, increased calcium uptake by the fetus and placenta or due to increased distal tubular reabsorption of calcium, which is likely to be independent of sodium reabsorption, as implied by several studies that were able to demonstrate reduced fractional excretion of calcium in patients with preeclampsia [25–28].

However, the finding of our study is different from that by Tejaswi et al who in their prospective cohort study of 100 pregnant women between 20–28 weeks gestation, aged less than 35 years found no significant difference in the mean urinary calcium levels, but reported that urinary calcium creatinine ratio is a good predictor of preeclampsia [33]. The average mean arterial blood pressure at entry into the study also did not differ significantly between those that subsequently developed preeclampsia and remained normotensive. This may have influenced the ability of the study to detect any difference in urinary calcium excretion.

Prajapati in a prospective study also found that urinary calcium excretion was not significantly different between groups of normotensives, preeclamptic and pregnancy- induced hypertensive patients [35]. This study involved a relatively large sample size of with calcium estimation done using spot urine samples. However, unlike our study, participants were recruited between 20-30 weeks gestation but only 16 women out of the total sample population of 456 women developed preeclampsia [35]. Hence, this may also have affected the ability of the study to detect a difference.

Further analysis revealed that there was a statistically significant difference between urinary calcium levels in normotensive participants and participants with mild as well as preeclampsia with severe features. However, no significant difference existed between the urinary calcium levels in

participants with mild preeclampsia and those with preeclampsia and severe features. The clinical implication of this finding is that urinary calcium excretion may be a reliable tool for determining the occurrence of preeclampsia but not the severity. This finding mirrors the study of Anandpara et al, who also did not show any significant difference in urinary calcium excretion between participants with mild preeclampsia and those with severe features [35].

Our study finding of no significant association between the severity of preeclampsia and urinary calcium level may be due to the fact that preeclampsia is a continuous spectrum of progressive multisystemic disease with the possibility of having a severe disease e.g. end-organ dysfunction even in the presence of perceived mild features like mild hypertension or absence of proteinuria [1]. Another possible reason for this finding is that the criteria for the determination of the severity of preeclampsia as defined by various clinical practice guidelines (CPGs) is froth with a lot of inconsistencies [1]. Some CPGs; for instance, define severe preeclampsia as the occurrence of the disease at less than 34 weeks' gestation, hence a severe disease in a particular CPG may be considered a mild disease in another CPG [33].

This observed association of low urinary calcium levels in preeclamptic women may mean that urinary calcium level may play a role in the identification, but, not in the categorization of preeclampsia and it may also not be a marker of severity of preeclampsia. However, whether the hypocalciuria is a cause or a consequence of preeclampsia still remains to be clarified.

However, there is need for further robust studies involving larger population of preeclamptic women to investigate any association between pre-eclampsia, and calcium excretion in the urine.

The strength is attributed to its relatively large sample size in a homogenous population of pregnant women which is sufficient to detect effect and increase the reliability of the obtained results. However, we are limited by the fact that the study is a one centre cross-sectional study which may not be able to show cause effect relationship between low urinary calcium and preeclampsia in the entire Sub-Saharan Africa.

Conclusions

This study revealed a significantly lower level of urinary calcium among preeclamptic participants in comparison with their healthy normotensive counterparts. However, there was no significant difference in the urinary calcium level in participants with mild and severe preeclampsia. The finding of low levels of urinary calcium in preeclamptic participants suggests that urinary calcium excretion may have a role in the aetiopathogenesis of preeclampsia. Considering the cost effectiveness and wide availability of tools for urinary calcium estimation, it holds a promising future for early diagnosis of preeclampsia.

Author Contributions: Conceptualization, M. C. C., O. N., K. S. O., S. I. O., F. D., E. O.; methodology, M. C. C., O. N., K. S. O., S. I. O., F. D., E. O.; validation, M. C. C., O. N., U. A. O., S. I. O., F. D., E. O.; formal analysis, M. C. C., O. N., U. A. O.; investigation, M. C. C., O. N., U. A. O., S. I. O., F. D., E. O.; data curation, M. C. C., O. N., U. A. O.; writing – original draft preparation, U. A. O., O. N., M. C. C., K. S. O., S. I. O., F. D., E. O.; writing – review and editing, U. A. O., O. N., M. C. C., K. S. O., S. I. O., F. D., E. O.; visualization, U. A. O., O. N., M. C. C., K. S. O., S. I. O., F. D., E. O.; supervision, M. C. C., K. S. O., S. I. O., F. D.; project administration, O. N., U. A. O.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: Sincere appreciation to all our medical house officers, health information department and nurses who helped immensely during patient recruitment data collection. You are highly appreciated.

Funding: None.

Data and materials availability: This will be provided anytime upon request from the 1st and corresponding author of this manuscript.

Disclaimer: We sincerely confirm and affirm that no Artificial Intelligence technologies were used in any form at any stage during the preparation of this manuscript.

References

1. Abdul AE, Oloyede T, Yusuf S, Gambo A. Comparative study of serum calcium in pre-eclamptic and normotensive pregnant women at Federal Teaching Hospital Katsina. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology.* 2023; 12(9): 2595–2599.https://doi.org/10.18203/2320-1770.ijrcog20232710.
2. Chukwunyere C, Awonuga D, Olunuga T, Udenze I. Comparison of serum calcium level in hypertensive and normotensive pregnant women. *Nigerian Journal of Medicine.* 2020; 29(4): 555.https://doi.org/10.4103/NJM.NJM_32_20.
3. Gasnier R, Valério EG, Vettorazzi J, Barros EG. et al. Calciuria and preeclampsia: A case–control study. *J ObstetGynaecol Res* 2012; 38: 674–680. https://doi.org/10.1111/j.1447-0756.2011.01774.x.
4. Oluwole AA, Fasesin TT, Okunowo A, Olorunfemi G, Okunade KS. Urinary Nephrin Levels Among Pregnant Women With Preeclampsia in Lagos, Southwest Nigeria: An Analytical Cross-Sectional Study. *Cureus*. 2023; 27: 15(11): e49472. https://doi.org/10.7759/cureus.49472.
5. Mansur JL, Oliveri B, Giacoia E, Fusaro D, Costanzo PR. Vitamin D: Before, during and after Pregnancy: Effect on Neonates and Children. *Nutrients.* 2022; 14(9): 1900. 2022; (1): 9–11. https://doi.org/10.3390/nu14091900.
6. Dwarkanath P, Muhihi A, Sudfeld CR, Wylie BJ, Wang M, Perumal N, Thomas T, Kinyogoli, SM, Bakari M, Fernandez R, Raj JM, Swai NO, Buggi N, Shobha R, Sando MM, Duggan CP, Masanja HM, Kurpad AV, Pembe AB, & Fawzi WW. Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy. *The New England journal of medicin*e. 2024; 390(2): 143–153. https://doi.org/10.1056/NEJMoa2307212.

7. Jikamo B, Adefris M, Azale T, Alemu K. Cultural adaptation and validation of the Sidamic version of the World Health Organization Quality-of-Life-Bref Scale measuring the quality of life of women with severe preeclampsia in southern Ethiopia. *Health and quality of life outcomes,* 2021; 19(1): 239. https://doi.org/10.1186/s12955-021-01872-z.
8. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstetrics and gynecology.* 2020; 135(6): e237–e260. https://doi.org/10.1097/AOG.0000000000003891.
9. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, Challenges, and Perspectives. *Circulation research.* 2019; 124(7): 1094–1112. https://doi.org/10.1161/CIRCRESAHA.118.313276.
10. Atluri N, Beyuo TK, Oppong SA, Moyer CA, Lawrence ER. Challenges to diagnosing and managing preeclampsia in a low-resource setting: A qualitative study of obstetric provider perspectives from Ghana. *PLOS global public health*. 2023; 3(5): e0001790. https://doi.org/10.1371/journal.pgph.0001790.
11. Ma'ayeh M, Costantine MM. Prevention of preeclampsia. *Seminars in fetal & neonatal medicine.* 2020; 25(5): 101123. https://doi.org/10.1016/j.siny. 2020.101-123.
12. Kokori E, Aderinto N, Olatunji G, Komolafe R, Babalola EA, Isarinade DT, Moradeyo A, Muili AO, Yusuf IA, Omoworare OT. Prevalence and materno-fetal outcomes of preeclampsia/eclampsia among pregnant women in Nigeria: a systematic review and meta-analysis. *Eur J Med Res.* 2024; 29(1): 482. https://doi.org/10.1186/s40001-024-02086-x.
13. Tesfa E, Munshea A, Nibret E, Gizaw ST. Association of maternal serum magnesium with pre-eclampsia in African pregnant women: a systematic review and meta-analysis. Int Health. 2024; 16(1): 14–22. https://doi.org/10.1093/inthealth/ihad026.
14. Roberts JM. Preeclampsia epidemiology(ies) and pathophysiology(ies). Best practice & research. *Clinical obstetrics & gynaecology.* 2024; 94: 102480. https://doi.org/10.1016/j.bpobgyn.2024.102480.
15. Ugwu AO, Owie E, Oluwole AA, Soibi-Harry AP, Garba SR, Okunade KS, Makwe CC, Omisakin SI, Ani-Ugwu NK , Ojiefoh LG, Okafor IT, Egba A , Olatunji RA, Yusuf-Awesu SA. Maternal and Perinatal Outcomes of Preeclampsia at a Tertiary Hospital in Lagos, Nigeria. *International Journal of Medicine and Health Development.* 2020; 27(2): 197–200. https://doi.org/10.4103/ijmh.IJMH_46_2.
16. Ugwu AO, Oluwole AA, Okunade KS. The predictive significance of serum cystatin C and free subunit of β-Human chorionic gonadotropin in pregnant women with preeclampsia in Lagos. *HJOG*. 2022; 21 (1): 35–46. https://doi.org/10.33574/hjog.0404.
17. Ugwuja EI, Famurewa AC, Ikaraoha CI. Comparison of Serum Calcium and Magnesium Between Preeclamptic and Normotensive Pregnant Nigerian Women in Abakaliki, Nigeria. *Ann Med Health Sci Res.* 2016; 6(1): 33–37. https://doi.org/10.4103/2141-9248.180269.
18. Eslamzadeh A, Kashani SMA, Asadi N, et al. Serum Calcium and Magnesium Levels in Women Presenting with Pre-eclampsia: A Systematic Review and Meta-analysis Based on Observational Studies. *Galen Med J.* 2023; 12: 1–19. https://doi.org/10.31661/gmj.v12i.3151.
19. Samaha II, Donayeva A, Abdelazim IA. The relation between serum uric acid and severity of preeclampsia in pregnant women: a cross-sectional study. *PrzMenopauzalny.* 2023; 22(3): 130–134. https://doi.org/10.5114/pm.2023.131328.
20. Sabitha BT, Rudrappa G, Javarappa D. Study of serum and urinary calcium levels in pregnancy induced hypertension cases in and around Chitradurga. *Global Journal of Medicine Research.* 2014; 14(4): 1–4. https://medicalresearchjournal.org/index.php/GJMR/article/view/855.
21. Ingec M, Nazik H, Kadanali S. Urinary calcium excretion in severe preeclampsia and eclampsia. *Clin Chem Lab Med*: 2013; 44: 51–53. https://doi.org/10.1515/cclm.2006.010.
22. Yule CS, Ambia AM, Duryea EL, McIntire DD, Nelson DB. The effect of normal saline on renal function and electrolytes in women with preeclampsia. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*. 2022; 35(21): 4110–4115. https://doi.org/10.1080/14767058.2020.1847071.
23. Tesfa E, Munshea A, Nibret E, Gizaw ST. Association of maternal serum magnesium with pre-eclampsia in African pregnant women: a systematic review and meta-analysis. *Int Health.* 2024; 16(1): 14–22. https://doi.org/10.1093/inthealth/ihad026.
24. Wadhwani N, Dangat K, Randhir K. Longitudinal Assessment of Calcium and Magnesium Levels in Women with Preeclampsia. *Biol Trace Elem Res.* 2023; 201(7): 3245–3255. https://doi.org/10.1007/s12011-022-03440-y.
25. McMaster KM, Kaunitz AM, Burbano de Lara P, Sanchez-Ramos L. A systematic review and meta-analysis of hypocalciuria in pre-eclampsia. *Int J Gynaecol Obstet.* 2017; 138(1): 3–11. https://doi.org/10.1002/ijgo.12165.
26. Jagu L, Orugbo VP, Okonta P. A cohort study on use of the spot urine calcium-creatinine ratio for prediction of antepartum preeclampsia among high-risk pregnant women in Delta State, Nigeria. *Journal of Surgery and Medicine.* 2022; 6(7): 693–699. https://doi.org/10.28982/josam.993621.
27. Lu X, Wang Y, Geng N, Zou Z, Feng X, Wang Y, Xu Z, Zhang N, Pu J. Dysregulated Mitochondrial Calcium Causes Spiral Artery Remodeling Failure in Preeclampsia. *Hypertension*. 2024; 81(11): 2368–2382. https://doi.org/10.1161/HYPERTENSIONAHA.124.23046.
28. 28. Brown MA, Magee LA, Kenny LC. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension*. 2018; 72(1): 24–43. https://doi.org/10.1161/HYPERTENSIONAHA.117.10803.
29. Liu H, Ning F, Lash GE. Contribution of vascular smooth muscle cell apoptosis to spiral artery remodeling in early human pregnancy. *Placenta*. 2022; 120: 10–17. https://doi.org/10.1016/j.placenta.2022.02.005.
30. Staff AC, Fjeldstad HE, Fosheim IK, Moe K, Turowski G, Johnsen GM, Alnaes-Katjavivi P, Sugulle M. Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. *American journal of obstetrics and gynecology.* 2022; 226(2S): S895–S906. https://doi.org/10.1016/j.ajog.2020.09.026.
31. Owusu Darkwa E, Antwi-Boasiako C, Djagbletey R, Owoo C, Obed S, Sottie D. Serum magnesium and calcium in preeclampsia: a comparative study at the Korle-Bu Teaching Hospital, Ghana. *Integr Blood Press Control.* 2017; 10: 9–15. https://doi.org/10.2147/IBPC.S129106.
32. Pal A, Roy D, Adhikary S, Roy A, Dasgupta M, Mandal AK. A prospective study for the prediction of preeclampsia with urinary calcium level. *J Obstet Gynaecol India. 2*012; 62(3): 312–316. https://doi.org/10.1007/s13224-012-0223-z.

33. Agarwal A, Diksha S, Goel JK. Study the Correlation of Urinary Calcium-Creatinine Ratio as a Predictor of Pre-Eclampsia. *JMSC*. 2022; 10(09): 38–44. https://dx.doi.org/10.18535/jmscr/v10i9.08.
34. Tejaswi MS, Kanthi Mangala J, Vinya P. Urine Calcium-Creatinine Ratio in Prediction of Pre-eclampsia. *J Obstet Gynecol India*. 2023; 73: 51–56. https://doi.org/10.1007/s13224-022-01712-0.
35. Prajapati KB, Nakum KD. Prospective study to analyze calcium creatinine ratio in a spot sample of urine for early prediction of hypertensive disorder in pregnancy. *IJMBS*. 2020; 4(3): 52–56. https://doi.org/10.32553/ijmbs.v4i3.1027.
36. Anandpara GK, Savadi BV, Rawal Y. Study of random urinary calcium/creatinine ratio as a predictor of preeclampsia in and around Chitradurga. *Int J Adv Biochem Res*. 2020; 4(1): 12–15. https://doi.org/10.33545/26174693.2020.v4.i1a.41.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15602

Depression, Anxiety and Stress Symptoms and Substance Use among Health Care Students in Turkey during the COVID-19 Pandemic

Şeyma Zehra Altunkurek[1], Esra Nur Demir[1]

[1]*Department of Public Health Nursing, Gulhane Faculty of Nursing, University of Health Sciences, Ankara, Turkey*

Received: 2024-07-30.
Accepted: 2024-11-11.

J Clin Med Kaz 2024; 21(6): 66–72

Corresponding author:
Şeyma Zehra Altunkurek.
Email: seymazehra.altunkurek@sbu.edu.tr.
ORCID: 0000-0002-1464-8313.

Abstract

Aim: People of all ages have been physically and psychologically impacted by the COVID-19 pandemic throughout the world. Due to their predisposition to high levels of stress, anxiety, and sadness in general, university students are especially susceptible to the psychological effects of COVID-19. The purpose of this study was to assess the perspectives of health care students regarding substance abuse, stress and anxiety, and depression within the COVID-19 pandemic.

Materials and methods: This cross-sectional survey includes 1126 university students. The data collecting forms were the Descriptive Info Form and the Depression, Anxiety and Stress Scale (DASS). ANOVA, post hoc tests (Tukey, LSD), and t-tests were used to analyze the individuals' scale scores and descriptive characteristics.

Results: The mean depression, anxiety and stress score was 16.280±7.942, 17.837±8.257, and 17.686±8.247, respectively. In this study, statistically significant differences were found in terms of gender, education level, income level, use of any addictive substance, use of any addictive substance by a relative, changes in substance use during the pandemic period and mean DASS subscale score ($p<0.05$).

Conclusions: Among university students studying health care, correlations between substance abuse and symptoms of stress, anxiety, and depression were found throughout the epidemic. Health experts may find it helpful to organize initiatives to lessen substance addiction in order to assist pupils in overcoming psychological issues during trying times like the COVID-19 pandemic.

Keywords: Anxiety, Addiction, COVID-19, Depression, Students, Stress

Introduction

In Wuhan, China, the first coronavirus infection case of 2019 (COVID-19) was reported in December of that year [1]. The global pandemic of COVID-19 is affecting individuals worldwide and has emerged as a significant public health concern [2]. The COVID-19 pandemic was labeled a "pandemic" by the World Health Organization (WHO) in March 2020 after it was originally categorized as a "international public health emergent situation" in January 2020 [3]. According to the World Health Organization's most recent figures, 6.64 million people have died as a result of the COVID-19 pandemic, and 646 million individuals have infected the virus [3]. In Turkey, 16.9 million individuals have been diagnosed with COVID-19, and 101 thousand individuals have died [3]. Throughout the COVID-19 outbreak, many measures have been taken and changes have been made to stop the expansion of the virus [4]. One of these was the implementation curfews, home quarantine and isolation to prevent the spread of the pandemic, which resulted in education systems being forced to use online platforms [5]. These

changes negatively affected individuals' social lives [6]. The pandemic also caused psychological problems in individuals [7]. According to a study in China, symptoms of anxiety, depression and stress increased among individuals at the onset of the pandemic [8,9]. Lin reviewed the perceptions of people regarding COVID-19 and reported that experiences of loss, grief, anxiety, fear of being sick and stigmatization during the pandemic caused psychosocial problems [10].

Although COVID-19 has affected all layers of society, university students may be the group most affected by this situation [11]. For university students forced to stay at home and fully dependent on online education, this situation has emerged as unusual and unexpected, especially for those who have no experience with e-learning or the necessary facilities [12]. In these circumstances, students faced psychological problems caused by the pandemic as well as uncertainties related to their education [6]. The stress and subjective well-being levels of university students increased and decreased, respectively, throughout the outbreak [13]. Kimhi et al. stated that an increase in feelings of stress and fear among college students in Israel led to a reduce in their stages of hope and morale [14]. University students also showed notable increases in unhealthy habits during the pandemic [16, 17], including smoking, drinking alcohol, using drugs, and not exercising [15]. In their study of university students, Sander et al. observed that the severity of mental issues and alcohol and drug usage were enhanced during the pandemic [18]. In a research among French university students, Bourion-Bédès et al. reported a rise in cigarette usage during the pandemic [16]. According to a survey by Gritsenko et al. of university students in Belarus and Russia, during the COVID-19 epidemic, there was a surge in the use of cigarettes and alcohol by students [19]. In a study involving Chinese university students, Ahmed et al. found that the pandemic period raised students' alcohol consumption to a dangerous level [20].

According to the literature, children were more prone to experience stress, anxiety, smoking, and drug use throughout the COVID-19 period. In addition, studies carried out in a number of countries have examined the stress, anxiety, and depression levels of college students as well as their perspectives on drug addiction throughout the pandemic. Turkey hasn't, however, produced many studies. The current study looked at students' opinions about substance usage, stress and anxiety symptoms, and depression levels at a health sciences university in light of the COVID-19 epidemic.

Materials and methods

The University of Health Sciences conducted this cross-sectional survey in April and May of 2021. The Gülhane University of Health Sciences Scientific Research Ethics Committee has approved this study (No. 2021/162). Regarding the subject matter of this essay, the writers have no relevant conflicts of interest to declare. Each author takes ownership of the article. 21000 University of Health Sciences students—14915 undergraduates and 6185 associate degree holders—made up the study population. The required sample size for this non-homogeneous population was estimated using the sampling formula to be n = 1016 with a 95% confidence interval and ± 3% sampling error. A total of 1126 individuals were contacted for this investigation. Google Forms was used in the creation of the dataset. It was collected using a random sampling method via WhatsApp. The participants were informed of the goal of the study at the outset of the data collecting form, and their consent was obtained. Participants received notification that no personal information will be shared with third parties and that their responses would never be utilized in conjunction with their identities. The Depression, Anxiety, and Stress Scale and sociodemographic characteristics comprise the two sections of the survey.

The sociodemographic characteristics questionnaire consisted of 12 questions to determine the sociodemographic characteristics and addictive substance (cigarettes, alcohol, etc.) use of the participants participating in this study.

- **Depression, Anxiety and Stress Scale:** To measure the levels of stress, anxiety, and depression, the 42-item DASS was used. The scale is divided into three smaller scales, with 14 items on each scale that are rated from 0 to 3, with 0 denoting nothing at all and 3 denoting a lot or the majority of the time. Every subscale has a possible score between 0 and 42. Depression scores vary from 0 to 9, with mild depression being represented by 10 to 13, moderate depression by 14 to 20, severe depression by 21 to 27, and extremely severe depression by 28 points or higher. The range of scores is as follows: 0–7 denotes a normal state; 8–9, mild anxiety; 10–14, moderate anxiety; 15–19, severe anxiety; and 20 and higher, extremely severe anxiety. The stress rating system is as follows: Normal stress is indicated by a score of 0–14, mild stress by 15–18, moderate stress by 19–25, severe stress by 26–33, and extremely severe stress by 34 and higher. In the initial investigation, the scale's subdimensions of tension, anxiety, and sadness had Cronbach's alphas of 0.90, 0.91, and 0.84. The validity and reliability of the scale were assessed for the Turkish population by Akin and Çetin [21]. The depression subdimension had internal consistency coefficients (Cronbach's alpha) of 0.92, the anxiety subdimension of 0.86, and the stress subdimension of 0.88, according to the authors' findings. In our study, the Cronbach's alpha values for the stress, anxiety, and depression aspects were 0.93, 0.92, and 0.93, respectively.

Statistical analysis

A statistical application called SPSS 21 was used to analyze the data. The descriptive traits of the subjects and the scale scores were examined using T tests, one-way analysis of variance (ANOVA), and post hoc (Tukey, LSD) analyses.

Results

This study included 1126 participants: 46.6% were male, 53.4% were female, 44.4% were nursing students, and 49.3% had a middle-income level. The sample's characteristics are displayed in Table 1. The participants' average age was 21.23 years (SD = 4.16). According to the DASS 42, the average scores for depression, anxiety, and stress were as follows: moderate (16.28±7.94) for depression, severe (17.83±8.25) for anxiety, and medium (17.68±8.24) for stress.

When the mean scores of the depression, anxiety and stress levels of the participants were evaluated according to the scores obtained for each subscale of the DASS, the frequency of moderate depression was 37.7%, there were 44.8% cases of really severe anxiety and 27.5% cases of moderate stress (Table 3).

In the present study, the mean anxiety score of women (17.35±8.60) was significantly lower than that of men (18.38±7.80) ($p<0.05$). When the depression, anxiety and stress subscale scores were compared according to who the participants lived with, the scores for those living alone were 18.88±6.95, 20.57±6.74, and 20.41±6.79, respectively, and were greater than those for those living with family and friends ($p<0.05$).

When students' depression (19.37±6.28), anxiety (21.71±6.65) and stress (20.43±7.03) scores were analyzed

Table 1 Distribution of participants by characteristics (n=1126)

Characteristics		N %
Sex	Female	601%53.4
	Male	525%46.6
Number of siblings	1	219%19.4
	2	694%61.6
	3	213%18.9
Living situation	Family	389%34.5
	Friends	644%57.2
	Alone	93%8.3
Faculty	Nursing	500%44.4
	Vocational School of Health	202%17.9
	Pharmacy	101%9.0
	Dental	203%18.0
	Medicine	120%10.7
Family situation	Parents together	1035%91.9
	Separated parents	91%8.1
Income Level	Low	162%14.4
	Middle	555%49.3
	High	409%36.3
Do you use any addictive substances (tobacco, alcohol or drugs)?	Yes	383%34.0
	No	743%66.0
Do you know anyone in your life who uses addictive substances (tobacco, alcohol, or drugs)?	Yes	570%50.6
	No	556%49.4
When did you start using any addictive substance (tobacco, alcohol or drugs)?	1 year ago	50%13.1
	2 years ago	115%30.0
	3 years ago or more	120%31.3
	Pandemic Period	98%25.6
Has there been any change in your addictive substance use during the pandemic (tobacco, alcohol or any other substance)?	Do not use	740%65.7
	No change	123%10.9
	Increased	263%23.4
How would you describe your mood during the pandemic?	Concerned	204%18.1
	Unhappy	204%18.1
	Scared	101%9.0
	Happy	79%7.0
	Bored	538%47.8

Table 2 DASS subscale scores of participants

	Mean (SD)
DASS Depression score	16.28±7.94
DASS Anxiety score	17.83±8.25
DASS Stress score	17.68±8.24

Table 3 Severity of the participants' depression, anxiety and stress (N=1126)

Severity	Depression	Anxiety	Stress
	N %	N %	N %
Normal	226% 20.1	131%11.6	422%37.5
Mild	178%15.8	58% 5.2	205%18.2
Moderate	424%37.7	203%18.0	310%27.5
Severe	207%18.4	230%20.4	153%13.6
Extremely severe	91%8.1	504%44.8	36%3.2

according to the faculty they studied at, the scores of medical faculty students were higher than those of the remaining pupils, and a statistically significant distinction was discovered between them. ($p<0.05$). The depression rating of middle-income participants was 16.90±8.09, the anxiety score was 18.66±8.24, and the stress score was 18.445±8.238, which were higher than those of participants with low and high incomes ($p<0.05$). Those who felt fear during the pandemic had a depression score of 18.32±7.46, an anxiety score of 19.87±7.63, and a stress score of 19.72±7.77. The scores of the participants who experienced fear during the pandemic were significantly greater than those of the participants who were anxious, unhappy, happy or bored ($p<0.05$) (Table 4).

In the present study, the mean depression score of the participants who used addictive substances (17.16±7.70) was greater than that of the participants who did not use addictive substances (15.82±8.03) ($p=0.007$). The individuals who used addictive substances had an average anxiety level (18.85±8.01) of greater than that of the participants without addictive substance use (17.31±8.33) ($p=0.003$). The individuals who used addictive substances had an average stress level (18.5±8.24) of greater than that of the participants without addictive substance use (17.26±8.22) ($p=0.017$). The mean depression score (16.85±8.34) of the participants with relatives who used addictive substances was greater than that (15.69±7.46) of the participants without relatives with addictive substance use ($p=0.014$). Participants who knew someone who used addictive drugs had a mean anxiety score of 18.32±8.31, which was higher than the mean anxiety score of 17.33±8.17 for those who did not know anybody who used addictive substances ($p=0.045$).

Those who experienced elevated stress during the pandemic time had mean depression ratings of 16.67±7.95, which was higher than those who did not experience elevated stress during the pandemic period (14.25±7.56) ($p=0.001$). Participants who experienced elevated stress during the pandemic (18.26±8.18) had mean anxiety scores that were higher than those of participants who did not experience elevated stress during the pandemic (15.62±8.27) ($p=0.001$). Furthermore, the participants who reported higher levels of stress had a DASS stress subscale score of 18.08±8.27, which was higher than the participants who reported lower levels of stress ($p=0.001$). During the pandemic period, 25.6% of participants started using addictive substances. The DASS depression subscale score of participants whose use of addictive substances did not change during the pandemic was 17.94±7.38, the anxiety subscale score was 19.65±8.27, and the stress score was 19.260±8.348. These scores were significantly greater than the scores of participants who did not use addictive substances during the pandemic and those whose use increased ($p<0.05$) (Table 5).

Discussion

Using online surveys, this study looked at how stress, anxiety, and depression symptoms changed during the COVID-19 pandemic in 2021, as well as college students' use of addictive substances. The findings indicated a correlation between an increase in the severity of anxiety and depressed symptoms and a rise in the use of addictive substances. Over half of the university students who responded to this study said they felt more anxious, frightened, bored, and nervous throughout the pandemic. The students' mean DASS subscale scores revealed that their levels of stress, anxiety, and depression were respectively moderate, severe, and mild. A study among Jordanian health care students, in contrast to ours, found modest levels of anxiety [22]. In contrast to these investigations, depression, anxiety, and stress levels were shown to be normal in another study involving other

Table 4 Comparison of participant characteristics and DASS scores

Characteristic	N %	Depression	Anxiety	Stress
Sex		Mean±SD	Mean±SD	Mean±SD
Female	601%53.4	16.08±8.26	17.35±8.60	17.72±8.50
Male	525%46.6	16.51±7.57	18.39±7.80	17.64±7.97
t=		-0,911	-2,100	0,181
p=		0.360	0.035	0.857
Living situation				
Family	389%34.5	15.50±8.09	16.83±8.40	16.77±8.26
Friends	644%57.2	16.38±7.91	18.04±8.27	17.84±8.34
Alone	93%8.3	18.88±6.95	20.57±6.74	20.41±6.79
F=		7.021	8.287	7.677
p=		0.001	0.001	0.001
Post Hoc=		3>1, 3>2 (p<0.05)	2>1, 3>1, 3>2 (p<0.05)	2>1, 3>1, 3>2 (p<0.05)
Faculty				
Nursing	500%44.4	15.94±9.60	16.18±9.50	17.61±9.51
Vocational School of Health	202%17.9	16.72±6.29	19.42±6.86	17.93±7.19
Pharmacy	101%9	16.52±5.93	19.89±6.37	18.28±6.84
Dental	203%18	14.72±5.94	17.00±6.52	15.70±6.53
Medicine	120%10.7	19.37±6.28	21.71±6.65	20.43±7.03
F=		7.044	16.423	6.593
p=		0.001	0.001	0.001
Post Hoc=		5>1, 5>2, 5>3, 2>4, 5>4 (p<0.05)	2>1, 3>1, 5>1, 5>2, 2>4, 3>4, 5>4 (p<0.05)	5>1, 5>2, 1>4, 2>4, 3>4, 5>4 (p<0.05)
Income Level				
Low	162%14.4	16.51±8.40	17.58±8.59	17.97±8.51
Middle	555%49.3	16.90±8.09	18.66±8.24	18.445±8.238
High	409%36.3	15.33±7.45	16.81±8.02	16.540±8.041
F=		4.706	6.060	6.459
p=		0.009	0.002	0.002
Post Hoc=		2>3 (p<0.05)	2>3 (p<0.05)	2>3 (p<0.05)
How would you describe your mood during the pandemic?				
Concerned	204% 18.1	16.50±8.27	18.04±8.67	18.08±8.78
Unhappy	204% 18.1	17.16±8.00	17.91±8.03	17.97±8.42
Scared	101% 9	18.32±7.46	19.87±7.63	19.72±7.77
Happy	79% 7	15.19±8.20	17.64±8.51	17.05±8.25
Bored	538% 47.8	15.63±7.75	17.37±8.22	17.13±8.00
F=		3.638	2.007	2.457
p=		0.006	0.091	0.044
Post Hoc=		3>4, 2>5, 3>5 (p<0.05)		3>4, 3>5 (p<0.05)

F: ANOVA; t: Independent samples t test; Post Hoc: Tukey, LSD

Table 5 Comparison of participants' attitudes toward substance abuse and mean DAS scores

Characteristics	N %	Depression	Anxiety	Stress
		Mean±SD	Mean±SD	Mean±SD
Do you use any addictive substances (tobacco, alcohol or drugs)?				
Yes	383%34	17.16±7.70	18.85±8.01	18.50±8.24
No	743%66	15.82±8.03	17.311±8.33	17.26±8.22
t=		2.699	2.986	2.388
p=		0.007	0.003	0,017
Do you know anyone in your life who uses addictive substances (tobacco, alcohol, or drugs)?				
Yes	570%50.6	16.85±8.34	18.32±8.31	18.03±8.48
No	556%49.4	15.69±7.46	17.33±8.17	17.32±7.99
t=		2.449	2.003	1.433
p=		0.014	0.045	0.152
Increased stress during the pandemic				
Yes	942%83.7	16.67±7.95	18.26±8.18	18.08±8.27
No	184%16.3	14.25±7.56	15.62±8.27	15.64±7.80
t=		3.80	3.99	3.69
p=		0.001	0.001	0.001
When did you start using any addictive substances (tobacco, alcohol or any other substance)?				
1 years ago	50%13.1	18.10±7.09	20.12±7.55	19.68±7.92
2 years ago	115%30	16.04±7.10	18.73±7.24	17.87±7.34
3 Years and More	120%31.3	17.70±8.35	18.81±8.46	19.06±8.76
Pandemic Period	98%25.6	17.34±7.80	18.39±8.57	17.93±8.72
F=		1.279	0.528	0.900
p=		0.281	0.663	0.441
Has there been any change in your addictive substance use during the pandemic period (tobacco, alcohol or any other substance)?				
Not used	740%65.7	15.83±8.04	17.32±8.33	17.249±8.230
No change	123%10.9	17.94±7.38	19.65±8.27	19.260±8.348
Increased	263%23.4	16.76±7.80	18.44±7.87	18.179±8.161
F=		4.379	5.157	3.769
p=		0.013	0.006	0.023
Post Hoc=		2>1 (p<0.05)	2>1 (p<0.05)	2>1 (p<0.05)

F: ANOVA Test; t: Independent samples t test; Post Hoc: Tukey, LSD

university students [23]. Rehman et al. found that students had modest stress levels and moderate levels of anxiety and sadness in their study done during the pandemic [24]. These findings imply that health care students experience high levels of anxiety and despair due to their familiarity with severe suffering and their awareness of the pandemic's effects and scope.

Anxiety levels varied significantly when the mean DASS subscale score was broken down by sex in this study. Consequently, the mean anxiety score of male students was higher than that of female students. In contrast to our results, girls fared better than males on stress, anxiety, and depression measures in a research among Turkish university students who were not pursuing medical degrees during the COVID-19 epidemic [25]. Talapko et al. found that female sex was linked to higher DASS subscale scores in their research of health care students [26]. In line with the results of these investigations, a research carried out in Helsinki during the COVID-19 epidemic showed that female pupils outperformed their male counterparts on the DASS subscale [27]. The findings show that when faced with tough situations like pandemics, female pupils are more prone to have a fragile mental health state. Studies have shown that female students were more likely to be depressed and anxious [28, 29].

When the students' mean scores in our study were categorized by the faculty they were enrolled in, a substantial difference was discovered. As a result, students in the medical faculty had significantly higher mean scores for depression, stress, and anxiety when compared to students in other faculties. An Egyptian study [30] found that anxiety and despair are common among medical students. In Brazil, moderate-to-severe symptoms of sorrow and anxiety were reported by 46.17% of medical students [31]. According to study, university education departments' students tend to be less depressed, anxious, and stressed than their medical department counterparts [32]. These results demonstrated that both medical and non-medical students' mental health might benefit from attentive coping techniques.

The living situation of the students were shown to be significantly correlated with their mean DASS score. Accordingly, the mean depression score of the students who lived alone was greater than that of the students who lived with their families, while the mean anxiety and stress scores were greater for the students living with friends than for the students living with their families. Similar to our study, Aylie et al.'s investigation among Ethiopian university students during the pandemic found that those who did not reside with their family experienced significant levels of anxiety and anxiety severity [33].

In many studies conducted among university students, living with friends, living in dormitories and not living with family increased individuals' depression, anxiety and stress levels [26,34,35]. Those who stayed with their relatives reported being less anxious. Being away from home and the pandemic's negative consequences on students' lives were risk factors for mental health conditions such sadness, stress, and anxiety. These findings imply that stress, anxiety, and depression were negatively impacted by social isolation during the epidemic.

The study revealed a noteworthy association between the average DASS subscale score and the students' economic income level. Consequently, it was discovered that people with medium earnings scored higher on sadness, stress, and anxiety than people with high incomes. Depression among students during the COVID-19 epidemic was shown to be more common in individuals with lower means, according to Sander et al. A person's and their family's income declining is one of the causes contributing to an increase in anxiety and stress levels. At this stage, school administrators and institutions should identify students in need of economic support and inform them of and promote the necessary scholarships and funding sources.

In addition, during the pandemic period, students felt anxious, bored and scared, with increased stress levels. The COVID-19 pandemic, which affected the entire world, left students feeling nervous, depressed, anxious, tired, gloomy, stressed, and unhappy with life [36]. A different study found that students who had anxiety or depression during the COVID-19 pandemic also experienced tension, fear, or nervousness [8,9]. In the Bashir et al. research, about half of the health sciences students experienced depression during the pandemic [37]. The impact of this time period on people's mental health endures even when the epidemic and its limitations have been gone. Multidisciplinary research is essential for offering families and students training, adaptive strategies, and psychological support.

According to our research, most people did not see any appreciable changes in their use of alcohol, cigarettes, or other substances throughout the pandemic. Of those surveyed, 25% indicated they started using alcohol, cigarettes, or other drugs during the pandemic, and 23.4% reported their use of these drugs increased during the outbreak. There has been a rise in the use of drugs and alcohol by participants in another study among Turkish university students [38]. In Poland, the majority of university students surveyed claimed that the epidemic had had no discernible impact on their use of hard drugs, alcohol, nicotine, marijuana, THC, or other substances. A nearly similar proportion of students reported rising and falling alcohol and cigarette intake. A much larger number of respondents reported decreases rather than increases in the use of marijuana, THC, or hard drugs [39]. Many studies conducted during the COVID-19 pandemic found a correlation between an increase in alcohol consumption and an increase in alcohol usage overall [40]. These results might indicate that university students who were isolated from the outside world during the pandemic and had to stay at home due to quarantine used more alcohol, cigarettes, and other drugs as a coping mechanism for their lack of sociability. During our analysis, we found a strong relationship between the average scores on the DASS subscales and the use of any kind of drug (such as alcohol, cigarettes, etc.). Thus, students who used any form of addictive substance displayed higher levels of stress, anxiety, and despair in comparison to students who did not use any addictive substances. According to Dogan-Sander et al.'s study, depression and alcohol usage rose among college students during the pandemic [18]. These findings imply that students lack appropriate coping mechanisms and suffer from depression, anxiety, and stress during significant emergencies like epidemics. There are various restrictions on this study. First, it was not possible to ask questions about addictive behavior and depressive symptoms separately. The study's religious views and ideals were taken into consideration while asking about addictive drugs like alcohol, cigarettes, and others in a single question. Second, as only self-report measures were used, generalizability may be restricted because the results are restricted to a single Turkish health care university.

Conclusion

It was found that the study participants had moderate sadness and severe anxiety. During the epidemic, those with high scores for stress, anxiety, and sadness also used addictive substances. Medical faculty students exhibited higher levels of stress, anxiety, and depression than other students studying in health-related areas. Furthermore, it was shown that 25% of the participants began using drugs or alcohol during the epidemic. These findings suggest that health professionals

working in the fields of psychiatry and public health should undertake interdisciplinary research, trainings, and workshops to help students develop personal coping strategies and support networks in the event of various unforeseen circumstances, like pandemics, and to stop mental health issues like anxiety, stress, and depression from persisting after these events have passed.

Author Contributions: Conceptualization, E. N. D., Ş. Z. A.; methodology, E. N. D., Ş. Z. A.; validation, E. N. D., Ş. Z. A.; formal analysis, E. N. D., Ş. Z. A.; investigation, E. N. D., Ş. Z. A.; literature search: E. N. D.; data curation, E. N. D., Ş. Z. A.; writing – original draft preparation, E. N. D., Ş. Z. A.; writing – review and editing, E. N. D., Ş. Z. A.; visualization, E. N. D., Ş. Z. A.; supervision, not applocable; project administration, not applicable; funding acquisition, not applocable. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: We would like to thank all students for their contribution to the research.

Funding: None.

Data availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: The study was approved by the Gülhane University of Health Sciences Scientific Research Ethics Committee (No. 2021/162).

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020; 382(8): 727–733. https://doi.org/10.1056/NEJMoa2001017.
2. Bhattarai A, Karki B. COVID-19 pandemic and mental health issues. *J Lumbini Med Coll.* 2020; 8(1): 181–182.
3. World Health Organization. Conflict in Israel and the Occupied Palestinian Territory. Geneva, Switzerland: World Health Organization; 2022.
4. Rogowska AM, Pavlova I, Kuśnierz C, Ochnik D, Bodnar I, Petrytsa P. Does physical activity matter for the mental health of university students during the COVID-19 pandemic? *J Clin Med.* 2020; 9(11): 3494. https://doi.org/10.3390/jcm9113494.
5. Xiong, J, Lipsitz O, Nasri F, Lui L, Gill H, Phan L, Chen-Li D, Iacobucci M, Ho R, Majeed A, McIntyre R. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *Journal of Affective Disorders.* 2020; 277: 55–64. https://doi.org/10.1016/j.jad.2020.08.001
6. Sahu P. Closure of universities due to coronavirus disease 2019 (COVID-19): impact on education and mental health of students and academic staff. *Cureus*. 2020; 12(4): e7541. https://doi.org/10.7759/cureus.7541.
7. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther.* 2020; 14(1): 58–60. https://doi.org/10.5582/ddt.2020.01012.
8. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int J Environ Res Public Health.* 2020; 17(5): 1729. https://doi.org/10.3390/ijerph17051729.
9. Wang X, Hegde S, Son C, Keller B, Smith A, Sasangohar F. Investigating mental health of US college students during the COVID-19 pandemic: cross-sectional survey study. *J Med Internet Res.* 2020; 22(9): e22817. https://doi.org/10.2196/22817.
10. Lin CY. Social reaction toward the 2019 novel coronavirus (COVID-19). *Soc Health Behav.* 2020; 3(1): 1–2. https://doi.org/10.4103/SHB.SHB_11_20.
11. Asici E, Günlü A. Üniversite öğrencilerinin gözünden COVID-19 salgini: Nitel bir araştirma. *Gençlik Araştirmalari Dergisi.* 2021; 9(Özel Sayi): 1–25. https://doi.org/10.52528/genclikarastirmalari.770078
12. Hamaideh SH, Al-Modallal H, Tanash MA, Hamdan-Mansour A. Depression, anxiety and stress among undergraduate students during COVID-19 outbreak and "home-quarantine". *Nursing Open.* 2022; 9(2): 1423–1431. https://doi.org/10.1002/nop2.918
13. Recchi E, Ferragina E, Helmeid E, Pauly S, Safi M, Sauger N, Schradie J. The "eye of the hurricane" paradox: an unexpected and unequal rise of well-being during the COVID-19 lockdown in France. *Res Soc Stratif Mobil.* 2020; 68: 100508. https://doi.org/10.1016/j.rssm.2020.100508.
14. Kimhi S, Eshel Y, Marciano H, Adini B. A renewed outbreak of the COVID-19 pandemic: a longitudinal study of distress, resilience, and subjective well-being. *Int J Environ Res Public Health.* 2020; 17(21): 7743. https://doi.org/10.3390/ijerph17217743,
15. Mack DL, DaSilva AW, Rogers C, Hedlund E, Murphy EI, Vojdanovski V, Plomp J, Wang W, Nepal SK, Holtzheimer PE, Wagner DD, Jacobson NC, Meyer ML, Campbell AT, Huckins JF. Mental health and behavior of college students during the COVID-19 pandemic: longitudinal mobile smartphone and ecological momentary assessment study, part II. *J Med Internet Res.* 2021; 23(6): e28892. https://doi.org/10.2196/28892.
16. Bourion-Bédès S, Tarquinio C, Batt M, Tarquinio P, Lebreuilly R, Sorsana C, Legrand K, Rousseau H, Baumann C. Psychological impact of the COVID-19 outbreak on students in a French region severely affected by the disease: results of the PIMS-CoV 19 study. *Psychiatry Res.* 2021; 295: 113559. https://doi.org/10.1016/j.psychres.2020.113559.
17. Bourion-Bédès S, Tarquinio C, Batt M, Tarquinio P, Lebreuilly R, Sorsana C, Legrand K, Rousseau H, Baumann C. Stress and associated factors among French university students under the COVID-19 lockdown: the results of the PIMS-CoV 19 study. *J Affect Disord.* 2021; 283: 108–114. https://doi.org/10.1016/j.jad.2021.01.041.
18. Dogan-Sander E, Kohls E, Baldofski S, Rummel-Kluge C. More depressive symptoms, alcohol and drug consumption: increase in mental health symptoms among university students after one year of the COVID-19 pandemic. *Frontiers in Psychiatry.* 2021; 12: 790974. https://doi.org/10.3389/fpsyt.2021.790974.
19. Gritsenko V, Skugarevsky O, Konstantinov V, Khamenka N, Marinova T, Reznik A, Isralowitz R. COVID 19 fear, stress, anxiety, and substance use among Russian and Belarusian university students. *International journal of mental health and addiction.* 2021; 19:

2362–2368. https://doi.org/10.1007/s11469-020-00330-z.
20. Ahmed MZ, Ahmed O, Aibao Z, Hanbin S, Siyu L, Ahmad A. Epidemic of COVID-19 in China and associated psychological problems. *Asian Journal of Psychiatry.* 2020; 51: 102092. https://doi.org/10.1016/j.ajp.2020.102092.
21. Akin A, Çetin B. The depression anxiety and stress scale (DASS): the study of validity and reliability. *Educ Sci Theory Pract.* 2007; 7(1): 260–268.
22. Almhdawi KA, Alazrai A, Obeidat D, Altarifi AA, Oteir AO, Aljammal AH, Arabiat AA, Alrabbaie H, Jaber H, Almousa KM. Healthcare students' mental and physical well-being during the COVID-19 lockdown and distance learning. *Work*. 2021; 70(1): 3–10. https://doi.org/10.3233/WOR-205309.
23. Cam HH, Ustuner Top F, Kuzlu Ayyildiz T. Impact of the COVID-19 pandemic on mental health and health-related quality of life among university students in Turkey. *Current Psychology.* 2022; 41(2): 1033–1042. https://doi.org/10.1007/s12144-021-01674-y
24. Rehman U, Shahnawaz MG, Khan NH, Kharshiing KD, Khursheed M, Gupta K, Kashyap D, Uniyal R. Depression, anxiety and stress among Indians in times of COVID-19 lockdown. *Community Ment Health J.* 2021; 57(1): 42–48. https://doi.org/10.1007/s10597-020-00664-x.
25. Cam HH, Ustuner Top F, Kuzlu Ayyildiz T. Impact of the COVID-19 pandemic on mental health and health-related quality of life among university students in Turkey. *Current Psychology.* 2022 Feb; 41(2): 1033-42. https://doi.org/10.1007/s12144-021-01674-y.
26. Talapko J, Perić I, Vulić P, Pustijanac E, Jukić M, Bekić S, Meštrović T, Škrlec I. Mental health and physical activity in health-related university students during the COVID-19 pandemic. *Healthcare*. 2021; 9 (7): 801. https://doi.org/10.3390/healthcare9070801.
27. Škrlec I, Talapko J, Pustijanac E, Meštrović T. Depression, anxiety, stress and physical activity in health-related university students during COVID-19. *Medical Sciences Forum.* 2021; 4 (1): 43. https://doi.org/10.3390/ECERPH-3-09028.
28. Wathelet M, Duhem S, Vaiva G, Baubet T, Habran E, Veerapa E, Debien C, Molenda S, Horn M, Grandgenèvre P, Notredame Ch-E, D'Hondt F. Factors Associated With Mental Health Disorders Among University Students in France Confined During the COVID-19 Pandemic. *JAMA Netw. Open.* 2020; 3: e2025591. https://doi.org/10.1001/jamanetworkopen.2020.25591.
29. Schlichtiger J, Brunner S, Steffen J, Huber BC. Mental health impairment triggered by the COVID-19 pandemic in a sample population of German students. *J. Investig. Med.* 2020; 68: 1394–1396. https://doi.org/10.1136/jim-2020-001553.
30. Soltan MR, Soliman SS, Dawoud ME. A study of anxiety, depression and stress symptoms among Fayoum medical students during COVID-19 lockdown, Egypt. The Egyptian Journal of Neurology, *Psychiatry and Neurosurgery.* 2021; 57(1): 1–6. https://doi.org/10.1186/s41983-021-00377-2.
31. SartoraoFilho CI, Rodrigues WC, de Castro RB, Marcal AA, Pavelqueires S, Takano L, de Oliveira WL, Neto CI. Impact of Covid-19 pandemic on mental health of Medical students: A cross-sectional study using GAD-7 and PHQ- 9 questionnaires. medRxiv. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.06.24.20138925v1. https://doi.org/10.1101/2020.06.24.20138925.
32. Pesen A, Mayda AS. Depression, anxiety, stress levels and related factors of medical faculty students. Sak Med J. 2020; 10(2): 240–252.
33. Aylie NS, Mekonen MA, Mekuria RM. The psychological impacts of COVID-19 pandemic among university students in bench-sheko zone, South-West Ethiopia: a community-based cross-sectional study. *Psychol Res Behav Manag.* 2020; 13: 813–821. https://doi.org/10.2147/PRBM.S275593
34. Karaca A, Yildirim N, Ankarali H, Açikgöz F, Akkuş D. Nursing students' perceived levels of clinical stress, stress responses and coping behaviors. *J Psychiatr Nurs.* 2017; 8(1): 32–39. https://doi.org/10.14744/phd.2017.22590
35. Lester D. College student stressors, depression, and suicidal ideation. *Psychol Rep*. 2014; 114(1): 293–296. https://doi.org/10.2466/12.02.PR0.114k10w7.
36. Sever M, Özdemir S. The experience of being a student during the coronavirus (COVID-19) process: a photovoice study. *Community Soc Work.* 2020; 31: 1653–1679. https://doi.org/10.33417/tsh.778615.
37. Bashir TF, Hassan S, Maqsood A, Khan ZA, Issrani R, Ahmed N, Bashir EF. The psychological impact analysis of novel COVID-19 pandemic in health sciences students: a global survey. *Eur J Dent.* 2020; 14(S 01): S91-6. https://doi.org/10.1055/s-0040-1721653.
38. Bulgan C, Demirel G. Evaluation of alcohol, substance and antidepressant drug use of university students during the COVID-19 pandemic. *Anatolian Current Medical Journal.* 2023; 5(1): 1–6. https://doi.org/10.38053/acmj.1169944.
39. Jodczyk AM, Kasiak PS, Adamczyk N, Gębarowska J, Sikora Z, Gruba G, Mamcarz A, Śliż D. PaLS Study: Tobacco, alcohol and drugs usage among Polish University students in the context of stress caused by the COVID-19 pandemic. *International Journal of Environmental Research and Public Health.* 2022; 19(3): 1261. https://doi.org/10.3390/ijerph19031261.
40. Fila-Witecka K, Senczyszyn A, Kołodziejczyk A, Ciułkowicz M, Maciaszek J, Misiak B, Szczes´niak D, Rymaszewska J. Lifestyle Changes among Polish University Students during the COVID-19 Pandemic. *Int. J. Environ. Res. Public Health.* 2021; 18(18): 9571. https://doi.org/10.3390/ijerph18189571.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15614

Assessment of Outcomes of the Modified Stoppa Approach in the Treatment of Acetabular Fractures: A Retrospective Cohort Study

Nurgeldi Manap[1], Nagmet Mursalov[1], Mukhtar Abilmazhinov[2]

[1]Department of Traumatology [5], National Scientific Center of Traumatology and Orthopedics named after Academician N. D. Batpenov, Astana, Kazakhstan
[2]Department of Traumatology and Orthopedics, Astana Medical University, Astana, Kazakhstan

Received: 2024-05-27.
Accepted: 2024-11-20.

J Clin Med Kaz 2024; 21(6): 73–78

Corresponding author:
Nurgeldi Manap.
E-mail: nurgeldi.manap@gmail.com.
ORCID: 0000-0002-2766-4072.

Abstract

Aims. To evaluate the efficacy of the modified Stoppa approach for surgical treatment of pelvic bone injuries based on clinical (sex distribution, fracture type), surgical (duration of operation, intraoperative blood loss, incision length, quality of reduction), and functional outcome (hip joint function).

Materials and methods. A total of 31 patient were included in a retrospective cohort study from 2019 until March 2022 with various injuries of acetabulum in the N.D. Batpenov National Scientific Center of Traumatology and Orthopaedics (NSCTO).The inclusion criteria for this study were: patients with acetabulum injuries, and who underwent surgical interventions using one of two surgical approaches (modified Stoppa, ilioinguinal approaches), patients over 18 years old. Exclusion criteria: other operative approaches to pelvic bones and patients under 18 years of age. 21 patients underwent surgery with the use of modified Stoppa approach (group A) and 10 surgeries were performed using the ilioinguinal approach (group B). Efficiency was evaluated by comparison of duration of surgical procedures, amount of blood lossbetween groups, size of skin incision, quality of reduction and functional outcomes.

Results. There are males – 18(58.1%), females – 13(41.9%) in the study. The clinical study results showed that average volume of intraoperative blood loss and size of skin incision were significantly less during Stoppa approach then ilioinguinal approach though average duration of surgical procedures did not reveal significant differences between two groups. Average duration of surgical procedures did not reveal significant differences between two groups – 109.5 min (±54.7) among group A and 126 min (±58.9) in group B. The volume of intraoperative blood loss averaged 338±254.5 ml of blood for the total sample. The volume of intraoperative blood loss was 525.0 ±322.5 ml of blood in group B, which is more than twice the estimated blood loss for group A (250 ±157.3 ml). When using a Stoppa approach, the length of the cutaneous surgical incision averaged at 8.8 ± 1.5 cm, while with an ilioinguinal approach, this value was estimated at 20.6 ± 8.5 cm, which suggests a favorable cosmetic effect of Stoppa approach.

Conclusion. The positive results obtained with the modified Stoppa approach, which are reflected in a reduction in the length of the skin incision and the amount of intraoperative blood loss, suggest that the use of this approach in clinical practice provides an opportunity to improve the surgical treatment of acetabular fractures by obtaining variability in the study of surgical approach. Nevertheless, the frequency and complexity of the occurring pelvic bone injuries dictate the need for further search and improvement of more optimal access options for surgical treatment.

Keywords: acetabulum, osteosynthesis, Stoppa approach, ilioinguinal approach.

Introduction

Introduction. Acetabulum fractures are among the most challenging to treat due to the intricate nature of the required surgery, making them some of the most difficult procedures for orthopedic surgeons [1]. Achieving an accurate anatomical reduction of fractures and reconstructing the joint are fundamental to treating acetabulum fractures, a consensus shared by most orthopedic surgeons [2]. Selecting the appropriate surgical method for treating fractures of the anterior pelvic ring and acetabulum is crucial for ensuring accurate fracture realignment and minimizing complications [2, 3]. Since Letournel introduced the ilioinguinal approach (IA) [4], it has become a widely adopted method for addressing pelvic ring and acetabulum fractures. The IA approach offers several advantages, including excellent visibility of the acetabulum fracture, minimal risk of sciatic nerve damage, a discreet postoperative scar, and a swift recovery [5]. It is noted that the rate of anatomical recovery reaches from 45% to 74% [6, 7]. Only from early 1990s the modified Stoppa approach, introduced by R. Stoppa, was initially employed in pelvic surgery as a less traumatic alternative [8-10].

Comparison of operative approaches in acetabulum fractures was previously carried out using the AO/ASIF classification system for fractures [11] or E. Letournel [12-15]. The type of fracture determines the selection of approach to the acetabulum.M. Erem et al. (2019) argue that to enhance functional outcomes, the selection of one or two approaches should be based on the fracture's type and location [13]. The literature suggests that specialists, having gained experience in treating acetabulum fractures, primarily considered fractures of the acetabulum columns when selecting operative approaches.

In cases of fractures involving the anterior column and the anterior wall of the acetabulum, the authors typically employed the ilioinguinal or Stoppa approaches. Deng C. et al. (2018) used a combination of ilioinguinal and Kocher-Langenbeck approaches in surgical treatment of 31 cases of acetabulum fractures [12].

In 1993, Hirvensalo et al. initially documented the modified Stoppa approach (MSA) for the treatment of pelvic ring or acetabulum fractures. MSA offers the advantage of minimizing surgical trauma, offering excellent visualization, and easing the reduction and fixation of fragments displaced towards the medial side [9, 10, 16].

The modified Stoppa approach is becoming increasingly popular worldwide. This is because it is potentially less invasive than the ilioinguinal approach and provides excellent visualization of the entire pelvic rim from the pubic bone to the sacroiliac joint, including direct visualization of the quadrilateral plate [17]. The adoption of the anterior intrapelvic approach also led to the development of new instruments and implants [18]. It is challenging to compare surgical approaches, but the studies by Rocca et al. and the meta-analysis by Meena et al., both conclude that MSA (anterior intrapelvic approach) is preferable over the iliopubic approach [19, 20].

The objective of this study is to examine Stoppa access in more detail, and to evaluate the efficiency of the modified Stoppa approach in comparison with ilioinguinal approach for the surgical management of pelvic bone injuries. Subsequently, we aim to add knowledge to consider the feasibility of wide application of Stoppa approach as the method of choice in our clinical practice.

Materials and methods

From the beginning of 2019 to March 2022, the Department of Traumatology performed surgery on 63 patients with various injuries of the pelvic bones. The inclusion criteria for this study were: patients with acetabulum injuries, according to the Judet-Letournel classification, except for fractures of the posterior wall of the acetabulum, and who underwent surgical interventions using one of two surgical approaches (modified Stoppa, ilioinguinal approaches), patients over 18 years old, as our clinic only treats adult patients. Exclusion criteria: other operative approaches to pelvic bones, patients with fractures of the posterior wall of the acetabulum, according to the Judet-Letournel classification, and patients under 18 years of age. During the study, according to the exclusion criteria 10 patients underwent surgery utilizing the Kocher-Langenbeck approach. In addition, 22 other patients underwent surgeries due to fractures of other pelvic bones, without involvement of the acetabulum, were not included in this study (Figure 1). Thirty-one surgeries were performed for the various injuries of the acetabulum in the Department of Traumatology. In this study, a retrospective cohort study was conducted. This study design was chosen because we have only started using the Stoppa approach in the last couple of years, and the idea of evaluating and comparing the two approaches came later.

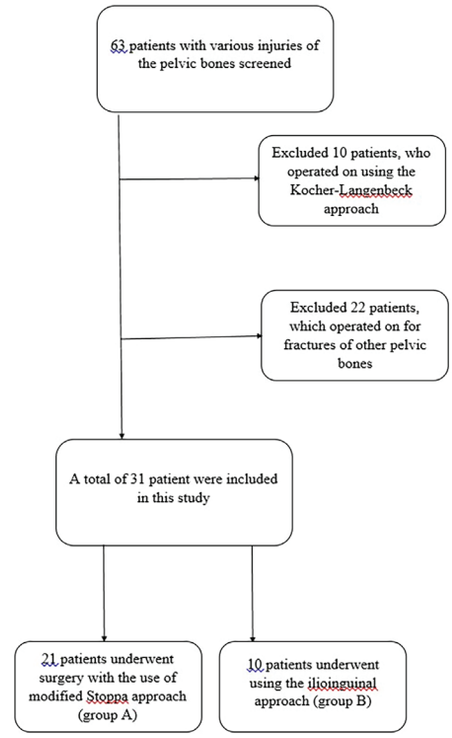


Figure 1 – Flow-chart of inclusion of patients in the study

Pre-operative preparations

Upon the patients' arrival to our emergency department, we ensured that they properly resuscitated and stabilized hemodynamically. We utilized conventional methods of the skeletal traction on their distal femur, and administered low molecular weight heparin subcutaneously as a prophylaxis against deep vein thrombosis. We routinely conducted pelvic X-ray, computed tomography (CT) scan with angiography and three-dimensional (3D) reconstruction. In addition, one day prior to surgery, we reevaluated and prepared for routine procedures such as enemas, urinary catheterization, and blood transfusion.

Surgical interventions

Patients in group A underwent surgery using a modified Stoppa approach. The operation is performed under endotracheal anesthesia. A soft tissue incision measuring 9.0 cm in size

was made transversely 2 cm above the symphysis. The skin-subcutaneous layer was mobilized from the fascia at a distance of 6 cm from the edges of the wounds. The rectus abdominis fascia was dissected vertically along its fibers. The Retzius space was dissected bluntly. Subperiosteal dissection was performed alongside the pubic bone. An elevator was installed. The left and right pubic bones were exposed for 4 cm along the upper, posterior, and anterior surfaces. A sharp Hohmann retractor was positioned over the pubic tubercle to facilitate retraction of the rectus muscle. The superior iliac crest fascia, inferior obturator fascia were separated from the pelvis to expose the pubic bone, the terminal line, and the quadrangular surface. Consequently, a square space was allocated, while the obturator nerve was mobilized (Figure 2).

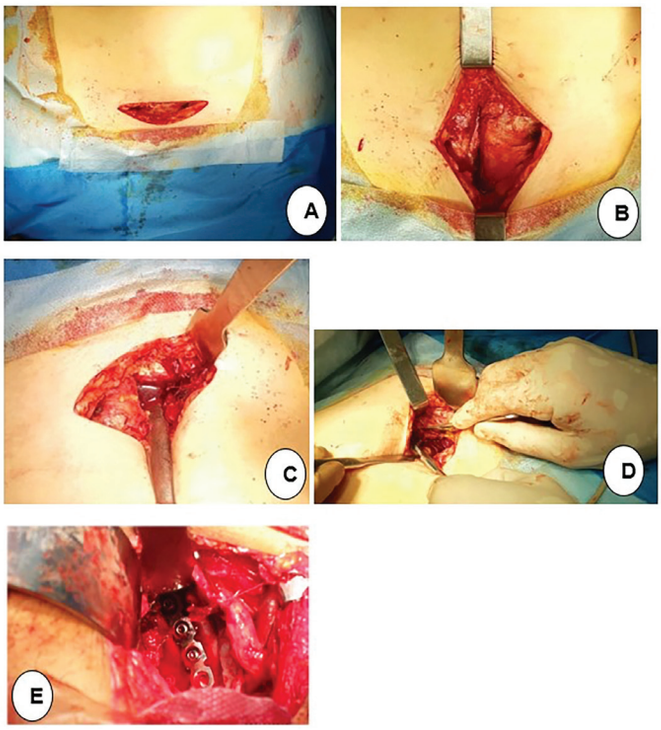


Figure 2 – Stages of modified Stoppa approach to an acetabular fracture: 9,0 cm skin incision 2 cm above the symphysis (A). The rectus abdominis fascia is dissected vertically along its fibers. Blunt dissection of the Retzius space is performed. Subperiosteal dissection is performed along the pubic bone (B). Blunt dissection of the Retzius space is performed. An elevator is installed (C). A sharp Hohmann retractor is placed over the pubic tubercle to retract the rectus muscle. The superior iliac crest fascia and inferior obturator fascia are separated from the pelvis to expose the pubic bone, the terminal line, and the quadrangular surface (D). Intraoperative reduction and fixation of fracture (E).

Next, the terminal line and the revision of the fracture site were highlighted. The fracture ends were cleaned, the fragments were repositioned using pelvic clamps and a picador. At the end, the plate was adapted and placed along the terminal line on the pelvic bone. The plate was fixed with cortical screws (Figure 3).

Patients in Group B underwent surgery utilizing the ilioinguinal approach. Unlike the Stoppa approach, this approach usually requires a larger incision. The incision site begins at the intersection of the lateral and medial quarter lines connecting the umbilicus to the anterior superior iliac spine (ASIS), continuing in a slightly convex curve towards the distomedial direction to the intersection of the medial and medial thirds of the line joining the ASIS to the symphysis. The ilioinguinal approach provides an overview of the anterior and posterior sections of the acetabulum.

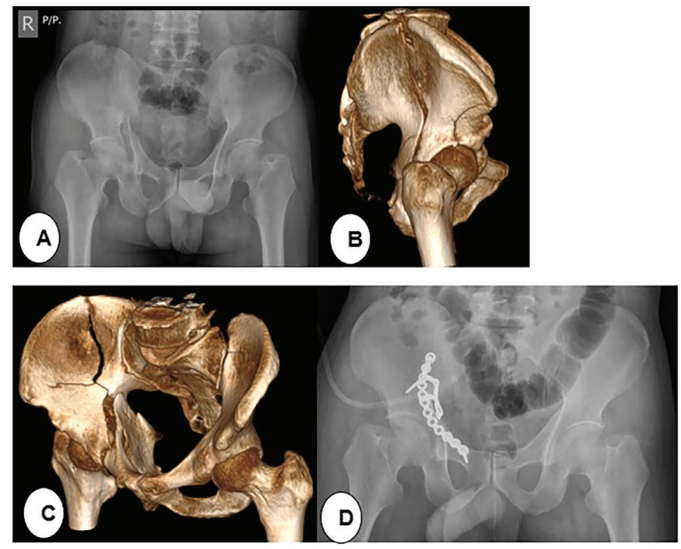


Figure 3 – Acetabular fracture after falling from a height was present in a 53-year-old male patient. The patient was operated on the 10th day after trauma with a modified Stoppa approach. Preoperative x-ray and CT sections: A) preoperative direct x-ray, B,C) preoperative axial CT section, D) X-ray on postoperative day 1. The postoperative reduction was assessed as an anatomical reduction.

Efficiency was evaluated by comparison the average duration of the operation and length of incision, the median amount of blood lost during surgery between the groups. Quality of reduction was evaluated according to the Matta reduction criteria on pelvic X-rays by measuring the diastasis between bone fragments according to the method: 0-1 mm displacement was classified as anatomical, 2-3 mm as imperfect, and >3 mm as poor. [21].

The functional assessment of the patients was carried out by applying the Harris Hip Score (HHS) postoperativelyby clinical examination and testing of the hip joint. [22, 23].

Statistical analysis was carried out using STATA statistical software. Quantitative variables were described using the mean and standard deviation. Frequency and percentage were employed to describe qualitative variables. The distribution of quantitative variables was assessed using the histogram and Shapiro-Wilk test. The distribution of patients by gender with different operative accesses was compared using a Chi-square test. Parameters such as the incision length, the duration of the operation and the quantity of intraoperative blood loss were compared utilizing the Student's t-test. Proportion of patients with missing data was negligible and did not require statistical handling.

Results

The range of age in our study was 19-77 years. Two groups did not differ on their ages with mean age for groupA being 39.4 years (±13.3) and 42.5 years (±18.2) among group B. No statistically significant difference in the distribution of sexes was observed. Both groups are slightly more represented by males, 57.1% in group A and 60% in group B (Table 1).

Table 1 text

Variable	Total (N=31)	Group A (N=21)	Group B (N=10)	p-value
Age, mean (±SD)	40.4 (±14.8)	39.4 (±13.3)	42.5 (±18.2)	0.6
Gender, N (%) Female Male	 13 (41.9%) 18 (58.1%)	 9 (42.9%) 12 (57.1%)	 4 (40%) 6 (60%)	0.88

Twenty (64.5%) fractures were classified as simple and 11 (35.5%) fractures were classified as complex acetabular fractures. Among the simple fractures, there were 11 (35.48%) fractures of the anterior column, 5 (16.13%) fractures of the anterior wall of the acetabulum, 2 (6.45%) cases of transverse fractures, and 2 (6.45%) posterior column acetabulum fractures. Also, two (6.45%) anterior semitransverse fractures, 2 (6.45%) transverse plus posterior wall fractures, 6 (19.35%) cases of two-column acetabulum fractures, 1 (3.23%) T-shaped fracture were classified as complex fractures (Table 2).

Acetabular fractures occurred as isolated injuries in 18 patients, while 27 had associated injuries, including 7 head injuries, 4 rib fractures, 7 upper limb injuries, and 3 lower limb injuries, and 6 had associated spinal injuries (Table 3).

In 2 cases, patients had complications in the form of post-traumatic neuropathy of the sciatic nerve.

Average duration of surgical procedures did not reveal significant differences between two groups – 109.5 min (±54.7) among group A and 126 min (±58.9) in group B. The volume of intraoperative blood loss averaged 338±254.5 ml of blood for the total sample. The volume of intraoperative blood loss was 525.0 ±322.5 ml of blood in group B, which is more than twice the estimated blood loss for group A (250 ±157.3 ml). Also note worthy is a cosmetic defect when using two approaches, which was estimated by the length of the skin incisions. Thus, when using a Stoppa approach, the length of the cutaneous surgical incision averaged at 8.8 ± 1.5 cm, while with an ilioinguinal approach, this value was estimated at 20.6 ± 8.5 cm, which also shows a statistically significant difference (Table 4).

Table 2 text

Type of fracture	Number of cases	Percentage
Anterior wall	5	16,13
Anterior column	11	35,48
Transverse	2	6,45
T-Shaped	1	3,23
Posterior column	2	6,45
Transverse with posterior wall	2	6,45
Anterior column with posterior hemi transverse	2	6,45
Associated both column	6	19,35
Total	31	100

Table 3 text

18	isolated acetabular injuries
7	head injuries
4	rib fractures
7	upper limbs
3	lower limbs
6	spine

Table 5 text

_____	Group A (N=21)	Group B (N=10)
Radiological outcome (Matta)		
Anatomical (<1 mm)	8 (38.1%)	3 (30%)
Imperfect (2-3 mm)	10 (47.6%)	5 (50%)
Poor (>3 mm)	3 (14.3%)	2 (20%)
Harris Hip Score		
Excellent (90-100)	7 (33.3%)	3 (30%)
Good (80-89)	10 (47.6%)	4 (40%)
Fair (70-79)	3 (14.3%)	2 (20%)
Poor (<70)	1 (4.8%)	1 (10%)

Table 4 text

Variable	Total (N=31)	Group A (N=21)	Group B (N=10)	p-value
Incision length in cm, mean (±SD)	12.6 (±7.4)	8.8 (±1.5)	20.6 (±8.5)	0.001
Duration of operation in min, mean (±SD)	115 (±55.7)	109.5 (±54.7)	126 (±58.9)	0.44
Blood loss in ml, mean (±SD)	338 (±254.5)	250 (±157.3)	525 (±322.5)	0.003

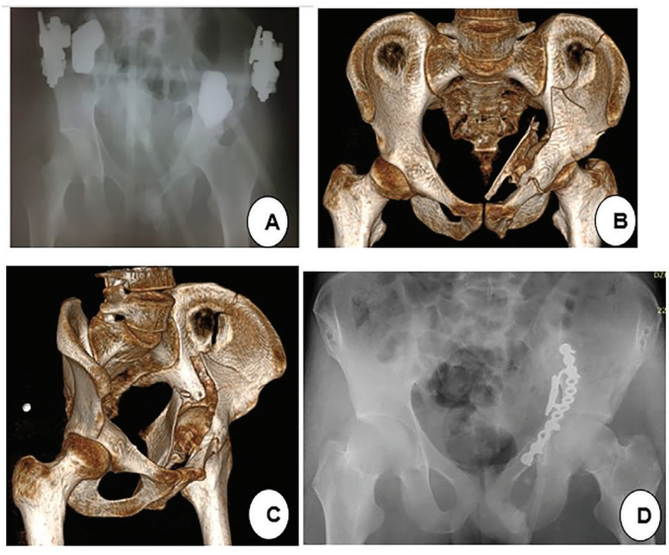


Figure 3 – A 26-year-old patient with a both column fracture of the acetabulum. Preoperative x-ray and CT sections: A) preoperative direct x-ray, B,C) preoperative CT sections, D) X-ray on postoperative day 1.

When assessed on radiography, the quality of reduction was rated as anatomical in 8 (%) cases, imperfect in 10 (%) cases and poor in 3 (%) cases in group A based on Matta criteria. Meanwhile in group B, it was rated as anatomical in 3 (%) cases, imperfect in 5 (%) cases and poor in 2 (%) cases (Table 5, Figure 4).

According to the Harris Hip score, the functional results were in group A excellent in 7 (33.3%) cases, good in 10 (47.6%) cases, fair in 3 (14.3%) cases, and poor in 1 (4.8%) cases. Whereas in group B, the results were excellent in 3 (30%) cases, good in 4 (40%) cases, fair in 2 (20%) cases, and poor in 1 (10%) cases at the 1 year follow up (Table 5).

Discussion

Based on the data obtained, it can be concluded that there are advantages of the modified Stoppa approach in contrast to the ilioinguinal approach. It is regarding the shorter length of the surgical incision and the reduced quantity of intraoperative blood loss.

Similar to our result, several studies showed a smaller amount of blood loss when using Stoppa approach [24-27]. However, these studies report a short duration of surgery, which does not correspond to our results. In our study there were no significant differences in amount of blood loss between two groups. This could be due to limited sample size as well as the difference in the quality of technical equipment that was used in this study.

Based on the data obtained during our study, we can conclude that the widespread use of the Stoppa surgical approach in the future is completely justified, since it has a number of advantages over other approaches. However, this does not mean that classical approaches, such as the ilioinguinal

approach, have completely lost their effectiveness. The selection of surgical approach should be considered in accordance with the type and nature of the fracture, the chosen surgical tactics, and the selection of the implant. It is also worth considering the fact that skilled surgeons can achieve a positive result by using both classical approaches and modern minimally invasive approaches.

The modified Stoppa approach has some limitations, including potential challenges associated with reducing and stabilizing fractures involving the posterior column, as well as limitations in visualizing certain areas such as head of femur, labrum, and articular surface of the acetabulum which results insufficient cleansing of the joint. This is due to the fact that this access provides a view of the acetabulum from the inside of the pelvic ring, and anatomically there is no way to fully reach the hip joint. Therefore, for fractures of the posterior column and posterior wall of the acetabulum, it is advisable to consider the use of a combined anterior intrapelvic approach(MSA), as well as the Kocher-Langenbeck approach for detailed visualization of the entire acetabulum and hip joint.

Most of the fractures in our study are associated with damage to the acetabular anterior column, which differs from some studies where damage to both columns was predominant [28].

The modified Stoppa approach offers a viable alternative in situations requiring anterior access to the acetabulum, although it may not entirely replicate the effectiveness of the traditional ilioinguinal approach.

The modified Stoppa approach is suitable for various types of fractures, including anterior wall, anterior column, both columns, anterior column, posterior hemitransverse, and some transverse and T-shaped fractures. This approach is particularly effective for transverse and T-shaped fractures when the fracture line is positioned high and in close proximity to the sciatic notch. It is less invasive than the inguinal approach since it does not involve opening the inguinal canal and its contents.

Based on the above, it can be concluded that the optimal path for the development of surgical treatment for acetabular fractures in our clinical practice involves the widespread adoption of new minimally invasive surgical approaches, such as the anterior intra-pelvic approach and the pararectal approach, as well as the development of new implants that provide better anatomical reduction and are easily contourable. This also requires the improvement of training for trauma surgeons, who should be capable of applying both traditional and new approaches in the treatment of acetabular fractures.

Conclusion

The advantages of using a modified Stoppa approach include a better cosmetic effect compared to other approaches, a reduction in soft tissue injury, a more optimal overview of the surgical field. In summary, this study demonstrates that the modified Stoppa approach is both safe and efficient for fixing acetabulum fractures. Thus, our results confirm the opinion that this minimally invasive method represents a valuable alternative to the ilioinguinal approach for surgical management of acetabulum fractures. All the above determines the prospects for further use of low-traumatic access as a method of choice in the surgery of fractures of the acetabulum, anterior pelvic ring.

Author Contributions: Conceptualization, N.M. and N.M.; methodology, N.M., N.M. and M.A.; validation, N.M. and N.M.; formal analysis, N.M. and M.A.; investigation, N.M. and N.M.; resources, N.M. and N.M.; data curation, N.M.; writing – original draft preparation, N.M.; writing – review and editing, N.M., N.M. and M.A.; visualization, N.M.; supervision, M.A.; project administration, N.M. and M.A.; funding acquisition, N.M., N.M. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: This research is funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (№ BR11065157).

References

1. Antell NB, Switzer JA, Schmidt AH. Management of acetabular fractures in the elderly. *J Am AcadOrthop Surg.* 2017; 25(8): em585. https://doi.org/10.5435/JAAOS-D-15-00510.
2. Park KS, Chan CK, Lee GW et al. Outcome of alternative approach to displaced acetabular fractures. *Injury.* 2017; 48(2): em93.https://doi.org/10.1016/j.injury.2016.11.029.
3. Kacra BK, Arazi M, Cicekcibasi AE, et al. Modified medial Stoppa approach for acetabular fractures: an anatomic study. *J Trauma.* 2011; 71(5): em1344. https://doi.org/10.1097/TA.0b013e3182092e8b.
4. Letournel E. Acetabulum fractures: classification and management. *Clin Orthop Relat Res.* 1980; 151: 81–106. https://doi.org/10.1097/00003086-198009000-00012.
5. Rocca G, Spina M, Mazzi M. Anterior combined endopelvic (ACE) approach for the treatment of acetabular and pelvic ring fractures: a new proposal. *Injury*. 2014; 45(12): em15. https://doi.org/10.1016/j.injury.2014.10.016.
6. Briffa N, Pearce R, Hill AM, Bircher M. Outcomes of acetabular fracture fixation with ten years' follow-up. *J Bone Joint Surg Br*. 2011; 93(2): em236. https://doi.org/10.1302/0301-620X.93B2.24056.
7. Fensky F, Lehmann W, Ruecker A, Ruecker JM. Ilioinguinal approach: indication and technique. *J Orthop Trauma.* 2018; 32(1): em13. https://doi.org/10.1097/BOT.0000000000001194.
8. Cole JD, Bolhofner BR. Acetabular fracture fixation via a modified Stoppa limited intrapelvic approach. Description of operative technique and preliminary treatment results. *Clin Orthop Relat Res.* 1994; (305): em123. https://doi.org/10.1097/00003086-199408000-00015.
9. Hirvensalo E, Lindahl J, Böstman O. A new approach to the internal fixation of unstable pelvic fractures. *Clin Orthop Relat Res*. 1993; 1(12): em32. https://doi.org/10.1097/00003086-199312000-00007.
10. Hirvensalo E, Lindahl J, Kiljunen V. Modified and new approaches for pelvic and acetabular surgery. *Injury*. 2007; 38(4): em441. https://doi.org/10.1016/j.injury.2007.01.020.

11. Negrin LL, Seligson D. Results of 167 consecutive cases of acetabular fractures using the Kocher-Langenbeck approach: a case series. *J Orthop Surg Res.* 2017; 26(4): em66. https://doi.org/10.1186/s13018-017-0563-6.
12. Deng C, Ni WD, Guo SQ, Luo G, Shui W, Qiao B. Operative treatment of delayed acetabular fractures through combined anterior and Kocher-Langenbeck approaches. *ZhonghuaWaiKeZaZhi.* 2018; 56(3): em200. https://doi.org/10.3760/cma.j.issn.0529-5815.2018.03.006.
13. Erem M, Copuroglu C, Copuroglu E, Ciftdemir M, Ozcan M, Saridogan K. Effects of the incısıon preference ın acetabular surgery on the postoperatıve functıonal outcomes. *Niger J Clin Pract.* 2019; 22(6): em868. https://doi.org/10.4103/njcp.njcp_455_18.
14. Frietman B, Biert J, Edwards MJR. Patient-reported outcome measures after surgery for an acetabular fracture. *Bone Joint J.* 2018; 100(5): em645. https://doi.org/10.1302/0301-620X.100B5.BJJ-2017-0871.R3..
15. Liu ZJ, Jia J, Zhang YG, Tian W, Jin X, Hu YC. Internal Fixation of Complicated Acetabular Fractures Directed by Preoperative Surgery with 3D Printing Models. *Orthop. Surg.* 2017; 9(2): em260. https://doi.org/10.1111/os.12324.
16. Wu H, Zhang L, Guo X, Jiang X. Meta-analysis of modified Stoppa approach and ilioinguinal approach in anterior pelvic ring and acetabular fractures. *Medicine.* 2020; 99: 4(e18395). https://doi.org/10.1097/MD.0000000000018395.
17. Sagi HC, Afsari A, Dziadosz D. The anterior intra-pelvic (modified Rives-Stoppa) approach for fixation of acetabular fractures. *J Orthop Trauma.* 2010; 24: 263–270. https://doi.org/10.1097/BOT.0b013e3181dd0b84.
18. Gras F, Marintschev I, Grossterlinden L, Rossmann M, Graul I, Hofmann GO, Rueger J, Lehmann W. The anterior intrapelvic approach for acetabular fractures using approachspecific instruments and an anatomical-preshaped 3-dimensional suprapectineal plate. *J Orthop Trauma.* 2017; 31: e210–e216. https://doi.org/10.1097/BOT.0000000000000829.
19. Rocca G, Spina M, Mazzi M. Anterior combined endopelvic (ACE) approach for the treatment of acetabular and pelvic ring fractures: a new proposal. *Injury*. 2014; 45(Suppl 6): S9–S15. https://doi.org/10.1016/j.injury.2014.10.016.
20. Meena S, Sharma PK, Mittal S, Sharma J, Chowdhury B. Modified Stoppa approach versus ilioinguinal approach for anterior acetabular fractures; a systematic review and meta-analysis. Bull Emerg Trauma. 2017: 5: 6–12.
21. Matta JM. Fractures of the acetabulum: accuracy of reduction and clinical results in patients managed operatively within three weeks after the injury. *J Bone Joint Surg Am.* 1996; 78(11): 1632e1645.
22. Haddad RJ, Cook SD, Brinker MR. A comparison of three varieties of noncemented porous-coated hip replacement. *J Bone Joint Surg Br.* 1990; 72(1): 2e8.
23. Kavanagh BF, Fitzgerald JRH. Clinical and rentgenographic assessment of total hip arthroplasty: a new hip score. *Clin Orthop Relat Res*. 1985; 13: 3e40.
24. Shazar N, Eshed I, Ackshota N, Hershkovich O, Khazanov A, Herman A. Comparison of acetabular fracture reduction quality by the ilioinguinal or the anterior intrapelvic (modified Rives-Stoppa) surgical approaches. *J Orthop Trauma.* 2014; 28(6): em319. https://doi.org/10.1097/01.bot.0000435627.56658.53.
25. Chen K, Ji Y, Huang Z, Navinduth R, Yang F, Sun T, Xiong Z, Yao Sh, Ahn J, Guo X. Single modified ilioinguinal approach for the treatment of acetabular fractures involving both columns. *J Orthop Trauma*. 2018; 32(11): em434. https://doi.org/10.1097/BOT.0000000000001303.
26. Yao S, Chen K, Ji Y, Zhu F, Zeng L, Xiong Z, Sun T, Yang F, Liu J, Guo X. Supra-ilioinguinal versus modified Stoppa approach in the treatment of acetabular fractures: reduction quality and early clinical results of a retrospective study. *Journal of Orthopaedic Surgery and Research*. 2019; 14(1): em9. https://doi.org/10.1186/s13018-019-1428-y.
27. Al Adawy AS, Abdel Aziz AH, El Sherief FA, Mahmoud WS, Mabrook M, El-Sayed Hassan Y. Modified Stoppa as an alternative surgical approach for fixation of anterior fracture acetabulum: a randomized control clinical trial. *Journal of Orthopaedic Surgery and Research.* 2020; 15(1): em12. https://doi.org/10.1186/s13018-020-01660-3.
28. Verbeek DO, Ponsen KJ, van Heijl M, Goslings JC. Modified Stoppa approach for operative treatment of acetabular fractures: 10-year experience and mid-term follow-up. *Injury*. 2018; 49(6): em1140. https://doi.org/10.1016/j.injury.2018.03.031.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15615

Risk Factors for Mortality in Low Birth Weight Infants with Respiratory Distress Syndrome

Arailym Abilbayeva[1], Anel Tarabayeva[1], Nishangul Bozhbanbayeva[2], Dinara Yelyubayeva[3]

[1]Shortanbayev General Immunology department, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
[2]Neonatology department, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
[3]Intensive care unit, The Center for Perinatology and Pediatric Cardiac Surgery, Almaty, Kazakhstan

Received: 2024-07-26.
Accepted: 2024-11-20.

J Clin Med Kaz 2024; 21(6): 79–84

Corresponding author:
Arailym Abilbayeva.
Email: arailym2686@gmail.com.
ORCID: 0000-0001-5081-5492.

Abstract

Objective: To study the structure of concomitant pathologies in low birth weight premature newborns with respiratory distress syndrome (RDS). To identify mortality risk factors in these newborns.

Materials and methods: Data from 374 premature newborns weighing less than 1500 g and gestational age less than 32 weeks with RDS treated in the intensive care unit were analyzed.

Results: Several comorbidities were more common among children with RDS compared to children without RDS. Thus, disseminated intravascular coagulation syndrome (DIC) occurred 2 times, atelectasis 1.3 times, necrotizing enterocolitis (NEC) 2.4 times, and anemia 1.8 times more often among children with RDS compared to those without RDS.

In multivariate logistic regression, such factors as 1-3 points on the Apgar scale at 1 minute (OR - 2.478, 95% CI - 1.289-4.764, p = 0.007), 1-3 points on the Apgar scale at 5 minutes (OR - 3.754, 95% CI - 1.788-7.878, p<0.0001), DIC (OR -4.428, 95% CI -2.206-8.887, p<0.0001), NEC (OR - 4.508, 95% CI - 2.270-8.954, p<0.0001) showed a positive association with death in children with RDS.

When assessing the effect of the combination of DIC and NEC on death, it was found that the combination of these two pathologies in children with RDS increases the risk of death by more than 2 times. Thus, the area under the curve (AUC) for DIC was 0.283, for NEC the AUC was 0.335, and for the combination ICE+NEC it was 0.782).

Conclusions: The structure of comorbidities in low birth weight infants with RDS differs from that of infants without RDS. Premature infants with RDS were more likely to develop anemia, DIC, atelectasis, and NEC. The presence of comorbidities increases the risk of death in low birth weight infants with RDS. Low Apgar score, DIC syndrome, and NEC can increase the risk of death in low birth weight premature infants with RDS. It is anticipated that the collected data will enhance personalized care for low birth weight, premature infants with multiple health conditions, ultimately reducing mortality rates in this vulnerable patient group.

Keywords: respiratory distress syndrome, premature newborns, risk factors, mortality.

Introduction

Neonatal respiratory distress syndrome (RDS) is a serious breathing problem that primarily affects premature babies. This condition occurs when the lungs lack sufficient surfactant, a substance essential for proper lung function. RDS was first identified in 1959 and continues to be a significant cause of illness and death in newborns [1].

Approximately 1% of all live births are affected by RDS, but the risk is significantly higher for premature babies. The earlier a baby is born, the greater the risk and severity of RDS. For example, around 80% of infants born at 28 weeks gestational age develop RDS, while this figure rises to nearly 90% for those born at 24 weeks [2].

Although modern treatment and prevention methods, including antenatal corticosteroids, use, postnatal exogenous surfactant administration, early use of spontaneous continuous positive airway pressure in the newborn, have improved the prognosis for

neonates with RDS [3], this pathology continues to be one of the main causes of neonatal morbidity and mortality, primarily among low birth weight preterm infants [4].

Key risk factors for premature infant mortality can be both maternal and premature infant factors. Maternal factors include maternal age, bad habits, preeclampsia, parity, mode of delivery, and maternal complications. Child factors include gestational age, congenital anomalies, neonatal infections, and perinatal asphyxia [5].

There are several other pathologies also associated with the incomplete formation of organs and a decrease in their adaptive capabilities to new conditions required at birth. These primarily include diseases such as bronchopulmonary dysplasia (BPD), diseases of the central nervous system such as intraventricular hemorrhage (IVH), periventricular hemorrhagic infarction (PVHI), and periventricular leukomalacia (PL), as well as retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and others [6, 7]. It should be noted that some of these diseases, in turn, could also cause death in premature newborns.

Currently, the significance of such biomarkers as low birth weight, severe prematurity, Apgar values, and some others in neonatal mortality has been well studied [8, 9, 10]. However, the extent to which the combination of pathologies associated with prematurity increases the risk of death in low birth weight newborns has not been sufficiently studied.

Objective of the study: to study the structure of concomitant pathologies in low birth weight premature newborns with respiratory distress syndrome (RDS); to identify mortality risk factors in these newborns.

Materials and method

The study design is an observational retrospective case-control study. The medical records of 374 premature babies weighing less than 1500 grams and born before 32 weeks who had respiratory distress syndrome (RDS) in the neonatal intensive care unit at the Center for Perinatology and Pediatric Cardiac Surgery in Almaty between 2021 and 2023 were studied. Clinical data, including Apgar scores, birth weight, gender and gestational age were obtained from medical records. The presence of complications such as intraventricular hemorrhage, atelectasis, DIC syndrome, necrotizing enterocolitis were determined based on neonatal intensive care unit (NICU) records. Inclusion criteria: premature infants weighing less than 1500 g, gestational age less than 32 weeks with RDS. Exclusion criteria: full-term babies, preterm babies born at 33 weeks or later and weighing over 1500 grams without RDS.

Data analysis

Statistical data processing was carried out using IBM SPSS Statistics 23.0. Continuous data was presented as mean ± standard deviation, while categorical data was presented as percentages and counts. The following variables were examined: gender, Apgar score at 1 and 5 minutes, presence of intraventricular hemorrhage, disseminated intravascular coagulation, atelectasis, necrotizing enterocolitis, anemia, and pneumonia. The method of contingency tables with $\chi 2$ assessment was used to compare qualitative variables. A univariate logistic regression was used to identify factors associated with death in preterm infants. The statistically significant parameters were further analyzed using multivariate logistic regression. ROC analysis was carried out to assess the prognostic significance of the totality of identified factors in the development of death. Differences were considered statistically significant at $p \leq 0.05$.

Ethical approval

The study was approved by the Ethics Committee of the Asfendiyarov Kazakh National Medical University (Min. No. 8 (144), November 3, 2023). The clinic administration was informed of the study, and clinic employees participated in this study. The data can be published publicly without any objections.

Results

1. Descriptive characteristics of the study group

The main characteristics of the study group are shown in Table 1.

Table 1 Descriptive characteristics of the study group

№	Parameters	Total number of premature babies with RDS (n=374)
1	**Gender**	
	female	178 (48%)
	male	196 (52%)
2	**Weight, (M±m)**	1037,32±15,7
3	**Gestational age, (M±m)**	27,91±0,13
4	**Apgar scores at 1 minute**	
	1-3 scores	183 (49%)
	4 scores or more	191 (51%)
5	**Apgar scores at 5 minutes**	
	1-3 scores	64 (17%)
	4 scores or more	310 (83%)
6	**Intraventricular hemorrhage (IVH)**	
	yes	176 (47%)
	no	198 (53%)
7	**Disseminated intravascular coagulation syndrome (DIC syndrome)**	
	yes	215 (57%)
	no	159 (43%)
8	**Atelectasis**	
	yes	209 (56%)
	no	165 (44%)
9	**Pneumonia**	
	yes	323 (86%)
	no	51 (14%)
10	**Necrotizing enterocolitis (NEC)**	
	yes	65 (17%)
	no	309 (83%)
11	**Anemia**	
	yes	166 (44%)
	no	208 (56%)

In this study, the number of males and females was 196 (52%) and 178 (48%). The average weight of premature newborns was 1037.32 g. The mean gestational age was 27.91 weeks. 1-3 points on the Apgar score at 1 minute were noted in 49% of children. At the same time, at the 5th minute, 1-3 points on the Apgar score were recorded in 17% of premature infants. The presence of IVH and DIC was diagnosed in 47% and 57%, respectively. At the same time, in these premature infants, atelectasis and pneumonia were detected in 56% and 86%, respectively. NEC was detected in 17%, and anemia in 44% of children.

2. The structure of concomitant diseases in low birth weight premature neonates with RDS

Comparative data on the presence of concomitant diseases in premature infants with and without RDS is presented in Table 2.

Table 2 Comparative analysis of data from premature infants with and without RDS

№	Parameters	RDS presence (n=374)	RDS absence (n=85)	P
1	**IVH**			
	yes	176 (47%)	45 (53%)	0,328
	no	198 (53%)	40 (47%)	
2	**DIC syndrome**			
	yes	215 (58%)	24 (28%)	<0,0001
	no	159 (42%)	61 (72%)	
3	**Atelectasis**			
	yes	209 (56%)	36 (42%)	0,025
	no	165 (44%)	49 (58%)	
4	**NEC**			
	yes	65 (17%)	7 (8%)	0,037
	no	309 (83%)	78 (92%)	
5	**Anemia**			
	yes	166 (44%)	21 (25%)	<0,0001
	no	208 (56%)	64 (75%)	
6	**Pneumonia**			
	yes	323 (86%)	68 (80%)	0,137
	no	51 (14%)	17 (20%)	

Comparative analysis of premature infant data with and without RDS revealed several statistically significant differences between the indicators (Table 2). Among children with RDS, DIC was 2 times more common than in the group of children without RDS. There were 1.3 times more children with atelectasis in the group with RDS compared to the group without RDS. In the group of children with RDS, the presence of NEC was 17% of the total number of the study group, while in the group without RDS, there was only 7%. In children with RDS, anemia was 1.8 times more common compared to children without RDS. No differences were found for pneumonia and IVH.

3. Mortality risk factors in low birth weight premature infants with RDS

3.1 Comparative analysis of parameters of low birth weight newborns with fatal outcome

A comparative analysis of the parameters of low birth weight premature infants with fatal outcomes in the presence of RDS is presented in Table 3.

Table 3 Comparative analysis of deceased and surviving premature infants with RDS

№	Parameters	Dead premature babies (n=114)	Surviving premature babies (n=260)	P
1	**Gender**			
	female	49 (43%)	129 (50%)	0,238
	male	65 (57%)	131 (50%)	
2	**Apgar scores at 1 minute**			
	1-3 scores	91 (80%)	92 (35%)	<0,0001
	4 scores or more	23 (20%)	168 (65%)	
3	**Apgar scores at 5 minutes**			
	1-3 scores	45 (39%)	19 (7%)	<0,0001
	4 scores or more	69 (61%)	241 (93%)	
4	**IVH**			
	yes	71 (62%)	105 (40%)	<0,0001
	no	43 (38%)	155 (60%)	
5	**DIC syndrome**			
	yes	100 (88%)	115 (44%)	<0,0001
	no	14 (12%)	145 (56%)	
6	**Atelectasis**			
	yes	92 (91%)	117 (44%)	<0,0001
	no	22 (9%)	143 (56%)	
7	**NEC**			
	yes	46 (40%)	19 (7%)	<0,0001
	no	68 (60%)	241 (93%)	
8	**Anemia**			
	yes	55 (48%)	111 (43%)	0,320
	no	59 (52%)	149 (57%)	
9	**Pneumonia**			
	yes	93 (82%)	230 (88%)	0,074
	no	21 (18%)	30 (12%)	

The number of deceased premature infants, whose condition was assessed by the Apgar score at 1-3 points at the 1st minute, was 2.3 times higher compared to surviving infants (80% versus 35%, p<0.001). At the same time, 1-3 points on the Apgar score at the 5th minute were noted 5.6 times more often among deceased premature infants (39% versus 7%, p<0.0001). The presence of IVH and DIC was also more often recorded among deceased infants compared to surviving infants (62% versus 40%, p<0.0001) and (88% versus 44%, p<0.001), respectively. Of the other factors, in the group of deceased children compared to the group of surviving children, atelectasis (91% versus 44%, p<0.001) and NEC (40% versus 7%, p<0.001) were more common. Other parameters did not show significant differences.

3.2 Evaluation of the association of low birth weight preterm infants' characteristics with mortality

All the studied factors that showed significant differences in the comparative analysis (Table 3) were analyzed in the regression analysis to identify their association with the fatal outcome. The results are presented in Table 4.

Table 4 Evaluation results of the association of low birth weight preterm infants' characteristics with mortality

№	Parameters	Unadjusted odds ratio, 95% CI	p	Adjusted odds ratio, 95% CI	p
1	**Apgar scores at 1 minute**				
	4 scores or more	reference		reference	
	1-3 scores	7.225 (4.281-12.193)	**<0,0001**	2,478 (1,289-4,764)	**0,007**
2	**Apgar scores at 5 minutes**				
	4 scores or more	reference		reference	
	1-3 scores	8.272 (4.543-15.063)	**<0,0001**	3,754 (1,788-7,878)	**<0,0001**
3	**Atelectasis**				
	no	reference		reference	
	yes	5.111 (3.022- 8.644)	**<0,0001**	1,803 (0,941-3,455)	0,076
4	**DIC syndrome**				
	no	reference		reference	
	yes	9.006 (4.891-16.584)	**<0,0001**	4,428 (2,206-8,887)	**<0,0001**
5	**NEC**				
	no	reference		reference	
	yes	8.581 (4.716 - 15.610)	**<0,0001**	4,508 (2,270-8,954)	**<0,0001**
6	**IVH**				
	no	reference		reference	
	yes	2.437 (1.550-3.833)	**<0,0001**	1,648 (0,940-2,888)	0,081

In the univariate logistic regression model, all factors showed an association with death: 1-3 points on the Apgar score at the 1st minute (OR- 7.225, 95% CI- 4.281-12.193, p<0.0001), 1-3 points on the Apgar score at the 5th minute (OR- 8.272, 95% CI- 4.543-15.063, p<0.0001), atelectasis (OR- 5.111, 95% CI- 3.022-8.644, p<0.0001), DIC (OR- 9.006, 95% CI- 4.891-16.584, p<0.0001), NEC (OR- 8.581, 95% CI 4.716 - 15.610, p<0.0001) and IVH (OR – 2.437, 95% CI 1.550-3.833, p<0.0001).

However, when testing these factors in a multivariate logistic regression model, only 1-3 points on the Apgar score at the 1st minute (OR - 2.478, 95% CI - 1.289-4.764, p = 0.007), 1-3 points on the Apgar score at the 5th minute (OR - 3.754, 95% CI - 1.788-7.878, p < 0.0001), DIC syndrome (OR - 4.428, 95% CI - 2.206-8.887, p < 0.0001), NEC (OR - 4.508, 95% CI - 2.270-8.954, p < 0.0001) confirmed the association with a fatal outcome in children with RDS.

3.3 Evaluation of the prognostic significance of a set of factors for fatal outcome in low birth weight premature infants with RDS

A ROC analysis was conducted to identify which factors had the highest prognostic value. Acceptable and good area under the curve values should be greater than 0.7 [11].

The results are presented in Table 5 and Figure 1.

Table 5 ROC analysis results

№	Parameters	Area under the curve	Standard error	p
1	DIC syndrome	0,283	0,027	<0,0001
2	NEC	0,335	0.033	<0,0001
3	DIC syndrome+NEC (Predicted probability)	0,782	0.025	<0,0001

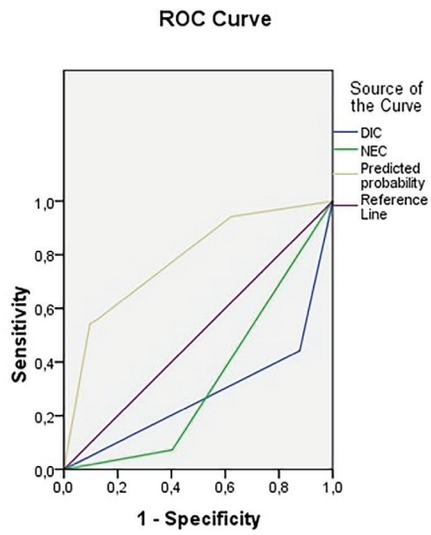


Figure 1 – ROC curves for DIC, NEC and their combination for predicting mortality in low birth weight preterm infants with RDS

ROC curves were created to assess how well DIC syndrome, NEC, and their combination predicted mortality in low birth weight preterm infants with RDS. The area under the curve for DIC syndrome was 0.283. At the same time, this indicator for NEC was 0.335. The area under the curve for the combination of DIC syndrome and NEC was 0.782 (Figure 1).

Discussion

This study was initiated due to the limited understanding of the interplay between respiratory distress syndrome (RDS) and other health conditions in premature, low-birth-weight infants, and the impact of these comorbidities on mortality rates.

Analysis of the concomitant pathologies structure in low birth weight premature newborns with respiratory distress syndrome

It has been found that low birth weight newborns with RDS, born at a low gestational age, are characterized by the presence of several concomitant diseases. In general, the data obtained are consistent with the studies of other authors [12-14].

Moreover, the main concomitant pathology in newborns both with and without RDS was pneumonia. These data indicate the predominant influence of prematurity on the risk of developing respiratory pathologies. A significant contributor to the high mortality rate among these infants is the requirement for mechanical ventilation and other forms of respiratory support. This can harm lung tissue [15], worsen RDS, and lead to ventilator-induced pneumonia [16]. Surprisingly, when newborns who survived were compared to those who didn't, no difference was found in the rate of pneumonia. It is believed that this is due to improved management and therapeutic strategies, which reduce the impact of pneumonia on mortality in this group of newborns.

It was also noticed that there were significant differences in the structure of concomitant diseases in low birth weight infants with and without RDS. Thus, infants with RDS were significantly more likely to have such diseases as anemia, DIC, atelectasis, and NEC. It is believed that the prevalence of these diseases in newborns with RDS is associated with the pathogenesis of these pathologies. Thus, the high frequency of anemia in RDS can be explained by bidirectional cause-and-effect relationships. On the one hand, neonatal anemia is also a consequence of prematurity and contributes to the development of hypoxia. In turn, hypoxia suppresses the development of epithelial cells and contributes to their death, simultaneously reducing the production of pulmonary surfactant, thus being a risk factor for RDS [17]. On the other hand, respiratory disorders can be a risk factor for hemorrhages, which increases the risk of anemia [18]. Atelectasis is also often associated with RDS. This is due to the similarity of the pathogenesis of these diseases. Both of these pathologies are associated with reduced surfactant production in premature infants. In addition, invasive respiratory support, often necessary for RDS, can contribute to the development of atelectasis [19].

An interesting feature of the study is the higher incidence of NEC in neonates with RDS. Although NEC is an independent disease, as is RDS, which is formed as a result of prematurity, our data confirm the presence of a multifactorial biological connection in critical illnesses, including cross-talk between the intestine and the lung, the so-called "lung-gut" axis [20]. As for the high incidence of DIC syndrome in RDS, it is hypothesized that this is due to the coagulation profile characteristic of RDS, which is manifested by hypocoagulation and high hyperfibrinolytic potential [21], as well as the birth of children with a low score on the Apgar score in the first and fifth minutes, which indicates hypoxia and its influence on the development of DIC.

Identification mortality risk factors in these newborns

Another objective of this study was to examine risk factors for mortality in the context of comorbidities. When analyzing risk factors for mortality in the study group, it was found that in

addition to the Apgar score, NEC and DIC are also risk factors for mortality. Well-studied risk factors for mortality are the Apgar score at the first and fifth minute and the use of advanced resuscitation after birth. The Apgar score at the first minute reflects how well the baby tolerated the birth process, and the Apgar score at the fifth minute reflects how well the baby feels after birth.

At the same time, it is considered that the identified association of NEC and DIC on mortality in neonates with RDS reflects their impact on mortality in preterm infants in general, and is not a feature of infants with RDS. In particular, NEC is the leading cause of death due to gastrointestinal diseases in preterm infants, affecting 5-12% of neonates born with very low birth weight. Moreover, mortality rates among newborns who require surgical intervention are estimated at 20–30% [22]. DIC is also a serious complication of the neonatal period in low birth weight infants and can either develop independently or be a manifestation of NEC in severe cases [23]. Considering that both DIC and NEC were more common in newborns with RDS and were identified as risk factors for death, the role of the synergistic effect of these two pathologies on mortality in such children was analyzed. It was found that the combination of these two pathologies increases the risk of death by two times.

This study differs from other similar studies in that it examines a specific population of extremely preterm infants born before 32 weeks, classified as extremely low birth weight (ELBW) and very low birth weight (VLBW) infants, without controlling for factors such as weight and gestational age, the effects of which have already been widely studied in previous studies. Moreover, the influence of concomitant pathologies, as well as their combination, on the lethal outcome in this category of newborns was studied.

Thus, in addition to previously studied factors such as low birth weight and gestational age, it was found that in the group of low birth weight premature infants with RDS, a combination of DIC syndrome and NEC made a significant contribution to the development of a fatal outcome.

A weakness of the study is the lack of analysis of the influence of social and maternal factors on the studied characteristics of newborns. In the future, we plan to conduct such an analysis. Also, the results of this study are specific to premature infants weighing less than 1500 g and with a gestational age of less than 32 weeks, and therefore cannot be applied to other categories of newborns.

The study's strength is its ability to assess how the interplay of different health conditions influences mortality rates in extremely premature infants with respiratory distress syndrome. It is thought that our findings will contribute to lower mortality rates in low-birth-weight premature infants with RDS. By understanding the structure of concomitant pathologies and identifying mortality risk factors in preterm infants with RDS has direct implications for clinical decision-making and patient care.

Conclusion

The structure of comorbidities in low birth weight infants with RDS differs from that of infants without RDS. Premature infants with RDS were more likely to develop anemia, DIC, atelectasis, and NEC.

The presence of comorbidities increases the risk of death in low birth weight infants with RDS. Low Apgar score, DIC syndrome, and NEC can increase the risk of death in low birth weight premature infants with RDS.

It is anticipated that the collected data will enhance personalized care for low birth weight, premature infants with multiple health conditions, ultimately reducing mortality rates in this vulnerable patient group.

Author Contributions: Conceptualization, A.T.; methodology, A.T. and A.A.; validation, A.A.; formal analysis, A.A.; investigation, A.A.; resources, N.B.; data curation, D.Y.; writing – original draft preparation, A.T. and A.A.; writing – review and editing, N.B.; visualization, A.A.; supervision, A.T.; project administration, A.A.; funding acquisition, A.A. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding information: This study is funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (grant no. AP22786227).

References

1. Yadav S, Lee B, Kamity R. Neonatal Respiratory Distress Syndrome. Treasure Island (FL): *StatPearls Publishing;* 2024.
2. Tana M, Tirone C, Aurilia C, Lio A, Paladini A, Fattore S, Esposito A, De Tomaso D, Vento G. Respiratory Management of the Preterm Infant: Supporting Evidence-Based Practice at the Bedside. *Children*. 2023; 10(3): 535. https://doi.org/10.3390/children10030535
3. Marinonio ASS, Costa-Nobre DT, Sanudo A, Miyoshi MH, Areco KCN, Kawakami MD, de Cassia Xavier R, Konstantyner T, Bandiera-Paiva P, Vieira de Freitas RM, Correia Morais LC, La Porte Teixeira M, Waldvogel BC, Kiffer CRV, Branco de Almeida MF, Guinsburg R. Temporal Trend and Risk Factors for Respiratory Distress Syndrome-Associated Neonatal Mortality in Preterm Infants: A Population-Based Study in a Middle-Income Country. *Am J Perinatol.* 2024; 41(S 01): e298–e304. https://doi.org/10.1055/s-0042-1754410.
4. Al-Momani MM. Admission patterns and risk factors linked with neonatal mortality: A hospital-based retrospective study. *Pak J Med Sci.* 2020; 36(6): 1371–1376. https://doi.org/10.12669/pjms.36.6.2281.
5. Tembo D, Abobo FDN, Kaonga P, Jacobs C, Bessing B. Risk factors associated with neonatal mortality among neonates admitted to neonatal intensive care unit of the University Teaching Hospital in Lusaka. *Sci Rep.* 2024; 14: 5231. https://doi.org/10.1038/s41598-024-56020-6.
6. Zivaljevic J, Jovandaric MZ, Babic S, Raus M. Complications of Preterm Birth—The Importance of Care for the Outcome: A Narrative Review. *Medicina.* 2024; 60(6): 1014. https://doi.org/10.3390/medicina60061014.
7. Ward RM, Beachy JC. Neonatal complications following preterm birth. *BJOG*. 2003; 110 (Suppl 20): 8-16. https://doi.org/10.1016/S1470-0328(03)00012-0.
8. Andegiorgish AK, Andemariam M, Temesghen S, Ogbai L, Ogbe Z, Zeng L. Neonatal mortality and associated factors in the specialized neonatal care unit Asmara, Eritrea. *BMC Public Health.* 2020; 20: 10. https://doi.org/10.1186/s12889-019-8118-x.

9. Daemi A, Ravaghi H, Jafari M. Risk factors of neonatal mortality in Iran: a systematic review. *Med J Islam Repub Iran.* 2019; 33: 87. https://doi: 10.34171/mjiri.33.87.
10. Batieha AM, Khader YS, Berdzuli N, Chua-Oon C, Badran EF, Al-Sheyab NA, Basha A.S, Obaidat A, Al-Qutob RJ. Level, Causes and Risk Factors of Neonatal Mortality, in Jordan: Results of a National Prospective Study. *Matern Child Health J.* 2016; 20(5): 1061–1071. https://doi.org/10.1007/s10995-015-1892-x.
11. Yang S, Berdine G. The receiver operating characteristic (ROC) curve. *The Southwest Respiratory and Critical Care Chronicles.* 2017; 5(19): 34–36. https://doi.org/10.12746/swrccc.v5i19.391.
12. Kiatchoosakun P, Jirapradittha J, Paopongsawan P, Techasatian L, Lumbiganon P, Thepsuthammarat K, Sutra S. Mortality and Comorbidities in Extremely Low Birth Weight Thai Infants: A Nationwide Data Analysis. *Children*. 2022; 9(12): 1825. https://doi.org/10.3390/children9121825.
13. Bhombal S, Chock VY, Shashidharan S. The impact of prematurity and associated comorbidities on clinical outcomes in neonates with congenital heart disease. *Semin Perinatol*. 2022; 46(4): 151586. https://doi.org/10.1016/j.semperi.2022.151586.
14. Ofek Shlomai N, Reichman B, Zaslavsky-Paltiel I, Lerner-Geva L, Eventov-Friedman S. Neonatal morbidities and postnatal growth failure in very low birth weight, very preterm infants. *Acta Paediatr.* 2022; 111(8): 1536–1545. https://doi.org/10.1111/apa.16380.
15. Kalikkot Thekkeveedu R, El-Saie A, Prakash V, Katakam L, Shivanna B. Ventilation-Induced Lung Injury (VILI) in Neonates: Evidence-Based Concepts and Lung-Protective Strategies. Journal of Clinical Medicine. 2022; 11(3): 557. https://doi.org/10.3390/jcm11030557.
16. Alriyami A, Kiger JR, Hooven TA. Ventilator-Associated Pneumonia in the Neonatal Intensive Care Unit. *Neoreviews*. 2022; 23(7): e448–e461. https://doi.org/10.1542/neo.23-7-e448.
17. Aslamzai M, Froogh BA, Mukhlis AH, Faizi OA, Sajid SA, Hakimi Z. Factors associated with respiratory distress syndrome in preterm neonates admitted to a tertiary hospital in Kabul city: A retrospective cross-sectional study. *Global Pediatrics.* 2023; 3: 100035. https://doi.org/10.1016/j.gpeds.2023.100035.
18. Wang TT, Zhou M, Hu XF, Liu JQ. Perinatal risk factors for pulmonary hemorrhage in extremely low-birth-weight infants. *World J Pediatr.* 2020; 16(3): 299–304. https://doi.org/10.1007/s12519-019-00322-7.
19. Santos AK, Silveira J, Neves VC, Zotz TGG, Motter AA, Andreazza M.G. Atelectasis and lung changes in preterm neonates in the neonatal period: a blind radiological report and clinical findings. *Rev Bras Ter Intensiva.* 2019; 31(3): 347–353. https://doi.org/10.5935/0103-507X.20190047.
20. Ziaka M, Exadaktylos A. Exploring the lung-gut direction of the gut-lung axis in patients with ARDS. *Crit Care.* 2024; 28(1): 179. https://doi.org/10.1186/s13054-024-04966-4.
21. Katsaras GN, Sokou R, Tsantes AG, Konstantinidi A, Gialamprinou D, Piovani D, Bonovas S, Kriebardis AG, Mitsiakos G, Kokoris S, Tsantes AE. Thromboelastometry in Neonates with Respiratory Distress Syndrome: A Pilot Study. *Diagnostics (Basel).* 2021; 11(11): 1995. https://doi.org/10.3390/diagnostics11111995.
22. Meister AL, Doheny KK, Travagli RA. Necrotizing enterocolitis: It's not all in the gut. *Exp Biol Med (Maywood).* 2020; 245(2): 85–95. https://doi.org/10.1177/1535370219891971.
23. Su Y, Xu RH, Guo LY, Chen XQ, Han WX, Ma JJ, Liang JJ, Hao L, Ren CJ. Risk factors for necrotizing enterocolitis in neonates: A meta-analysis. *Front Pediatr.* 2023; 10: 1079894. https://doi.org/10.3389/fped.2022.1079894.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15703

The Effect of Breast Cancer History on Bone Mineral Density in the Treatment of Postmenopausal Osteoporosis: One-Year Follow-Up Results

Yasemin Tombak[1], Ebru Karaca Umay[1], Fatma Nazli Unkazan[2], Ozgur Zeliha Karaahmet[1], Methiye Kubra Sezer[1], Ece Unlu Akyuz[1], Eda Gurcay[3]

[1]Physical Medicine and Rehabilitation, Ankara Etlik City Hospital, Ankara, Turkey
[2]Physical Medicine and Rehabilitation, Kirklareli University Faculty of Medicine, Kirklareli, Turkey
[3]Physical Medicine and Rehabilitation, University of Health Sciences, Gaziler Physical and Rehabilitation Medicine Education and Research Hospital, Ankara, Turkey

Received: 2024-10-12.
Accepted: 2024-12-09.

J Clin Med Kaz 2024; 21(6): 85–90

Corresponding author:
Yasemin Tombak.
Email: yasemintombak@hotmail.com.
ORCID: 0000-0003-0065-5376.

Abstract

Aim: Breast cancer patients who get certain chemotherapeutic agents are more likely to experience early menopause and to suffer osteoporotic fractures at a younger age. This study investigated the impact of breast cancer history on bone mineral density (BMD) levels in postmenopausal osteoporosis (OP) treatment.

Materials and Methods: This is a retrospective case-control study analyzed 65 female cases diagnosed with OP, including 32 patients with stable breast cancer who had undergone chemotherapy and/or radiotherapy but not within the last 5 years, and 33 matched controls. Demographic characteristics, total lumbar and femoral neck BMD levels and biochemical parameters were recorded for both groups.

Results: Before treatment, femoral neck T-score and serum Ca levels were lower in the patient group than in the control group (p=0.038, p=0.007, respectively). There was no difference between groups for the first year (p>0.05), but when the change within a group was examined, only the patient group showed a significant increase in femoral neck T-score and serum Ca levels (p=0.027, p=0.001, respectively). Patients who received radiotherapy had lower femoral neck BMD levels before and after treatment than those who did not receive radiotherapy (p=0.021, p=0.024, respectively), and the post-treatment recovery was not different (p>0.05).

Conclusion: This study demonstrated the success of osteoporosis treatment in patients with a previous diagnosis of breast cancer. Patients with breast cancer must be screened for osteoporosis and treated accordingly.

Keywords: bone mineral density; breast cancer; osteoporotic fractures; postmenopausal osteoporosis, screening

Introduction

In osteoporosis (OP), a systemic skeletal disorder, decreased bone density and degradation within the bone micro-architecture contribute to an increased fragile nature and a higher risk of fractures [1]. Based on the cause, it is divided into primary and secondary OP.

Primary OP consists of type 1 (postmenopausal) and type 2 (senile) OP. The biochemical phenomenon known as postmenopausal osteoporosis (OP) is typified by low bone mass and weakened microarchitecture as a result of the estrogens' no longer having a direct influence on osteoclasts [2]. Secondary OP is caused by a variety of disorders or medication use. Changes in lifestyle, genetic diseases, hypogonadal conditions, endocrine diseases, gastrointestinal diseases, hematological diseases, rheumatological and autoimmune diseases, neurological and musculoskeletal system difficulties, smoking and alcohol use, weight loss, and drugs (aromatase inhibitors, chemotherapeutics, etc.) are all potential causes [3].

Menopause causes rapid bone loss. Women may experience a loss up to 30% of their bone density over the first five years after menopause if estrogen is not present. Some chemotherapy agents used in breast cancer patients develop premature menopauses as well as elevate the possibility of osteoporotic fractures in these patients at early ages [4,5].

Bone mineral density (BMD), Z- and T-scores were all low in breast cancer patients, whereas the proportion of bone loss and osteoporosis were high [6].

As a consequence of this, according to current National Comprehensive Cancer Network guidelines, women receiving aromatase inhibitor (AI) treatment for breast cancer should have their BMD monitored with a baseline scan and then on a regular basis after that [7].

No research has been done to compare the efficacy of osteoporosis treatment in individuals with a history of breast cancer with those who have not. The focus of this study was to look into how BMD levels were affected by radiotherapy, chemotherapy, and breast cancer history both before and one year after osteoporosis treatment.

Materials and methods

Study design

This study was conducted after obtaining approval (Protocol No. P202300018 dated 31.03.2023) in the format required by the clinical research ethics committee of the local institute and under the principles set forth in the declaration of Helsinki. The study procedure was clarified to those who participated, and their written informed consent was collected in the manner mandated by the local institute's ethical committee.

This is a retrospective case-control study included 32 patients with breast cancer and a control group of 33 age-matched patients with osteoporosis, totaling 65 female cases. The records of 65 female patients who were followed up in the physical medicine and rehabilitation outpatient clinic were diagnosed with postmenopausal OP for the first time by lumbar and/or femoral neck BMD scanning were evaluated.

Stable breast cancer and OP patients who have a history of chemotherapy and/or radiotherapy but have not received chemotherapy and/or radiotherapy in the last 5 years, group 1 (n=32, patient group), those with OP diagnosis compatible with age and body mass index, group 2 (n=33, control group) were included in the study. Patients under 50 years of age, who had an additional disease other than a cancer history or were diagnosed with an additional disease during follow-up, were using irregular medication and were excluded from the study.

Demographics and Disease Characteristics

Demographic characteristics, total lumbar and femoral neck BMD levels, and biochemical parameters of all patients were recorded. Patients were questioned whether they had suffered a fracture or not.

The cancer stage of the patients with a history of cancer is presented in Table 1 with TNM (tumor, lymph node, metastasis) staging [8]. Oestrogen positivity, chemotherapy, and radiotherapy histories were questioned.

BMD measurements were conducted by a dual-energy x-ray absorptiometry (DEXA) instrument. Lumbar spine (L1-L4) total score and hip region (femoral neck), T-scores, and serum biochemical parameters measured according to standard protocols were recorded (T0). In all patient groups, 1200 mg calcium carbonate and vitamin D3 were administered along with alendronate (70 mg/wk) to correct the existing hypocalcemia and prevent hypocalcemia during treatment. Patients who attended regular check-ups and continued their medication were included. The (T1) values of the patients at the end of the first year were recorded.

Table 1 TNM staging of breast cancer

Stage	Notes
Stage 0	This N0 M0
Stage 1	
1a	Tmic N0 M0/T1 N0 M0
1b	T0 Nmic M0/Tmic Nmic M0/T1 Nmic M0
Stage 2	
2a	T0 N1 M0/T1 N1 M0/T2 N0 M0
2b	T2 N1 M0/T3 N0 M0
Stage 3	
3a	T0 N2 M0/T1 N2 M0/T2 N2 M0/T3 N1 M0/T3 N2 M0
3b	T4 N0 M0/T4 N1 M0/T4 N2 M0
3c	T1-4 N3 M0
Stage 4	Any T, Any N, M1

T: tumor, N: regional lymph nodes, M: metastasis, is: in situ, mic: micro invasion

Statistical analysis

It was found that 28 patients would be enough for each group to produce a power of 80% with a significance of 0.05, provided an effect size of 0.4 (Cohen's d) for the sample size. With a 10% standard deviation, the effect size was computed to find a 10% variation in the DEXA screening recommendation.

The Statistical Package for Social Sciences (SPSS) 22.0 for Windows was used to analyze the data. In descriptive statistics, data were expressed as median (25%-75% quartile range) for continuous variables, frequency, and percentage (%) for nominal variables. Normality was evaluated with the Kolmogorov-Smirnov test. None of the continuous variables were normally distributed. The Wilcoxon Signed Rank test was utilized to assess statistically significant variations in the group's repeated measurements. Statistically, the difference between the groups was evaluated with the Mann-Whitney-U test. $p<0.05$ scores were considered significant.

Results

The median age of the patient group was 58.2 years, whereas that of the control group was 57.6 years (p=0.182). The patient group's body mass index (BMI) was 29.5 kg/m2, while that of the control group was 29.7 kg/m2 (p=0.895). The patient and control groups shared similar demographic features. No fractures occurred in either patient group.

Table 2 Disease characteristics of patients with breast cancer:

	Patient Group (n=32) n (%), Median (%25-%75 quartile range)
Number of patients receiving chemotherapy	32 (100)
Number of patients receiving radiotherapy	13 (40.6)
Number of patients who underwent surgery	32 (100)
Affected breast	
Right	19 (59.4)
Left	13 (40.6)
Bilateral	0
Stage	
1a	7 (21.9)
2a	8 (25.0)
2b	9 (28.1)
3a	8 (25.0)
Untreated time (years)	7.28 (5.12-8.25)

Table 3 Comparison of pretreatment (T0) BMD and biochemical parameters of the groups

Parameter	Patient Group(n=32) Median (%25-%75 quartile range)	Control Group (n=33) Median (%25-%75 quartile range)	p
L1-4 total T score	-2.90 (-3.50_-1.95)	-2.80 (-3.12_-2.01)	0.171
Femur neck T score	-2.85 (-3.45_-2.10)	-2.15 (-2.92_-1.90)	**0.038**
Serum Ca (mg/dl)	7.10 (6.70-9.12)	9.80 (8.80-.11.15)	**0.007**
Serum P (mg/dl)	3.45 (2.85-4.40)	3.20 (2.91-3.98)	0.092
Serum ALP (U/l)	47.30 (31.15-94.22)	46.50 (34.15-97.24)	0.134
Serum PTH (ng/L)	28.12 (17.60-56.22)	26.20 (19.25-57.18)	0.592
Serum calcidiol (ng/mL)	21.18 (17.20-26.30)	23.45 (18.35-32.64)	0.357
Serum osteocalcin(µg/L)	9.60 (6.58-12.65)	8.85 (7.78-11.72)	0.172

BMD: Bone mineral density, Ca: calcium, P: phosphorus ALP: alkaline phosphatase, PTH: parathormone

Table 4 Comparison of BMD and biochemical parameters of the groups at the 1st year of treatment (T1)

Parameters	Patient Group(n=32) Median (%25-%75 quartile range)	Control Group (n=33) Median (%25-%75 quartile range)	p
Total lumbar (L1-4) T score	-2.60 (-3.32_-1.12)	-2.50 (-3.00_-1.92)	0.532
Total femoral neck T score	-2.05 (-3.01_-1.54)	-2.08 (-2.97_-2.06)	0.427
Serum Ca (mg/dl)	9.80 (8.62-11.38)	9.90 (8.70-11.15)	0.918
Serum P (mg/dl)	3.60 (2.92-4.32)	3.50 (3.04-4.25)	0.134
Serum ALP (U/l)	46.50 (21.12-98.24)	47.10 (27.18-96.44)	0.262
Serum PTH (ng/L)	28.21 (18.72-60.15)	26.95 (21.35-58.32)	0.098
Serum Calcidiol (ng/mL)	22.48(18.61-32.78)	22.50 (19.61-35.44)	0.699
Serum Osteocalcin (µg/L)	9.62 (7.76-11.28)	9.15 (7.92-11.05)	0.128

BMD: Bone mineral density, Ca: calcium, P: phosphorus ALP: alkaline phosphatase, PTH: parathormone

Table 5 Comparison of treatment changes in patient and control groups

Parameters	Patient Group(n=32) Median (%25-%75 quartile range)	Control Group (n=33) Median (%25-%75 quartile range)	p
Total lumbar (L1-4) T score	0.30 (0.18-0.80)	0.21 (0.16-0.69)	0.589
Total femoral neck T score	0.68 (0.37-0.80)	0.10 (-0.21-0.52)	**0.027**
Serum Ca (mg/dl)	2.26 (1.77_2.85)	0.0 (-0.10_0.10)	**0.001**
Serum P (mg/dl)	0.17 (-0.08-0.25)	0.25 (0.13-0.32)	0.253
Serum ALP (U/l)	-0.80 (-6.97-0.60)	-0.80 (-10.03-4.02)	0.940
Serum PTH (ng/L)	1.12 (0.09-3.93)	1.14 (0.75-2.10)	0.637
Serum Calcidiol (ng/mL)	1.41 (1.30-6.48)	1.29 (-0.95-2.80)	0.076
Serum Osteocalcin (µg/L)	0.02 (-1.37-1.18)	0.14 (-0.67-0.30)	0.154

Ca: calcium, P: phosphate, ALP: alkaline phosphatase, PTH: parathormone

All of the patients had received chemotherapy after surgery and were estrogen receptor-positive (n=32, 100%). The characteristics of the disease are presented in Table 2.

In terms of pre-treatment parameters between the groups, the patient group had lower serum Ca levels and a lower femoral neck T-score than the control group (p=0.038, p=0.007, respectively). In the first year, the two groups' results did not differ from one another (p>0.05), but when the change within the group was examined, the increase in the femoral neck T-score and serum Ca levels was significant in the patient group (p=0.027, p=0.001, respectively), while the change in the control group was not significant (p>0.05) (Tables 3-5).

The pre- and post-treatment evaluation results of the patients who had radiotherapy (n=13) and those who did not receive radiotherapy (n=19) are presented in Table 6.

The femoral neck BMD levels in the patients who underwent radiotherapy were lower at the beginning and after the treatment than the patients who did not receive radiotherapy (p=0.021, p=0.024, respectively), and the post-treatment recovery was not different (p>0.05) (Table 6).

Discussion

In our study, the effect of breast cancer history and bone mineral density (BMD) on postmenopausal osteoporosis (OP) treatment was investigated.

Table 6 Pretreatment (T0) and 1st year (T1) results of patients who received and did not receive radiotherapy (RT).

Parameters	Administered RT (n=13) Median (%25-%75 quartile range)		No RT (n=19) Median (%25-%75 quartile range)		P		
	T0	T1	T0	T1	P*	P#	P&
Total lumbar (L1-4) T score	-3.05 (-3.50_-2.31)	-2.75 (-3.32_-2.15)	-2.82 (-3.21_-1.95)	-2.57 (-2.80_-1.12)	0.246	0.392	0.308
Total femoral neck T score	-3.05 (-3.45_-2.32)	-2.38 (-3.01_-1.91)	-2.75 (-2.98_-2.10)	-1.81 (-2.56_-1.54)	**0.024**	**0.021**	0.127
Serum Ca (mg/dl)	7.05 (6.70-8.50)	9.72 (8.62-10.30)	7.24 (6.90-9.12)	9.95 (9.17-11.38)	0.542	0.724	0.361
Serum P (mg/dl)	3.30 (2.85-3.47)	3.45 (2.92-4.01)	3.55 (3.27-4.40)	3.75 (3.18-4.32)	0.458	0.337	0.872
Serum ALP (U/l)	46.65 (31.15-84.50)	45.58 (21.12-86.77)	48.27 (40.26-94.22)	47.63 (42.60-98.24)	0.265	0.185	0.644
Serum PTH (ng/L)	26.57 (17.60-48.67)	27.14 (18.72-58.21)	29.21 (20.15-56.22)	29.34 (24.21-60.15)	0.282	0.894	0.102
Serum Calcidiol (ng/mL)	19.11 (17.20-20.12)	21.33 (18.61-25.52)	22.25 (19.18-26.30)	24.15 (20.05-32.78)	0.169	0.203	0.836
Serum Osteocalcin (µg/L)	9.58 (6.58-10.05)	9.55 (7.76-10.28)	9.74 (7.21-12.65)	9.71 (8.85-11.28)	0.326	0.181	0.753

Ca: calcium, P: phosphate, ALP: alkaline phosphatase, PTH: parathormone
**: p value between groups before treatment*

#: p value between groups at the 1st year of treatment

&: p value between groups for change with treatment

Before treatment, femoral neck T-score and serum Ca levels were lower in the patient group than in the control group. There was no difference between groups for the first year, but when the change within a group was examined, only the patient group showed a significant increase in femoral neck T-score and serum Ca levels. Patients who received radiotherapy had lower femoral neck BMD levels before and after treatment than those who did not receive radiotherapy, and the post-treatment recovery was not different.

OP and breast cancer are prevalent diseases that affect people of similar ages in the postmenopausal period. This means that the primary risk factor for OP is estrogen deficiency while excess estrogen after menopause is considered to be the key risk factor for breast cancer [9].

Bisphosphonate therapy improves BMD in postmenopausal women using AI and premenopausal women with breast cancer who become amenorrheic throughout treatment, according to randomized, placebo-controlled clinical trials [10].

Bisphosphonates are the current gold standard for oral therapeutics in osteoporosis [11].

In our study, similar results were obtained at the end of the treatment between the patients diagnosed with osteoporosis and regardless of their history of breast cancer, and the patients who received and did not receive RT as a subgroup analysis.

In a study monitoring breast cancer patients scheduled for cytotoxic chemotherapy were assessed by measuring BMD in the 6th month before the start of chemotherapy, the percentage decreases in BMD in the lumbar spine, femoral neck and total hip were found to be $-2{,}36 \pm 2{,}90$, $-2{,}63 \pm 3{,}79$ and $-2{,}08 \pm 2{,}80$, respectively [12].

In our study, the patient group had lower femoral neck T-scores and serum Ca levels before treatment. This implies that BMD measures are impacted by breast cancer therapy. In the literature, which supports our hypothesis, BMD was assessed before starting AI treatment and at the 6th month of treatment in 45 patients included in a study by Erbag et al. [13] Femoral T-scores and BMD levels significantly decreased in the analysis of the patients with two measurement findings. In the analysis of the patients with two measurement results, a significant decrease was found in the femoral T-score and BMD values. When the lumbar vertebra T-scores of the patients were compared, it was found that the second measured vertebra T-score, Z-score, and BMD values were significantly lower. Based on these findings, it has been shown that AI treatment significantly affects BMD even in the first 6 months [13].

Following treatment, our study found no differences between the two groups. There was a significant increase in femoral neck T-score and serum calcium levels in the patient group after 1 year of treatment, but the control group did not experience any notable changes. Similarly in the literature, in a 2-year randomized double-blind placebo-controlled study by Greenspan et al. [14,15] weekly oral risedronate therapy was found to be beneficial for spine and hip BMD in postmenopausal breast cancer women with or without AI therapy.

In breast cancer, RT can be applied to the breast after breast-conserving surgery, to the chest wall, and regional lymph nodes after mastectomy. RT is used as palliative treatment in metastatic breast cancer [16]. Radiation-related bone complications include malignancy, fractures, growth arrest, and osteopenia. Certain complications, including osteopenia, can be reversed, and the

degree of these complications varies with dosage. After radiation therapy, insufficiency fractures are common complications that typically affect bones with the highest trabecular/cortical bone ratio and the highest physiological stress [17]. It has been reported that besides causing bone atrophy, radiotherapy can have a direct effect on the bone in the irradiated area and affect bone vascularity by changing it [18].

In our study, patients who received RT at baseline and afterward had lower femoral neck than those who did not receive RT. Recovery with treatment was also not different from the control group. That is, in our study, we see the negative effect of RT on bone, but the fact that treatment and recovery were not different between the two groups emerged as a pleasing result.

The fact that the BMD values before the cancer history were not known can be considered a limitation.

Conclusion

This study demonstrated the success of osteoporosis treatment in patients with a previous diagnosis of breast cancer. Patients with breast cancer must be screened for osteoporosis and treated accordingly.

Author Contributions: Conceptualization, Y.T., E.K.U.; drafting or revising critically, Y.T., E.K.U., E.U.A., E.G.; data collection or processing, E.K.U., F.N.U., M.K.S.; analysis or interpretation, Y.T., E.K.U., F.N.U., O.Z.K.; literature search, Y.T., E.K.U.; writing, Y.T., O.Z.K., E.U.A., E.G.; supervision: Y.T., E.K.U. All authors have read and agreed to the final version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

Ethics approval: The study protocol received institutional review board approval (dated 31.03.2023; Protocol No. P202300018) and all participants provided informed consent in the format required by the clinical research ethics committee of Kirklareli University, Kirklareli, Turkey.

Informed consent: All participants provided written informed consent in the format required by the clinical research ethics committee of the local institute.

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article. The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

References

1. Duque G, Troen BR. Understanding the mechanisms of senile osteoporosis: new facts for a major geriatric syndrome. *J Am Geriatr Soc*. 2008; 56(5): 935–941. https://doi.org/10.1111/j.1532-5415.2008.01764.x.
2. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. *Nat Rev Endocrinol.* 2013; 9(12): 699–712. https://doi.org/10.1038/nrendo.2013.179.
3. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S et al. Clinician's Guide to Prevention and Treatment of Osteoporosis [published correction appears in Osteoporos Int. 2015; 26: 2045-47]. *Osteoporos Int.* 2014; 25(10): 2359–2381. https://doi.org/10.1007/s00198-014-2794-2.
4. Mahon SM. Osteoporosis: A concern for cancer survivors. Oncol Nurs Forum. 1998; 25: 843–851.
5. Bruning PF, Pit MJ, de Jong-Bakker M, van den Ende A, Hart A, van Enk A. Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *Br J Cancer* 1990; 61(2): 308–310. https://doi.org/10.1038/bjc.1990.58.
6. Zhao F, Li C, Wang W, Zhang Y, Yao P, Wei X, Jia Y, Dang Sh, Zhang Sh. Machine learning predicts the risk of osteoporosis in patients with breast cancer and healthy women. *J Cancer Res Clin Oncol*. 2024; 150(2): 102. https://doi.org/10.1007/s00432-024-05622-8.
7. Gradishar WJ, Anderson BO, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goldstein LJ, Hayes DF, Hudis CA, Isakoff SJ, Ljung BM, Marcom PK, Mayer IA, McCormick B, Miller RS, Pegram M, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Smith ML, Soliman H, Somlo G, Ward JH, Wolff AC, Zellars R, Shead DA, Kumar R; National Comprehensive Cancer Network Breast Cancer Panel. Breast cancer version 3.2014. *J Natl Compr Canc Netw* 2014; 12: 542–590.
8. Edge SB, Byrd DR, Compton CC, editors. The American Joint Committee on Cancer: the 7th edition of AJCC cancer staging manual. Springer-Verlag, New York: Springer-Verlag; 2010. 347 p.
9. Fontanges E, Fontana A, Delmas PD. Osteoporosis and breast cancer. *J Bone Spine* 2004; 71(2): 102–110. https://doi.org/10.1016/j.jbspin.2003.02.001.
10. VanderWalde A, Hurria A. Aging and osteoporosis in breast and prostate cancer. *CA Cancer J Clin.* 2011; 61(3): 139–156. https://doi.org/10.3322/caac.20103.
11. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. *J Clin Endocrinol Metab.* 2020; 105(3): dgaa048. https://doi.org/10.1210/clinem/dgaa048.
12. Nisha Y, Dubashi B, Bobby Z, Sahoo JP, Kayal S, Ananthakrishnan R, Ganesan P. Cytotoxic chemotherapy is associated with decreased bone mineral density in postmenopausal women with early and locally advanced breast cancer. *Arch Osteoporos.* 2023; 18(1): 41. https://doi.org/10.1007/s11657-023-01231-z.
13. Erbag G. The risk of developing osteoporosis of the early-stage breast cancer patients using aromatase inhibitor. [DoctoralThesis]. Kocaeli University School of Medicine; 2011, Available from: https://acikbilim.yok.gov.tr/handle/20.500.12812/409288.
14. Greenspan SL, Vujevich KT, Brufsky A, Lembersky BC, van Londen GJ, Jankowitz RC, Puhalla SL, Rastogi P, Perera S. Prevention of Bone Loss with Risedronate in Breast Cancer Survivors: A Randomized, Controlled Clinical Trial. *Osteoporos Int.* 2015; 26(6): 1857–1864. https://doi.org/10.1007/s00198-015-3100-7.
15. Greenspan SL, Brufsky A, Lembersky BC, Bhattacharya R, Vujevich KT, Perera S, et al. Risedronate prevents bone loss in breast cancer survivors: a 2-year, randomized, double-blind, placebo-controlled clinical trial. *J Clin Oncol.* 2008; 26(16): 2644-52. https://doi.org/10.1200/JCO.2007.15.2967.

16. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med.* 2002; 347(8): 567–575. https://doi.org/10.1056/NEJMoa020128.
17. Pacheco R, Stock H. Effects of radiation on bone. *Curr Osteoporos Rep.* 2013; 11(4): 299–304. https://doi.org/10.1007/s11914-013-0174-z.
18. Shapiro CL, Van Poznak C, Lacchetti C, Kirshner J, Eastell R, Gagel R, Smith S, Edwards BJ, Frank E, Lyman GH, Smith MR, Mhaskar R, Henderson T, Neuner J. Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline. *J Clin Oncol.* 2019; 37(31): 2916–2946. https://doi.org/10.1200/JCO.19.01696.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15701

Development and Printing of a Customized 3D Model of a Solitary Humeral Cyst as a Stage in Surgical Treatment of Bone Defects Using Orgignal Bone Replased Material

Bakhtiyar Makhatov[1], Berik Tuleubayev[1], Amina Koshanova[1]

[1]Department of Surgery, NAO "Karaganda Medical University", Karaganda, Kazakhstan

Received: 2024-10-01.
Accepted: 2024-12-09.

J Clin Med Kaz 2024; 21(6): 91–94

Corresponding author:
Bakhtiyar Makhatov.
E-mail: mahatov@qmu.kz.
ORCID: 0009-0009-1262-6848.

Abstract

Objective: To study the possibilities of using 3D technology in preoperative planning and surgical treatment for solitary bone cyst.

Methods. As part of this work, a 3D model of a solitary cyst of the proximal humerus of a 14-year-old teenager was formed based on CT scans for printing a bone defect sample on a 3D printer.

Results. During processing, 3D slicer, 3D paint and Rhinoceros programs were used to create a virtual bone model and edit it further. Printing was done using ABS plastic and thermoplastic polyurethane using the FDM method. A comparison of the samples was made, taking into account the necessary characteristics for future filling of the model with bone plastic material and formation of an individualized graft.

Conclusion. The results of the study showed the feasibility and simplicity of the technique for creating and printing 3D bone models. This method can be fully utilized to create customized grafts that are identical in shape to the bone cyst.

Keywords: bone cyst, additive technologies, 3D technologies.

Introduction

Bone cysts (CC) are benign neoplasms that occur in bone tissue. They are most common in children (85% of cases) aged 5 to 15 years. CC ranks third in frequency of occurrence among all primary bone formations. The lesion can develop in any bone of the skeleton, but most often CC is localized in the proximal humerus (more than 50%) and femoral (25%) bones [2].

Despite the fact that several theories have been proposed to explain the development of bone cysts, the exact causes of their occurrence have not been fully studied.

Although bone cysts are usually benign, they can cause pain, bone deformity, and even fractures. In some cases, cysts can degenerate into malignant tumors.

Also, complications of this pathology are pain, bone deformity, and pathological fractures [15].

The only effective method of treating a bone cyst is surgical treatment. The most proven method is curettage of the cavity or radical excision of the cyst with replacement of the resulting defect. To date, the choice of material for bone grafting is extensive. Thanks to the ongoing research, the scientific community is offering more and more innovative, affordable, easy-to-use and effective materials for filling bone defects. Thus, one of the fairly developed areas in this field is the use of additive technologies in preoperative planning and modeling of bone defects.Modern 3D modeling capabilities in the arsenal of orthopedists make it possible to get a detailed idea of the structure and location of the cyst. This helps to plan a more accurate and less invasive operation [17].

The use of 3D-printed navigation templates and implants makes it possible to improve the accuracy and safety of the operation, as well as reduce the time of its implementation, which has a positive effect on the outcome of treatment due to a reduction in the surgical load and complete anatomical bone restoration [14]. Such technologies have been actively used over the past 10 years in many countries, including Russia [3]. The novelty of the research is due to the variety of software tools and the variety of materials used in additive technologies, as well as various applications of 3D modeling in operational techniques.

As part of this work, preoperative planning and modeling of a bone cyst of the upper third of the humerus of a 13-year-old patient was carried out using 3D-Slicer and Rhinoceros programs.

According to the information available to us, there has never been a study using this software in 3D modeling of bone cysts.

The purpose of this study is to explore the possibilities of using 3D technologies in preoperative planning and surgical treatment of solitary bone cysts.

This work is part of a study on the development and application of bone-plastic material with the addition of bone allograft, prepared using the Marburg bone bank technology. This type of allograft was chosen due to its proven clinical effectiveness both in emergency traumatological operations with a bone defect and in orthopedic restoration of bone integrity [1].

As part of this work, it is extremely important to obtain a detailed impression of the inner wall of the cyst in order to further fill the model with bone-plastic material and form a so-called primary bone filling. In the future, it is planned to develop a method for the surgical treatment of bone defects using pre-prepared bone fillings.

Materials and methods

We conducted a simulation of a solitary cyst of the proximal humerus of a 13-year-old patient.From the patient's medical history, the symptoms of the cyst were not noted, and therefore the initial diagnosis of the cyst occurred with a pathological fracture, which was noted a year before the treatment. After consolidation of the fracture, surgical treatment of the bone cyst in the volume of scraping the walls and filling the cyst with bone allograft was carried out as planned. During a follow-up examination, a recurrence of the cyst was noted a year later. Based on the CT scan of the shoulder joint at the time of diagnosis of recurrence, it was decided to simulate a cyst. The 3DSlicer program, version 5.6.2, was used for this purpose.

The 3D Slicer used in this study is a free, open source medical image processing software that works seamlessly on a personal computer and is compatible with various systems[8]. It allows you to significantly reduce the cost of medical services and is convenient for use in clinical research.

The first version of Slicer software was presented by David Goering in 1999 as part of his master's thesis at the Massachusetts Institute of Technology [9] It was based on the developments of MIT research groups and the Laboratory of Surgical Planning (SPL) [11]. Later, Steve Piper became the chief architect of the project and led its transformation into a full-fledged software package.

Since 1999, Slicer has been continuously developing under the leadership of Ron Kikinis in the SPL. Today, professional engineers, algorithm developers and scientists from various fields are working on its creation. IsomicsInc., Kitware Inc. and GE Global Research are also involved in the development process, as well as the Slicer user community.

Slicer was originally conceived as a system of neurosurgical guidance, visualization and analysis [9, 16]. Over the past decade, it has evolved into an integrated platform that is used in various clinical and preclinical studies, as well as for image analysis unrelated to medicine [11].

The initial processing was carried out in the Paint 3D application, as in the most accessible and widespread software for working with 3D models.

Paint 3D is a raster graphics editor and a program for 3D modeling and printing, introduced in the Windows 10 Creators Update. Designed by LIFT London Studio. Paint 3D includes the functions of the Microsoft Paint and 3D Builder applications, combining an easy hybrid 2D-3D editing method that allows users to select various shapes from the application, their personal computer [13].

With the help of this program, the cyst model was divided into two halves for ease of printing and further filling it as a mold for possible plastic materials based on bone allograft, and the dimensions were changed identically to the CT study data.

Subsequent processing was carried out in the Rhino® program (V 6.0 SR 23, Robert McNeel&Associates) - engineering software for 3D reconstruction of surfaces.

It is mainly used in industrial design, architecture, ship design, jewelry and automotive design, CAD/CAM design, rapid prototyping, reverse engineering, as well as multimedia and graphic design.

The model created in Rhino demonstrates NURBS surfaces (Flamingo rendering).

Rhino specializes in NURBS modeling. Plugins developed by McNeel include Flamingo (retrace rendering), Penguin (non-photorealistic rendering), Bongo (animation) and Brazil (complex rendering). There are over a thousand third-party plugins for Rhino. As with many other modeling programs, Rhino has its own scripting language based on Visual Basic, and the SDK allows you to read and write files directly [10].

Results

CT images in DICOM format were used in the simulation. The dimensions of the inner walls of the cyst are shown in Figure 1.

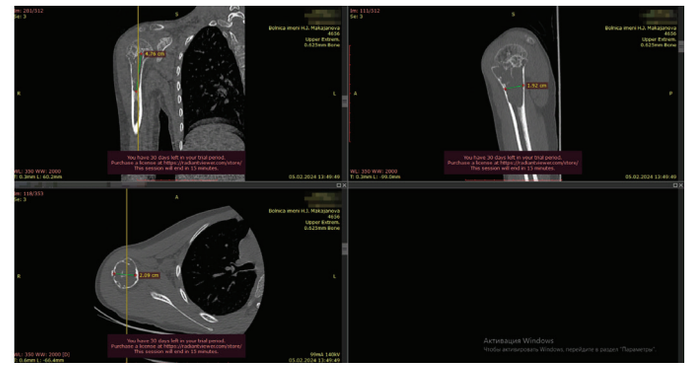


Figure 1 – Dimensions of the inner walls of the cyst on CT scans

Using the Thresholding tool from the Segment Editor set, the bone part of the images was selected directly. The presence of this tool helped to quickly separate the soft tissues that are not applicable for research on all layers, creating a three-dimensional model of all the bones available on the slices. The result is shown in Figure 2.

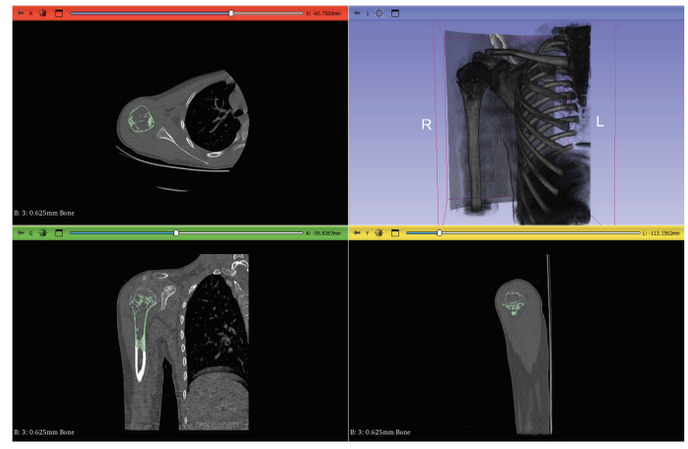


Figure 2– Screenshot of working in 3D Slicer

Next, using the Scissors tool from the same set, the scapula, clavicle and ribs, as well as the distal humerus, were isolated and removed. Thus, a 3D model of the proximal humerus with an existing cyst was obtained, which was exported in stl format. For greater printing convenience, the resulting sample was divided longitudinally into two parts in the Paint 3D program. The result is shown in Figure 3.

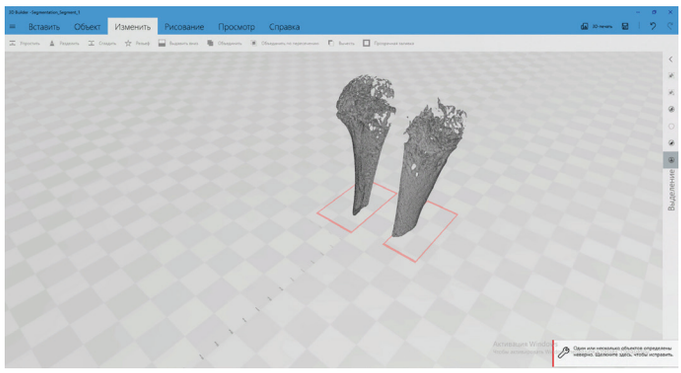


Figure 3 – 3D model of the proximal humerus

This model was printed by FDM printing on a commercial basis in the company "3DStudio" with white ABS plastic. The result is shown in Figure 4.

Figure 4 – Printed 3D model. ABS, FDM printing

As you can see, the printed model is well suited as a training material and as a sample for preoperative planning. However, for filling the mold with bone plastic material, it cannot be called successful due to the difficulties with filling voids and holes formed during the printing of growth zones. Thus, there was definitely a need for further processing with a detailed isolation of the cyst cavity itself and its separation from the cavities of the growth zones where possible.

In this connection, further, also on a commercial basis, the post-processing of the model in the Rhinoceros program was carried out by 3DStudio with further printing by FDM printing with PLA plastic. Due to the characteristics of the selected material, the sample turned out to be more flexible, easily removed from the frozen biocomposite without violating the integrity of the structure, preserving all the details of the inner surface of the bone cavity. The visually printed model is shown in Figure 5.

Figure 5 – Printed 3D model. Thermopolyuretan, FDM printing

Discussion

In this case, the demonstrative effectiveness of the proposed method is clearly visible.The resulting sample reflected all the irregularities and protrusions of the inner wall of the cyst, which, in fact, was a cast of the inner cavity of the cyst. The possibilities of visualization, analysis and processing of CT images available to orthopedists with the transformation of the latter into a 3D model are also clearly demonstrated.

However, given the young age of the patient and the presence of growth zones, the resulting sample is not suitable for the manufacture of adequate replacement material during preoperative planning.

It should be noted here that more detailed processing is possible only in 3D engineering design programs that require additional skills. This may be a difficulty for orthopedists planning surgical treatment with further filling with bone-plastic material or any similar technique involving the formation of a kind of "bone filling".

Despite this, the primary printed sample of a bone cyst is quite suitable for practicing the technique of scraping the walls of the cyst or completely removing the necessary area with the formation of individual tools and templates. Prepared guide templates are used to resect the required area both in the recipient's bone and in the donor allograft. This technique is quite actively used in Europe [5, 12, 4] and in mainland China [18, 7, 6]. The authors also note the disadvantages of the chosen technique, such as a large traumatization of the patient during surgery, a long period of rehabilitation, the need for a large amount of donor material and premature lysis of the allograft, leading to instability and rejection of the transplanted area.

The technology we have in development eliminates the above disadvantages due to the fact that the filling of the scraped cyst cavity occurs evenly, without damage to the cortical bone. The presence of an additional adhesive in the bone-plastic material makes it possible to solve the issue of early lysis of allograft. To date, in parallel with the work described above, a search is being carried out for a suitable adhesive composite and its optimal concentration in combination with bone allograft for sufficient stimulation of bone resorption.

Conclusions

The results of the work have shown the accessibility and simplicity of the technique of forming and printing 3D models of bone defects in the preoperative planning of their surgical treatment. This technique can be fully used to form customized grafts identical in shape to a bone cyst. This technique aims to obtain a negative bone cavity with a detailed repetition of the irregularities of the inner wall and volume of the cavity for the preoperative formation of a positive bone cyst from the original biocomposite. This study requires further work in terms of finding the optimal composition of the biocomposite and preclinical studies.

Author Contributions: Conceptualization, B. T.; methodology, B. T.; validation, B. M.; formal analysis, B. M.; investigation, B. M.; resources, not applicable; data curation, B. M.; writing – original draft preparation, B. M.; writing – review and editing, A. K; visualization, B. M.; supervision, B. T.; project administration, B. T.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. Arutjunjan MG. Zagotovka kostnogo allografta i ego primenenie v Respublike Kazahstan. In: Aktual'nye voprosy tkanevoj i kletochnoj transplantologii : Sbornik tezisov VII Vserossijskogo simpoziuma s mezhdunarodnym uchastiem, Astrahan', 27–28 aprelja 2017 goda [In Russian]. Astrahan: *Astrahanskij gosudarstvennyj medicinskij universitet,* 2017. P. 8–10.
2. Hotim OA. Sostojanie kostnoj tkani u detej s kostnymi kistami. In: Dostizhenija sovremennogo sestrinskogo dvizhenija i praktiki : sbornik materialov k 30-letiju vysshego sestrinskogo obrazovanija v Respublike Belarus [In Russian]. Grodno: *Grodnenskij gosudarstvennyj medicinskij universitet,* 2022. P. 139–141.
3. Jarikov AV, Gorbatov RO, Denisov AA, Smirnov II, Fraerman AP, Sosnin AG, Perl'mutter OA, Kalinkin AA. Primenenie additivnyh tehnologij 3d-pechati v nejrohirurgii, vertebrologii, travmatologii i ortopedii [In Russian]. *Klinicheskaja praktika*. 2021; 12(1): 90–104. https://doi.org/10.17816/clinpract64944.
4. Alessandri G, Frizziero L, Santi GM, Liverani A, Dallari D, Vivarelli L, Di Gennaro GL, Antonioli D, Menozzi GC, Depaoli A, Rocca G, Trisolino G. Virtual Surgical Planning, 3D-Printing and Customized Bone Allograft for Acute Correction of Severe Genu Varum in Children. *Journal Of Personalized Medicine.* 2022; 12(12): 2051. https://doi.org/10.3390/jpm12122051.
5. Ardente DF, Fusaro FM, Abad MP, Soldado F, Coll JQ. The utilization of computer planning and 3D-printed guide in the surgical management of a reverse Hill-Sachs lesion. *JSES Int.* 2020; 4(3): 569–573. https://doi.org/10.1016/j.jseint.2020.04.013.
6. Chen CJ, Brien EW. Early postoperative compilations of bone filling in curettage defects. *Journal of Orthopaedic Surgery and Research.* 2019; 4(1): 261. https://doi.org/10.1186/s13018-019-1297-4.
7. Dong C, Beglinger I, Krieg AH. Personalized 3D-printed guide in malignant bone tumor resection and following reconstruction-17 cases in pelvic and extremities. *Surgical Oncology-Oxford.* 2022; 42: 101733. https://doi.org/10.1016/j.suronc.2022.101733.
8. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, Bauer C, Jennings D, Fennessy F, Sonka M, Buatti J, Aylward S, Miller JV, Pieper S, Kikinis R. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magnetic Resonance Imaging.* 2012; 30(9): 1323–1341. https://doi.org/10.1016/j.mri.2012.05.001.
9. Gering DT. A system for surgical planning and guidance using image fusion and interventional. Thesis (S.M.). Cambridge: *Massachusetts Institute of Technology, Dept. of Electrical Engineering and Computer Science*, 2000.
10. 10. Gould L. 3D Modeling and Rendering for the Rest of Us – 2017. https://web.archive.org/web/20090709092144/.
11. 11. Grimson E, Leventon M, Ettinger G, Chabrerie A, Ozlen F, Nakajima S, Atsumi H, Kikinis R, Black P. Clinical experience with a high precision image-guided neurosurgery sy. Medical Image Computing and Computer-Assisted Intervention. In: Medical Image Computing and Computer-Assisted Intervention – MICCAI 1998. Lecture Notes in Computer Science, vol. 1496. Berlin: *Springer, Heidelberg,* 1998. https://doi.org/10.1007/BFb0056188.
12. Huotilainen E, Salmi M, Lindahl J. Three-dimensional printed surgical templates for fresh cadaveric osteochondral allograft surgery with dimension verification by multivariate computed tomography analysis. *Knee.* 2019; 26(4): 923–932. https://doi.org/10.1016/j.knee.2019.05.007.
13. Iizuka K. Welcome to the Wonderful World of 3D. *Optics and Photonics News.* 2007; 18(2): 24–29.
14. Meng M, Wang J, Sun T, Zhang W, Zhang J, Shu L, Li Zh. Clinical applications and prospects of 3D printing guide templates in orthopaedics. *Journal of Orthopaedic Translation.* 2022; 35: 22–41. https://doi.org/10.1016/j.jot.2022.03.001.
15. Nasri E, Reith JD. Aneurysmal bone cyst: a review. *Journal of Pathology and Translational Medicine.* 2023; 3(57): 81–87.
16. Gering DT, Nabavi A, Kikinis R, Hata N, O'Donnell LJ, Grimson WEL, Jolesz FA, Black PM, Wells WM. An Integrated Visualization System for Surgical Planning and Guidance Using Image Fusion and an Open MR. *Journal of Magnetic Resonance Imaging*. 2010; 13(6): 967–975. https://doi.org/10.1002/jmri.1139.
17. Wixted CM, Peterson JR, Kadakia RJ, Adams SB. Three-dimensional Printing in Orthopaedic Surgery: Current Applications and Future Developments. *JAAOS: Global Research and Reviews.* 2021; 5(4): e20.00230-11. https://doi.org/10.5435/JAAOSGlobal-D-20-00230.
18. Wu ZG, Fu J, Wang Z, Li XD, Li J, Pei YJ, Pei GX, Li D, Guo Z, Fan HB. Three-dimensional virtual bone bank system for selecting massive bone allograft in orthopaedic oncology. *International Orthopaedics.* 2015; 39 (6): 1151–1158. https://doi.org/10.1007/s00264-015-2719-5.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15702

Complete Blood Count (CBC) and Multivariate Analysis as Tools for Predicting Coronavirus (COVID-19) Infectious

Hafedah Noureldeen Elsharef[1], Mansour Awiadat Salem[2], Fatimah Nouri Mohammed Abdulwahid[1], Yasser Fathi Nassar[3]

[1]Department of Biology, Faculty of Education, University of Wadi Alshatti, Brack, Libya
[2]Department of Environmental Sciences, Faculty of Environment and Natural Resources, University of Wadi Alshatti, Brack, Libya
[3]Department of Mechanical and Renewable Energy Engineering, Faculty of Engineering, University of Wadi Alshatti, Brack, Libya

Received: 2024-09-21.
Accepted: 2024-12-09.

J Clin Med Kaz 2024; 21(6): 95–102

Corresponding author:
Hafedah Noureldeen Elsharef.
Email: h.elshref@wau.edu.ly.
ORCID: 0009-0006-9232-9277.

Abstract

The COVID-19 pandemic has affected millions worldwide in recent years. However, the epidemic's impact on the residents of the southern Libyan region has not been assessed. To investigate the spread of COVID-19 among the population, a study was conducted from March to June 2021. The study involved 146 people, 97 of whom were infected with COVID-19 and 49 were not infected. A complete blood count (CBC) and multivariate statistical analysis were used to determine the extent of the epidemic's spread in the study area. The CBC analysis used China's Tecom Science Corporation, model number TEK-5000. The results revealed that males (58.76%) were more affected than females (41.24%). The most affected age group was those under 46 (53.6%). The T-test analysis showed significant differences ($p > 0.01$) for each Red blood cell count (RBC), Mean corpuscular haemoglobin (MCH), Mean corpuscular haemoglobin concentration (MCHC), Red cell distribution width (RDW), Platelet count (PLT), White blood cell count (WBC), Platelet count (PLT), and granulocytes (GRA). However, the Hematocrit (HCT) was less than the significance level ($P < 0.05$), and there was no significant difference ($P > 0.05$) for Hemoglobin (HGB), Mean corpuscular volume (MCV), Lymphocyte (LYM), and Monocyte (MON) compared to the uninfected group. This study indicates that COVID-19 infection significantly affects the average values of blood tests, and changes in these values may cause complications for patients. Therefore, monitoring these changes in blood values is crucial to reducing the death rate among the infected.

Keywords: Complete Blood Count; COVID-19; Multivariate statistical analysis; infected; uninfected; T-test.

Introduction

The COVID-19 pandemic, discovered in Wuhan, China 2019, has caused widespread concern. Millions of people have been infected with the disease, quickly spreading globally [1,2]. COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily affects the respiratory system [3]. The disease has severely impacted life's health, social, and economic aspects [4,5]. While most individuals recover within a few days after experiencing mild symptoms such as fever, dry cough, and altered sense of taste and smell [6,7], patients with acute symptoms, especially those with pre-existing chronic conditions, can develop pneumonia and acute respiratory distress syndrome within days of contracting COVID-19, leading to increased mortality rates [7,8]. Although initial reports only linked COVID-19 to pneumonia, accumulating data reveals that coagulopathy and intravascular coagulation are also common among those infected and contribute to the high mortality rate [9,10]. Certain groups, including smokers, alcoholics, and those with a history of similar illnesses, are more susceptible to the disease. Elderly individuals with chronic conditions are more vulnerable to COVID-19 than younger,

healthier people [8,11]. Moreover, COVID-19 patients who are older and have diabetes, cardiovascular disease, or obesity are at a higher risk of hospitalization and death compared to those without these conditions [12,13]. Furthermore, older COVID-19 patients with diabetes, cardiovascular disease, or obesity are at a higher risk of hospitalization and death compared to those without these conditions [12,13]. Laboratory tests, such as a Complete Blood Count (CBC), provide crucial information about the stage and severity of COVID-19. Studies show that COVID-19 patients typically experience changes in red blood cells, haemoglobin levels, hematocrit levels, mean corpuscular volume, and monocyte and eosinophil levels. The average platelet volume is also a prognostic factor for COVID-19 patients [14]. Additionally, the concurrent consumption of alcohol and smoking is linked to more severe cases of COVID-19. Studies by Akman et al. [15] and Shivakumar et al. [16] assess the effectiveness of biomarkers from peripheral blood samples in diagnosing COVID-19 for patients visiting the emergency department. They find no significant difference between the positive and negative test groups regarding lymphocyte and platelet values ($p>0.05$). However, another study by Shivakumar et al. [16] identifies significant differences between infected and uninfected individuals in the neutrophil-to-lymphocyte ratio (NLR), platelet count, haemoglobin levels, and leukocyte count ($p<0.05$). The NLR is approximately 1.8 times higher in COVID-19 patients who survive than usual, differing from the trends observed in uninfected individuals. These findings are further supported by [17], who report that critically ill COVID-19 patients exhibit considerably higher NLRs than the uninfected group. In 2021, Pozdnyakova et al. [18] conducted a study investigating the clinical significance of changes in numerical peripheral blood parameters in predicting outcomes for COVID-19 patients; they also compared these changes between critical cases of COVID-19-positive and COVID-19-negative patients, and the study revealed significant variations in the white blood cell counts among all COVID-19 patients, which differed depending on the severity of their cases.

The first case of COVID-19 in Libya was reported on March 24, 2020. Initially confined to the southern region, the outbreak eventually spread to the western and eastern parts of the country. Estimates suggest COVID-19 has affected between 390,000 to 1.3 million people in Libya, accounting for approximately 14 to 20% of the population [19]. The Coronavirus (COVID-19) has spread frighteningly among people, forcing many residents to undergo a test to ensure they are not infected. It was necessary to find a fast and reliable way to verify this. Therefore, this study aimed to use the complete blood analysis (CBC) method to determine the possibility of infection with this virus.

Materials and methods

Study area

The study was conducted from March to June 2021 in the Al-Shatti region of southwest Libya, approximately 700 km south of Tripoli and 60 km north of Sebha. The Al-Shatii district is situated between latitudes 23° to 28.5° N and longitudes 10° to 16° E, with a population of roughly 100,000 individuals [20]. Blood samples for complete blood count (CBC) analysis were collected from patients admitted to the isolation centres in Brack and Algorda.

Collection of blood samples

This study included 146 patients, with 97 testing positive for COVID-19 via PCR and 49 testing negatives at the Brack Isolation Centre (BIC) and the filtration centres in Brack, Al-Qardah, and Al-Disa. The sampling technique is based on the procedure commonly used by other researchers; medical staff members took blood samples from patients admitted to the isolation centres who agreed to be part of this study, while the reference blood samples were taken from people who had no symptoms of convicted-19. Blood samples were collected using test tubes containing EDTA anticoagulant and were subsequently analyzed on the same day using a TEK-5000 CBC analyzer from Tecom Science Corporation, China.

Statistical Analysis

A multivariate analysis was conducted to examine the relationships between various CBC analyses. The Pearson correlation coefficient was used to measure the variability between the parameters and identify any correlations between them [21]. The data was analyzed using multivariate statistical analysis, which included descriptive statistics, correlation coefficients, and principal component analysis (PCA). Additionally, factor analysis, hierarchical cluster analysis (HCA), and T-test analysis were performed to compare the haematological parameters of infected and uninfected individuals. The analysis was carried out using SPSS version 26.

Results

Descriptive analysis

This study included 146 individuals and thoroughly examined the connection between infection and blood parameters. Out of these, 97 were infected (41.24% female, 58.76% male) with an average age of 47 years, and 49 were uninfected (61.22% female, 38.78% male) with an average age of 34 years. The complete blood count (CBC) analysis presented

Table 1 Descriptive analysis of the CBC for infected and uninfected individuals.

	Infected (n =97)						Uninfected (n = 49)					
	Min.	Max.	Mean	Med.	S. D	CV%	Min.	Max.	Mean	Med.	S. D	CV%
age	4.00	90.00	47.01	46.00	17.58	37.39	9.00	89.00	34.14	28.00	17.24	50.78
HGB (g/dl)	5.30	18.40	12.56	12.90	2.36	18.79	8.80	16.80	13.23	13.40	1.85	13.98
RBC(10^6/µl)	2.04	5.87	4.43	4.43	0.64	10.38	2.89	5.15	4.16	4.20	0.50	12.02
HCT(%)	15.27	50.91	37.38	37.80	5.91	15.81	23.50	45.00	35.35	35.20	4.61	13.04
MCV (fl)	66.30	105.50	85.19	85.60	7.68	9.01	66.70	106.50	85.43	85.50	6.80	7.96
MCH(pg)	18.60	35.30	28.41	28.50	3.12	10.98	19.80	36.90	31.90	32.50	3.52	11.03
MCHC(g/dl)	19.60	41.20	33.23	33.30	2.56	7.70	0.90	42.30	38.26	40.10	6.30	16.47
RDW(%)	10.00	20.90	13.63	13.20	2.16	16.17	11.90	23.30	18.36	19.10	3.24	17.65
PLT(10^3/µl)	57.00	693.00	263.13	244.00	100.98	38.38	110.00	460.00	208.49	206.00	64.18	30.78
WBC(10^3/µl)	1.88	16.70	7.30	6.70	3.28	44.93	2.00	13.10	5.93	5.70	2.00	33.73
LYM(10^3/µl)	0.25	4.50	2.06	1.90	1.01	49.03	0.70	5.80	2.14	2.00	0.89	41.59
MON(10^3/µl)	0.05	2.10	0.51	0.40	0.35	68.63	0.10	1.00	0.40	0.30	0.22	55.0
GRA(10^3/µl)	0.74	15.30	4.76	4.10	3.11	65.37	1.00	6.50	3.37	3.30	1.43	42.43

in Table 1 indicated notable differences between infected and uninfected individuals. Specifically, the levels of red blood cells (RBC), hematocrit (HCT), platelets (PLT), white blood cells (WBC), monocytes (MON), and granulocytes (GRA) were found to be higher in infected individuals compared to uninfected ones. Conversely, uninfected individuals exhibited higher levels of haemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW), and lymphocytes (LYM) than their infected counterparts.

Furthermore, the platelet count (PLT) displayed a high standard deviation, particularly within the infected group. It is noteworthy that the coefficient of variation (CV%) for variables such as haemoglobin (HGB), red blood cells (RBC), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and red cell distribution width (RDW) indicates a symmetrical distribution of these variables.

The degree of variation in CV values can be classified as follows: low (<10%), moderate (10% to 20%), high (20% to 30%), and very high (>30%). Typically, CV values range from 5% to 50%, with values below 1% rare. Variables with a CV% lower than 20% indicate a symmetrical distribution [22]. When the CV% values are low, the mean values align with the median, indicating homogeneity in the collected specimens [23].

Multivariate statistical analysis

Correlation analysis

Table 2 presents the results of the Pearson correlation coefficient analysis conducted on CBC and the age of infected individuals. The study reveals a strong positive correlation between HGB, RBC, HCT, MCV, MCH, and MCHC (r=0.701, 0.919, 0.494, 0.595, and 0.408), respectively. Additionally, there is also a strong positive correlation between RBC and HCT (r=0.773), HCT and MCV and MCH (r=0.527 and 0.493), MCV and MCH (r=0.786), MCH and MCHC (r=0.538), PLT and WBC, MON, GRA (r=0.403, 0.492, and 0.302, respectively), WBC, MON, and GRA (r=0.383 and 0.919, respectively), and MON and GRA (r=0.269).

Table 2 Correlation analysis of infected and uninfected people

		HGB	RBC	HCT	MCV	MCH	MCHC	RDW	PLT	WBC	LYM	MON	GRA
Infected (n=97)	HGB	1											
	RBC	0.701**	1										
	HCT	0.919**	0.773**	1									
	MCV	0.494**	-0.056	0.527**	1								
	MCH	0.595**	0.022	0.493**	0.786**	1							
	MCHC	0.408**	0.035	0.176	0.222*	0.538**	1						
	RDW	-0.289**	-0.078	-0.303**	-0.348**	-0.294**	-0.229*	1					
	PLT	-0.151	-0.171	-0.222*	-0.047	-0.132	-0.031	0.223*	1				
	WBC	-0.104	-0.121	-0.101	0.078	-0.067	-0.073	0.129	0.403**	1			
	LYM	0.022	0.170	0.086	-0.139	-0.141	-0.153	0.090	0.186	0.162	1		
	MON	0.077	-0.004	0.063	0.203*	0.015	-0.060	0.139	0.492**	0.383**	0.122	1	
	GRA	-0.107	-0.209*	-0.124	0.105	-0.026	-0.020	0.071	0.302**	0.919**	-0.118	0.269**	1
Uninfected (n=49)	HGB	1											
	RBC	0.596**	1										
	HCT	0.861**	0.807**	1									
	MCV	0.406**	-0.258	0.343*	1								
	MCH	0.571**	-0.313*	0.202	0.760**	1							
	MCHC	0.391**	-0.193	0.009	0.249	0.652**	1						
	RDW	-0.043	-0.419**	-0.440**	-0.103	0.362*	0.419**	1					
	PLT	-0.074	0.368**	0.217	-0.221	-0.455**	-0.493**	-0.466**	1				
	WBC	-0.048	0.306*	0.072	-0.376**	-0.392**	-0.145	-0.250	0.147	1			
	LYM	0.176	0.356*	0.186	-0.305*	-0.171	0.140	-0.128	0.075	0.705**	1		
	MON	-0.186	0.362*	0.074	-0.430**	-0.572**	-0.498**	-0.396**	0.573**	0.630**	0.464**	1	
	GRA	-0.184	0.135	-0.064	-0.302*	-0.379**	-0.219	0-.200	0.099	0.881**	0.308*	0.462**	1

Table 3 Principle component analysis for infected people.

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
HGB	3.647	30.388	30.388	3.647	30.388	30.388	2.688	22.402	22.402
RBC	2.443	20.362	50.750	2.443	20.362	50.750	2.554	21.281	43.683
HCT	1.751	14.592	65.341	1.751	14.592	65.341	1.989	16.576	60.259
MCV	1.065	8.876	74.218	1.065	8.876	74.218	1.675	13.958	74.218
MCH	0.876	7.303	81.520						
MCHC	0.833	6.939	88.459						
RDW	0.695	5.789	94.248						
PLT	0.428	3.565	97.813						
WBC	0.125	1.044	98.857						
LYM	0.085	0.712	99.569						
MON	0.036	0.297	99.867						
GRA	0.016	0.133	100.000						

Extraction Method: Principal Component Analysis.

The analysis also shows a high negative correlation between HBC and RDW (r=-0.289), HCT and RDW and PLT (r=0.303 and -0.222, respectively), MCV and RDW (r=0.348), MCH and RDW (r=-0.294), and a positive correlation between RDW and PLT (r=0.223), GRA and Age (r=0.205). Furthermore, there is a negative correlation between RBC and GRA (r=-0.209), HCT and PLT (r=-0.222), MCH and RDW (r=-0.294), and MCHC and RDW (r=-0.229). In uninfected individuals, a strong positive correlation exists between HGB and RBC, HCT, MCV, MCH, and MCHC with correlation coefficients of 0.596, 0.861, 0.406, 0.571, and 0.391, respectively. Similarly, there is a positive correlation between RBC and HCT, PLT with correlation coefficients of 0.807 and 0.368, respectively. Additionally, MCV is positively correlated with MCH (r=0.760), MCH is positively correlated with MCHC (r=0.652), and MCHC is positively correlated with RDW (r=0.419). There is also a positive correlation between PLT and MON (r=0.573), and WBC is positively correlated with LYM, MON, and GRA with correlation coefficients of 0.705, 0.630, and 0.881, respectively.

Table 4 Rotated Component Matrix for infected people.

	Component			
	1	2	3	4
MCH	0.910	0.158	-0.039	-0.022
MCV	0.840	0.154	0.139	0.063
MCHC	0.639	0.005	-0.091	-0.053
RDW	-0.437	-0.165	-0.006	0.370
RBC	-0.129	0.940	-0.096	-.036
HCT	0.397	0.893	-0.024	-0.037
HGB	0.522	0.808	-0.044	0.000
GRA	0.020	-0.115	0.977	0.067
WBC	-0.063	-0.019	0.924	0.289
PLT	-0.025	-0.209	0.227	0.777
MON	0.135	0.043	0.263	0.753
LYM	-0.291	0.292	-0.141	0.520

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.
Rotation converged in 6 iterations.

Furthermore, 13 LYM is positively correlated with MON (r=0.464), and MON is positively correlated with GRA (r=0.462). On the other hand, there is a high negative correlation between RBC and RDW (r=-0.419), HCT and RDW (r=-0.440), MCV and WBC, and MON with correlation coefficients of -0.376 and -0.430, respectively. Additionally, MCH is negatively correlated with PLT, WBC, MON, and GRA with correlation coefficients of -0.455, -0.392, -0.572, and -0.397, respectively. MCHC is negatively correlated with PLT and MON with correlation coefficients of -0.493 and -0.498, respectively. Moreover, RDW negatively correlates with PLT and MON, with correlation coefficients of -0.466 and -0.396, respectively. In addition, there is a positive correlation between RBC, LYM and MON, with correlation coefficients of 0.356 and 0.362, respectively. Furthermore, MCH is positively correlated with RDW (r=0.362), and LYM is positively correlated with GRA (r=0.308). Conversely, there is a negative correlation between RBC and MCV (r=-0.313) and MCV and GRA (r=-0.302).

Principle Component Analysis (PCA)

The dataset was analyzed using principal component analysis to uncover any hidden patterns. The study revealed four eigenvalues greater than 1.00 before and after rotation. By reducing the initial dimension of the COVID-19-infected individual dataset, four components - PC1, PC2, PC3, and PC4 - were obtained, which account for 74.218% of the data variation. Table 3 displays the initial component matrix, with PC1, PC2, PC3, and PC4 explaining 30.388%, 20.362%, 14.592%, and 8.876% of the total variance, respectively. The dataset structure was examined by analyzing the loadings of components and rotated components in Table 4. The loading plots of the rotated components and data groups offered a more transparent and more readily understandable view of the results. PC1 exhibited the maximum MCH, MCV, MCH, and RDW loading in negative values, while PC2 showed loading by RBC, HCT, and HGB. PC3 had loading by GRA and WBC, and PC4 with PLT, MON, and LYM.

The initial dimension of the uninfected dataset was also reduced, with four components explaining 84.381% (Table 5). PC1 explained 35.919% and was loaded with MCHC, PLT, RDW, and MON. PC2 explained 24.308% and had loaded with HCT, HGB, and RBC.

Table 5 Principle component analysis for uninfected people.

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	4.310	35.919	35.919	4.310	35.919	35.919	2.827	23.556	23.556
2	2.917	24.308	60.226	2.917	24.308	60.226	2.771	23.091	46.646
3	1.857	15.472	75.698	1.857	15.472	75.698	2.662	22.179	68.826
4	1.042	8.682	84.381	1.042	8.682	84.381	1.867	15.555	84.381
5	0.674	5.618	89.999						
6	0.513	4.275	94.275						
7	0.381	3.171	97.446						
8	0.210	1.754	99.199						
9	0.083	0.690	99.889						
10	0.007	0.057	99.946						
11	0.004	0.035	99.981						
12	0.002	0.019	100.000						

Extraction Method: Principal Component Analysis.

PC3 explained 15.472% and was loaded with WBC, GRA, and LYM, while PC4 explained 8.682% and was loaded with MCV and MCH. The results highlight the differences between the PCA of CBC and the age of infected and uninfected people, which we attribute to the COVID-19 pandemic.

Cluster analysis

The clustering method involves identifying segments within a dataset and assigning each observation to a specific cluster. The aim is to minimize variation within a dendrogram (24). Two dendrogram clusters were identified, representing infected and uninfected individuals. For infected individuals (Figure 1), cluster A was further divided into two sub-clusters: sub-cluster A1 included HGB-HCT and RBC, while sub-cluster A2 consisted of MCV, MCH, and MCHC. Likewise, cluster B was subdivided into three smaller clusters: B1(i) contained WBC and GRA, B1(ii) included RDW, and B1(iii) comprised PLT-MON. The variables within each cluster were found to be comparable and correlated. Sub-cluster B2 contained the LYM variable. For uninfected individuals, the hierarchical clustering revealed two main clusters (Figure 2), A and B. Cluster A was divided into two sub-clusters: A1 included WBC-GRA, LYM, and PLT-MON, while A2 contained HGB-HCT and RBC. Cluster B was split into two sub-clusters: MCV-MCH and MCHC, while the other contained only RDW.

Independent samples T-test

In Table 7, the results of a T-test show that individuals infected with COVID-19 have similar levels of HGB, MCV, LYM, and MON as uninfected individuals. The probability value is higher than the significance level of 0.05, indicating no significant differences in these parameters. However, levels of HCT, RBC, MCHC, MCH, RDW, PLT, WBC, and GRA differ significantly, with probability values lower than the significance level of 0.05.

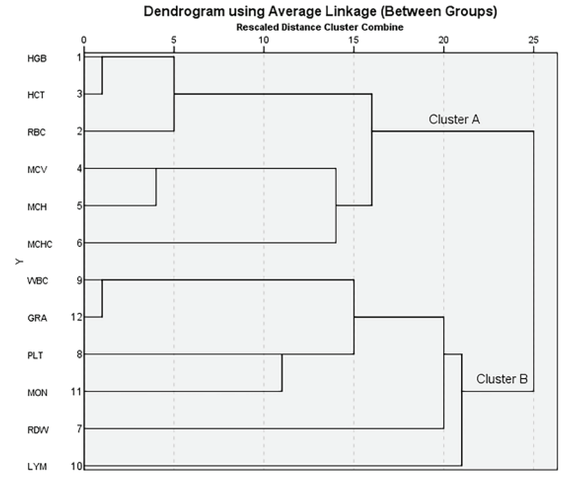


Figure 1 – Cluster analysis of individuals with COVID-19

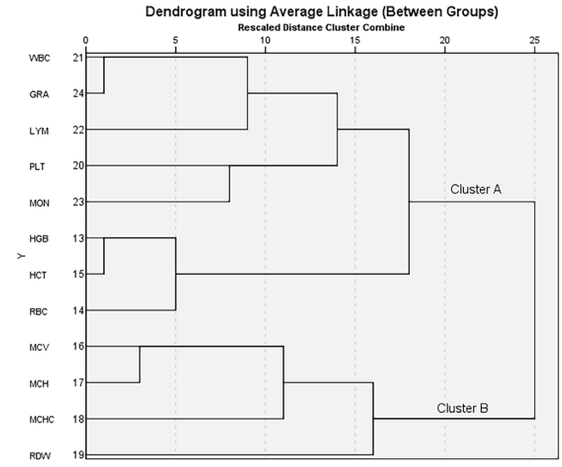


Figure 2 – Cluster analysis of uninfected individuals with COVID-19

Table 6 Rotated Component Matrix for uninfected people

	Component			
	1	2	3	4
MCHC	0.842	0.180	-0.016	0.150
PLT	-0.747	0.194	0.007	-0.209
RDW	0.746	-0.278	-0.214	-0.259
MON	-0.561	0.077	0.548	-0.326
HCT	-0.189	0.935	0.017	0.253
HGB	0.272	0.899	-0.046	0.273
RBC	-0.316	0.847	0.158	-0.306
WBC	-0.118	0.069	0.973	-0.156
GRA	-0.186	-0.164	0.870	0.006
LYM	0.160	0.352	0.688	-0.319
MCV	0.117	0.147	-0.232	0.922
MCH	0.626	0.202	-0.235	0.646

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

Rotation converged in 6 iterations.

Discussion

This study found that the majority of COVID-19 cases were among males (58.76%) with an average age of 47. In contrast, another study reported an equal ratio of male-to-female infection [25], possibly because males are more susceptible to COVID-19 infection than females, possibly because of biological differences in the immune system and genetic factors [26, 27]. Additionally, lifestyle factors such as smoking, drinking alcohol, and not following recommended social distancing regulations contribute to the higher infection rate in males [28]. On the other hand, females have been reported to behave more responsibly towards the COVID-19 crisis than men [26], which is consistent with other studies [28-30].

The study also found differences between infected and uninfected individuals through cluster analysis. Grouping of HGB-HCT in one cluster was acceptable since HGB and RBC are used to calculate HCT [31, 32], which could be attributed to the significant impact of COVID-19 on HGB, HCT, and RBC [33]. COVID-19 can lead to respiratory distress, affecting the blood's oxygen-carrying capacity and leading to hypoxia [34]. It may also directly infect bone marrow elements, resulting in abnormal hematopoiesis or triggering an autoimmune response against blood cells [35]. The second variable affected by COVID-19 was WBCs, which could be attributed to various factors, including an induced inflammatory response, immune system activation, and direct infection of immune cells, leading

to changes in WBC levels, including MON and LYM, causing their dysfunction [36]. T-test analysis showed higher RBC and HCT levels in infected patients compared to MCH and MCHC levels in uninfected patients. Previous studies [29, 37] have reported significantly lower RBC levels in severely ill patients. Similarly, Berzuini et al. [38] have reported a decline in RBC among COVID-19 patients, while Mei et al. (2020) [39] found considerably lower RBC, HGB, and HCT levels in severe cases. The results of our study show that the average HGB level is within the normal range, which differs from other studies. It has been suggested that COVID-19 patients have higher levels of HGB than uninfected individuals, possibly due to factors such as smoking and chronic diseases that were not excluded from the study by Usul et al. [17]. The average MCV values did not significantly differ between the two groups. Still, there was a notable decrease in the average RDW value among COVID-19 patients compared to uninfected individuals, contradicting previous studies [29, 40]. Additionally, it was reported that the morphological parameters of RDW were significantly higher in patients with severe COVID-19 [41]. The results also indicated a significant increase in the overall white blood cell (WBC) count in COVID-19 patients. On the other hand, other studies suggest that specific changes in blood cells can help diagnose and predict the progression of COVID-19 in patients infected with SARS-CoV-2 [29, 42]. COVID-19-positive patients have higher rates of anaemia and thrombocytopenia compared to those who test negative [43]. The results showed no significant difference in lymphocyte (LYM) levels between the two groups. Still, lymphopenia is commonly observed in COVID-19 patients [18, 44, 45] and is often associated with the severity of COVID-19 infection [46], which is consistent with findings reported by [29]. The results also demonstrated a significant increase in platelet (PLT) levels for the infected group, contrasting with previous reports. The monocyte (MON) count did not show a significant difference between the two groups, contradicting previous reports which indicated a substantial reduction in monocyte counts in COVID-19 patients [47]. Monocytes typically migrate to infection sites to combat pathogens, which can further decrease their blood levels [48]. In severe cases of COVID-19, the number of monocytes in the bloodstream may decline even more. Patients with severe symptoms have been found to have lower monocyte levels compared to those with milder symptoms, suggesting a potential role for monocytes in the progression of the disease [45, 48]. The immune system's response to the virus can lead to immune fatigue and monocyte exhaustion [49].

Moreover, COVID-19 can trigger a cytokine storm, an excessive immune response that damages healthy tissues, leading to monocyte death and reduced blood levels [49]. Increased granulocyte (GRA) in COVID-19 patients indicates severe respiratory tract infections and potential central nervous system involvement. Conversely, recovered patients may exhibit lower GRA levels, possibly due to decreased immunological activity [35]. Furthermore, COVID-19 infection can cause variations in GRA, leading to changes in blood test results [50].

Conclusion

The study used various statistical analysis techniques such as correlation coefficient, principal component analysis, cluster analysis, and T-test to distinguish between the Complete Blood Count (CBC) profiles of COVID-19-infected and uninfected individuals. The findings suggest that CBC analysis is valuable for diagnosing infection and assessing disease severity. Regular CBC monitoring is essential for observing changes in COVID-19 patients, potentially reducing the mortality rate. A CBC test can quickly determine disease severity when RT-PCR testing or trained medical personnel are unavailable. The results indicate that COVID-19 significantly impacts the health of those infected, with older individuals being the most affected and men showing greater susceptibility to the disease than women. Complications such as increased red blood cell count and hematocrit concentration can present patient problems, while elevated platelet numbers may lead to blood clots. Consequently, the study supports CBC analysis as a reliable method for predicting COVID-19 infection and determining its severity.

Author Contributions: Conceptualization, E. H. and S. M.; methodology, E. H. and A. F.; validation, E. H. and A.F.; formal analysis, M. S. and E. H.; investigation, E. H. and A. F.; resources, E. H, M. S. and A. F.; data curation, M. S., N. Y and E. H.; writing – original draft preparation, E. H. and S. M.; writing – review and editing, E. H. and S. M.; visualization, E. H. and A. F.; supervision, S. M. and N. Y.; project administration, E. H. and S. M.; funding acquisition, No fund. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: The authors would like to thank the staff of isolation and filtration centres in the Alshati district and the Central Brack Hospital for assisting in performing part of the CBC analysis.

Funding: None.

Ethical Statement: This study was approved by the Research Ethics Committee, Faculty of Laboratory Technology University of Wadi Alshatti, in the third meeting of the scientific committee on January 23 2021.

References

1. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). 2023; August 18. In: Stat Pearls [Internet]. Treasure Island (F.L.). StatPearls Publishing; 2024.
2. Brancaccio M, Mennitti C, Gentile A, Correale L, Buzzachera CF, Ferraris C, Montomoli C, Frisso G, Borrelli P, Scudiero O. Effects of the COVID-19 Pandemic on Job Activity, Dietary Behaviors and Physical Activity Habits of University Population of Naples, Federico II-Italy. *Int J Environ Res Public Health.* 2021; 18(4): 1502. https://doi.org/10.3390/ijerph18041502.
3. Sharma A, Tiwari S, Deb MK, Marty JL. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a global pandemic and treatment strategy. *Int J Antimicrob. Agents.* 2020; 56(2): 106054. https://doi.org/10.1016/j.ijantimicag.2020.106054.
4. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). *Indian J Pediatr*. 2020; 87(4): 281–286. https://doi.org/10.1007/s12098-020-03263-6.
5. Alsrhani A, Junaid K, Younas S, Hamam SSM, Ejaz H. Covid-19 Pandemic: Through the Lens of Science, a Painstaking Review. *Clin Lab.* 2020; 66(10). https://doi.org/ 10.7754/Clin.Lab.2020.200642.

6. Thakar A, Panda S, Sakthivel P, Brijwal M, Dhakad S, Choudekar A, Kanodia A, Bhatnagar S, Mohan A, Maulik SK, Dar L. Chloroquine nasal drops in asymptomatic & mild COVID-19: An exploratory randomized clinical trial. *Indian J Med Res.* 2021; 153(1 & 2): 151–158. https://doi.org/ 10.4103/ijmr.IJMR_3665_20.
7. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, Abosalif KOA, Ahmed Z, Younas S. COVID-19 and comorbidities: Deleterious impact on infected patients. *J Infect Public Health.* 2020; 13(12): 1833–1839. https://doi.org/ 10.1016/j.jiph.2020.07.014.
8. Zuo MZ, Huang YG, Ma WH, Xue ZG, Zhang JQ, Gong YH, Che L; Chinese Society of Anesthesiology Task Force on Airway Management; Airway Management Chinese Society of Anesthesiology Task Force. Expert Recommendations for Tracheal Intubation in Critically Ill Patients with Noval Coronavirus Disease 2019. Chin Med Sci J. 2020; 35(2): 105–9. https://doi.org/ 10.24920/003724.
9. Levi M, Iba T. COVID-19 coagulopathy: is it disseminated intravascular coagulation? *Intern Emerg Med.* 2021; 16(2): 309–312. https://doi.org/10.1007/s11739-020-02601-y.
10. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol.* 2021; 113(1): 45–57. https://doi.org/10.1007/s12185-020-03029-y.
11. Zamboni P. COVID-19 as a Vascular Disease: Lesson Learned from Imaging and Blood Biomarkers. *Diagnostics (Basel)*. 2020; 10(7): 440. https://doi.org/ 10.3390/diagnostics10070440.
12. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA.* 2020; 323(16): 1612–1614. https://doi.org/10.1001/jama.2020.4326.
13. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M; COVID-19 Lombardy ICU Network. Risk Factors Associated with Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med.* 2020; 180(10): 1345–1355. https://doi.org/10.1001/jamainternmed.2020.3539.
14. Djakpo DK, Wang Z, Zhang R, Chen X, Chen P, Antoine MMLK. Blood routine test in mild and common 2019 coronavirus (COVID-19) patients. *Biosci. Rep.* 2020; 40(8): BSR20200817. https://doi.org/ 10.1042/BSR20200817.
15. Akman C, Bakırdöğen S. The role of serum inflammatory markers, albumin, and haemoglobin in predicting the diagnosis in patients admitted to the emergency department with a pre-diagnosis of COVID-19. *Rev Assoc Med Bras.* 1992. 2021; 67 (Suppl 1): 91–96. https://doi.org/10.1590/1806-9282.67.Suppl1.20200917.
16. Shivakumar BG, Gosavi S, Ananda Rao A, Shastry S, Raj SC, Sharma A, Suresh A, Noubade R. Neutrophil-to-Lymphocyte, Lymphocyte-to-Monocyte, and Platelet-to-Lymphocyte Ratios: Prognostic Significance in COVID-19. Cureus. 2021; 13(1): e12622. https://doi.org/ 10.7759/cureus.12622.
17. Usul E, Şan İ, Bekgöz B, Şahin A. Role of haematological parameters in COVID-19 patients in the emergency room. *Biomark Med*. 2020; 14(13): 1207–1215. https://doi.org/10.2217/bmm-2020-0317.
18. Pozdnyakova O, Connell NT, Battinelli EM, Connors JM, Fell G, Kim AS. Clinical Significance of CBC and WBC Morphology in the Diagnosis and Clinical Course of COVID-19 Infection. *Am J Clin Pathol.* 2021; 155(3): 364–-375. https://doi.org/10.1093/ajcp/aqaa231.
19. Bredan A, Bakoush O. COVID-19 epidemic in Libya. *Libyan J Med.* 2021; 16(1): 1871798. https://doi.org/10.1080/19932820.2021.1871798.
20. Salem MA, Bedade DK, Al-Ethawi L, Al-Waleed SM. Assessment of physiochemical properties and concentration of heavy metals in agricultural soils fertilized with chemical fertilizers. *Heliyon.* 2020; 6(10): e05224. https://doi.org/10.1016/j.heliyon. 2020.e05224.
21. Batabyal AK. Correlation and multiple linear regression analysis of groundwater quality data of Bardhaman District, West Bengal, India. Int. J of Res. in Chem. and Environ. (IJRCE), 2014; 4(4): 42–51.
22. Gill JL. Design and analysis of experiments in the animal and medical sciences. Arnes, The Iowa State University Press, 1987; 1: 1–411.
23. Salah EA, Turki AM, Mahal SN. Chemometric evaluation of the heavy metals in urban soil of Fallujah City, Iraq. *J of Environ. Prot*. 2015; 6(11), 1279. https://doi.org/10.4236/jep.2015.611112.
24. Qasrawi R, Abu Al-Halawa D. Cluster Analysis and Classification Model of Nutritional Anemia Associated Risk Factors Among Palestinian Schoolchildren, 2014. *Front Nutr.* 2022; 9: 838937. https://doi.org/10.3389/fnut.2022.838937.
25. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, Liu S, Yang JK. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Health.* 2020; 8: 152. https://doi.org/ 10.3389/fpubh.2020.00152.
26. Bwire GM. Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? S.N. *Compr Clin Med.* 2020; 2(7): 874–876. https://doi.org/10.1007/s42399-020-00341-w.
27. Zhong R, Chen L, Zhang Q, Li B, Qiu Y, Wang W, Tan D, Zou Y. Which Factors, Smoking, Drinking Alcohol, Betel Quid Chewing, or Underlying Diseases, Are More Likely to Influence the Severity of COVID-19? *Front Physiol.* 2021; 11: 623498. https://doi.org/10.3389/fphys.2020.623498.
28. Liang C, Cao J, Liu Z, Ge F, Cang J, Miao C, Luo J. Positive RT-PCR test results after consecutively negative results in patients with COVID-19. *Infect Dis (Lond).* 2020; 52(7): 517–519. https://doi.org/10.1080/23744235.2020.1755447.
29. Elderdery AY, Elkhalifa A M E, Alsrhani AZK, Alsurayea S M, Escandarani FK, Alhamidi AH. Idris HME, Abbas A M, Shalabi MG, Mills J. Complete blood count alterations of COVID-19 patients in Riyadh, Kingdom of Saudi Arabia. *J of Nanomaterials,* 2022; 1–6. https://doi.org/10.1155/2022/6529641.
30. Usul E, Şan İ, Bekgöz B, Şahin A. Role of haematological parameters in COVID-19 patients in the emergency room. *Biomark Med*. 2020; 14(13): 1207–1215. https://doi.org/10.2217/mm-2020-0317.
31. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020; 46(5): 846–848. https://doi.org/10.1007/s00134-020-05991-x.
32. Everitt BS, Landau S, Leese M, Stahl D. Cluster Analysis. 5th ed. *John Wiley and Sons, Chichester,* UK, 2011: 71–110. https://doi.org/10.1002/9780470977811.
33. Zini G, Bellesi S, Ramundo F, d'Onofrio G. Morphological Anomalies of Circulating Blood Cells in COVID-19. American Journal of Hematology. 2020; 95: 870-872. https://doi.org/10.1002/ajh.25824.

34. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. *Curr. Probl. Cardiol.* 2020; 45(8): 100618. https://doi.org/10.1016/j.cpcardiol.2020.100618.
35. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin. *Chim. Acta*. 2020; 506: 145–148. https://doi.org/10.1016/j.cca.2020.03.022.
36. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, Chen L, Li M, Liu Y, Wang G, Yuan Z, Feng Z, Zhang Y, Wu Y, Chen Y. Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). *Front Immunol.* 2020; 11: 827. https://doi.org/10.3389/fimmu.2020.00827.
37. Yuan X, Huang W, Ye B, Chen C, Huang R, Wu F, Wei Q, Zhang W, Hu J. Changes of haematological and immunological parameters in COVID-19 patients. *Int J Hematol.* 2020; 112(4): 553–559. https://doi.org/10.1007/s12185-020-02930-w.
38. Berzuini A, Bianco C, Migliorini AC, Maggioni M, Valenti L, Prati D. Red blood cell morphology in patients with COVID-19-related anaemia. *Blood Transfus.* 2021; 19(1): 34–36. https://doi.org/10.2450/2020.0242-20.
39. Mei Y, Weinberg SE, Zhao L, Frink A, Qi C, Behdad A, Ji P. Risk stratification of hospitalized COVID-19 patients through comparative studies of laboratory results with influenza. *EClinicalMedicine.* 2020; 26: 100475. https://doi.org/10.1016/j.eclinm.2020.100475.
40. Lee JJ, Montazerin SM, Jamil A, Jamil U, Marszalek J, Chuang ML, Chi G. Association between red blood cell distribution width and mortality and severity among patients with COVID-19: A systematic review and meta-analysis. *J Med Virol.* 2021; 93(4): 2513–2522. https://doi.org/ 10.1002/jmv.26797.
41. Li YX, Wu W, Yang T, Zhou W, Fu YM, Feng QM, Ye JM. Characteristics of peripheral blood leukocyte differential counts in patients with COVID-19 [In Chinese]. *Zhonghua Nei Ke Za Zhi.* 2020; 59(0): E003.
42. Khartabil TA, Russcher H, van der Ven A, de Rijke YB. A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients. *Crit Rev Clin Lab Sci.* 2020; 57(6): 415–431. https://doi.org/10.1080/10408363.2020.1774736.
43. Fan BE. Hematologic parameters in patients with COVID-19 infection: a reply. *Am J Hematol*. 2020; 95(8): E215. https://doi.org/10.1002/ajh.25847.
44. Chen ZH, Li YJ, Wang XJ, Ye YF, Wu BL, Zhang Y, Xuan WL, Bao JF, Deng XY. Chest CT of COVID-19 in patients with a negative first RT-PCR test: Comparison with patients with a positive first RT-PCR test. *Medicine (Baltimore).* 2020; 99(26): e20837. https://doi.org/ 10.1097/MD.0000000000020837.
45. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, Zhang M, Tan J, Xu Y, Song R, Song M, Wang L, Zhang W, Han B, Yang L, Wang X, Zhou G, Zhang T, Li B, Wang Y, Chen Z, Wang X. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. *J Transl Med.* 2020; 18(1): 206. https://doi.org/10.1186/s12967-020-02374-0.
46. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, Yang D, Zhang G, Li H, Chen F, Xu Y, Chen M, Gao Z, Yang J, Dong J, Liu B, Zhang X, Wang W, He K, Jin Q, Li M, Wang J. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. *Cell Host Microbe.* 2020; 27(6): 883–890.e2. https://doi.org/10.1016/j.chom.2020.04.017.
47. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395(10223): 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
48. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, Marron TU, Xie H, Patel M, Tuballes K, Van Oekelen O, Rahman A, Kovatch P, Aberg JA, Schadt E, Jagannath S, Mazumdar M, Charney AW, Firpo-Betancourt A, Mendu DR, Jhang J, Reich D, Sigel K, Cordon-Cardo C, Feldmann M, Parekh S, Merad M, Gnjatic S. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020; 26(10): 1636–1643. https://doi.org/10.1038/s41591-020-1051-9.
49. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020; 8(5): 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5.
50. Letícia de Oliveira Toledo S, Sousa Nogueira L, das Graças Carvalho M, Romana Alves Rios D, de Barros Pinheiro M. COVID-19: Review and hematologic impact. *Clin Chim. Acta.* 2020; 510: 170–176. https://doi.org/10.1016/j.cca.2020.07.016.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15729

Determination of Gynecologic Cancer Awareness and Attitudes Towards Screening in Women Aged 20–65

Kübra Demirkaya[1], Funda Akduran[2]

[1]Faculty of Health Sciences, Sakarya University, Sakarya, Turkey
[2]Internal Medicine Nursing Department, Faculty of Health Sciences, Sakarya University, Sakarya, Turkey

Received: 2024-10-30.
Accepted: 2024-12-18.

J Clin Med Kaz 2024; 21(6): 103–109

Corresponding author:
Funda Akduran.
Email: fsevgi@sakarya.edu.tr.
ORCID: 0000-0001-7009-3562.

Abstract

Aim: Gynecological cancers are among the top ten cancers in terms of mortality and incidence among women in our country. Enhancing awareness is crucial to reducing the morbidity and mortality of these cancers. Women with increased awareness are more likely to have positive attitudes towards cancer screenings and to undergo such tests, thereby lowering their risk. Study aims to assess gynecological cancer awareness, attitudes towards screenings, and influencing factors among women aged 20–65.

Material and methods: This descriptive and correlation study's population comprised 5,504 female patients in the gynecology and obstetrics, a sample of 272 patients was selected. Data were collected through a patient information form, a gynecological cancer awareness scale, and a cancer screening attitudes scale, and analyzed with SPSS.

Results: The participants had an average age of 29.00 ± 5.942. Of them, 94.5% were married, 96% had not received gynecological cancer education previously, and 90.1% had not undergone cancer screening before. Non-smokers and those who had received gynecologic cancer education before had statistically higher mean total scale scores (p<0,05). Those with higher education, employed individuals, regular exercisers, those who had previously received gynecological cancer education, and those who had previously undergone cancer screenings had statistically higher average scores on the cancer screening attitude scale (p<0,05).

Conclusion: It was found that women's attitudes toward cancer screenings and their awareness of gynecological cancers were above average. There was a statistically significant positive correlation between awareness and attitude. This result shows that women with increased awareness of gynaecological cancers also have positive attitudes towards cancer screening. Therefore, women should be educated on how to prevent gynaecological cancers through not smoking, education, employment and regular exercise.

Keywords: gynecological cancer awareness, women, attitudes towards cancer screenings.

Introduction

Cancer encompasses a variety of diseases characterized by uncontrolled cell growth, varying by bodily location and clinical presentation. As per the 2022 global cancer report by the International Agency for Research on Cancer (IARC) under the World Health Organization (WHO), an estimated 20 million new cancer diagnoses and 9.7 million fatalities occurred globally. Gynecological cancers make up about 15% of all cancer cases and 10% of cancer-related deaths, representing a substantial cause of illness and death in women, second only to breast cancer. Worldwide, the most prevalent cancers in women are breast, lung, colorectal, and cervical cancers; in Turkey, cervical cancer ranks among the top five [1]. Data from the 2020 "Turkey Cancer Statistics" report indicate that among the ten most common cancers in Turkish women are gynecological cancers, including cervical and ovarian cancers [2, 3]. Gynecological cancers are prominent in terms of both mortality and incidence, highlighting the necessity of heightened awareness and proactive screening attitudes to reduce their impact on women's health [4, 5].

In Turkey, national-level screenings are conducted for breast, colorectal, and cervical cancer types, as recommended by the WHO [6]. Among gynecological

cancers, cervical cancer, which is screened at the national level, is the fourth leading cause of death among women worldwide. In Turkey, cervical cancer screening is conducted using Human Papilloma Virus (HPV) and Pap smear tests. The WHO highlights that cervical cancer, despite being a significant risk, is a "preventable cause of death." Therefore, worldwide screening for cervical cancer is recommended [7–9]. Early diagnosis, awareness and taking preventive measures for gynecological cancers are of great importance in reducing mortality rates due to these cancers [10]. Low cancer awareness is a risk factor for late diagnosis, and therefore, women's awareness of gynecological cancers should be increased. Women with heightened awareness are more likely to have a positive attitude toward cancer screening tests and take preventive measures in a timely manner, thereby reducing the risk of cancer occurrence [11, 12].

For cancer screening programs to be effective, there is a need for societal awareness and a positive attitude toward cancer screenings. Continuously raising awareness through education and planning to foster positive attitudes and behaviors toward cancer screenings should be among the primary objectives for community-based screenings [13–15].

The unique aspect of this study is that, while previous research has separately examined gynecological cancer awareness and attitudes toward cancer screenings, no study has simultaneously assessed both aspects.

Based on these reasons, the aim of this research is to determine the gynecological cancer awareness and attitudes toward cancer screenings among women aged 20–65.

Research Questions

The research questions in our study were as follows:

1. What is the awareness of gynaecological cancer and attitudes towards screening among women aged 20-65?
2. What is the awareness of gynaecological cancer and attitudes towards screening among women aged 20-65 according to their socio-demographic characteristics?
3. Is there an association between cervical cancer awareness and attitudes towards screening among women aged 20-65?

Materials and Methods

Study Design and Sample

This research was designed as descriptive and correlational.

Study Location and Duration

The study took place from May 2024 to July 2024 in the gynecology and obstetrics department of a teaching and research hospital in a provincial center.

Study Population and Sample

The study population included female patients admitted to the gynecology and obstetrics department of the specified hospital (N=5504). In determining the sample, 95% confidence interval was used. The sample size was calculated using the formula for a known population, and the stratified random sampling method, specifically "Neyman Allocation," was utilized. This resulted in a final sample of 272 patients.

Women were included in the study if they voluntarily consented, were hospitalized in the gynecology and obstetrics unit, were married, aged between 20 and 65, were at least literate, had no gynecological cancer diagnosis, and had no cognitive, visual, or orthopedic limitations that would hinder completion of the data collection forms.

Data Collection Instruments

Data were gathered using the "Patient Information Form," the "Gynecological Cancer Awareness Scale" (GCAS), and the "Attitude Towards Cancer Screenings Scale".

Patient Information Form

This form, crafted by the researchers with reference to existing literature [11,13,16-18], consists of 14 questions that capture sociodemographic data (age, marital status, residence, education level, occupation, income, exercise habits) and health-related details (smoking and alcohol use, history of cancer diagnosis, and family history of cancer).

Gynecological Cancer Awareness Scale (GCAS)

Developed by Dal and Ertem, this scale measures gynecological cancer awareness among married women aged 20-65 [17]. The scale's Turkish version was validated and found reliable by the original authors. Comprising 41 items across four subscales, it utilizes a five-point Likert scale, with scores ranging from 41 to 205. Items 20-41 of the GCAS constitute the sub-dimension of 'Awareness of Routine Control and Serious Disease Perception in Gynaecological Cancers'; items 3-11 constitute the sub-dimension of 'Awareness of Gynaecological Cancer Risks'; items 14-19 constitute the sub-dimension of 'Awareness of Gynaecological Cancer Prevention'; and items 1-2, 12-13 constitute the sub-dimension of 'Awareness of Early Diagnosis and Information in Gynaecological Cancers'. Higher scores reflect greater awareness levels. The scale's Cronbach's alpha was calculated at 0.944, while in this study, it was found to be 0.845.

Attitude Towards Cancer Screenings Scale

This scale was created by Yıldırım Öztürk and colleagues [18], with validation and reliability confirmed in Turkish by the original team. The scale contains 24 items in a single dimension, also using a five-point Likert scale, yielding scores from 24 to 120. Scores closer to 24 suggest a negative attitude toward cancer screenings, whereas scores nearer to 120 indicate a positive outlook. Its Cronbach's alpha was calculated at 0.957, and in this study, it was found to be 0.953.

Data Collection

The researcher administered the forms face-to-face, explaining the study's objectives and detailing the forms. Each session lasted about 20 minutes per participant.

Data Analysis

Data analysis was performed using IBM SPSS Statistics 23. The normality of the data distribution was examined, and parametric tests were employed accordingly. The conformity of the data to a normal distribution was assessed on the basis of skewness and kurtosis values. The presence of skewness and kurtosis values within certain limits indicates that the data follow a normal distribution. In this context, the ranges of -1.5 to +1.5 suggested by Tabachnick and Fidell (2007) are commonly used reference intervals. In this study, these criteria were also used to assess the normal distribution. Frequency distributions were used for categorical variables, and descriptive statistics (mean, standard deviation, minimum, and maximum) were calculated for numerical variables. To assess differences in two-category variables, the "independent t-test" was applied, while "one-way analysis of variance" (ANOVA) was used for variables with more than two categories. Homogeneity of variances was checked with Levene's test, and post-hoc tests (Bonferroni or Tamhane's T2) were applied to explore group differences. Pearson correlation

analysis assessed relationships between numerical variables, and reliability of the scales was evaluated using Cronbach's alpha.

Ethical Considerations

Institutional approval was obtained from the training and research hospital before the study commenced. Ethical approval was also secured from the affiliated university's Non-Interventional Clinical Research Ethics Committee (24.05.2024-E-71522473-050.04-364032-145). Permissions were granted by the original authors for the scales used in data collection. Participants were informed about the study's aims, assured of data confidentiality, and provided with an "Informed Voluntary Consent Form" to document their consent. The research adhered to ethical principles, including "Informed Voluntary Consent, Confidentiality, Respect for Privacy and Autonomy," and followed the Declaration of Helsinki.

Results

The participants' mean age was 29.00±5.942. Findings revealed that 94.5% were married, 79.4% were housewives, 58.5% did not exercise regularly, 96% had no prior education on gynecological cancers, and 90.1% had not undergone cancer screenings (Table 1).

Table 1 Distribution of Sociodemographic Characteristics of Women (n=272)

Variables		**Min.-Max.**	**Mean.±SD**
Age (years)		20-51	29.00±5.942
		n	**%**
Marital status	Married	257	94,5
	Single	15	5,5
Place of residence	Village	53	19,5
	Town	108	39,7
	County	111	40,8
Educational background	Illiterate	6	2,2
	Primary	28	10,3
	Secondary	145	53,3
	Higher education	70	25,7
	Graduate	23	8,5
Employment status	Civil servant	15	5,5
	Worker	22	8,1
	Retired	3	1,1
	Housewife	216	79,4
	Unemployed	4	1,5
	Other	12	4,4
Exercise regularly	Doing	113	41,5
	It doesn't	159	58,5
Income level	Income is lower than expense	63	23,2
	Income equals expense	169	62,1
	Income is higher than expense	40	14,7
Alcohol	Using	3	1,1
	Doesn't use	269	98,9
Cigarette	Using	49	18,0
	Doesn't use	223	82,0
The presence of cancer	Yes	2	0,7
	No	270	99,3
Presence of cancer in the family or environment	Yes	105	38,6
	No	167	61,4
Previous gynecological cancer education	Yes	11	4,0
	No	261	96,0
Previous cancer screening	Yes	27	9,9
	No	245	90,1
Total		272	100

**Participants selected more than one option*

The Cronbach's alpha value for the Attitude Towards Cancer Screenings Scale was calculated as 0.845, with a mean score of 93.18±15.151. For the Gynecological Cancer Awareness Scale (GCAS), the Cronbach's alpha values and mean scores for each subscale were as follows: the "Awareness of Routine Check-ups and Perception of Serious Illness in Gynecological Cancers" subscale had a mean score of 80.92±17.266; "Awareness of Gynecological Cancer Risks" scored 26.31±5.984; "Awareness of Prevention in Gynecological Cancers" scored 20.33±5.276; and "Awareness of Early Diagnosis and Knowledge in Gynecological Cancers" scored 14.99±4.191. The total scale mean was 142.56±26.912 (Table 2).

The mean scores of the Attitude Towards Cancer Screenings Scale were compared based on the participants' sociodemographic characteristics. The analysis revealed that the mean scores of those with higher education (undergraduate and graduate degrees), those who were employed, those who exercised regularly, those who had previously received gynecological cancer education, and those who had undergone cancer screenings were statistically significantly higher ($p<0.05$) (Table 3).

The Gynecological Cancer Awareness Scale (GCAS) mean scores were compared across participants' sociodemographic factors. Analysis indicated that non-smokers scored significantly higher in the subscales "awareness of prevention in gynecological cancers" and "awareness of early diagnosis and knowledge in gynecological cancers," as well as in the overall scale score, compared to smokers ($p<0.05$). Likewise, women who had prior education on gynecological cancers scored significantly higher in the subscales "awareness of routine check-ups and perception of serious illness in gynecological cancers," "awareness of prevention in gynecological cancers," and "awareness of early diagnosis and knowledge in gynecological cancers," along with the total scale score, compared to those without such education ($p<0.05$).

Prior cancer screening was also a significant factor. Women who had undergone cancer screenings had significantly higher scores across all GCAS subscales and the total scale score compared to those who had not ($p<0.05$) (Table 4).

The relationship between the scales was analyzed, revealing a statistically significant positive correlation between the Attitude Towards Cancer Screenings Scale and the Gynecological Cancer Awareness Scale (GCAS), including its subscale and overall scores (Table 5).

Discussion

In this study, which assessed gynecological cancer awareness and attitudes toward cancer screenings among women hospitalized in the obstetrics and gynecology departments of a provincial training and research hospital, the mean Gynecological Cancer Awareness Scale (GCAS) score was 142.56±26.912 (As the score approaches 120, it reflects a positive attitude towards cancer screenings. Therefore, participants' attitudes towards cancer screenings were found to be positive) and the Attitude Towards Cancer Screenings Scale mean score was 93.18±15.151 (Since higher scores on the scale indicate greater awareness, participants' overall gynecological cancer awareness was above average) (Table 2). Given that the possible GCAS scores range from 41 to 205 and Attitude Towards Cancer Screenings scores range from 24 to 120, the participants demonstrated above-average awareness of gynecological cancers and positive attitudes toward cancer screenings.

The literature supports these findings. Gözüyeşil et al. (2020) observed similar results among women registered at a

Table 2 The Descriptive Statistics of the Scales

Scale	Bottom dimension	Cronbach's alfa	Min-Max	Mean±SD
Attitude Scale Towards Cancer Screening		0,845	24-120	93.18±15.151
Gynecologic Cancers Awareness Scale	1st Sub-Dimension: Routine control and awareness of serious disease perception in gynecologic cancers	0,957	22-110	80.92±17.266
	Sub-Dimension 2: Awareness of gynecological cancer risks	0,835	9-45	26.31±5.984
	3rd Sub-Dimension: Awareness of prevention of gynecological cancers	0,805	6-30	20,33±5,276
	Sub-Dimension 4: Early diagnosis and information awareness in gynecologic cancers	0,853	4-20	14.99±4.191
	Total	0,953	41-205	142,56±26,912

Table 3 Comparison of mean scores of the Attitude Scale towards Cancer Screening according to sociodemographic characteristics

Variable		n	Mean	SD	t/F	p
Marital status	Married	257	93,33	15,253	0,694	0,488
	Single	15	90,53	13,479		
Place of residence	Village	53	92,57	16,402	0,353	0,703
	Town	108	94,13	14,184		
	County	111	92,54	15,530		
Educational background	Primary+illiterate	34	90,26	14,714	4,940	**0,008***
	Secondary	145	91,34	14,764		
	Higher education+graduate	93	97,10	15,278		
Employment status	Working	49	98,71	15,028	2,863	**0,005***
	Not working	223	91,96	14,938		
Exercise regularly	Doing	113	95,76	14,396	2,392	**0,017***
	It doesn't	159	91,34	15,448		
Income level	Income is lower than expense	63	91,92	15,597	0,316	0,729
	Income equals expense	169	93,69	14,428		
	Income is higher than expense	40	92,98	17,548		
Alcohol	Using	3	102,67	6,429	1,091	0,276
	Doesn't use	269	93,07	15,192		
Cigarette	Using	49	89,78	15,594	-1,742	0,083
	Doesn't use	223	93,92	14,985		
The presence of cancer	Yes	2	98,50	19,092	0,498	0,619
	No	270	93,14	15,156		
Presence of cancer in the family or environment	Yes	105	93,35	15,507	0,152	0,880
	No	167	93,07	14,970		
Previous gynecological cancer education	Yes	11	105,64	11,066	3,748	**0,003***
	No	261	92,65	15,090		
Previous cancer screening	Yes	27	101,26	12,439	2,962	**0,003***
	No	245	92,29	15,181		

Table 5 Correlation between scales

Parameters			Attitude Scale Towards Cancer Screenings	GCAS				
				Sub-Dimension 1	Sub-Dimension 2	Sub-Dimension 3	Sub Dimension 4	Sum
Attitude Scale Towards Cancer Screenings		r	1	,344*	,169*	,252*	,305*	,356*
		p		,001	0,005	,001	,001	,001
GCAS	**Sub-Dimension 1**	r		1	,311*	,656*	,671*	,944*
		p			,001	,001	,001	,001
	Sub-Dimension 2	r			1	,302*	,312*	,529*
		p				,001	,001	,001
	Sub-Dimension 3	r				1	,665*	,787*
		p					,001	,001
	Sub Dimension 4	r						,786*
		p						,001
***p<0.05**	**Total**	r						1
		p						

Table 4 Comparison of Gynecological Cancer Awareness Scale score and sub-dimension score averages according to sociodemographic characteristics

Variables		n	Gynecologic Cancers Awareness Scale									
			Sub-Dimension 1		Sub-Dimension 2		Sub-Dimension 3		Sub Dimension 4		Sum	
			Place.	**SD**	**Place.**	**SD**	**Place.**	**SD**	**Place.**	**SD**	**Place.**	**SD**
Marital status	Married	257	**81,20**	17,183	**26,45**	5,921	**20,46**	5,277	**15,05**	4,120	**143,15**	26,673
	Single	15	76,20	18,621	24,00	6,772	18,13	4,912	14,07	5,351	132,40	29,890
t/p			1,090/0,277		1,544/0,124		1,665/0,097		0,880/0,380		1,508/0,133	
Place of residence	To the village	53	79,66	17,967	28,17	5,320	19,89	5,105	14,70	3,714	142,42	24,401
	Town	108	80,35	15,369	25,62	5,853	20,45	4,992	14,96	3,924	141,39	24,376
	District	111	82,08	18,700	26,10	6,271	20,42	5,648	15,16	4,658	143,77	30,366
t/p			0,213/0,808		0,223/0,800		0,233/0,793		3,406/0,035*		0,449/0,639	
Difference									a<b			
Educational background	Primary education+illiterate	34	77,03	19,847	26,44	6,421	19,32	4,903	14,32	3,983	137,12	30,430
	Secondary educationb	145	**81,97**	15,047	26,01	5,718	20,32	4,918	14,88	3,841	143,19	23,715
	Higher education+graduatec	93	80,71	19,368	**26,73**	6,259	**20,72**	5,915	**15,41**	4,753	**143,57**	30,140
F/p			1,141/0,321		0,414/0,661		0,873/0,419		0,941/0,392		0,799/0,451	
Employment status	Running	49	**81,43**	21,534	**27,73**	6,197	**20,84**	6,209	**15,88**	5,247	**145,88**	32,194
	Nonoperating	223	80,81	16,236	26,00	5,904	20,22	5,057	14,80	3,909	141,83	25,633
t/p			0,226/0,821		1,846/0,066		0,741/0,460		1,637/0,103		0,953/0,341	
Exercise regularly	Doing	113	**82,34**	17,465	**26,36**	5,435	**21,05**	5,158	**15,49**	4,147	**145,24**	26,537
	It doesn't	159	79,92	17,108	26,28	6,361	19,82	5,315	14,64	4,200	140,65	27,098
t/p			1,139/0,256		0,117/0,907		1,912/0,057		1,644/0,101		1,387/0,167	
Income level	Income is lower than expense	63	82,05	16,376	26,56	5,769	19,75	5,013	14,89	3,806	143,24	25,343
	Income equals expense	169	81,41	16,458	26,17	5,887	20,51	5,218	15,22	4,204	143,30	25,648
	Income is higher than expense	40	77,10	21,458	26,55	6,809	20,50	5,957	14,20	4,692	138,35	34,010
F/p			1,182/0,308		0,134/0,875		0,502/0,606		0,981/,376		0,572/0,565	
Alcohol	Using	3	82,67	22,301	26,33	6,110	21,33	6,110	14,67	1,155	145,00	35,553
	Doesn't use	269	80,90	17,255	26,31	5,994	20,32	5,278	15,00	4,213	142,53	26,886
t/p			0,176/0,861		0,006/0,995		0,330/0,741		-0,135/0,893		0,158/0,875	
Cigarette	Using	49	77,20	18,576	25,02	5,750	17,78	4,870	13,35	4,381	133,35	27,449
	Doesn't use	223	**81,74**	16,900	**26,60**	6,009	**20,89**	5,205	**15,35**	4,070	**144,58**	26,427
t/p			-1,671/0,096		-1,675/0,095		-3,838/0,001*		-3,083/0,002*		-2,676/0,008*	
The presence of cancer	Yes	2	**105,00**	2,828	**30,00**	1,414	**24,50**	0,707	**20,00**	0,000	**179,50**	4,950
	No	270	80,74	17,204	26,29	5,997	20,30	5,283	14,96	4,184	142,29	26,821
t/p			1,990/0,048*		0,874/0,383		1,122/0,263		1,702/0,090		1,959/0,051	
Presence of cancer in the family or environment	Yes	105	**81,59**	15,935	**27,12**	5,513	**20,44**	4,622	**15,38**	4,063	**144,53**	23,498
	No	167	80,50	18,088	25,80	6,223	20,26	5,661	14,75	4,263	141,32	28,852
t/p			0,505/0,614		1,780/0,076		0,278/0,781		1,213/0,226		0,959/0,338	
Previous gynecological cancer education	Yes	11	**92,91**	17,260	**29,27**	9,034	**24,45**	4,698	**17,64**	3,107	**164,27**	28,513
	No	261	80,42	17,116	26,19	5,813	20,16	5,236	14,88	4,199	141,64	26,511
t/p	Yes		**2,370/0,018***		1,681/0,094		**2,676/0,008***		**2,150/0,032***		**2,765/0,006***	
Previous cancer screening	No	27	**85,81**	14,537	**29,11**	6,589	**20,78**	5,079	**16,33**	4,715	**152,04**	21,887
	Yes	245	80,38	17,483	26,00	5,846	20,28	5,305	14,84	4,113	141,51	27,246
t/p			1,555/0,121		**2,588/0,010***		0,463/0,644		1,758/0,080		1,938/0,054	

Sub-Dimension 1 = "Awareness of routine control and serious disease perception in gynecologic cancers", Sub-Dimension 2 = "Awareness of gynecological cancer risks", Sub-Dimension 3 = "Awareness of prevention of gynecological cancers", Sub-Dimension 4 = "Early diagnosis and information awareness in gynecological cancers"
*t=Independent sample t-test, F=Oneway ANOVA, *=p<0.05*

family health center, reporting above-average gynecological cancer awareness [16]. Tekbaş (2023) found moderate awareness among postmenopausal women aged 45-50 [19], while Şenol et al. (2021) reported higher awareness levels among reproductive-age women than among postmenopausal women [20]. The present study also suggests that high awareness among participants could relate to their predominantly reproductive-age status. Similarly, Atlas et al. (2022) found slightly above-average awareness scores in a sample of 400 women attending a regional training hospital, observing that factors such as age, education, occupation, family structure, residence, and alcohol use influenced awareness levels [21]. In contrast, this study found no significant effect of marital status, education level, employment, regular exercise, income, alcohol use, or personal/family cancer diagnosis on awareness.

However, non-smoking, prior gynecological cancer education, and undergoing cancer screenings were associated with significantly higher awareness levels ($p<0.05$). Prior education on gynecological cancers has been shown to increase screening awareness; Al-Amro et al. (2020) also found that education increased the likelihood of cervical cancer screening [22]. The limited availability of screening tests for gynecological cancers outside of cervical cancer emphasizes the need to raise awareness about early detection and treatment [23]. Promoting awareness will encourage healthy habits, increase interest in educational resources, and support participation in appropriate age-related screening tests.

When participants' screening attitudes were analyzed by sociodemographic characteristics (Table 3), women with higher education levels (undergraduate or graduate), those employed, those who exercised regularly, and those who had undergone prior gynecological cancer education or screening showed both statistically significant ($p<0.05$) and higher mean scores, reflecting more positive attitudes. A higher education level was linked to a more positive attitude toward cancer screenings, consistent with other studies indicating that both higher education (at least a bachelor's degree) and specific cancer education positively influence awareness and attitudes [16, 17, 24]. Studies frequently show that higher education correlates with positive screening attitudes [15, 25–27]. In line with these findings, Chali et al. (2021) observed that those with low or no literacy had less positive attitudes and lower screening participation [28]. Some research, however, suggests that education level does not significantly impact attitudes toward screenings [29, 30].

These findings indicate that individuals with higher education levels approach screening with greater awareness, demonstrating positive attitudes and a better understanding of early cancer diagnosis's importance as education increases. Studies show that individuals with higher physical activity levels are more likely to participate in various cancer screenings [31]. In this study, women who exercised regularly also showed more positive screening attitudes, with significant results ($p<0.05$). While some studies confirm that exercise positively affects attitudes and awareness of cancer [32], others suggest no significant impact of regular exercise on screening attitudes [18].

A significant association was also found between women's screening attitudes and their screening history ($p<0.05$). Among the participants, 27 had undergone cancer screening, while 245 had not. Those with a screening history scored higher (101.26±12.43) compared to those without (92.29±15.18) (Table 3). Although most participants (n=245) had not been screened, they generally had positive attitudes toward screenings. Common reasons for not undergoing screenings included fear, lack of information on screening locations, insufficient knowledge, and perceived irrelevance due to a mean participant age of 29.00±5.942. Koç et al. (2023) reported a positive correlation between attitudes towards cervical cancer screening and willingness to receive the HPV vaccine, suggesting that positive attitudes promote healthy lifestyle behaviors [33]. The correlation analysis also demonstrated a positive association between the Attitude Towards Cancer Screening Scale and the GCAS, including all subscale scores ($p<0.05$) (Table 5). Thus, women with greater awareness of gynecological cancers tend to have more favorable screening attitudes. Positive attitudes toward screenings are crucial for early diagnosis and treatment, emphasizing the importance of healthcare providers reaching target groups and promoting active participation in screenings. Accurate, reliable information can enhance women's awareness, foster positive attitudes, and increase screening participation.

This study's findings show that education, regular exercise, prior information, and screening history positively impact gynecological cancer awareness and screening attitudes. Actively planned early diagnosis and screening programs, community-wide engagement, and timely healthcare referrals are vital to reducing cancer incidence and mortality. Addressing the community's information needs and providing reliable, comprehensive information on early cancer screening programs through healthcare providers can positively impact women's awareness and attitudes toward early gynecological cancer detection and treatment.

Limitations of the Study

This study has certain limitations. Conducted in a single center, its findings are not generalizable to the wider population. Future research could involve larger sample sizes and multiple centers for broader applicability.

Conclusion

Participants exhibited positive attitudes toward cancer screenings and above-average awareness of gynecological cancers. Higher scores in attitudes were associated with higher education, employment, regular exercise, previous gynecological cancer education, and past cancer screenings. Additionally, non-smoking and prior education on gynecological cancers were linked to increased awareness of cancer prevention, early diagnosis, and knowledge. Participants who had undergone cancer screenings displayed a greater awareness of gynecological cancer risks, and a statistically significant positive correlation was identified between attitudes and awareness.

Educational programs should aim to increase women's knowledge of risk factors, symptoms, and screening tests for gynecological cancers. These programs should be accessible and easy to understand, aligned with women's health needs and literacy levels, and conducted regularly. Furthermore, integrating technology, such as artificial intelligence and mobile applications, into these educational efforts can enhance remote learning, supporting improved awareness and attitudes.

Author Contributions: Conceptualization, F. A., K. D.; methodology, F. A., K. D.; validation, not applicable; formal analysis, not applicable; investigation, F. A., K. D.; resources, not applicable; data curation, not applicable; writing – original draft preparation, F. A., K. D.; writing – review and editing, F. A., K. D.; visualization, not applicable; supervision, not applicable; project administration, not applicable; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: The authors extend their gratitude to all participants for their involvement in this study.

Funding: TÜBİTAK 2209/A University Students Research Projects Support Program.

1. Global Cancer Statistics (GLOBOCAN) 2022 (version 1.1). 08.02.2024. https://gco.iarc.who.int.
2. Başara BB, Çağlar İS, Aygün A, Özdemir B, Kulali B, Ünal G, ve diğerleri. *Türkiye Sağlık İstatistikleri Yıllığı* 2022. Sağlık Bilgi Sistemleri Genel Müdürlüğü, Sağlık Bakanlığı; 2024: 45–46.
3. Tolunay T, Kaygusuz S, Keskinkılıç B, Özsarı S, Gökler ME, Türkyılmaz M, ve diğerleri. *Türkiye Kanser İstatistikleri* 2018. Halk Sağlığı Genel Müdürlüğü, Sağlık Bakanlığı; 2022.
4. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021; 71(4). https://doi.org/10.3322/caac.21654.
5. Gözüyeşil E, Arıöz Düzgün A, Ünal Aslan KS. Kadınların serviks kanseri önleme ve erken tanı konusundaki tutumlarının değerlendirilmesi. *STED.* 2019; 28(4): 229–238.
6. Sağlık Bakanlığı, Halk Sağlığı Genel Müdürlüğü, Kanser Dairesi. Kanser taramaları. https://hsgm.saglik.gov.tr/tr/kanser-taramalari.html.
7. Small W Jr, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider et al. Cervical cancer: A global health crisis. *Cancer.* 2017; 123(13): 2404–2412. https://doi.org/10.1002/cncr.30667.
8. Stelzle D, Tanaka LF, Lee KK, Khalil AI, Baussano I, Shah ASV, McAllister DA, Gottlieb SL, Klug SJ, Winkler AS, Bray F, Baggaley R, Clifford GM, Broutet N, Dalal Sh. Estimates of the global burden of cervical cancer associated with HIV. *The Lancet.* 2020; 9(2): e161–e169. https://doi.org/10.1016/S2214-109X(20)30459-9.
9. Guida F, Kidman R, Ferlay J, et al. Global and regional estimates of orphans attributed to maternal cancer mortality in 2020. *Nat Med*. 2022; 28: 2563–2572. https://doi.org/10.1038/s41591-022-02109-2.
10. World Health Organization (WHO), Cervical cancer. https://www.who.int/health-topics/cervical-cancer#tab=tab_2.
11. Uludağ G, Gamsızkan Z, Sungur MA. Kadınların serviks kanseri ve tarama ile ilgili sağlık inançlarının değerlendirilmesi. *Düzce Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi.* 2021; 10(3): 357–362. https://doi.org/10.33631/duzcesbed.749205.
12. Şen SK, Öztürk YK. Sağlık algısı ile kanser tarama farkındalığı arasındaki ilişki. Turk J Fam Med Prim Care. 2020; 24(4): 175–183.
13. Altun Y. Kadınların kanser taramalarına katılımını etkileyen faktörler. *TJFMPC*. 2020; 14(2): 210–215.
14. Özsöyler M, Çapar ZG, Keser M. Knowledge and attitudes about cancer screening tests of 35 years old and over who applied to family medicine policlinic. Forbes J Med. 2023; 4(1): 76–83.
15. Babaoğlu A, Büyüközmen E, Can F. İzmir'de toplulukta kanser tarama testleri farkındalığı ve bireylerin kanser tarama testlerine katılımını etkileyen faktörler. Med J West Black Sea. 2021; 5(2): 173–181.
16. Gözüyeşil E, Arıöz Düzgün A, Taş F. Evaluation of gynecological cancer awareness of women's applying for a family health center. *Turk J Fam Med Prim Care.* 2020; 14(2): 177–185.
17. Alp Dal N, Ertem G. Jinekolojik kanser farkındalık ölçeğinin geliştirilmesi. *J Human Soc Sci Res.* 2017; 6(5): 2351–2367. https://dergipark.org.tr/tr/pub/itobiad/issue/31500/314332.
18. Yıldırım Öztürk EN, Uyar M, Şahin TK. Development of an Attitude Scale for Cancer Screening. *Turk J Oncol.* 2020; 35(4): 394–404. https://doi.org/10.5505/tjo.2020.2341.
19. Tekbaş S. Menopoz sonrası kadınlarda sağlıklı yaşam davranışlarının jinekolojik kanser farkındalığına etkisinin değerlendirilmesi. *TJFMPC*. 2023; 17(3): 398–406.
20. Kaya Ş, Senol D, Polat F, Doğan M. Jinekolojik kanser farkındalığı: üreme çağındaki ve menopoz sonrası kadınlar. *TJFMPC*. 2021; 15(1): 56–62.
21. Atlas B, Er Güneri S. Kadınların jinekolojik kanserler konusundaki farkındalığı ve bu farkındalığı etkileyen faktörler. *İKÇÜSBFD*. 2022; 7(1): 77–85.
22. Al-Amro SQ, Gharaibeh MK, Oweis AI. Factors associated with cervical cancer screening uptake: implications for the health of women in Jordan. *Infectious Diseases in Obstetrics and Gynecology* 2020; 9690473. https://doi.org/10.1155/2020/9690473.
23. Al Qadire M. Awareness of cancer signs and barriers to help seeking: a national survey. *J Cancer Educ.* 2018; 33(6): 1206–1212.
24. Coşkun S. Effect of health responsibility and health literacy on gynecological cancer awareness of university working women. *Turk J Public Health.* 2023; 21(2): 209–222.
25. Erkal E. Determining ındividuals' attitudes toward cancer screening and their ınfluential factors. *Makara J Health Res*. 2022; 26(2): 6. https://doi.org/10.7454/msk.v26i2.1336.
26. Huang J, Choi P, Pang TWY, Chen X, Wang J, Ding H, Jin Y, Zheng Z-J, Wong MCS. Factors associated with participation in colorectal cancer screening: A population-based study of 7200 individuals. *Eur J Cancer Care.* 2021; 30: e13369. https://doi.org/10.1111/ecc.13369.
27. Jalalabadi NZ, Rahimi B, Foroumandi M, Lackey A, Peiman S. Willingness to participate in a lung cancer screening program: Patients' attitudes towards United States Preventive Services Taskforce (USPSTF) recommendations. *Eur J Intern Med*. 2022; 98: 128–129. https://doi.org/10.1016/j.ejim.2021.12.004.
28. Chali K, Oljira D, Sileshi T, Mekonnen T. Knowledge on cervical cancer, attitude toward its screening, and associated factors among reproductive age women in Metu Town, Ilu Aba Bor, South West Ethiopia, 2018: community-based cross-sectional study. *Cancer Rep*. 2021; 4: e1382. https://doi.org/10.1002/cnr2.1382.
29. Uysal N, Ünal F, Toprak F. Kadınların sağlık algılarını, kanser taramalarına yönelik tutumlarını ve etkileyen faktörleri belirleme. *Adnan Menderes Üniversitesi Sağlık Bilimleri Dergisi.* 2022; 6(1): 65–76. https://doi.org/10.46237/amusbfd.926839.
30. Yegenler F, Tunc Karaman S, Yegenler B, Basat O. Evaluation of attitudes and behaviors towards cancer screening in people 30–70 years old. *Eur J Hum Health.* 2023; 3(2): 15–25.
31. Coups EJ, Manne SL, Meropol NJ, Weinberg DS. Multiple behavioral risk factors for colorectal cancer and colorectal cancer screening status. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(3): 510–516. https://doi.org/10.1158/1055-9965.EPI-06-0143.
32. Niederdeppe J, Lee T, Robbins R, Kim HK, Kresovich A, Kirshenblat D, et al. Content and effects of news stories about uncertain cancer causes and preventive behaviors. *Health Commun*. 2014; 29(4): 332–346. https://doi.org/10.1080/10410236.2012.755603.
33. Koç Ö, Baltacı N, Doğan Yüksekol Ö. Kadınların serviks kanseri taraması inançlarının HPV aşısına yönelik inançları ile ilişkisi. *TJFMPC*. 2023; 17(1): 31–34.

CONTENTS

(E-ISSN 2313-1519)
JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN