JCMK

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

EFQM
Recognised for exellence
5 star

TÜV CERT
Management system as per
ISO 9001:2000

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 Russian Science Citation Index, "Cyberleninka" scientific electronic library, Index Copernicus International, Google Scholar, CrossRef. DOAJ.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

Scientific and practical journal

JCMK
JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

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

TREATMENT OF TUMORS AND PARASITIC CYSTS USING HIGH-INTENSITY FOCUSED ULTRASOUND

The latest HIFU installation- JC therapy has been in use in NSMC since January 2010. This installation allows noncontact complete eliminating the endogenic tumor using high intensity focused ultrasound without cutting the tissues and injury of not affected organs.

NSMC successfully treats: mammary and alvus fibroadenoma; breast cancer; liver tumors and cysts (primary liver cancer, liver metastases, echinococcosis, alveococcosis); benign and malignant pancreatic tumors; benign and malignant tumors of kidneys; osteogenic and myelosarkoma of extremities (soft tissues and bones cancer of the extremities).

HIFU-therapy of echinococcosis and alveococcosis developed in the clinic is the one and only in the world and is an alternative to surgical treatment of this disease, causing the economic feasibility.

Acknowledgment to JCMK Editorial Board and Peer-Reviewers for contribution in 2023

Yekaterina Dotsenko

Executive Secretary of the Journal of Clinical Medicine of Kazakhstan
On behalf of the editorial team of the Journal of Clinical Medicine of Kazakhstan, we would like to express our appreciation to all editorial and advisory board members, reviewers and authors who contributed to this journal in year 2023.

EDITORIAL AND ADVISORY BOARD MEMBERS IN 2023

PEER-REVIEWERS WHO CONTRIBUTED TO THIS JOURNAL IN 2022

Abduzhappar Gaipov (Kazakhstan)
Ahmet Gudeloglu (Turkey)
Aigul Kaliyeva (Kazakhstan)
Ainur B. Kumar (Kazakhstan)
Aizada Marat (Kazakhstan)
Akbope Myrkassymova (Kazakhstan)
Ali Cihat Yildirim (Turkey)
Ali Muhtaroglu (Turkey)
Ali Sürmelioğlu (Turkey)
Alimzhan Muxunov (Kazakhstan)
Alina Ogizbayeva (Kazakhstan)
Aliya Kabylbekova (Kazakhstan)
Aliya Smagulova (Kazakhstan)
Alpamys Issanov (Kazakhstan)
Amangali Akanov (Kazakhstan)
Amin Zollanvari (Kazakhstan)
Anara Abbay (Kazakhstan)
Anel Tarabayeva (Kazakhstan)
Aniya Seipenova (Kazakhstan)
Ankit Kumar (India)
Ankur Munjal (United Kingdom)
Antonio Sarria-Santamera (Spain)
Apexa B Shukla (India)
Arif Aydin (Turkey)
Arnur Gusmanov (Kazakhstan)
Arpana Haritwal (India)
Ashish Jaiman (India)
Ashish Joshee (India)
Assylzhan Messova (Kazakhstan)
Aydin Sarihan (Turkey)
Aykut Turhan (Turkey)
Aylin Aydın Sayılan (Turkey)
Ayşin Kılınç Toker (Turkey)
Aysun Özlü (Turkey)
Azar Abiyev (Turkey)
Aziz Serkan Senger (Turkey)
Bakhytbek Zhalmagambetov (Kazakhstan)
Balkenzhe Imankulova (Kazakhstan)
Basim Almothfar (Iraq)
Bauyrzhan Omarkulov (Kazakhstan)
Betül Orhan Kiliç (Turkey)
Bülent Işık (Turkey)
Burak Sayar (Turkey)
Buse Güler (Turkey)
Capros Hristiana Capros (Moldova)
Cennet Yildiz (Turkey)
Çetin Murat Altay (Turkey)
Chandeep Singh (India)
Chang Wook (Republic Of Korea)
Cihan Bedel (Turkey)
Damir Biktashev (Kazakhstan)
Daniya Serdaliyeva (Kazakhstan)
Daniyar Kanzhigalin (Kazakhstan)
Dastan Nabiyev (Kazakhstan)
Demet Celik (Turkey)
Devdatta Suhas Neogi (United Kingdom)
Devinder Pal Singh (India)
Dilber Kocaşaban (Turkey)
Dilek Konuksever (Turkey)
Dinara Jumadilova (Kazakhstan)
Dmitriy Viderman (Kazakhstan)
Doskhan Kozhakhmet (Kazakhstan)
Duygu Kayar Calili (Turkey)
Eda Ay (Turkey)
Eduard A. Shuralev (Russia)
Elif Baki (Turkey)
Emrah Ay (Turkey)

Emre Bilgin (Turkey)
Emrullah Durmus (Turkey)
Ercan Aydin (Turkey)
Erkut Etçioğlu (Turkey)
Ernar Tursynbet (Kazakhstan)
Ersin Kuloglu (Turkey)
Ertan Altaylı (Turkey)
Evelina Koldarova (Uzbekistan)
Faruk Karandere (Turkey)
Furkan Bodur (Turkey)
Galiya Orazova (Kazakhstan)
Galymzhan Kuatbay (Kazakhstan)
Gamze Temiz (Turkey)
Gaukhar Bakhtiyarova (Kazakhstan)
Gaukhar Kuanyshbayeva (Kazakhstan)
Gulbanu Shaimerdenova (Kazakhstan)
Gulnar Shalgumbayeva (Kazakhstan)
Gurpreet Singh Walia (India)
Hamza Okuyan (Turkey)
Hanna Elbahsir Mohamed (Qatar)
Hatice Şeyma Akça (Turkey)
Hilal Baş (Turkey)
Hüseyin Erdem (Turkey)
Ibrahim Toker (Turkey)
İlkay Ceylan (Turkey)
Irina Mekhantseva (Kazakhstan)
Iroda Mammadinova (Kazakhstan)
İsa Ardahanlı (Turkey)
Jatin Prakash (India)
Kajelcha Fikadu (Ethiopia)
Kakharman Yesmembetov (Kazakhstan)
Kamilla Mussina (Kazakhstan)
Kamilya Kedelbaeva (Kazakhstan)
Kanat Batyrbekov (Kazakhstan)
Kapil Rampal (India)
Karina Nukeshtayeva (Kazakhstan)
Kulpash Kaliaskarova (Kazakhstan)
Kuralay Atageldiyeva (Kazakhstan)
Kuralay Kongrtay (Kazakhstan)
Leila Razakhani (Iran)
Lina Zaripova (Kazakhstan)
Madina Syzdykova (Kazakhstan)
Malika Khaiitova (Kazakhstan)
Manav Raghuvanshi (United Kingdom)
Mariya Derbak (Ukraine)
Mariya Dmitriyeva (Kazakhstan)
Mayra Ashirova (Kazakhstan)
Mehmet Argun (Turkey)
Meliha Ergün Orhon (Turkey)
Merve Küçüker (Turkey)
Metin Yildiz (Turkey)
Mohammad Maaz Ahmad (India)
Muharrem Ozkaya (Turkey)
Mukhit Dossov (Kazakhstan)
Murat Kerkutluoglu (Turkey)
Mustafa Boğan (Turkey)
Nagehan Ümit Karacan (Turkey)
Naresh Kumar (India)
Nataliya Chekalina (Ukraine)
Nazire Kiliç Şafak (Turkey)
Neslihan İlkkaz (Turkey)
Nicel Yıldız Silahlı (Turkey)
Nilay Gökbulut (Turkey)
Olayinka Rasheed Ibrahim (Nigeria)
Olga An (Kazakhstan)
Onur Avci (Turkey)
Oya Güven (Turkey)

PEER-REVIEWERS WHO CONTRIBUTED TO THIS JOURNAL IN 2022

Pelin Dilsiz (Turkey)
Petar Jovan Avramovski (Macedonia)
Pooja Agrawal (India)
Prajna Anirban (India)
Prithpal Singh Matreja (India)
Ramazan Yuksel (Turkey)
Raushangul Magzumova (Kazakhstan)
Reyhan Aydın Doğan (Turkey)
Rinat Aitbekov (Kazakhstan)
Rohat Ak (Turkey)
Rumiyya Zakariyya Karimova (Azerbaijan)
Ruslan Bilal (Kazakhstan)
Sagar Anil Kurkure (India)
Sandeep Kumar (India)
Saniya Saussakova (Kazakhstan)
Satabdi Saha (India)
Saule Balmagambetova (Kazakhstan)
Sauran Yerdessov (Kazakhstan)
Seda Keskin (Turkey)
Selman Belviranlı (Turkey)
Selmin Köse (Turkey)
Serdar Özdemir (Turkey)
Serhat Şahinoğlu (Turkey)
Serik Aitaliyev (Kazakhstan)
Sevda Canbay Durmaz (Turkey)

Sholpan Daniyarova (Kazakhstan)
Suat Ekin (Turkey)
Susheela Taxak (India)
Tamara Prokopiyeva (Kazakhstan)
Tansu Erakgün (Turkey)
Tatyana Li (Kazakhstan)
Tatyana Vasiliyevna Polukchi (Kazakhstan)
Teuku Muhammad Yus (Indonesia)
Ulan Zhaparov (Kazakhstan)
Ulanbek Balpukov (Kazakhstan)
Ümit Ali Malçok (Turkey)
Ümran Karaca (Turkey)
Vitaliy Sazonov (Kazakhstan)
Vladimir Dikolayev (Kazakhstan)
Yaşar Duranoğlu (Turkey)
Yasemin Şanlı (Turkey)
Yerzhan Sharapatov (Kazakhstan)
Yodang Yodang (Indonesia)
Yousra Samir Ghoweba (UAE)
Yuliya Semenova (Kazakhstan)
Zeynep Kizilcik Özkan (Turkey)
Zhalaliddin Makhammajanov (Kazakhstan)
Zhanar Yermakhanova (Kazakhstan)
Zhenisgul Tlegenova (Kazakhstan)

Questioning editors who blame COVID-19 for their editorial failures

Jaime A. Teixeira da Silva[1]

[1]Independent researcher, Miki-cho, Japan

Corresponding author:
Jaime A. Teixeira da Silva.
E-mail: jaimetex@yahoo.com;
ORCID: 0000-0003-3299-2772.

Abstract

The Covid-19 pandemic has provided an opportunity to appreciate how delays in medical treatments can negatively impact the healthcare of patients in need. However, not much – if anything – has been researched on how the pandemic has been used as an excuse within professional settings. In this letter,, I take note of a personal case in which an editor of a ranked and indexed medical journal, having taken four months to issue a desk rejection, promptly blamed Covid-19 for the journal's editorial failures, without providing proof of this claim. Currently, editors who issue such statements cannot be held accountable, and the system of publication needs to change in order to prevent editors from making such ludicrous claims without publicly verifiable evidence. Absent concrete measures to safe-guard authors' rights to know why their papers' intellect has been held up for so long, they become victims of a system that offers unprecedented unchecked powers to editors.

Key words: editorial irresponsibility; honesty; predatory publishing; scientific ethos; truth

Dear *Journal of Clinical Medicine of Kazakhstan* **Editors,**

One of the most commonly observed secondary consequences of the COVID-19 pandemic, at its height, were delays in medical treatments, including valid reasons and excuses to blame COVID-19 for inefficiencies and delays[1], but beyond healthcare settings, the use of COVID-19 as an invalid "excuse" does not appear to have been studied extensively.

A submission by the author to an indexed healthcare journal (*Health Care Analysis*) published by Springer Nature was met with a desk rejection after waiting more than 4 months. In that period of time, the competitive advantage of the work was reduced. An apology was offered, accompanied by an odd reason: "Apologies for the delay, our editorial processes and response time continues to be impacted as a result of the effects of the COVID-19 pandemic." In other words, even though authors are victimized by editorial inefficiency, there are absolutely no negative consequences for the editor, journal or publisher, reputational or otherwise. This is completely incorrect and unfair, especially with respect to tardy desk rejections[2]. There are no support structures to offer authors who are victimized by editorial inefficiencies, no accountability, and no consequences for the perpetrators of such actions, in this case editors. Unfairly-induced stresses caused by professional victimization undoubtedly impact scientists with families.

WHO and the US CDC, among other leading healthcare organizations, now consider the COVID-19 pandemic to be over, although societies and medical communities need to take precautionary measures to avoid flare-ups in infections, and thus possible deaths [3].One of the issues that was raised initially, when the pandemic was still having a dramatic impact on many global societies, was how individuals might abuse it for unfair personal and professional gains[4]. It is likely that individuals were too preoccupied with their own struggles, health and otherwise[5], to be able to focus enough attention on such abusive practices.

This letter reflects on a potentially abusive or even predatory editorial practice, namely to blame COVID-19 for direct or indirect editorial failures, such as delayed desk rejections that might take months to achieve, but which should in principle be screened within at most a few days or a week or two. More importantly, it is argued that editors have the responsibility of offering proof to support their claims that COVID-19 was responsible for editorial failures, delays or inefficiencies. Absent concrete, publicly verifiable proof, arguments by editors should be considered null and void, and thus inadmissible to a paper's rejection from a journal.

In such a case, authors should be able to exercise their rights, not only to demand proof, but in the case where they feel that they have been treated unfairly, or that their work or intellect has been grossly mishandled by the journal editor, to initiate an investigation and seek

justice, including but not limited to, a fresh and rapid evaluation of their work in a conflict-free environment. Absent proof, and absent the ability of an author to fairly challenge editors who make such potentially ludicrous claims without proof, are such journals not operating on a principle of "junk" management that victimizes authors unfairly [6]?

Editors who issue tardy desk rejections or excuses for poor editorial handling have the opportunity of doing the right thing, by offering proof to support their excuse, and to thus prove that their rejections are realistic.

References

1. Madsen SMD, Rawashdeh YF. Assessing timeline delays associated with utilization of ultrasound diagnostics in paediatric acute scrotum, pre and per COVID-19 pandemic. *Journal of Pediatric Urology,* 2023; 19(5): 653.e1–653.e7. https://doi.org/10.1016/j.jpurol.2023.07.003.

2. Teixeira da Silva JA, Al-Khatib A, Katavić V, Bornemann-Cimenti H. Establishing sensible and practical guidelines for desk rejections. *Science and Engineering Ethics*. 2018; 24(4): 1347–1365. https://doi.org/10.1007/s11948-017-9921-3.

3. Chirico F, Teixeira da Silva JA. What should happen after the COVID-19 pandemic ends? A global plan is needed to address "endemic" COVID-19 and prevent future pandemics. *Journal of Health and Social Sciences*. 2023; 8(1): 9–12. https://doi.org/10.19204/2023/whts1.

4. Teixeira da Silva JA. Use of Covid-19 as an illegitimate excuse, or as a scape-goat. *Gazeta Médica*. 2020; 7(4): 396–397. https://doi.org/10.29315/gm.v7i4.409.

5. Teixeira da Silva JA. Corona exhaustion (CORONEX): Covid-19-induced exhaustion grinding down humanity. *Current Research in Behavioral Sciences*. 2021; 2: 100014. https://doi.org/10.1016/j.crbeha.2021.100014.

6. Teixeira da Silva JA. Junk science, junk journals, and junk publishing management: risk to science's credibility. *Philosophia*. 2023; 51(3): 1701–1704. https://doi.org/10.1007/s11406-022-00590-0.

Late post-COVID syndrome: clinical complications beyong 12 weeks

Shynar S. Nurusheva[1], Saule T. Abisheva[1], Anilim B. Abisheva[1], Kristina S. Rutskaya-Moroshan[1], Serik A. Shaimerdenov[2]

[1]*Department of Family Medicine №1, Astana Medical University, Astana, Kazakhstan*
[2]*Administration department, City polyclinic №4, Astana, Kazakhstan*

Corresponding author:
Nurusheva Shynar Sabyrbekovna.
E-mail: nurusheva-95@mail.ru;
ORCID: 0009-0001-2101-6680.

Abstract

The persistent and diverse manifestations of post-COVID syndrome present a significant challenge for global healthcare. Beyond the acute phase of infection, individuals continue to grapple with lingering symptoms affecting various organ systems, including the respiratory, cardiovascular, neurological, and endocrine systems. In the respiratory realm, symptoms such as cough, dyspnea, and fatigue endure, particularly in those with a history of severe COVID-19. The cardiovascular impact manifests as chest pain, arrhythmias, and heightened risks of thromboembolic events, emphasizing the intricate connection between COVID-19 and cardiovascular complications. Neurological complications, ranging from headaches to more severe disorders, further contribute to the complex sequelae of post-COVID syndrome. Additionally, disruptions in the endocrine system, including new-onset diabetes and thyroid abnormalities, pose long-term challenges for affected individuals. The review discusses the clinical management challenges posed by the multifaceted nature of post-COVID complications and the necessity for tailored multidisciplinary approaches. A holistic and compassionate response to the long-term effects of COVID-19 requires collaboration across healthcare professionals, researchers and the broader community. By navigating these challenges collectively, we can pave the way for a more comprehensive and effective approach to post-COVID care.

Keywords: Post-COVID syndrome, respiratory complications, cardiovascular complications, neurological complications, endocrine complications, diabetes inset.

Introduction

The initial focus on COVID-19 primarily revolved around understanding and managing the acute phase of infection. However, as time has progressed, attention has shifted to the considerable number of individuals experiencing persistent symptoms well beyond the acute phase and the interest still exists [1, 2]. Termed post-COVID syndrome, this phenomenon has sparked a new frontier of research and clinical consideration. According to the WHO-lead Delphi process, post-COVID-19 syndrome is defined as a condition that emerges in individuals with a history of probable or confirmed SARS-CoV-2 infection, typically appearing three months after the onset of COVID-19, and is defined by symptoms lasting at least two months without explanation from an alternative diagnosis [3].

An early meta-analysis investigating post-COVID syndrome revealed a noteworthy statistic: more than 60% of individuals who had survived a SARS-CoV-2 infection experienced diverse complications three months after the initial infection [4]. This underscores the substantial and lasting impact of the virus on a significant portion of the population, necessitating an in-depth examination of the clinical manifestations of post-COVID syndrome (Figure 1). In alignment with the ever-evolving landscape of post-COVID healthcare and considering its effect across diverse medical disciplines, this review aims to present a thorough exploration of post-COVID syndrome's clinical manifestations.
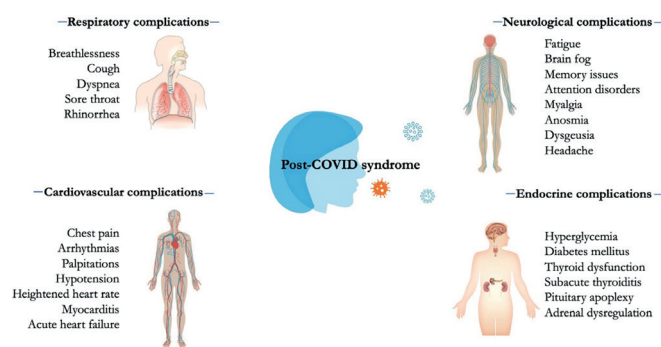
Figure 1 - Clinical complications of COVID-19 appearing after 12 weeks after the initial infection.

Effect on the Respiratory System

Considering that COVID-19 often causes problems with breathing, it's important to focus on the respiratory system when studying its lasting effects. After hospital discharge, certain symptoms, including cough, exertional dyspnea, sore throat, rhinorrhea, muscle aches, and fatigue, may persist for prolonged durations, particularly among individuals who have undergone severe COVID-19 [5]. Notably, those patients who experienced acute respiratory distress syndrome (ARDS) and had invasive mechanical ventilation (IMV) therapy face the heightened risk of developing chronic respiratory failure and enduring lung fibrosis [5, 6].

According to the prospective cohort study from the UK, 39% of patients had breathlessness symptoms and approximately 13% had a cough at 12-week follow-up [7]. A persistent cough can disrupt sleep patterns, leading to fatigue and daytime drowsiness. Sleep disturbances contribute to a decreased overall sense of well-being and can hinder the recovery process. Another prospective cohort study in the Netherlands, including 2113 participants, revealed that at the 3-month follow-up, 71% reported dyspnea (compared to 90% during the infection), 29% had a cough (compared to 68% during the infection), 26% experienced a sore throat (compared to 62% during the infection), and 24% reported pain or a burning sensation in the lungs (compared to 61% during the infection) [8]. Dyspnea can restrict physical activities, making even routine tasks challenging. Individuals may experience difficulty walking, climbing stairs, or engaging in exercise, leading to a decreased ability to participate in daily life activities.

A study from Stanford University showed that at 3-months follow-up, the rate of chest pain, cough, rhinorrhea, and sore throat did not differ significantly between severe and mild COVID groups; however, the rate of dyspnea was higher in the first group (p=0.006) [9]. This study shows the absence of a correlation between the severity of COVID-19 during hospitalization and the extent of symptoms during follow-up, as observed in previous research [10]. It highlights the need for a nuanced understanding of the varied and unpredictable nature of post-COVID effects on individuals' health.

Effect on the Cardiovascular System

While post-COVID complications commonly manifest as dyspnea and fatigue, persistent symptoms such as chest pain, olfactory and gustatory dysfunction, headaches, and gastrointestinal and cardiac-related issues may endure for up to six months [11, 12]. Within the realm of post-COVID syndrome, individuals commonly experience a range of cardiovascular events, including arrhythmias, palpitations, hypotension, heightened heart rate, venous thromboembolic diseases,

myocarditis, and acute heart failure [13]. This diverse array of cardiovascular complications underscores the intricate impact that the syndrome can have on the cardiovascular system.

In a 76-patient observational follow-up study at Wuhan Union Hospital, 62% reported chest tightness and palpitations three months after infection [14]. The high levels of troponin-I, which is related to the contraction of the heart muscle, in the blood during the illness were strongly connected with feeling tired after leaving the hospital (correlation coefficient 0.782, p = 0.008). Additionally, having low levels of lymphocytes during the illness was linked to feelings of tightness in the chest and heart palpitations during physical activity after leaving the hospital (correlation coefficient: −0.285, p = 0.027; correlation coefficient: −0.363, p = 0.004, respectively) (14). Recently, a meta-analysis of seven studies involving 8,126,462 participants showed that combined odds ratios for cardiovascular outcomes were notably higher in post-COVID cases (OR > 1, p < 0.05) compared to controls [15].

A long-term study conducted in China examined the post-COVID in patients who had been hospitalized and released from Renmin Hospital of Wuhan University. The study compared this group with a set of volunteers who did not have COVID-19 and lived in the urban area of Wuhan during the outbreak. Three months post-discharge, 11.2% of COVID survivors exhibited an increased resting heart rate, 4.8% reported discontinuous flashing, and 1.3% were diagnosed with new hypertension (16). In the comparison group, there was no significant increase in heart rate (p<0.001), only one case of discontinuous flashing (p<0.01), and no instances of newly diagnosed hypertension (p=0.20) [16].

The potential link between cardiovascular complications post-COVID and angiotensin-converting enzyme 2 (ACE2) expression in the heart is plausible. SARS-CoV-2, the virus causing COVID-19, binds to membrane-bound ACE2, leading to internalization by the host cell [17]. These findings suggest COVID-19-induced cardiovascular damage, although discerning whether these symptoms are part of the general post-COVID aftermath or a result of a complex interplay of factors poses a challenge for clinicians.

Neurological Complications

In addition to respiratory and cardiovascular complications, post-COVID patients commonly exhibit neurological manifestations such as headaches, peripheral neuropathy symptoms, memory issues, difficulties in concentration, and sleep disorders. A comprehensive meta-analysis of studies conducted from January 1st, 2020, to August 1st, 2021, involving a total of 10,530 patients, revealed the prevalence of post-COVID-19 neurological symptoms. The overall prevalence rates were as follows: 37% fatigue, 32% brain fog, 28% memory issues, 22% attention disorders, 17% myalgia, 12% anosmia, 10% dysgeusia, and 15% headache [18]. Notably, the prevalence of neurological symptoms tended to be lower in hospitalized patients compared to non-hospitalized individuals. Furthermore, the occurrence of fatigue, brain fog, and headaches was higher in assessments conducted at or beyond six months (long-term) compared to assessments between three and six months (mid-term) [18].

In a prospective cohort study, Rass et al. identified the emergence of neurological disorders in 17% of patients during the 3-month follow-up post-COVID-19 [19]. This prevalence exhibited a pronounced elevation among patients in the Intensive Care Unit (ICU), encompassing conditions such as polyneuro/myopathy, mild encephalopathy, and parkinsonism. This research indicated that individuals with severe COVID-19 were more predisposed to enduring neurological symptoms at follow-up compared to those with milder courses [19]. A

similar trend was observed by Taquet et al., who identified a significantly heightened prevalence of neurological disorders among hospitalized COVID-19 patients, particularly those requiring ICU admission [20].

In the realm of Post-COVID Neurological Syndrome (PCNS), there exists a spectrum of less common yet noteworthy disorders, including Guillain-Barré syndrome (GBS), polyneuropathy, myopathy, encephalopathy, post-infectious transverse myelitis, seizures, parkinsonism, orthostatic hypotension associated with vasovagal syncope, strokes, and neuro-ophthalmological issues such as post-infectious optic neuritis [21]. These less frequent manifestations reveal a nuanced neurological landscape in the aftermath of COVID-19, extending beyond the commonly observed symptoms. During the 12-week follow-up period, a subset of individuals exhibited these disorders, shedding light on the diverse and potentially prolonged neurological impact attributed to post-COVID complications [19]. This delineation serves to underscore the multifaceted nature of post-COVID neurological sequelae, necessitating comprehensive exploration for a holistic understanding and effective management.

Effect on the Endocrine System

Similar to its impact on various organ systems, COVID-19 influences the human endocrine system in several ways [22]. The recognized endocrine manifestations of COVID-19, primarily observed during the acute phase, encompass dysglycemia, new-onset diabetes mellitus, euthyroid sick syndrome, subacute thyroiditis (SAT), and pituitary apoplexy. Post-COVID syndrome disrupts endocrine regulation, affecting various mechanisms such as those related to the thyroid [22, 23], pituitary [24, 25], adrenal [26, 27], and gonadal [28]. Reduced thyroid function (hypothyroidism) can lead to symptoms such as fatigue, weight gain, intolerance to cold, dry skin, and constipation. As it was discussed before, one of the most prevalent cases of post-COVID syndrome is fatigue. The connection between COVID-19 and the pituitary gland lies in the expression of Angiotensin-Converting Enzyme-2 (ACE-2) receptors on the surface of pituitary cells [25, 26]. The pituitary gland is a crucial part of the endocrine system, regulating the release of various hormones that control essential bodily functions. Post-COVID syndrome may impact the normal functioning of the gland and disrupt the hormonal balance.

The binding of SARS-CoV-2 to angiotensin-converting enzyme-2 (ACE-2) receptors results in an overexpression of angiotensin II, potentially impairing insulin secretion and contributing to disruptions in glucose metabolism, which may lead to the development of diabetes [29]. According to a prospective observational study, 10% of initially non-diabetic patients developed new-onset pre-diabetes, and 14% developed new-onset diabetes mellitus (DM) within three months after the infection [30]. Additionally, at the same follow-up time, 17% of initially pre-diabetic patients had developed DM. The consequences of new-onset diabetes mellitus following SARS-CoV-2 infection are particularly concerning for individuals with pre-existing predispositions. Predisposed individuals, such as those with a family history of diabetes or other risk factors, may experience exacerbated challenges in glucose regulation due to the added burden of COVID-19-induced diabetes [31, 32]. This dual impact could lead to a more complex and difficult-to-manage metabolic condition, posing heightened risks for adverse outcomes and potentially complicating the overall health status of these individuals.

A recent study revealed that, after a 3-month follow-up, 10% of initially non-diabetic patients developed new-onset diabetes mellitus (DM). The most common risk factors associated with this development were a high dose of steroids (p<0.001), a family history of DM (p=0.001), excess weight (p<0.001), and fungal infection (p<0.001) (32). The results of this study also indicated that individuals experiencing new-onset diabetes exhibited a more severe infection, necessitating oxygen supplementation and ICU admission. Additionally, they demonstrated elevated levels of inflammatory markers compared to non-diabetic patients. These findings align with those of Li et al., who reported that individuals with newly diagnosed diabetes and hyperglycemia frequently presented with more severe symptoms and higher inflammatory marker levels [33]. As per a comprehensive meta-analysis, individuals with COVID-19-associated new-onset diabetes mellitus (NODM) exhibited the highest mortality rate (24.96%), surpassing patients with pre-existing diabetes mellitus (DM) (16.03%) and non-diabetic patients (9.29%) (29). Moreover, COVID-19-associated NODM patients experienced the most significant adverse effects, followed by individuals with pre-existing DM, COVID-19-associated hyperglycemia, and non-diabetic patients.

Implications and Future directions

The diverse and persistent nature of post-COVID complications poses significant challenges for clinicians. Tailored and multidisciplinary approaches are essential to address the range of symptoms affecting the respiratory, cardiovascular, neurological, and endocrine systems. Developing comprehensive clinical guidelines that integrate evolving knowledge about post-COVID manifestations is crucial for optimizing patient care. Moreover, the long-term nature of post-COVID syndrome implies continued healthcare resource utilization. Hospitals and healthcare systems need to anticipate and plan for ongoing support, including specialized clinics, rehabilitation services, and mental health resources. This necessitates a strategic allocation of resources to meet the evolving needs of individuals experiencing persistent symptoms.

As the understanding of post-COVID syndrome advances, public health strategies must adapt to address the long-term health consequences. Education campaigns should focus on raising awareness about the potential for lingering symptoms and the importance of seeking medical attention for persistent health issues. Public health interventions should extend beyond the acute phase of the pandemic to provide sustained support for those affected. In addition, the psychological impact of persistent symptoms should not be underestimated. Mental health support must be integrated into post-COVID care plans, acknowledging the potential for anxiety, depression, and other mental health challenges. Research into effective mental health interventions for individuals grappling with the psychological toll of post-COVID syndrome is imperative.

Conclusion

Considering the abovementioned complexities, a comprehensive understanding of post-COVID syndrome's diverse manifestations is crucial for effective clinical management. Continued research and exploration of the long-term effects of COVID-19 are essential for developing targeted interventions and support strategies for individuals experiencing persistent symptoms. The evolving landscape of post-COVID healthcare underscores the need for a multidisciplinary approach to address the intricate interplay of symptoms across different organ systems.

References

1. Fernández-de-Las-Peñas C. One year later: Prevalence of long-COVID symptoms. *European Journal of Internal Medicine.* 2023; 115: 37-8. https://doi.org/10.1016/j.ejim.2023.07.001.

2. Welte T. Post-COVID syndrome-more questions than answers. *Deutsches Ärzteblatt International.* 2022; 119(10): 165. https://doi.org/10.3238/arztebl.m2022.0154.

3. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *The Lancet Infectious Diseases.* 2022; 22(4): e102-e7. https://doi.org/10.1016/S1473-3099(21)00703-9.

4. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *European journal of internal medicine.* 2021; 92: 55-70. https://doi.org/10.1016/j.ejim.2021.06.009.

5. Esendağli D, Yilmaz A, AkÇAy MŞ, Özlü T. Post-COVID syndrome: pulmonary complications. Turkish journal of medical sciences. 2021; 51(7): 3359-71. https://doi.org/10.3906/sag-2106-238.

6. Leask A. COVID-19: is fibrosis the killer? J*ournal of Cell Communication and Signaling.* 2020; 14: 255. https://doi.org/10.1007/s12079-020-00569-0.

7. Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax.* 2021; 76(4): 399-401. https://doi.org/10.1136/thoraxjnl-2020-216086.

8. Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ open research.* 2020; 6(4). https://doi.org/10.1183/23120541.00542-2020.

9. Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M, et al. Patients with uncomplicated coronavirus disease 2019 (COVID-19) have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic. *Clinical Infectious Diseases.* 2021; 73(3): e826-e9. https://doi.org/10.1093/cid/ciab103.

10. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: what is long-COVID and how should we manage it? *Lung.* 2021; 199: 113-9. https://doi.org/10.1007/s00408-021-00423-z.

11. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *European heart journal.* 2020; 41(22): 2070-9. https://doi.org/10.1093/eurheartj/ehaa408.

12. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ. 2021; 372. https://doi.org/10.1136/bmj.n136.

13. Visco V, Vitale C, Rispoli A, Izzo C, Virtuoso N, Ferruzzi GJ, et al. Post-COVID-19 syndrome: involvement and interactions between respiratory, cardiovascular and nervous systems. *Journal of clinical medicine.* 2022; 11(3): 524. https://doi.org/10.3390/jcm11030524.

14. Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, et al. Three-month follow-up study of survivors of coronavirus disease 2019 after discharge. Journal of Korean medical science. 2020; 35(47). https://doi.org/10.3346/jkms.2020.35.e418.

15. Shrestha AB, Mehta A, Pokharel P, Mishra A, Adhikari L, Shrestha S, et al. Long COVID syndrome and cardiovascular manifestations: a systematic review and meta-analysis. *Diagnostics.* 2023; 13(3): 491. https://doi.org/10.3390/diagnostics13030491.

16. 16. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clinical microbiology and infection.* 2021; 27(1): 89-95. https://doi.org/10.1016/j.cmi.2020.09.023.

17. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. American Journal of Physiology-Heart and Circulatory Physiology. 2020. https://doi.org/10.1152/ajpheart.00217.2020.

18. Premraj L, Kannapadi NV, Briggs J, Seal SM, Battaglini D, Fanning J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis. *Journal of the neurological sciences.* 2022; 434: 120162. https://doi.org/10.1016/j.jns.2022.120162.

19. Rass V, Beer R, Schiefecker AJ, Kofler M, Lindner A, Mahlknecht P, et al. Neurological outcome and quality of life 3 months after COVID-19: A prospective observational cohort study. *European journal of neurology.* 2021; 28(10): 3348-59. https://doi.org/10.1111/ene.14803.

20. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry.* 2021; 8(5): 416-27. https://doi.org/10.1016/S2215-0366(21)00084-5.

21. Okrzeja J, Garkowski A, Kubas B, Moniuszko-Malinowska A. Imaging and neuropathological findings in patients with Post COVID-19 Neurological Syndrome – A review. *Frontiers in Neurology.* 2023; 14: 1136348. https://doi.org/10.3389/fneur.2023.1136348.

22. Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. *Journal of endocrinological investigation.* 2020; 43: 1027-31. https://doi.org/10.1007/s40618-020-01276-8.

23. Popescu M, Ghemigian A, Vasile CM, Costache A, Carsote M, Ghenea AE. The new entity of subacute thyroiditis amid the COVID-19 pandemic: from infection to vaccine. *Diagnostics.* 2022; 12(4): 960. https://doi.org/10.3390/diagnostics12040960.

24. Ilera V, Delfino LC, Zunino A, Glikman P, Drnovsek M, Reyes A, et al. Correlation between inflammatory parameters and pituitary-thyroid axis in patients with COVID-19. *Endocrine.* 2021; 74: 455-60. https://doi.org/10.1007/s12020-021-02863-2.

25. Finsterer J, Scorza FA. The pituitary gland in SARS-CoV-2 infections, vaccinations, and post-COVID syndrome. *Clinics*. 2023; 78. https://doi.org/10.1016/j.clinsp.2022.100157.

26. Geslot A, Chanson P, Caron P, editors. Covid-19, the thyroid and the pituitary – The real state of play 2022: *Elsevier*. https://doi.org/10.1016/j.ando.2021.12.004.

27. Kanczkowski W, Gaba WH, Krone N, Varga Z, Beuschlein F, Hantel C, et al. Adrenal gland function and dysfunction during COVID-19. *Hormone and Metabolic Research*. 2022; 54(08): 532-9. https://doi.org/10.1055/a-1873-2150.

28. Moreno-Perez O, Merino E, Alfayate R, Torregrosa ME, Andres M, Leon-Ramirez JM, et al. Male pituitary-gonadal axis dysfunction in post-acute COVID-19 syndrome-Prevalence and associated factors: A Mediterranean case series. *Clinical Endocrinology*. 2022; 96(3): 353-62. https://doi.org/10.1111/cen.14537.

29. Shrestha DB, Budhathoki P, Raut S, Adhikari S, Ghimire P, Thapaliya S, et al. New-onset diabetes in COVID-19 and clinical outcomes: A systematic review and meta-analysis. *World Journal of Virology*. 2021; 10(5): 275. https://doi.org/10.5501/wjv.v10.i5.275.

30. Keerthi BY, Sushmita G, Khan EA, Thomas V, Cheryala V, Shah C, et al. New onset diabetes mellitus in post-COVID-19 patients. *Journal of family medicine and primary care*. 2022; 11(10): 5961. https://doi.org/10.4103/jfmpc.jfmpc_316_22.

31. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *Journal of diabetes science and technology*. 2020; 14(4): 813-21. https://doi.org/10.1177/1932296820924469.

32. Dambal A, Nekkanti A, Yashika C. The incidence, risk factors, and outcome of new-onset diabetes among post-COVID-19 patients: A single-center study. *Asian Journal of Medical Sciences*. 2023; 14(3). https://doi.org/10.3126/ajms.v14i3.51510.

33. Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes, obesity and metabolism*. 2020; 22(10): 1897-906. https://doi.org/10.1111/dom.14099.

Low renin forms of monogenic hypertension: review of the evidence

Ugochi Chinenye Okorafor[1], Uchechi Chioma Okorafor[2]

[1]Department of Cardiology, Meridian Cardiac Center, Festac Town, Lagos, Nigeria
[2]Department of Medicine and Surgery, College of Medicine, University of Ibadan, University Of Ibadan, Ibadan, Nigeria.

Abstract

Background: Monogenic hypertension syndromes result from a single genetic mutation and present with severe, refractory hypertension, distinct laboratory abnormalities, and a positive family history. These syndromes are often unrecognized or misdiagnosed as essential hypertension, thus preventing proper treatment. The rise of molecular genetics has brought these conditions to the limelight, and physicians must be kept abreast of the latest in this field. This paper aims to educate doctors to recognize and institute appropriate management early to prevent end-organ damage.

Discussion: These syndromes all affect sodium transport in the distal nephron of the kidneys. However, they are divided based on the location of the primary disorder, i.e., the adrenal glands or the distal nephron and discussed in that manner. Tables provide an overview of the different syndromes and provide essential information in a snapshot.

Conclusion: The widespread availability of genetic testing facilities will aid in the earlier diagnosis of these conditions to prevent morbidity.

Keywords: Apparent Mineralocorticoid Excess; Congenital Adrenal Hyperplasia; Familial Hyperaldosteronism; Gordon Syndrome; Hypertension; Liddle Syndrome.

Introduction

Hypertension is a significant risk factor in the development of cardiovascular diseases (CVD) [1] and is also a major contributor to the global burden of disease [2]. Defined as systolic blood pressure (SBP) of 140mmHg or more and/or diastolic blood pressure (DBP) of 90mmHg or more [3], it is responsible for one in eight deaths globally [4]. Monogenic hypertension syndromes have distinct causative genetic mutations with identifying clinical and/or laboratory characteristics [5, 6]. They are subserved by abnormally high sodium transport in the distal nephron [7–9]. Of particular note is their presentation in childhood with severe, refractory hypertension, propensity to develop end-organ failure and associated family history [10]. This paper discusses low renin monogenic hypertension disorders. They are grouped as adrenal gland and distal nephron disorders based on their pathophysiology. We aim to educate physicians on best management practices. Table 1 provides an overview of these syndromes and their management.

Methods

Searches were conducted in Google Scholar and PubMed. Search terms included "monogenic hypertension", "low renin hypertension", "familial hyperaldosteronism", "congenital adrenal hyperplasia", "secondary hypertension", "Liddle syndrome", "Gordon syndrome", "Geller syndrome", "apparent mineralocorticoid excess", and "familial glucocorticoid resistance".

Inclusion criteria
1. Articles included in the review had to be written in English.
2. Articles had to have been released between September 2018 and August 2023.
Exclusion criteria
1. Publications noted to not have passed through the peer review process.
2. Articles not published in English.
3. Publications released before September 2018 and after August 2023.

Eighty-two articles and books were retrieved and reviewed, after which 56 were selected for discussion.

Table 1					Overview of low-renin monogenic hypertension syndromes	
Syndrome	Gene locus	Affected gene	Gene product	Mode of Inheritance	Pathophysiology	Management
Familial Hyperaldosteronism-1	8q24.3	CYP11B1/ CYP11B2 gene chimera	Aldosterone synthase	AD	GOF mutation in the chimeric gene allows aldosterone synthase to be responsive to ACTH stimulation	Glucocorticoids (dexamethasone or prednisolone), MR antagonists (spironolactone or eplerenone), ENaC blockers (amiloride or triamterene)
Familial Hyperaldosteronism-2	3q27.1	CLCN2	Voltage-gated chloride channel-2	AD	GOF mutation in the affected gene allows for the synthesis of an overly permeable chloride channel with cell membrane depolarisation and production of aldosterone synthase	MR antagonists, unilateral adrenalectomy
Familial Hyperaldosteronism-3	11q24.3	KCNJ5	GIRK4	AD	GOF mutation in the KCNJ5 leads to loss of selectivity in the gene product, GIRK4	MR antagonists, bilateral adrenalectomy
Familial Hyperaldosteronism-4	16p13.33	CACNA1H	α-subunit of CaV3.2 (T-type calcium channel)	AD	Intracellular calcium ion influx secondary to GOF mutation in the responsible gene with stimulation of aldosterone synthase synthesis	No specific treatment. MR antagonists can be used.
Congenital Adrenal Hyperplasia Type IV	8q24.3	CYP11B1	11β-hydroxylase	AR	Accumulation of DOC and deoxycortisol which both have mineralocorticoid effect	Glucocorticoids, MR antagonists, Calcium channel blockers
Congenital Adrenal Hyperplasia Type V	10q24.32	CYP17A1	17α-hydroxylase	AR	Increased production of DOC with excessive activity at the MR	MR antagonists
Familial Glucocorticoid Resistance	5q31-q32	NR3C1	Glucocorticoid receptor	AD,AR	LOF mutation in the affected gene encodes for a glucocorticoid receptor unresponsive to cortisol. Accumulation of cortisol (which has mineralocorticoid activity) causes excess MR activation	Dexamethasone
Liddle syndrome	16p12.2	SCNN1B	ENaC β-subunit	AD	Reduced degradation of ENaCs secondary to the mutations causes increased sodium and water reabsorption	ENaC blockers, dietary sodium restriction
	16p12.2	SCNN1G	ENaC γ-subunit	AD		
	12p13.31	SCNN1A	ENaC α-subunit	AD		
Geller syndrome	4q31.23	NR3C2	Mineralocorticoid receptor	AD	GOF mutation in the MR makes it sensitive to progesterone, a natural antagonist	ENaC blockers, finerenone, dietary sodium restriction
Apparent Mineralocorticoid Excess	16q22.1	HSD11B2	11β-hydroxysteroid dehydrogenase type II	AR	Defects in the metabolism of cortisol cause its accumulation and excess activity at the MR	MR antagonists, dietary sodium restriction, ENaC blockers, Calcium channel blockers
Gordon syndrome	1q31-q42	Not known	Not known	AD	All mutations known to Gordon syndrome work to upregulate the NCC in the distal nephron resulting in increased sodium reabsorption and hypertension	Thiazide diuretics, dietary sodium and potassium restriction
	17q21.2	WNK-4	With-no-lysine kinase 4	AD		
	12p13.33	WNK-1	With-no-lysine kinase 1	AD		
	5q31.2	KLHL3	Kelch-like 3	AD,AR		
	2q36.2	CUL3	Cullin3	AD		

ACTH – Adrenocorticotropic Hormone, AD – Autosomal dominant, AR – Autosomal recessive, DOC – deoxycorticosterone, ENaC – Epithelial sodium channel, GOF – Gain of function, LOF – Loss of function, MR – Mineralocorticoid receptor, NCC – Sodium-chloride cosymporter.

Discussion

A. Disorders of the Adrenal Gland
• Familial Hyperaldosteronism Type 1 (FH-1)

First described in 1966 and also known as Glucocorticoid-remediable aldosteronism (GRA), FH-1 is an autosomal dominant condition resulting from a mutation on chromosome 8q24.3 [11, 12]. A chimeric gene resulting from the crossing over of genes typically near each other, namely CYP11B1 and CYP11B2 (which encode 11β-hydroxylase and aldosterone synthase, respectively), is produced during DNA replication in individuals with this condition [12]. This mutant gene was identified by Lifton and colleagues in 1992 and encodes for aldosterone synthase that is responsive to adrenocorticotropic hormone (ACTH) stimulation [13, 14]. Aldosterone is now produced in the zona glomerulosa and alongside cortisol in the zona fasciculata of the adrenal glands [15]. This leads to supraphysiologic aldosterone concentrations in the bloodstream, increased sodium and water reabsorption, mild hypokalemia,

Overview of Familial Hyperaldosteronism

TYPE	GENE LOCUS	AFFECTED GENE	GENE PRODUCT	AD/AR	GOF/LOF	AGE AT ONSET
FH-1	8q24.3	CYP11B1/CYP11B2 chimeric gene	Aldosterone synthase	AD	GOF	Variable
FH-2	3q27.1	CLCN2	Voltage-gated chloride channel 2	AD	GOF	Variable
FH-3	11q24.3	KCNJ5	GIRK-4	AD	GOF	Infancy/early childhood
FH-4	16p13.3	CACNA1H	CaV3.2	AD	GOF	Variable

AD – Autosomal dominant, AR – Autosomal recessive, FH – Familial hyperaldosteronism, GOF – Gain of function, LOF – Loss of function

metabolic alkalosis, low plasma renin levels, and hypertension [16, 17].

These patients have been noted to have a higher risk of hemorrhagic strokes and, even when normotensive, have increased left ventricular wall thickness with diastolic dysfunction [18, 19]. Diagnosis is conclusive with genetic testing [20]. Additional laboratory investigations include plasma aldosterone and renin levels alongside testing for aldosterone suppression levels with dexamethasone [21]. Treatment involves glucocorticoid replacement (i.e., dexamethasone or prednisolone) at the lowest dose to allow for disease remission and also prevent Cushing syndrome [22]. Mineralocorticoid antagonists (i.e., spironolactone or eplerenone) and epithelial sodium channel (ENaC) blockers can serve as adjuncts for better blood pressure control [23].

• Familial Hyperaldosteronism Type 2 (FH-2)

FH-II is caused by mutations in the CLCN2 gene on chromosome 3q27.1 [12]. This gene encodes ClC-2, a voltage-gated chloride channel in zona glomerulosa cells [16]. The mutant gene produces a defective chloride channel with increased permeability, thereby causing depolarization of the cell membrane and influx of calcium intracellularly, resulting in the activation of aldosterone synthesis [18]. Inheritance is thought to be likely autosomal dominant with incomplete penetrance [21]. The gold standard for diagnosis remains genetic analysis, and management of these patients is through the administration of mineralocorticoid receptor (MR) antagonists and unilateral adrenalectomy [16].

• Familial Hyperaldosteronism Type 3 (FH-3)

FH-3 is very rare and occurs secondary to gain-of-function mutations in the KCNJ5 gene located on chromosome 11q24.3 [19, 24]. KCNJ5 encodes for a potassium channel in the zona glomerulosa called GIRK4 which loses its selectivity for potassium with mutations in the gene [22]. This leads to sodium influx into the cells with resultant membrane depolarisation, intracellular calcium entry and aldosterone synthesis [15, 25]. The result is severe hypertension, hypokalemia and bilateral adrenal hyperplasia [16]. Diagnosis is made using genetic testing and adrenal computed tomography [26]. Owing to the variety of phenotypes these patients may present with, bilateral adrenalectomy is recommended in these patients if MR blockers cannot stabilize the blood pressure [25, 27]. Unilateral adrenalectomy has been erroneously trialled in the management of markedly elevated blood pressure and plasma aldosterone in a patient with FH-III [25]. The case highlights the problems faced by managing physicians and the propensity for the development of complications at an early age.

• Familial Hyperaldosteronism Type 4 (FH-4)

This condition results from mutations in CACNA1H, located on chromosome 16p13.3 and encodes the α-subunit of CaV3.2, a T-type calcium channel expressed abundantly in the zona glomerulosa [22, 26]. Wild-type CACNA1H allows the calcium channel to be open transiently [12]. However, the mutant form of the gene impairs the channel's deactivation,

resulting in an influx of calcium ions into the zona glomerulosa cells, thus signalling aldosterone synthesis [18].

The disorder is inherited in an autosomal dominant fashion and demonstrates incomplete penetrance with highly variable clinical presentations [19]. FH-4 has no specific treatment, but mineralocorticoid antagonists and adrenalectomy have improved hypertension in these patients [26]. Table 2 below describes the salient characteristics of the familial hyperaldosteronism syndromes.

• Congenital Adrenal Hyperplasia (CAH)

One of the most commonly occurring genetic disorders of the adrenal glands, CAH is a group of autosomal recessive disorders responsible for defects in the pathways of steroid hormone synthesis [23, 28]. The most common of these disorders is 21-hydroxylase deficiency, which accounts for 90-99% of cases [29, 30]. However, these cases do not present with hypertension [23].

11β-hydroxylase deficiency, also known as Type IV CAH, accounts for 5-8% of all CAH cases and is the second most common form of the disorder [12, 31]. It is caused by mutations affecting the CYP11B1 gene on chromosome 8q24.3 [23]. The deficiency prevents the hydroxylation of deoxycorticosterone and deoxycortisol to form corticosterone and cortisol, respectively, thus leading to the accumulation of steroid precursors with a mineralocorticoid effect (especially 11-deoxycorticosterone) [12]. Hypokalemia and low-renin hypertension are secondary to increased sodium reabsorption [17, 31]. Hypertension occurs in at least one-third of cases and is of varying severity [32]. Genetic testing confirms the presence of a mutation in the CYP11B1 gene, but the condition is suspected with elevated basal 11-deoxycortisol [21]. Treatment of hypertension occurs with optimal glucocorticoid replacement; however, MR antagonists such as spironolactone are used alone or with a calcium channel blocker (CCB) when blood pressure control remains inadequate [32].

Type V CAH, caused by 17α-hydroxylase deficiency, is the second form of CAH that can cause low renin hypertension. This rare enzyme deficiency occurs in 1 in 50,000 of the population [31]. Located on chromosome 10q24.32 [12], the defective gene and the resultant loss of enzyme activity cause an increase in the production of deoxycorticosterone and corticosterone at the expense of cortisol and adrenal androgens [31]. The accumulated deoxycorticosterone results in excess mineralocorticoid activity with resultant hypokalemia and hypertension [23]. Molecular testing for the presence of CYP17A1 mutations confirms the diagnosis [32]. MR antagonists help alleviate the hypertension [32].

• Familial Glucocorticoid Resistance (FGR)

Loss-of-function mutations in the NR3C1 gene on chromosome 5q31-q32 [16]. The affected gene encodes the glucocorticoid receptor, rendering it unresponsive to circulating cortisol [17]. The lack of inhibitory feedback on the hypothalamic-pituitary-adrenal axis leads to the overproduction of ACTH, deoxycorticosterone (DOC), corticosterone and

adrenal androgens [33]. This leads to excessive MR activation (as cortisol also has a high affinity for the MR) with subsequent sodium ion overabsorption and hypertension [26].

Patients present with high serum cortisol levels without the peripheral stigmata of Cushing's syndrome, hypokalemia, metabolic alkalosis, and hypertension [34]. Diagnosis is through genetic analysis with background elevated serum cortisol levels [16]. Treatment is through oral dexamethasone, a mineralocorticoid-sparing glucocorticoid [11].

B. Disorders of the Distal Nephron
• Liddle Syndrome

First identified by Liddle et al. in 1963 [16,31], Liddle syndrome is caused by activating (gain-of-function) mutations in the genes (SCNN1A, SCNN1B, SCNN1G) that encode the subunits of the aldosterone-regulated epithelial sodium channels (ENaC) [35,36]. A table collating basic information on the 3 types of Liddle syndrome is attached below (Table 3).

Table 3	Liddle syndrome		
TYPE	GENE LOCUS	AFFECTED GENE	GENE PRODUCT
LS-1	16p12.2	SCNN1B	ENaC β-subunit
LS-2	16p12.2	SCNN1G	ENaC γ-subunit
LS-3	12p13.31	SCNN1A	ENaC α-subunit

ENaC – Epithelial sodium channel, LS – Liddle syndrome

Although the worldwide prevalence of the condition is unknown [37], Liddle syndrome is regarded as the most common form of monogenic hypertension [26]. This condition, also known as pseudohyperaldosteronism, is inherited in an autosomal dominant manner with variable penetrance, thus allowing for variability in phenotypes [38–40]. Less than 50 different disease-causing mutations have been identified, with mutations in the SCNN1B gene being the most common [41].

Mutations in the subunits of the ENaCs reduce the rate at which these channels are degraded, leading to increased sodium and water reabsorption and account for hypertension in these patients [42]. Other typical features include hypokalemia, metabolic alkalosis, low serum renin and aldosterone levels [43]. Long-term complications result from hypertension-related organ damage, such as retinopathy, encephalopathy, nephrocalcinosis, cerebrovascular ischemia, left ventricular hypertrophy, and myocardial infarction [42, 44]. Genetic testing allows for early diagnosis of Liddle syndrome and subsequent management [45].

Treatment of hypertension involves dietary sodium limitations and ENaC blockers such as amiloride and triamterene [28, 46].

• Gordon Syndrome

Also known as familial hyperkalemic hypertension or pseudohypoaldosteronism type 2 (PHA2) [45], Gordon syndrome results from mutations identified in 5 different chromosomes [23]. A table detailing these mutations is attached below (Table 4).

PHA2 differs from PHA1, which is associated with hypotension [21]. All five mutations are involved in the regulation of the sodium-chloride cosymporter (NCC) located in the distal nephron [47]. The overall effect of these mutations is the upregulation of the NCC within the distal nephron with increased sodium reabsorption, reduced expression of renal outer medullar K1 channel, and subsequent hyperkalemia and hypertension [31]. Inheritance has been identified to occur in an autosomal dominant or recessive manner, depending on the phenotype [48].

The age of onset of symptoms varies widely [33]. Clinical and laboratory features include hypertension, hypercalcemia, hyperchloremic metabolic acidosis, hypercalciuria and hyperkalemia [49]. A clinical history, laboratory investigations and genetic testing are essential for making a diagnosis [12]. Treatment is achieved by dietary sodium and potassium restriction together with thiazide diuretics as they inhibit the NCC [16].

• Geller Syndrome

Geller syndrome is an autosomal dominant disorder resulting from a gain-of-function mutation in the MR [50]. It is also known as Constitutive Activation of the Mineralocorticoid Receptor or Pregnancy-exacerbated Hypertension which is misleading as the condition also affects non-pregnant females and men [12, 16]. Less than 10 cases have been reported since its initial description in 2000 by Geller et al [50]. The causative mutation affects the hormone-binding domain of the receptor and results from the substitution of leucine for serine at amino acid 810 in chromosome 4q31 [12, 17]. This results in the mutant mineralocorticoid receptor being activated by aldosterone and steroids such as progesterone, a natural antagonist [21]. This receptor is also sensitive to cortisone and 11-dehydrocorticosterone in non-pregnant women and males and spironolactone, which is contraindicated in its management [31, 33].

Patients present with low-renin hypertension at an early age, which worsens with pregnancy, low serum aldosterone and low-to-normal potassium levels [26]. Hypertension and hypokalemia have been noted to peak within the third trimester [17]. Definitive diagnosis, as for a lot of these monogenic disorders, is through genetic testing for the mutations in the MR [50]. Treatment includes limitation of dietary salt, and epithelial sodium channel antagonists such as amiloride and finerenone (a nonsteroidal selective antagonist of the mutant MR) [26, 31, 33]. Close monitoring of fetal and maternal conditions while managing blood pressure and serum potassium levels during pregnancy is the mainstay of treatment [50]. Blood pressure and serum potassium levels return to normal in the postpartum period [17].

• Apparent Mineralocorticoid Excess (AME)

Apparent Mineralocorticoid Excess (AME), more specifically known as Classic AME [51], is an infrequent monogenic hypertensive disorder with about 100 reported

Table 4	Gordon syndrome					
TYPE	GENE LOCUS	AFFECTED GENE	GENE PRODUCT	AGE AT DIAGNOSIS	AD/AR	GOF/LOF
PHA2A	1q31-q42	Not known	Not known	Adolescence/Adulthood	AD	-
PHA2B	17q21.2	WNK4	With no lysine kinase 4	Adolescence/Adulthood	AD	LOF
PHA2C	12p13.33	WNK1	With no lysine kinase 1	Adolescence/Adulthood	AD	GOF
PHA2D	5q31.2	KLHL3	Kelch-like 3	Infancy/Childhood	AD, AR	LOF
PHA2E	2q36.2	CUL3	Cullin 3	Infancy/Childhood	AD	LOF

AD – Autosomal dominant, AR – Autosomal recessive, GOF – Gain of function, LOF – Loss of function, PHA – Pesudohypoaldosteronism.

cases worldwide [52]. First reported in the 1970s [53], it was not until 1995 that the first mutation was found [52]. AME is an autosomal recessive disorder caused by a deficiency in the 11β hydroxysteroid dehydrogenase type II enzyme (11βHSD2) secondary to loss-of-function biallelic mutations in the HSD11B2 gene located on the chromosome 16q22.1 [54, 55]. This enzyme is expressed primarily in sodium-transporting epithelia such as the distal nephron [47] and is responsible for the peripheral conversion of cortisol to cortisone [56]. Over 50 pathogenic mutations in the HSD11B2 gene have been reported worldwide [56].

HSD11B2 prevents the activation of the MR by cortisol (which has mineralocorticoid activity) by its conversion to cortisone, which cannot bind to the receptor [12]. With mutations in the gene, cortisol is not metabolized and thus can activate the MR. Affected patients present in infancy with failure to thrive, polyuria, polydipsia, metabolic alkalosis, severe hypertension, hypokalemia, low serum renin, and aldosterone levels [31, 33]. In severe cases, these patients may come down with hypercalciuria, muscle paralysis secondary to severe hypokalemia, renal medullary cysts and nephrocalcinosis [8, 28]. End-organ damage to the heart (LVH), retina (hypertensive retinopathy), central nervous system (stroke) and aortic insufficiency is not uncommon and occurs secondary to hypertension [16, 33].

Diagnosis is ideally through genetic testing, but the 24-hour serum or urinary cortisol to free cortisone ratio is high in these cases [21, 56]. This condition can be mistaken for Bartter syndrome, which can be prevented through blood pressure measurements, serum renin, and aldosterone quantification [36].

Partial deficiency of the 11βHSD2 enzyme (nonclassic AME) presents in adulthood and may be indistinguishable from essential hypertension [31, 36] and is characterized by high serum cortisol to cortisone ratio, normal or slightly elevated blood pressure, normal or low aldosterone and low renin [56]. These patients have elevated microalbuminuria, plasminogen activator inhibitor-1 (PAI-1) and high-sensitivity C-reactive protein (hs-CRP), suggesting that the condition causes a pro-inflammatory state along with vascular and renal problems [51].

Both phenotypes respond to MR antagonists such as spironolactone or eplerenone and a salt-limited diet [56]. Dexamethasone may be used at the lowest effective dose in classic AME to prevent growth retardation [21]. In refractory cases, amiloride and calcium channel blockers may also be prescribed [33]. Renal transplantation has been reported to offer a cure for the condition [12].

Conclusion

Diagnosis of monogenic hypertension syndromes is increasing globally due to the advances in molecular testing techniques. It is plausible that some cases are wrongly diagnosed as primary or essential hypertension when, in fact, they are monogenic in origin. This could lead to a wrongful diagnosis of resistant hypertension, inherently leading to end-organ damage. Physicians catering to adults and children alike should be on the lookout for cases of poorly controlled hypertension associated with biochemical abnormalities, all in the setting of a strong family history. A good history, with specific laboratory investigations and genetic testing (if available), can lead to early diagnosis and reduce morbidity and mortality in these patients. It is also imperative that genetic testing becomes more available and accessible to prevent misdiagnosis.

References

1. Buffolo F, Monticone S, Pecori A, Pieroni J, Losano I, Cavaglià G, et al. The spectrum of low-renin hypertension. *Best Pract Res Clin Endocrinol Metab*. 2020 May 1; 34(3):101399. https://doi.org/10.1016/j.beem.2020.101399.
2. Zöller B, Manderstedt E, Lind-Halldén C, Halldén C. Rare-variant collapsing analyses of arterial hypertension in the UK biobank. *J Hum Hypertens*. 2023: 1-3. https://doi.org/10.1038/s41371-023-00829-7.
3. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol*. 2021; 18(11): 785-802. https://doi.org/10.1038/s41569-021-00559-8.
4. Mamdouh H, Alnakhi WK, Hussain HY, Ibrahim GM, Hussein A, Mahmoud I, et al. Prevalence and associated risk factors of hypertension and pre-hypertension among the adult population: findings from the Dubai Household Survey, 2019. *BMC Cardiovasc Disord*. 2022; 22(1): 1-9. https://doi.org/10.1186/s12872-022-02457-4.
5. Lu YT, Fan P, Zhang D, Zhang Y, Meng X, Zhang QY, et al. Overview of Monogenic Forms of Hypertension Combined With Hypokalemia. *Front Pediatr*. 2021; 8: 543309. https://doi.org/10.3389/fped.2020.543309
6. Padmanabhan S, Dominiczak AF. Genomics of hypertension: the road to precision medicine. *Nat Rev Cardiol*. 2021; 18(4): 235-50. https://doi.org/10.1038/s41569-020-00466-4
7. Boder P, Mary S, Mark PB, Leiper J, Dominiczak AF, Padmanabhan S, et al. Mechanistic interactions of uromodulin with the thick ascending limb: perspectives in physiology and hypertension. *J Hypertens*. 2021; 39(8): 1490-504. https://doi.org/10.1097%2FHJH.0000000000002861. PMID: 34187999 PMCID: PMC7611110
8. Yadav M, Sinha A, Hari P, Bagga A. Impaired Distal Tubular Acidification, Renal Cysts and Nephrocalcinosis in Monogenic Hypertension. *Indian J Pediatr*. 2021 Jun 1; 88(6): 579–81. https://doi.org/10.1007/s12098-020-03516-4.
9. Precone V, Krasi G, Guerri G, Stuppia L, Romeo F, Perrone M, et al. Monogenic hypertension. *Acta Bio Medica: Atenei Parmensis*. 2019; 90 (10): 50-52. https://doi.org/10.23750%2Fabm.v90i10-S.8759. PMID: 31577254 PMCID: PMC7233634
10. Lalji R, Tullus K. Causes of Secondary Hypertension in Children and Adolescents. In: Lurbe E, Wühl E, editors. Hypertension in Children and Adolescents. Updates in Hypertension and Cardiovascular Protection. *Springer, Cham*. 2019. p. 111-30 https://doi.org/10.1007/978-3-030-18167-3_8.

11. Lin YF, Peng KY, Chang CH, Hu YH, Wu VC, Chueh JS, et al. Adrenalectomy Completely Cured Hypertension in Patients with Familial Hyperaldosteronism Type i Who Had Somatic KCNJ5 Mutation. *J Clin Endocrinol Metab*. 2019 Nov 1; 104(11): 5462–6. https://doi.org/10.1210/jc.2019-00689.

12. Raina R, Krishnappa V, Das A, Amin H, Radhakrishnan Y, Nair NR, et al. Overview of monogenic or Mendelian forms of hypertension. *Front Pediatr*. 2019 Jul 1; 7: 263. https://doi.org/10.3389/fped.2019.00263.

13. Levanovich PE, Diaczok A, Rossi NF. Clinical and Molecular Perspectives of Monogenic Hypertension. *Curr Hypertens Rev*. 2020; 16(2): 91–107. https://doi.org/10.2174/1573402115666190409115330. PMID: 30963979 PMCID: PMC7499356.

14. Sanga V, Seccia TM, Rossi GP. A systematic review of pathophysiology and management of familial hyperaldosteronism type 1 in pregnancy. *Endocrine*. 2021 Oct; 74(1): 5-10. https://doi.org/10.1007/s12020-021-02763-5.

15. Stowasser M, Wolley M, Wu A, Gordon RD, Schewe J, Stölting G, et al. Pathogenesis of familial hyperaldosteronism type II: new concepts involving anion channels. *Curr Hypertens Rep*. 2019 Apr;21:1-0. https://doi.org/10.1007/s11906-019-0934-y.

16. Park SJ, Shin JI. Diagnosis and Treatment of Monogenic Hypertension in Children. *Yonsei Med J*. 2023 Feb;64(2):77. https://doi.org/10.3349%2Fymj.2022.0316. PMID: 36719014. PMCID: PMC9892546.

17. Garg AK, Parajuli P, Mamillapalli CK. Pregnancy complicated by hypertension and hypokalemia. *American Journal of Kidney Diseases*. 2020 Oct 1; 76(4): A21-2. https://doi.org/10.1053/j.ajkd.2020.04.012.

18. Seidel E, Schewe J, Scholl UI. Genetic causes of primary aldosteronism. *Exp Mol Med*. 2019; 51(11): 1-2. https://doi.org/10.1038/s12276-019-0337-9.

19. Pecori A, Monticone S, Losano I, Cavaglià G, Pieroni J, Veglio F, Mulatero. Familial Hyperaldosteronism. In: Morganti A, Agabiti Rosei E, Mantero F. editors. Secondary Hypertension. Updates in Hypertension and Cardiovascular Protection. *Springer, Cham*. 2020. p. 79-93. https://doi.org/10.1007/978-3-030-45562-0_5.

20. Sanga V, Lenzini L, Seccia TM, Rossi GP. Familial hyperaldosteronism type 1 and pregnancy: successful treatment with low dose dexamethasone. *Blood Press*. 2021; 30(2): 133–7. https://doi.org/10.1080/08037051.2020.1863771.

21. He X, Modi Z, Else T. Hereditary causes of primary aldosteronism and other disorders of apparent excess mineralocorticoid activity. *Gland Surg*. 2020; 9(1):150. https://doi.org/10.21037%2Fgs.2019.11.20. PMID: 32206607 PMCID: PMC7082269.

22. Pons Fernández N, Moreno F, Morata J, Moriano A, León S, De Mingo C, et al. Familial hyperaldosteronism type III a novel case and review of literature. *Rev Endocr Metab Disord*. 2019; 20: 27-36. https://doi.org/10.1007/s11154-018-9481-0.

23. Garofalidou T, Munroe PB. Molecular pathophysiology of systemic hypertension. In: Clinical Molecular Medicine: Principles and Practice. *Elsevier*; 2019. p. 169–87. https://doi.org/10.1016/B978-0-12-809356-6.00011-3.

24. Alam S, Goyal A, Kandasamy D, Bansal VK, Asuri K, Agarwal S, et al. Resistant Hypertension Due to Familial Hyperaldosteronism Type III: First Report From Indian Sub-Continent. *J Endocrine Soc*. 2021; 5 (1): A115-6. https://doi.org/10.1210/jendso/bvab048.314.

25. Takizawa N, Tanaka S, Nishimoto K, Sugiura Y, Suematsu M, Ohe C, et al. Familial Hyperaldosteronism Type 3 with a Rapidly Growing Adrenal Tumor: An In Situ Aldosterone Imaging Study. *Curr Issues Mol Biol*. 2022; 44(1): 128–38. https://doi.org/10.3390/cimb44010010.

26. Mashmoushi A, Wolf MTF. A narrative review of Hyporeninemic hypertension-an indicator for monogenic forms of hypertension. Pediatric Med. 2022; 5: 21. https://doi.org/10.21037%2Fpm-21-48. PMID: 36325202.

27. Mourtzi N, Sertedaki A, Markou A, Piaditis GP, Charmandari E. Unravelling the Genetic Basis of Primary Aldosteronism. *Nutrients*. 2021; 13(3): 875. https://doi.org/10.3390/nu13030875.

28. Raina R, Mahajan Z, Sharma A, Chakraborty R, Mahajan S, Sethi SK, et al. Hypertensive Crisis in Pediatric Patients: An Overview. Front Pediatr. *Frontiers Media S.A.;* 2020; 8: 588911. https://doi.org/10.3389/fped.2020.588911.

29. van der Grinten HLC, Speiser PW, Faisal Ahmed S, Arlt W, Auchus RJ, Falhammar H, et al. Congenital Adrenal Hyperplasia—Current Insights in Pathophysiology, Diagnostics, and Management. Endocr Rev. Endocrine Society; 2022; 43(1): 91–159. https://doi.org/10.1210/endrev/bnab016.

30. Nordenström A, Lajic S, Falhammar H. Long-Term Outcomes of Congenital Adrenal Hyperplasia. Endocrinol Metab (Seoul). *Korean Endocrine Society;* 2022; 37(4): 587-98. https://doi.org/10.3803/EnM.2022.1528.

31. Athimulam S, Lazik N, Bancos I. Low-Renin Hypertension. *Endocrinol Metab Clin North Am*. 2019; 48(4): 701-15. https://doi.org/10.1016/j.ecl.2019.08.003.

32. Tosun BG, Guran T. Congenital adrenal hyperplasia and hypertension. In: Endocrine Hypertension: From Basic Science to Clinical Practice. Elsevier; 2022. p. 113–25. https://doi.org/10.1016/B978-0-323-96120-2.00015-7.

33. Khandelwal P, Deinum J. Monogenic forms of low-renin hypertension: clinical and molecular insights. *Pediatr Nephrol*. 2022; 37(7): 1495–509. https://doi.org/10.1007/s00467-021-05246-x.

34. Martins CS, de Castro M. Generalized and tissue specific glucocorticoid resistance. *Mol Cell Endocrinol*. 2021; 530: 111277. https://doi.org/10.1016/j.mce.2021.111277.

35. Kozina AA, Trofimova TA, Okuneva EG, Baryshnikova N V., Obuhova VA, Krasnenko AY, et al. Liddle syndrome due to a novel mutation in the γsubunit of the epithelial sodium channel (ENaC) in family from Russia: A case report. *BMC Nephrol*. 2019; 20(1): 389. https://doi.org/10.1186/s12882-019-1579-4.

36. Allen GT, Shipman AR, Darragh-Hickey C, Flowers KC, Kaur S, Shipman KE. Investigative algorithms for disorders affecting alkalosis: a narrative review. *J Lab Precis Med*. 2022; 7. https://doi.org/10.21037/jlpm-22-8.

37. Lu YT, Liu XC, Zhou ZM, Zhang D, Sun L, Zhang Y, et al. A Novel Frame-Shift Mutation in SCNN1B Identified in a Chinese Family Characterized by Early-Onset Hypertension. *Front Cardiovasc Med*. 2022; 9: 896564. https://doi.org/10.3389/fcvm.2022.896564.

38. Enslow BT, Stockand JD, Berman JM. Liddle's syndrome mechanisms, diagnosis and management. *Integrated Blood Pressure Control*. 2019: 13-22. https://doi.org/10.2147/IBPC.S188869.

39. Aksoy OY, Bastug F, Celik B, Uytun S. Hypokalemia and hypertensive urgency in a 10-year-old boy: Questions. *Pediatr Nephrol*. 2021; 36(11): 3627–8. https://doi.org/10.1007/s00467-021-05058-z.

40. Mareš Š, Filipovský J, Vlková K, Pešta M, Černá V, Hrabák J, et al. A novel nonsense mutation in the β-subunit of the epithelial sodium channel causing Liddle syndrome. *Blood Press*. 2021; 30(5): 291–9. https://doi.org/10.1080/08037051.2021.1942785.

41. Qu Y, Lu Y, Zhang D, Liu X, Fan P, Chen J, et al. Identification of a novel frameshift mutation in the SCNN1B causing Liddle syndrome. Sci Bull (Beijing). 2023; 68(4): 383–7. https://doi.org/10.1016/j.scib.2023.02.006. PMID: 36774301.

42. Akram S, Rehman A, Khan MA. Liddle Syndrome in a Six-Year-Old Girl: A Case Report. *Journal of Islamabad Medical & Dental College*. 2021; 10(2): 116–9. https://doi.org/10.35787/jimdc.v10i2.642.

43. Steyn N, Chale-Matsau B, Abera AB, Van Biljon G, Pillay TS. Neonatal presentation of a patient with Liddle syndrome, South Africa. *Afr J Lab Med*. 2023; 12(1):1-6. https://dx.doi.org/10.4102/ajlm.v12i1.1998.

44. Brower RK, Ghlichloo IA, Shabgahi V, Elsholz D, Menon RK, Vyas AK. Liddle Syndrome due to a Novel c.1713 Deletion in the Epithelial Sodium Channel β-Subunit in a Normotensive Adolescent. *AACE Clin Case Rep*. 2021; 7(1): 65–8. https://doi.org/10.1016/j.aace.2020.11.017.

45. Yang Y, Wu C, Qu D, Xu X, Chen L, Sun Q, et al. Liddle syndrome misdiagnosed as primary aldosteronism is caused by inaccurate aldosterone-rennin detection while a novel SCNN1G mutation is discovered. *Blood Press*. 2022; 31(1): 139–45. https://doi.org/10.1080/08037051.2022.2088471.

46. Teoh Z, Shah S. A case report of three children with secondary hypertension caused by Liddle syndrome. *Clin Nephrol Case Stud*. 2020; 8(01): 37–40. https://doi.org/10.5414%2FCNCS109972.

47. Pratamawati TM, Alwi I. Summary of Known Genetic and Epigenetic Modification Contributed to Hypertension. *International Journal of Hypertension*. 2023; 2023. https://doi.org/10.1155/2023/5872362.

48. Mabillard H, Sayer JA. The molecular genetics of gordon syndrome. *Genes (Basel)*. 2019; 10(12): 986. https://doi.org/10.3390/genes10120986.

49. Asadi S. The Role Of Genetic Mutations In Genes WNK1,WNK4, CUL3, KLHL3 In Gordon's Syndrome. *Journal of Genetics and Genetic Engineering*. 2019; 3(1): 18–21. https://doi.org/10.3390/genes10120986.

50. Hindosh N, Hindosh R, Dada B, Bal S. Geller Syndrome: A Rare Cause of Persistent Hypokalemia During Pregnancy. *Cureus*. 2022; 14(6). https://doi.org/10.7759/cureus.26272.

51. Carvajal CA, Tapia-Castillo A, Vecchiola A, Baudrand R, Fardella CE. Classic and nonclassic apparent mineralocorticoid excess syndrome. *J Clin Endocrinol Metab*. 2020; 105(4): e924-36. https://doi.org/10.1210/clinem/dgz315.

52. Fan P, Lu YT, Yang KQ, Zhang D, Liu XY, Tian T, et al. Apparent mineralocorticoid excess caused by novel compound heterozygous mutations in HSD11B2 and characterized by early-onset hypertension and hypokalemia. *Endocrine*. 2020; 70(3): 607–15. https://doi.org/10.1007/s12020-020-02460-9.

53. Albalawi AD, Al-Issa SD, AlHissi MA, Aljurayyan AN, Khoder JJ, Al-Jurayyan NA. Hereditary forms of apparent mineralocorticoid excess (AME): Report of a further case and literature review. *World J Biol Pharm Sci*. 2023; 15(1):180–4. https://doi.org/10.30574/wjbphs.2023.15.1.0284.

54. Kucuk N, Yavas Abali Z, Abali S, Canpolat N, Yesil G, Turan S, et al. A rare cause of hypertension in childhood: Questions. *Pediatr Nephrol*. 2020; 35(1): 77–8. https://doi.org/10.1007/s00467-019-04326-3.

55. Verma S, Dabadghao P, Moirangthem A. Apparent mineralocorticoid excess - A rare cause of endocrine hypertension. *Indian Pediatr Case Rep*. 2022; 2(1): 36. https://doi.org/10.4103/ipcares.ipcares_312_21.

56. Lu YT, Zhang D, Zhang QY, Zhou ZM, Yang KQ, Zhou XL, et al. Apparent mineralocorticoid excess: comprehensive overview of molecular genetics. *J Transl Med. BioMed Central Ltd*. 2022; 20(1): 500. https://doi.org/10.1186/s12967-022-03698-9.

Fetal growth restriction - clinical manifestations through the perspective of pathophysiological changes

Capros Hristiana Capros[1], Voloceai Victoria[1], Cotelea Veronica[1], Mitriuc Diana[1], Pavlenco Angela[1]

[1]Department of Obstetrics and gynecology, State Medical University "N.Testemitanu", Chisinau, Republic of Moldova

Corresponding author:
Capros Hristiana Capros.
E-mail: caproscristina@yahoo.com;
ORCID: 0009-0002-1517-2342.

Abstract

Intrauterine restriction of fetal growth is one of the most interestings and nowadays intensively studied problems of modern obstetrics. Fetal growth restriction can lead to significant obstetric complications, as well as consequences after delivery. For the obstetricians the fetal growth means iatrogenic prematurity, fetal distress, perinatal morbidity but also long term consequences as metabolic disease, cardiovascular pathology and Alzhaimer disease. There was considerable controversy as to how fetal growth restriction should be defined and diagnosed. Biometric and biophysical tests have been proposed to diagnose growth restriction, but until recently there were no unanimously accepted standards for the diagnosis of this pathology. This definition was reached in 2021 by the FIGO publication. Under the condition of intrauterine hypoxia adaptation mechanisms are activated. Understanding the ongoing pathophysiological process of adaptation in a hypoxic media helps to better understand proposed diagnosis criteria and the classification.

Key words: fetal growth restriction, hypoxia adaptation.

Introduction

Birth weight is one of the parameters used to describe the "health" of the newborn. Thus, the healthy newborn is a child born at 37-42 weeks' gestation, with a birth weight of 2500-4000 g and who during the examination looks vigorous, without congenital developmental anomalies or other pathological signs [1].

Fetal weight depends on genetically predetermined growth potential (parental weight, sex, ethnicity), but can be modulated by internal (fetal, placental, maternal) and external factors. Low fetal weight at birth can be an indicator of pathological damage, associated with perinatal complications, but it can also be found if low weight is genetically determined (constitutionally small newborns) [2].

A "normal" fetus, with "appropriate for gestational age" growth, is one that maintains constant growth and whose biometric parameters (cranial circumference, abdominal circumference, biparietal diameter, estimated weight) lie between the 10th and 90th percentiles [3]. A fetus whose estimated mass and/or abdominal circumference falls on the growth curves below the 10th percentile is defined as a "small for gestational age" (SGA) fetus. In the case of intrauterine growth restriction, fetal growth will be affected by an external or internal factor, fetal growth will be diminished, flattened, most frequently, lower than the 10th percentile [4].

The group of fetuses with a weight below the 10th percentile is a heterogeneous group and includes:

1) constitutionally small fetuses (50-70%);

2) fetuses who are small due to the action of an etiological factor, and in this case the diagnosis is fetal growth restriction (FGR).

Fetal growth restriction is the third leading cause of perinatal death. In specialized literature, this pathology is associated with iatrogenic prematurity, intraventricular hemorrhage, necrotizing enterocolitis, convulsions, sepsis, respiratory distress syndrome, retinopathy of prematurity, cerebral palsy, perinatal death [5]. Along with the profound perinatal impact, the consequences may continue into adulthood in the form of metabolic disease as a result of prenatal reprogramming and compensatory postnatal growth. It is now well established that children born with intrauterine growth restriction have poorer school performance and lower rates of neurobehavioral development. Adults who suffered intrauterine growth restriction have an increased risk of metabolic syndrome, hypertension, insulin resistance and type 2 diabetes, coronary heart disease and stroke [6].

Methods and materials

Research was conducted in international databases PubMed, Cochrane Library, and DOAJ by applying the key words and the combinations of terms including pregnancy, oxygen, fetal growth restriction, hypoxia, adaptation, hypoxic stress. The authors then compiled and analyzed the data, attempting to answer the following questions:

1. What are the hypoxic modifications in the growth restricted fetus?

2. What are long term and short term complications of these modifications?

3. Is there an interrelation between the hypoxic modification in fetuses and criteria proposed for diagnosis of FGR?

References from primary and review articles were cross-referenced to identify additional reports that met the inclusion criteria but were not identified by the initial search. Excluded were short reports, case reports, and letters to the editor.

Results

Antepartum fetal assessment is based on the hypothesis that the fetus responds to progressive hypoxia with a series of biophysical changes that can be detected by instrumental investigations.

Physiological and pathological mechanisms in intrauterine hypoxia have been studied since the 17th century, the first publication on fetal respiration appeared in 1674 - "De respiratione foetus in utero et ovo" by John Mayow [7]. Until now, the focus of international study is on the physiological reactions during the exposure to hypoxic episodes during intrauterine life and the cardiovascular adaptation of the fetus [8].

The heart rate, breathing, muscle tone and other biophysical activities of the fetus are dependent on the level of oxygenation. Under conditions of hypoxic stress, physiological adaptation mechanisms are activated. This determines the centralization of blood circulation for the protection of vitally important organs [9]. Thus, in the experimental and human models, under conditions of hypoxia, vasodilatation was determined in the vessels of the heart, central nervous system and adrenal glands, and in the vessels of other fetal regions – vasoconstriction (Figure 1). In the animal models, there was 70% increasing blood flow through the cerebral vessels in the hypoxic fetuses in comparison with the controls [10]. Prospective studies on fetal vessels confirmed higher middle adrenal artery-peak systolic velocity and increasing of the fetal adrenal gland dimensions in the pregnancies with FGR [11]. Finally, the greater vessel lumen diameter profiles were obtained for the right coronary artery, left coronary circumflex artery, and left anterior descending artery in the FGR in comparison with the normal weight fetuses [12]. An increase of the pulsatility index in tibial arteries as a sign of remarkable constriction of the peripheral arteries was found in human growth restricted fetuses [13]. Absolute brain volume did not differ between the chronic hypoxia fetuses and controls, indicating protection of brain growth. However, the liver and lung volumes were 22 and 27% smaller in the fetuses exposed to chronic maternal hypoxia compared to controls [14]. In the same time, the elevations in uric acid and other ammoniagenic amino acids identified in studies supports the global metabolic changes in a sheep model of intrauterine growth restriction fetuses [15].

The redistribution of blood flow has the following consequences: decreased fetal movements due to vasoconstriction on the striated muscles, decreased renal perfusion and the development of oligoamnios, asymmetric growth with decreased abdominal diameters, intrauterine growth restriction, fetal death [16].
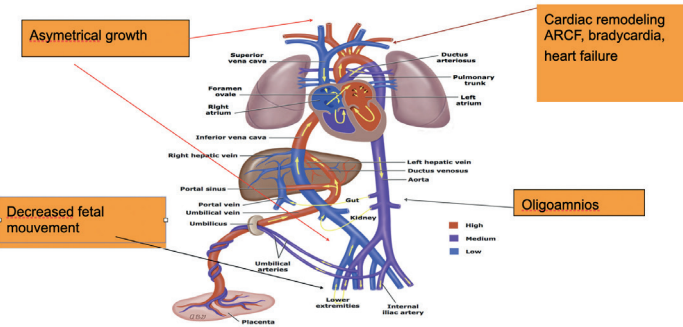
Figure 1 - Fetal response to hypoxia. Short term complications.

It should be noted that fetal biophysical parameters can also be affected by factors unrelated to hypoxemia, such as gestational age, maternal medication, sleep-wake rhythm, and fetal anomalies [17]. These parameters are taken into consideration during the antenatal assessment [18].

Centralisation of the circulation to the vital organs, eg. towards the fetal heart, the fetal brain and fetal adrenal glands have as consequences the cerebral vasodilation and cardiac remodeling. Vasoconstriction on the peripheral segments (renal, digestive, striated muscles) is responsible for the clinical manifestation of FGR such as oligoamnios, asymmetrical growth and decreased fetal movements.

Discussion

FGR of the fetus is defined as the inability to reach its growth potential corresponding to its gestational age, due to one or more determining factors. Classically, the factors involved in the occurrence of fetal growth restriction are divided into: maternal, fetal and placental (table 1) [19]. The detailed collection of anamnesis at the preconception visit or at the first antenatal visit allows the identification of patients with risk factors for the development of fetal growth restriction and their more careful monitoring during pregnancy [20]. Considering the association of fetal growth restriction and genetic syndromes, aneuploidy and intrauterine infection, a careful evaluation of the parents' morphotype, personal and family medical history is indicated [21].

Table 1	Maternal, fetal, and placental factors in fetal growth restriction
Maternal factors	Age <20 and >35 years Primiparity or multiparity Chronic hypertension, preeclampsia, pregnancy-induced hypertension History of preeclampsia, fetal growth restriction in previous pregnancies Causes of chronic hypoxia (cyanotic heart disease, anemia, hemoglobinopathy) Antiphospholipid syndrome, systemic lupus erythematosus, autoimmune diseases, diabetes with vascular damage Unfavorable socioeconomic environment Use of tobacco, alcohol, drugs Malnutrition/underweight or obesity Uterine malformations, uterine hypoplasia
Fetal factors	Infections: toxoplasmosis, rubella, chicken pox, cytomegalovirus, syphilis, parvovirus, enterovirus, herpes, Epstein-Barr virus Chromosomal abnormalities Genetic syndromes Multiple pregnancy
Placental factors	Placental insufficiency, usually as part of preeclamptic syndrome Placental infarction Placenta previa Placental chorioangioma Pathology of the cord: velamentous insertion, veridical ombilical knot

For the diagnosis of fetal growth restriction, biometric tests and fetal functional tests are combined. An important condition for the ultrasonographic examination is the accurate assessment of the gestational age. Thus, the first step in the evaluation of a pregnant woman with a risk of reduced fetal growth is the correct assessment of the gestation period by taking into account the date of the last menstruation and/or the ultrasound data from the first trimester of pregnancy [22]. Considering the association of fetal growth restriction with chromosomal abnormalities, genetic syndromes, intrauterine infection, a careful and detailed evaluation of the fetal anatomy will be performed each time. Following the ultrasound examination, the presence/absence of fetal structural abnormalities, markers for genetic pathology, chromosomal abnormalities, polyhydramnios, markers for intrauterine infection will be noted. In case of suspicion of growth restriction due to chromosomal or genetic causes, the pregnant woman will be consulted in order to perform non-invasive antenatal tests, amniocentesis; when an infectious cause is suspected, serological tests will be performed [23].

Table 2	Ultrasonographic tests used for the diagnosis of fetal growth restriction
Biometric tests	**Functional tests**
Estimated Fetal Weight (GFE) Biparietal diameter (DBP) Cranial Circumference (CC) Abdominal circumference (CA) Femur length (LF)	Evaluation of pulsatility indices at the level of the uterine arteries Evaluation of the pulsatility index at the level of the umbilical artery Evaluation of the pulsatility index at the level of the middle cerebral artery Calculation of cerebroplacental ratio Assessment of amniotic fluid volume Evaluation of the fetal biophysical score Cardiotocography with the non-stress test Doppler flow evaluation at the level of the ductus venosus Doppler flow evaluation at the level of the aortic isthmus

During the ultrasonography examination the fetal biometric and functional parameters are evaluated: the biparietal diameter, the cephalic circumference, the abdominal circumference, the femoral lengths with the calculation of the fetal weight, the uterine artery pulsatility index, umbilical cerebral Doppler, and the cerebroplacental index [24]. All the results are expressed in percentile. To establish the diagnosis, the presence of one major pathological parameter or two minor parameters is necessary. The major parameters are: estimated fetal weight or abdominal circumference less than 3rd percentile, flattening of the growth curve, absent or reverse-flow umbilical Doppler. The minor parameters are: estimated fetal weight or abdominal circumference less than the 10th percentile, pathological Doppler on the uterine arteries, increased resistance on the umbilical artery, pathological cerebroplacental index [25].

The proposed criteria perfectly reflect the fetal answer to hypoxia, and not only the general compensating mechanism, but also the tiny modifications that occur in the fetal cardiovascular system depending on the gestational term of installation of hypoxia. So knowing FIGO diagnosis criteria helps us also to describe the ongoing processes in a hypoxic intra-uterin media [26].

The current classification proposes the differentiation of fetal growth restriction according to the onset of the pathological process: FGR with early onset is diagnosed up to 32 gestational weeks and FGR with late onset, after 32 gestational weeks. This classification corresponds to the clinical course of the disease [27].

Early-onset fetal growth restriction is frequently associated with preeclampsia, severe placental insufficiency. This insufficiency translates into pathological Doppler on the uterine arteries. Insufficient transit through the placenta causes chronic fetal hypoxia. Fetal condition deteriorates with progression to hypoxia and decompensated acidosis. Decompensated acidosis translates negative or reverse flow Doppler on the umbilical artery, decreased resistance in the cerebral artery and pathological venous duct. The latency of severe fetal damage may vary in individual cases, but normally lasts for weeks [28]. It can be associated with antenatal death, or neonatal morbidity. Late-onset growth restriction is associated with preeclampsia only in about 10% of cases. Fetal adaptation to hypoxia results in blood redistribution phenomena, with cerebral vasodilation and vasoconstriction in the peripheral segment, due to which the cerebroplacental ratio is pathological. Fetal damage occurs rapidly, suddenly, manifesting as fetal distress during labor and neonatal acidosis, and impairment of neurological development after delivery [29, 30]. Centralisation of the circulation in intrauterine life induces long duration vasospasm in the renal arteries, digestive system vessels and is responsible for the late clinical consequences such as metabolic syndrome, diabetes, kidney disease. The cardiac remodeling due to vasodilation in the coronary segment increases the risk of cardiac pathology in adult life (Figure 2) [31].
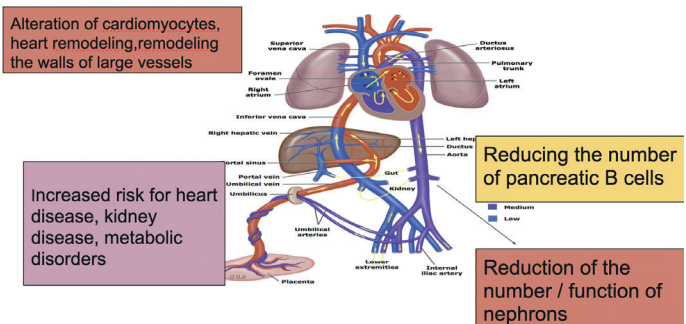
Figure 2 - Fetal response to hypoxia. Long term consequences

Conclusion

The fetus responds to progressive hypoxia with a series of pathophysiological changes. In conditions of hypoxic stress, physiological adaptation mechanisms that are activated determine the centralization of blood circulation to ensure the protection of organs of vital importance: vasodilation is determined in the vessels of the heart, central nervous system and adrenal glands, and in other fetal regions - vasoconstriction. These effects will determine short term complications in the restricted fetus that are nowadays used for the diagnosis: growth retardation, oligoamnios, pathological Doppler, fetal rhythm anomalies etc. The exposure of the fetus to the hypoxic media during prenatal life will induce long term system modifications causing adult pathology : metabolic syndrome, diabetes, renal disease, cardiac pathology.

References

1. ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol.* 2013; 121(5): 1122-1133. https://doi.org/10.1097/01. AOG.0000429658.85846.f9. PMID: 23635765.
2. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl.* 2006; 450: 76-85. https://doi.org/10.1097/10.1111/j.1651-2227.2006.tb02378.x. PMID: 16817681.
3. Nardozza LM, Araujo Júnior E, Barbosa MM, Caetano AC, Lee DJ, Moron AF. Fetal growth restriction: current knowledge to the general Obs/Gyn. *Arch Gynecol Obstet.* 2012; 286(1):1-13. https://doi.org/10.1007/s00404-012-2330-6. Epub 2012 Apr 24. PMID: 22526452.
4. Damhuis SE, Ganzevoort W, Gordijn SJ. Abnormal Fetal Growth: Small for Gestational Age, Fetal Growth Restriction, Large for Gestational Age: Definitions and Epidemiology. *Obstet Gynecol Clin North Am.* 2021; 48(2): 267-279. https://doi.org/10.1016/j. ogc.2021.02.002. PMID: 33972065.
5. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol (Lausanne).* 2019; 10: 55. https://doi.org/10.3389/fendo.2019.00055. PMID: 30792696; PMCID: PMC6374308.
6. D'Agostin M, Di Sipio Morgia C, Vento G, Nobile S. Long-term implications of fetal growth restriction. *World J Clin Cases.* 2023; 11(13): 2855-2863. https://doi.org/10.12998/wjcc.v11.i13.2855. PMID: 37215406; PMCID: PMC10198075.
7. Mayow, J. Tractatus quinque medico-physici; Quorum primus agit De salnitro, et spiritu nitro-aereo; Secundus De respiratione; Tertius De respiratione foetus in utero, et ovo; Quartus De motu musculari, et spirtitibus animalibus; Ultimus De rhachide. E. Theatro Sheldonian, Oxonii. 1674
8. Capros H, Scoricova I, Mihalcean L. Intrauterine growth restriction: contemporary issues in diagnosis and management. *The Moldovan Medical Journal.* 2017; 60 (2): 26-31. ISSN 2537-6373.
9. Maršál K. Physiological adaptation of the growth-restricted fetus. *Best Pract Res Clin Obstet Gynaecol.* 2018; 49: 37-52. https://doi. org/10.1016/j.bpobgyn.2018.02.006. Epub 2018 Feb 24. PMID: 29753694.
10. Cahill LS, Hoggarth J, Lerch JP, Seed M, Macgowan CK, Sled JG. Fetal brain sparing in a mouse model of chronic maternal hypoxia. *Journal of Cerebral Blood Flow & Metabolism.* 2019; 39(6):1172-1184. https://doi.org/10.1177/0271678X17750324.
11. Uyan Hendem, Derya, Ocal, Fatma Doga, Oluklu, Deniz, et al. Evaluation of fetal middle adrenal artery Doppler and fetal adrenal gland size in pregnancies with fetal growth restriction: a case-control study. *Journal of Perinatal Medicine.* 2023; 51 (4): 492-499. https:// doi.org/10.1515/jpm-2022-0270.
12. Garcia-Canadilla P, de Vries T, Gonzalez-Tendero A, Bonnin A, Gratacos E, Crispi F, et al. Structural coronary artery remodelling in the rabbit fetus as a result of intrauterine growth restriction. *PLoS One.* 2019; 14(6): e0218192. https://doi.org/10.1371/journal. pone.0218192. PMID: 31226127; PMCID: PMC6588274.
13. Norvilaitė K, Ramašauskaitė D, Bartkevičienė D, Šliachtenko A, Kurmanavičius J. Fetal Tibial Artery Doppler in Late IUGR Fetuses: A Longitudinal Study. *J Clin Med.* 2022; 12(1): 82. https://doi.org/10.3390/jcm12010082. PMID: 36614891; PMCID: PMC9821295.
14. Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. APMIS. 2018; 126(7): 561-569. https://doi.org/10.1111/apm.12849. PMID: 30129125.
15. Chang EI, Wesolowski SR, Gilje EA, Baker PR 2nd, Reisz JA, D'Alessandro A, et al. Skeletal muscle amino acid uptake is lower and alanine production is greater in late gestation intrauterine growth-restricted fetal sheep hindlimb. *Am J Physiol Regul Integr Comp Physiol.* 2019 1; 317(5): R615-R629. https://doi.org/10.1152/ajpregu.00115.2019. Epub 2019 Sep 4. PMID: 31483682; PMCID: PMC6879841.
16. Boddy K, Dawes GS, Fisher R, Pinter S, Robinson JS. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. *J Physiol.* 1974; 243(3): 599-618. https://doi.org/10.1113/jphysiol.1974.sp010768. PMID: 4475694; PMCID: PMC1330726.
17. Indications for Outpatient Antenatal Fetal Surveillance: ACOG Committee Opinion, Number 828. *Obstet Gynecol.* 2021; 137(6): e177-e197. https://doi.org/10.1097/AOG.0000000000004407. PMID: 34011892.
18. Capros H, Mihalcean L, Surguci M. Fetal growth restriction. New terminology and classification. *Obstetrics and Gynaecology of Saint-Petersburg.* 2020; 1(2): 6-10. ISSN: 2541-8491.
19. Unterscheider J, O'Donoghue K, Malone FD. Guidelines on fetal growth restriction: a comparison of recent national publications. *Am J Perinatol.* 2015; 32(4): 307-16. https://doi.org/10.1055/s-0034-1387927. Epub 2014 Sep 13. PMID: 25217738.
20. Royal College of Obstetricians and Gynaecologists. The Investigation and Management of the Small-for-Gestational-Age Fetus. RCOG Green-top Guideline No. 31.
21. Vayssière C, Sentilhes L, Ego A, Bernard C, Cambourieu D, Flamant C et al. Fetal growth restriction and intra-uterine growth restriction: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. *Eur J Obstet Gynecol Reprod Biol.* 2015; 193: 10-8. https://doi.org/10.1016/j.ejogrb.2015.06.021. Epub 2015 Jul 2. PMID: 26207980.
22. Lausman A, Kingdom J; Maternal fetal medicine committee. Intrauterine growth restriction: screening, diagnosis, and management. *J Obstet Gynaecol Can.* 2013; 35(8): 741-748. English, French. https://doi.org/10.1016/S1701-2163(15)30865-3. PMID: 24007710.
23. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T et al. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. *Ultrasound Obstet Gynecol.* 2019; 53(6): 715-723. https://doi.org/10.1002/uog.20272. PMID: 31169958.

24. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol.* 2016; 48(3): 333-9. https://doi.org/10.1002/uog.15884. PMID: 26909664.

25. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet.* 2021; 152 (51): 3-57. https://doi.org/10.1002/ijgo.13522. PMID: 33740264; PMCID: PMC8252743.

26. Lees CC, Romero R, Stampalija T, Dall'Asta A, DeVore GA, Prefumo F, et al. Clinical Opinion: The diagnosis and management of suspected fetal growth restriction: an evidence-based approach. *Am J Obstet Gynecol.* 2022; 226(3): 366-378. https://doi.org/10.1016/j.ajog.2021.11.1357. Epub 2022 Jan 10. PMID: 35026129; PMCID: PMC9125563.

27. Lawin-O'Brien AR, Dall'Asta A, Knight C, Sankaran S, Scala C, Khalil A, et al. Short-term outcome of periviable small-for-gestational-age babies: is our counseling up to date? *Ultrasound Obstet Gynecol.* 2016; 48(5): 636-641. https://doi.org/10.1002/uog.15973. PMID: 27854384.

28. Visser GH, Nicholson WK, Barnea ER, Ramasauskaite D, Nassar AH; FIGO Safe Motherhood, Newborn Health Committee. FIGO position paper on reference charts for fetal growth and size at birth: Which one to use? *Int J Gynaecol Obstet.* 2021; 152(2): 148-151. https://doi.org/10.1002/ijgo.13500. Epub 2020 Dec 29. PMID: 33247958.

29. Morris RK, Malin G, Robson SC, Kleijnen J, Zamora J, Khan KS. Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. *Ultrasound Obstet Gynecol.* 2011; 37(2): 135-42. https://doi.org/10.1002/uog.7767. Epub 2011 Jan 12. PMID: 20922778.

30. Baschat AA. Neurodevelopment following fetal growth restriction and its relationship with antepartum parameters of placental dysfunction. *Ultrasound Obstet Gynecol.* 2011; 37(5): 501-14. https://doi.org/10.1002/uog.9008. PMID: 21520312.

31. Crispi F, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. *Am J Obstet Gynecol.* 2018 Feb; 218 (2S): 869-879. https://doi.org/10.1016/j.ajog.2017.12.012. PMID: 29422215.

High-risk human papillomaviruses L1 gene isolates identified in Western Kazakhstan

Saule K. Balmagambetova[1], Elena V. Zholdybayeva[2], Oxana V. Zavalennaya[3], Ainur Amanzholkyzy[4], Victoria I. Kononets[5], Gulmira M. Zharmakhanova[5], Nadiar M. Mussin[6], Lazzat M. Zhamaliyeva[7], Nurgul M. Kereyeva[1]

[1]Department of Oncology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[2]Shared laboratory, National Center for Biotechnology, Astana, Kazakhstan
[3]PCR laboratory, Scientific-Production Center, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[4]Department of Physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[5]Department of Natural Science Disciplines, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[6]Department of Transplantology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[7]Department of Family Medicine, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

Abstract

Kazakhstani researchers reported a significant prevalence of highly carcinogenic human papillomavirus types in the country.

The article **aimed** to present HPV L1 gene sequencing developments in women affected with cervical cancer throughout the western part of Kazakhstan with provided findings on the geographic pathways of obtained isolates.

Methods. The HPV L1 gene was amplified using the consensus primers MY09HPV 5'-CGTCCMARRGGAWACTGATC-3' and MY11HPV 5' – GCMCAGGGWCATAAYAATGG-3'. The purified DNA was used as the target for direct nucleotide sequencing. Phylogenetic analyses were conducted using the MegAlign program from the LASERGENE software package (version 6.0; DNA star, Madison, WI) and MEGA version 5.0 software. A multiple alignment was created through Clustal W software, and the neighbor-joining method was used to construct the phylogenetic tree.

Results. Of 70 HPV samples transported to the Astana shared laboratory for gene L1 sequencing, only ten appeared fit to obtain isolates (14.3%). The viral load of the samples ranged from 3.3 to 8.2, and the range of DNA concentration was from 8.16 to 69.6 ng/uL. Not yet registered in the world genebank, a unique HPV16 Kazakhstani isolate with its own branch was revealed in Aktobe. An isolate of potentially carcinogenic HPV53 forming a remote cluster with KF436822/1, KU951264.1 – Southwest China, and 97% identity with EU056643.1 – Ireland, and acted as a single agent for invasive cervical cancer was identified.

In general, the sequencing findings indicate the variety of ways for HPV pervasion into the western region of Kazakhstan: North and South America, Europe, and Asia.

The study was recorded in the ISRCTN registry, No. 7154910, 02/01/2018.

Keywords: Human papillomavirus, gene sequencing, isolates, gene L1, cervical cancer, western Kazakhstan.

Introduction

Cervical cancer remains a substantial health problem for women globally, requiring more effective prevention and control strategies. Despite plenty of various screening modalities, the incidence of cervical cancer in the world has demonstrated an increase of 68.5% since 1990 [1]. Human papillomaviruses (HPVs) are a causative factor for cervical cancer onset, as high-risk HPV DNA presents in 99.7% of cervical cancer specimens [2, 3]. HPVs constitute a large, diverse family of about 200 fully characterized types. In total, four groups are currently classified, including group 1, containing types of highly carcinogenic risk (HR-HPV); probably carcinogenic, such as type 68 (group 2a); possibly carcinogenic, such as 26, 53, 66, 67, 70, 73 and 82 types, considered potential carcinogens, with an arguable and still not thoroughly defined role in carcinogenesis (group 2b); not classified (group 3); and, possibly not carcinogenic types (group 4)

[4]. A growing number of proofs of HPV's continuous evolution resulted in clear molecular-biological evidence of the uniquely high carcinogenicity of types currently classified as probably / possibly carcinogenic [5, 6].

Some sources mentioned particular areas of Asia as countries with the lowest cervical cancer rates [7], but subsequent studies have proven this is not true. The first Kazakh researcher to study the HPV prevalence was M. Buleshov (2011). Buleshov et al. found that out of 17,000 women tested in South Kazakhstan, 1,870 were HPV-positive (11%). Their findings were then widely cited in international HPV bulletins [8-10]. However, more recent authors reported higher rates of HPV infection in various regions of the country, within 25% [11] and even higher. Among Kazakhstani women attending the gynecologic clinics, high-risk HPV was found in 39%, and 13% were infected with multiple HR-HPV types [12]. All homeland researchers report the predominance of the most carcinogenic HPV type 16 in the swabs of Kazakhstani women [11-14]. In the five Central Asian countries that were formerly part of the Soviet Union (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan), cervical cancer incidence and mortality rates are far higher than those in most Western and high-income nations and are increasing [15]. Experts from the International Agency for Research on Cancer (IARC) Information Centre on HPV reported the prevalence of HPV16 and/or HPV18 among Kazakhstani women with normal cytology as 3.4%, with low-grade cervical lesions (LSIL/CIN-1) 21.2%, with high-grade cervical lesions (HSIL/CIN-2/CIN-3/ CIS) 42.1%, and in cervical cancer cases 68.9%, respectively. Meanwhile, the crude incidence rate of cervical cancer per 100,000 women is 18.4. As to the HPV vaccine, it is unavailable and has not been introduced for now [16]. As known, the pilot HPV vaccination program started in Kazakhstan in 2013 but then was discontinued. Recent studies have shown that contrary attitudes towards HPV vaccination exist among Kazakhstani women, with approximately half having positive and almost half having negative or neutral attitudes towards the vaccine [17]. Nonetheless, the Kazakh Institute of Oncology and Radiology reported that the program relaunch is scheduled for 2024.

According to the nomenclature of HPV established by the International Committee on Taxonomy of Virus (ICTV), each HPV type can be differentiated into phylogenetic lineages in terms of geographic distribution, pathogenicity, regulation of transcription, and immunological response [18, 19, 20]. The HPV16 type has accordingly been divided into four phylogenetic lineages: A, B, C, and D. The lineage D consists of the three sub-lineages: D1, D2, and D3, that include Asian-American and North American sequences. HPV intratypic molecular variants can be distinguished based on oncogenic potentials despite their phylogenetic relatedness. Reportedly, the HPV16 lineage D appears more carcinogenic than other lineages [21].

The HPV genome is an 8,000 base pair (bp), double-stranded, circular DNA packaged within a protein capsid. The prototypical genome encodes 6 early genes (E1, E2, E4, E5, E6, and E7) and 2 late genes (L1 and L2) [22]. Specifically, the L1 gene encodes the major capsid protein, which forms a pentameric capsomer that self-arranges into a 72-subunit icosahedral capsid. The capsid is essential for viral binding and entry into host-specific tissues [23]. Furthermore, the L1 coding sequences of the immunogenic surface loops are distinctively poorly conserved due to selective pressures for mutagenesis and immune evasion [24].

Research on HPV gene sequencing that focuses on the geographic locations of the found isolates has not yet been performed in Kazakhstan. Making a nationwide map of HPV responsible for cervical cancer onset in local women and identifying HPV lineages and the isolates' countries of origin appears to be one of the foreground tasks for Kazakhstani researchers.

The purpose of HPV L1 gene sequencing in the present work was to confirm the HPVs identification established by PCR typing and to clarify the geographical distribution of identified HPV types circulating in the western region of Kazakhstan.

Thus, the article **aimed** to present HPV L1 gene sequencing developments in women affected with cervical cancer throughout the western part of Kazakhstan and provide findings on the geographic pathways of the obtained isolates.

Methods

This research constituted a part of a large multipurpose project on HPV infection in western Kazakhstan, with the published protocol [25]. The study protocol (version_2) was approved by the University Local Ethical Committee (Ref. 1 dated 09.01.2016). The work was carried out using the checklist of mandatory items for observational studies (STROBE) and STREGA for studies with genetic material. The informed consent form was developed based on WHO recommendations, and all participants who signed the form were informed of the research objectives. The patients' rights were protected.

Test systems "Quantum-21" (Russian manufacturing) were used for qualitative and quantitative detection of total HPV 21 types (6, 11, 16, 18, 26, 31, 33, 35, 39, 44, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82). Of them, thirteen are highly carcinogenic, five are possibly/probably carcinogenic (26, 53, 66, 73, 82), and three are low carcinogenic types (6, 11, 44). DNA extraction for further L1 gene sequencing was performed with QIAamp DNA Mini Kit (Qiagen Ltd, Crawley, UK). All details on HPV detection in samples collected in women with newly diagnosed cervical cancer through the PCR Real-time method were published [25].

Description of HPV L1 gene sequencing
Amplification of PCR products:
Human papillomavirus fragment amplification was performed using universal primers:
MY09HPV – 5' – CGTCCMARRGGAWACTGATC-3'
and MY11HPV – 5' – GCMCAGGGWCATAAYAATGG.
The reaction mixture contained 50 pmol of each primer (MY09/11) 1x PCR buffer with KCl (Fermentas), six mM MgCl2, 200 mmol of each dNTP, and 2 U of Taq polymerase (Taq DNA Polymerase (recombinant, Fermentas). The PCR program was run on a GeneAmp amplifier 9700 (Applied Biosystems). It included long-term denaturation at 95°C for 5 minutes, 40 cycles at 95°C for 1 minute, 55°C for 1 minute, and 72°C for 1 minute, and final elongation at 72°C for 7 minutes.
Electrophoretic analysis of amplification products:
The amplified target DNA fragments were analyzed by separating DNA fragments in an agarose gel (agarose concentration from 2%) in the presence of an intercalating agent, ethidium bromide, which was used for further DNA visualization. Electrophoresis was performed in a PowerPac horizontal electrophoresis chamber and a BioRad Electrophoretic bath current source. 1x TAE buffer was used as electrode buffer.
The results were documented using the Gel Doc (Bio-Rad) gel documentation system with Quantity One software (Bio-Rad). The molecular sizes of the analyzed DNA samples were determined by comparing their electrophoretic mobility in the gel with the mobility of markers – a DNA fragment of a known molecular weight. "DNA Ladder 1kb" (Fermentas) was used as a molecular weight marker.

Determination and analysis of nucleotide sequences:

PCR products were purified from unbound primers by an enzymatic method using Exonuclease I (Fermentas) and alkaline phosphatase (Shrimp Alkaline Phosphatase, Fermentas).

To eliminate non-specific fragments, an additional method was used to purify PCR products by precipitation in the presence of polyethylene glycol (PEG 6000), based on early papers showing an inverse relationship between the percentage concentration of PEG and the size of the purified double-stranded DNA molecules.

Purification included:

– adding an equal volume of the prepared PEG mixture (52.4 PEG 6000, 40 ml 3M NaOAc pH 5.2, 1.32 ml 1M MgCl2, and up to 200 ml deionized water) to the PCR product;

– intensive mixing on a vortex for 20 seconds;

– keeping at room temperature for 30 minutes;

– centrifugation at 13 thousand rpm for 10 minutes;

– removal of the supernatant;

– washing the precipitate with 80% ethanol and eluting the DNA in water.

The sequencing reaction was performed using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) according to the manufacturer's instructions, followed by separating the fragments on a 3730xl DNA Analyzer (Applied Biosystems).

Nucleotide sequences obtained using forward and reverse primers were analyzed and combined into a joint sequence using SeqScape 2.6.0 software (Applied Biosystems).

The resulting nucleotide sequences were identified using the BLAST function in the international Gene Bank database (http://www.ncbi.nlm.nih.gov/). The genotype was determined by the maximum percentage of identity of the analyzed sequence to the reference samples in the Gene Bank. Phylogenetic analyses were conducted using the MegAlign program from the LASERGENE software package (version 6.0; DNA star, Madison, WI) and with MEGA version 5.0 software, http://www.megasoftware.net). A multiple alignment was created through Clustal W software, and the neighbor-joining method was used to construct the phylogenetic tree.

Results

For research, 70 samples were transported to the shared laboratory of the National Scientific Center for Biotechnology (Astana), but successful sequencing was performed only in 10 cases (14.3%). The overall effectiveness of L1 gene sequencing: of seven samples isolated in Aktau, two were sequenced successfully; of eight samples from Uralsk, one was sequenced; of three samples from Atyrau, sequencing failed in all cases. Fifty-two samples from Aktobe resulted in seven successful developments.

| Table 1 | Results of successful sequencing of the HPV L1 gene isolated in cervical cancer patients in western Kazakhstan. |

№	Sample code	Viral load/ per sample	Region	Identified types	DNA concentration, ng/uL	Performing a sequence of the HPV L1 gene
1	2a/2/1	3,3*103	Aktau	18	69.6	An isolate similar to KC470221.1, country of origin the USA
2	3/2/189	8,2*103	Aktau	33	53.0	Isolate KC706450.1 from Saudi Arabia
3	2a/4/12	5,5 * 103	Uralsk	53	42.22	An isolate forming a remote cluster with KF436822/1, KU951264.1 – Southwest China, 97% identity with EU056643.1 – Ireland
4	4/1/27	6,7*103	Aktobe	16	24.66	A sequence similar to the EU918764 isolate from China is obtained
5	2a/1/30	7,1*103	Khromtau, Aktobe	16	25.84	An isolate similar to KU951264/1 was obtained, forming a separate cluster with AJ617545.1, the country of origin for both isolates is Cyprus
6	2a/1/34	7,4*103	Khromtau, Aktobe	16	28.0	Common cluster with isolates KU707481.1 (country – Netherlands), GQ465900 (country – Canada)
7	5/1/2	3,5*103 7,2*103	Aktobe, Shalkar	6 16	11.5	An isolate of genotype 16 similar to isolate AJ617545.1 from Cyprus
8	5/1/3	6,2*103	Aktobe, Temir	16	8.16	An isolate of genotype 16 similar to isolate EF133498.1, country – Portugal
9	4/1/314	6,5*103	Aktobe, Kayndy	31	22.0	An isolate of genotype 31, similar to isolate KX514424.1, country – Brazil
10	2a/1/2	5,2*103	Aktobe, Alga	16	19.3	An authentic isolate from the Aktobe region, not represented yet in the world Genbank

Table 1 displays the summarized results of the HPV L1 gene sequences obtained. The viral load of the samples, measured in 103 genomic equivalents (GE) per sample, ranged from 3.3 to 8.2, and the range of DNA concentration was broad, from 8.16 to 69.6 ng/uL (Table 1).

Mangystau samples

Results of the primary nucleotide sequence of sample 2a/2/1 (Aktau), identified with existing nucleotide sequences using the BLAST program, are shown in Figure 1.

Nucleotide sequence of HPV 2a/2/1 (Aktau, HPV18):

TTTAACAATATGTGCTTCTACACAGTCTATCCTGTA CCTGGGCAATATGATGCTACCAAATTTAAGCAGTATAG CAGACATGTTGAAGAATATGATTTGCAGTTTATTTTTCA GTTATGTACTATTACTTTAACTGCAGATGTTATGTCCTAT ATTCATAGTATGAATAGCAGTATTTTAGAGGATTGGAAC TTTGGTGTTCCCCCCCCGCCAACTACTAGTTTGGTGGA TACATATCGTTTTGTACAATCTGTTGCTATTACCTGTCA AAAGGATGCTGCACCAGCTGAAAATAAGGATCCCTAT GATACGTTAAAGTTTTGGAATGTGGATTTAAAGGAAAA GTTTTCTTTAGACTTAGA

The identity with the isolate KC470221.1 (country of origin – the USA) is 99%. A phylogenetic tree was built for sample 2a/2/1 (Aktau) (Figure 2).

Sequences producing significant alignments:

Select: All None Selected:0

Alignments | Download ˅ | GenBank | Graphics | Distance tree of results

	Description	Max score	Total score	Query cover	E value	Ident	Accession
☐	Human papillomavirus type 18 isolate Qv28775, complete genome	656	656	100%	0.0	99%	KC470221.1
☐	Human papillomavirus type 18, isolate IS768, major capsid protein L1 (L1) gene, partial cds	656	656	100%	0.0	99%	U45893.1
☐	Human papillomavirus type 18 isolate Z100, complete genome	651	651	100%	0.0	99%	KC470222.1
☐	Human papillomavirus type 18 isolate Rw57, complete genome	651	651	100%	0.0	99%	KC470219.1
☐	Human papillomavirus type 18 isolate Rw687, complete genome	651	651	100%	0.0	99%	KC470218.1
☐	Human papillomavirus type 18 isolate Rw750, complete genome	651	651	100%	0.0	99%	KC470217.1
☐	Human papillomavirus type 18 isolate Z53, complete genome	651	651	100%	0.0	99%	KC470216.1
☐	Human papillomavirus type 18 isolate Z52, complete genome	651	651	100%	0.0	99%	KC470214.1
☐	Human papillomavirus type 18 isolate MI_142_09 L1 protein gene, partial cds	651	651	100%	0.0	99%	JF728188.1
☐	Human papillomavirus type 18 isolate Qv03814, complete genome	651	651	100%	0.0	99%	EF202154.1
☐	Human papillomavirus type 18, isolate IS168, major capsid protein L1 (L1) gene, partial cds	651	651	100%	0.0	99%	U45892.1
☐	Human papillomavirus type 18 isolate BF380, complete genome	645	645	100%	0.0	99%	KC470228.1
☐	Human papillomavirus type 18 isolate Qv12693, complete genome	645	645	100%	0.0	99%	KC470227.1
☐	Human papillomavirus type 18 isolate Z125, complete genome	645	645	100%	0.0	99%	KC470226.1
☐	Human papillomavirus type 18 isolate BF172, complete genome	645	645	100%	0.0	99%	KC470225.1
☐	Human papillomavirus type 18 isolate BF288, complete genome	645	645	100%	0.0	99%	KC470224.1
☐	Human papillomavirus type 18 isolate BF309, complete genome	645	645	100%	0.0	99%	KC470223.1

Figure 1 - BLAST data for HPV18 (Mangystau, sample 2a/2/1)

Synthetic construct codon-modified HPV18 L1 protein gene, complete cds
viruses | 2 leaves
Human papillomavirus type 18 isolate Qv03132, complete genome
Human papillomavirus type 18 isolate CC1 L1 capsid protein gene, partial cds
Human papillomavirus type 18 isolate Qv29226, complete genome
Human papillomavirus type 18, isolate IS002, major capsid protein L1 (L1) gene, partial cds
Human papillomavirus type 18 variant, partial sequence
Human papillomavirus type 18 complete sequence
Human papillomavirus - 18 clone L0011 L1 protein gene, partial cds
viruses | 27 leaves
viruses | 4 leaves
viruses | 18 leaves
Human papillomavirus type 18 isolate MI_239_09 L1 protein gene, partial cds
Human papillomavirus type 18 isolate MI_430_09 L1 protein gene, partial cds
Human papillomavirus type 18 isolate MI_296_09 L1 protein gene, partial cds
Human papillomavirus type 18 isolate MI_47_09 L1 protein gene, partial cds
Human papillomavirus type 18 isolate S4 L1 protein (L1) gene, partial cds
Human papillomavirus type 18 isolate Z135, complete genome
Human papillomavirus type 18 isolate Qv26861, complete genome
Human papillomavirus type 18, isolate IS326, major capsid protein L1 (L1) gene, partial cds
Human papillomavirus isolate LSM4 capside major protein (L1), partial cds
Human papillomavirus isolate LSCJ1 capside major protein (L1), partial cds
Human papillomavirus isolate LSCC capside major protein (L1), partial cds
Human papillomavirus isolate LSML1 capside major protein (L1), partial cds
Human papillomavirus isolate LSCM capside major protein (L1), partial cds
Human papillomavirus type 18, isolate IS168, major capsid protein L1 (L1) gene, partial cds
Human papillomavirus type 18 isolate Z100, complete genome
Human papillomavirus type 18 isolate MI_142_09 L1 protein gene, partial cds
Human papillomavirus type 18 isolate Z52, complete genome
viruses | 5 leaves
Human papillomavirus type 18 isolate Rw687, complete genome
Human papillomavirus type 18 isolate Rw57, complete genome
viruses | 14 leaves
lcl|Query_89223
viruses | 3 leaves

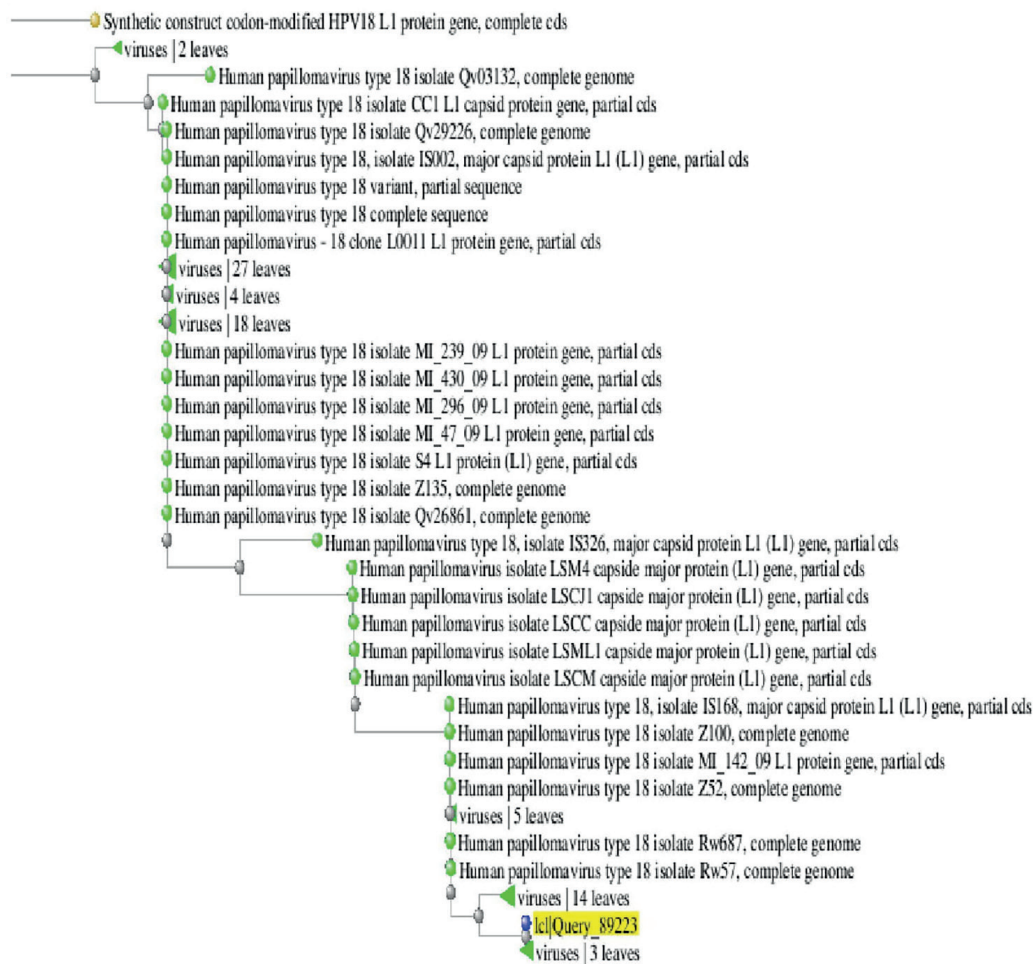**Figure 2** - HPV18 (Mangystau, sample 2a/2/1), phylogenetic tree

Sequences producing significant alignments:

Select: All None   Selected:0

Description	Max score	Total score	Query cover	E value	Ident	Accession
Human papillomavirus type 33 isolate 3 major capsid protein L1 (l1) gene, partial cds	592	592	100%	2e-165	99%	KC706450.1
Human papillomavirus type 33 isolate S5 L1 protein (L1) gene, partial cds	592	592	100%	2e-165	99%	JQ902114.1
Human papillomavirus type 33 isolate RW926, complete genome	592	592	100%	2e-165	99%	HQ537694.1
Human papillomavirus type 33 isolate Z84, complete genome	592	592	100%	2e-165	99%	HQ537693.1
Human papillomavirus type 33 isolate RW702, complete genome	592	592	100%	2e-165	99%	HQ537692.1
Human papillomavirus type 33 isolate BF266, complete genome	592	592	100%	2e-165	99%	HQ537691.1
Human papillomavirus type 33 isolate Qv35834, complete genome	592	592	100%	2e-165	99%	HQ537690.1
Human papillomavirus type 33 isolate Qv32494, complete genome	592	592	100%	2e-165	99%	HQ537688.1
Human papillomavirus isolate 1514 L1 protein gene, partial cds	592	592	100%	2e-165	99%	GU797244.1
Human papillomavirus type 33 isolate 3 major capsid protein L1 (L1) gene, complete cds	592	592	100%	2e-165	99%	GQ479014.1
Human papillomavirus type 33 isolate 2 major capsid protein L1 (L1) gene, complete cds	592	592	100%	2e-165	99%	GQ479013.1
Human papillomavirus isolate 06JAN_PHL_MY061_02 L1 capsid protein (L1) gene, partial cds	592	592	100%	2e-165	99%	EU911184.1
Human papillomavirus isolate 06JAN_PHL_MY035_06 L1 capsid protein (L1) gene, partial cds	592	592	100%	2e-165	99%	EU911114.1
Human papillomavirus type 33 strain SRB170AK L1 protein (L1) gene, partial cds	592	592	100%	2e-165	99%	EU779744.1
Human papillomavirus type 33 isolate Bsb-98 major capsid protein L1 gene, partial cds	592	592	100%	2e-165	99%	DQ486473.1
Human papillomavirus isolate PT170-04 L1 protein gene, partial cds	592	592	100%	2e-165	99%	DQ111016.1
Human papillomavirus type 33, isolate IS267, major capsid protein L1 (L1) gene, partial cds	592	592	100%	2e-165	99%	U45895.1
Human papillomavirus type 33, complete genome	592	592	100%	2e-165	99%	M12732.1
Human papillomavirus type 33 isolate 2207 major capsid protein L1 gene, partial cds	588	588	99%	2e-164	99%	EU056640.1

Figure 3 - The BLAST program data for HPV33 (Mangystau, sample 3/2/189)

The following sequence in Table 1 is also isolated in Aktau (Mangystau region). Figure 3 presents BLAST data for this sample (HPV33).

As can be seen from the results, the identity is 99%. The first in the GenBank alignments is isolate KC706450.1, corresponding to the HPV33 genotype detected in Saudi Arabia.

Nucleotide sequence of HPV33 sample 3/2/189 (Mangystau region):

ACCACTCGCAGTACTAATATGACTTTATGCACACA AGTAACTAGAaGACAGTACATATAAAAATGAAAATTTT AAAGAATATATAAGACATGTTGAAGAATATGATCTACA GTTTGTTTtTCAACTATGCAAAGTTACCTTAACTGCAGA- AGTTATGACATATATTCATGCTATGAATCCAGATATTTTA GAAGATTGGCAATTTGGTTTAACACCTCCTCCATCTGC TAGTTTACAGGATACCTAAAGGTTTGTTACCTCTCAGG CTATTACGTGTCAAAAAACAAGTACCTCCAAAGGAAA AGGAAGACCCCTTAGGTAAATATACATTTT

The phylogenetic tree of sample 3/2/189 with isolates presented in Genbank (sample marked in yellow) is shown in Figure 4.
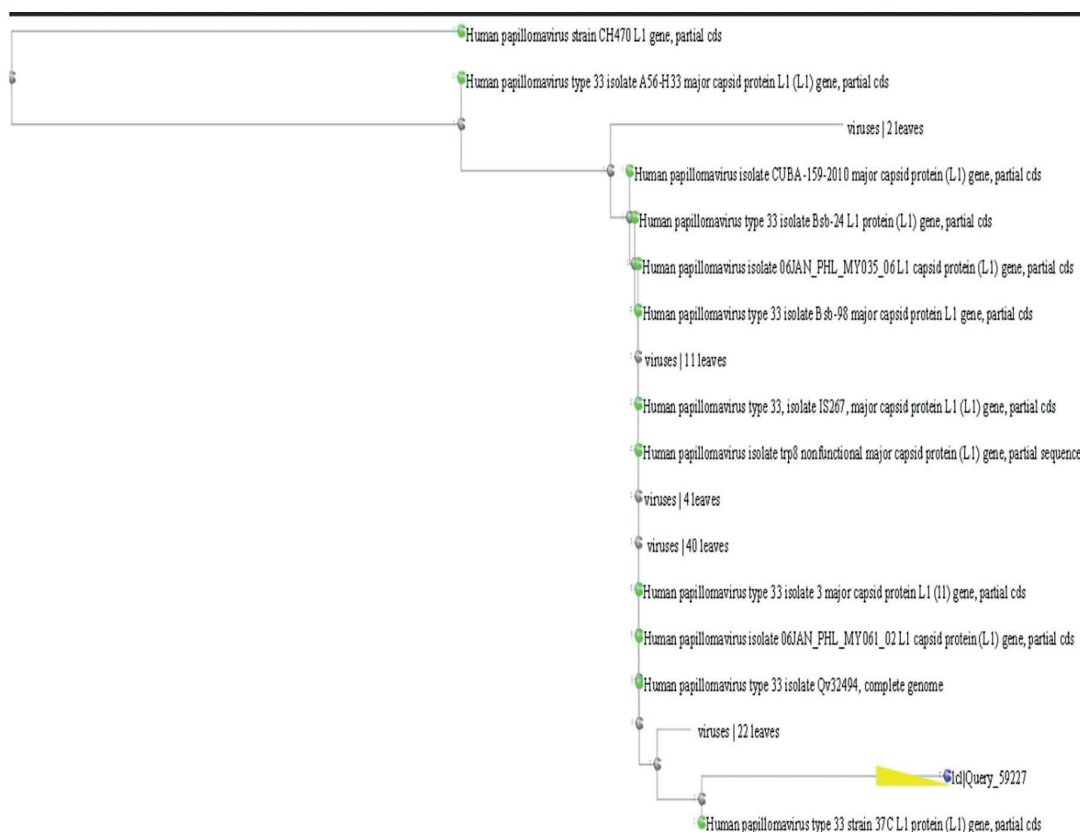

Figure 3 - HPV33 (Mangystau, sample 3/2/189), phylogenetic tree

Uralsk samples

Only one sample from Uralsk was fit for sequencing. An isolate genotype 53 (potentially / possibly carcinogenic) was obtained as a separate cluster from those from Southwest China and Ireland (identity 97%).

Aktobe samples

Sample 4/1/27 (HPV16), primary nucleotide sequence:
CAGTAAAGGATCCTAATTGTTACTGTTGTAGATA
CTACACGCAGTACACAATATGTCATGTATGGTGGCTGC
CATATGCTACCTCTGATACTACATATTAAAGTACTAAC
TTTAAAGAGTATCTACGACATGGGGAGGAATATGATTT
ACAGTTTATTTTTCAACTGTGCAAAATAACCTTATCTGC
AGACGTTATGACATACATTCATTCTATGAATTCCGCTAT
TTTGGAGGACTGGAATTTTGGACTACCCCCTCCCCCCT
GAGGCTCATTAGAAGATACTTATAGGTTTGTAACCTCC
CAGGCCATTGCTTGTCAAAAACATGCCCCTCCAACAC
CTAAAGAAGATCCCCTTAAAAAATACGCTTTTTGGGAA
GTAAATTTAAAGGAAAAGTTTTCTGCAGACCTAGATCA
GTTTCCCCCTTGGACGAAA

Figure 5 shows a print screen of the BLAST program results and the percent identity of the existing nucleotide sequences with the tested sample.

Description	Max score	Total score	Query cover	E value	Ident	Accession
Human papillomavirus type 16 isolate LZcc11-16, complete genome	590	590	94%	9e-165	93%	EU918764.1
Human papillomavirus type 16 isolate PT 62-05 L1 protein gene, partial cds	588	588	96%	3e-164	92%	EF133498.1
Human papillomavirus type 16 isolate PT 59-05 L1 protein gene, partial cds	588	588	96%	3e-164	92%	EF133497.1
Human papillomavirus proviral partial L1 gene for major capsid protein, isolate CY07-118	586	586	96%	1e-163	92%	AJ617545.1
Human papillomavirus type 16 isolate CNA138, complete genome	584	584	94%	4e-163	93%	KP212157.1
Human papillomavirus type 16 isolate CNA34, complete genome	584	584	94%	4e-163	93%	KP212153.1
Human papillomavirus type 16 isolate CNA33, complete genome	584	584	94%	4e-163	93%	KP212152.1
Human papillomavirus type 16 isolate CNA20, complete genome	584	584	94%	4e-163	93%	KP212151.1
Human papillomavirus type 16 isolate CNA15, complete genome	584	584	94%	4e-163	93%	KP212150.1
Human papillomavirus type 16 strain IR isolate IR-59 L1 protein (L1) gene, complete cds	584	584	94%	4e-163	93%	KP161014.1
Human papillomavirus type 16 strain IR isolate IR-44 L1 protein (L1) gene, complete cds	584	584	94%	4e-163	93%	KP160999.1
Human papillomavirus type 16, complete genome	584	584	94%	4e-163	93%	KF880690.1
Human papillomavirus type 16 isolate IR-32 L1 (L1) gene, complete cds	584	584	94%	4e-163	93%	KM058666.1
Human papillomavirus type 16 isolate IR-31 L1 (L1) gene, complete cds	584	584	94%	4e-163	93%	KM058665.1
Human papillomavirus type 16 isolate IR-19 L1 (L1) gene, complete cds	584	584	94%	4e-163	93%	KM058654.1
Human papillomavirus type 16 isolate IR-9 L1 (L1) gene, complete cds	584	584	94%	4e-163	93%	KM058645.1
Human papillomavirus type 16 isolate IR-1 L1 (L1) gene, complete cds	584	584	94%	4e-163	93%	KM058637.1
Human papillomavirus type 16 isolate IR-0 L1 (L1) gene, complete cds	584	584	94%	4e-163	93%	KM058636.1
Human papillomavirus type 16 isolate 16-Anhui12 from China, complete genome	584	584	94%	4e-163	93%	KC935953.1
Human papillomavirus type 16 isolate 78SE major capsid protein L1 (L1) gene, partial cds	584	584	94%	4e-163	93%	KJ467234.1
Human papillomavirus type 16 isolate 32SE major capsid protein L1 (L1) gene, partial cds	584	584	94%	4e-163	93%	KJ467230.1

Figure 5 - BLAST data for HPV16 (Aktobe, sample 4/1/27)

Figure 6 - HPV16 (Aktobe, sample 4/1/27), phylogenetic tree

The first in the table is the accession EU918764, which was isolated in China in 2007, but the percentage of identity with the tested sample is 93%. The phylogenetic tree of sample 4/1/27 with isolates presented in Genbank (sample marked in yellow) is displayed in Figure 6.

The explored sample forms a somewhat isolated branch, having a common node with the CNA33 isolate.

Identification of the genotype 16 Kazakhstani isolate from Aktobe, having its own branch, appears to be the study's most important finding. Unique sample 2a/1/2 (Aktobe, Alga district) and its nucleotide sequence:

CAGTAAAGGATCCTAATTGTTACTGTTGTAGATA CTACACGCAGTACACAATATGTCATGTATGGTGGCTGC CATATGCTACCTCTGATACTACATATTAAAGTACTAACT

TTAAAGAGTATCTACGACATGGGGAGGAATATGATHA CAGTTTATTTTTCAACTGTGCAAAATAACCTTATCTGCA GACGTTATGACATACATTCATTCTATGAATTCCGCTATT TTGGAGGACTGGAATTTTGGACTACCCCCTCCCCCCTG AGGCTCATTAGAAGATACTTATAGGTTTGTAACCTCCC AGGCCATTGCTTGTCAAAAACATGCCCCTCCAACACCT AAAGAAGATCCCCTTAAAAAATACGCTTTTTGGGAAGT AAATTTAAAGGAAAAGTTTTCTGCAGACCTAGATCAGT TTCCCCCCTTGGACGAAA

The results of identifying the sample with the BLAST program are shown in Figure 7.

The figure shows that the identity of the studied isolate with those deposited in Genbank reached only 93% percent.
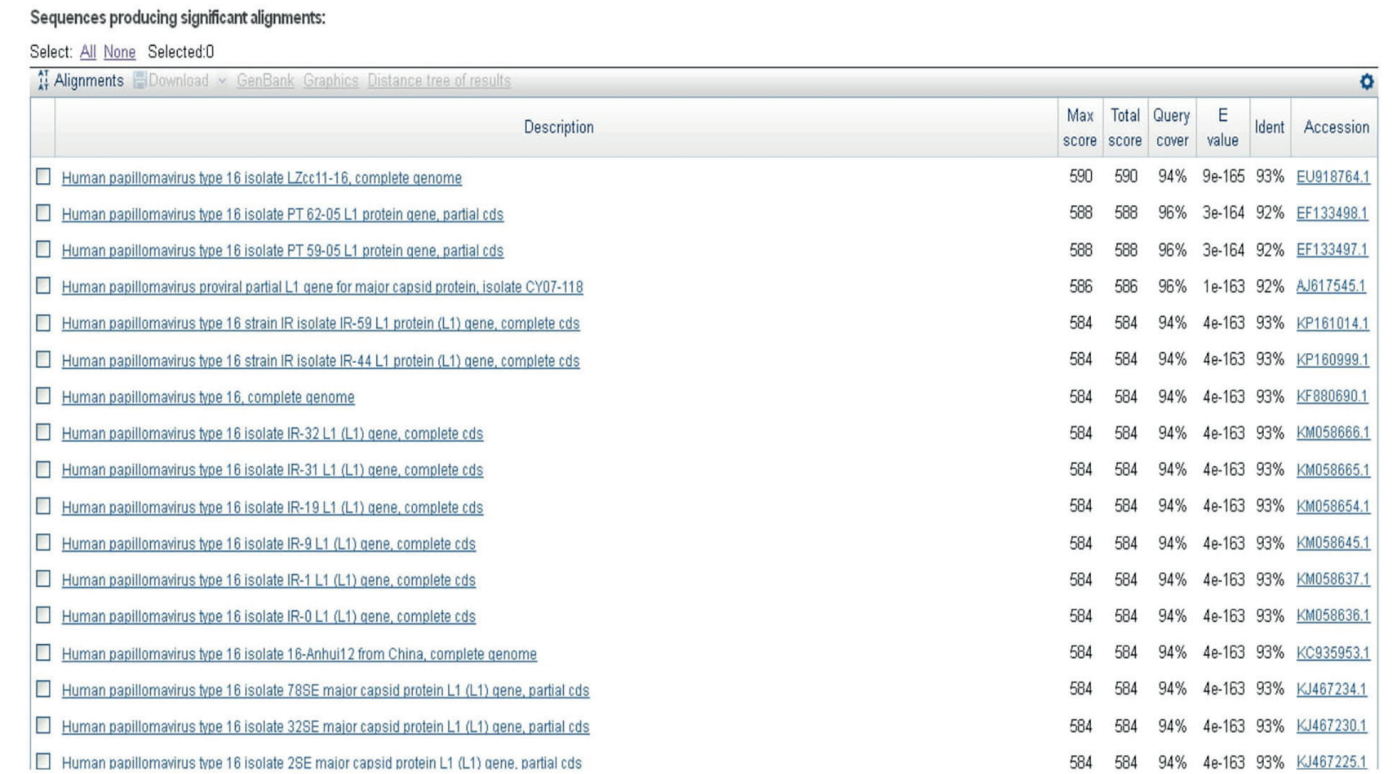
Figure 7 - BLAST data for HPV16 (Aktobe, Alga district, sample 2a/1/2)

The program Mega 6.0 was used to construct the phylogenetic tree (Figure 8).
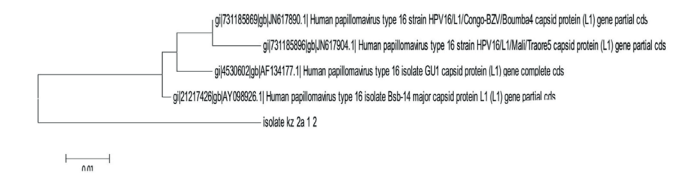
Figure 8 - HPV16 (Aktobe, sample 2a/1/2), phylogenetic tree

The presence of the Kazakh isolate's separate branch is seen in the figure. Further data collection is needed to build a phylogenetic tree and clarify the data obtained on the Kazakh HPV16 unique isolate.

The data from the presented study on the detected HPV types are summarized on the map of Western Kazakhstan (Figure 9). Regrettably, the findings are incomplete – there is a lack of data from the Atyrau region and insufficient data from Oral terrains. The research towards detecting all available information on HPV distribution to compile a complete map of the prevalence of HPV types in the Western region and throughout the country needs to be continued.

Figure 9 - HPV types detected in the western region of Kazakhstan

Discussion

As stated previously, the most convenient object for HPV gene sequencing is the L1 gene, often sequenced for additional genotype identification. Comparison of HPV 6b, 11, 16, 18, 31, and 33 sequences showed that the most conserved regions are within the open reading frames (ORFs) of the E1 and L1 genes (E, early; L, late). These HPV genes are responsible for virus replication. Two highly conserved 20 bp sequences were found in the L1 ORF, common to all sequenced HPV types [26, 27]. As known, HPV16 variants, classified based on less than 10% nucleotide variations in the major capsid (L1 ORF), contribute to persistent infection leading to cancer development. L1 protein forms the cornerstone of HPV structure and antigenicity [23]. Nowadays, all licensed HPV recombinant vaccines are designed based on HPV major capsid L1 protein [27]. But to explore the genetic variability of isolates, genomic regions E6/E7 are used, i.e., genes responsible for the expression of oncoproteins. Researchers observed thousands of unique HPV16 genomes exploring the E7 region. They reported that very few women shared the identical HPV16 sequence, which should stimulate a careful re-evaluation of the clinical implications of HPV mutation rates, transmission, clearance, and persistence [28].

In our study, the results of HPV L1 gene sequencing evidence that the geographical introduction of obtained isolates in western Kazakhstan is extensive and various. In fact, we established pervasion of HPV infection from almost all continents, excluding Africa and Australia. For types 18 and 33 circulating in the Mangistau region, we found an introduction from North America and the Arabian Peninsula. At the same time, researchers from Saudi Arabia established that HPVs circulating in their territory formed a closed cluster with African, Asian, East Asian, and American HPVs distributed into multiple lineages from various geographical locations [29].

We found that the isolate HPV53 from Uralsk was presented as a separate cluster from those from Southwest China and Ireland. Canada and the Netherlands have been identified as the geographic locations for the isolate obtained in the Khromtau sight of Aktobe. Other countries of origin for the Aktobe samples were the following: Brazil, South America (sample isolated in the Kayndy site), Cyprus (isolates obtained in the districts of Khromtau and Shalkar), Portugal (the isolate was obtained in the Temir district), and China.

We believe that the work done has resulted in two indisputable achievements. In the Alga area, an original isolate of genotype 16 has been detected as a separate branch for which it is necessary to complete the phylogenetic tree. The isolate has not yet been entered into the world Genbank, and the registration process should be commenced as the tree is built. Considering that HPV16 is the predominant type among HPV-infected women in western Kazakhstan (26.4% prevalence), besides it is the causative factor for 54.1% of women affected with cervical cancer, any research into the nature and behavior of this genotype seems very important [11].

In Uralsk, we detected a case of cervical cancer caused by HPV53 (sample 2a/4/12). The value of this sample's successful sequencing is that the apparent carcinogenicity of one of the so-called "potentially carcinogenic" HPV types was confirmed. By definition, highly carcinogenic types are those capable of causing invasive cancer by acting as a single agent. Moreover, we established the geographic path for this isolate, which forms a remote cluster with KF436822/1, KU951264.1 – Southwest China, and 97% identity with EU056643.1 – Ireland.

However, the work was accompanied by significant disadvantages. The first and the most prominent is unsatisfactory productivity, only 14.3% of successful cases. As known, collection, storage, and transport significantly affect the quality of the samples. In our study, some examples showed a very low viral load, and some lacked DNA, thus failing to obtain the L1 gene sequences in 60 cases. Specialists from the shared laboratory practiced repeated attempts to optimize the PCR conditions and the sequencing procedure, as well as additional experiments (reamplification, re-sequencing), but without success. Meanwhile, the sampling and transportation of the biomaterial were carried out according to the Instructions of the transport medium manufacturer – the Russian company "DNA-technologies". However, it cannot be denied that there were certain deviations from Instruction during the transportation of samples by train or plane due to some lack of control by the project staff.

One of the limitations is some incompleteness of work. Identifying the lineages for HPV16 isolates would be beneficial, given the different carcinogenicity of the four HPV16 lineages. The subsequent research on the genetic features of HPV types circulating in Kazakhstan should include these issues. Moreover, there is a need to generate complete genome sequence information to provide a clearer picture of the genetic diversity and evolution of HPVs in the country.

In general, the sequencing findings indicate the variety of ways for HPV pervasion into the western region of Kazakhstan. The presence of HPV53 as a single agent for invasive cervical cancer (sample 2a/4/12) confirms the current viewpoint on the particularities of HPV behavior – high genetic variability and a tendency to constant evolution. It is necessary to continue the research cycle and complete the Kazakhstani isolate of type HPV16 registration process in the world Genbank.

References

1. Zhang X, Zeng Q, Cai W, Ruan W. Trends of cervical cancer at global, regional, and national level: data from the Global Burden of Disease study 2019. *BMC Public Health*. 2021; 21(1): 894. https://doi.org/10.1186/s12889-021-10907-5.

2. zur Hausen H. Papillomaviruses in the causation of human cancers – a brief historical account. Virology. 2009; 384(2): 260-5. https://doi.org/10.1016/j.virol.2008.11.046.

3. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999; 189(1): 12–19. https://doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F.

4. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer*. 2009; 4: 17-29. https://doi.org/10.1186/1750-9378-4-8.

5. Halec G, Alemany L, Lloveras B, Schmitt M, et al. Retrospective International Survey and HPV Time Trends Study Group. Pathogenic role of the eight probably/possibly carcinogenic HPV types 26, 53, 66, 67, 68, 70, 73 and 82 in cervical cancer. *J Pathol* 2014; 234: 441-51. ttps://doi.org/10.1002/path.4405.

6. McBride AA. Human papillomaviruses: diversity, infection and host interactions. *Nat Rev Microbiol* 2022; 20(2): 95–108. https://doi.org/10.1038/s41579-021-00617-5.

7. Shrestha AD, Neupane D, Vedsted P, Kallestrup P. Cervical Cancer Prevalence, Incidence and Mortality in Low and Middle Income Countries: A Systematic Review. *Asian Pac J Cancer* 2018; 19(2): 319-24. https://doi.org/10.1111/ecc.13207.

8. Rogovskaya SI, Shabalova IP, Mikheeva IV, Minkina GN, Podzolkova NM, Shipulina OY, Sultanov SN, Kosenko IA, Brotons M, Buttmann N, Dartell M, Arbyn M, Syrjänen S, & Poljak M. Human papillomavirus prevalence and type-distribution, cervical cancer screening practices and current status of vaccination implementation in Russian Federation, the Western countries of the former Soviet Union, Caucasus region and Central Asia. *Vaccine* 2013; 31 Suppl 7: H46–H58. https://doi.org/10.1016/j.vaccine.2013.06.043.

9. De Vuyst H, Alemany L, Lacey C, Chibwesha CJ, Sahasrabuddhe V, Banura C, Denny L, Parham GP. The burden of human papillomavirus infections and related diseases in sub-saharan Africa. *Vaccine* 2013; 31 Suppl 5: F32-46. https://doi.org/10.1016/j.vaccine.2012.07.092.

10. European Cancer Organisation. Putting HPV on the Map: The State of HPV Prevention Programmes in the WHO European Region. Available at: [https://www.europeancancer.org/resources/256:hpv-prevention-programmes.html] (Accessed 27 Apr 2022.)

11. Balmagambetova SK, Tinelli A, Urazayev ON, Sakieva KZ, Koyshybaev AK, Zholmukhamedova DA, et al. HPV Types Distribution in General Female Population and in Women Diagnosed with Cervical Cancer Across Western Kazakhstan. *Asian Pac J Cancer* 2019; 20(4): 1089-96. https://doi.org/10.31557/APJCP.2019.20.4.1089.

12. Babi A, Issa T, Issanov A, Akilzhanova A, Nurgaliyeva K, Abugalieva Z, et al. Prevalence of high-risk human papillomavirus infection among Kazakhstani women attending gynecological outpatient clinics. *Int J Infect Dis* 2021; 109: 8-16. https://doi.org/10.1016/j.ijid.2021.06.006.

13. Aimagambetova G, Azizan A. Epidemiology of HPV Infection and HPV-Related Cancers in Kazakhstan: a Review. *Asian Pac J Cancer Prev* 2018; 19(5): 1175-80. https://doi.org/10.22034/APJCP.2018.19.5.1175.

14. Niyazmetova L, Aimagambetova G, Stambekova N, et al. Application of molecular genotyping to determine prevalence of HPV strains in pap smears of Kazakhstan women. Int J Infect Dis 2016; 54: 85-8. https://doi.org/10.1016/j.ijid.2016.11.410.

15. Aimagambetova G, Chan CK, Ukybassova T, Imankulova B, Balykov A, Kongrtay K, et al. Cervical cancer screening and prevention in Kazakhstan and Central Asia. J Med Screen. 2021; 28(1): 48-50. https://doi.org/10.1177/0969141320902482.

16. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Kazakhstan. Summary Report 22 October 2021. [Date Accessed]

17. Aimagambetova G, Babi A, Issa T, Issanov A. What Factors Are Associated with Attitudes towards HPV Vaccination among Kazakhstani Women? Exploratory Analysis of Cross-Sectional Survey Data. *Vaccines (Basel)*. 2022;10(5): 824. https://doi.org/10.3390/vaccines10050824.

18. Pal A, & Kundu R. Human Papillomavirus E6 and E7: The Cervical Cancer Hallmarks and Targets for Therapy. *Front Microbiol* 2020; 10: 3116. https://doi.org/10.3389/fmicb.2019.03116.

19. Van Doorslaer K. Revisiting Papillomavirus Taxonomy: A Proposal for Updating the Current Classification in Line with Evolutionary Evidence. *Viruses* 2022; 14(10): 2308. https://doi.org/10.3390/v14102308.

20. Bhattacharjee R, Das SS, Biswal SS, Nath A, Das D, Basu A, Malik S, Kumar L, et al. Mechanistic role of HPV-associated early proteins in cervical cancer: Molecular pathways and targeted therapeutic strategies. *Crit Rev Oncol Hematol* 2022; 174: 103675. https://doi.org/10.1016/j.critrevonc.2022.103675.

21. Vonsky M, Shabaeva M, Runov A, Lebedeva N, Chowdhury S, Palefsky JM, & Isaguliants M. Carcinogenesis Associated with Human Papillomavirus Infection. Mechanisms and Potential for Immunotherapy. *Biochemistry. Biokhimiia* 2019; 84(7): 782–799. https://doi.org/10.1134/S0006297919070095.

22. Sayers EW, Cavanaugh M, Clark K, Ostell J, Pruitt KD, & Karsch-Mizrachi I. GenBank. *Nucleic Acids Res* 2020; 48(D1): D84–D86. https://doi.org/10.1093/nar/gkz956.

23. Mane A, Patil L, Limaye S, Nirmalkar A, Kulkarni-Kale U. Characterization of major capsid protein (L1) variants of Human papillomavirus type 16 by cervical neoplastic status in Indian women: Phylogenetic and functional analysis. *J Med Virol* 2020; 92(8): 1303-08. https://doi.org/10.1002/jmv.25675.

24. Shen-Gunther J, Cai H, Zhang H and Wang Y. Abundance of HPV L1 Intra-Genotype Variants With Capsid Epitopic Modifications Found Within Low- and High-Grade Pap Smears With Potential Implications for Vaccinology. *Front Genet* 2019; 10: 489. https://doi.org/10.3389/fgene.2019.00489.

25. Bekmukhambetov YZ, Mynbaev OA, Tinelli A, Balmagambetova SK, Koyshybaev AK, Urazayev ON, Ismagulova EK, et al. Human Papillomavirus related issues in western Kazakhstan: Protocol for a comprehensive study. *Rus Open Med J*. 2018; 7(4): e0408. https://doi.org/10.15275/rusomj.2018.0408.

26. Yu L, Majerciak V, Zheng ZM. HPV16 and HPV18 Genome Structure, Expression, and Post-Transcriptional Regulation. Int J Mol Sci. 2022; 23(9): 4943. doi: 10.3390/ijms23094943. Erratum in: *Int J Mol Sci*. 2022; 23(14). https://doi.org/10.3390/ijms23094943.

27. Oumeslakht L, Ababou M, Badaoui B, Qmichou Z. Worldwide genetic variations in high-risk human papillomaviruses capsid L1 gene and their impact on vaccine efficiency. *Gene* 2021; 782:145533. https://doi.org/10.1016/j.gene.2021.145533.

28. Nelson CW, & Mirabello L. Human papillomavirus genomics: Understanding carcinogenicity. *Tumour Virus Res* 2023; 15: 200258. https://doi.org/10.1016/j.tvr.2023.200258.

29. Sait K, Turki R, Abuzenadah AM, Jiffri OH, Bohmaidah A, Sohrab SS. Genetic diversity and phylogenetic analysis of HPV 16 & 18 variants isolated from cervical specimens of women in Saudi Arabia. *Saudi J Biol Sci*. 2019; 26(2): 317-24. https://doi.org/10.1016/j.sjbs.2018.05.005.

Analysis of the effectiveness of intrapleural analgesia after minimally invasive coronary artery bypass grafting on a beating heart

Mukhit Dossov[1], Serik Seitenov[1], Baurzhan Babashev[1], Azhar Zhailauova[1], Arman Kazmagambetov[1], Ruslan Kulchukov[1], Rustam Salakhanov[1], Akerke Bekseitova[1]

[1]Anesthesiology & ICU Department Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan

Corresponding author:
Mukhit Dossov.
E-mail: dossovmukhit@gmail.com;
ORCID: 0009-0000-3291-362X.

Abstract

Purpose: To determine the effectiveness of intrapleural analgesia (IPA) for pain relief after minimally invasive coronary artery bypass surgery on a beating heart.

Methods: We prospectively studied 35 patients who underwent coronary artery bypass grafting on a beating heart through a mini thoracotomy access on the left. Patients were divided into two groups: group I received IPA with a catheter (n=16) and group II patients were not introduced intrapleural analgesia (n=19). Postoperative pain was assessed according to the visual analogue scale (VAS), consumption of analgesics, extubation time, arterial blood gas parameters. Adequacy of respiration and lung ventilation were estimated by electrical impedance tomography.

Results: Extubation time after surgery did not differ in both groups. Arterial oxygen partial pressure was higher (p<0.05) in the first group (160.82±46.98) compared to the second group (111.42±49.26). Regarding the EIT in the quadrant mode, distribution of tidal volume was better in the first group (p<0.05) in the 2nd, 3rd quadrant and in the layer mode, the second layer of the first group showed better results compared to the same layer of the second group. After extubation, average pain score according to VAS was four points for the first group and six points for the second group. On the 1st and 2nd day pain scores were the same in both groups. Postoperative analgesia by promedol was required only for 1 patient (6.25%) from the first group, and 14 patients from the second group (73.7%). Additionally, tramadol was administered to 43.5% (7 patients) of the first group and 26.3% (5 patients) of the second group.

Conclusion: IPA can be used as one of the effective treatments for postoperative pain in minimally invasive coronary artery bypass surgeries. IPA promotes less use of opioids. An improvement in respiration was observed with reduction in postoperative pain.

Keywords: postoperative pain, intrapleural, analgesia, electrical impedance tomography.

Introduction

Lately, minimally invasive procedures in cardiac surgery (MICS) are gaining popularity and this poses certain challenges for anesthesiology practice [1]. Minimally invasive direct coronary artery bypass (MIDCAB) being commonly applied subtype of MICS where revascularization takes place through conjunction of the left internal thoracic artery (ITA) and left anterior descending artery, nowadays are implemented worldwide more often [2]. The mini-thoracotomy approach for these surgeries may require more personalized pain management techniques to minimize postoperative pain. The relief of postoperative pain after MIDCAB is necessary to ensure a complete and rapid recovery [3]. Management of pain after minimally invasive procedures remains a major challenge, and the pursuit of an optimal pain control strategy still continues.

Poorly controlled pain can lead to limited chest expansion, ineffective cough, hypoxia, atelectasis, and eventually respiratory failure and pneumonia. Besides, poor analgesia delays early extubation, one of the factors that decreases number of days spent in hospital, as well as

overall morbidity and mortality [4]. Opioids have traditionally been the cornerstone of pain management, but all current guidelines recommend minimizing their use due to numerous side effects the most prominent of which are CNS and respiratory depression [5,6]. Despite these new recommendations, evidence to support a single pain management strategy is limited. Multimodal pain management strategies being a part of Enhanced Recovery after Surgery programs (ERAS) to reduce postoperative morbidity and mortality associated with poorly controlled pain after thoracotomy [7, 8], occupies a special place in addressing multifactorial pathophysiology of thoracotomy pain.

Multimodal analgesia involves the use of two or more anesthetics and analgesics that have different mechanisms of action and allows achievement of adequate pain relief with a minimum side effect [3, 4, 6, 9]. For this purpose, systemic and regional methods are applied. In modern practice, there are several methods of pain relief after thoracotomy one of them being intrapleural analgesia (IPA). Although in guidelines accepted in 2016 intrapleural analgesia is not recommended as a single technique for post operative management after thoracic surgeries [10], non-inferiority of the procedure was not supported and application of IPA is regarded as a part of multimodal analgesia under the supervision of the signs for a possible local anesthetic systemic toxicity, cardiac and CNS toxicities being the most detrimental [11].

The review on thoracic regional anesthesia conducted by Joshi et al. evaluated the sole efficacy of IPA versus other thoracic regional anesthesia techniques such as epidural analgesia (EA) and thoracic paravertebral block (PVB) based on three studies [12]. In the first study, Bachmann-Mennenga et al. deduced inferiority of IPA based on the conclusion that seven out of ten patients receiving IPA required additional opioids for pain management compared to other groups receiving EA or PVB [9]. Wedad et al. found out superiority of paravertebral block compared to the EA or IPA [13] and the last study included in the review analyzed thirty-two patients in each group [14] and did not distinguish any difference in pain scores along with morphine consumption in patients receiving EA or IPA accordingly. In the earlier review conducted by Karmakar and Ho application of IPA was shown to be preferable when other thoracic blocks including epidural and paravertebral are non-advisory. Effectiveness of IPA versus epidural anesthesia (EA) was contradictory in several studies [15]. The first study mentioned in review demonstrated superiority of IPA versus EA provided with the same local anesthetic amount and analgesia duration in terms of substantial decrease in mean blood pressure in case of epidural anesthesia [16] which is an intolerable outcome for minimally invasive heart surgeries performed without cardiopulmonary bypass. In contrast, the second study showed higher effectiveness of EA compared to IPA in terms of better values of negative inspiratory pressure and tidal volume with reduced number of consumed opioids, although with higher extent of induced hypotension in case of EA [17]. The last study conducted by Short et al. presented equal effectiveness of IPA and systemic opioid approach supporting better outcomes after applying IPA to avoid circulatory depression in case of epidural anesthesia and respiratory depression in case of opioid usage [18]. It should be again noted that the studies conducted in both reviews were limited by the amount of the patients involved and study design applied making the statistical evidence relatively indecisive. Application of the cross over design would include a crucial parameter such as drug metabolism consideration to equilibrate the duration of the analgesic effect.

Recently IPA were gaining popularity again. According to the review on multimodal anesthesia management techniques during minimally invasive cardiac surgeries conducted in 2021 [3], IPA provides deeper analgesic effect due to ability to be continuously delivered, although correct placement of the catheter is vital. Another recent review comparing the benefits of EA to IPA demonstrated superiority IPA by resulting in the [19] less value of Visual pain score in patients receiving IPA compared to EA group with other respiratory and hemodynamics parameters being similar [19]. Ishikawa et al. applied IPA and EA after thoracoscopic surgery showing that delivery of IPA analgesia did not require additional analgesic management compared to EA group [20].

IPA has been used in practice for a long time, but summarizing all available literature, there is little research on IPA effectiveness in MIDCAB grafting surgeries. In our practice, in search of effective methods of analgesia after MIDCAB grafting, we started to apply IPA and compare its analgesic effect with the control group. The primary goal of the study is to assess IPA analgesic effect in terms of hemodynamics, respiratory parameters and data from arterial blood gases in both groups. The secondary goal is to assess IPA analgesia by comparing visual analogue scale scores in control and treatment groups.

Materials and methods

We prospectively studied 35 cardiac patients who underwent off-pump coronary artery bypass (OPCAB) through a mini-thoracotomy access on the left (5th ICS thoracotomy). Approval from the ethical committee was obtained before the start of the study. Selected patients initially did not have respiratory distress and their division was randomized in two groups. The first group consisted of patients receiving intrapleural analgesia (n=16) and the second group represented patients free from intrapleural analgesia (n=19). Division on groups was carried out randomly by physicians not involved in the study. Sample size was gathered according to the available spots for MIDCAB surgery during the time of prospective study. Participants were preoperatively examined in a standard manner, preanesthetic evaluation was performed and informed consent on application of intrapleural anaesthesia as well as on the participation in the study was received. All patients underwent multi-component general anesthesia with double-lumen endotracheal tube (one lung ventilation: left bronchus intubation) of an appropriate size depending on patient's height and weight. Position control and fixation of the endotracheal tube were performed under fiberoptic bronchoscopy control. Intraoperatively invasive monitoring of systolic blood pressure, diastolic blood pressure, central venous pressure (CVP), continuous electrocardiographic (ECG) monitoring, blood saturation (SpO2), capnography (etCO2), ABGs (initial and final), temperature, Activated Clotting Time (ACT) were recorded.

Technique for inserting an intrapleural catheter. After induction into anesthesia and tracheal intubation, the patients of the first group underwent the installation of an intrapleural catheter. In the right lateral recumbent position, at the level of the 6th ICS on the left along the scapular line (between the posterior axillary and paravertebral lines), the pleural cavity was punctured with a Tuohy needle connected to a syringe of 3-4 ml of saline and a 0.9% sodium chloride system through a three-way valve with the purpose of pneumothorax prevention. After puncture of the pleural cavity, an epidural catheter was installed with the side holes 5-8 cm deep from the tip of the needle, then the needle was removed, the catheter was fixed to the skin with

adhesive tape and marked [21]. Patency check was performed by injection of 5 ml 0.9% sodium chloride saline. The left half of the patient's chest was elevated with a roller placed under the left scapula. Re-examination of endotracheal tube positioning was checked under fiberoptic bronchoscopy control after changing patient's position. After the start of the surgery, one-lung ventilation was performed during the main stage, with the left lung being turned off under strict monitoring of vital signs.

Estimated dosage of heparin for coagulation was 150 units/kg administered as a bolus. Target activated clotting time was 200 seconds. Upon completion of the aorto-coronary bypass, inactivation of heparin was performed with protamine. Towards the end of the surgery, reintubation was performed with a conventional endotracheal tube according to patient's height and weight. Following the surgery, patients were hospitalized in ICU. Initial data was recorded: age, gender, body mass index (BMI), diagnosis and comorbidities, ASA classification. In the postoperative period, the following parameters were recorded: systolic and diastolic blood pressure, pulse rate, blood saturation, extubation time. Postoperative pain intensity was assessed using a visual analogue scale (VAS) from 0 to 10 points (0 – no pain, 10 – the most severe pain). Postoperatively, degree of pain was monitored continuously and assessed three times by the same employee: after extubation, at 08:00 am on the 1st day and at the same time on the 2nd day postoperatively, and the assessment was carried out by nurses and physicians not involved in the study. The parameters of ABGs were assessed on the first two days postoperatively. The amount of opioid and non-opioid analgesics used after surgery as long as the frequency of administration was recorded. Also, the length of stay (LOS) in ICU, the duration of inpatient treatment was recorded. In the first group (n=16), bupivacaine 0.25% 20 ml was injected into the intrapleural catheter as an analgesia postoperatively before extubation. After injection, the pleural cavity drainage was closed, the patient the patient was placed horizontally for 15 minutes, after which the pleural cavity drainage was opened. If the patients from the first group experienced pain, an additional dose of analgesic was administered in the amount of 0.25% 20 ml. All patients underwent analgesia with trimeperidine and tramadol after assessing the pain syndrome according to VAS which value should be more or equal to four. To assess the adequacy of breathing after extubation and on the first day postoperatively, electrical impedance tomography (Dräger PulmoVista® 500) of the lungs was performed at the level of the 4th-5th intercostal space. Electrical impedance tomography (EIT) was performed in two modes with the division of the estimated level of lung fields into "layers" and "quadrants". On the screen, the picture of the examined area (slice) of the lungs in the "layers" mode is divided into 4 layers from the sternum to the spine, in the "quadrants" mode, the examined area of the lung slice is divided into 4 quadrants: the anterior right – 1st quadrant, the anterior left – 2nd quadrant, back right – 3rd quadrant and back left – 4th quadrant.

The study did not include patients who underwent repeated thoracotomy due to bleeding, as long as patients who underwent sternotomy. Statistical processing of the obtained data was carried out in STATA program according to nonparametric descriptive methodology, applying Mann-Whitney U test.

Results

The compared groups did not differ in terms of diagnosis and comorbidities. According to the general characteristics of the group (Table 1), there was no variability in sex and age. Also,

Table 1	Basic Data by groups			
Patient's Data	All (N=35)	Group I (N=16)	Group II (N=19)	p-value
Age, mean (SD±)		60.1 (8.83)	61.56 (8.98)	0,632
BMI, n(%)				0,153
<18.5	0	0	0	
18.5 < 25	9 (25.71)	5 (55.56)	4 (44.44)	
25 < 30	12 (34.29)	4 (33.33)	8 (66.67)	
30 <	14 (40)	10 (71.43)	4 (28.57)	
Gender, n(%)				0,929
Female	9 (25.71)	5 (55.56)	4 (44.44)	
Male	26 (74.29)	14 (53.85)	12 (46.15)	
LOS in ICU n(IQR)	2 (1-2)	2 (1-3)	2 (2-2)	0,552
LOS inpatient (IQR)	10 (8-13)	10 (8-15)	10 (8-12)	0,806
3rd grade	9 (25.71)	5 (55.56)	4 (44.44)	
4th grade	26 (74.29)	14 (53.85)	12 (46.15)	

BMI – body mass index, ICU – Intensive Care Unit

the risk of ASA stratification, the duration of ICU hospitalization and the duration of inpatient treatment did not differ between the groups.

In the first group, ten patients had BMI over 30, while in the second group, there were only 4 people with such BMI. Though, statistical significance was not revealed. All patients underwent multicomponent anesthesia, induction with propofol following maintenance anesthesia with sevoflurane. Difference in drug dosages during anesthesia was not observed. The average duration of anesthesia was 195 minutes, the duration did not differ significantly between groups. The amount of fentanyl used in the first group was 700 mcg and 800 mcg in the second group (p>0.05).

Intraoperative hemodynamic data are presented in the following Table 3. According to the analysis, significant differences in SBP, DBP and HR in the groups was not noted.

According to the analysis of hemodynamic parameters after surgery, the first day and the second day showed a difference (p<0.05) in heart rate. The mean value for the first group was statistically significantly lower (80±10.7) than the mean value for the second group (90.1±12.13). However, no difference was noted in SBP, DBP and HR between those days.

The duration of mechanical ventilation (median (IQR) minutes) in the postoperative period for the first and the second group was 232.5 (187.5-340) minutes and 230 (170-280) minutes accordingly, that is, the extubation time for the groups was the same (p> 0.05).

Analyzing data on arterial blood gases in the postoperative period, the following data were obtained. A significant difference (p < 0.05) was revealed in the partial pressure of oxygen in arterial blood, which was higher in the first group (160.82±46.98) compared to the second group (111.42±49.26). Considering the level of partial pressure of carbon dioxide there was a hypercapnic trend for the latter group where IPA was not implemented.

Glucose level from ABGs parameter, being an indirect sign of the body's stress response on the first two days postoperatively, did not show any difference between the groups. Overall, patients in both groups showed the average glucose value higher than normal due to stress response to surgery. The analysis of the results of electrical impedance tomography (EIT) which was

Table 2   Duration of anesthesia and amount of fentanyl used during anesthesia

	All (N=35)	Group I (N=16)	Group II (N=19)	p-value
Duration of anesthesia (min) median(IQR)	195 (165-240)	192.5 (177.5-207.5)	195 (155-280)	0,816
Fentanyl used (ampoules), mean(SD±)	8 (6-8)	7 (5-8)	8 (7-9)	0,174

Table 3   Hemodynamic parameters

	All (N=35)	Group I (N=16)	Group II (N=19)	p-value
Hemodynamic parameters during anesthesia				
SBP mmHg., mean(SD±)	122.28 (14.22)	125.5 (12.43)	119.58 (15.38)	0,225
DBP mmHg., mean(SD±)	66.06 (9.21)	65.5 (9.97)	66.53 (8.76)	0,748
HR per min, mean(SD±)	75.57 (15.01)	72.75 (12.22)	77.95 (16.97)	0,314
Hemodynamic parameters during anesthesia 1st day postoperatively				
SBP mmHg., mean(SD±)	121.88 (12.43)	123.06 (10.74)	120.89 (13.91)	0,614
DBP mmHg., mean(SD±)	65.31 (9.78)	63.5 (10.19)	66.84 (9.41)	0,321
HR per min, mean(SD±)	85.48 (12.2)	80 (10.07)	90.1 (12.13)	0,01
Hemodynamic parameters during anesthesia 2nd day postoperatively				
SBP mmHg., mean(SD±)	124.69 (13.64)	124.07 (12.86)	125.16 (14.52)	0,825
DBP mmHg., mean(SD±)	70.42 (8.19)	67.5 (5.85)	72.58 (9.11)	0,07
HR per min,, mean(SD±)	87.64 (9.92)	84.57 (6.86)	89.89 (11.33)	0,129

SBP – systolic blood pressure, DBP – diastolic blood pressure. HR – heart rate.

Table 4   ABGs parameters postoperatively

	Group I (N=16)	Group II (N=19)	p-value
ABGs parameters after extubation			
pH, median(IQR)	7.38 (7.34-7.39)	7.36(7.3-7.38)	0,178
pO2 mmHg, mean(SD±)	160.82 (46.98)	111.42 (49.26)	0,004
pCO2 mmHg, median(IQR)	37.15 (33.4-41.2)	40.5 (37.4-47.7)	0,016
Lactat mmol/L, median(IQR)	1.2 (0.92-1.65)	1.2 (1.03-1.4)	0,855
BE mmol/L, mean(SD±)	-3.07 (2)	-3.61 (2.61)	0,507
Glucose mmol/l, median(IQR)	7.8 (6.6-8.8)	7.8 (6.7-8.4)	0,89
ABGs parameters 1st day postoperatively			
pH, median(IQR)	7.39 (7.37-7.42)	7.37 (7.34-7.4)	0,078
pO2 mmHg, mean(SD±)	99.26 (25.58)	99.01 (33.89)	0,981
pCO2 mmHg, median(IQR)	35.95 (35.15-39.7)	40.8 (34.6-43.8)	0,111
Lactat mmol/L, median(IQR)	1.41 (1.05-1.67)	1.46 (1.13-2.1)	0,529
BE mmol/L, mean(SD±)	15.44 (7.96)	12.95 (7.41)	0,345
Glucose mmol/l, median(IQR)	8.25 (7.2-8.7)	8.25 (7.1-8.7)	0,835
ABGs parameters 2nd day postoperatively			
pH, median(IQR)	7.4 (7.39-7.44)	7.4 (7.38-7.41)	0,239
pO2 mmHg, mean(SD±)	94.78 (21.58)	85.96 (20.12)	0,256
pCO2 mmHg, median(IQR)	36.8 (34.4-40.2)	39 (36.4-41.4)	0,243
Lactat mmol/L, median(IQR)	1.04 (0.93-1.35)	1.04 (1-1.5)	0,607
BE mmol/L, mean(SD±)	-0.9 (2.5)	-1.14 (2.1)	0,776
Glucose mmol/l, median(IQR)	7 (6.7-8.5)	7.3 (6.2-8.5)	0,48

Table 5   Results of EIT of the lungs after surgery

	Group I (N=16)	Group II (N=19)	p-value
EIT results, day 1			
RI 1st quadrant, mean(SD±)	16.07 (9.25)	22.5 (10.92)	0,095
RI 2nd quadrant, mean(SD±)	34.36 (5.51)	28.58 (8.49)	0,037
RI 3rd quadrant, mean(SD±)	37.07 (6.85)	29.7 (5.79)	0,003
RI 4th quadrant, mean(SD±)	12.78 (8)	17.35 (7.82)	0,12
RI 1st layer, mean(SD±)	28.21 (11.36)	23.94 (12.01)	0,327
RI 2nd layer, mean(SD±)	29.53 (11.72)	20.36 (6.84)	0,015
RI 3rd layer, mean(SD±)	29.5 (8.42)	31.11 (8.59)	0,602
RI 4th layer, mean(SD±)	20.93 (8.81)	16.23 (8.15)	0,134
EIT results, day 2			
RI 1st quadrant, mean(SD±)	16.8 (7.86)	22.37 (10.75)	0,103
RI 2nd quadrant, mean(SD±)	33.8 (10.94)	30.68 (8.87)	0,365
RI 3rd quadrant, mean(SD±)	34.67 (7.94)	34.89 (8.91)	0,938
RI 4th quadrant, mean(SD±)	12.06 (6.25)	12.84 (6.37)	0,724
RI 1st layer, mean(SD±)	32.27 (8.19)	27.74 (11.13)	0,197
RI 2nd layer, mean(SD±)	26.53 (13.06)	15.6 (8.55)	0,008
RI 3rd layer, mean(SD±)	32.27 (7.97)	31.42 (11.96)	0,815
RI 4th layer, mean(SD±)	16.4 (8.27)	15.74 (8.92)	0,825

RI – region of interest, EIT – electrical impedance tomography.

carried out to study the adequacy of breathing postoperatively showed the results represented in the Table 5. In the quadrant mode 2nd and 3rd field of study as well as the 2nd slice in the layer mode showed larger values (p<0.05) in comparison to the second group demonstrating better respiratory dynamics after IPA implementation.

EIT in the quadrant mode performed on the second day post surgically showed no differences in both groups, but in the layer's mode, a difference was found with a large value on the 2nd layer (26.53 ± 13.06) of the first group compared to the second group (15.6± 8.55) where intrapleural blockade has not been performed.

Table 6   Postoperative VAS pain scores and pain relief

Pain assessment	Group I(N=16)	Group II (N=19)	p-value
VAS after extubation, median(IQR)	4 (3-5)	6 (5-7)	
VAS Day 1, median(IQR)	3 (3-3)	3 (3-4)	
VAS Day 2, median(IQR)	2 (2-2)	2 (2-3)	
Analgesia, n (%)			
Bupivacaine in IP catheter 2-fold injection.	12 (75)	0	
Number of patients received Trimeperidine 20mg IM (%)	1 (6.25)	14 (73.7)	
Number of patients received Tramadol IM			0,012
Tramadol 100 mg/day	1 (6.25)	10 (52.6)	
Tramadol 200 mg/day	8 (50)	4 (21.05)	
Tramadol 300 mg/day	7 (43.75)	5 (26,3)	

VAS is a visual analogue scale. IP – intrapleural.

An important point of the study was the assessment of pain relief. All patients underwent analgesia with trimeperidine and tramadol, if necessary, after assessment of pain by VAS. The first group (n=16) after surgery in the ICU before extubation was additionally injected with bupivacaine through intrapleural catheter, with subsequent intubation per need. The results of the analysis of postoperative pain relief are presented in Table 6.

According to VAS, the intensity of pain after extubation was less in the first group and averaged four points (in the second group, the average score was six). Dynamically, pain scores according to VAS on the first two days were the same in both groups. In the first group, bupivacaine was administered twice in 75% (12) patients, i.e. before extubation and in dynamics after an average of 8 hours. In the remaining quarter of the first group, bupivacaine was not administered repeatedly. Postoperative analgesia with additional trimeperidine application was necessary for one patient in the former group (6.25%) and for fourteen patients from the latter group (73.7%). Pain relief with a single tramadol dose was required for one (6.25%) patient from the first group and ten (52.6%) patients from the second group. Double administration of tramadol during the day was observed in eight (50%) and four (21.05%) patients, while injection of tramadol three times per day was required in seven (43.5%) and five (26.3%) of patients from the former and latter groups accordingly. Significant difference (p = 0.012) in the frequency of prescribed tramadol was observed.

Discussion

Pain after cardiothoracic surgery is an indication for multimodal analgesia. There are different methods of regional analgesia and anesthesia, which can reduce surgical stress and postoperative pain [2, 8]. Analyzing existing literature, there are very few studies related to intrapleural blockade during MICS on a beating heart. In our study, we used the method of an intrapleural analgesia. Bupivacaine was administered as the local anesthetic for pain relief due to its long duration of action, and the dosage was chosen after a review of the literature describing the use of 0.25% bupivacaine as a sufficient dose.

The literature describes the effectiveness of intrapleural blockade with 8 ml of 0.25% bupivacaine in contrast to thoracic epidural anesthesia in MIDCAB [22] according to VAS values, but in this study a lower dose was used, and it required repeated administration of IPA over time. In our study, the use of bupivacaine at a dose of 20 ml of 0.25% showed an improvement in oxygenation and ventilation on the first day after surgery according to EIT findings and ABGs parameters. Although one lung ventilation technique by itself poses higher risk for the atelectasis formation, possible atelectasis formation is expected to be equally distributed in both groups since one lung ventilation was performed in both groups. The only difference is the administration of intrapleural analgesia resulting in different density measurements by EIT. Thus, application of IPA revealed a more adequate distribution of the volume of ventilation on the side of surgical intervention and less tachycardia compared to the control group.

Cogan J et al. from the Montreal Heart Institute reports the effectiveness of intrapleural administration of bupivacaine in drainage tubes inserted into the pleural space which they widely use. But this technique requires application of more careful aseptic techniques with each injection. The intrapleural catheterization we use is established before surgery and the rules of care are the same as for central venous catheters, and there is no risk of depressurization of pleural drains [23].

With intrapleural analgesia, opioid analgesics were used significantly less, confirming the data of other authors [3, 4, 5, 22, 23]. Comparatively, the second group consumed more trimeperidine. But fifty per cent of patients in the first group required repeated administration of tramadol. Significant differences in VAS were not observed between the groups. Recently, several authors report the benefit of opioid-free analgesia in cardiac surgery patients [24]. Also, Carlos et al supports the effectiveness and decreased need for opioids in intercostal block compared with other methods, but this technique requires additional tools such as an ultrasound device for navigating intercostal block [25].

Halide Ogus et al found benefits of intrapleural analgesia over placebo in patients with COPD after CABG sternotomy. Intrapleural analgesia improved lung function parameters, provided a good level of pain relief, and allowed rapid mobilization which led to decrease in postoperative respiratory complications [26]. According to the results of our study, with intrapleural blockade, there are better indicators of oxygenation in arterial blood gas parameters and more adequate distribution of tidal volume in the lung fields according to EIT.

Conclusion

IPA can be used as one of the effective methods for postoperative pain management. IPA promotes less opioid use, and there has been an improvement in respiration with a reduction in postoperative pain. IPA is safe and one of the effective methods of postoperative analgesia in MIDCAB.

References

1. Ali JM, PhD. Abu-Omar Ya, Minimally invasive cardiac surgery – a Fad or the Future? *J Thorac Dis*. 2021 Mar; 13(3): 1882–1885. https://doi.org/10.21037/jtd-2020-mics-12.

2. Marin-Cuartas M, et al. Minimally invasive coronary artery surgery: Robotic and nonrobotic minimally invasive direct coronary artery bypass techniques. *JTCVS Techniques,* 2021; 10: 170–177. https://doi.org/10.1016/j.xjtc.2021.10.008.

3. White A, Patvardhan Ch, Falter F. Anesthesia for minimally invasive cardiac surgery. *J Thorac Dis*. 2021; 13(3): 1886–1898. https://doi.org/10.21037/jtd-20-1804.

4. Sherazee EA, Chen SA, Li D, Frank P, Kiaii B. Pain Management Strategies for Minimally Invasive Cardiothoracic Surgery. *Innovations (Phila)*. 2022; 17(3): 167-176. https://doi.org/10.1177/15569845221091779.

5. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg*. 2019; 55: 91–115. https://doi.org/10.1093/ejcts/ezy301.

6. Wick EC, Grant MC, and Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. *JAMA Surg*. 2017; 152: 691–697. https://doi.org/10.1001/jamasurg.2017.0898.

7. Piccioni F, Segat M, Falini S, et al. Enhanced recovery pathways in thoracic surgery from Italian VATS Group: perioperative analgesia protocols. *J Thorac Dis*. 2018; 10: 555–563. https://doi.org/10.21037/jtd.2017.12.86.

8. Zaouter C, Oses P, Assatourian S, et al. Reduced length of hospital stay for cardiac surgery-implementing an optimized perioperative pathway: prospective evaluation of an Enhanced Recovery After Surgery program designed for mini-invasive aortic valve replacement. *J Cardiothorac Vasc Anesth*. 2019; 33: 3010–3019. https://doi.org/10.1053/j.jvca.2019.05.006.

9. Bachmann-Mennenga B, et al. Intercostal nerve block, interpleural analgesia, thoracic epidural block or systemic opioid application for pain relief after thoracotomy? *European Journal of Cardio-Thoracic Surgery*. 1993; 7(1): 12–18. https://doi.org/10.1016/1010-7940(93)90141-W.

10. Chou R, et al. (2016) 'Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council', *The Journal of Pain*. 2016; 17(2): 131–157. https://doi.org/10.1016/j.jpain.2015.12.008.

11. Demmy TL, et al. Chest tube–delivered bupivacaine improves pain and decreases opioid use after thoracoscopy. *The Annals of Thoracic Surgery*. 2009; 87(4): 1040–1047. https://doi.org/10.1016/j.athoracsur.2008.12.099.

12. Joshi GP, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. *Anesthesia & Analgesia*. 2008; 107(3): 1026–1040. https://doi.org/10.1213/01.ane.0000333274.63501.ff.

13. Wedad M, Zaki MK, Haleem M. The effect of addition of wound infiltration with local anesthetics to interpleural block on post-thoracotomy pain, pulmonary function and stress response in comparison to thoracic epidural and paravertebral block. *Egypt J Anaesth* 2004; 20: 67–72.

14. Brockmeier V, et al. Interpleural or thoracic epidural analgesia for pain after thoracotomy. A double-blind study. *Acta Anaesthesiologica Scandinavica*. 1994; 38(4): 317–321. https://doi.org/10.1001/jamanetworkopen.2021.33394.

15. Karmakar MK and Ho AM-H. Acute pain management of patients with multiple fractured ribs. *The Journal of Trauma: Injury, Infection, and Critical Care*. 2003; 54(3): 615–625. https://doi.org/10.1097/01.TA.0000053197.40145.62.

16. Shinohara K, et al. Interpleural block for patients with multiple rib fractures: Comparison with epidural block. *The Journal of Emergency Medicine*. 1994; 12(4): 441–446. https://doi.org/10.1016/0736-4679(94)90337-9.

17. Luchette FA, et al. Prospective evaluation of epidural versus intrapleural catheters for analgesia in chest wall trauma. *The Journal of Trauma: Injury, Infection, and Critical Care*. 1994; 36(6): 865–870. https://doi.org/10.1097/00005373-199406000-00018.

18. Short K, Scheeres D, Mlakar J, Dean R. Evaluation of intrapleural analgesia in the management of blunt traumatic chest wall pain: a clinical trial. *Am Surg*. 1996; 62: 488–493.

19. Yu S, et al. Regional analgesia for minimally invasive cardiac surgery. Journal of Cardiac Surgery. 2019; 34(11), pp. 1289–1296. https://doi.org/10.1111/jocs.14177.

20. Ishikawa Y, et al. Intrapleural analgesia using Ropivacaine for postoperative pain relief after minimally invasive thoracoscopic surgery. *Annals of Thoracic and Cardiovascular Surgery*. 2012; 18(5): 429–433. https://doi.org/10.5761/atcs.oa.11.01854.

21. Dravid RM, Paul RE. Interpleural block – part 1. *Anesthesia*. 2007; 62(10): 1039-1049. https://doi.org/10.1111/j.1365-2044.2007.05183.

22. Mehta Ya. A comparative evaluation of intrapleural and thoracic epidural analgesia for postoperative pain relief after minimally invasive direct coronary artery bypass surgery. *Journal of Cardiothoracic and Vascular Anesthesia*. 1998; 12(2): 162-165. https://doi.org/10.1016/S1053-0770(98)90324-X.

23. Cogan J, André M. Injection of Bupivacaine into the Pleural and Mediastinal Drains: A Novel Approach for Decreasing Incident Pain After Cardiac Surgery – Montreal Heart Institute Experience. *Journal of Pain Research*. 2020; 13: 3409–3413. https://doi.org/10.2147/JPR.S279071.

24. Carlos E, et al. Assessment of Intercostal Nerve Block Analgesia for Thoracic Surgery A Systematic Review and Meta-analysis. *JAMA Network Open*. 2021; 4(11): e2133394. https://doi.org/10.1001/jamanetworkopen.2021.33394.

25. Landry E, et al. A Successful Opioid-Free Anesthetic in a Patient Undergoing Cardiac Surgery. *Journal of Cardiothoracic and Vascular Anesthesia*. 2019; 33(9): 2517-2520. https://doi.org/10.1053/j.jvca.2018.11.040.

26. Ogus H, et al. Effects of Intrapleural Analgesia on Pulmonary Function and Postoperative Pain in Patients With Chronic Obstructive Pulmonary Disease Undergoing Coronary Artery Bypass Graft Surgery. *Journal of Cardiothoracic and Vascular Anesthesia*. 2007; 21 (6): 816-819. https://doi.org/10.1053/j.jvca.2007.05.002.

Perceptions regarding autism spectrum disorders among population of Kazakhstan

Laura Kozhageldiyeva[1,2], Lyazzat Kosherbayeva[1,2], Zhanara Sabyrdilda[1,2], Assem Kaukenova[1], Sandugash Kurmanalina[1]

[1]Department of Science, SDU University, Kaskelen, Kazakhstan
[2]Department of health policy and management, School of Public Health, Kazakh National Medical University, Almaty, Kazakhstan

Corresponding author:
Laura Kozhageldiyeva.
E-mail: smstrainerkz@gmail.com;
ORCID: 0000-0003-0553-8988.

Abstract

Introduction. The increase in the number of patients with autism spectrum disorders around the world leads to the need for public of its symptoms, for early detection and comprehensive care. The increase of public health literacy allows to improve and ease perception of population, families with ASD people. The purpose of the study is to understand the population's perceptions of ASD in Kazakhstan.

Methods. A developed questionnaire in Kazakh and Russian languages was contributed among population of all regions of Kazakhstan during the first half of 2023. Survey provided using the online Google platform. 410 respondents attended the survey. Statistical analyses were performed using the SPSS13.

Results. The questionnaire was developed using simulation situations, where the respondent chose the most suitable answer. It was found that the willingness to fully accept a child with ASD is not at a high level, regardless of residence (urban, rural). Fear and curiosity were noted as a high response among the population when simulating the situation of a child with ASD on the street. Despite a high level of willingness to help families, respondents identified gaps in knowledge or methods of helping children with ASD. It is known that children with ASD, depending on the severity of the condition, can study at school along with neurotypical children. There was a reluctance among the population to attend schools with neurotypical children, develop friendships, and even live in their neighborhoods.

Conclusion

Changes in legislative acts, the development of Roadmaps for children with disabilities are only the tip of the iceberg in the formation of tolerance for people with disabilities. The creation of a host society should be a key factor in the organizations involved in shaping public opinion. Considering that this issue concerns all structures and areas, not only social programs, it is necessary to develop activities for various segments of the population on awareness and training in helping families with ASD.

Keywords: autism spectrum disorders, population, perception, Kazakhstan.

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects communication skills, manifests itself in repetitive movements or behavior [1]. According to a systematic review, the median prevalence of ASD is 100/10,000 populations [2], usually males in comparison to female 3:1 [3]. ASD is influenced by both genetic and environmental factors that lead to impaired brain development [4].

The difficulty in providing timely assistance is the late diagnosis. Often parents or caregivers notice speech delay or other symptoms of ASD at a later age, thus the average age of ASD diagnosis is 3-4 years. In this regard, some countries have introduced screening programs, such as The American Academy of Pediatrics (AAP) guidelines recommend autism specific screening at 18 months and again at 24 or 30 months. There is no gold standard for the treatment of ASD, so the main method is to focus on individual approach to providing care by multidisciplinary team. The main assistance is provided by the health, social support and educational services. However, the main therapy includes behavioral and environmental changes [5].

Low awareness of ASD has been identified in a number of studies [6, 7, 8], including developed and developing countries. Subsequently, this fact leads to misconceptions about the causes of ASD, which leads to stigma and negative impact on families affected by ASD [9]. In addition, parents or caregivers with ASD are prone to psychological disorders, manifested in the form of anxiety or stress [10, 11, 12].

In Kazakhstan last reforms in ASD included changes in different areas and levels of care provision. Thus, screening tools such as M-CHART/R-F for primary care and ADOS and ADI-R for Mental health units and centers were introduced. These changes were reflected in legal acts and developed clinical protocols in health in Kazakhstan. The review of legal acts of social support showed that ASD was included in disability list in 2015 and parents/caregivers are provided by financial aid. Day-care and full-time centers that belong to social support system are providing care to families with children with disabilities based on revised Standards. Being an integral part of care for children with autism Educational system has undergone changes as well. M-CHART/R-F was included in Psychological medical pedagogical committees and screening age was changed from 3 to 0. Network of rehabilitation centers and offices of psychological and pedagogical correction as well as inclusivity in primary and secondary schools are also the part of reforms in the last 5 years. Moreover, Project financed by Ministry of Science include the development of web-site platform for different type of stakeholders, which will allow them to obtain the necessary information regarding regulations, guidelines for child care and in general about the course of ASD and other. Thus, the purpose of the study is to understand the population's perceptions of ASD in Kazakhstan.

Methods

Data collection: Based on literature review [6, 8, 13], a questionnaire was developed in Kazakh and Russian languages, which included the demographic part, as well as questions on the perception of the population about ASD (Appendix 1). The survey was conducted in the first half of 2023 using the online Google platform. The survey was sent out through primary health care workers to families with neurotypical children through WhatsApp messages by the research group of this Project. Respondents participated in the survey voluntarily,

anonymously, and had the opportunity to leave the survey any time. The survey covered all the regions of Kazakhstan.

Inclusion criteria: voluntary consent of the patient to participate in the study, age of 18 years and older, resident of Kazakhstan, patient of any gender.

Exclusion criteria: completed or partial refusal to participate in the questionnaire, age under 18 years.

Data analysis: The representative group consisted of 374 people. However, taking into account 20% of possible missing data, it was planned to include 449 respondents. As a result, after removing incomplete answers, the results of 410 respondents were included in the analysis.

The sample size of this study was based on the cross-sectional study design formula, so the sample size calculation formula is:

$$n = deff \times \frac{N \cdot \hat{p}(1-\hat{p})}{(N-1)\frac{d^2}{z_\propto^2} + \hat{p}(1-\hat{p})}$$

Where
n= sample size
N= 19 832 737 (population size)
Deff=1 (design effect-random sampling)
$\hat{p}$ =0,5 (the estimated proportion – such studies have not been conducted in Kazakhstan, so we chose 50% of the population know about ASD)
d= 0.05 (desired absolute precision or absolute level of precision)
$z_\propto$ =1,96 (z-score)

We compare data between urban and rural residents to understand the preference activity based on regional perspectives. Statistical analyses were performed using the SPSS13, where a descriptive analysis was performed and variables were tested using a chi-square test. Statistical significance was determined by p-values <0.05.

Results

The survey involved 410 participants, in which female respondents presented more in urban areas, aged 25-44 years. Demographics characteristics of the participants are given in the Table 1.

| Table 1 | Demographics characteristics of the participants |

Characteristics		Total (n=410; %)	Urban (n=310; %)	Rural (n=100; %)
Gender	Male	114(27,8%)	64(20,6%)	50(50,0%)
	Female	296(72,2%)	246(79,4%)	50(50,0%)
Age group	18-24	52(12,7%)	44(14,2%)	8(8,0%)
	25-34	123(30,0%)	103(33,2%)	20(20,0%)
	35-44	126(30,7%)	101(32,6%)	25(25,0%)
	45-54	62(15,1%)	41(13,2%)	21(21,0%)
	55-64	26(6,3%)	14(4,5%)	12(12,0%)
	65-74	16(3,9%)	5(1,6%)	11(11,0%)
	75 years and older	5(1,2%)	2(0,6%)	3(3,0%)
Level of education	High	256(62,4%)	217(70,0%)	39(39,0%)
	College	89(21,7%)	62(20,0%)	27(27,0%)
	School	48(11,7%)	20(6,5%)	28(28,0%)
	Unfinished school	17(4,1%)	11(3,5%)	6(6,0%)
Occupation	Employed (full-time, part-time, self-employed	251(61,2%)	204(65,8%)	47(47,0%)
	Unemployed	32(7,8%)	22(7,1%)	10(10,0%)
	Pensioner	32(7,8%)	12(3,9%)	20(20,0%)
	Student	39(9,5%)	27(8,7%)	12(12,0%)
	Housewife	56(13,7%)	45(14,5%)	11(11,0%)

Slightly more than a third of the population participating in the survey noted that there were no acquaintances with ASD, while the rest said that they knew less than 5 people with ASD. About 13.2% of the respondents noted their acquaintance with more than 5 people with ASD, most likely, these are the respondents, who are in the group of parents of children with ASD, and 12.7% of the survey participants indicated that they were not sure. There no significant differences between urban and rural respondents (p=0,702, Figure 1).
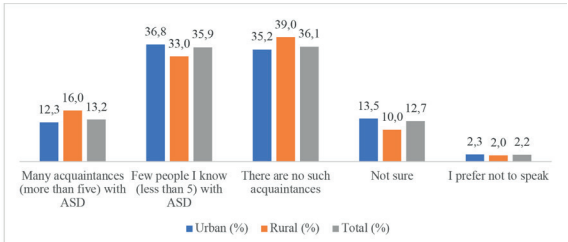

Figure 1 - The number of people with ASD in the respondent's environment

In order to understand the perception of people with ASD, a task was given, with questions where the respondent had to present the situation and give probable reflection. Tasks were adapted from the life of an autistic children. For instance, when the child is with his mother somewhere on the street or in a store, and suddenly there is a noise, to which the child begins to react through plugging ears, falling to the floor, and other similar types of behavior. In this situation, the greater number of rural respondents compared with urban noted that they would extremely likely feel frightened (p=0,004), curious (p=0,001), threat (p<0,001) and very likely embarrassed (p=0,003), Irritability (p=0,002), Surprise (p=0,002, Table 2).

The largest number of respondents in both regions noted the probability that the child is special (p<0.001). However, more rural residents note that the child looks dangerous than urban (40.3%) (p<0.001). On the positive side, the population believes that the child may be upset and ready to help (p=0,131), and ready to offer help to mother and/or child (p=0.001). However, the most respondents of both regions would have no idea what to do (p<0.001), which means they do not know how can they help. Almost twice as many rural as urban residents believe that the child is like most other children of that age (p=0.003) and that the child is likely to be spoiled and his/her parent allows the child to get away with bad behavior (p= 0.001, Table 1). If the respondents would had been told that in the presented situation the child is with autism, then 41.2% would not change their attitude to the situation, while a third of 29.8% were not sure what their behavior would be and 21.5% would change their views on this situation (Table 2).

If a close friend's child is diagnosed with autism 76.1% will feel anxious, only 31.7%, curious to know more (p=0.066) and ready to help for him 66.8%. Pity for the child (p=0.007) and would feel sorry for a friend (p=0.002) will feel half of the respondents (Table 2). Rural residents note great concern if a

Table 2	Respondents' perception with ASD child situation.				
Questions		Total (n=410,%)	Urban (n=310,%)	Rural (n=100,%)	p-value
Frightened	Extremely likely	149(36,3%)	99(31,9%)	50(50,0%)	0,004
	Very likely	86(21,0%)	65(21,0%)	21(21,0%)	
	More likely	71(17,3%)	57(18,4%)	14(14,0%)	
	Hardly	79(19,3%)	71(22,9%)	8(8,0%)	
	Not sure	19(4,6%)	13(4,2%)	6(6,0%)	
	I prefer not to speak	6(1,5%)	5(1,6%)	1(1,0%)	
Embarrassment	Extremely likely	80(19,5%)	56(18,1%)	24(24,0%)	0,003
	Very likely	114(27,8%)	76(24,5%)	38(38,0%)	
	More likely	70(17,1%)	57(18,4%)	13(13,0%)	
	Hardly	108(26,3%)	91(29,4%)	17(17,0%)	
	Not sure	31(7,6%)	27(8,7%)	4(4,0%)	
	I prefer not to speak	7(1,7%)	3(1,0%)	4(4,0%)	
Curiosity	Extremely likely	130(31,7%)	83(26,8%)	47(47,0%)	0,001
	Very likely	55(13,4%)	38(12,3%)	17(17,0%)	
	More likely	83(20,2%)	68(21,9%)	15(15,0%)	
	Hardly	96(23,4%)	84(27,1%)	12(12,0%)	
	Not sure	38(9,3%)	31(10,0%)	7(7,0%)	
	I prefer not to speak	8(2,0%)	6(1,9%)	2(2,0%)	
Irritability	Extremely likely	101(24,6%)	77(24,8%)	24(24,0%)	0,002
	Very likely	105(25,6%)	65(21,0%)	40(40,0%)	
	More likely	49(12,0%)	36(11,6%)	13(13,0%)	
	Hardly	105(25,6%)	91(29,4%)	14(14,0%)	
	Not sure	42(10,2%)	35(11,3%)	7(7,0%)	
	I prefer not to speak	8(2,0%)	6(1,9%)	2(2,0%)	
Surprise	Extremely likely	86(21,0%)	62(20,0%)	24(24,0%)	0,002
	Very likely	114(27,8%)	74(23,9%)	40(40,0%)	
	More likely	69(16,8%)	54(17,4%)	15(15,0%)	
	Hardly	95(23,2%)	84(27,1%)	11(11,0%)	
	Not sure	36(8,8%)	30(9,7%)	6(6,0%)	
	I prefer not to speak	10(2,4%)	6(1,9%)	4(4,0%)	
Threat	Extremely likely	134(32,7%)	86(27,7%)	48(48,0%)	<0,001
	Very likely	53(12,9%)	39(12,6%)	14(14,0%)	
	More likely	57(13,9%)	41(13,2%)	16(16,0%)	
	Hardly	118(28,8%)	106(34,2%)	12(12,0%)	
	Not sure	34(8,3%)	29(9,4%)	5(5,0%)	
	I prefer not to speak	14(3,4%)	9(2,9%)	5(5,0%)	
What do you think about the child					
Child seems to be a special	Extremely likely	124(30,2%)	77(24,8%)	47(47,0%)	<0,001
	Very likely	157(38,3%)	119(38,4%)	38(38,0%)	
	More likely	97(23,7%)	85(27,4%)	12(12,0%)	
	Hardly	15(3,7%)	15(4,8%)		
	Not sure	12(2,9%)	10(3,2%)	2(2,0%)	
	I prefer not to speak	5(1,2%)	4(1,3%)	1(1,0%)	
Child looks dangerous	Extremely likely	100(24,4%)	67(21,6%)	33(33,0%)	<0,001
	Very likely	83(20,2%)	46(14,8%)	37(37,0%)	
	More likely	48(11,7%)	40(12,9%)	8(8,0%)	
	Hardly	137(33,4%)	125(40,3%)	12(12,0%)	
	Not sure	33(8,0%)	25(8,1%)	8(8,0%)	
	I prefer not to speak	9(2,2%)	7(2,3%)	2(2,0%)	
The child is upset and would like to help	Extremely likely	99(24,1%)	67(21,6%)	32(32,0%)	0,131
	Very likely	114(27,8%)	82(26,5%)	32(32,0%)	
	More likely	130(31,7%)	106(34,2%)	24(24,0%)	
	Hardly	34(8,3%)	27(8,7%)	7(7,0%)	
	Not sure	27(6,6%)	23(7,4%)	4(4,0%)	
	I prefer not to speak	6(1,5%)	5(1,6%)	1(1,0%)	
The child is similar to most other children of this age	Extremely likely	85(20,7%)	54(17,4%)	31(31,0%)	0,003
	Very likely	114(27,8%)	79(25,5%)	35(35,0%)	
	More likely	87(21,2%)	71(22,9%)	16(16,0%)	
	Hardly	80(19,5%)	69(22,3%)	11(11,0%)	
	Not sure	36(8,8%)	31(10,0%)	5(5,0%)	
	I prefer not to speak	8(2,0%)	6(1,9%)	2(2,0%)	
The child is spoiled and his/her parent allows the child to get away the punishment with bad behavior	Extremely likely	118(28,8%)	84(27,1%)	34(34,0%)	0,001
	Very likely	79(19,3%)	49(15,8%)	30(30,0%)	
	More likely	56(13,7%)	42(13,5%)	14(14,0%)	
	Hardly	100(24,4%)	89(28,7%)	11(11,0%)	
	Not sure	46(11,2%)	38(12,3%)	8(8,0%)	
	I prefer not to speak	11(2,7%)	8(2,6%)	3(3,0%)	
I have no idea what to do	Extremely likely	87(21,2%)	54(17,4%)	33(33,0%)	<0,001
	Very likely	109(26,6%)	73(23,5%)	36(36,0%)	
	More likely	97(23,7%)	82(26,5%)	15(15,0%)	
	Hardly	47(11,5%)	43(13,9%)	4(4,0%)	
	Not sure	40(9,8%)	34(11,0%)	6(6,0%)	
	I prefer not to speak	30(7,3%)	24(7,7%)	6(6,0%)	
Offer help to mother and/or child	Extremely likely	84(20,5%)	55(17,7%)	29(29,0%)	0,001
	Very likely	119(29,0%)	80(25,8%)	39(39,0%)	
	More likely	133(32,4%)	110(35,5%)	23(23,0%)	
	Hardly	41(10,0%)	38(12,3%)	3(3,0%)	
	Not sure	28(6,8%)	24(7,7%)	4(4,0%)	
	I prefer not to speak	5(1,2%)	3(1,0%)	2(2,0%)	
After this situation, if the respondent is informed that the child had autism, then the probability of changing the initial reaction to the situation	Yes	88(21,5%)	75(24,2%)	13(13,0%)	0,001
	No	169(41,2%)	136(43,9%)	33(33,0%)	
	Not sure	122(29,8%)	82(26,5%)	40(40,0%)	
	Prefer not to say	31(7,6%)	17(5,5%)	14(14,0%)	

child with autism lives in the neighborhood (74.0%), and if a child with autism studies along with neurotypical children 68.0% (p<0.001), as well as if a child becomes friends with an autistic child 73.0 %, and be his best friend 66,0% (Table 3).

Table 3	Respondents reflection with ASD child			
If a close friend's child is diagnosed with autism, how would you react?		Total (n=410,%)	Urban (n=310,%)	Rural (n=100,%)	P value
Worry about the child's future	Yes	312(76,1%)	244(78,7%)	68(68,0%)	
	No	54(13,2%)	28(9,0%)	26(26,0%)	<0,001
	not sure	44(10,7%)	38(12,3%)	6(6,0%)	
Curious to know more	Yes	130(31,7%)	96(31,0%)	34(34,0%)	
	No	170(41,5%)	122(39,4%)	48(48,0%)	0,066
	not sure	110(26,8%)	92(29,7%)	18(18,0%)	
Indifferent	Yes	82(20,0%)	52(16,8%)	30(30,0%)	
	No	229(55,9%)	176(56,8%)	53(53,0%)	0,008
	not sure	99(24,1%)	82(26,5%)	17(17,0%)	
Pity for the child	Yes	199(48,5%)	148(47,7%)	51(51,0%)	
	No	127(31,0%)	88(28,4%)	39(39,0%)	0,007
	not sure	84(20,5%)	74(23,9%)	10(10,0%)	
Would feel sorry for a friend (p=0.002)	Yes	213(52,0%)	165(53,2%)	48(48,0%)	
	No	113(27,6%)	73(23,5%)	40(40,0%)	0,002
	not sure	84(20,5%)	72(23,2%)	12(12,0%)	
Wouldn't know what to do (p=0.015)	Yes	175(42,7%)	124(40,0%)	51(51,0%)	
	No	124(30,2%)	91(29,4%)	33(33,0%)	0,015
	not sure	111(27,1%)	95(30,6%)	16(16,0%)	
Embarrassment (p=0.023)	Yes	135(32,9%)	93(30,0%)	42(42,0%)	
	No	158(38,5%)	119(38,4%)	39(39,0%)	0,023
	not sure	117(28,5%)	98(31,6%)	19(19,0%)	
Proud that my friend is looking for a diagnosis (p<0.001)	Yes	199(48,5%)	143(46,1%)	56(56,0%)	
	No	110(26,8%)	76(24,5%)	34(34,0%)	<0,001
	not sure	101(24,6%)	91(29,4%)	10(10,0%)	
Ask how I can help them	Yes	274(66,8%)	221(71,3%)	53(53,0%)	
	No	84(20,5%)	51(16,5%)	33(33,0%)	<0,001
	not sure	52(12,7%)	38(12,3%)	14(14,0%)	
The family, in which the autistic child was born, moved to a neighboring house	Very concerned	83(20,2%)	48(15,5%)	35(35,0%)	
	Concerned	111(27,1%)	72(23,2%)	39(39,0%)	
	Indifference	113(27,6%)	100(32,3%)	13(13,0%)	
	Very indifferent	31(7,6%)	27(8,7%)	4(4,0%)	<0,001
	Not sure	53(12,9%)	47(15,2%)	6(6,0%)	
	I prefer not to speak	19(4,6%)	16(5,2%)	3(3,0%)	
The autistic child was in class with a child from your family	Very concerned	37(9,0%)	11(3,5%)	26(26,0%)	
	Concerned	151(36,8%)	109(35,2%)	42(42,0%)	
	Indifference	107(26,1%)	92(29,7%)	15(15,0%)	
	Very indifferent	57(13,9%)	47(15,2%)	10(10,0%)	<0,001
	Not sure	42(10,2%)	38(12,3%)	4(4,0%)	
	I prefer not to speak	16(3,9%)	13(4,2%)	3(3,0%)	
A child in your family befriended a autistic child	Very concerned	63(15,4%)	38(12,3%)	25(25,0%)	
	Concerned	135(32,9%)	87(28,1%)	48(48,0%)	
	Indifference	109(26,6%)	95(30,6%)	14(14,0%)	
	Very indifferent	46(11,2%)	40(12,9%)	6(6,0%)	<0,001
	Not sure	39(9,5%)	35(11,3%)	4(4,0%)	
	I prefer not to speak	18(4,4%)	15(4,8%)	3(3,0%)	
Your child's new best friend was autistic	Very concerned	49(12,0%)	22(7,1%)	27(27,0%)	
	Concerned	143(34,9%)	102(32,9%)	41(41,0%)	
	Indifference	112(27,3%)	95(30,6%)	17(17,0%)	
	Very indifferent	45(11,0%)	39(12,6%)	6(6,0%)	<0,001
	Not sure	42(10,2%)	36(11,6%)	6(6,0%)	
	I prefer not to speak	19(4,6%)	16(5,2%)	3(3,0%)	

Discussion

Based on the answers of the respondents, it can be seen that many of them have heard about ASD and many of them are familiar with ASD. Many respondents, in particular in rural areas, note that the behavior of a child with autism can be dangerous. This result is consistent with other similar studies [13, 14, 15]. Despite the fact that many respondents are ready to help parents of children with ASD, there is low awareness of how to do this. The low awareness of population about ASD and their needs in education and other activities indicated in researches provided by Anwar et al., Alsehemi et al., Wei et al. [6, 8, 16]. In addition to the population, limited knowledge and self-efficacy in working with autistic people is noted among health care and social service professionals [17].

Children with ASD, depending on the severity of the condition, can study at school along with neurotypical children. The results of the study showed that parents prefer to send their children in a regular classroom, but the main factor is directed to the learning experience and skills of the teachers [18, 19]. In this regard, the early detection of children with ASD and their adaptation to society is important [20]. For example, Roula Choueiri et al. presented strategies for healthcare professionals to find culturally appropriate ways to address family problems associated with ASD and ensure early identification of children with ASD [21]. The reforms carried out in the educational sector in Kazakhstan allow children with ASD to study in inclusive classes. The introduction of teacher-assistant and psychological-pedagogical support service supposes the improvement of the educational skills of children with ASD in schools. The above-mentioned events are the steps to develop the inclusive society. However, our results show that the society is not sufficiently prepared for the contact of neurotypical children with children with ASD, especially in rural areas.

For the effective implementation of programs (health, education and social services) in providing complex support to children with ASD in the country, it is necessary to take measures to improve public awareness of ASD, as well as their behavior in relation to the perception of families with children with ASD. According to the authors, educational activities can be provided through primary health care (by early symptoms of the disease for families of planning children), through educational organizations (at parent-teacher meetings of schools) and through local executive bodies.

In the world practice (The All Party Parliamentary Group on Autism report 2017) teachers and leaders are called to consider autism as a difference, not a deficit. Institutions are to conduct peer education and raise awareness by celebrating Autism Awareness Week and focus on embracing difference and see it in positive light, which increases public awareness and acceptance of children with ASD.

Conclusion

Families with children with ASD go through different steps when receiving assistance from various agencies, public and private. Society is an integral part of the life of children with ASD, and early socialization is the key to their successful immersion in society. The

ASD perception and level of understanding of the population is a key factor in the readiness to accept people with ASD, which should be an indicator of the activities of structures that form public opinion. It is necessary to consider the inclusion of information and educational activities about autism at the level of local executive bodies, continuous monitoring of the level of acceptance by society of persons with disabilities. Various channels for shaping public opinion such as the use of the media, social media, direct learning and campaigns need to be included in the action plans of the entities.

Appendix 1.

Questionnaire to population perception of children with ASD
Dear respondent!

We invite you to take part in the study on "Integration of children with autism spectrum disorder into the socio-educational environment based on comprehensive support: challenges and advantages". The purpose of our survey is to examine public awareness of autism spectrum disorders. The project is carried out by the research group of Institution "SDU University". Participation in the survey will take approximately 30 minutes. This survey is devoted to study the public opinion. There are no right or wrong answers. Participation in the survey is completely voluntary. The study was approved by the local ethics committee.

If you would like more information about the project, please contact Lead Researcher – Lyazzat through +7 705 120 4652. Your responses will be de-identified and stored under data protection requirements and will not be disclosed to other organizations for marketing or research purposes. Responses from everyone participating in the survey will be combined for analysis. Consent form: click the "Agree" button to confirm: your voluntary participation and you are over 18 years old.

You can end your participation at any stage of the survey

Please, choose the appropriate answer:
1. Sex
a) Male
b) Female
2. Your age
a) 18-24
b) 25-34
c) 35-44
d) 45-54
e) 55-64
f) 65-74
g) 75 age and above
3. Choose your region
a) Astana city
b) Almaty city
c) Akmola oblast
d) Aktobe oblast
e) Almaty oblast
f) Atyrau oblast
g) West-Kazakhstan oblast
h) Zhambyl oblast
i) Karaganda oblast
j) Kostanai oblast
k) Kyzylorda oblast
l) Mangystau oblast
m) Turkestan oblast
n) Pavlodar oblast
o) North-Kazakhstan oblast
p) West-Kazakhstan oblast
q) Shymkent city
r) Abai oblast
s) Zhetysu oblast
t) Ulytau oblast
4. Residence type:
a) City
b) Rayon level
5. Degree of education
a) University degree
b) Secondary-specialty degree (college, etc.)
c) High school (grade 11 completed)
d) Secondary school (grade 9 completed)
6. Your activities
a) Employed (full-time, part-time, self-employed)
b) Unemployed
c) Retired
d) Student
e) Housewife
f) Other (please, specify) _____

7. Do you know anyone who diagnosed with autism (or autism spectrum disorder)?
a. Me/myself
b. Close relative
c. Another family member
d. Friend
e. Familiar one
f. Colleague
g. Somebody else _____
h. No such acquaintances
i. Prefer not to speak

8. Do you think there are many children or adults with autism (or autism spectrum disorder), would you say that you have...?
a. Many people I know (more than five) with autism or autism spectrum disorder
b. Few acquaintances (less than 5) with autism or autism spectrum disorder
c. No such acquaintances
d. Not sure
e. Prefer not to speak

9. Now we will ask you to imagine yourself in the following situation

You are shopping for a new TV at a hardware store and notice at the end of the corridor a mother with a boy/girl who is around 12 years old. The boy/girl seems slightly worried, and <his/her> mother continues to speak to <him/her> in a soothing tone. Suddenly, a demonstration of a vacuum cleaner begins near the mother and child, and <boy/girl> reacts to the noise by covering <his/her> ears, falling to the floor, squealing uncontrollably and rocking back and forth. The salesman rushes to the mother and child to ask what's wrong, which further upsets <boy/girl> and <he/she> starts hitting <himself>.

9.1 People may experience different thoughts and emotions when they find themselves in such a situation. If you were in this situation, how likely is it that you would feel...?

	Extremely likely	Very likely	More likely	Hardly	Not sure	I prefer not to talk
Frightened						
Confusion						
Curiosity						
Irritation						
Sympathy						
Astonishment						
Threat						

9.2 You are still thinking about the situation...How likely is it that you think...?

	Extremely likely	Very likely	More likely	Hardly	Not sure	I prefer not to talk
<boy/girl> seems like an interesting child						
<boy/girl> looks dangerous						
<boy/girl> is upset and I would like to help						
<boy/girl> looks like most other boys [girls] this age						
boy/girl> is spoiled and his/her parent allows the child to get away with bad behavior						
I have no idea what to do						

9.3 You are still thinking about the situation...How likely is it that you think...?

	Extremely likely	Very likely	More likely	Hardly	Not sure	I prefer not to talk
Smile mother						
Comment on another customer's behavior						
Offer help to mother and/or child						
Leave the store quickly						
Focus on studying the assortment of televisions on display and pretend not to notice						
Invite mom to bring water						
Complain about the store staff						

9.4. Why do you think <boy/girl> behaved this way?

	Extremely likely	Very likely	More likely	Hardly	Not sure	I prefer not to talk
<he/she> acted like most other <boys/girls> of that age						
<He/She> has anxiety disorder						
<He/She> suffers from Attention Deficit Hyperactivity Disorder (ADHD)						
<He/she> suffers from obsessive-compulsive disorder (OCD)						
<He/She> has a mental retardation						
<He/She> has schizophrenia						
Not sure						
Prefer not to speak						

10. Imagine that a close friend's child is diagnosed with autism...Which of the following, if any, do you think BEST describes your initial reaction? If one of your close friend's children has already been diagnosed with autism, please think about what your initial reaction was when you were told about it.

	Yes	No	Not sure
Concern for the child's future			
Curious to know more			
Disinterest			
Pity for the child			
I would feel sorry for my friend			
Wouldn't know what to do			
Embarrassment			
Proud of my friend seeking a diagnosis			
Ask how I can help them			

11. If one of your colleagues has already been diagnosed with autism, please describe your initial reaction when you were told this

a. Disbelief

b. Anxiety

c. Try to learn more about autism

d. Ask them (i.e. a colleague) about autism

e. Avoid them

f. I expect that I will receive autism training in my workplace.

g. I'm proud of them

h. Ask how I can help them

i. Other (SPECIFY)

j. None of the above

k. Not sure

l. I prefer not to talk

12. And, thinking about an autistic child, would you be concerned or not concerned if...

	Very concerned	Concerned	Indifference	Very indifferent	Unsure	Prefer not to say
A family with an autistic child moved into a neighboring house						
The autistic child was in a class with a child from your family						
A child from your family has become friends with an autistic child						
Your child's new best friend was autistic						

Thank you for participation!

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders 2013. 5th ed. https://doi-org.ezproxy.frederick.edu/10.1176/appi.books.9780890425596.

2. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, Yusuf A, Shih A, Elsabbagh M. Global prevalence of autism: A systematic review update. *Autism Res*. 2022; 15(5): 778-790. https://doi.org/10.1002/aur.2696.

3. Loomes R, Hull L, Mandy WPL. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017; 56: 466-74. https://doi.org/10.1016/j.jaac.2017.03.013.

4. Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. *Transl Pediatr*. 2020; 9(1): 55-65. https://doi.org/10.21037/tp.2019.09.09.

5. Mughal S, Faizy RM, Saadabadi A. Autism Spectrum Disorder. [Updated 2022 Jul 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK525976/.

6. Alsehemi MA, Abousaadah MM, Sairafi RA, Jan MM. Public awareness of autism spectrum disorder. *Neurosciences (Riyadh)*. 2017; 22(3): 213-215. https://doi.org/10.17712/nsj.2017.3.20160525.

7. Chansa-Kabali T, Nyoni J, Mwanza H. Awareness and Knowledge Associated with Autism Spectrum Disorders Among University Students in Zambia. *J Autism Dev Disord*. 2019; 49(9): 3571-3581. https://doi.org/10.1007/s10803-019-04044-7.

8. Wei H, Li Y, Zhang Y, Luo J, Wang S, Dong Q, Tao Y, Gong L, Feng Y, Shi M, Cao Z, Liu Y, Chen L, Liu X, Dai Y, Qu L, Song Z, Chen J, Li T, Cheng Q. Awareness and knowledge of autism spectrum disorder in Western China: Promoting early identification and intervention. *Front Psychiatry*. 2022; 13: 970611. https://doi.org/10.3389/fpsyt.2022.970611.

9. Castillo A, Cohen SR, Miguel J, Warstadt MF. Short report: Perceptions of causes and common beliefs of autism spectrum disorder in the U.S. *Res. Autism Spectr. Disord*. 2020; 70. https://doi.org/10.1016/j.rasd.2019.101472.

10. Kosherbayeva L, Tolganbaeva K, Kurmanalina S, Kozhageldiyeva L. Psychological support for parents raising children with autism spectrum disorders. Nauka i Zdravookhranenie [Science & Healthcare]. 2023; 25(3): 214-222. https://doi.org/10.34689/SH.2023.25.3.028.

11. Lai WW, Goh TJ, Oei TP, Sung M. Coping and Well-Being in Parents of Children with Autism Spectrum Disorders (ASD). *J Autism Dev Disord*. 2015; 45(8): 2582-93. https://doi.org/10.1007/s10803-015-2430-9.

12. Keenan BM, Newman LK, Gray KM, Rinehart NJ. Parents of Children with ASD Experience More Psychological Distress, Parenting Stress, and Attachment-Related Anxiety. *J Autism Dev Disord*. 2016; 46(9): 2979-91. https://doi.org/10.1007/s10803-016-2836-z.

13. Jones SC, Akram M, Gordon CS, Murphy N, Sharkie F. Autism in Australia: Community Knowledge and Autistic People's Experiences. J Autism Dev Disord. 2021; 51(10): 3677-3689. https://doi.org/10.1007/s10803-020-04819-3.

14. Brewer N, Zoanetti J, Young RL. The influence of media suggestions about links between criminality and autism spectrum disorder. *Autism*. 2017; 21: 117–121. https://doi.org/10.1177/1362361316632097.

15. King C, Murphy G. A Systematic Review of People with Autism Spectrum Disorder and the Criminal Justice System. *Journal of Autism and Developmental Disorders*. 2014; 44: 2717–2733. https://doi.org/10.1007/s10803-014-2046-5.

16. Anwar MS, Tahir M, Nusrat K, Khan MR. Knowledge, Awareness, and Perceptions Regarding Autism Among Parents in Karachi, Pakistan. *Cureus*. 2018; 10(9): e3299. https://doi.org/10.7759/cureus.3299.

17. Corden K, Brewer R, Cage E. A Systematic Review of Healthcare Professionals' Knowledge, Self-Efficacy and Attitudes Towards Working with Autistic People. *Rev J Autism Dev Disord*. 2022; 9: 386–399. https://doi.org/10.1007/s40489-021-00263-w.

18. Carter M, Stephenson J, Clark T, Costley D, Martin J, Williams K, et al. Perspectives on regular and support class placement and factors that contribute to success of inclusion for children with ASD. *Journal of International Special Needs Education*. 2014; 17(2): 60–69. https://doi.org/10.9782/2159-4341-17.2.60.

19. Skokut M, Robinson S., Openden D, et al. Promoting the Social and Cognitive Competence of Children with Autism: Interventions at School. *Contemp School Psychol*. 2008; 13: 93–108. https://doi.org/10.1007/BF03340945.

20. Zwaigenbaum L, Bauman ML, Choueiri R, Fein D, Kasari C, Pierce K, Stone WL, Yirmiya N, Estes A, Hansen RL, McPartland JC, Natowicz MR, Buie T, Carter A, Davis PA, Granpeesheh D, Mailloux Z, Newschaffer C, Robins D, Smith Roley S, Wagner S, Wetherby A. Early Identification and Interventions for Autism Spectrum Disorder: Executive Summary. *Pediatrics*. 2015; 136(1): 1-9. https://doi.org/10.1542/peds.2014-3667B.

21. Choueiri, R., Garrison, W.T. & Tokatli, V. Early Identification of Autism Spectrum Disorder (ASD): Strategies for Use in Local Communities. *Indian J Pediatr*. 2023; 90: 377–386. https://doi.org/10.1007/s12098-022-04172-6.

Examination of the effects of primary dysmenorrhea on daily life of young women and treatment approaches

Ayşe Çuvadar[1], Elnaz Karamelikli[1]

[1]*Department of Midwifery, The Faculty of Health Sciences, Karabuk University, Karabuk, Turkey*

Corresponding author:
Ayşe Çuvadar.
E-mail: aysecuvadar@karabuk.edu.tr;
ORCID: 0000-0002-7917-0576.

Abstract

Aim: Dysmenorrhea is a condition characterized by pain during or before menstruation. This study aims to investigate how dysmenorrhea affects the quality of life of young women and explore effective treatment approaches.

Methods: The research data in descriptive and cross-sectional types were collected using a personal information form containing students' socio-demographic characteristics and a Visual Analog Scale (VAS). A total of 336 students diagnosed with dysmenorrhea and willing to participate in the study were included.

Results: The mean VAS scale score used to determine the severity of dysmenorrhea in the participants was 6.51±2.10. Among the participants who chose Complementary and Alternative Treatment (CAT), 81.8% preferred lying down for rest, and 72.9% opted for applying heat to the abdomen. A statistically significant difference was found in the use of analgesics and CAT methods for dysmenorrhea control based on a family history of dysmenorrhea and the impact of dysmenorrhea on daily life (p<0.05). When the relationship between some categorical characteristics of the students and their belief in and use of CAT methods was examined, a statistically significant relationship was found between nationality (Turkish and foreign) and belief in CAT methods (p<0.05).

Conclusion: This study demonstrates that dysmenorrhea can impact the daily lives of young women and highlights the utilization of various treatment methods. Analgesic medication and TAT methods are commonly preferred for managing this condition. Future research could provide further insights into dysmenorrhea management and aid in developing more effective strategies to improve the quality of life for young women.

Keywords: Dysmenorrhea, menstrual cycle, student, complementary and alternative therapy, quality of life.

Introduction

Dysmenorrhea is a significant issue that affects women's health, characterized by pain during menstruation, typically accompanied by typical symptoms such as abdominal pain or stomach cramps that can radiate to the lower back, along with problems like fatigue, nausea, vomiting, headaches, and diarrhea [1, 2]. The prevalence of dysmenorrhea in adolescents worldwide varies between 41.7% and 94%. This variation is attributed to factors such as the age of menarche, genetics, Body Mass Index (BMI), diet, duration of menstrual bleeding, smoking, coffee consumption, and physical activity [3]. In our country, according to data from the Ministry of Health, dysmenorrhea is observed in adolescents at a rate of 60% and in adults at a rate of 45%[4]. Dysmenorrhea can be primarily categorized into two types: primary and secondary. Primary dysmenorrhea is defined as painful menstruation that occurs without pelvic pathology and typically begins with the onset of the ovulatory cycle, often 6 to 12 months after menarche. In this type of dysmenorrhea, there is no underlying pathology.

On the other hand, secondary dysmenorrhea arises due to an organic pathological condition or pain symptoms associated with menstruation [5]. For young women, dysmenorrhea can emerge as a problem that negatively impacts their learning activities and may require serious treatment1. Research indicates that the consequences of dysmenorrhea can lead to school absenteeism, lower academic performance, significant limitations in daily activities, decreased participation in sports activities, and weakening of peer relationships[6,7].

Dysmenorrhea can be addressed through both pharmacological and non-pharmacological methods. In this context, pharmacological and non-pharmacological approaches can be utilized to treat dysmenorrhea[1]. Complementary and Alternative Treatment (CAT) methods are widely preferred to reduce the side effects of medications, promote healthy behaviors, support

traditional treatments, enhance the immune system, improve quality of life, reduce pain, and support both physical and mental healing[8].

Aim: In Turkey, although there are various CAT methods available, there is a lack of sufficient research regarding the types of these methods, their prevalence in dysmenorrhea treatment, and their effectiveness at the national level. This study aims to investigate how dysmenorrhea affects the quality of life of young women and to examine effective treatment approaches. By doing so, we aim to contribute to a better understanding of dysmenorrhea and the development of improved treatment strategies.

Research Questions

1. What are the effects of primary dysmenorrhea on the quality of life of young women?

2. How is the impact of dysmenorrhea on daily life assessed among young women?

3. What are the preferences and effects of Complementary and Alternative Treatment (CAT) methods in managing dysmenorrhea among young women?

4. What is the relationship between the use of analgesic drugs and CAT methods in treating dysmenorrhea?

Methods

Design: This descriptive and cross-sectional study, conducted between February and June at a University's Faculty of Health Sciences, aims to examine how dysmenorrhea affects the quality of life of young women and investigate effective treatment approaches.

Population and Sample of the Study: The study population comprises female students in a University's Faculty of Health Sciences. The sample size for the study was calculated using the formula for situations where the frequency of the event in the population is unknown, utilizing the OpenEpi software. With a 95% confidence level and a 5% margin of error, the sample size was determined to be 310 individuals. A total of 336 students who had dysmenorrhea and agreed to participate were included in the research.

Data Collection Tools: The data for the research were collected through a "Personal Information Form", consisting of 33 questions that inquired about students' socio-demographic characteristics and their knowledge of coping methods for dysmenorrhea, and by using the Visual Analog Scale (VAS), administered online.

Personal Information Form: The form, prepared by the researchers after conducting a literature review, consists of three sections: The first section contains questions (1-14) about students' demographic information. The second section includes questions (15-31) related to menstruation and dysmenorrhea experiences. The third section contains questions about students' knowledge of CAT methods for coping with dysmenorrhea.

Visual Analog Scale (VAS): The research measured the severity of dysmenorrhea in students using the VAS. VAS is a scale used to measure subjective perceived pain intensity. It consists of numerical values ranging from 0 to 10 cm or 0 to 100 to determine the intensity of pain numerically. "0" represents no pain, while "10" or "100" represents the most severe pain. VAS has been widely used in many studies to assess the severity of dysmenorrhea in women[9-12].

Data Collection: The data for the research were collected online between February and June 2023. Research forms were distributed to students diagnosed with dysmenorrhea studying in the Faculty of Health Sciences through WhatsApp® groups.

Data Analysis: The data were analyzed using the SPSS 26 program. Descriptive statistics such as mean, standard deviation, median, minimum-maximum values, percentages, and frequency values were calculated for the obtained data. For the data analysis, the chi-square ($\chi 2$) test was used to compare categorical characteristics related to students' demographic features, menstruation and dysmenorrhea experiences, and CAT methods. The normality of continuous variables was assessed using histogram graphic testing, Skewness, and Kurtosis values. Kurtosis and Skewness values within the range of -2.0 to +2.0 are generally considered to indicate a normal distribution. Independent variables showing a normal distribution were analyzed using the t-test, and the One-Way Analysis of Variance (ANOVA) Test was used for multiple comparisons. A significance level of $p<0.05$ was considered statistically significant.

Ethical Aspects of the Research: Ethical approval was obtained from the Karabük University Non-Interventional Clinical Research Ethics Committee (Number: E-77192459-050.99-223775, Decision: 2023/1259). After obtaining ethical approval, the researchers obtained informed consent from the participants.

Results

When the distribution of students' socio-demographic characteristics was examined, it was found that the average age was 20.88±1.96 years, the average body mass index (BMI) was 22.13 ± 3.59, 47.9% were enrolled in the midwifery department, 44.6% were in the first year, 78.3% were Turkish citizens, 3% were married, 85.7% did not smoke, and 11.9% used hormonal medication. Among those using hormonal medication, it was determined that 42.5% used it primarily for irregular menstruation.

Additionally, the average age of menarche for the students was 13.30±1.39 years, and the average severity of dysmenorrhea was 6.51±2.10.

CAT: Complementary and Alternative Treatment

It was observed that 80.1% of the students had their daily lives affected due to dysmenorrhea complaints, and as a result, 25.9% of them had absenteeism from school. Furthermore, 64.9% of the students used any analgesic for dysmenorrhea complaints, and 35.8% obtained the medication from the pharmacy themselves. Among them, 66.1% used analgesic medication when the pain was very severe, and 45.2% used CAT methods along with analgesics.
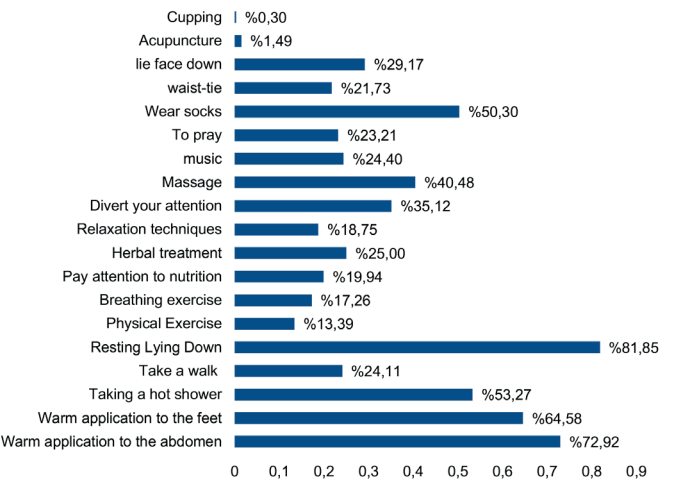

Figure 1 - Findings regarding alternative methods used by students to cope with dysmenorrhea (n=336)

Table 1	Findings Regarding Students' Menstrual Periods (n=336)

Features	n (%)
Menstrual Cycle Pattern	
Regular	258 (76,8)
Irregular	78 (23,2)
Menstrual Cycle Interval	
21 days or less	27 (8)
Every 22- 35 days	290 (86,3)
36 days or more	19 (5,7)
Menstrual Cycle Duration	
less than 3 days	10 (3,0)
Between 3-5 days	234 (69,6)
Between 6-8 days	76 (22,6)
More than 8 days	16 (4,8)
Time of onset of dysmenorrhea	
Before menstruation	89 (26,5)
First day of menstruation	127 (37,8)
2nd and 3rd day of menstruation	101 (30,1)
During menstruation	19 (5,7)
Family history of dysmenorrhea	
Yes	223 (66,4)
No	113 (33,6)
The Effect of Dysmenorrhea on Daily Life	
Affecting	272 (80,1)
Does not affect	64 (19,9)
The level of its impact on daily life	
Absenteeism from school	87 (25,9)
Absenteeism from work	23 (6,8)
Difficulty communicating with people	60 (17,9)
Information about menstrual period	
Yes	305 (90,8)
No	31 (9,2)
Time of Receiving Information	
Before first menstruation	218 (64,9)
After menstruation	118 (35,1)
Use of analgesics in dysmenorrhea control	
Yes	218 (64,9)
No	118 (35,1)
Her situation regarding the procurement of the medication (n=218)	
I buy it myself from the pharmacy	78 (35,8)
I buy it with a doctor's prescription	67 (30,7)
I get it from members of my family	65 (29,8)
I get it from my friends	8 (3,7)
Analgesic use time (n=218)	
When the pain is very severe	144 (66,1)
On the first day of my period	74 (33,9)
Use of other methods together with analgesic drugs (CAT)	
Analgesic drugs	66 (19,6)
Analgesic drugs+ CAT	152 (45,2)
Only CAT	118 (35,1)
Belief in the CAT Method	
Believes a little	139 (41,4)
Believes	160 (47,6)
Does not believe	37 (11,0)

When the findings regarding the CAT methods used by students were evaluated, it was observed that they mostly used methods such as resting in a lying position (81.8%), applying warmth to the abdomen (72.9%), and applying warmth to the feet (64.6%). Additionally, it was determined that students used acupuncture (1.49%) and cupping therapy (0.3%) the least among CAT methods.

The analysis results indicated that the VAS (pain scale) score average for Turkish students was 6.37 ± 2.007, while for foreign national students, it

Table 2	Comparison of VAS Scale Average Scores According to Students' Socio-demographic Characteristics

Variables	Groups	Number(n)	X̄±SS	Statistical significance	P
Marital Status	Single	326	6,52 ± 2,102	t = ,480	0,631
	Married	10	6,20 ± 2,201		
Nationality	T.C	263	6,37 ± 2,007	t = -2,436	**0,015***
	Foreign	73	7,04 ± 2,354		
Presence of smoking status	No	288	6,45± 2,106	t = 1,283	0,200
	Yes	48	6,88 ± 2,059		
Alcohol consumption status"	No	274	6,51 ± 2,123	t = -0,139	0,890
	Yes	62	6,55 ± 2,022		
Chronic disease	No	303	6,45 ±2,058	t = -1,662	0,097
	Yes	33	7,09 ± 2,429		
Menstrual Cycle Pattern	Irregular	78	6,79 ± 2,140	t = 1,344	0,180
	Regular	258	6,43 ± 2,087		
History of Dysmenorrhea in the Family	No	113	6,07 ± 2,215	t = -2,785	**0,006***
	Yes	223	6,74 ± 2,010		
Information about the menstrual period	No	31	6,87 ± 2,217	t = 0,990	0,323
	Yes	305	6,48 ± 2,090		
Use of analgesics in dysmenorrhea control	No	118	5,64 ± 2,130	t = -5,859	**0,001***
	Yes	218	6,99 ± 1,933		
The Effect of Dysmenorrhea on Daily Life	Does not affect	64	4,11± 1,605	t = -12,225	**0,001***
	Affecting	272	7,08 ± 1,782		
Type of residence	Lalone at home	25	6,56 ± 2,256	F = 1,255	0,290
	Stays in dormitory	84	6,86 ± 1,877		
	Lives at home with her family	195	6,34 ± 2,127		
	Lives at home with friends	32	6,66 ± 2,350		
Menstrual Cycle Interval	21 days or less1	27	7,48 ± 1,649	F =5,018***	**0,007***
	Every 22- 35 days2	290	6,37 ± 2,114		
	36 days or more3	19	7,32 ± 2,029		
Analgesic use time	Not taking1	118	5,64 ± 2,130	F= 22,441****	**0,001***
	When the pain is very severe2	144	6,69 ± 1,803		
	On the first day of my period3	74	7,57 ± 2,055		
Use of other methods together with analgesic drugs (CAM)	Analgesic + CAM1	152	7,10 ± 1,826	F= 17,984*****	**0,001***
	Only Analgesic drugs2	66	6,64 ± 2,130		
	Only CAM3	118	6,51 ± 2,102		
Belief in the CAM Method Believes a little Believes Does not believe	Believes	160	6,48 ± 2,071	F= ,052	0,950
	Does not believs	37	6,59 ± 2,166		
	Blieves a little	139	6,53 ± 2,134		

p <0,05, t = t test in independent groups, F = One-way analysis of variance = * Games-Howell, Posthoc Benferroni Alpha=,016, CAT: Complementary and ** Alternative Treatment
3<2 ,3<1 = ***** ,2<3 ,1<3 ,1<2 = **** ,2<1 = ***

Variables	Groups	Number(n)	X̄±SS	Statistical significance	P
Warm application to the abdomen.	Yes	245	6,66 ± 2,076	t = -2,045	**0,042***
	No	91	6,13 ± 2,135		
Warm application to the feet	Yes	217	6,63 ± 2,100	t = -1,319	0,188
	No	119	6,63 ± 2,098		
Taking a hot shower	Yes	179	6,45 ± 1,983	t = 0,632	0,528
	No	157	6,59 ± 2,233		
Take a walk	Yes	81	6,35 ± 2,157	t = 0,831	0,406
	No	255	6,57 ± 2,085		
Resting Lying Down	Yes	275	6,42 ± 2,069	t = 1,797	0,073
	No	61	6,95 ± 2,209		
Physical Exercise	Yes	45	6,31 ± 2,162	t = 0,698	0,485
	No	291	6,55 ± 2,094		
Breathing exercise	Yes	58	6,76 ± 1,895	t = -0,971	0,332
	No	278	6,46 ± 2,142		
Pay attention to nutrition	Yes	67	6,12 ± 2,121	t = 1,726	0,085
	No	269	6,61± 2,089		
Herbal treatment	Yes	84	6,71 ± 2,086	t = -1,004	0,316
	No	252	6,45 ± 2,107		
Relaxation techniques	Yes	63	6,63 ± 2,058	t = -0,502	0,616
	No	273	6,49 ± 2,115		
Divert your attention	Yes	118	6,50 ± 1,977	t = 0,095	0,924
	No	218	6,52 ± 2,171		
Massage	Yes	136	6,31 ± 2,152	t = 1,485	0,139
	No	200	6,66 ± 2,061		
Music	Yes	82	6,27 ± 2,103	t =1,223	0,222
	No	254	6,59 ± 2,100		
To pray	Yes	78	6,49 ± 2,266	t = 0,133	0,895
	No	258	6,52 ± 2,054		
Wear socks	Yes	169	6,53 ± 2,107	t = -0,155	0,877
	No	167	6,50 ± 2,102		
waist-tie	Yes	73	6,82 ± 2,213	t = -1,413	0,159
	No	263	6,43 ± 2,066		
lie face down	Yes	98	6,88± 1,912	t = -2,039	**0,042***
	No	238	6,37 ± 2,161		
Acupuncture	Yes	5	5,80 ± 1,789	t = ,766	0,444
	No	331	6,53 ± 2,107		
Cupping	Yes	1	7,00	t = -0,231	0,818
	No	335	6, 51± 2,105		

Table 3 — Comparison of VAS Scale Average Scores According to the CAT Methods Used by Students

was 7.04 ± 2.354. The difference between the VAS score averages of Turkish and foreign national students was statistically significant (p <0.05) (Table 2).

Among students with a family history of dysmenorrhea, those who used pain relievers, and those whose daily lives were affected by dysmenorrhea, the VAS scale score averages were higher compared to other students, and this difference was statistically significant (p<0.05) (Table 2).

It was found that the VAS scale scores of students varied statistically significantly among groups based on menstrual cycle intervals, F (2,333) = 5.018, p=0.007, Ƞ2=0.29. Accordingly, the VAS scale score averages of students with menstrual cycle intervals of 21 days and below (7.48 ± 1.649) were higher than the VAS scale score averages of students with menstrual cycle intervals of 22-35 days (6.37 ± 2.114). This difference was statistically significant (p<0.05) (Table 2).

The comparison of VAS scale scores among groups based on students' use of Analgesic and CAT methods for dysmenorrhea control showed statistically significant differences between groups,

F (2,333) = 5.018, p=0.007, Ƞ2=0.29. Accordingly, the VAS scale score averages were higher in students who used both analgesics and CAT methods (7.10 ± 1.826) and in students who used only analgesic medication (6.73 ± 2.152) compared to students who used only CAT methods (5.64 ± 2.130), and this difference was statistically significant (p<0.001). Post-hoc analysis revealed no statistically significant differences among other group comparisons (Table 2).

When the VAS scale score averages were compared according to the CAT methods used by students, statistically significant differences were found between those who used warm abdominal application and those who used the supine lying method (p<0.05). The other methods had no statistically significant difference in VAS scale score averages.

When the relationship between some categorical characteristics of the students and their belief in and use of CAT methods was examined, a statistically significant relationship was found between nationality (Turkish and foreign) and belief in CAT methods (p<0.05). Additionally, a statistically significant relationship was found between having a family history of dysmenorrhea and the use of both Analgesic and CAT methods (p<0.001) (Table 4).

Discussion

In this study, we aimed to examine the impact of primary dysmenorrhea on the daily lives of young women and their treatment approaches. According to the research results, the average severity of dysmenorrhea in the students was determined to be 6.51±2.10. 64.9% of the participants used analgesics to cope with dysmenorrhea, while 35.1% preferred CAT methods. Among them, 81.8% stated that they rested lying down, and 72.9% applied heat to the abdomen.

Primary dysmenorrhea, without pelvic pathology, is one of the most common complaints related to women's health[14-15].

Although various pain measurement methods exist in the literature, VAS is commonly preferred to assess dysmenorrhea pain. In the current study, VAS was also used, and the average pain severity according to VAS in women with dysmenorrhea was determined to be 6.51±2.10 (on a scale of 0-10). When looking at studies in the literature, Yılmaz et al.[16] found an average pain severity of 6.35±1.97 in women with dysmenorrhea; Helwa et al.[17] found an average pain severity of 6.79±2.64 in women with dysmenorrhea; Yılmaz and Başer[18] reported 6.3±2.02. The study findings are consistent with the literature.

The overall dysmenorrhea severity in young women can vary, but it is generally moderate. However, this can vary for each individual, and the severity of pain can change depending on personal experiences and the factors involved.

Our research observed that 64.9% of young women with dysmenorrhea used analgesic medication to cope with pain, and an increase in pain severity led to a higher utilization of pharmacological methods. However, different results have been obtained on this topic when reviewing the literature. Yılmaz et al.[16] found that 51% of the participants used analgesic medication, and medication use significantly increased with the severity of pain. Ataş et al.[7] found that 81.6% of students used

| Table 4 | Comparison of Some Socio-Demographic Characteristics of Students with their Belief in and Use of CAT Methods |

Socio-Demographic Characteristics			The Belief in the CAT Method			Total	x2	p
			Believes	Does not believe	Partially believes			
Grade level	1.	n	56	20	74	150	17,107	0,009*
		%	37,3	13,3	49,3	100,0		
	2.	n	34	3	26	63		
		%	54,0	4,8	41,3	100,0		
	3.	n	27	6	22	55		
		%	49,1	10,9	40,0	100,0		
	4.	n	43	8	17	68		
		%	63,2	11,8	25,0	100,0		
Nationality	T.C	n	138	27	27	263	11,532	0,003*
		%	52,5	10,3	37,3	100,0		
	Foreign	n	22	10	41	73		
		%	30,1	13,7	56,2	100,0		
Marital status	Single	n	154	37	135	326	1,475	0,479
		%	47,2	11,3	41,4	100,0		
	Married	n	6	0	4	10		
		%	60,0	0,0	40,0	100,0		
		%	47,5	11,9	40,6	100,0		
Status of Receiving Menstruation Information	No	n	11	3	17	31	2,609	0,271
		%	35,5	9,7	54,8	100,0		
	Yes	n	149	34	122	305		
		%	48,9	11,1	40,0	100,0		
			Use of Analgesic and CAT methods					
			Analgesic +CAT	Analgesic	CAT	Total		
Nationality	T.C	n	121	47	95	263	2,440	0,295
		%	46,0	17,9	36,1	100,0		
	Foreign	n	31	19	23	73		
		%	42,5	26,0	31,5	100,0		
History of Dysmenorrhea in the Family	Yes	n	117	40	66	223	14,399	0,001*
		%	52,5	17,9	29,6	100,0		
	No	n	35	26	52	113		
		%	31,0	23,0	46,0	100,0		
The Effect of Dysmenorrhea on Daily Life	Affecting	n	140	50	82	272	23,469	0,001*
		%	51,5	18,4	30,1	100,0		
	Does not affect	n	12	16	36	64		
		%	18,8	25,0	56,3	100,0		

analgesics. Lete et al.[19] reported a medical treatment method utilization rate of 60.1%, while Kuşaslan Avcı and Sarı[20] found that 34.4% resorted to medical methods. This indicates different approaches to managing dysmenorrhea; individual differences play a significant role.

According to the results of our research, 47.6% of the students believed in Traditional and Complementary Treatment (CAT) methods, while 41.4% partially believed in them. However, it was observed that only 35.1% used exclusively CAT methods to cope with dysmenorrhea. The most commonly preferred CAT methods were as follows: lying down and resting (81.8%), applying heat to the abdomen (72%), applying heat to the feet (64.6%), and taking a hot shower (53.2%). These results are similar to the study conducted by Ataş et al.[7] In this study when looking at pain coping methods, the most frequently used methods were lying down and resting (72%) and lying in the prone/fetal position (57.9%), followed by applying heat to the lower abdomen (49%, 52.2%, 67.2%). In Oyardı and Karakaş's study[21], it was found that 57% of the students partially believed in traditional and complementary treatment methods, and the most commonly preferred methods were drinking herbal tea (37%), massage (32%), and applying heat (22.4%).

Additionally, in another study, it was observed that 93.2% of students followed a low-fat diet, 81.8% engaged in exercise, 41.8% applied abdominal massage, and 34.5% applied heat to the abdomen to alleviate dysmenorrhea symptoms[22]. These findings indicate that young women commonly prefer CAT methods to cope with dysmenorrhea, and these methods play a significant role in overall health practices. A study conducted with midwifery students in Turkey found that all students had knowledge about the menstrual cycle. When looking at the time of initial knowledge acquisition, 66.4% had acquired this knowledge before they started menstruating[20]. In our study, we observed that 90.8% of the students were informed about the menstrual cycle, and 64.9% acquired this knowledge before their first menstruation. Our research also revealed that 25.9% of students did not attend school due to complaints of dysmenorrhea, and 17.9% had difficulty communicating with others. In the study by Yılmaz and Başer[18], 11.8% of those who experienced dysmenorrhea at a disturbing level and 56.1% of those who experienced it severely reported that it affected their school performance and attendance. In another study, 15.5% of students mentioned that they could not attend classes and school due to dysmenorrhea[21].

In our study, those with a family history of dysmenorrhea had higher VAS scale mean scores, and the difference was

statistically significant. In the study by Habibi et al.[23], 58.8% of the participants reported a family history of dysmenorrhea (27.8% mother, 18.4% sister), and family history was reported as the most important factor affecting the severity of dysmenorrhea (β=-0.294, p<0.05).

Our study observed that students affected by dysmenorrhea in their daily lives had higher VAS scale mean scores compared to other students, and the difference was statistically significant. Therefore, it can be said that students with severe dysmenorrhea have higher pain intensity, which can more significantly affect their daily lives.

In conclusion, dysmenorrhea can affect the quality of life of young women. Especially, the severity of dysmenorrhea can impact students' daily activities and lead to the preference of different coping methods.

Our study observed that the use of analgesic drugs was common, and with the increase in pain intensity, pharmacological methods were more frequently used. Traditional and Complementary Treatment methods were also preferred in coping with dysmenorrhea. Additionally, students with a family history of dysmenorrhea had higher pain intensity.

The results of this study indicate that dysmenorrhea can affect the daily lives of young women and that different coping strategies are used. It should be noted that the methods individuals prefer and the severity of pain can vary according to personal experiences. Future studies may provide further insights into the management of dysmenorrhea and help us develop more effective strategies to improve the quality of life of young women.

Particularly, it is essential to investigate alternative and effective approaches to the treatment of dysmenorrhea. Furthermore, further research is needed to understand young women's coping strategies with dysmenorrhea and provide them with more support. The results of this study can serve as a foundation for healthcare professionals and researchers, offering a better understanding to enhance the quality of life for young women.

Conclusıon

In conclusion, it was observed that various coping methods are employed for the management of dysmenorrhea, significantly impacting the lives of young women. Our research revealed that analgesic medications are commonly used, and as the severity of pain increases, pharmacological methods are more frequently preferred. Traditional and Complementary Treatment methods are also chosen for coping with dysmenorrhea. Additionally, students with a family history of dysmenorrhea were observed to experience higher pain intensity.

The findings of this study can provide a foundation for healthcare professionals and researchers to develop more effective strategies in understanding and managing the issue of dysmenorrhea, which greatly affects the daily lives of young women. It is especially essential to explore alternative and effective approaches to the treatment of dysmenorrhea. Furthermore, more research is needed to comprehend the coping strategies of young women with dysmenorrhea and to offer them additional support.

References

1. Trisnawati Y. Hipnoterapi Untuk Menurunkan Nyeri Dismenore: Tinjauan Literatur. Prepotıf. *Jurnal Kesehatan Masyarakat. 2*023; 7(1): 640-647.
2. Mizam AK. Pengaruh Hipnoterapi Terhadap Penurunan Skala Nyeri Dismenore. *Media Husada Journal Of Nursing Science.* 2021; 1(1): 69–72. https://doi.org/10.33475/mhjns.v1i1.7.
3. Ningrum AG, Setyowati D, Sema, MOK. Hubungan Aktivitas Fisik dengan Dismenore Primer pada Remaja Putri: Systematic Review. *Jurnal Ilmiah Universitas Batanghari Jambi.* 2023; 23(2): 1997-2000. https://doi.org/10.33087/jiubj.v23i2.3577.
4. Ryan SA. The Treatment of Dysmenorrhea. *Pediatr Clin North Am.* 2017; 64(2): 331–342. https://doi.org/10.1016/j.pcl.2016.11.004.
5. De Sanctis V, Soliman A, Bernasconi S, Bianchin L, Bona G, Bozzola M, et al. Definition and self-reported pain intensity in adolescents with dysmenorrhea: a debate report. *Rivista Italiana di Medicina dell'Adolescenza.* 2016; 14(2). https://doi.org/10.1016/j.pcl.2016.11.004.
6. Iravani M. Effects of thymus vulgaris extract on primary dysmenorrhea. *J Med plants.* 2008; 8: 54-5.
7. Ataş K, Poyraz İşleyen T, Kaya Mutlu E. The Incidence of Dysmenorrhea in University Students During the COVID-19 Pandemic and Social Isolation Process. *A Cross-Sectional StudyTurkiye Klinikleri Journal of Health Sciences.* 2023; 8(2). https://doi.org/10.5336/healthsci.2022-93857.
8. Özkan A, Hiçerimez A. Determination of the frequency, types and effectiveness of descriptive and alternative applications used in premenstrual syndrome during the covid normalızatıon period. *Gevher Nesibe Journal of Medıcal and Health Sciences.* 2023; 8(2): 292-301. https://doi.org/10.5281/zenodo.7922528.

9. Kurt N, Bozkır Ç, Koca HÜ. The Relationship Between Dysmenorrhea and Emotional Eating in Young Women. *Journal of Infant, Child and Adolescent Health*. 2023; 3(1): 42-51.

10. Lidia A, and Romadhona Haque B. Efektivitas Senam Kombinasi Dismenore Terhadap Penurunan Tingkat Dismenore Pada Siswi SMPN 2 Setu Kabupaten Bekasi Tahun 2023. Innovative: *Journal Of Social Science Research*. 2023; 3(3): 6885-6895.

11. Della M, Follona W, Aticeh A. Hubungan Tingkat Stres dan Perilaku Konsumsi Makanan Cepat Saji Terhadap Kejadian Dismenore Pada Remaja Putri. *Muhammadiyah Journal of Midwifery*. 2023; 4(1): 34-46. https://doi.org/10.24853/myjm.4.1.34-46.

12. Sönmezer E, Yosmaoğlu HB. Changes of Menstrual Attitude and Stress Perception in Women with Dysmenorrhea. *Turkish Journal of Physiotherapy and Rehabilitation.*. 2014; 2(25): 1-7. https://doi.org/10.7603/s40680-014-0008-7.

13. George D, Mallery P. IBM SPSS statistics 26 step by step: *A simple guide and reference Routledge*. 2019; 113-118. https://doi.org/10.4324/9780429056765.

14. Kurt N, Bozkır Ç, Koca HÜ. Determining the relationship between dysmenorrhea and emotional eating in young women. *Journal of Infant, Child and Adolescent Health.* 2023; 3(1): 42-51.

15. Çay B, Saka S. The Effect of Short Term Aerobic Exercise on Dysmenorrhea in Young Adults. *Health Pro Res*. 2020; 2(3): 94-101.

16. Yılmaz T, Nuraliyeva Z, Dinç H. The Coping Methods of Young Women with Dysmenorrhea. *Jaren*. 2020; 6(2): 294-9. https://doi.org/10.5222/jaren.2020.48344.

17. Helwa HAA, Mitaeb AA, Al-Hamshri S, Sweileh WM. Prevalence of dysmenorrhea and predictors of its pain intensity among Palestinian female university students. *BMC women's health*. 2018; 18(18): 1-11. https://doi.org/10.1186/s12905-018-0516-1.

18. Yılmaz FA, Başer M. The Effects of Dysmenorrhea on School Performance. Gümüşhane UniversityJournal Of HealthSciences. 2016; 5(3): 29-33.

19. Lete I, Duenas JL, Serrano I, Doval JL, Martinez-Salmean J, Coll C, et al. Attitudes of Spanish women toward premenstrual symptoms, premenstrual syndrome and premenstrual dysphoric disorder: results of a nationwide survey. European journal of obstetrics, gynecology, and reproductive biology. 2011; 159(1): 115-118. https://doi.org/10.1016/j.ejogrb.2011.06.041.

20. Kuşaslan Avcı D, Sarı E. Approach to Dysmenorrhea and Effect of Dysmenorrhea on Social Life and School Performance in the University Students. *Van Medical Journal. Der.* 2018; 25(2): 188-193. https://doi.org/10.5505/vtd.2018.65807.

21. Oyardı G, Karakaş S. oping Methods Used by University Students Experiencing Primary Dysmenorrhea Traditional and Complementary Treatment Practices: *A Cross-Sectional Study. Turkiye Klinikleri Journal of Nursing Sciences*. 2023; 15(1). https://doi.org/10.5336/nurses.2022-91453.

22. Eser A, Kaya N. Dysmenorrhea Problems of Midwifery Students at a University in Terms of Some Related Variables. *Mersin University Faculty of Medicine Lokman Hekim Medical History and Folkloric Medicine Journal.* 2023; 13(1): 168-179. https://doi.org/10.31020/mutftd.1166386.

23. Habibi N, Huang MS, Gan WY, Zulida R, Safavi SM. Prevalence of primary dysmenorrhea and factors associated with its intensity among undergraduate students: a cross-sectional study. *Pain Manag Nurs*. 2015; 16(6): 855-61. https://doi.org/10.1016/j.pmn.2015.07.001.

Epidemiology of glomerular diseases in Kazakhstan during the period of 2014-2019: data from the Unified national electronic healthcare system

Ainur Assan[1], Gulnur Zhakhina[2], Zakira Kerimbayeva[3], Ikilas Moldaliyev[1], Dmitriy Sychev[4], Saltanat Tuganbekova[5], Abduzhappar Gaipov[2]

[1]*Faculty of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University, Turkestan, Kazakhstan*
[2]*Department of Medicine, Nazarbayev University School of Medicine, Astana, Kazakhstan*
[3]*Department of Public Health and Management, NJSC "Astana Medical University", Astana, Kazakhstan*
[4]*Faculty of Medicine, Russian Medical Academy of Continuous Professional Education, Ministry of Healthcare, Moscow, Russia*
[5]*Department of Nephrology, NJSC "Astana Medical University", Astana, Kazakhstan*

Corresponding author:
Ainur Assan.
E-mail: ainur.assan@ayu.edu.kz;
ORCID: 0000-0003-3313-0699.

Abstract

Brief Description: The investigation of glomerular disease prevalence is vital for comprehending chronic kidney disease development, particularly in regions like Kazakhstan and Central Asia, where confirming data is lacking. This study focuses on the epidemiology of glomerular diseases, utilizing registered cases of glomerular diseases in the national electronic health system.

Research Methods: The research involves data from 31,421 patients recorded in the Unified National Electronic Healthcare System database, covering glomerular diseases with ICD-10 codes N01-N08 between 2014 and 2019. Descriptive statistics encompass demographic characteristics, all-cause mortality, prevalence and incidence rates, and comorbidities.

Results: Results reveal a substantial rise in diagnosed cases from 7,756 (2014) to 30,686 (2019), with corresponding all-cause mortality increasing from 254 to 1,025. Also, new cases went up from 4,875 (2014) to 6,320 (2019). Over the period, 51% were women, 49% were men, and 67% were of Kazakh ethnicity. Russian nationality constituted 16%, and other ethnic groups comprised 17%. Diabetes mellitus emerged as the primary comorbidity, associated with 20% of cases.

Conclusion: This is the first descriptive study in Central Asia scrutinizing the epidemiology of patients with glomerular diseases (ICD-10 code N01-N08) using administrative healthcare data in Kazakhstan. The findings indicate an escalation in prevalence and mortality, coupled with a gradual increase in incidence among glomerular disease patients from 2014 to 2019. The study underscores the pivotal role of diabetes mellitus as a predominant comorbidity in this context.

Keywords: glomerular disease, prevalence, comorbidity, incidence, Kazakhstan.

Introduction

Glomerular diseases constitute a group of relatively rare immunomediated disorders characterized by damage to the glomerular compartment of renal nephrons [1]. Glomerular disease can be triggered by various inflammatory conditions such as vasculitis and systemic lupus erythematosus, or infections such as streptococcal, HIV, hepatitis B and C, and endocarditis [2]. One of the most common negative consequences of poorly controlled glomerular disease is the development of chronic kidney disease, eventually requiring renal replacement therapy [3]. In the United States, glomerular disease accounts for 10-15% of end-stage renal failure cases, often leading to comorbidities [4, 5].

Reports indicate that 10% of dialysis patients suffer from chronic glomerular disease, making it the third most common cause of end-stage renal failure in the U.S., surpassed only by hypertension and diabetes mellitus [6]. However, in Kazakhstan and Central Asian countries, glomerular diseases are considered the primary cause of terminal kidney failure, although there is a lack of confirming data.

According to data from the American Medicare program cohort, 18.7% of German citizens with chronic kidney disease and 30–36% of children and adolescents in the U.S. with end-stage renal failure are attributed to glomerular disease. Additionally, several ethnic groups, including African Americans, Hispanics, Asians, and Indigenous peoples in Australia and Canada, have a higher likelihood of developing glomerular disease, which may also be more severe in these populations [4]. However, there is limited data for Kazakhstan regarding the role and prevalence of glomerular disease in the development of terminal chronic kidney failure.

Apart from the prevalence of glomerular disease, the financial costs of patient medical care and treatment play a crucial role in the increasing significance of the disease. The common pathogenetic mechanism for glomerular disease is immunomediated, involving both humoral and cellular responses [5]. Depending on the cause of glomerular disease, treatment may include various methods, including the administration of immunosuppressants, steroids, monoclonal antibodies, and plasmapheresis [5]. Immunosuppressants typically cost between $10,000 and $14,000 annually.

Managing glomerular disease entails not only healthcare but also a financial burden for both the patient and the state. In Kazakhstan, the government provides free medications for patients with glomerular disease. As one of the burdensome medical conditions, the epidemiology of glomerular disease in Kazakhstan will be explored in this study. Therefore, studying the prevalence and incidence of glomerular pathology in the population is crucial for assessing the need for immunosuppressive therapy. The aim of this study is to investigate the epidemiology of glomerular diseases using registered cases of glomerular disease in a Unified National Electronic Healthcare System.

Methodology

Study Population

The study included patients entered into the database of the Unified National Electronic Healthcare System. Initial data on 31,421 patients with glomerular diseases with ICD-10 codes N01-N08 from 2014 to 2019 were extracted from the database in Microsoft Excel format. The flow-chart diagram of cohort set-up (data management and cleaning) is presented in Figure 1. The annual incidence of glomerular diseases was presented in a graphical format. The number of deaths per year was also shown on the graph. Detailed information on data sources is provided in the supplementary material. The total population in Kazakhstan and its regions was obtained from the Statistics Committee of the Ministry of National Economy of the Republic of Kazakhstan (2019) [7].

Exposure and Covariates

Individual patient data included age, gender, ethnicity, place of residence, comorbidities, and outcomes. Information on age and death (if applicable) was obtained through linkage with the Population Registry using the Registry Number (RPN number). Age was categorized into five groups (under 18 years, 18–34 years, 35–50 years, 51–70 years, and over 70 years), ethnic groups included Kazakhs, Russians, and others (including Uzbeks, Uighurs, Ukrainians, Koreans, and 37 other
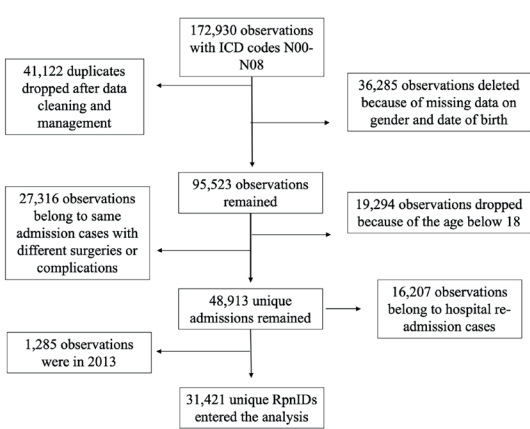

Figure 1 - Flow-chart of cohort set-up

ethnic groups). Comorbidities were categorized as hypertension, diabetes mellitus, cardiovascular diseases, heart failure, atherosclerotic heart disease, cerebrovascular events/transient ischemic attacks, peripheral vascular disease, and chronic obstructive pulmonary disease. Comorbidities are mutually exclusive among the study patients.

Outcome Assessment

The prevalence, incidence, and overall mortality of patients were studied. The prevalence of glomerular disease patients was examined over six consecutive years (2014–2019). The number of incident cases of glomerular disease was obtained from the Unified National Electronic Healthcare System database. For each year, the periodic prevalence per 100,000 population was calculated by dividing the number of cases of glomerular disease by the population of that year, multiplied by 100,000, and presented on a graph. Similarly, the overall mortality rate in Kazakhstan per 100,000 population was calculated and presented on a graph. Data on overall mortality and corresponding dates were obtained from the Republican Center for Healthcare Development (RCHD) and the population registry. Incidence rates of glomerular disease were calculated by dividing the number of new cases by the population of that year and multiplying by 100,000. Population data for Kazakhstan and its regions were obtained from the Statistics Committee (2019) [7].

Statistical analysis

The data are presented as percentages for categorical variables. Incidence, prevalence, and all-cause mortality rates were calculated by dividing absolute numbers by the population size of the corresponding year and multiplying by 100,000. Population sizes for each year were obtained from the Statistics Committee within the Ministry of National Economy of the Republic of Kazakhstan[7]. The association between variables was tested using the Chi-squared test after checking for corresponding assumptions. The significance level was set at 0.05. Data cleaning, which involved identifying and removing duplicate cases, as well as data management tasks such as labeling all data, creating new variables, and categorizing them, were carried out using STATA version 16.1. Data visualization was conducted using GraphPad Prism version 9.5.

Results

Demographic Data

Demographic information regarding the cohort is presented in Table 1. From 2014 to 2019, a total of 15,970 (51%) females and 15,451 (49%) males were registered with a diagnosis of glomerular disease. Ethnically, 67% of the patients were of Kazakh origin, 16% were of Russian nationality, and 17% belonged to other ethnic groups.

Table 1	Baseline characteristics of the population			
	Total (n = 31,421)	Female (n = 15,970; 51%)	Male (n = 15,451; 49%)	p-value
Age, n (%)				<0.001
=< 17 y.o.	9,024 (29)	3,822 (24)	5,202 (34)	
18-34 y.o.	5,042 (16)	2,431 (15)	2,611 (17)	
35-50 y.o.	4,833 (15)	2,387 (15)	2,446 (16)	
51-70 y.o.	9,804 (31)	5,596 (35)	4,208 (27)	
>= 71 y.o.	2,718 (9)	1,731 (11)	984 (6)	
Ethnicity, n (%)				<0.001
Kazakh	20,993 (67)	10,363 (65)	10,630 (69)	
Russian	5,074 (16)	2,909 (18)	2,165 (14)	
Other	5,354 (17)	2,698 (17)	2,656 (17)	
Living area, n (%)				<0.001
Urban	19,762 (64)	10,240 (65)	9,522 (63)	
Rural	11,124 (36)	5,428 (35)	5,642 (37)	
Comorbidities, n (%)				
HTN	4,534 (14)	2,588 (16)	1,946 (13)	<0.001
DM	6,193 (20)	3,771 (24)	2,422 (16)	<0.001
CVD	4,673 (15)	2,415 (15)	2,258 (15)	0.206
HF	1,609 (5)	757 (5)	852 (6)	0.002
ASHD	1,376 (4)	669 (4)	707 (5)	0.094
Dysrhythmia	284 (1)	96 (1)	188 (1)	<0.001
CVA/TIA	742 (2)	382 (2)	360 (2)	0.717
PVD	1,088 (3)	687 (4)	401 (3)	<0.001
COPD	757 (2)	348 (2)	409 (3)	0.007
Liver Disease	259 (1)	114 91)	145 (1)	0.028
Outcome, n (%)				0.620
Alive	27,404 (87)	13,943 (87)	13,461 (87)	
Deceased	4,017 (13)	2,027 (13)	1,990 (13)	

Abbreviations: HTN – hypertension, DM – Diabetes Mellitus, CVD – cardiovascular disease, HF – heart failure, ASHD - Atherosclerotic Heart Disease, CVA/TIA - Cerebrovascular Accident / Transient Ischemic Attack, PVD - Peripheral Vascular Disease, COPD - Chronic Obstructive Pulmonary Disease

Prevalence and Incidence per 100,000 Population

The prevalence and incidence in 2014 were 45.1 and 28.4 per 100,000 population, respectively. These figures differed from the data in 2019 (166.8 and 34.4, respectively) (Figure 2b and 3b). The absolute number of patients with a confirmed diagnosis sharply increased from 7,756 to 30,686 between 2014 and 2019 (Figure 2a). Additionally, the number of new cases increased from 4,875 in 2014 to 6,320 in 2019 (Figure 3a).
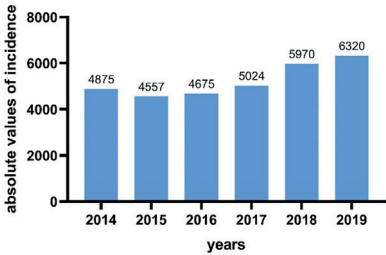

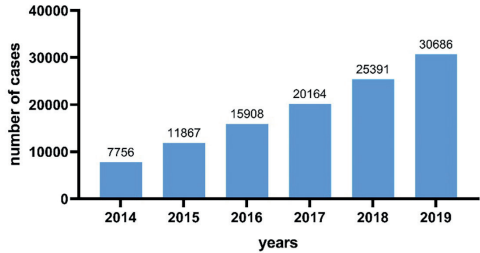Figure 3a - Absolute values of incidence of Glomerular Diseases in Kazakhstan per each year between 2014-2019

Figure 2a - Absolute values of prevalence of Glomerular Diseases in Kazakhstan between 2014-2019 years
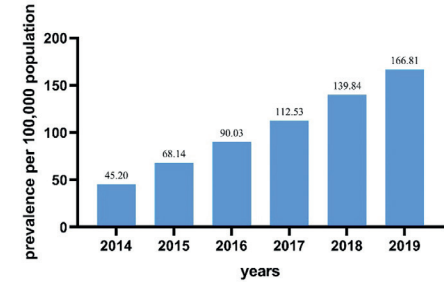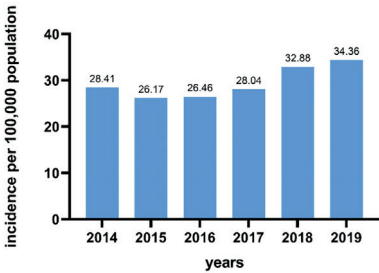

Figure 3b - Incidence rate of Glomerular Diseases per 100,000 population in Kazakhstan between 2014-2019

All-cause Mortality per 100,000 Population

Figure 3b illustrates the all-cause mortality per 100,000 population from 2014 to 2019. The all-cause mortality in 2014 was 1.48 per 100,000 population, increasing to 5.57 in 2019. This significant rise is also evident in the absolute mortality values for 2014 and 2019, which were 254 and 1,025, respectively (Figure 4a).
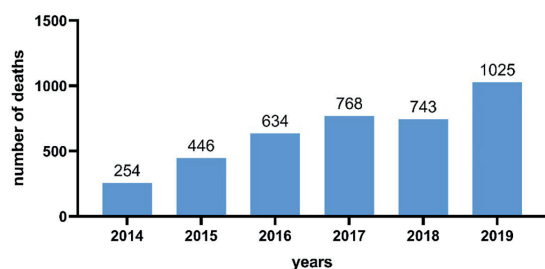

Figure 2b - Prevalence of Glomerular Diseases per 100,000 population in Kazakhstan between 2014-2019 years

Figure 4a - Absolute numbers of all-cause mortality in Kazakhstan between 2014-2019 years
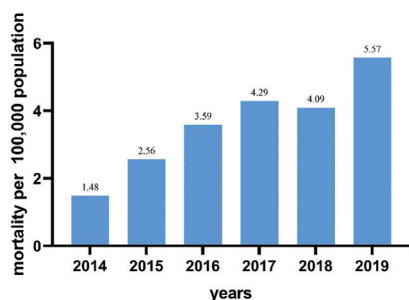

Figure 4b - All-cause mortality per 100,000 population in Kazakhstan between 2014-2019 years

Discussion

This is the first Central Asian study investigating the epidemiology of patients with glomerular diseases using administrative health data recently provided in Kazakhstan. The results of this study demonstrated an increase in the prevalence and mortality, as well as in the incidence of patients with glomerular disease from 2014 to 2019. In this patient cohort, diabetes mellitus was the most prevalent comorbidity associated with glomerular diseases. The majority of patients belonged to the age category of 51–70 years. Additionally, the overwhelming majority of patients (64%) resided in urban regions.

The increasing prevalence of glomerular diseases in Kazakhstan highlights an urgent public health issue that requires comprehensive investigation. Upon meticulous examination of potential risk factors, the interplay of genetic predisposition, aging, environmental influences, and socio-economic factors emerges as a complex nexus contributing to the growing burden of glomerular diseases [8]. As diagnostic challenges persist and treatment accessibility remains inconsistent, it is recommended to explore more precise screening methods, such as kidney biopsies for patients, and establish a national registry based on biopsy results [9]. Patients with glomerular disease in this study were collected solely based on their ICD-10 codes, which were assigned by patients' blood sample analysis. However, for more accurate diagnostic studies, patients should undergo kidney biopsy and be registered in a database, as practiced in more developed countries [9].

Our previous preliminary research revealed that glomerular diseases constitute only 9% of all causes of CKD, while arterial hypertension, along with other cardiovascular diseases and diabetes, accounts for the majority of CKD at 44%, 31%, and 11%, respectively [10]. Nevertheless, the diagnostic and treatment costs for glomerular diseases necessitate significant financial investments in healthcare, considering the morphological verification of the diagnosis and prolonged immunosuppressive therapy [11].

In a meta-analysis of kidney biopsy registries, researchers identified 16 major national catalogs worldwide, including Europe, South America, Asia, and Canada [12]. Notably, none of these catalogs includes Kazakhstan; currently, the country lacks a registry of morphologically verified glomerular disease cases. Based on kidney biopsy results, immunosuppressants and other forms of therapy are typically prescribed. Such data can predict the need for patients' immunosuppressants and medication requirements.

The study also points to an increase in all-cause mortality in Kazakhstan, necessitating a comparative analysis with other similar countries to understand the underlying factors contributing to this trend. The prevalence of non-communicable diseases, such as cardiovascular and respiratory diseases, may significantly contribute to the higher mortality rates in Kazakhstan compared to countries with similar demographic and socio-economic indicators.

The observed increase in incidence can be explained by several factors such as the prevalence of hypertension and diabetes, the aging population, poor diagnosis practices, poor data accuracy, and infectious diseases. More effective preventive measures and public health interventions can curb disease onset, potentially leading to a decline in incidence. Increasing public awareness and educational campaigns promoting a healthy lifestyle and risk-reduction strategies can influence population behavior, thereby reducing the overall risk of new cases [13]. However, it is important to note that while an increase in incidence signifies poor disease prevention and management, the simultaneous increase in disease prevalence suggests that affected patients are living longer with the condition. This shift underscores the need for a thorough understanding of disease dynamics, considering not only the frequency of new cases but also the duration and impact of the disease on affected individuals.

Various factors contribute to the fact that most patients reside in urban areas. Urban regions often have higher population density and expanded access to medical facilities, which can lead to increased awareness, diagnosis, and disease information dissemination [14].

The prevalence of comorbidities among individuals with glomerular diseases in Kazakhstan presents a compelling picture, demonstrating the relationship between kidney health and systemic diseases. Notably, diabetes mellitus is the primary comorbidity, illustrating an interesting link between glomerular diseases and metabolic disorders [15]. The high incidence of diabetes in this context not only exacerbates the burden of lifestyle-related diseases but also underscores the bidirectional influence between kidney function and metabolic health.

Furthermore, cardiovascular diseases are the second most prevalent comorbidity, emphasizing the profound consequences of glomerular diseases for the cardiovascular system. The connection between glomerular diseases and cardiovascular complications can be explained by common risk factors and underlying pathophysiological mechanisms. It is known that patients with glomerular disease develop common cardiovascular risk factors such as hypertension and hyperlipidemia. A study by Hutton et al. (2017) demonstrated that patients with glomerular disease, chronic kidney disease (CKD), and reduced estimated glomerular filtration rate (eGFR), not receiving active immunosuppressive therapy, face a significant three-year risk of cardiovascular events (9.2%). However, this risk seems to be substantially similar to CKD patients with similar characteristics but without glomerular diseases. This suggests that the increased risk of cardiovascular diseases in patients with glomerular disease may be associated with pre-existing cardiovascular risk factors and kidney function levels rather than the glomerular disease itself [16].

Hypertension, as the third most common comorbidity, highlights the mutual relationship between elevated blood

pressure and renal insufficiency [17]. The interaction between glomerular diseases and hypertension creates additional challenges for effective treatment and requires a comprehensive approach to addressing both conditions. This triad of common comorbidities - diabetes, cardiovascular diseases, and hypertension - calls for the development of comprehensive healthcare strategies aimed not only at kidney health but also at a broader spectrum of systemic diseases, facilitating integrated treatment and improved outcomes for people suffering from glomerular diseases in Kazakhstan.

The study is limited by certain factors, including the absence of a morphological diagnosis and kidney biopsy in the examined patients. Additionally, recorded ICD-10 codes based on blood samples may contain inaccuracies arising from human errors and may not truly reflect the actual epidemiological trends of glomerular disease. Therefore, it is crucial to further validate the study results by comparing them with the actual kidney biopsy results of patients. The retrospective design of the study may introduce inherent limitations, as it relies on previously recorded data, potentially leading to incomplete or inconsistent information. Prospective studies may offer more robust data collection and reduce the impact of retrospective limitations. Another limitation was that the study didn't have data on patient history about medical records, medication usage, or lifestyle factors that could impact the depth of the study findings.

Conclusion

The study examined the morbidity, prevalence of glomerular diseases, and all-cause mortality in Kazakhstan from 2014 to 2019. The most common comorbidities with glomerular disease in the Kazakhstani population were diabetes mellitus, cardiovascular diseases, and hypertension. Over this period, there was a significant increase in prevalence and the number of deaths from all causes, and an increase in the incidence rate. This research demonstrated the need for more precise diagnostic methods such as kidney biopsy and morphological verification of the diagnosis. These methods can enhance kidney disease screening, preventing its progression into a chronic form and predicting the need for immunosuppressive therapy.

References

1. Chadban SJ, Atkins RC. Glomerulonephritis. *Lancet* (London, England). 2005; 365(9473): 1797–1806. https://doi.org/10.1016/S0140-6736(05)66583-X.
2. National Health Service. Glomerulonephritis overview. *NHS.* 2023; https://www.nhs.uk/conditions/glomerulonephritis/#:~:text=Causes%20of%20glomerulonephritis,HIV.
3. Guo Q, Wu S, Xu C, Wang J, Chen J. Global Disease Burden From Acute Glomerulonephritis 1990-2019. *Kidney international reports.* 2021; 6(8): 2212–2217. https://doi.org/10.1016/j.ekir.2021.04.038.
4. Wetmore JB, Guo H, Liu J, Collins AJ, Gilbertson DT. The incidence, prevalence, and outcomes of glomerulonephritis derived from a large retrospective analysis. *Kidney international.* 2016; 90(4):853–860. https://doi.org/10.1016/j.kint.2016.04.026.
5. Kazi AM, Hashmi MF. Glomerulonephritis. statpearls. 2023; https://www.ncbi.nlm.nih.gov/books/NBK560644/.
6. Salifu OM. Chronic Glomerulonephritis. Medscape. November 2022; https://emedicine.medscape.com/article/239392-overview?Form=fpf.
7. Statistics committee Ministry of National Economy of the Republic of Kazakhstan. Main Socio-Economic Indicators 2019. http://stat.gov.kz/.
8. Obrador GT, Schultheiss UT, Kretzler M, Langham RG, Nangaku M, Pecoits-Filho R, Pollock C, Rossert J, Correa-Rotter R, Stenvinkel P, Walker R, Yang CW, Fox CS, & Köttgen A. Genetic and environmental risk factors for chronic kidney disease. *Kidney international supplements.* 2017; 7(2): 88–106. https://doi.org/10.1016/j.kisu.2017.07.004.
9. Brachemi S, Bollée G. Renal biopsy practice: What is the gold standard? *World journal of nephrology.* 2014; 3(4): 287–294. https://doi.org/10.5527/wjn.v3.i4.287.
10. Zhakhina G, Gaipov A, Mussina K, Yerdessov S, Gusmanov A, Sakko Y, Syssoyev D, Kim V, Kuanshgaliyeva Z, Turebekov D. WCN23-1016 current epidemiology and forecasting the trend of chronic kidney disease in Kazakhstan. *Kidney International Reports.* 2023; 8(3):181. https://doi.org/10.1016/j.ekir.2023.02.402.
11. Gordon EJ, Prohaska TR, Sehgal AR. The financial impact of immunosuppressant expenses on new kidney transplant recipients. *Clinical transplantation.* 2008; 22(6): 738–748. https://doi.org/10.1111/j.1399-0012.2008.00869.x.
12. Dendooven A, Peetermans H, Helbert M, Nguyen TQ, Marcussen N, Nagata M, Gesualdo L, Perkowska-Ptasinska A, Capusa C, López-Gómez JM, Geddes C, Abdul-Hamid MA, Segelmark M, Yahya, R., Garau M, Villanueva R, Dorman A, Barbour S, Cornet R, Hopfer H, Amann K, Leh S. Kidney Biopsy Codes for Pathologists project (www.kibico.org). Coding practice in national and regional kidney biopsy registries. *BMC nephrology.* 2021; 22(1): 193. https://doi.org/10.1186/s12882-021-02365-3.
13. Muxunov A, Bulanov N, Makhmetov S, Sharapov O, Abdullaev S, Loboda O, Aiypova D, Haziyev E., Rashidov, I., Tchokhonelidze, I., Okpechi, I. G., & Gaipov, A. Awareness of chronic kidney disease and its risk factors in the former Soviet Union countries. *Electronic Journal of General Medicine.* 2023; 20(6): em528. https://doi.org/10.29333/ejgm/13517.
14. Chen X, Orom H, Hay JL, Waters EA, Schofield E, Li Y, Kiviniemi MT. Differences in Rural and Urban Health Information Access and Use. The *Journal of rural health: official journal of the American Rural Health Association and the National Rural Health Care Association.* 2019; 35(3):405–417. https://doi.org/10.1111/jrh.12335.

15. Galiyeva D, Gusmanov A, Sakko Y, et al. Epidemiology of type 1 and type 2 diabetes mellitus in Kazakhstan: data from unified National Electronic Health System 2014–2019. *BMC Endocr Disord.* 2022; 22: 275. https://doi.org/10.1186/s12902-022-01200-6.
16. Hutton HL, Levin A, Gill J, Djurdjev O, Tang M, Barbour SJ. Cardiovascular risk is similar in patients with glomerulonephritis compared to other types of chronic kidney disease: a matched cohort study. *BMC nephrology.* 2017; 18(1): 95. https://doi.org/10.1186/s12882-017-0511-z.
17. Yerdessov S, Kadyrzhanuly K, Sakko Y, Gusmanov A, Zhakhina G, Galiyeva D, Bekbossynova M, Salustri A, Gaipov A. Epidemiology of Arterial Hypertension in Kazakhstan: Data from Unified Nationwide Electronic Healthcare System 2014–2019. *Journal of Cardiovascular Development and Disease.* 2022; 9(2): 52. https://doi.org/10.3390/jcdd9020052.

Relationship between coronavirus anxiety, resilience, and attitudes toward complementary and alternative treatment among patients admitted to the COVID-19 Outpatient Clinic

Ahmet Karakoyun[1], Emel Bahadir-Yilmaz[2], Arzu Yüksel[3]

[1]Department of Physical Medicine and Rehabilitation at the Faculty of Medicine, Aksaray University, Aksaray, Turkey
[2]Department of Psychiatric Nursing at the Faculty of Health Sciences, Giresun University, Giresun, Turkey
[3]Department of Psychiatric Nursing at the Faculty of Health Sciences, Aksaray University, Aksaray, Turkey

Corresponding author:
Emel Bahadir-Yilmaz.
E-mail: ebahadiryilmaz@yahoo.com;
emel: bahadir.yilmaz@giresun.edu.tr;
ORCID: 0000-0003-1785-3539.

Abstract

Aim: During the COVID-19 pandemic, the studies showed an increase in complementary and alternative therapy use. This study aimed to determine the relationship between coronavirus anxiety, resilience, and attitudes toward complementary and alternative treatment among patients admitted to the COVID-19 outpatient clinic.

Material and methods: This is a descriptive and relational study. The sample consisted of 364 patients who applied to the pandemic outpatient clinic of a training and research hospital in Turkey. Data were collected using the Coronavirus Anxiety Scale, Brief Resilience Scale, and Scale for Attitudes toward Complementary and Alternative Medicine. The Mann–Whitney U test, the Kruskal–Wallis test, and the Spearman correlation test were used in data analysis.

Results: There was a moderate and negative correlation (r = −0.332) between attitudes toward complementary and alternative medicine and coronavirus anxiety, and a moderate and positive correlation (r = 0.348) between attitudes toward complementary and alternative medicine and resilience (p < 0.01). Additionally, there was a moderate and negative correlation between coronavirus anxiety and resilience (r = −0.667; p < 0.01).

Conclusion: In the COVID-19 pandemic process, it is essential to follow up on patients' complementary and alternative medicine use, inform them, and determine their causes.

Keywords: anxiety, psychological resilience, complementary and alternative medicine, COVID-19

Introduction

Coronavirus disease 2019 (COVID-19), transmitted from sick people or carriers, causes symptoms such as fever, respiratory failure, dry cough, muscle, chest and joint pain, and pneumonia [1, 2]. The disease increases cardiovascular risk, causing diseases such as arrhythmia, heart attack, myocarditis, and pericarditis [3]. Hematological complications such as thromboembolism and thrombocytopenia, autoimmune complications such as hemolytic anemia and thyroid diseases, and complications related to the respiratory, renal, and neurological systems are also seen [1, 4].

The lethal effect of the disease has been increasing gradually; however, a definitive treatment remains unknown. Current treatment in many countries has been directed at disease symptoms. Antiviral treatment and plasma therapy are applied, and vaccination studies are continuing rapidly to find a definitive treatment against the virus. Complementary and alternative medicine (CAM) methods are given alone or in combination with standard therapy to prevent or treat COVID-19 [5, 6]. Food and herbs can contribute to the treatment and prevention of the disease. It can also be used to manage and prevent infection and strengthen immunity [7].

During the COVID-19 pandemic, the use of complementary and alternative therapy has increased. A study conducted in China showed that about 26% of patients diagnosed with COVID-19 used CAM products and home-made medicines during and even after their

treatment, and a study in Nepal found that the use of medicinal herbs helped prevent or treat the COVID-19 disease [8, 9]. Further, a study carried out in Bangladesh revealed that more than half of the participants were using drugs and herbal food/products to prevent the disease [10]. Therefore, this study aimed to determine the relationship between coronavirus anxiety, resilience, and attitudes toward complementary and alternative treatment among patients admitted to the COVID-19 outpatient clinic.

Material and methods

Design

This descriptive and relational study enrolled patients who registered in the pandemic outpatient clinic of a training and research hospital located in the city of Aksaray in the Central Anatolia Region of Turkey between October and December 2020.

Study population and sample

The study included individuals suspected for COVID-19 who applied to the pandemic outpatient clinic and who were above 18 years of age and conscious and did not have any mental problems and communication difficulties. The data was collected via Google form. The study objective was explained to the patients who applied to the outpatient clinic, and the phone numbers or e-mails of the patients who wanted to participate in the volunteer were taken and a link to the Google form was sent.

The sample size was calculated using the Brief Resilience Scale (BRS). The mean and standard deviation (9.76 ± 2.61) obtained in one study were used [11]. The following formula was used for the calculation: $n = (t^2 * s^2) / d^2$ [12]. The sample size was calculated as 105 and the sample of the study consisted of 365 volunteers.

Data collection tools

Data were collected using the "Patient Information Form," "Coronavirus Anxiety Scale," "Brief Resilience Scale," and "Scale for Attitudes toward CAM."

Patient information form

In the first part of the form, questions on the patient's age, educational status, occupation, and economic status were included, followed by questions regarding having a chronic disease, pain, and respiratory distress in the second part.

Coronavirus Anxiety Scale (CAS)

The scale was developed by Lee [13]. Turkish validity and reliability study was conducted by Evren et al. [14]. The scale consisted of five items and each item is scored between 0-4. The highest score that can be obtained from the scale is 20. An increase in the mean score is associated with higher COVID-19 anxiety. The Cronbach's alpha coefficient of the CAS was 0.80. In this study, it was 0.90.

The Brief Resilience Scale (BRS)

The scale was developed by Smith et al. [15]. Turkish reliability and validity study was conducted by Doğan [16]. There are six items in the scale and each item is scored between 1 and 5. The highest score that can be obtained from the scale is 30. An increase in the mean score is associated with higher resilience. In present study, the Cronbach alpha coefficient of the scale was 0.89.

Scale for Attitudes toward CAM (SACAM)

The SACAM was developed by Araz and Harlak [17]. It consists of eight items and each item is scored between 1 and 5. Four items assess the patients' attitudes toward complementary medicine and four items evaluate their attitudes toward alternative medicine. The Cronbach Alpha coefficient for internal consistency was 0.85, the Complementary Medicine

Subscale score was 0.77, and the Alternative Medicine Subscale score was 0.76. The lowest score was 8 and the highest was 40. Higher scores show positive attitudes toward CAM. In this study, it was 0.91.

Data evaluation

The study's data were analyzed with the SPSS (Statistical Package for Social Science for Windows 24.0) program. Statistics such as mean and standard deviation were used to present descriptive data. Data were not normally distributed according to the Kolmogorov–Smirnov test. Therefore, analyses were performed using the Mann–Whitney U, Kruskal–Wallis, and Spearman correlation tests. $p < 0.05$ level was accepted statistically significant.

Ethical approval

Before the study started, written permissions were obtained from the Training and Research Hospital and University Human Research Ethics Committee (date, October 1, 2020; No., 2020/09-19). The purpose of the study was explained to the patients before the data were collected. It is stated that the information obtained will only be used for scientific purposes. The principles of the Declaration of Helsinki were taken into account at each stage of the study. The authors report no actual or potential conflict of interest.

Results

The average age of the patients participating in the study was 38.04 ± 12.51 (min = 18; max = 77). Table 1 presents the following: 43.4% of the participants are between the ages 18 and 34, 54.7% are women, and 71.7% are married. 47.5% are exercising during the pandemic process. Moreover, 72.3% of them had a positive coronavirus test, and 88.6% of those who have positive coronavirus tests were treated at home. Only 22.5% of them have a chronic disease and 73.1% have pain complaints.

The CAS average of the participants was 4.76 ± 4.67; the BRS mean score was 18.30 ± 5.55; and the mean SACAM score was 15.73 ± 5.47 (Table 2).

There was a moderate and negative correlation ($r = -0.332$) between the SACAM and CAS scores of the participants and moderate and positive correlation ($r = 0.348$) between the SACAM and BRS scores ($p < 0.01$). Additionally, there was a moderately and negatively significant correlation between the CAS and BRS scores ($r = -0.667$; $p < 0.01$) (Table 3).

The mean CAS score of the participants was high in women (5.80 ± 4.94); those aged 52 and over (8.78 ± 4.87), married (5.50 ± 4.76), having children (5.75 ± 4.78), and living in the village (8.12 ± 6.63); primary school graduates (8.51 ± 4.88); those whose income are equal to their expenses (5.43 ± 4.77); those who do not exercise during the pandemic process (5.76 ± 5.13); those who have a positive coronavirus test (5.65 ± 4.82); those who are hospitalized (10.56 ± 5.49); those with chronic diseases (8.46 ± 5.27); those who experience pain (5.82 ± 4.82); and those whose pain extremely affects their daily life (8.71 ± 5.06) ($p < 0.05$) (Table 4).

In contrast, the mean BRS score was high in males (19.83 ± 5.66); those between 18 and 34 years (20.28 ± 4.97), who are single (20.66 ± 4.92), having no children (20.53 ± 4.98), and living in the city (18.88 ± 5.20); those with postgraduate education (22.03 ± 3.80); those whose incomes are less than their expenses (21.06 ± 4.17); those who exercise during the pandemic process (20.09 ± 4.79); those who have a negative coronavirus test (21.25 ± 4.27); those who receive their treatment at home (17.65 ± 5.32); those who do not have chronic diseases (19.23 ± 5.04); and those who have no pain (21.19 ± 4.62; $p < 0.05$) (Table 4).

Table 1	Socio-demographic characteristics of participants (n=364)		
Characteristics		n	%
Age, year			
18-34		158	43.4
35-51		156	42.9
≥ 52		50	13.7
Gender			
Female		199	54.7
Male		165	45.3
Marital status			
Married		261	71.7
Single		103	28.3
Having a child			
Yes		248	68.1
No		116	31.9
Place of residence			
City		294	80.8
Town		46	12.6
Village		24	6.6
Educational status			
Primary school		72	19.8
High school		81	22.2
Two-year college degree		49	13.5
Bachelor degree		131	36.0
Postgraduate degree		31	8.5
Income status			
High		113	31.0
Moderate		189	52.0
Low		62	17.0
Exercising during the pandemic			
Yes		173	47.5
No		191	52.5
Coronavirus test			
Positive		263	72.3
Negative		101	27.7
Hospitalization (n = 263)			
Yes		30	11.4
No		233	88.6
Having a chronic disease			
Yes		82	22.5
No		282	77.5
Having pain complaints			
Yes		266	73.1
No		98	26.9
Regions where pain is felt			
Neck		87	10.6
Back		182	22.2
Shoulder		46	5.6
Arms		38	4.6
Waist		122	14.9
Hip		85	10.5
Knee		58	7.1
Legs		157	19.2
Feet		43	5.3
Effect of pain on daily life			
Never		118	32.4
Little		132	36.3
High		114	31.3

Table 2	Mean scores of the sample on the CAS, BRS, and SACAM.		
	Mean ± SD	Median	Min-Max
Coronavirus Anxiety Scale (CAS)	4.76 ± 4.67	3	0-16
Brief Resilience Scale (BRS)	18.30 ± 5.55	19	6-30
Scale for Attitudes toward Complementary and Alternative Medicine	15.73 ± 5.47	15	8-37
Attitudes towards alternative medicine	7.67 ± 2.84	8	4-19
Attitudes towards complementary medicine	8.05 ± 2.98	8	4-18

Table 3	Correlation between the CAS, BRS, and SACAM scores			
		CAS	BRS	SACAM
CAS	r	1		
	p	-		
BRS	r	-0.667*	1	
	p	0.000	-	
SACAM	r	-0.332*	0.348*	1
	p	0.000	0.000	-

* Correlation is significant at the 0.01 level. CAS = Coronavirus Anxiety Scale; BRS = Brief Resilience Scale; SACAM = Scale for Attitudes toward Complementary and Alternative Medicine.

As seen in Table 4, the mean SACAM score is high in men (16.56 ± 6.19); those who are between ages 18 and 34 (16.41 ± 4.90), single (16.46 ± 5.24), having no children (16.09 ± 4.89), and living in the city (16.15 ± 5.44); those with a postgraduate education (19.38 ± 7.39); those whose incomes are less than their expenses (17.08 ± 4.97); those who exercise during the pandemic process (16.72 ± 5.51) and have a negative coronavirus test (17.24 ± 5.23); those who receive their treatment at home (15.35 ± 5.37); those who do not have chronic disease (16.52 ± 5.53); those who have no pain (17.72 ± 5.85); and those whose pain does not affect their daily life at all (17.91 ± 5.71; p < 0.05).

Discussion

The coronavirus anxiety levels of the patients who applied to the clinic were found to be low. However, the anxiety level was high in women; those aged 52 and above; those who are married, have children, live in villages, and are primary school graduates; those whose income is equal to their expenses; those who do not exercise during the pandemic process; those who have positive coronavirus tests; those who are hospitalized; those who have chronic disease; those who have pain; and those whose pain affects their daily life considerably. Similarly, Lee et al. found that age, gender, and education affected dysfunctional coronavirus anxiety [18]. In another study conducted in the general population, the anxiety levels of those who were over the age of 30, women, high education level, married, and non-governmental workers were found to be increased [19]. Accepting the factors obtained in this study as risk factors in terms of coronavirus anxiety enables problem identification in the early stage and supported and resolved with appropriate interventions.

This study revealed that the resilience of the patients who applied in the COVID-19 outpatient clinic was at a significant level. In addition, men, young people, single people, those who do not have children, those who live in the city, those who have a high education level, those who have low income, those who

Characteristics	Coronavirus Anxiety X ± SD	Resilience X ± SD	Attitudes toward CAM X ± SD
Gender			
Female	5.80 ± 4.94	17.04 ± 5.15	15.04 ± 4.71
Male	3.52 ± 3.99	19.83 ± 5.66	16.56 ± 6.19
z	-4.682	-4.795	-2.082
p	0.000	0.000	0.037
Age, year			
18-34	3.05 ± 3.79	20.28 ± 4.97	16.41 ± 4.90
35-51	5.21 ± 4.54	17.44 ± 5.12	15.71 ± 6.05
≥ 52	8.78 ± 4.87	14.74 ± 6.19	13.60 ± 4.82
x^2	56.596	39.862	14.604
p	0.000	0.000	0.001
Marital status			
Married	5.50 ± 4.76	17.37 ± 5.52	15.44 ± 5.55
Single	2.91 ± 3.88	20.66 ± 4.92	16.46 ± 5.24
z	-5.284	-4.895	-2.103
p	0.000	0.000	0.035
Having a child			
Yes	5.75 ± 4.78	17.26 ± 5.51	15.56 ± 5.73
No	2.67 ± 3.64	20.53 ± 4.98	16.09 ± 4.89
z	-6.353	-5.031	-1.631
p	0.000	0.000	0.103
Place of residence			
City	4.24 ± 4.18	18.88 ± 5.20	16.15 ± 5.44
Town	6.39 ± 5.37	16.17 ± 6.19	14.23 ± 5.93
Village	8.12 ± 6.63	15.37 ± 6.72	13.33 ± 3.82
x^2	10.316	16.868	13.829
p	0.006	0.000	0.001
Educational status			
Primary school	8.51 ± 4.88	13.88 ± 5.72	12.83 ±4.30
High school	4.34 ± 4.54	18.79 ± 5.26	15.39 ± 5.18
Two-year college degree	4.28 ± 4.41	19.83 ± 4.89	16.04 ± 4.97
Bachelor degree	3.54 ± 3.77	18.98 ± 4.84	16.54 ± 5.17
Postgraduate degree	3.09 ± 3.96	22.03 ± 3.80	19.38 ± 7.39
x^2	52.044	61.905	38.678
p	0.000	0.000	0.000
Income status			
High	4.64 ± 4.61	18.66 ± 5.55	16.10 ± 5.97
Moderate	5.43 ± 4.77	17.19 ± 5.63	15.06 ± 5.25
Low	2.96 ± 3.97	21.06 ± 4.17	17.08 ± 4.97
x^2	14.549	24.936	10.058
p	0.001	0.000	0.007
Exercising during the pandemic			
Yes	3.66 ± 3.82	20.09 ± 4.79	16.72 ± 5.51
No	5.76 ± 5.13	16.68 ± 5.71	14.83 ± 5.30
z	-3.357	-5.548	-3.724
p	0.001	0.000	0.000
Coronavirus test			
Positive	5.65 ± 4.82	17.17 ± 5.58	15.14 ± 5.46
Negative	2.45 ± 3.28	21.25 ± 4.27	17.24 ± 5.23
z	-6.169	-6.123	-3.968
p	0.000	0.000	0.000
Hospitalization (n=263)			
Yes	10.56 ± 5.49	13.43 ± 6.20	13.56 ± 6.04
No	5.02 ± 4.35	17.65 ± 5.32	15.35 ± 5.37
z	-5.068	-3.764	-2.410
p	0.000	0.000	0.016
Having a chronic disease			
Yes	8.46 ± 5.27	15.10 ± 6.05	13.01 ± 4.33
No	3.69 ± 3.87	19.23 ± 5.04	16.52 ± 5.53
z	-7.033	-5.377	-5.603
p	0.000	0.000	0.000
Pain			
Yes	5.82 ± 4.82	17.24 ± 5.50	14.99 ± 5.15
No	1.90 ± 2.59	21.19 ± 4.62	17.72 ± 5.85
z	-7.526	-5.883	-4.430
p	0.000	0.000	0.000
Effect of pain on daily life			
Never	2.03 ± 2.56	21.03 ± 4.42	17.91 ± 5.71
Little	3.80 ± 3.35	19.06 ± 4.95	15.40 ± 5.15
High	8.71 ± 5.06	14.61 ± 5.32	13.84 ± 4.79
x^2	107.625	75.632	37.056
p	0.000	0.000	0.000

Table 4 The comparison of the socio-demographic characteristics between mean scores of the sample on the CAS, BRS, and SACAM.

exercise during the pandemic process, those who have negative coronavirus test, those who receive their treatment at home, those who do not have chronic diseases, and those who have no pain had higher psychological resilience. Contrary to the findings obtained in this study, in a study conducted with hemodialysis patients, those with good income were found to have higher psychological resilience, whereas gender, marital status, education level, and history of chronic disease were not found to be effective [20]. Moreover, in a study conducted in arthritis patients during the COVID-19 pandemic, it was found that they had higher psychological resilience than healthy controls [21]. Therefore, we conclude that the disease process can increase resilience by activating coping skills and adaptability and that some sociodemographic characteristics can affect the level of resilience.

Exercising in quarantine during the pandemic process increased resilience by leading to higher locus of control, self-efficacy, and optimism and that gender had a crucial effect on this relationship [22]. In a study conducted with menopausal women during the pandemic process, it was found that doing physical activity improved quality of life and increased resilience [23]. Another study showed that regular physical activity during the quarantine process increased psychological resilience and reduced depressive symptoms along with positive affect, improving focus of control, optimism, and self-efficacy [24]. In line with the results of this study, we can say that the participants who exercise during the pandemic process have higher psychological resilience.

The participants' level of attitude toward complementary and alternative therapy was found to be low. However, men, young people, single individuals, those who do not have children, those who live in the city, those who have a high education level, those who have low income, those who exercise during the pandemic process, those who have negative coronavirus test, those who receive their treatment at home, those who do not have chronic diseases, and those who do not have pain and whose pain does not affect daily life at all had more positive attitudes. In a study conducted at the isolation center during the COVID-19 process, it was determined that approximately one third of the participants used CAM products during treatment and after discharge [8]. As mentioned, in a study conducted during the pandemic process, it was found that 57.6% of the participants took herbal products and that women, young people, those with a high level of education, single individuals, and those living in the city used herbal products more [10]. Studies on SACAM during the COVID-19 pandemic process are limited. However, in the third version of the National COVID-19 Diagnosis and Treatment Guidelines in China, traditional herbal Chinese medicine was proposed as a treatment during the pandemic [25]. World Health Organization declared that it will support scientifically proven traditional medical support in the fight against COVID-19 [26]. In recent days, the use of complementary alternative medicine to prevent or treat coronavirus disease in Turkey has been frequently reported, and its benefits, harms, and side effects have been discussed [27]. In this respect, it should be kept in mind that the use of products that are not scientifically proven may cause unwanted side effects. The low attitudes toward CAM use in this study can be considered as a good result in this sense.

This study found that as the resilience increased, the coronavirus anxiety levels of the participants decreased. Similarly, in a study conducted with doctors during the pandemic process, an inverse relationship was determined between anxiety and resilience [28]. In a study conducted with nurses, a strong relationship was found between coronavirus-related anxiety and

resilience [29]. Further, in another study with healthcare workers, high resilience was associated with low COVID-19 anxiety [30]. In studies conducted with the general population during the pandemic process, a negative relationship was found between anxiety and resilience [31,32]. In fact, resilience was defined as the ability to cope with difficult life events such as illness and disasters and to recover again [33]. It can be said that the disease process during pandemic improves the resilience level, and the anxiety level decreases as the level of psychological resilience increases.

A strong relationship between the participants' attitudes toward complementary and alternative medicine and coronavirus anxiety was observed, and as their CAM attitudes increased positively, their anxiety levels decreased. Similarly, in a study conducted with patients with solid tumors, the anxiety levels of those using CAM were found to be lower than those of who did not use it, and it was found to be associated with anxiety [34]. In another study conducted with cancer patients, no significant relationship was found between CAM use and anxiety level [35]. There was no other study conducted on this subject during the pandemic process. However, it was stated that complementary and integrative medicine can strengthen mental and physical health and reduce symptoms such as anxiety and depression in COVID-19 patients [36].

Conclusion

In conclusion, it was determined that patients who applied to the COVID-19 outpatient clinic had low coronavirus anxiety and attitudes toward CAM, and their psychological resilience levels were good. Chiefly, as the psychological resilience levels of the participants increased, their coronavirus anxiety and attitude toward CAM decreased. This finding is believed to provide crucial contributions to experimental studies on the subject. In this regard, psychological resilience-based psychosocial interventions have been recommended for individuals diagnosed with COVID-19 who are under hospital or home treatment. It was predicted that these interventions could reduce or improve mental symptoms such as anxiety. Identifying sociodemographic characteristics that pose a risk for coronavirus anxiety, performing mental follow-up of the person who is thought to be at risk, and supporting them with psychosocial interventions may as well be beneficial in reducing mortality and morbidity.

References

1. Fernandes PMP, Mariani AW. Life post-COVID-19: Symptoms and chronic complications. *Sao Paulo Med J.* 2021; 139(1): 1-2. https://doi.org/10.1590/1516-3180.2021.139104022021.
2. Şenyiğit A. COVID-19 pandemic; clinical findings, diagnosis, treatment and prevention. *Dicle Medical Journal.* 2021; 48(special issue): 176-186. https://doi.org/10.5798/dicletip.1005418.
3. Alosaimi B, AlFayyad I, Alshuaibi S, Almutairi G, Alshaebi N, Alayyaf A, et al. Cardiovascular complications and outcomes among athletes with COVID-19 disease: A systematic review. *BMC Sports Sci Med Rehabil.* 2022; 14: 74. https://doi.org/10.1186/s13102-022-00464-8.
4. Yazdanpanah N, Rezaei N. Autoimmune complications of COVID-19. *J Med Virol.* 2022; 94(1): 54-62. https://doi.org/10.1002/jmv.27292.
5. Ang L, Song E, Lee HW, Lee MS. Herbal medicine for the treatment of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of randomized controlled trials. *J Clin Med.* 2020; 9(5): 1583. https://doi.org/10.3390/jcm9051583.
6. Shankar A, Dubey A, Saini D, Prasad CP. Role of complementary and alternative medicine in prevention and treatment of COVID-19: an overhyped hope. Chin J Integr Med. 2020; 26(8): 565–7. https://doi.org/10.1007/s11655-020-2851-y.
7. Panyod S, Ho CT, Sheen LY. Dietary therapy and herbal medicine for COVID-19 prevention: a review and perspective. *J Tradit Complement Med.* 2020; 10: 420–7. https://doi.org/10.1016/j.jtcme.2020.05.004.
8. Charan J, Bhardwaj P, Dutta S, Kaur S, Bist SK, Detha MD, et al. Use of complementary and alternative medicine (CAM) and home remedies by COVID-19 patients: a telephonic survey. *Indian J Clin Biochem.* 2021; 36(1): 108–11. https://doi.org/10.1007/s12291-020-00931-4.
9. Khadka D, Dhamala MK, Li F, Aryal PC, Magar PR, Bhatta S, et al. The use of medicinal plant to prevent COVID-19 in Nepal. *J Ethnobiol Ethnomed.* 2020. https://doi.org/10.21203/rs.3.rs-88908/v1.
10. Ahmed I, Hasan M, Akter R, Sarkar BK, Rahman M, Sarker S, et al. Behavioral preventive measures and the use of medicines and herbal products among the public in response to Covid-19 in Bangladesh: a cross-sectional study. *PLoS One.* 2020; 15(12): e0243706. https://doi.org/10.1371/journal.pone.0243706.
11. Satici SA, Kayis AR, Satici B, Griffiths MD, Can G. Resilience, hope, and subjective happiness among the Turkish population: fear of COVID-19 as a mediator. *Int J Ment Health Addiction.* 2020. https://doi.org/10.1007/s11469-020-00443-5.
12. Aktürk Z, Acemoğlu H. Sağlık çalışanları için araştırma ve pratik istatistik: örnek problemler ve SPSS çözümleri (2nd ed.). İstanbul, Turkey: *Anadolu Ofset*; 2011. (in Turkish).
13. Lee SA. Coronavirus Anxiety Scale: A brief mental health screener for COVID-19 related anxiety. *Death Stud.* 2020; 44(7): 393–401. https://doi.org/10.1080/07481187.2020.174848116.

14. Evren C, Evren B, Dalbudak E, Topcu M, Kutlu N. Measuring anxiety related to COVID-19: a Turkish validation study of the Coronavirus Anxiety Scale. Death Stud. 2022; 46(5): 1052-1058. https://doi.org/10.1080/07481187.2020.1774969.

15. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Jennifer Bernard J. The brief resilience scale: assessing the ability to bounce back. *Int J Behav Med.* 2008; 15(3): 194–200. https://doi.org/10.1080/10705500802222972.

16. Doğan T. Kısa Psikolojik Sağlamlık Ölçeği'nin Türkçe uyarlaması: geçerlik ve güvenirlik çalışması. *The Journal of Happiness & Well-Being.* 2015; 3(1): 93–102.

17. Araz A, Harlak H. Developing a scale for attitudes towards complementary and alternative medicine. *Turk J Public Health.* 2006; 4(2): 47–54.

18. Lee SA, Jobe MC, Mathis AA. Mental health characteristics associated with dysfunctional coronavirus anxiety. *Psychol Med* 2021;51(8):1403-1404. https://doi.org/10.1017/S003329172000121X.

19. Islam S, Ferdous Z, Potenza MN. Panic and generalized anxiety during the COVID-19 pandemic among Bangladeshi people: an online pilot survey early in the outbreak. *J Affect Disord.* 2020; 276: 30–7. https://doi.org/10.1016/j.jad.2020.06.049.

20. Karadag E, Ugur O, Mert H, Erunal M. The relationship between psychological resilience and social support levels in hemodialysis patients. J Basic Clin Health Sci. 2019; 3(1): 9–15. https://doi.org/10.30621/jbachs.2019.469.

21. Ciaffi J, Brusi V, Lisi L, Mancarella L, D'Onghia M, Quaranta E, et al. Living with arthritis: a "training camp" for coping with stressful events? A survey on resilience of arthritis patients following the COVID-19 pandemic. *Clin Rheumatol.* 2020; 39: 3163–70. https://doi.org/10.1007/s10067-020-05411-x.

22. Carriedo A, Cecchini JA, Fernandez-Rio J, Mendez-Gimenez A. Resilience and physical activity in people under home isolation due to COVID-19: a preliminary evaluation. *Ment Health Phys Act.* 2020a; 19: 100361. https://doi.org/10.1016/j.mhpa.2020.100361.

23. Coronado PJ, Fasero M, Otero B, Sanchez S, de la Viuda E, Ramirez-Polo I, et al. Health-related quality of life and resilience in peri- and postmenopausal women during Covid-19 confinement. *Maturitas.* 2021; 144: 4–10. https://doi.org/10.1016/j.maturitas.2020.09.004.

24. Carriedo A, Cecchini JA, Fernandez-Rio J, Mendez-Gimenez A. COVID-19, psychological well-being and physical activity levels in older adults during the nationwide lockdown in Spain. *Am J Geriatr Psychiatry.* 2020b; (11): 1146–55. https://doi.org/10.1016/j.jagp.2020.08.007.

25. Li Y, Li J, Zhong D, Zhang Y, Guo Y, Clarke M, et al. Clinical practice guideliness and experts' consensuses of traditional Chinese herbal medicine for novel coronavirus (COVID-19): protocol of a systematic review. Chin. *J. Integr. Med.* 2020; 26(10): 786–93. https://doi.org/10.1186/s13643-020-01432-4.

26. World Health Organization. WHO supports scientifically-proven traditional medicine. Available from https://www.afro.who.int/news/who-supports-scientifically-proven-traditional-medicine. Accessed November 11, 2021.

27. Konakci G, Ozgursoy-Uran BN, Erkin O. In the Turkish news: coronavirus and "alternative & complementary" medicine methods. *Complement Ther Med.* 2020; 53: 102545. https://doi.org/10.1016/j.ctim.2020.102545.

28. Mosheva M, Hertz-Palmor N, Ilan SD, Matalon N, Pessach IM, Afek A, et al. Anxiety, pandemic-related stress and resilience among physicians during the COVID-19 pandemic. *Depress Anxiety.* 2020; 37(10): 965–71. https://doi.org/10.1002/da.23085.

29. Labraque LJ, De los Santos JAA. COVID-19 anxiety among front-line nurses: predictive role of organisational support, personal resilience and social support. *J Nurs Manag.* 2020; 28: 1653–61. https://doi.org/10.1111/jonm.13121.

30. Barzilay R, Moore TM, Greenberg DM, DiDomenico GE, Brown LA, White LK, et al. Resilience, COVID-19-related stress, anxiety and depression during the pandemic in a large population enriched for healthcare providers. *Transl Psychiatry.* 2020; 10: 291. https://doi.org/10.1038/s41398-020-00982-4.

31. Havnen A, Anyan F, Hjemdal O, Solem S, Riksfjord MG, Hagen K. Resilience moderates negative outcome from stress during the COVID-19 pandemic: a moderated-meditation approach. *Int J Environ Res Public Health.* 2020; 17: 6461. https://doi.org/10.3390/ijerph17186461.

32. Ran L, Wang W, Ai M, Kong Y, Chen J, Kuang L. Psychological resilience, depression, anxiety, and somatization symptoms in response to COVID-19: a study of the general population in China at the peak of its epidemic. *Soc Sci Med.* 2020; 262: 113261. https://doi.org/10.1016/j.socscimed.2020.113261.

33. Öz F, Bahadır-Yılmaz E. Ruh sağlığının korunmasında önemli bir kavram: psikolojik sağlamlık. *Sağlık Bilimleri Fakültesi Hemşirelik Dergisi.* 2009; 16(3): 82–9.

34. Jang A, Kang DH, Kim DU. Complementary and alternative medicine use and its association with emotional status and quality of life in patients with a solid tumor: a cross-sectional study. *J Altern Complement Med.* 2017; 23(5): 362–9. https://doi.org/10.1089/acm.2016.0289.

35. Kalender ME, Buyukhatıpoglu H, Balakan O, Suner A, Dirier A, Sevinc A, et al. Depression, anxiety and quality of life through the use of complementary and alternative medicine among breast cancer patients in Turkey. *J Cancer Res Ther.* 2014; 10(4): 962–6. https://doi.org/10.4103/0973-1482.138010.

36. Seifert G, Jeitler M, Stange R, Michalsen A, Cramer H, Brinkhaus B, et al. The relevance of complementary and integrative medicine in the COVID-19 pandemic: a qualitative review of the literature. *Front Med.* 2020; 7: 587749. https://doi.org/10.3389/fmed.2020.587749/.

Maternal-fetal attachment among pregnant women at risk for mental health: a comparative study

Sümeyye Barut[1], Esra Sabancı Baransel[2]

[1]Department of Midwifery, Faculty of Health Sciences, Fırat University, Elazığ, Turkey
[2]Department of Midwifery, Faculty of Health Sciences, Inönü University, Malatya, Turkey

Corresponding author:
Esra Sabancı Baransel.
E-mail: esraa.sabancii@gmail.com;
ORCID: 0000-0001-6348-2084.

Abstract

Background: Mental problems (stress, anxiety, and depression) experienced by the pregnant negatively affect the life and health of the fetus in the future and may increase the complications seen in pregnancy, delivery and postpartum.

Aim: In this study, it was aimed to determine maternal-fetal attachment among pregnant women at risk for mental health.

Methods: This cross-sectional study was conducted with 404 women between June 10, 2023 and September 30, 2023 in the obstetrics and gynecology outpatient clinics of a private hospital in eastern Türkiye. Data were collected with the Personal Information Form, the Maternal Antenatal Attachment Scale (MAAS), and the General Health Questionnaire (GHQ-28). The data were evaluated according to the General Health Questionnaire (GHQ-28) mean score, by dividing them into two groups as those at risk for mental health and those without risk for mental health.

Results: The MAAS mean score of the women participating in the study was 67.78±9.66, and the mean scores of the subscales of "Attachment Quality" and "Time Spent on Attachment" of the MAAS were 40.82±55.33 and 26.95±5.62, respectively; it was determined that the mean score they got from the GHQ-28 was 2.98±3.81. Between the groups with high-risk and non-risky pregnancies, the mean scores of the MAAS and the subscale of Attachment Quality were found to be higher in non-risky pregnancies (p<0.05). Additionally, it was determined that the mean score of "Time Spent on Attachment" of non-risky pregnant women was higher than that of high-risk pregnant women, but there was no statistically significant difference between the groups (p> 0.05). The GHQ-28 mean score was lower in non-risky pregnant women (p<0.05).

Conclusion: In the study, it was determined that the maternal-fetal attachment levels of pregnant women with psychological risk were low. Therefore, the results suggest that it is necessary to determine mental problems in pregnant women and to conduct screening programs more frequently.

Keywords: Attachment, maternal, mental health, pregnant,

Introduction

The pregnancy process is a period that is considered as a preparation stage for motherhood and aimed to provide a positive experience, with various changes in female anatomy, physiology, and psychology [1]. If the expectant mother cannot cope with the intense changes and stress factors she encounters during pregnancy, the risk of developing mental illnesses may increase. Stress and mental disorders experienced during pregnancy can negatively affect both the mother and the fetus [2, 3]. Previous studies in the literature presented that depression and anxiety are the most common mental illnesses during pregnancy [4, 5]. In a study evaluating anxiety and depression during pregnancy, it was determined that 26.9% of Turkish women and 9.5% of Hispanic women had anxiety and depression [6]. In a study conducted in Turkey in 2009, it was determined that 27.9% of pregnant women had depression, and there was a positive relationship between depression and anxiety. In a systematic review and meta-analysis conducted in 2021, the prevalence of depression was found to be 30.3% in low-income countries, 30.8% in middle-income countries, and 18.1% in high-income countries. In the study conducted by Fawcett et al., it was determined that anxiety disorders were seen at a rate of 20.7% [7]. Mental illnesses among pregnant women can affect the pregnant woman and the fetus in many ways. The maternal attachment that develops in this process may be affected by the mental state of the pregnant woman.

Maternal attachment begins with pregnancy and continues throughout life [8]. Attachment is viewed as a psychological process. Feelings related to attachment enable the development of maternal identity and affection for the baby. From the beginning of pregnancy, the woman perceives her baby both as a part of herself and as a new individual. The attachment process includes a multifactorial process such as maternal health, psychosocial health, stress, environmental factors, receiving prenatal care, baby's gender, spouse's approach, and unwanted pregnancy. It was determined that there is a positive relationship between the psychosocial health of pregnant women and the role of motherhood [9]. Mental problems (stress, anxiety, and depression) experienced by the pregnant negatively affect the life and health of the fetus in the future and may increase the complications seen in pregnancy and delivery [10, 11]. Problems that negatively affect neonatal health such as prematurity delivery, low birth weight, and fetal growth retardation may arise [12]. Mental health problems experienced during pregnancy may negatively affect the mother and baby bonding during infancy and may cause the child to lead an unhealthy social life in the future [13].

It is known to be effective onIn addition, mental health problems negatively affect family health. For these reasons, mothers should be carefully screened during pregnancy not only physically but also in terms of mental health, and the risks should be determined. The most important task in this regard falls to midwives and nurses working in primary care.

For this reason, it was aimed to determine maternal-fetal attachment levels among pregnant women at risk for mental health. It is hoped that the findings obtained in this study would guide midwives and nurses in terms of health protection and the services they provide for pregnant women at risk for mental health. The findings of this study would guide healthcare professionals by emphasizing the importance of evaluating the mental health of pregnant women.

Research questions:

1. What is the maternal-fetal attachment level of pregnant women at risk for mental health?

Materials and Methods

This cross-sectional study was conducted between June 10, 2023 and September 30, 2023 in the obstetrics and gynecology outpatient clinics of a private hospital in eastern Türkiye. Pregnant women who applied to gynecology outpatient clinics were included in the sample of the study by utilizing the random sampling method. In the study, the sample size was determined as at least 385 in the 5% error level, 80% power, and 95% confidence interval, when the power analysis was performed together with the sample calculation of the unknown population. The study was completed with 404 pregnant women who volunteered to participate in the study. The data were evaluated according to the General Health Questionnaire (GHQ-28) score, by dividing them into two groups as those at risk for mental health and those without risk for mental health. In the study, those with a total score of GHQ-28 survey above 4 were considered at risk for mental health, and those with a score of 4 points and below were considered not at risk for mental health.

Inclusion criteria: Being 18 years of age and older and being pregnant.

Exclusion criteria: Being a woman with a previous psychological disorder and not being diagnosed with a high-risk pregnancy (multiple pregnancies, gestational diabetes, diabetes, preeclampsia, with risks to the fetus such as congenital anomalies etc).

Data Collection Tools

Data were collected with the Personal Information Form, the Maternal Antenatal Attachment Scale (MAAS), and the General Health Questionnaire (GHQ-28).

Personal Information Form: It was created by researchers in order to determine some personal characteristics of pregnant women. In this form, some sociodemographic (age, educational level, employment, income level, family type, duration of the marriage, the status of being married willingly, the status of the relationship with the spouse, etc.), obstetric characteristics of women, and some factors that may affect attachment (parity, trimester, having a desired pregnancy, feeling of the baby's movements, having the pregnancy after the application of assisted-reproduction treatment, knowing the baby's gender, requesting to know the baby's gender, hospitalization during pregnancy, etc.) are included in this form [14-16].

General Health Questionnaire (GHQ-28): This questionnaire was developed by Goldberg in 1972 and its validity and reliability study in Turkiye was established by Kılıç in 1999 [17, 18]. The questionnaire is a screening test that was developed to determine the mental health problems of society, encountered outside of psychiatric clinics, and that individuals can fill in themselves. The aim of the questionnaire is to determine the disorders that lead the individual to apply to a clinic other than psychiatry, with a mental problem. The questionnaire has 4 subscales (somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression) and consists of 28 questions. The subscales are independent of each other. The questions consist of four-item answers, "less than usual" and "more than usual", questioning the individual's recent complaints. The four-item response scale was used as a two-item scale in which the first two items were scored as negative and the last two items were scored as positive, which is the "GHQ type scoring" method developed by Goldberg. Accordingly, items a and b were taken as "(0) zero", and items c and d as "(1) one". The four-item response has the benefit of avoiding the tendency to mark the extreme or middle answers. After the application, a minimum of 0 and a maximum of 28 points are obtained. Those with a total score between 0 and 4 are considered normal in terms of mental health, and those above 4 points are considered high-risk in terms of mental health [16, 18, 19]. The Cronbach's alpha reliability coefficient of the scale was calculated as 0.94. In this study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.88.

Maternal Antenatal Attachment Scale (MAAS): The Turkish validity and reliability study of the scale developed by Condon was performed by Gölbaşı et al. [20, 21]. The 19-item scale focuses on the pregnant woman's feelings, attitudes, and behaviors towards the fetus. The scale is in the form of a 5-point Likert-type and items are scored between 1 and 5 (5 represents very strong feelings towards the fetus; 1 represents the absence of feelings towards the fetus). The lowest "19 points" and the highest "95 points" can be obtained from the scale. High scores on the scale indicate a high degree of attachment. The calculation is made by reversing items 1, 3, 5, 6, 7, 9, 10, 12, 15, 16, and 18 on the scale. The scale consists of two subscales. Its subscales are the Attachment Quality (items 3, 6, 9, 10, 11, 12, 13, 15, 16, and 19) and the Time Spent on Attachment (items 1, 2, 4, 5, 8, 14, 17, and 18). The 7th item of the scale is added to the total score in the assessment of attachment, without being included in the subscales. The Cronbach's alpha reliability coefficient of the scale was calculated as 0.79 [21]. In this study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.80.

Statistical analysis

The data of the study were analyzed with SPSS 25.0 for Windows software (SPSS, Chicago, Il, USA). While reporting the results, pregnant women were divided into 2 groups: (1) those with high-risk pregnancies and (2) healthy pregnant women who did not have high-risk pregnancies. Descriptive statistics were given as numbers and percentages. The chi-square test was used to compare the difference between the groups, and the t-test was used for the two-group comparisons for the variables meeting the parametric test conditions. Statistical significance was determined as $p<0.05$.

Ethics

Before the data were collected, ethical approval was obtained from the Health Sciences, Non-Interventional Clinical Research and Publication Ethics Committee of İnönü University (Decision Number: 2023/4596, Date: 05.02.2023). In addition, prior to the application of the data collection tools, the consent of the participants was obtained by creating an information letter about the research and data collection tools. Participation in the study was carried out on a voluntary basis.

Results

The comparison of the sociodemographic characteristics of the participants according to their statuses of having high-risk or non-risky pregnancies is presented in Table 1. It was determined that the mean age of the participants with high-risk pregnancies was 27.83±5.25, and the mean age of those with non-risky pregnancies was 27.53±5.12. It was determined that there were statistically significant differences between the groups in terms of income level, family type, and the status of the relationship with the spouse of women with high-risk and non-risky pregnancies ($p<0.05$). However, it was determined that there were not any statistically significant differences between the groups in terms of educational level, employment, duration of the marriage, and the status of being married willingly ($p>0.05$; Table 1).

Table 1	Comparison of the participants' sociodemographic characteristics according to their statuses of having high-risk or non-risky pregnancies (n= 404)						
Characteristics	High-risk (n=114)		Non-risky (n=290)		Total (n=404)		Test and p value
	n	%	n	%	n	%	
Age, year (mean±SD)	27.84±4.61		27.86±5.28		28.68±5.72		t=-0.048 p=0.960
Educational Level							
≤ Middle School or Lower	71	62.3	183	63.1	254	62.9	χ2=0.590
≤ High School	30	26.3	81	27.9	111	27.5	p=0.744
≥ University or Higher	13	11.4	26	9.0	39	9.7	
Employment							
Employed	11	9.6	44	15.2	55	13.6	χ2=2.123
Unemployed	103	90.4	246	84.8	349	86.4	p=0.145
Income Level							
Good	5	4.4	22	7.6	27	6.7	χ2=6.664
Moderate	60	52.6	181	62.4	241	59.7	p=0.036
Low	49	43.0	87	30.0	136	33.7	
Family Type							
Nuclear Family	22	19.3	90	31.0	292	72.3	χ2=5.625
Extended Family	92	80.7	200	69.0	112	27.7	p=0.018
Duration of the Marriage							
1	34	29.8	77	26.6	111	27.5	χ2=0.440
≥ 2	80	70.2	213	73.4	293	72.5	p=0.507
The Status of Being Married Willingly							
Present	108	94.7	273	94.1	381	94.3	χ2=0.055
Absent	6	5.3	17	5.9	23	5.7	p=0.815
The Status of the Relationship with the Spouse							
Good	94	82.5	264	91.0	358	88.6	χ2=6.131
Moderate	19	16.7	24	8.3	43	10.6	p=0.047
Bad	1	0.9	2	0.7	3	0.7	

x²: Chi-square test

Comparison of the obstetric characteristics of the participants according to their statuses of having high-risk or non-risky pregnancies is presented in Table 2. It was determined that there were statistically significant differences between the groups in terms of the trimester, having a desired pregnancy, feeling of the baby's movements, having the pregnancy after the application of assisted-reproduction treatment, knowing the baby's gender, whether the baby's gender was the desired one, and hospitalization during pregnancy ($p<0.05$). However, it was determined that there was no statistically significant difference between the groups in terms of parity ($p>0.05$; Table 2).

In Table 3, the distribution of the mean scores of the GHQ-28, MAAS, and its subscales are presented. The MAAS mean score of the women participating in the study was found to be 67.78±9.66. In addition, it was determined that the mean score of the MAAS's subscale of the **"Attachment Quality"** was 40.82±55.33, and the mean score of the MAAS's subscale of the **"Time Spent on Attachment"** was 26.95±5.62. The GHQ-28 mean score was found to be 2.98±3.81.

The comparison of the mean scores of the GHQ-28, AEAS, and its subscales according to the participants' statuses of having high-risk or non-risky pregnancies is presented in Table 4. It was determined that the AEAS and its subscale of quality of attachment mean scores were higher in high-risk and non-risky pregnancies, and the differences between the groups were statistically significant ($p<0.05$). Additionally, it was determined that the mean score of "time in attachment mode" of non-risky pregnant women was higher than that of high-risk pregnant

Table 2 — Comparison of the obstetric characteristics of the participants according to their statuses of having high-risk or non-risky pregnancies (n= 404)

Characteristics	High-risk (n=114)		Non-risky (n=290)		Total (n=404)		Test and p value
	n	%	n	%	n	%	
Parity							
Multiparous	63	55.3	163	56.2	226	55.9	χ2=0.030
Primiparous	51	44.7	127	43.8	178	44.1	p=0.863
Trimester							
Trimester I	29	25.4	27	9.3	56	13.9	χ2=17.901
Trimester II	20	17.5	58	20.0	78	19.3	p<0.001
Trimester III	65	57.0	205	70.7	270	66.8	
Having a Desired Pregnancy							
Present	82	72.8	236	82.1	321	79.5	χ2=4.61
Absent	32	27.2	54	17.9	83	20.5	p=0.037
Feeling of the Baby's Movements							
Present	89	78.1	258	89.0	347	85.9	χ2=8.016
Absent	25	21.9	32	11.0	57	14.1	p=0.005
Having the Pregnancy after the Application of Assisted-Reproduction Treatment	17	14.9	22	7.6	39	9.7	χ2=5.036
Present	97	85.1	268	92.4	365	90.3	p=0.025
Absent							
Knowing the Baby's Gender							
Present	84	73.7	242	83.4	326	80.7	χ2=5.008
Absent	30	226.3	48	16.6	78	19.3	p=0.025
Whether the baby's gender was the desired one	55	48.2	121	41.7	176	43.6	χ2=9.665
Yes	39	34.2	74	25.5	113	28.0	p=0.008
No	20	17.5	95	32.8	115	28.5	
It does not matter							
Hospitalization during Pregnancy							
Present	78	69.3	245	15.9	323	20.0	χ2=13.170
Absent	36	30.7	45	84.1	81	80.0	p=0.001

x^2: Chi-square test

Table 3 — Distribution of the mean scores of the GHQ-28, MAAS, and its subscales (n=404)

Scales	Min-Max	Mean ± SD
MAAS	32-90	67.78±9.66
Attachment Quality	18-50	40.82±55.33
Time Spent on Attachment	10-40	26.95±5.62
GHQ-28	0-25	2.98±3.81

SD: Standard Deviation, MAAS: Maternal Antenatal Attachment Scale; GHQ-28: General Health Questionnaire

women, but there was no statistically significant difference between the groups (p> 0.05). It was determined that the GHQ-28 mean score of the non-risky pregnant women was lower and the difference between the groups was statistically significant (p<0.05; Table 4).

According to the study findings, it can be said that the total DSPAS score of pregnant women at risk is lower, and the quality of attachment sub-dimension score is lower than those who do not have a risky pregnancy.

Table 4 — Comparison of the mean scores of the GHQ-28, MAAS, and its subscales according to the participants' statuses of having high-risk or non-risky pregnancies (n = 404)

Variables	High-risk (n=114)	Non-risky (n=290)	Test*	p value	Confidence intervals	
	Mean±SD	Mean±SD			Lower	Upper
MAAS	65.67±9.58	68.61±9.59	2.769	p=0.006	0.850	5.019
Attachment Quality	38.57±5.84	41.71±4.85	5.690	p<0.001	2.027	4.266
Time Spent on Attachment	26.89±5.82	27.10±5.11	-0.341	p=0733	-1.371	0.947
GHQ-28	7.40±4.16	1.24±1.65	-21.303	p<0.001	-6.957	-5.366

SD: Standard Deviation, *: Independent samples t-test, MAAS: Maternal Antenatal Attachment Scale
GHQ-28: General Health Questionnaire

Discussion

In this study, in which maternal-fetal attachment was evaluated among pregnant women at risk for mental health, it was determined that pregnant women at risk for mental health had a higher rate of poor income and extended family type than those without risk, and the rate of those who expressed good relationship with their spouse was lower. Women are more likely to encounter psychological problems such as stress due to negative life experiences such as violence, low income, excessive workload, and challenging living conditions throughout their lives, so psychological problems are more common among women [22]. In the literature, mental problems in high-risk pregnancies were extensively investigated [10, 15], but pregnant women with mental health risks were neglected [22-24]. It has been seen that the results related to income and family type are supported by the literature. Pregnancy is a unique period of life for women and their partners. While the woman and her husband experience happiness, joy, and excitement upon receiving the

news of pregnancy, each individual perceives the physical and psychological changes experienced with pregnancy differently and may show different reactions, and the relationship with the spouse may change. The factors affecting the adjustment to pregnancy can be listed as the spouse's attitude towards pregnancy, having a high-risk pregnancy, the status of having a desired pregnancy, having a desired gender for the baby, and mental illnesses [25-28]. When the obstetric characteristics of pregnant women with and without risk for mental health were examined, it was seen that there were differences between the groups in terms of the trimester, having a desired pregnancy, feeling the baby's movements, having the pregnancy after the application of assisted-reproduction treatment, knowing the baby's gender, whether the baby's gender was the desired one, and hospitalization during pregnancy, and the results of the present study are similar to the literature [25].

In the study, it was determined that the GHQ-28 mean score of all participants was 2.98, MAAS mean score was 67.78, the mean score of the MAAS's subscale of the "Attachment Quality" was 40.82, and the mean score of the MAAS's subscale of the "Time Attachment Mode" was 26.95. There are many studies in which antenatal maternal attachment levels were evaluated with similar and different scales [29, 30]. In a study using the same scale, the MAAS mean score was found to be 75, and the mean scores of the subscales of the "Attachment Quality" and "Time Spent on Attachment" were found to be 40 and 30, respectively [31]. In another study, the MAAS mean score was found to be 71, and the mean scores of the subscales of the "Attachment Quality" and "Time Spent on Attachment" were calculated as 41 and 25, respectively [32]. It is known that as MAAS scores increase, attachment also increases. In these studies, it was seen that the mean scores of attachment are higher than the results of the present study. This difference is thought to be due to the inclusion of mentally high-risk pregnant women in the sample.

In the study, when the antenatal attachment levels of pregnant women with and without risk for mental health were compared, it was determined that the attachment level of pregnant women with psychological risk was low. Again, it was determined that the mean score of the subscale of the "Attachment Quality", which is one of the MAAS's subscales, was lower in mentally risky pregnant women. Although there is no study in the literature evaluating the antenatal maternal attachment level of mentally risky pregnancies, there are many studies evaluating attachment in high-risk pregnancies [14, 15, 25, 33, 34]. Mother-infant attachment during pregnancy includes the woman's perception of herself as a mother during pregnancy, her emotional interaction with the baby, and the processes of forming the identity of motherhood. There are many factors that cause mental problems during pregnancy [14, 15, 25, 33, 34]. In addition, weak mother-infant attachment can increase mental problems such as anxiety [15]. Training programs with the presence of social support may affect this process [35, 36].

While the increase in mental problems such as anxiety during pregnancy affects attachment negatively, the fact that weak prenatal attachment can also pave the way for mental problems such as anxiety shows that these concepts may have an opposite relationship with each other. As a result, it is thought that stress, anxiety, and attachment problems during pregnancy negatively affect women's mental health, and thus, affect the health of the mother, fetus, and newborn, and consequently, family and community health [15].

It was determined that there was a difference between the groups in terms of some criteria evaluated in the present study. It was mentioned in the literature that attachment and mental problems are affected by these features [15, 37-39]. It was determined that the social environment and cultural structure of the pregnant woman, family type (extended family), income level (low socio-economic level), having an undesired pregnancy (unplanned pregnancy), substance use (cigarette and alcohol), relationship with the spouse, having a planned pregnancy, baby's gender, and social support systems affect the pregnant's mental problems, such as stress, anxiety, and depression [40-42]. For this reason, it is thought that the similarities and differences between the results of the present study and the studies in the literature are due to social and obstetric characteristics such as the relationship with the spouse, social support, the gender of the baby, and hospitalization. Additionally, the education and counseling received during pregnancy was not questioned in the study. The education regarding pregnancy, birth or postpartum period received by the group with and without risk in terms of mental health may have affected these results.

Limitations

This study has some limitations. First of all, the risks in pregnancy were handled in a general way, and no grouping was made according to the type and severity of the risk. This might have affected the results. However, the results of the present study are similar to the studies in the literature, indicating that this risk is low. Secondly, it is related to screening tests used to identify mental risks such as GHQ-28. Although these tools have high sensitivity and specificity, they cannot be used instead of clinical examination. Thirdly, inclusion and exclusion criteria, data collection methods, or possible methodological problems, conducting the study in a single center might have affected the results. Another limitation is that complications that may affect the mental state of the mother and the attachment of the fetus were not taken into account in the current study.

Despite these limitations, it is thought that the present study is the first study to examine the effects of maternal-fetal attachment levels among pregnant women at risk for mental health in the same study.

Conclusion and recommendations

In the study, it was determined that the attachment levels of pregnant women at psychological risk were significantly lower than those of pregnant women without psychological risk. Therefore, the results suggest that it is necessary to determine mental problems in pregnant women and to conduct screening programs more frequently. GHQ-28 was used in the study to determine psychological risk. Evidence-based effective screening strategies may be developed in further studies. It is recommended to execute more studies for the purpose of developing interventions on the subject. Subsequent studies can be carried out by limiting or expanding the study population in terms of the economic status of the pregnant woman, the quality and quantity of training received for the newborn during birth and postpartum. Effective screening may be helpful in identifying the risks early and avoiding the effects of those risks.

acquisition – not applicable. All authors have read and agreed to the published version of the manuscript.

References

1. Can R, Yılmaz S, Çankaya S, Kodaz N. Gebelikte yaşanan sorunlar ve yaşam kalitesi ile ilişkisi. Sağlık ve Toplum. 2019; 29(2): 59-64.

2. Dağlar G, Nur N. Gebelerin stresle başa çıkma tarzlarının anksiyete ve depresyon düzeyi ile ilişkisi. *Cumhuriyet Medical Journal.* 2014; 36(4): 429–441. https://doi.org/10.7197/cmj.v36i4.5000076793.

3. Yılmaz SD, Beji NK. Gebelerin stresle başa çıkma, depresyon ve prenatal bağlanma düzeyleri ve bunları etkileyen faktörler. *Genel Tip Dergisi.* 2010; 20(3): 99–108.

4. Jha S, Salve HR, Goswami K, Sagar R, Kant S. Burden of common mental disorders among pregnant women: a systematic review. Asian journal of psychiatry. 2018; 36: 46-53. https://doi.org/10.1016/j.ajp.2018.06.020.

5. Wu Y, Zhang C, Liu H, Duan C, Li C, Fan J, et al. Perinatal depressive and anxiety symptoms of pregnant women during the coronavirus disease 2019 outbreak in China. *American journal of obstetrics and gynecology.* 2020; 223(2): 240.e1–240.e9. https://doi.org/10.1016/j.ajog.2020.05.009.

6. González-Mesa E, Kabukcuoglu K, Blasco M, Körükcü O, Ibrahim N, González-Cazorla A, et al. Comorbid anxiety and depression (CAD) at early stages of the pregnancy. A multicultural cross-sectional study. *Journal of affective disorders.* 2020; 270: 85-89. https://doi.org/10.1016/j.jad.2020.03.086.

7. Fawcett EJ, Fairbrother N, Cox ML, White IR, Fawcett JM. The prevalence of anxiety disorders during pregnancy and the postpartum period: a multivariate Bayesian meta-analysis. *The Journal of clinical psychiatry.* 2019; 80(4): 1181. https://doi.org/10.4088/JCP.18r12527.

8. Koptur A, Emül TG. Fetüs Ve Yenidoğanda Bağlanmanin Iki Yüzü: Maternal Ve Paternal Bağlanma. *Ege Üniversitesi Hemşirelik Fakültesi Dergisi.* 2017; 33(3): 138-152.

9. Hülya U, Özkan H. Gebelerin Psikososyal Sağlık Durumları İle Annelik Rolü Algısı Arasındaki İlişki. *Adnan Menderes Üniversitesi Sağlık Bilimleri Fakültesi Dergisi.* 2023; 7(1): 115-126. https://doi.org/10.46237/amusbfd.1169109.

10. Atasever İ, çelik AS. Prenatal stresin ana-çocuk sağliği üzerine etkisi. *Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi.* 2018; 21(1): 60-68.

11. Bock J, Wainstock T, Braun K, Segal M. Stress in utero: prenatal programming of brain plasticity and cognition. *Biological psychiatry.* 2015; 78(5): 315-326. https://doi.org/10.1016/j.biopsych.2015.02.036.

12. Dağlar G, Naim N, Bilgiç D, KADIOĞLU M. Gebelİkte duygulanim bozUKluĞu. *Kadın Sağlığı Hemşireliği Dergisi.* 2016; 2(1): 27-40.

13. Kesebir S, Kavzoğlu SÖ, Üstündağ MF. Bağlanma ve psikopatoloji. Psikiyatride Güncel Yaklaşımlar. 2011; 3(2): 321-342.

14. Ataman H, Akarsu Ö, Budak Mİ. Üçüncü Trimesterdeki Yüksek Riskli Gebelerde Evlilik Uyumu ve Prenatal Bağlanma Arasındaki İlişkinin Belirlenmesi. *Turkish Journal of Family Medicine and Primary Care.* 2022. 16(4): 670-680. https://doi.org/10.21763/tjfmpc.1097177.

15. Baltacı N, Başer M. Riskli gebelerde yaşanan anksiyete, prenatal bağlanma ve hemşirenin rolü. Dokuz Eylül Üniversitesi Hemşirelik *Fakültesi Elektronik Dergisi.* 2020; 13(3): 206-212. https://doi.org/10.46483/deuhfed.565338.

16. Ayvaz S, Hocaoğlu Ç, Tiryaki A, Ak İ. Trabzon il merkezinde doğum sonrası depresyon sıklığı ve gebelikteki ilişkili demografik risk etmenleri. Türk Psikiyatri Dergisi. 2006; 17(4): 243-251.

17. Goldberg P. The detection of psychiatric illness by questionnaire. *Maudsley monograph.* 1972.

18. Kıllıç C. Genel sağlık anketi: Güvenilirlik ve geçerlilik çalışması. *Türk Psikiyatri Dergisi.* 1996; 7(1): 3-9.

19. Kaplan Ö, Çağlı F. Postpartum Dönemdeki Kadınların Pandemi Sürecinde Sosyal Destek Düzeyleri, Ruh Sağlığı Durumları ve İlişkili Faktörler.

20. Condon JT. The assessment of antenatal emotional attachment: development of a questionnaire instrument. *British journal of medical psychology.* 1993; 66(2): 167-183. https://doi.org/10.1111/j.2044-8341.1993.tb01739.x.

21. Golbasi Z, Ucar T, Tugut N. Validity and reliability of the Turkish version of the Maternal Antenatal Attachment Scale. *Japan Journal of Nursing Science.* 2015; 12(2): 154-161. https://doi.org/10.1111/jjns.12052.

22. Koyun A, Taşkın L, Terzioğlu F. Yaşam dönemlerine göre kadın sağlığı ve ruhsal işlevler: Hemşirelik yaklaşımlarının değerlendirilmesi. *Psikiyatride Güncel Yaklaşımlar.* 2011; 3(1): 67-99.

23. Yıldırım AD, Şahin NH. Riskli gebelerde prenatal Bağlanma ve risklerin Değerlendirilmesi. *Online Türk Sağlık Bilimleri Dergisi.* 2020; 5(4): 661-672. https://doi.org/10.26453/otjhs.750158.

24. Yıldız NG, Aydın K, Yıldız H. Türkiye'de sağlık sistemi: Sosyoekonomik faktörler ve sağlık hizmetlerine erişimde yaşanan eşitsizlikler. Disiplinlerarası Tıp ve Sağlık Bilimleri Kavramlar, Araştırmalar ve Uygulama. 2022.

25. Aksoy YE, Turfan EÇ, Yılmaz SD. Normal ve riskli gebeliklerde sağlıklı yaşam biçimi davranışlarının değerlendirilmesi. *Perinatal Journal/Perinatoloji Dergisi.* 2017; 25(1): 6-31. https://doi.org/10.2399/prn.17.0251006.

26. Arslan S, Gülşen O, Coşkun AM, Temiz F. Kadınların gebeliği algılama durumu ve bunu etkileyen faktörler. *Sağlık Bilimleri ve Meslekleri Dergisi.* 2019; 6(1): 179-192. https://doi.org/10.17681/hsp.432333.

27. Öngay E. Düşük yapan kadınların algıladıkları stres ile eş desteği arasındaki ilişki: Sağlık Bilimleri Enstitüsü; 2019.

28. Özbek Z, Beydağ KD. Yüksek riskli gebelerde eş desteği ve gebelik stresi arasındaki ilişki. *Mersin Üniversitesi Sağlık Bilimleri Dergisi*. 2021; 15(2): 144-155. https://doi.org/10.26559/mersinsbd.950382.

29. Badem A, Zeyneloğlu S. Gebelerin prenatal bağlanma düzeyleri ve etkileyen faktörlerin belirlenmesi. *Kırşehir Ahi Evran Üniversitesi Sağlık Bilimleri Dergisi*. 2021; 1(1): 37-47.

30. Gül F. Doğum Sonu Depresyon Danışmanlığında Anne-Bebek Bağlanmasını Güçlendiren ve Annenin Kendini Toparlama Gücünü Artıran Uygulamalar. 2022.

31. Şahin M. Gebelerde Travmatik Doğum Algısı ve Anne Bağlanması İlişkisi: Sağlık Bilimleri Enstitüsü; 2020.

32. Uçar T, Sabancı E, Karataş Okyay E. The Effect of Interconceptional Duration on Maternal Fetal Attachment and Psychosocial Health. *Journal of Current Researches on Health Sector*. 2018; 8(1): 75-88.

33. Özkahraman-Koç Ş, Ersoy S, Yıldırım B, Ersoy İH. Anxiety, depression, and prenatal attachment levels in pregnant women with gestational diabetes mellitus. *Int J Clin Exp Med*. 2019; 12(5): 6078-6086.

34. Tsakiridis I, Bousi V, Dagklis T, Sardeli C, Nikolopoulou V, Papazisis G. Epidemiology of antenatal depression among women with high-risk pregnancies due to obstetric complications: a scoping review. *Archives of gynecology and obstetrics*. 2019; 300: 849-859. https://doi.org/10.1007/s00404-019-05270-1.

35. Palma E, Armijo I, Cifuentes J, Ambiado S, Rochet P, Díaz B, et al. Hospitalisation in high-risk pregnancy patients: is prenatal attachment affected? *Journal of Reproductive and Infant Psychology*. 2021; 39(1): 30-42. https://doi.org/10.1080/02646838.2020.1740661.

36. Teskereci G, Aysun Ü, Özbek N, Koçak B. Prenatal Bağlanmayı Destekleyici Bakım Uygulamaları. *Psikiyatride Güncel Yaklaşımlar*. 2021; 13(4): 805-819. https://doi.org/10.18863/pgy.883104.

37. Aydın R, Güven DY, Karahan N. Sen de dinle: Yüksek riskli gebeliklerde stresle baş etmede müzikle terapinin etkisi. *Necmettin Erbakan Üniversitesi Sağlık Bilimleri Fakültesi Dergisi*. 2019; 2(1): 19-24.

38. Bedaso A, Adams J, Peng W, Sibbritt D. The relationship between social support and mental health problems during pregnancy: a systematic review and meta-analysis. *Reproductive health*. 2021; 18(1): 1-23. https://doi.org/10.1186/s12978-021-01209-5.

39. Fındıklı E. Perinatal Dönemde Ruh Sağlığı Sorunları, Yaygınlığı, Neden ve Sonuçları: Derleme. *Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi Dergisi*. 2022; 17(2): 213-221. https://doi.org/10.17517/ksutfd.1111035.

40. Aksoy A, Aksu A, Yilmaz DV, Degirmenci F, Celebi A. Ucuncu Trimesterdeki Gebelerin Prenatal Baglanma ile Sosyal Destek Duzeyleri Arasindaki Iliski ve Etkileyen Faktorler. *Journal of Education and Research in Nursing*. 2021; 18(2): 138-145.

41. Çelik AS, Atasever İ. Gebelerde Algılanan Stres Düzeylerinin ve Etkileyen Faktörlerin Belirlenmesi. *Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi*. 2020; 23(2): 267-276.

42. Özçetin YSÜ, Erkan M. Yüksek riskli gebelerde psikolojik sağlamlık, algılanan stres ve psikososyal sağlık. *Cukurova Medical Journal*. 2019; 44(3): 1017-1026. https://doi.org/10.17826/cumj.502989.

Iron deficiency anemia in pediatric children at Kalmunai North Base Hospital, Sri Lanka

Seyid Mohamed Moulana Seyida Afreen[1,2], Muneeb Muhamed Musthafa[1], Rajavarthani Sanjeev[3], Somasundaram Norman Roshanth[4]

[1]Department of Biosystem Technology, Faculty of Technology, South Eastern University of Sri Lanka, Oluvil, Sri Lanka
[2]Al-Manar central College, Kalmunai, Sri Lanka
[3]Department of Human Biology, Faculty of Health-Care Sciences, Eastern University, Sri Lanka, Batticalo, Sri Lanka
[4]Pediatric unit, Base Hospital, Kalmunai North, Sri Lanka

Corresponding author:
Muneeb M. Musthafa.
E-mail: Muneeb@seu.ac.lk;
ORCID: 0000-0002-3936-1095.

Abstract

Objective: This study's aim was to estimate association between the iron deficiency anemia (IDA) and associated risk factors among children at Kalmunai north in Sri Lanka during COVID-19.

Material and Methods: During the pandemic, 101 children aged between 1and 14 years were involved in the cross sectional study. Hemoglobin levels, serum ferritin and C-reactive protein (CRP) were measured to determine anemia. Additionally, dietary intake, socioeconomic status, and demographic information were collected through interviews with the caregivers. Chi-square tests and Pearson correlation were used to investigate connections between IDA and other factors such as demographic characteristics and eating habits. In addition, a multivariate regression analysis was performed to identify independent predictors of IDA.

Results: 7.9% of children were found to be anemic at Kalmunai Base Hospital. Low dietary iron consumption was revealed as a significant risk factor for IDA. Meat, liver, fish, chicken, fresh milk, dark green leafy vegetables, and black tea were found to be independent predictors of IDA, explaining 57.7% of the variation in IDA frequency (R² value = 57.7%; P< 0.001). Consuming dark green leafy vegetables, poultry, liver, beef, and fish are linked to a lower incidence of IDA in children. On the other hand, a higher risk of IDA appears to be associated with increased consumption of fresh milk and black tea. In conclusion, this study focuses on Dietary factors, especially the consumption of particular foods, were found to be significant contributors of IDA, even if demographic parameters did not differ significantly from IDA. Strategies to increase iron intake and dietary diversity, particularly among young children, are critical in the fight against IDA.

Keywords: Pediatric children, Hemoglobin, Iron deficiency anemia and Dietary habits, Iron rich food

Introduction

Iron deficiency anemia (IDA) is still a global public health concern that affects people of all ages. However, its frequency in pediatric groups is particularly concerning, given the potential for long-term developmental and health effects [1]. In recent years, healthcare providers and academics have focused more attention on understanding and resolving this condition, realizing the enormous impact it can have on children's growth, cognition, and overall well-being [1].

(IDA) is a condition in which the body's iron stores are depleted, resulting in insufficient production of hemoglobin, the protein responsible for transporting oxygen in the blood [2]. The degree of deficiency has little

bearing on the non-specific symptoms of ID and IDA. Clinically, children may exhibit symptoms like exhaustion, shortness of breath, palpitations, vertigo, headaches, and restless legs [3]. It can lead to serious public health problems, including a rise in childhood illnesses and deaths, as well as impaired immune system, mental, and physical development, decreased physical activity, low endurance, and poor learning in both infants and adolescents, as well as a lifelong reduction in serotonin levels and dopamine receptors [3–5].

Despite significant advances in healthcare and child well-being in recent decades, the frequency of IDA among Sri Lankan pediatric patients remains a major concern. Although there aren't many studies on nutritional

deficiency anemia in the nation, the Ampara district of Sri Lanka hasn't been the subject of any research on IDA in children.This study was aimed in order to determine the severity of IDA and the demographics and eating habits associated with the presence of IDA among children at Base Hospital, Kalmunai North.

This study is significant on several levels. For starters, it adds to the body of knowledge on iron deficiency anemia by shining light on its specific patterns and issues in the context of Sri Lankan pediatric healthcare. Second, it has the potential to inform healthcare policies and interventions aimed at lowering the burden of IDA among Sri Lankan children, hence increasing their overall health and well-being. Third, it is hoped that the findings of this study will help with the development of suitable strategies to enhance complementary feeding and consumption of iron-rich diets, hence reducing the risk of IDA in children.

Materials and Methods

A cross-sectional study design was used in this study to investigate the risk factors for IDA in pediatric children at the pediatric clinic and ward at Base Hospital, Kalmunai North in the Ampara district, which is located at latitude 7°25'12.1"N and longitude 81°49'20.4"E. Kalmunai Hospital, which acted as a primary healthcare centre for paediatric children in the Kalmunai region of Sri Lanka. The paediatric section at the hospital was the major location for data gathering. Pediatric patients aged 1 to 14 years who were hospitalized to or received outpatient care at Kalmunai Hospital during the study period from January to April 2022 were included in the study. The sample was chosen at random, with attempts taken to guarantee representation from various age groups and genders.Using the sample size calculator, the sample size was determined.

There were two population statistical formulas used:

$$(ss = t2 \times p \times (1-p)/e2$$

i.e. t – Coefficient for confidence level, p – Prevalence rate, e –precision rate.
The second formula:

$$ss\ final = ss\ theoretical * 1/\%\ response\ * 1/\%\ eligibility * 1/\%\ valid$$

A 6% prevalence of anemia [6], a 5% margin of error, a 95% confidence level, and a 5% expected non-response rate were used. The study's final required minimum sample size was 101. Potentially fewer children were hospitalized for treatment or diagnosis as a result of the COVID-19 pandemic's dynamic impact on the healthcare system. The sample size represents the subset of children who could access healthcare services during this challenging period.

Excluded from the data collection were children getting anemia treatment, those who had undergone blood transfusions prior to the four-month period, and parents who chose not to voice their concerns.A questionnaire that was administered by an interviewer was utilized to gather socio demographic, socioeconomic, and clinical data. Two knowledgeable nutrition professionals evaluated the surveys.

An experienced phlebotomist used aseptic techniques to collect 5 ml of blood in plain tubes (2 ml) and EDTA tubes (3 ml) from each study participant. Following collection, the samples were delivered within two hours to the Aqsha Medical Laboratory. Serum ferritin, Hb levels, and CRP (C-reactive protein) were measured. Hemoglobin was estimated using automated hematology analyzer (BC6800, Mindray, China).

A blood sample of two milliliters was taken up into the simple tubes and centrifuged. Blood and serum were clearly separated from one another. Following that, serum was added to the fully automatic biochemical analyzer (BS480 China). Serum ferritin and CRP levels were then assessed. HB levels, serum ferritin, and CRP were used to determine an IDA status.

In order to evaluate anemia (Hb <11 g/dl) and iron deficiency (SF< 15 µg/l), WHO established cut-off levels were utilized. When CRP is more than 5.0 mg/l, as determined by the assessment, an acute phase of infection has been detected [7]. Detected infected children were treated in the ward and after their recovery they were included in our study. Children were classified as having severe, moderate, mild and normal iron level according to WHO [8]. The classification of Hb is below in table1.

Table 1	Classification of IDA according to WHO (Hb level are in the table)		
Children	Non-anaemia	Anaemia (g/dl)		
		Mild	Moderate	Severe
6–59 months	11	10.0–10.9	7.0–9.9	<7.0
5–11 years	11.5	11.0–11.4	8.0–10.9	<8.0
12–14 years	12	11.0–11.9	8.0–10.9	<8.0

All laboratory activities were subject to strict adherence to specific standard operating procedures and manufacturer's instructions. In keeping with this, monitoring of samples were used. The expiration dates on all chemicals and quality control samples were examined. An individual identification number was used to record laboratory results on typical report formats.

The Social Package for Social Science (SPSS) version 21 (IBM Corp., Chicago, Illinois, USA) was utilized for accurate data entry. Based on HB levels, serum ferritin, and CRP, IDA status was determined. To ascertain the relationship between IDA and dietary consumption of foods high in iron, Pearson correlation was performed. In order to assess the link between IDA and demographic characteristics, the Pearson Chi-square test was utilized. Multi regression analysis was then utilized to evaluate the relationship between dietary habits, demographic features and IDA. For statistical significance, a p-value of less than 0.05 was utilized as the threshold.

Results

In this study, we noticed that 60% of patients came to the clinic primarily for chronic condition management and follow-up care, whereas the remaining 40% were admitted to the ward for acute illnesses or acute on chronic illness (A sudden worsening of a pre- existing chronic condition). Some (No:14) children in the study had co-morbidities, such as asthma and epilepsy which complicated their clinical profile. There were 54% male and 47% female among the children. Eight children in all (7.9%) were found to have IDA.

Table 2	Proportion of IDA severity among children at Base hospital, Kalmunai according to Hb level			
Age group (Years)	No of children	Mild (10-10.9 g/dl) %	Moderate (7-9.9 g/dl) %	Severe (<7 g/dl) %	Total Anaemic %
1 - 3	38	2	1	0	37.5
4 - 6	24	0	3	0	37.5
7 - 10	26	0	1	1	25
11-14	13	0	0	0	0
Total IDA %		25	62.5	12.5	100

Age, sex, family income, sector, and mothers' level of education were found that did not differ significantly with IDA from other children. However, it was shown that there was a significant relationship between IDA and child bearing interval (P < 0.001) and number of children (P< 0.005) as given in Table 3.

Table 3	Relationship between IDA with independent demographic variables					
variable	IDA				Mean Hb ± SD (g/dl)	P value
	No	%	Yes	%		
Age						
1-3	38	92.7 %	3	7.9%	12.58±1.1	0.620
4-6	24	88.9%	3	12.5%	12.38±1.4	
7-9	26	89.5%	2	7.6%	12.13±1.7	
10-14	13	100%	0	0%	12.79±0.9	
Gender						
Male	49	90.7%	5	9.3%	12.35±1.2	0.593
Female	44	93.6%	3	6.4%	12.62±1.4	
Sector						
Urban	48	96.0%	2	4.0%	12.76±1.0	0.149
Rural	45	88.2%	6	11.8%	12.18±1.4	
Educational level of mother						
Grade 1-5	5	100%	0	0%	12.27±.4	0.675
grade 6-11	63	90%	7	10%	12.28±1.3	
Grade 12-13	21	95.5%	1	4.5%	13.07±1.1	
higher studies	4	100%	0	0%	12.83±1.1	
Children number						
1	43	97.7%	1	2.3%	12.78±.9	0.018*
2	22	91.7%	2	8.3%	12.45±1.0	
3	19	90.5%	2	9.5%	12.30±1.2	
4	7	87.5%	1	12.5%	12.06±2.5	
5	2	50%	2	50%	10.97±1.8	
Child bearing interval						
1 year	4	50%	4	50%	10.65±2.4	0.000**
2 year	26	89.7%	3	10.3%	12.58±1.2	
3 year	20	100%	0	0%	12.71±0.6	
4 year	15	93.8%	1	6.2%	12.60±1.3	
> 4 year	28	100%	0	0%	12.63±0.8	
Monthly income						
<20 000	27	84.4%	5	15.6%	11.92±1.3	0.118
20 000-40 000	52	94.5%	3	5.5%	12.59±1.3	
>40 000	14	100%	0	0%	13.26±0.8	

Refers to Significance at 0.05
Refers to significance at 0.01
Hb- Hemo globin, SD- standard deviation

When food intake is taken into account, there is a significant relationship between Hb level and foods like orange guava and dates, green leafy vegetables, chicken, meat, liver, fish, prawns, and eggs, dairy products like chocolate and cheese, and beverages like black tea and fresh milk as given in Table 4.

According to the findings of the multiple regression analysis (R^2 value = 57.7%; P< 0.001, Dark green leafy vegetables, meat, liver, fish and chicken were decreased the IDA . Fresh milk, and black tea were the positive factors of IDA as given in Table 5. None of the other characteristics under analysis were discovered to be independent predictors of IDA.

Estimated multiple regression equation from table 6.

$Y = 17.394 - 0.402X_1 - 0.422X_2 - 0.421X_3 - 0.427X_4 - 0.343X_5 + 0.157X_6 + 0.287X_7$.

Consumption of dark green leafy vegetables, poultry, liver, beef, and fish was connected with a negative coefficient, indicating that increasing consumption of these foods is linked to a lower risk of IDA. Black tea and fresh milk consumption have a positive coefficient, indicating that increasing use of black tea and fresh milk is connected with an increased risk of IDA.

Overall, the findings imply that eating dark green leafy vegetables, poultry, liver, beef, and fish is related with a lower risk of IDA in children. Higher consumption of black tea and fresh milk, on the other hand, appears to be connected with an increased risk of IDA.

Discussion

Age, gender, family income, sector, and mothers' level of education did not influence the link with IDA, according to the study's findings, which is in line with the findings of other earlier research [9, 10]. However, according to other studies, socioeconomic level significantly affects the prevalence rates of IDA [9, 10] there does not appear to be agreement regarding the importance of socioeconomic status as a risk factor for IDA [11]. Although children between the ages of 4 and 6 had a higher IDA turnout (11.1%). In this research, there was no evidence of a significant association between a child's gender and their hemoglobin level (p=0.593). However, male children had a slightly greater prevalence of IDA. The outcomes of earlier research are supported by this result [11, 12]. In comparison to urban areas, where IDA prevalence was just 4%, rural areas had an incidence rate of 11.8%. The prevalence of IDA was found to be lower in urban samples than in rural ones, according to Rashid's research [13], and this result is in line with his findings. Little education was held by the mother of anemic children. Children were found to frequently have anemia, and the majority of their parents had little to no college education [14], findings that were similar to those of the current study. In a study of children aged 6-59 months conducted in Bangladesh, those with higher education were a smaller amount likely to be anemic than those with lower education, elementary school, or secondary education. The significant IDA factor was the number of children per family (p = 0.018). Hb level and childbearing interval showed a significant correlation (p < 0.001). Although the number of children and Childbearing interval had a significant correlation with IDA in chi square analysis (P = 0.018, p < 0.001), the multiple regression analysis revealed no effect after correcting for other variables.

Meat, poultry, fresh milk, fish, dark green leafy vegetables, black tea, and liver products were all discovered to be strongly and independently related with IDA. Which agrees with earlier results published. The study found a significant association between green leafy vegetables and Hb levels. This is because it has been shown that a rich source of iron is found in green leafy vegetables [15]. Similar research shown that when children had a composite green leafy vegetable powder as opposed to just the typical stew and soup provided by the school food program, their mean hemoglobin concentration improved considerably [15]. Fish, liver, poultry, beef, shrimp, and eggs were strongly negatively correlated with IDA. This might be because foods containing animal meat, like cattle, pork, lamb, chicken, and fish, are a good source of dietary iron [16]. According to studies by [17, 18] irregular meat and vegetable diet was found to be a significant predictor of anemia in school-aged children. This fact backs up the study's findings. Fresh milk and black tea exhibited a substantial and favorable relationship with IDA. This might be because tea polyphenols create insoluble iron-tannin complexes in the gastrointestinal lumen [19]. How effectively iron is absorbed may be impacted by the fact that cow's milk has roughly four times as much calcium as human milk [20]. Time separating consuming cow milk and black tea with main meal is good for healthy life.

Table 4	Relationship between IDA with food consumption among the children					

Fruits	Daily	3Time/week (%)	Weekly (%)	Monthly (%)	Rare/Never (%)	P value
Orange						Pearson correlation-0.214*
Normal children	0	9.7	34.4	55.9	0	Significant (2 tailed) 0.032
IDA children	0	0	0	100	0	
Banana						
Normal children	12.9	25.8	30.1	26.9	4.3	Pearson correlation0.098
IDA children	37.5	12.5	25	25	0	Significant (2 tailed) 0.329
Papaya						
Normal children	0	1.1	22.6	63.5	12.9	Pearson correlation-0.170
IDA children	0	0	0	62.5	37.5	Significant (2 tailed)0.090
Guava						
Normal children	0	2.2	48.4	40.9	8.6	Pearson correlation-0.272**
IDA children	0	0	0	50	50	Significant (2 tailed) 0.006
Dates						
Normal children	4.3	4.3	4.3	77.4	9.7	Pearson correlation-0.226*
IDA children	0	0	0	75	25	Significant (2 tailed) 0.023
Star gooseberry						
Normal children	1.1	23.7	34.4	19.4	21.5	Pearson correlation-0.098
IDA children	0	0	12.5	50	37.5	Significant (2 tailed) 0.328
Pomegranate						
Normal children	1.1	23.7	34.4	19.4	21.5	Pearson correlation-0.195
IDA children	0	0	12.5	50	37.5	Significant (2 tailed) 0.050
vegetables	Daily (%)	3Time/week (%)	Weekly (%)	Monthly (%)	Rare/Never (%)	
Green leafy vegetable						
Normal children	10.8	54.8	28	4.3	2.2	Pearson correlation -0.282**
IDA children	0	0	37.5	62.5	0	Significant (2 tailed) 0.004
Beans						
Normal children	2.2	16.1	23.7	46.2	11.8	Pearson correlation-0.046
IDA children	0	0	37.5	25	37.5	Significant (2 tailed) 0.647
Tomato						
Normal children	11.8	31.2	37.6	15.1	4.3	Pearson correlation-0.099
IDA children	12.5	0	37.5	50	0	Significant (2 tailed) 0.323
Potato						
Normal children	5.4	19.4	52.7	22.6	0	Pearson correlation 0.067
IDA children	12.5	12.5	62.5	12.5	0	Significant (2 tailed) 0.505
Beets						
Normal children	0	0	14	50.5	35.5	Pearson correlation 0.066
IDA children	0	12.5	12.5	50	25	Significant (2 tailed) 0.511
Leeks						
Normal children	0	0	20.4	66.7	12.9	Pearson correlation -0.149 Significant (2 tailed) 0.137
fish						
Normal children	30.1	60.2	7.5	1.1	1.1	Pearson correlation -0.379**
IDA children	0	0	87.5	12.5	0	Significant (2 tailed) 0.000
Chicken						
Normal children	1.1	10.8	60.2	26.9	1.0	Pearson correlation -0.463**
IDA children	0	0	25	62.5	12.5	Significant (2 tailed) 0.000
Liver						
Normal children	0	0	21.5	59.1	19.4	Pearson correlation-0.371**
IDA children	0	0	0	37.5	62.5	Significant (2 tailed) 0.000
Red meat						
Normal children	0	7.5	9.7	23	59.1	Pearson correlation-.395**
IDA children	0	0	0	0	100	Significant (2 tailed) 0.000
shrimp						
Normal children	0	5.4	31.2	37.6	25.8	Pearson correlation-0.280**
IDA children	0	0	0	25	75	Significant (2 tailed) 0.005
Egg						

Normal children	33.3	48.4	14	2.2	2.2	Pearson correlation-0.202* Significant (2 tailed) 0.043
IDA children	0	12.5	62.5	12.5	12.5	
Yoghurt						
Normal children	4.3	22.6	37.6	31.2	4.3	Pearson correlation 0.157 Significant (2 tailed) 0.117
IDA children	0	37.5	62.5	0	0	
Chocolate						
Normal children	14	26.9	28	29	2.2	Pearson correlation 0.274** Significant (2 tailed) 0.006
IDA children	75	25	0	0	0	
Cheese						
Normal children	0	5.4	7.5	25.8	61.3	Pearson correlation 0.229* Significant (2 tailed) 0.021
IDA children	0	12.5	37.5	37.5	12.5	
Black tea						
Normal children	28	21.5	7.5	18.3	24.7	Pearson correlation 0.283** Significant (2 tailed) 0.004
IDA children	62.5	25	12.5	0	0	
Fresh milk						
Normal children	3.2	2.2	3.2	43	48.4	Pearson correlation 0.283** Significant (2 tailed) 0.004
IDA children	0	12.5	62.5	25	0	
Coffee						
Normal children		2.2	1.1	33.3	63.4	Pearson correlation 0.131 Significant (2 tailed) 0.193

Correlation is significant at 0.05 levels (2-tailed)
**Correlation is significant at 0.01 levels (2-tailed)

Table 5	The estimated multiple regression result is presented below

Variables	R value	R² value	Adjusted R Square	P value	F value
Predictors: (Constant), fresh milk, meat, Dark green leafy vegetable, Black tea, liver, fish, chicken	0.760a	0.577	0.545	0.000a	18.130

Table 6	The coefficient values of selected food items

Coefficientsa

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	17.394	0.912		19.073	< 0.001
Dark green leafy vegetable (X1)	-0.402	0.104	-0.268	-3.873	< 0.001
Chicken (X2)	-0.422	0.146	-0.224	-2.897	0.005
Liver (X3)	-0.421	0.143	-0.213	-2.935	0.004
Meat (X4)	-0.427	0.105	-0.303	-4.079	< 0.001
Fish (X5)	-0.343	0.126	-0.203	-2.716	0.008
Black tea (X6)	0.157	0.058	0.192	2.715	0.008
fresh milk (X7)	0.287	0.099	0.207	2.887	0.005

a. Dependent Variable: IDA

Sig – significant

Conclusion

The results highlight the role that dietary factors play in the development of IDA, with inadequate iron consumption being found to be a major risk factor. Interestingly, eating dark green leafy vegetables, chicken, liver, beef, and fish were linked to a decreased frequency of IDA. This highlights the importance of varied and nutrient-rich diets in preventing IDA in children. In contrast, consuming more black tea and fresh milk was associated with a higher risk of IDA. Even though there were no statistically significant differences between demographic factors and IDA, the study emphasizes the need for focused efforts to increase intake of iron-rich foods and dietary diversification, particularly for young children.

References

1. East P, Lozoff B, Blanco E, Delker E, Delva J, Encina P et al. Infant iron deficiency, child affect, and maternal unresponsiveness: Testing the long-term effects of functional isolation. *Dev Psychol*. 2017; 53(12): 2233–44. https://doi.org/10.1037/dev0000385.
2. Mettananda S, Williams S. Clinical and laboratory evaluation of childhood anaemia. *Sri Lanka J Child Heal*. 2020; 49(1): 64–70. https://doi.org/10.4038/sljch.v49i1.8901.
3. Singh S, Parihar S. Prevalence of anemia in under five-year-old children: a hospital-based study. *Int J Contemp Pediatr*. 2019; 6(2): 842–7. https://doi.org/10.18203/2349-3291.ijcp20190740.
4. El-mansoury A. Prevalence of iron deficiency anaemia among children under the age of 5 years in paediatric hospitals-Benghazi , Libya. *J Heal Sci Nurs*. 2020; 3(6): 1–13. https://doi.org/10.22259/2639-3581.0301004.

5.   World Health Organization. Global Accelerated Action for the Health of Adolescents (AA-HA!) Guidance to Support Country Implementation Who. 2017. 44 p. Available from: https://apps.who.int/iris/bitstream/handle/10665/255415/9;jsessionid=B309C8C56E5EEFA24FA2F606422AB847?sequence=1.

6.   Uragoda C., Goonaratna C, Silva J. Anaemia in children : are we using the correct prevention strategies? *Ceylon Med J.* 2017; 62(2): 73–6. https://doi.org/10.4038/cmj.v62i2.8469.

7.   Melbye H, Hvidsten D, Holm A, Nordbø SA, Brox J. The course of C-reactive protein response in untreated upper respiratory tract infection. 2004: 653–8.

8.   WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. *World Health Organization.* 2011. 1–6 p. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Haemoglobin+concentrations+for+the+diagnosis+of+anaemia+and+assessment+of+severity#1.

9.   KDHS. Kenya. Kenya Demographic and Health Survey. National Council for Population and Development, Central Bureau of Statistics and Ministry of National Planning and Development, Nairobi, Kenya. 2008. 455 p.

10. Khan JR, Awan N, Misu F. Determinants of anemia among 6-59 months aged children in Bangladesh: Evidence from nationally representative data. *BMC Pediatr.* 2016; 16(1): 1–12. https://doi.org/10.1186/s12887-015-0536-z.

11. Rashid M, Flora M, Moni M, Akhter A, Mahmud Z. Reviewing Anemia and Iron Folic Acid Supplementation Program in Bangladesh - A Special Article. *Bangladesh Med J.* 2010; 39(3): 5–10.

12. Enid A. Meso level situational analysis of nutritional status of children and prevalence of anaemia among children, adolescent girls and pregnant women in selected districts of India. 2015. 1–542 p.

13. Hussein MD, Mohamed S. Prevalence of anaemia in preschool children in Karma Albalad area, Northern State, Sudan. *East Mediterr Heal J.* 2014; 20(1): 33–8. https://doi.org/10.26719/2014.20.1.33.

14. Agbaire PO, Eoyan OO. Nutritional and antinutritional levels of some local vegetables from Delta State, Nigeria. *African J Food Sci.* 2012; 6(1): 8–11. https://doi.org/10.5897/AJFS111.175.

15. Jackson J, Williams R, McEvoy M, MacDonald-Wicks L, Patterson A. Is higher consumption of animal flesh foods associated with better iron status among adults in developed countries? A systematic review. *Nutrients.* 2016; 8(2): 1–27. https://doi.org/10.3390/nu8020089.

16. Djokic D, Drakulovic MB, Radojicic Z, Crncevic Radovic L, Rakic L, Kocic S, et al. Risk factors associated with anemia among Serbian school-age children 7-14 years old: Results of the first national health survey. *Hippokratia.* 2010; 14(4): 252–60.

17. Kaya M, Pehlivan E, Aydoğdu İ, Genç M, Güneş G. Iron Deficiency Anaemia Among Students of Two Primary Schools at Different Socioeconomic Conditions in Malatya, Turkey. Indian J Pediatr. 2002; 69 (7): 60716.

18. Timothy AM, Lynch SR, Cook JD. Inhibition iron absorption. Am J Clin Nutr. 1983; 37: 416–20. Available from: http://ehis.ebscohost.com.ezproxy.endeavour.edu.au:2048/eds/detail?sid=204ba0a7-cbb1-4777-bd0c-d3513ddb194d%40sessionmgr10&vid=15&hid=107&bdata=JnNpdGU9ZWRzLWxpdmU%3D#db=mdc&AN=6402915.

19. Hallberg L, Hulthén L. Prediction of dietary iron absorption: An algorithm for calculating absorption and bioavailability of dietary iron. *Am J Clin Nutr.* 2000; 71(5): 1147–60. https://doi.org/10.1093/ajcn/71.5.1147.

20. Hallberg L, Rossander-Hultén L, Brune M, Gleerup A. Bioavailability in man of iron in human milk and cow's milk in relation to their calcium contents. *Pediatr Res.* 1992; 31(5): 524–7. https://doi.org/10.1203/00006450-199205000-00024.

The need for orthopedic dental services for the elderly population of Kazakhstan

Naziya A. Kamiyeva[1], Kubeisin D. Altynbekov[2], Nurmukhamet S. Ruzuddinov[3], Zuliya R. Rizabekova[4]

[1]Department of Public Health, Kazakhstan's School of Public Health, Kazakhstan Medical University, Almaty, Kazakhstan
[2]Department of Prosthodontics dentistry, Kazakh National Medical University, Almaty, Kazakhstan
[3]Department of Clinical Disciplines, Al Farabi Kazakh National University, Almaty, Kazakhstan
[4]Department of Dentistry of children, Kazakh National Medical University, Almaty, Kazakhstan

Corresponding author:
Naziya A. Kamiyeva.
E-mail: kamieva.n@kaznmu.kz;
ORCID: 0000-0002-2956-2168.

Abstract

Objective: To determine the orthopedic dental status of the elderly population of Kazakhstan using clinical and diagnostic determinants.

Methods: The dental status of 708 patients from three institutions in Almaty, Kazakhstan, was recorded using WHO dental questionnaires. The patients were divided into groups according to their age and sex, and modern statistical methods were used to process the data. Through the construction of tables and graphs, calculation of relative values, and assessment of the reliability of the differences in the data, we determined if there were any differences between the groups.

Results: The study revealed that most patients who needed orthopedic dental care were 60 years of age and older. The older the age of patients with registered diagnoses of partial and complete adentia, the greater the need for removable prosthetics. The most common type of orthopedic treatment required for these patients was removable dentures. Analysis of the quantitative relationship between the need for orthopedic dental care and patients' gender revealed the following patterns: the critical value of Chi-square at the significance level $p \leq 0.0001$ was 23.95, the exact Fisher criterion was 0.0000 ($p=0.0000$), and the calculated Cramer's V criterion and the conjugacy coefficient showed the relationship between the variables were at the levels of 0.17 and 0.18, respectively.

Conclusions: Owing to the aging population in Kazakhstan, and indeed the world, the problem of medical adaptation and social rehabilitation of older age groups is pertinent, and our findings argue that the introduction of geriatric dental services in Kazakhstan is warranted.

Keywords: gerontology, orthopedic dentistry, elderly, geriatric.

Introduction

The world's population is steadily aging, resulting in an increase in the proportion of people over 60 years old today compared to 40 years ago [1, 2]. According to UN forecasts, by 2050, the number of elderly people will exceed 2 billion and make up more than 20% of the global population. Presently, this figure does not exceed 11%, and in 1950 it was 8% [3, 4]. Experts forecast that depopulation and population aging will continue; consequently, the ratio of age groups will change and will affect social and economic well-being. Similar demographic phenomena occur in the Republic of Kazakhstan. Unfortunately, the elderly sector of the population in the Republic of Kazakhstan does not receive the necessary attention

regarding dental care [5-7]). Oral health is known to affect a person's general health, and most elderly people need extensive, multifunctional dental treatment to preserve their oral health [8-11]. Thus, the requirement for a geriatric dentistry service in the Republic of Kazakhstan is evident. Dental services like orthopedic dentistry should also include fully covered gerontology services [12].

In 1983, the International Association for Gerontology (IAG) began to apply the concept of Gerontostomatology, the science of dentistry in elderly people, which is considered a separate discipline of dentistry and not a special part of gerontology [13]. Many epidemiological surveys conducted in other countries have revealed the unsatisfactory condition of the oral cavity in older age

groups. Physiological aging processes affect the human dental system through changes in the structure of teeth and a decrease in the number of teeth [14]. Poor oral health, including edentulism, changes in the oral mucosa, and inferior removable dentures, in combination with chronic general somatic diseases, significantly reduces the body's adaptive capabilities, seriously affecting the quality of life in the elderly [15]. Furthermore, oral health is an important and integral part of systemic health and can influence systemic conditions [16]. Preserving the health of the elderly can be aided by restoring the chewing apparatus, allowing efficient chewing of food and functioning of the entire digestive system, which, in turn, prevents serious somatic diseases and diseases of the gastrointestinal tract. In this regard, the improvement of orthopedic dental care for elderly people is the most urgent task today in dentistry [17].

In the Republic of Kazakhstan, databases measuring the number of patients with socially significant diseases are being created. Analysis of this data reveals a high level of morbidity within the elderly population. High morbidity rates among the elderly population are associated with a relatively low level of accessibility to highly qualified medical care [18]. Many sociodemographic, behavioral, medical, and financial barriers related to the accessibility and utilization of dental services have been observed in the elderly populations of all countries [19]. Given the momentum and extent of the current population growth, access to dental care is essential to influence quality of life in elderly people. The introduction of gerontodentistry will provide an opportunity to extensively improve elderly health, but it will undoubtedly take a lot of time for a global transformation. This work will help to draw attention to the urgent need for gerontological services, and the need to include dental care in its services. Orthopedic dental care, in addition to the being one of the most needed services among the elderly and one of the most expensive dental services, unfortunately is not included in the services of medical insurance. The first impetus to address this issue, at the first stage, is a revision of the areas covered by medical insurance by the state to include dentistry, which would significantly improve the dental condition of the Kazakhstan population. The introduction of dental services to the list of insured medical care will facilitate the financing of the population and be fundamental in the concept of improving oral health services.

The purpose of this study was to identify problems in orthopedic dentistry among the elderly, justifying the creation of a gerontological service.

Methods

Assessment of Orthopedic Dental Status

The orthopedic dental status of 708 patients from the Center for the Provision of Special and Social Services, the WWII Veterans' Polyclinic, and the dental clinic of Asfendiyarov NMU JSC, in Almaty, Kazakhstan, between 2015 and 2021 was determined using special questionnaires recommended by WHO (2013). Patients were divided into the following age groups: 45–59 years old (9.9%), 60–74 years old (46.9%), 75–90 years old (37.4%), and over 90 years old (5.8%). Orthopedic dental status was assessed, revealing the presence of single crowns; bridges; combined, partial, or completely removable dentures; and the complete absence of dentures. The need for orthopedic dental care was determined by considering the presence of defects in the dentition, the complete absence of teeth, the presence of dentures in need of replacement, and the absence of dentures according to the following five criteria:

1. The need for prosthetics is not required i.e., the absence of defects in the dentition, and the condition of the natural teeth and existing prostheses is satisfactory. There are no indications for prosthetics.

2. The need for non-removable prostheses. Defects of the dentition of Kennedy class III (no more than three teeth), Kennedy class IV (no more than four teeth), and satisfactory condition of natural teeth. Indications for the manufacture of non-removable prostheses.

3. The need for a partial removable prosthesis. Defects of the dentition of Kennedy class I and II, extensive defects of class III (absence of more than three teeth), or class IV (absence of more than four teeth).

4. The need for combined prosthetics (partial removable and non-removable prostheses). A combination of defects of Kennedy class I, II, III, and IV. Indications for a bridge prosthesis (Kennedy class I, III, and IV) or a partial removable prosthesis (Kennedy class I and II).

5. The need for a complete removable prosthesis or a combination of a partial removable and a complete removable prosthesis. Complete absence of teeth on one jaw and a partial absence of teeth on the other jaw. Complete absence of teeth on both jaws.

Research Design

The design of the study in this paper is of a mixed type, including a cross-sectional and retrospective analysis.

Statistical Analysis

Modern statistical methods were used to process the data, including grouping by gender and age, construction of tables and graphs, calculation of relative values, and assessment of the reliability of the differences in the data.

For the conjugacy tables, the significance of the differences between the actual (revealed as a result of the study) quantitative or qualitative characteristics of the sample in each category and the theoretical amount expected in the studied groups with the validity of the null hypothesis was evaluated using the criterion Chi-square (χ^2). Then the value of the criterion χ^2 was calculated using the formula:

$$\chi^2 = \sum_{i=1}^{r} \sum_{j=1}^{c} \frac{(O_{ij} - E_{ij})^2}{E_{ij}}$$

where i is the row number (from 1 to r), j is the column number (from 1 to c), Oij is the actual number of observations in cell ij, E_{ij} is the expected number of observations in cell ij.

For multi-field tables, to assess the strength of the relationship between nominal/categorical variables, it is more appropriate to apply Cramer's V criterion (Cramer's V). The values of both criteria vary from 0 to 1. This criterion can be calculated by the formula:

$$V = \sqrt{\frac{\chi^2}{n * (r-1) * (c-1)}}$$

The obtained value of Cramer's V criterion is interpreted according to the recommendations of Rea & Parker.

The conjugacy coefficient is a measure of the strength of the relationship based on the criterion χ^2. The conjugacy coefficient was calculated using the formula:

$$c = \sqrt{\frac{\chi^2}{\chi^2 + n}}$$

where n is the sample size, and χ^2 is the value of the Chi-square criterion. Conjugacy coefficients range between 0 (no relationship) to values approaching 1 (strong relationship) but do not reach 1.

Statistical and mathematical data processing was carried out using the software packages SPSS version 22.0 and Statistica version 6.0 on a personal computer Aspire E 15 Intel Core i5 2.8 GHz.

Results

Older Patients Have a Greater Probability of Adentia

Comparative analysis between the patients' diagnoses and ages revealed a statistically significant relationship between the 45–59 years and the 60–74 years age groups ($p \leq 0.01$) with a calculated odds ratio (OR) of 2.60; the 45–59 years and over 90 years age groups (OR=3.61; $p \leq 0.01$); adentia and 75–90 years age group (OR = 2.15; $p \leq 0.05$); adentia and the over 90 years age group (OR=3.02; $p \leq 0.01$); crown defect and 45–59 years age group (OR=2.04; $p \leq 0.05$); breakdown of the prosthesis and the 75–90 years age group (OR=2.54; $p \leq 0.01$), and the breakdown of the prosthesis and the over 90 years age group (OR=7.44; $p \leq 0.001$). In other cases, there was a uniform percentage distribution both in terms of ages and diagnoses with ORs in the range of 0.25–1.66 ($p \geq 0.05$). Kruskal-Wallis analysis of variance in the context of age (66.77; $p \leq 0.0001$) and in the context of diagnosis (40.76; $p \leq 0.0001$) helped conclude that the older the patient (75–90 years and older than 90 years), the more pathologies were observed: combined class 30.6%–34.1%, adentia 37.0%–51.2%, crown defect 4.5%, and prosthesis breakage 2.3%–7.3%. Conversely, in younger patients (45–59 years and 60–74 years), pathology varied between the age groups (45–59 years: 17.1%–21.1%; 60–74 years: 10.0%–6.6%; 75–90 years: 12.9%–7.2%, and over 90 years: 11.4%–3.9%).

Thus, assessment of the quantitative relationship between diagnoses and patients' ages revealed that the critical value of χ^2 at the significance level $p \leq 0.0001$ was 97.60, the Spearman correlation coefficient was 0.22 (p=0.0001), and the calculated Cramer's V criterion and the conjugacy coefficient showed an average relationship between the studied variables at the levels of 0.21 and 0.35, respectively. Based on the data, the older the age, the greater the probability of adentia.

Older Patients Have a Greater Need for Orthopedic Dental Care

Comparative analysis of the need for orthopedic dental care and patients' age found a statistically significant relationship between no need and age 60–74 years ($p \leq 0.05$) with a calculated OR of 3.02 and between a need and age over 90 years ($p \leq 0.05$; OR = 3.16) (Table 1 and Figures 1 and 2). In other cases, there was a uniform percentage distribution both in terms of age and the need for orthopedic dental care with calculated ORs in the range 0.30–1.78 ($p \geq 0.05$). Kruskal-Wallis analysis of variance in the context of age (29.57; $p \leq 0.0001$) and in the context of the need for orthopedic dental care (8.47; $p \leq 0.03$) helped conclude that older patients (75–90 years and older than 90 years), had a greater need for orthopedic dental care (35.8%–53.7%), whereas, for younger patients (45–59 years and 60–74 years), the need was not registered, meaning dental care, but not orthopedic dental care, was required (72.9%–68.1%).

Thus, when assessing the quantitative relationship between the need for orthopedic dental care with patients' age, the following patterns were revealed: the critical value of χ^2 at the significance level $p \leq 0.0001$ was 39.92, the Spearman correlation coefficient was -0.09 ($p \leq 0.003$), and the calculated Cramer's V criterion and the conjugacy coefficient showed a weak and average relationship between the studied variables at the levels of 0.16 and 0.23, respectively.

Table 1		Quantitative relationship between the need for orthopedic dental care and patients' age				
			Age				Total
Indicators			45–59 years old	60–74 years old	75–90 years old	Over 90 years old	Total
Need for orthopedic dental care	Not registered	Absolute number	4	37	10	1	52
		Total %	0.6%	5.2%	1.4%	0.1%	7.3%
	No	Absolute number	15	69	95	22	201
		Total %	2.1%	9.7%	13.4%	3.1%	28.4%
	Yes	Absolute number	51	226	160	18	455
		Total %	7.2%	31.9%	22.6%	2.5%	64.3%
Total		Absolute number	70	332	265	41	708
		Total %	9.9%	46.9%	37.4%	5.8%	100.0%
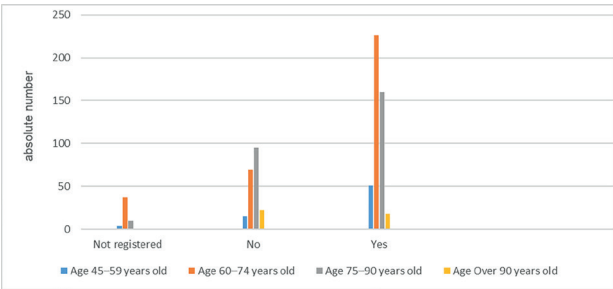
Figure 1 - Quantitative relationship between the need for orthopedic dental care and patients' age
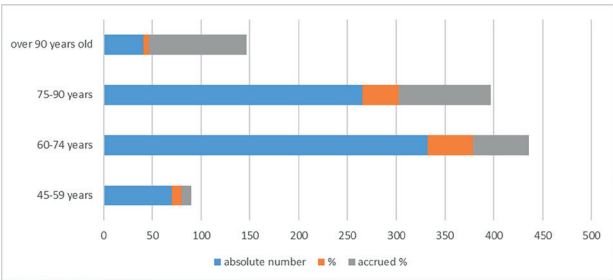
Figure 2 - Graph showing the total number of patients in each age group requiring orthopedic dental care

The Need for Orthopedic Dental Care Does Not Depend on Gender

Comparison of the need for orthopedic dental care with patients' gender showed a statistically significant difference ($p \leq 0.0001$) between "no need" and "need" (19.2% vs. 49.8% in men and 80.8% vs. 50.2% in women) with a calculated relative risk of 4.15 (Table 2 and Figure 3).

Thus, when assessing the quantitative relationship between the need for orthopedic dental care with patients' gender, the following patterns were revealed: the critical value of χ^2 at the significance level $p \leq 0.0001$ was 23.95, the exact Fisher criterion was 0.0000 (p=0.0000), and the calculated Cramer's V criterion and the conjugacy coefficient showed a weak relationship with variables of 0.17 and 0.18, respectively.

Table 2 Quantitative relationship between the need for orthopedic dental care and patients' gender

Indicators			Gender		Total
			Male	Female	
Need for orthopedic dental care	Not registered	Absolute number	10	42	52
		% by line	19.2%*	80.8%*	100.0%
		% by column	2.8%	12.1%	7.3%
		Total %	1.4%	5.9%	7.3%
	No	Absolute number	100	101	201
		% by line	49.8%*	50.2%*	100.0%
		% by column	27.8%	29.0%	28.4%
		Total %	14.1%	14.3%	28.4%
	Yes	Absolute number	250	205	455
		% by line	54.9%	45.1%	100.0%
		% by column	69.4%	58.9%	64.3%
		Total %	35.3%	29.0%	64.3%
Total		Absolute number	360	348	708
		% by line	50.8%	49.2%	100.0%
		% by column	100.0%	100.0%	100.0%
		Total %	50.8%	49.2%	100.0%
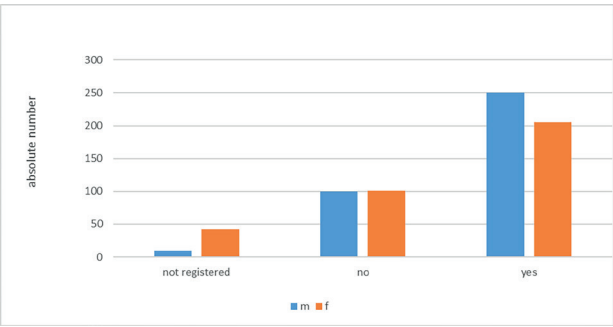
Figure 3 - Quantitative relationship between the need for orthopedic dental care and patients' gender

Discussion

Aging is, unfortunately, an irreversible, continuous and universal process that concerns all living beings, and which leads to a gradual decline in all functions. Comfortable aging depends on various factors including physiological, psychological and economic factors. According to activity theory, socially active individuals have high life satisfaction and positive attitudes towards old age. Attitudes toward old age in one study suggests that perceptions of social exhaustion play an important role in reinforcing negative attitudes toward old age [20].

Our study of 708 patients from Almaty, Kazakhstan, showed that older patients (75–90 years and older than 90 years) had more pathologies upon diagnosis, whereas younger patients (45–59 years and 60–74 years), had pathologies varying within the age groups. In summary, older patients had more missing teeth or even a complete absence of teeth.

We found no significant relationship between diagnosis and gender in line with the literature. Oral disease arises from problems related to oral hygiene, malnutrition, vitamin deficiencies, malocclusion, and other causes that do not depend on gender.

Assessment of the quantitative relationships between the age and gender of patients and their leading clinical diagnostic and therapeutic indicators revealed weak- and medium-level relationships that were statistically reliable. Patients' diagnoses and treatment can be managed through the development of scientific and practical recommendations that will improve medical knowledge.

At the same time, it is necessary to take into account the attitude of elderly people toward the condition of their teeth and oral cavity, their care, their possible reduced interest in life, their attitude to dental care, and their fear of paying for the treatment provided [21].

According to the results of the study in Iran, 32% of the participants corresponded to retirees with low income and socioeconomic status, which could limit the maintenance and fulfillment of their basic needs such as food, health, and shelter. A valuable point in this study is the fact that this population lived in their own homes, which leads not only to less economic expenditure but also to emotional stability at this stage. Galvezet al. [22] among the elderly in Chiclayo [23] found that most of them did not work because they were retired and also belonged to one of the social groups with the lowest socioeconomic income. In this sense, according to some authors, the difference between a healthy old age and a sick elderly person is the amount of money available, so the acquisition of economic resources that can provide decent care in old age should be considered at the young adult stage. that lead to a good quality of life [24, 25].

If we consider the average monthly pension of those living in the "Center for the Provision of Special and Social Services" in Almaty is approximately 70,000–80,000 tenge, and this dental treatment is not included in the scope of guaranteed free provision, it is clear that there is an acute need for orthopedic care. This issue needs government support since the ability to chew is fundamental to a person's quality of life, allowing a full diet, aesthetic appearance, and the capability to communicate normally and lead an active lifestyle [10, 11]. UN experts classify Kazakhstan as a country with accelerated aging rates, and according to their forecasts, 25% of the country will be elderly by 2050.

Therefore, orthopedic dental care should be an essential service. In view of the above, balancing the population requires the adoption of appropriate population policies and decades of planning and implementation in structural, substantive and functional areas in an integrated manner and in different dimensions. For example, forecasting sufficient budgets while a significant portion of the population is shifting from productive to consumptive. Part of this budget is needed for adaptive spaces and services in various areas for older people and caregivers (who devote some of their time and attention to these people).

Conclusions

The novelty of this work lies not only in the identification of an urgent problem that has not been studied in Kazakhstan before, but also in the fact that rational solutions are proposed. Due to the fact that this topic has not previously been raised in our country, to begin with, we had to identify this problem among the elderly, taking as a basis only one city of Almaty and its several sites. A key strategy to solve this issue is the creation of gerontological care programs involving dental care, and peculiarity orthopedic care. We understand that this may require a lot of financial and time resources. The most important starting point is to change the concept of medical insurance, namely the involvement of the dental services. In the Republic of Kazakhstan, there are no official data on the accessibility of medical organizations, including dental services, for elderly people with high levels of morbidity and disability. This study revealed an urgent need to improve gerontostomatology services in the Republic of Kazakhstan.

References

1. Atchison KA, Dolan TA. Development of the geriatric oral health assessment index. *J Dent Educ.* 1990; 54: 680-687. https://doi.org/10.1002/j.0022-0337.1990.54.11.tb02481.x.

2. Issrani R, Ammanagi R, Keluskar V. Geriatric dentistry – meet the need. *Gerodontology.* 2012; 29: e1-e5. https://doi.org/10.1111/j.1741-2358.2010.00423.x.

3. León S, Giacaman RA. Proposal for a Conceptual Framework for the Development of Geriatric Dentistry. *J Dent Res.* 2022; 101(3): 247-252. https://doi.org/10.1177/00220345211042268.

4. Bleiel D, Nitschke I, Noack MJ, Barbe AG. Impact of care level, setting and accommodation costs on a newly developed oral care nursing plan format for elderly patients with care needs – Results from a cross-sectional study. *Int J Dent Hyg.* 2022; 20: 543–552. https://doi.org/10.1111/idh.12525.

5. D'Addazio G, Santilli M, Sinjari B, Xhajanka E, Rexhepi I, Mangifesta R, et al. Access to Dental Care—A Survey from Dentists, People with Disabilities and Caregivers. *Int J Environ Res.* 2021; 18(4): 1556. https://doi.org/10.3390/ijerph18041556.

6. Ikebe K, Matsuda K, Morii K, Furuya-Yoshinaka M, Nokubi T, Renner RP. Association of masticatory performance with age, posterior occlusal contacts, occlusal force, and salivary flow in older adults. *Int J Prosthodont.* 2006; 19(5): 475-481. https://doi.org/10.3390/jcm12020593.

7. Kaye EK, Valencia A, Baba N, Spiro A, III, Dietrich T, Garcia RI. Tooth Loss and Periodontal Disease Predict Poor Cognitive Function in Older Men. *J Am Geriatr Soc.* 2010; 58: 713-718. https://doi.org/10.1111/j.1532-5415.2010.02788.x.

8. Kenny RA, Coen RF, Frewen J, Donoghue OA, Cronin H, Savva GM. Normative Values of Cognitive and Physical Function in Older Adults: Findings from The Irish Longitudinal Study on Ageing. *J Am Geriatr Soc.* 2013; 61: 279-290. https://doi.org/10.1111/jgs.12195.

9. Okada T, Ikebe K, Inomata C, Takeshita H, Uota M, Mihara Y, et al. Association of periodontal status with occlusal force and food acceptability in 70-year-old adults: from SONIC Study. *J Oral Rehabil.* 2014; 41: 912-919. https://doi.org/10.1111/joor.12214.

10. Paganini-Hill A, White SC, Atchison KA. Dentition, dental health habits, and dementia: the Leisure World Cohort Study. *J Am Geriatr Soc.* 2012; 60(8): 1556-1563. https://doi.org/10.1111/j.1532-5415.2012.04064.x.

11. Ibolya Czibere , Andrea Rácz , Henrietta Szilvási , Zita Szikszai , Sándor Imre. Examination of life quality, mental conditions and cognitive status of people over the age of 90: results of a hungarian local research. *Cent Eur J Public Health* 2019; 27 (1): 17–23 https://doi.org/10.21101/cejph.a3561.

12. Kausova GK, Kamieva NA. On the issue of age-related changes in the oral cavity in the elderly. Kazakhstan's medical university (KSPH). 2018; 98-100. Available from: https://www.elibrary.ru/item.asp?id=36880178.

13. Walls AW, Steele JG, Sheiham A, Marcenes W, Moynihan PJ. Oral health and nutrition in older people. *J Public Health Dent.* 2000; 60(4): 304-307. https://doi.org/10.1111/j.1752-7325.2000.tb03339.x.

14. Vigild M. Denture status and need for prosthodontic treatment among institutionalized elderly in Denmark. *Community Dent Oral Epidemiol.* 1987; 15(3): 128-133. https://doi.org/10.1111/j.1600-0528.1987.tb00499.x.

15. Abbas MJ, Albaai FS, Hussein HM, Mahmood AA. Importance of preventive dentistry in the elderly: A personal approach. *Dent Res J.* 2022; 19; 11. Available from: https://www.drjjournal.net/text.asp?2022/19/1/11/338774.

16. Rejnefelt I, Anderson P, Renvert S. Oral health status in individuals with dementia living in special facilities. *Int J Dent Hyg.* 2006; 4: 67-71. https://doi.org/10.1111/j.1601-5037.2006.00157.x.

17. White S, Griffiths R, Baxter M, Beanland T, Cross J, Dhesi J et al. Guidelines for the peri-operative care of people with dementia. *Anaesthesia.* 2019; 74: 357-372. https://doi.org/10.1111/anae.14530.

18. Martins AM, Guimaraes LS, Campos CH, Kuchler EC, Pereira DM, Maia LC, Antunes LS, Antunes LA. The effect of complete dentures on edentulous patients' oral health-related quality of life in lomg-term: A systematic review and meta-analysis. Available from: https://www.drjjournal.net/text.asp?2021/18/1/65/324024.

19. Tsakos G, Watt RG, Rouxel PL, de Oliveira C, Demakakos P. Tooth loss associated with physical and cognitive decline in older adults. *J Am Geriatr Soc.* 2015; 63 (1): 91-99. https://doi.org/10.1111/jgs.13190.

20. Aykut Aydın, Aylin Aydın Sayılan. Attitudes toward successful aging in individuals with chronic disease aged 65 or over. *Journal of clinical medicine of Kazakhstan.* 2021; 18 (2): 39-43. https://doi.org/10.23950/jcmk/9736.

21. Yen Chun G. Liu, Shou-Jen Lan, Hirohiko Hirano, Li-min Lin, Kazuhiro Hori, Chia-shu Lin, Samuel Zwetchkenbaum, Shunsuke Minakuchi, Andy Yen-Tung Teng. Update and review of the gerodontology prospective for 2020's: Linking the interactions of oral (hypo)-functions to health vs. systemic diseases. *Journal of Dental Sciences.* 2021; 6(2): 757-773. https://doi.org/10.1016/j.jds.2020.09.007.

22. Abbas, Maha Jamal1; Albaaj, Firas Saddam Oglah2; Hussein, Hashim M.3,; Mahmood, Athraa A.4 Importance of preventive dentistry in the elderly. A personal approach. *Dental Research Journal.* 2022; 19(1): 11. https://doi.org/10.4103/1735-3327.338774.

23. Gálvez JM, Vélez CD, Segura MAA, González LM, Benavides JP. Perception of the quality of life related to health of older residents in the city of Chiclayo. *Acta Med Peru.* 2009; 26: 230-238. https://doi.org/10.35663/amp.

24. Wong R, Espinoza M. Mexican senior adult in the broad socioeconomic context: *Health and aging. Public Health Mexico.* 2007; 49: 436-447. https://doi.org/10.1590/S0036-36342007001000002.

25. Saxena A, Nagarajappa R, Naik D, Abid M, Ramesh G. Assessing the effect of oral diseases on oral health related quality of life of institutionalized elderly using Oral Health Impact Profile (OHIP-14) questionnaire: A pilot study. *Rocz Panstw Zakl Hig.* 2020; 71: 349-353. https://doi.org/10.32394/rpzh.2020.0130.

Trends of violence against health care workers and facilities: understanding the unheard

Sonia Mukhtar[1], Waleed Rana[2], Shamim Mukhtar[3]

[1]Institute of Clinical Psychology, University of Management and Technology, Lahore, Pakistan
[2]Hainan Medical University, Hainan General Hospital, Haikou, China
[3]College of Earth & Environmental Sciences, University of the Punjab, Lahore, Pakistan

Corresponding author:
Waleed Rana.
E-mail: waleedrana312@gmail.com;
ORCID: 0000-0002-6679-5112.

Abstract

This article evaluated trends of violence against healthcare workers and healthcare facilities. It further assessed risk factors, perpetuating, precipitating, and predicting factors. This article presented a framework on how to address, minimize and control the violence against healthcare workers and facilities in an effective way. It further presented a framework for policy developers and decision makers to ensure the safety and protection of the healthcare profession.

Keywords: Healthcare workers, healthcare facilities, COVID-19, violence, policy making

"I have been slapped, pushed, hair pulled, stalked, harassed, and verbally abused," says Dr. John Doe of the Sheikh Zaid Hospital of Pakistan

When health-care workers are subjected to more acts of violence than police officers and prison guards then imperativeness of this matter cannot be overlooked. Situations such as these indicate prevalence of violence towards healthcare personnel at healthcare facilities [1]. Healthcare personnel's violence appears to be the underreported but alarmingly ubiquitous and persistent problem [2].

Operational definitions

Healthcare refers to the facilities, services and activities that ensure, delivered and access for the wounded and sick in the context under consideration that grouped into four main categories, doctors, nurses, paramedical staff and administrative staff.

Health-care facilities includes health-care centers, first aid posts, blood transfusion centers, clinics, medical laboratories, medical and pharmaceutical stores, medical vehicles (ambulances, civilian or military medical ships or aircrafts carrying medical supplies or equipment) of *healthcare personnel* consists of doctors, nurses, physiotherapists, pharmacists, ambulance drivers, paramedics, support staff (ward orderlies, gate keepers), administrative staff, medical rescue workers, clinical professionals, social and community workers and volunteers, local health providers including polio teams, and midwives are subjected to violence. In health-care settings, possible sources of violence include patients, visitors, intruders and coworkers [3, 4].

Violence is defined as the intentional or accidental use of physical force perceived or real, threatened or actual, interpersonal or collective against oneself or another person, or against a group or community which results in or has likelihood to result in harm or death, physiological, verbal, sexual or psychological harm, deprivation or under-development. The National Institute for Occupational Safety and Health (NIOSH) defines *workplace violence* as violence acts such as physical assaults and threats towards people at work or on duty [5, 6]. *Violence against health-care* consists of acts or threats of violence that hinder, obstruct or adversely affect the deliverance or access to healthcare. *Violence against health-care personnel* includes physical, verbal psychological harm or death while performing their

duties [7]. *Violence against patients* includes physical, verbal, or psychological harm in getting medical care in the form of killing, injuring, deliberate failure or denial of medical assistance [8].

Violence against healthcare providers

Violence against health-care has become an epidemic, with almost equal intensity of COVID-19 pandemic, threatening to dissuade the entire health system throughout the industrialized, developing and transitional countries. The prevalence of physical and non-physical violence against health-care constitutes from 8% to 38% observed during the COVID-19 pandemic [9]. Most violence incidents are perpetrated by patients and visitors, even become the subject of individualistic, collective or political violence [10]. Health-care personnel especially individuals from BIPOC, women, and minority workers are the most vulnerable professionals susceptible to workplace violence [11, 13]. Reports have indicated responses of health-care personnel from different countries ranging from physical or psychological violence: 76% in Bulgaria; 67% in Australia; 61% in South Africa; 60% in health centers in Portugal; 54% in Thailand; and 47% in Brazil [14]. *Violence against lady health-care workers* has increased drastically in Pakistan especially during Pakistan's polio eradication struggles. Besides 110,000 lady health-care workers in Pakistan negotiation access and security interests remains same [15-16]. Physical, non-physical assaults and aggression are common occurrences at many parts of Pakistan varying from aggression to harassment [17]. Such violence against health-care workers has negative influence on their occupational performance, well-being and consequently impact patient's health and satisfaction as shown by a study conducted during the peak of COVID-19 pandemic [18]. A study conducted by the ICRC in Karachi and Peshawar indicated that ambulance drivers are at higher risk, other drivers' unwillingness to let the ambulance past, afar location of hospitals with trauma wards, general lack of respect towards medical profession. [19,20]. In Karachi, Pakistan's largest city, 130 doctors were killed and 150 kidnapped between 2012 and 2014 [21-22].

4Ps (precipitating, predisposing, perpetuating, predictive factors)

Studies conducted by International Committee of the Red Cross (ICRC) has indicated the following findings: health-care personnel were subjected to threats, physical assaults by patients and relatives, deprivation of their liberty, and coerced to act against health-care ethics; health-care facilities were effected against, inside, or within the perimeter through attack, disruptive armed entry, takeover, or looting such as bombing, burning or harming during the conduct of hostilities; break-ins and forced entry including pillage, robberies for perpetrating violence against health-care facilities often resulting the deaths of patients, bystanders, relatives and health-care personnel; obstruction of passage of ambulance and drivers of medical transports carrying patient; health-care personnel resulting in health-care personnel and patients were effected by threats and deprivation liberty, and health-care facility involved in the loss of resources to the suspension of health-care services.

The growing epidemic rate of violence, after the pandemic of COVID-19, against healthcare workers and healthcare facilities has been prevalent; however recent attention to this problem's magnitude is due to various factors [23, 24]. First, risk of verbal and physical violence has expanded across diverse types of healthcare settings, globally. Second, recent media attention to global school, workplace and religious citing's shootings raised the level of conscious awareness of dimensions of violence converting sensationalism into habituation or desensitization towards violence. Third, various psychological studies have observed the insurgence of decreased job satisfaction, increased occupational strain and poor wellbeing as a consequence of physical or nonphysical violence.

Furthermore, the escalating risk in the healthcare facilities is due to increased drug and alcohol use by patients, or presence of any form of weapon, or unhealthy coping skills, or long waiting times, and increased number of patients with violence history, mental health issues like dementia or psychosis. Healthcare workers' uniform of identification that instigated security and reverence has transformed into a threat for them [25].

It appears as the mainstream media stagger in comprehending violence against healthcare personnel and advertently or inadvertently conveys the message of 'do no harm' at the expense of personal risk. In an episode of House M.D (Season 1, Episode 15), a brother of the patient slapped Dr. Chase across the face but Dr. Chase 'decided' to silently endure without reporting [26]. Social media has expanded, exposed and expedited health-care data or information into a highly research issue on the internet. This accessibility and liberty have paved the way to give voice of the unheard health-care workers' issues to the masses – allowing individuals to share their experiences about service provisions, procedures, and treatment management for definitive diagnosis.

The role of culture in confluence of nature of service healthcare workers provide may render some particularly at risk of experiencing violence and even death. In global context, having more representation of women in healthcare system including majority of nurses and auxiliary nurses, and community outreach workers who are targeted by violence led to higher number of incidents involving women healthcare workers. In Pakistan, male gynecologists are specifically threatened or killed under the pretense of perceived violation of women's privacy. This intersection between job specialization, gender, culture and violent incidents may point towards a possible gendered exposure towards violence [27-30].

Impact of violence towards healthcare providers

The effect of threats and attacks against healthcare severely impacted entire healthcare system and has become the key humanitarian challenge of this time. So much a talk of efforts to reduce child mortality, to improve maternal health, to tackle stigmas against mental health, and to fight against diseases such as polio which majorly exist in Pakistan – it will take decades to rebuild the system if magnitude, patterns, intensity and dynamics of this issue left unacknowledged [31].

Many studies in the developed countries have focused on violence and associated factors at psychiatric and psychological facilities at hospitals, emergency departments, public sector hospitals, welfare sectors, and nursing homes [32-35]. Many developing countries including Pakistan remained in the want of more scientific researches to explore further factors of violence, aggression and gendered hatred towards women (misogyny, sexism, sexual assault, rape, harassment and bullying) in health-care setting to help in addressing policies and training to deal with such incidents [36-39].

More research required in low resource settings of developing and underdeveloped countries to evaluate negative outcomes and impact on the occupational motivation, and physical and psychological wellbeing of the health-care workers. It will establish the course of action of different setting for interventions

to prevent violence against health-care for emergency and non-emergency settings through ensuring physical security of health-care facilities and treatment /management of high-risk patients or visitors, respectively. Poor political or economic stability, unemployment, poverty, deprivation of basic human rights political agitation give birth to anger, frustration, and importance resulting in more outbursts of violence against anyone

In Pakistan, 77% medical employees have experienced both physical and nonphysical assault. But only a fraction of actual cases gets reported like a trend seen in violence faced by young doctors in Pakistan [40]. Low rate of reporting may be due to lack of support from management, vague reporting procedures, and policies or laws in this regard and a perceived moral obligation of acceptance of violence at workplace including unpreparedness to cope with violence at workplace [41]. A problem that can only be dealt with thorough training in healthy working practices, de-escalation techniques with the assistance of institutional policies and occupational safety policies for the violence-free workplace.

Lack of understanding of the duties of medical personnel and unmet unreasonable expectations in terms of treatment, management, prescriptions of medicine can lead to violent encounters [42]. If patients who have non-emergency states denied hospitalization at emergency department or given simple treatment then the chance of violent episode from patient or visitors could occur. Studies conducted at psychological hospitals indicated that, on average, two aggressive assaults per week takes place [43]. Such aggressive incidents, active aggression, and relational aggression lead to chronic fatigue, intolerance, impatience, absence of frustration tolerance, and lack of sympathy towards patients. Therefore, violence in general is more prevalent in the society [44-47].

Health-care facilities in emergency department are subjected to over-crowding, insufficient number of medical and nursing staff, delay of laboratory tests or diagnostic imaging, and other health condition as one of the cardinal issues of health-care workers encountered. Violence occurs if the service is unsteady or health access is limited or delayed. Conflict with health-care workers at health-care facilities occur during times of high activity and interaction with multiple patients at a time or during meal times, visiting hours or patient transportation as a result of disciplinary action such as restraints of eatables for patients [48].

In humanitarian implication such as natural disasters (earthquakes, floods, dust storm, tsunami) or anthropogenic disaster (mass destruction, bombing, terrorism acts) tend to cause extended suffering to the people resulting in loss of health resources, water supply, nutrition, shelter, and obstruction of access to health-care facilities. This conditional conflict or violence again health-care or health-care facilities leads to collapse of social, economic, and political infrastructure – reformed through developing policies and protocols, health-care protection laws, reinforcing networks, emergency conditions and evaluating services during peace and conflict.

The frequency and intensity of violent events has direct proportionality with the probability of mental health issues [49]. The other consequences consist of negative emotions, and negative behavioral manifestations including burnout, negative self- concept towards oneself and the others, psychosocial complaints, and emotional- behavioral issues [50]. Many studies comprising of responses to violence against health- care across different countries, cultures, settings and emotional reactions including fear, anger, anxiety, and uncertainty and intention to quit profession [51-53].

Biopsychosocial model

An individual's defense mechanisms, coping strategies, risk assessment and management, assertive communication, resilience, empathy, and innate personality act as influential factors in any context, situation and environment in establishing a response continuum [54]. This triggers physical responses such as metabolic functions, immune system, tense up muscles and increasing heart rate to prepare for urgent action – F4 (Fight – Flight – Freeze – Fawn) response. This establishes an individual's reaction to the situational triggers who choose to respond to violence from multiple options: avoidance, denial, discussion, reporting, counseling and prosecution [55]. Emotional reactions to violence include shock, disbelief, anger, frustration, apprehension, high stress level, burnout, loss of self-esteem and professional competence, feeling of powerlessness, self-blame, avoidance of situations, lack of job motivation and job satisfaction, anxiety, depression, suicidal ideations, and other mental health concerns [3, 4]. Other responses could be high turnover, truancy, unsatisfactory job performance, relationship issues, sexual dysfunction, compromised ability to provide quality care to oneself and patient which was seen more prevalent and exacerbated during and post-COVID-19 pandemic [56].

Emotional behavioral reactions physical response (F4) to any situation varies individual to individual. If the health-care workers reluctantly tackle violent event as being a characteristic of the patient then the magnitude could be significant next time. This indicates the violence is not inevitable as health-care workers had assumed but situational. Short term exposure to violent incident become stressful event and long-term psychological reaction holds the beginning of Post-Traumatic Stress Disorder (PTSD).

The cluster of symptoms can be divided PTSD into acute or chronic PTSD which accounts duration and symptoms of persistent re-experiencing of the traumatic event; avoidance of similar situations and feeling anxiety, apathy, and hyper-sensitivity. Adjustment issues could become another factor for a victim in this situation. These mental health problems could be manifested in terms of inattentiveness, truancy, time off, psychosomatic complaints, emotional-behavioral reactions, psychosocial issues, relationship strains and occupational hazards. Sharing a traumatic event, no matter how trivial has cathartic outcome as a catalyst for optimism and change. And health-care facility could suffer from problems of recruitment and retention of staff after resignation.

An imminent need of a mental health practitioner for capacity building of healthcare workers to manage emotions after the encounter of violent incidents, and a research psychologist for consultation for development of training program for healthcare workers such as communication methods (aggressive, passive and assertive communication) to manage threatening situations (breaking bad news to patients and relatives, medical ethics, and ways to predict, prevent and pacify violence against healthcare workers. A research psychologist could publish manuals in esteemed journals, informative articles in impactful newspapers and magazines, coping strategies guidelines as part of curriculum modules.

Intervention and prevention

For intervention and prevention, a campaign could be initiated by taking an initiative and commencement of movement which aimed at addressing the issues of violence against healthcare workers, patients, and facilities by ensuring safety and quality deliverance of healthcare [57]. An initiative that should foster consolidation for identification, operationalization and

implementation of SMART (Specific, Measurable, Achievable, Relevant, Time-bound) goals to prevent violence and safeguard healthcare ought to be implemented.

The active mobilization of society is a key for support just as an adjoined community is a catalyst for change. It serves the purpose of prevention against violence through scientific research, debate, consultations, and workshops to create and strengthen awareness with practical steps to safeguard healthcare. This campaign could seek public communication to raise awareness on violence against healthcare by highlighting the concerns, humanitarian impact of violence and implementation strategies for the protection of healthcare. It consists of national and international organizations, indigenous research initiatives, academia, health professionals, government officials, non-government organizations, and more to advocate and implement measures for healthcare. Collective effort of humanitarian, development, and health communities with broader coalitions, formal or informal of different groups of society connected by interest in this issue are required to produce the monitored and measured results. Various indigenous and global initiatives and campaigns brought together under common action plan to address and prevent violence against healthcare. This common action plan seeks policy change, not only legislation but regulation and implementation (which requires time and commitment of authorities). A campaign could commission a brand-new framework for operational practices from existing data and literature.

A high-profile media campaign's impact can never be undervalued or undermined as media is the most powerful tool to modify behavioral patterns of people and alter cognitive schemas, *en masse*. Electronic, print and social media including television, radio, newspapers, blog, vlog, twitter, and others lay a foundation upon which journalists, healthcare providers, victims, rights advocates, public figures, public speakers, and medical and mental health professionals. Feasibility of changes, consolidation of practices, implementation of policies, commencement of laws and prompting behavioral change fosters a society free of violence against healthcare workers and facilities.

Legislative measures for the implementation of the international legal framework, dissemination and training should be implemented meanwhile, policy makers, NGOs, humanitarian agencies and stakeholders initiated national level course of action for domestic policies to undertake comprehensive analysis, including causes and effects of violence against health-care workers [58-63]. Pakistan Penal Code (PPC) accommodates a law, Section 153 – A which stated that "By words, either spoken or written, or by signs, or by visible representations or otherwise, that promote or incite, or attempt to promote or incite, on grounds of religion, race, place of birth, residence, language, caste or community or any other grounds whatsoever, disharmony or feelings of enmity, hatred or ill-will between different religious, racial, language or regional groups or castes or communities: or commits, or incites any other person to commit, any act which is prejudicial to the maintenance of harmony between different religious, racial, language or regional groups or castes or communities or any groups of persons identifiable as such on any ground whatsoever, and which disturbs or is likely to disturb public tranquility shall be punished with imprisonment for a term which may extend to five years.

Limitation towards achieving these goals is the paucity of consensuses standard definition of assault, misinformation, battery, threat or harassment among governmental domain so establishing standardized operational definition can be the logical way forward. Another obstruction is abstruse differentiation between intentional and inadvertent violence [64-66]. A vigilant distinction should be placed to determine whether the attack was prompted due to delirium, psychosis, or dementia, however, an action undertaken under the influence of alcohol and drugs is a crime even intoxication, drug seeking and withdrawal leading to violence cannot be overlooked as an excuse for abusing healthcare workers. Judiciary should intervene and matter should be immediately reported to the authority to prevent recidivism [67].

Healthcare ethics

Health-care ethics is the field of ethics to deal with the ethical issues in the practice of health-care. Ethical decision-making demands impartiality, confidentiality, regard for dignity of others in need, fair treatment, avoid inflicting harm and acting in the best interest of individuals and groups in times of peace, conflict and emergencies Healthcare personnel's task is to provide necessary care in the accordance of human physical and mental health. Healthcare personnel act in the best interest of patients with their consent. Healthcare workers' obligation required them to render immediate attention and requisite care without prejudice and discrimination against anyone. Healthcare workers ensure respect, privacy and confidentiality and disclose confidential information with the consent of patient or in case of threat of harm to patient or to others. Safe access to health-care personnel, facilities or equipment should not be impeded or compromised. By endorsing these ethical conditions will minimize the chance of a conflict or encounter of inflicted harm against health-care personnel [68]. Healthcare personnel in under no circumstance should accept and agree with inhuman or degrading treatment based on gender, race or any other factor and must never be present at and may take part in such acts [69]. Health-care personnel, health-care facilities must be respected by all [70-73].

Healthcare workers endure perceived personalization and social tolerance of violence and from the perception that the training of their profession implies the acceptance of violence and aggression (victimization of health-care personnel) [74]. Another challenge contributing to underreporting rooted in cultural, economic and political dynamic where healthcare personnel feel professional and ethical obligation to 'do no harm' to patients over their own wellbeing or their unwillingness to report to avoid stigmatization of perpetrator due to illness or impairment. The acceptance of violence with healthcare workers and at healthcare facilities should not be considered as a part of a job. A related factor that prevents healthcare workers from reporting include apprehension towards being perceived as unprofessional amongst peers, or indicator of poor performance or negligent towards the job, fear of personal and professional stigmatization, and lack of support from administration.

Healthcare facilities can reduce workplace violence by implementing an inclusive violence intervention and prevention program that constitutes commitment from upper management and participation from lower management, health and safety training, occupational setting's analysis and occupational hazard identification, recordkeeping, program evaluation, and hazard prevention and intervention.

Violence against health-care is a prevalent factor that affects human rights and public health worldwide with social, economic, and physical and mental health consequences against gender norms, individuals, families, communities and societies. More consequences could be of workplace under productivity, minimal job motivation, less inclination of job retention, mental

health complaints, physical injury and suicidal ideations. A need to foster partnership among and beyond the individuals, community and society of concern – collective effort by humanitarian, health communities, civil society organizations, and media and health professionals to raise awareness at domestic and global level: make health-care system safe, secure, and progressive under all circumstances.

References

1. Kingma M. Workplace violence in the health sector: a problem of epidemic proportion. *Int Nurs Rev.* 2001; 48: 129–130. https://doi.org/10.1046/j.1466-7657.2001.00094.x

2. Violence against healthcare workers can have a negative impact on World Health Organization (WHO). World report on violence and health. Geneva: *World Health Organization,* 2003.

3. Mukhtar S, Rana W. Biopsychosocial-Spiritual Model of COVID-19 for Healthcare Practitioners Amidst and Post-COVID-19. *Psychiatr Danub.* 2021; 33(4): 595-599. https://doi.org/10.24869/psyd.2021.595.

4. Mukhtar S, Rana W, Mukhtar S. The Development and Psychometric Properties of the Impact of Covid-19 Scale (Ic19-S): A Factor Analysis Approach. *Psychiatr Danub.* 2022; 34(10): 226-232. https://doi.org/10.1186/s40359-022-00778-9.

5. Schyve PM. The Joint Commission. Preventing Violence in the Health Care Setting. [Last accessed on 2022 April 19]. Available from: https://www.jointcommission.org/jc_physician_blog/violence_in_the_health_care_setting/.

6. Hartley D, Doman B, Hendricks SA, Jenkins EL, Non-fatal workplace violence injuries in the United States 2003-2004: a follow back study. *Work (Reading, Mass).* 2012; 42(1): 125-35. https://doi.org/10.3233/WOR-2012-1328.

7. Mukhtar S. Mental Wellbeing of Nursing Staff during the COVID-19 Outbreak: A Cultural Perspective. *Journal of Emergency Nursing.* 2020; 46(4), 426-427 https://doi.org/10.1016/j.jen.2020.04.003.

8. Mukhtar S, Mukhtar S, Rana W. COVID-19 Feminist Framework to Address Public Health Impact of Violence, Abuse, and Trauma in Children, Women, BIPOC, and LGBTQIA+ Community: A Preliminary Observation. *Asia Pacific Journal of Public Health.* 2021; 33(5), 645–647. HYPERLINK "https://doi.org/10.1177/10105395211014351/" https://doi.org/10.1177/10105395211014351.

9. Ullah I, Khan KS, Ali I, Ullah AR, Mukhtar S, de Filippis R, Malik NI, Shalbafan M, Hassan Z, Asghar MS. Depression and anxiety among Pakistani healthcare workers amid COVID-19 pandemic: A qualitative study. *Annals of Medicine and Surgery.* 2022; 78: 103863. https://doi.org/10.1016/j.amsu.2022.103863.

10. Occupational Safety and Health Administration (OSHA). Guidelines for preventing workplace violence for healthcare and social service workers. No. 3148-04R. 2015.

11. WHO. Violence against Health Workers. Available from: http://www.who.int/violence_injury_prevention/violence/workplace/en.

12. Mukhtar S. 8 minutes and 46 seconds of 'I Can't Breathe': A call for anti-racist feminist solidarity amid COVID-19. International Social Work. 2021; 64(2), 255-260. https://doi.org/10.1177/0020872820967417.

13. Rana W, Mukhtar S, Mukhtar S. Countering Emotional and Psychological Manipulation Abuse by Cultivating Resilience, Meaning, and Well-Being Among Victims of Male Intimate Partner Violence – Working Frontline Health Care Workers During COVID-19 Lockdown: A Qualitative Study. *Asia Pacific Journal of Public Health.* 2023. 34 (6-7): 671-674. https://doi.org/10.1177/10105395221107139.

14. U.S. Department of Labor. Occupational Safety and Health Administration: Guidelines for Preventing Workplace Violence for Health Care and Social Service Workers (OSHA3148-01R, 2004) 2007b. [Last retrieved on 2019 April 19]. Available from: http://www.osha.gov/index.html.

15. Violence: Occupational Hazards in Hospital. Cincinnati, OH, USA: National Institute for Occupational Safety and Health; 2002. Centers for Disease Control and Prevention.

16. Kamchuchat C, Chongsuvivatwong V, Oncheunjit S, Yip TW, Sangthong RJ. Workplace violence directed at nursing staff at a general hospital in southern Thailand. *Occup Health.* 2008; 50(2): 201-7. https://doi.org/10.1539/joh.O7001.

17. Mukhtar S, Mukhtar S. Letter to the Editor: Mental Health and Psychological Distress in People with Diabetes during COVID-19. *Metabolism.* 2020: 108, 154248. https://doi.org/10.1016/j.metabol.2020.154248.

18. Rana W, Mukhtar S, Mukhtar S. Job satisfaction, performance appraisal, reinforcement and job tasks in medical healthcare professionals during the COVID-19 pandemic outbreak. *The International Journal of Health Planning and Management.* 2022. https://doi.org/10.1002/hpm.3476.

19. Bullying of junior doctors in Pakistan: A cross-sectional survey. *Singapore Med J.* 2010; 51(7): 592-5.

20. Addressing violence against health care in Peshawar a mixed methods study. (2018). International committee of the Red Cross

21. A matter of life and death tackling violence against health care in Pakistan, Peru and El Salvador (2017). International Committee of the Red Cross.

22. lsaleem SA, Alsabaani A, Alamri RS, et al. Violence towards healthcare workers: A study conducted in Abha City, Saudi Arabia. *J Family Community Med.* 2018; 25(3): 188–193. https://doi.org/10.4103/jfcm.JFCM_170_17.

23. Mukhtar S. Mental Health and Psychosocial Aspects of Coronavirus Outbreak in Pakistan: Psychological Intervention for Public Mental Health Crisis. *Asian Journal of Psychiatry.* 2020; 51: 102069. https://doi.org/10.1016/j.ajp.2020.102069.

24. Mukhtar S. Pakistanis' mental health during the COVID-19. *Asian journal of psychiatry.* 2020: 51: 102127. https://doi.org/10.1016/j.ajp.2020.102127.

25. Findor MJ, McGovern PM, Wall M, et al. Risk factors for work related violence in a health care organization. *Inj Prev.* 2004; 10 (5): 296-302. https://doi.org/10.1136/ip.2003.004747.

26. Joey Arnello. House Wiki. Accessed April 16, 2019. https://house.fandom.com/wiki/Joey_Arnello.

27. IFRC. 2010. Global strategy on violence prevention, mitigation and response (2010–2020).

28. Mukhtar S. Public Health Aspects of Domestic/Intimate Partner Violence Abuse and Trauma (DIVAT) during COVID-19 Quarantine: Imbalanced Power Dynamic and Sexual, Emotional, and Psychological Abuse. *Asia Pac J Public Health.* 2023; 35(4): 301-303. https://doi.org/10.1177/10105395231164439.

29. Jessica Cadesky. Health Care in Danger and Gender. *Swedish Red Cross.* (2015).

30. Privitera M, Weisman R, Cerulli C, Tu X, Groman A. Violence toward mental health staff and safety in the work environment. *Occup Med.* 2005; 55: 480-86. https://doi.org/10.1093/occmed/kqi110.

31. Mukhtar S. Experiences, Challenges, and Lessons Learned From COVID-19: A Case Study of Mental Health in Pakistan. *Disaster Medicine and Public Health Preparedness.* 2024, 18, e11. https://doi:10.1017/dmp.2024.2

32. Chen WC, Hwu HGH, Kung SM, Chiu HJ, Wang JD. Prevalence and determinants of workplace violence of health care workers in a psychiatric hospital in Taiwan. *J Occup Health* 2008; 50: 2888-93. https://doi.org/10.1539/joh.L7132.

33. Ryan D, Maguire J. Aggression and violence- A problem in Irish Accident and Emergency departments? *J Nurs Manag.* 2006; 14(2): 106-15. https://doi.org/10.1111/j.1365-2934.2006.00571.x.

34. Schablon A, Zeh A, Wendeler D. Frequency and consequences of violence and aggression towards employees in the German healthcare and welfare system: a cross-sectional study. *BMJ Open.* 2012; 2: e001420. https://doi.org/10.1136/bmjopen-2012-00142015.

35. Algwaiz WM, Alghanim SA. Violence exposure among healthcare professionals in Saudi public hospitals. A preliminary investigation. *Saudi Med J.* 202; 33(1): 76-82.

36. Franz S, Zeh A, Schablon A, Kuhnert S, Nienhaus A. Aggression and violence against health care workers in Germany – a cross sectional retrospective survey. *BMC Health Services Research* 2010; 10: 5. https://doi.org/10.1186/1472-6963-10-51.

37. Qadri H, Kumar S, Rafique Khan H, et al. Changes in Lifestyle, Health Practices, and Perceived Anxiety amidst the COVID-19 Pandemic: A Cross-Sectional Study Conducted on the General Population of Pakistan. *Medical journal of the Islamic Republic of Iran.* 2021; 35 (1) :1382-1388. https://doi.org/10.47176/mjiri.35.195.

38. Rana W, Mukhtar S, Mukhtar, S. COVID-19 in Pakistan: Current status, challenges and recommendations. *Journal of Clinical Medicine of Kazakhstan.* 2020; 3(57): 48-52. https://doi.org/10.23950/1812-2892-JCMK-00766.

39. Mukhtar S, Mukhtar S. The Hidden Shadow Pandemic of Marital Rape During COVID-19 Pandemic Outbreak: A Critical Role of Women's March for Awareness of Rape, Consent, and Sexual and Reproductive Rights. *Journal of Psychosexual Health.* 2022; 4(2): 80-94. https://doi.org/10.1177/26318318221089415.

40. Habermann M, Uys L. Introductory remarks: violence in nursing– international perspectives. Violence in nursing International perspectives. *Frankfurt am Main: Peter Lang,* 2003. 13-27.

41. Sands N. An ABC approach to assessing the risk of violence of triage. *Australian Emergency Nursing Journal.* 2007; 10, 107-109. https://doi.org/10.1016/j.aenj.2007.05.002.

42. Celik SS, Celik Y, Agirbus I, Vgurluog O. Verbal and physical abuse against nurses in turkey. *International nursing review.* 2007; 54: 359-360. https://doi.org/10.1111/j.1466-7657.2007.00548.x.

43. Abbas MA, Fiala, LA, Abdel Rahman, AG, Fahim, AE. Epidemiology of work place violence against nursing staff in Ismailia Govern rate, Egypt. *Journal of the Egyptian Public Health Association.* 2010; 85: 1-5.

44. Mukhtar S, Mahmood Z. Moderating Role of Perceived Social Support between Perceived Parenting Styles and Relational Aggression in Adolescents. *J Aggress Maltreatment Trauma.* 2018; 27(8): 831-845. https://doi.org/10.1080/10926771.2018.1468842.

45. Mukhtar S, Mukhtar S, Mahmood Z. A Correlational Approach to Relational Aggression: Assessing Individual, Family and Classroom Variables/Determinants of Relational Aggression among Adolescents. *Bahria Journal of Professional Psychology.* 2022; 21(1): 28–51.

46. Mukhtar S. Dilemmas in School Counseling Services. *Bahria Journal of Professional Psychology.* 2019. 18(2): 21–32.

47. Mukhtar S, Mahmood Z. Prevalence and associated factors of relational aggression in educated adolescents. *Journal of Pakistan Psychiatric Society.* 2019; 16(2).

48. Sendzum, EK. Violence Towards nursing staff. In Emergency departments in one Turkish. *City in International Nursing review,* 2005. 52(2), 154-160. https://doi.org/10.1111/j.1466-7657.2005.00420.x.

49. Gerberich SG, Church TR, McGovern PM, Hansen HE, Nachreiner NM, Geisser MS, et al. An epidemiological study of the magnitude and consequences of work related violence: the Minnesota Nurses' Study. *Occup Environ Med* 2004; 61: 495-503.

50. Voyer P, Verreault R, Azizah G, Desrosiers J, Champoux N, Bèdard A. Prevalence of physical and verbal aggressive behaviors and associated factors among older adults in long-term care facilities. *BMC Geriatrics* 2005; 5: 1-13

51. Estryn-Behar M, van der Heijden B, Camerino D, Fry C, Le Nezet O, Conway PM, Hasselhorn HM. Violence risk in nursing-results from the European "NEXT" study. *Occup Med* 2008; 58: 107-14

52. Zeh A, Schablon A, Wohlert C, Richter D, Nienhaus A. Violence and Aggression in Care-Related Jobs - A Literature Overview (Artikel in German) Gewalt und Aggression in Pflegeund Betreuungsberufen Ein Literaturüberblick. *Gesundheitwesen* 2009; 71: 449-59.

53. Law Commission, 1995, Liability for all psychiatric illness, a consultation paper, No 137 HMSO, London, UK.

54. Mukhtar S. Feminism and gendered impact of COVID-19: Perspective of a counselling psychologist. *Gender, Work & Organization*, 2020; 27(5), 827-832. https://doi.org/10.1111/gwao.12482.

55. Mukhtar S. Domestic/Intimate Partner Violence, Abuse, and Trauma During COVID-19 Lockdown: Gaslighting, Non-consensual Condom Removal, Grooming, Coercive Control, Power Dynamic, and Sexual Entitlement in Emotional and Psychological Abuse. *Journal of Psychosexual Health.* 2024: 0(0). https://doi.org/10.1177/26318318231225050.

56. Lancaster Group, 2000, Stress and how to survive it, Nottingham, UK.

57. Changing behavior tackling violence against health care in Niger, the Central African Republic and Nigeria. *International Committee of the Red Cross.* 2018.

58. ICRC, Violent incidents affecting the delivery of health care – January 2012 to December 2013, ICRC, Geneva, 2014.

59. International Humanitarian Law requires healthcare facilities respected and protected without adverse distinction. IHL also provides framework of protecting healthcare during both peace and conflict.

60. Rana W, Mukhtar S, Mukhtar S, Mohiuddin G, Ehmad A. Psychological health of aging mental healthcare social workforce amidst coronavirus disease-2019 pandemic. *International Journal of Geriatric Psychiatry.* 2021; 36(3): 461-462. https://doi.org/10.1002/gps.5456.

61. Mukhtar S. Mental Health and Emotional Impact of COVID-19: Applying Health Belief Model for Medical Staff to General Public of Pakistan. *Brain Behavior, and Immunity.* 2020. https://doi.org/10.1016/j.bbi.2020.04.012.

62. Resolution 5 – Health Care in Danger. Respecting and Protecting Health Care. 31st International Conference of the International Red Cross and Red Crescent Movement, Geneva, Switzerland, 28 November-1 December 2011.

63. A matter of life and death tackling violence against health care in Pakistan, Peru and El Salvador (2017). International Committee of the Red Cross.

64. Mukhtar S. Psychological health during the coronavirus disease 2019 pandemic outbreak. *International Journal of Social Psychiatry,* 2020; 66(5): 512–516. https://doi.org/10.1177/0020764020925835.

65. Mukhtar S. Psychology and politics of COVID-19 misinfodemics: Why and how do people believe in misinfodemics? *International Sociology,* 2021; 36(1): 111-123. https://doi.org/10.1177%2F0268580920948807.

66. Aqsa Sajid. Violence against Healthcare in Pakistan: Social and Humanitarian Implications. Journal of pioneering medical sciences. 2016. Retrieved from http://blogs.jpmsonline.com/2016/01/05/violence-against-healthcare-in-pakistan-social-and-humanitarian-implications/.

67. Fitzwater E, Gates D. Violence and home healthcare. *Home Health Nurse.* 2000; 18: 596-605. https://doi.org/10.1097/00004045-200010000-00012.

68. Hasan MM, Sujan SH, Tasnim R, Siddique AB, et al. Joblessness and Suicidal Ideation Amidst COVID-19 Pandemic: A Cross-Sectional Pilot Survey in Bangladesh. *Am J Med Public Health.* 2021; 2 (4), 1027.

69. Mukhtar S. COVID-19 feminist framework and biopsychosocial-spiritual perspective for social workers and mental health practitioners to manage violence, abuse, and trauma against children, women, BIPOC, and LGBTQIA+ during and post-COVID-19. *International Social Work.* 2022; 66 (1). https://doi.org/10.1177/00208728211067158.

70. Ethical principles of health care in times of armed conflict and other emergencies (2018). International Committee of the Red Cross.

71. Mukhtar S. Preparedness and proactive infection control measures of Pakistan during COVID-19 pandemic outbreak. *Research in Social and Administrative Pharmacy.* 2020; 17 (1): 2052. https://doi.org/10.1016/j.sapharm.2020.04.011.

72. International Committee of the Red Cross, Preventing and Repressing International Crimes: Towards an 'Integrated' Approach Based on Domestic Practice: Report of the Third Universal Meeting of National Committees for the Implementation of International Humanitarian Law, Chapter 5, 2012, https://www.icrc.org/eng/resources/documents/publication/p4138.htm.

73. Mukhtar S, Rana W. COVID-19 and individuals with mental illness in psychiatric facilities. *Psychiatry Research.* 2020; 289: 113075. https://doi.org/10.1016/j.psychres.2020.113075.

74. Rana W, Mukhtar S, Mukhtar S. Mental Health of Medical Workers in Pakistan during the Pandemic COVID-19 Outbreak. *Asian Journal of Psychiatry.* 2020; 51: 102080. https://doi.org/10.1016/j.ajp.2020.102080.

Awake magic: glioblastoma resection under 5-aminolevulinic acid guidance during awake craniotomy. A case report with video demonstration

Aidos Moldabekov[1], Aiman Maidan[1], Nurzhan Ryskeldiyev[1], Nurali Ashirov[2], Serik Akshulakov[1]

[1]Department of Brain Neurosurgery, National Centre for Neurosurgery, Astana, Kazakhstan
[2]Department of Minimal Invasive Neurosurgery, National Centre for Neurosurgery, Astana, Kazakhstan

Corresponding author:
Aiman Maidan.
Email: maidanaiman@gmail.com;
ORCID: 0000-0003-3321-9714.

Abstract

An awake craniotomy's primary goal is to remove the tumor or damaged cells as much as possible without affecting the patient's capacity for clear thought or other crucial functions. This surgical procedure offers a better prognosis by balancing the maximum removal of lesions with the preservation of working zones. For patients with malignant gliomas, the current neurosurgical objective is to resection the large part of a tumor using contrast and not causing neurological deficits. Neurooncological patients are required to have further chemotherapy and radiotherapy, with a control MRI of the brain in 3 and 6 months. Real multidisciplinary work should be provided to improve each patient's quality of life and overall survival. This paper aims to report a single case of successful awake craniotomy with fluorescence guidance and discuss the outcomes of the performed surgery.

Keywords: awake craniotomy, gliolan, 5-aminolevulinic acid

Introduction

An *awake craniotomy* is a surgical procedure in which a patient is deliberately kept awake during the surgical process or a portion of the surgery [1]. The main objective of an awake craniotomy is to remove the tumor and preserve the patient's executive functions to think clearly and perform other essential duties. This surgery provides a better prognosis by balancing the maximal removal of the damaged cell structures while conserving functioning zones [2]. Maximal, safe contrast-enhancing tumor removal is the current neurosurgical priority for patients with malignant gliomas. However, only a small percentage of surgeons manage to remove the contrast-enhancing tumor completely [3]. This restriction is due, in part, to the difficulty of separating a living tumor from the nearby normal brain during surgery at the tumor boundary using traditional white-light microscopy. To get over this drawback, malignant gliomas are now treated with fluorescence-guided surgery (FGS) that makes use of 5-aminolevulinic acid (5-ALA). The use of FGS enables the intraoperative viewing of malignant glioma tissue and provides the neurosurgeon with independent neuronavigation and brain shift real-time guidance for separating the tumor from the normal brain [4]. Corns et al. [5] demonstrated the safety of glial tumor resection with awake craniotomy with 5-aminolevulinic acid guidance; our case report includes a video of the resection[1].

Case Presentation

A right-handed female patient, 55 years old, was admitted to our hospital with complaints of dizziness, lethargy, general weakness, distraction, disorientation in space and time, and memory distortion. According to the patient, she has been ill since June 1, 2022, when the complaints mentioned above abruptly began. On June 6, 2022, she was rushed to a nearby hospital, where doctors decided to perform MRI scans of her brain. An MRI revealed the tumor in the left frontotemporal region. The patient was admitted to our hospital, where a detailed neurological examination was provided. On admission, the consciousness was clear, and the Glasgow Coma Score of 15

1 The process of awake neurosurgery in our hospital is demonstrated here: https://vimeo.com/896060075.

points. She answered questions with slowness but answered some questions out of hand, sometimes corrected herself, and executed instructions. Although she was self-oriented, there was disorientation in space and time. Executive functions, criticism, and the adequacy of her condition were reduced. The Karnofsky Performance Score was 70%. A neurological examination of cranial nerves revealed central paresis of the right facial nerve (House-Brackmann score 3). Pharyngeal and palatine reflexes were reduced, with the soft palate and the tongue deviation to the right. Also, there were fibrillar twitches on the right half of the tongue. The speech therapist revealed dynamic aphasia of mild to moderate severity. Since our hospital started the project on glial tumors, we have provided 3T MRI examinations (Figure 1) for all patients with glial tumors; moreover, if we see that there is contrast enhancement, we do an operation with 5-aminolevulinic acid hydrochloride (GliolanR). Due to Broca area's involvement and risk of further deterioration of hemiparesis, the decision was made to perform an awake tumor removal. Specimens from the tumors are analyzed separately and are kept in our Biobank [6].
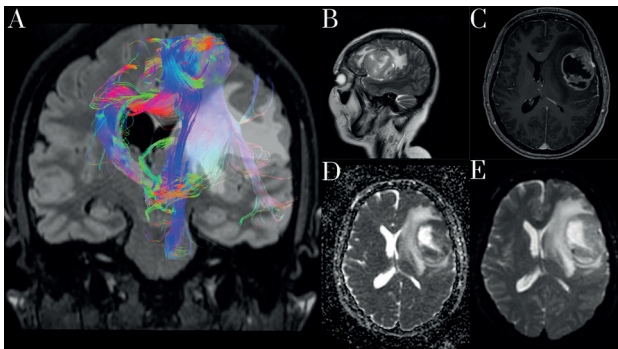
Figure 1 - A: DTI- MRI was performed and revealed displacement of corticospinal tracts on the left with the total destruction of associative and commissural pathways. B: T2WI that demonstrates the tumor in the left frontotemporal region, involving the speech center. C: Post-contrast images demonstrate enhancement, notice there was also a 13 mm dislocation of central structures. D and E: ADC (D) and DWI (E) images demonstrate the presence of areas of pronounced restriction of the diffusion coefficient in the tumor stroma. It presumes necrotic tissue in the tumor, which indicates a high-grade tumor.

Pre-operative preparation and surgery

The decision was made to use a neuronavigation system and mark the operation field on the projected image of the tumor (seen on video). The scalp block technique with 0.5% bupivacaine 40 ml was performed before Mayfield skull clamp placement. Sedation was achieved with 200 mg of dexmedetomidine and 0.2 mg of fentanyl, and we used the "asleep-awake-asleep" approach. Additionally, we used the local anesthetic during durotomy. To measure and view fluorescence working, a microscope called the Pentero 900 (Carl Zeiss Meditec AG, Obrekochen, Germany) with a fluorescent BLUE400 light module was employed. The surgery was performed with 5-ALA fluorescence and the speech and language therapist's control of the Broca center. Additionally, the patient was required to perform movements with the right hand and the right leg.

The tumor was meticulously removed using fluorescence, and all pathologic vessels were coagulated; however, there was a possibility to preserve functionally important vessels, as seen in the video. Because of the close relationship with Broca's area, when, during the operation, there were speech problems, the decision was made to stop the resection. Despite an intense residual fluorescence in Broca's region, resection was stopped because the patient experienced speech arrest during bipolar stimulation at a depth of the resection cavity.

Maximal resection and hemostasis were achieved, and the post-operative field was filled with hemostatic pads (Surgicel). The dura mater was tightly closed, and duraplasty was made. Muscles and skin were tightly sutured. The patient stayed in the intensive care unit for 1 day, and then, after a control post-operative CT, which showed a lesser deviation of the midline structures (Figure 2). the patient was transferred to the pathology department. The patient's speech and calculations improved, and she became more time-conscious.
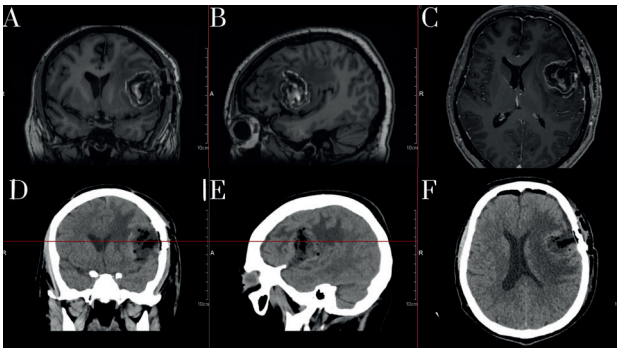
Figure 2 - A, B, C: Postoperative MRI demonstrates the contents of the signal intensity corresponding to the cerebrospinal fluid, with foci of high density on T1WI along the periphery of the bed and along the course of operative access, due to hemorrhagic and hemostatic components. D, E, and F postoperative CT scan demonstrates no apparent complication.

Histological findings

The glial fibrillary acidic protein (GFAP), a Ki-67 proliferation antigen, was detected using immunohistochemistry. IDH1 gene mutation, 1p-19q co-deletion status, ATRX gene mutation, and CDKN2A/2B gene mutation were all negative based on molecular genetic analysis. The presence of necrosis (Figure 3) and the morphological characteristics helped to confirm the diagnosis of glioblastoma, IDH-wildtype, WHO grade 4, and ICD-O code 9440/3.
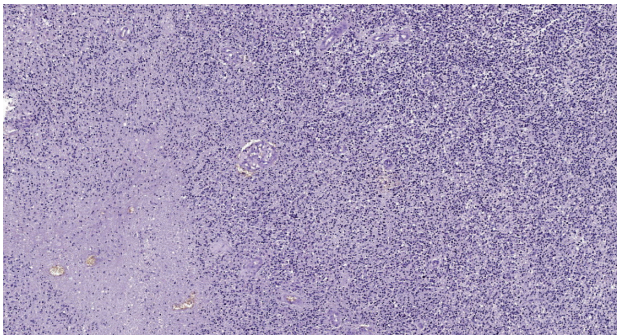

Figure 3 - Glioblastoma multiforme x 100. Stained with hematoxylin and eosin.

Three weeks after the operation, the patient was headed to the oncological treatment. Pre-treatment dosimetry planning was carried out on the TomoPlannig apparatus; the total radiotherapy dosage was counted as 60 Gy 5 times a week with a daily visual inspection. The patient also got the chemotherapy course, which consisted of a Temozolomide 140 mg per os daily. Three months later, after completion of radio and chemotherapy, the patient underwent a control MRI investigation with contrast (Figure 4).

The postoperative patient's Karnofsky Performance Score was 80%, and she started to work again as no neurological deficits were observed. Six months later, after another course of chemotherapy, there was thrombocytopenia; due to this diagnosis, the patient was temporarily withdrawn from the
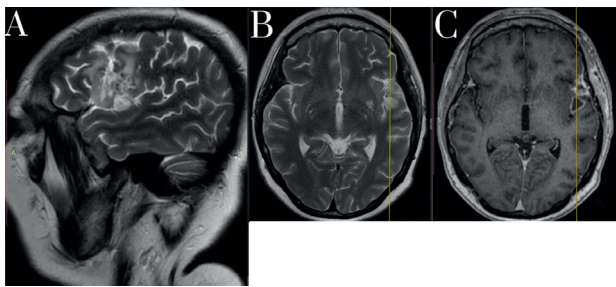
Figure 4 - 3 months follow-up MRI examination with contrast. A: Sagittal T2 Propeller view with an apparent decrease of enhancement. B: Axial T2 Propeller. C: Axial T1 fat-suppressed fast spoiled gradient echo with contrast enhancement on the periphery demonstrates slight residual tissue, not expanded over time.

treatment. After the course of virus-inactivated thrombocyte transfusion, her thrombocyte level eventually increased. The patient developed continued growth of glioblastoma at nine months, muscle strength of right limbs reduced to 3 points, and criticism reduced as well. She underwent one more resection surgery of the tumor of the left frontotemporal region using fluorescence. After her last operation, she has undergone one more chemotherapy cycle. The patient is alive at 1-year follow-up.

Discussion

Currently, the "gold standard" for the excision of tumors or lesions in or close to eloquent brain areas is awake craniotomy with brain imaging [7]. Excision of or damage to regions necessary for speech and motor control skills may result in severe neurological impairments. In 278 patients, Zhang et al. discovered a link between an awake craniotomy and a low rate of postoperative neurological deficits and gross total resection of tumors [2]. In Della Puppa et al.'s study, 31 patients underwent 5-ALA fluoresce surgery; after a 90-day assessment, there was a 3% rate of significant morbidity, and it is crucial to remember that 0% of patients who underwent surgery while awake presented with permanent morbidity [8]. Fluorescence guidance allows for visualization of the tumor extent and can provide information about vascular structures [9]. The unprecedentedly high sensitivity, specificity, and positive predictive value of tissue fluorescence following an oral dose of 5-ALA can provide information about tumor grade even during surgery [1, 10]. Postoperative MRI showed gross total resection was completed in 86% of surgeries operated with 5 ALA [11]. Neurocognitive functions should be evaluated before, during, and after surgery to predict the results and the outlook [12]. Due to preserved neurocognitive functions, 97% of patients who underwent awake surgery for an accidental low-grade glioma returned to work, highlighting the need for comprehensive intraoperative mapping to maintain a better quality of life [13]. Since the first description in the 19th century, different anesthesia methods have been suggested. Dr. Picconi, in his work [14], describes the method of asleep-awake-asleep as the safest one for brain mapping but mentions it requires excellent anesthesiology techniques to perform. According to Goettel et al., dexmedetomidine was as effective as propofol-remifentanil in sedating patients during awake craniotomy for supratentorial tumor removal. Dexmedetomidine was linked to fewer adverse respiratory events as well [15]. 93% of the patients underwent a gross full resection or a near-gross total resection, which is an optimal amount of resection [15].

The challenges of awake surgery with 5-ALA guidance could arise in the absence of fluorescence. In patients with cortical mapping and 5-ALA guidance, fluorescence was present in 50% of cases [11]. Only 12% of awake craniotomy patients demonstrated neurological complications that were either new or deteriorated from their previous deficiencies; however, 8% recovered within two months after the operation [15]. Transient aphasia developed in 14 patients, and permanent aphasia developed in 4 patients [11].

The right patient selection and patient counseling are crucial. Brain mapping requires a cooperative patient who can follow instructions during surgery; as a result, choosing the wrong patient might lead to an unsuccessful awake craniotomy [12]. Different authors proposed different approaches for awake neurosurgery [3]. However, our hospital prefers a combination of 5-aminolevulinic acid with awake neurosurgery. In the recent research of Gandhi et al., a comparative subgroup analysis of 5-ALA-guided versus traditional surgery revealed a 26% higher gross total resection rate in the 5-ALA subgroup [16]. A specialized biobank is essential in prospective oncological analysis. Our country's biobank [6] has been functional since 2018, and nowadays, we have more than 269 patients. Future research will be published in the future with details.

It will be possible to conduct a more in-depth study into the risk factors for various cancer subtypes, as well as provide appropriate prognostic indicators for survival and pharmacogenomics research with the use of biobank databases [17]. The research using data from the UK Biobank has discovered new susceptibility loci for certain malignancies, such as endometrial cancer, colon cancer, and cervical cancer - these studies are found to help comprehend the biochemical processes that underlie the growth of cancer [17].

Biobanks have been widely used for cancer prevention, diagnosis, and treatment and have been integrated into personalized medicine. Biobanks will unquestionably revolutionize research, enhance genetic research, and lead to the identification of new therapeutic targets [18]. IDH1 gene mutation, 1p-19q co-deletion status, ATRX gene mutation, and CDKN2A/2B gene mutation can be aimed in the future interdisciplinary oncology treatment of glioblastoma patients, which hopefully will increase their median survival.

It is currently proven that glioblastoma patients, in comparison to chemotherapy, surgical resection, or radiation alone, benefit from combination therapy, such as surgery or radiotherapy with chemotherapy, which may increase the likelihood of survival [19].

The paper reports on the excision of tumors by successful awake craniotomy with 5-ALA guidance and discusses the advantages and main challenges of this method. The paper considers only one case and builds assumptions around it. The awake craniotomy surgery is not performed frequently in our center; therefore, other literature reviews and case reports should be carefully considered.

Conclusion

Awake craniotomy with 5-ALA staining guidance maximizes the chances of gross total resection of infiltrative gliomas with visible fluorescence, allowing excision that would otherwise be missed without contrast, and aids in preserving executive and motor functions of the patients. Due to its high sensitivity and specificity, awake neurosurgery is considered potentially safe when combined with 5-aminolevulinic acid, and it provides maximal resection with vascular preservation. A multidisciplinary approach is essential in high-grade glial tumors. Specialized Biobank of CNS tumors will improve the quality of life and extend the life of neurosurgical patients.

References

1. Hadjipanayis CG, Widhalm G, Stummer W. What is the Surgical Benefit of Utilizing 5-Aminolevulinic Acid for Fluorescence-Guided Surgery of Malignant Gliomas? *Neurosurgery*. 2015; 77(5): 663-73. https://doi.org/10.1227/NEU.0000000000000929. PMID: 26308630; PMCID: PMC4615466.

2. Zhang JJY, Lee KS, Voisin MR, Hervey-Jumper SL, Berger MS, Zadeh G. Awake craniotomy for resection of supratentorial glioblastoma: a systematic review and meta-analysis. *Neuro-oncology advances*. 2020; 2(1): vdaa111. https://doi.org/10.1093/noajnl/vdaa111. PMID: 33063012; PMCID: PMC7542985

3. Sun R, Cuthbert H, Watts C. Fluorescence-Guided Surgery in the Surgical Treatment of Gliomas: Past, Present and Future. *Cancers (Basel)*. 2021; 13(14): 3508. https://doi.org/10.3390/cancers13143508. PMID: 34298721; PMCID: PMC8304525.

4. Kim RB, Cohen-Gadol AA. *Language Mapping for Glioma*. 2016 Jan 1 [cited 2023 Jul 13]; Available from: https://www.growkudos.com/publications/10.18791%252Fnsatlas.v4.ch02.7/reader.

5. Corns R, Mukherjee S, Johansen A, Sivakumar G. 5-aminolevulinic acid guidance during awake craniotomy to maximise extent of safe resection of glioblastoma multiforme. *BMJ Case Rep*. 2015; 2015: bcr2014208575. https://doi.org/10.1136/bcr-2014-208575.

6. Kasymova AB; Zhetpisbayev BB; Solodovnikov MP; Rakymzhan AK; Ryskeldiyev NA. Organizatsiya biobanka v neyrokhirurgii (Organization of biobank in neurosurgery) [In Russian]. *Nejrohirurgiâ i nevrologiâ Kazahstana (Neurosurgery and neurology of Kazakhstan)*. 2021; 64: 3-10. https://doi.org/10.53498/24094498_2021_3_3.

7. Kulikov A, Lubnin A. Anesthesia for awake craniotomy. *Curr Opin Anaesthesiol*. 2018; 31(5): 506-510. https://doi.org/10.1097/ACO.0000000000000625.

8. Della Puppa A, De Pellegrin S, d'Avella E et al. 5-aminolevulinic acid (5-ALA) fluorescence guided surgery of high-grade gliomas in eloquent areas assisted by functional mapping. Our experience and review of the literature. *Acta Neurochir*. 2013; 155(6): 965-972. https://doi.org/10.1007/s00701-013-1660-x.

9. Müther M et al. "5-Aminolevulinic Acid Fluorescence-Guided Resection of 18F-FET-PET Positive Tumor Beyond Gadolinium Enhancing Tumor Improves Survival in Glioblastoma." *Neurosurgery*. 2019; 85 (6): E1020-E1029. https://doi.org/10.1093/neuros/nyz199.

10. Save AV, Gill BJ, D'amico RS, Canoll P, Bruce JN. Fluorescein-guided resection of gliomas. *Journal of neurosurgical sciences*. 2019; 63(6): 648-655. https://doi.org/10.23736/S0390-5616.19.04738-6. PMID: 31961117.

11. Goryaynov SA, Buklina SB, Khapov IV et al. 5-ALA-guided tumor resection during awake speech mapping in gliomas located in eloquent speech areas: Single-center experience. *Front Oncol*. 2022; 12: 940951. Published 2022 Sep 23. https://doi.org/10.3389/fonc.2022.940951.

12. Zhang K, Gelb AW. Awake craniotomy: indications, benefits, and techniques. *Colombian Journal of Anesthesiology*. 2018; 46(2S): 46-51. https://doi.org/10.1097/CJ9.0000000000000045.

13. Duffau H. Updated perspectives on awake neurosurgery with cognitive and emotional assessment for patients with low-grade gliomas. *Expert Review of Neurotherapeutics*. 2021. Apr 3; 21(4): 463-73.

14. Piccioni F, Fanzio M. Management of anesthesia in awake craniotomy. *Minerva Anestesiologica*. 2008; 74(7-8): 393-408. PMID: 18612268.

15. Goettel N, Bharadwaj S, Venkatraghavan L, Mehta J, Bernstein M, Manninen PH. Dexmedetomidine vs propofol-remifentanil conscious sedation for awake craniotomy: a prospective randomized controlled trial. *British journal of anesthesia*. 2016; 116(6): 811-21. https://doi.org/10.1093/bja/aew024. Epub 2016 Apr 20. PMID: 27099154.

16. Groshev A, Padalia D, Patel S, et al. Clinical outcomes from maximum-safe resection of primary and metastatic brain tumors using awake craniotomy. *Clin Neurol Neurosurg*. 2017; 157: 25-30. https://doi.org/10.1016/j.clineuro.2017.03.017.

17. Gandhi S, Tayebi MA, Belykh E, Cavallo C, Zhao X, Syed MP et al. Survival Outcomes Among Patients with High-Grade Glioma Treated With 5-Aminolevulinic Acid-Guided Surgery: A Systematic Review and Meta-Analysis. *Frontiers in oncology*. 2019; 9: 620. https://doi.org/10.3389/fonc.2019.00620. PMID: 31380272; PMCID: PMC6652805.

18. Conroy MC, Lacey B, Bešević J, Omiyale W, Feng Q, Effingham M, Sellers J, Sheard S, Pancholi M, Gregory G, Busby J. UK Biobank: a globally important resource for cancer research. *British Journal of Cancer*. 2023; 16; 128(4): 519-27. https://doi.org/10.1038/s41416-022-02053-5.

19. Patil S, Majumdar B, Awan KH, Sarode GS, Sarode SC, Gadbail AR, Gondivkar S. Cancer oriented biobanks: A comprehensive review. *Oncol Rev*. 2018; 12(1): 357. https://doi.org/10.4081/oncol.2018.357. PMID: 30057691; PMCID: PMC6047884.

20. Wen J, Chen Wanbin, Zhu Y, Zhang P. Clinical features associated with the efficacy of chemotherapy in patients with glioblastoma (GBM): a surveillance, epidemiology, and end results (SEER) analysis. 2021 Jan 19 [cited 2023 Jul 13]; 21(1). Available from: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-021-07800-0.

Sudden infant death syndrome as a result of thymic-lymphatic dysgenesis

Saule Amangeldievna Mussabekova[1], Elena Igorevna Burkova[1], Kristina Ergardovna Dobler[2], Balzhan Smailovna Muldasheva[2], Zhan Zhumagulovich Atmtaev[2]

[1] Department of Morphology, Medical University of Karaganda, Karaganda, Kazakhstan
[2] Institute of Forensic Examinations in Karaganda, Center for Forensic Examination of the Ministry of Justice of the Republic of Kazakhstan, Karaganda, Kazakhstan

Corresponding author:
Elena Igorevna Burkova
e-mail: Alenushka_fiery@mail.ru
ORCID: 0000-0002-0062-4337

Abstract

Sudden infant death syndrome is one of the leading causes of post-neonatal mortality. The thymic-lymphatic condition in children is a clinically rare manifestation and difficult to diagnose condition, assessed as a background, realized in a number of cases of sudden death syndrome. However, the clinical and histopathological manifestations of thymic-lymphatic status may not be clearly expressed. We present an unusual case of sudden infant death syndrome as a result of thymic-lymphatic dysgenesis complicated by acute adrenal insufficiency.

Keywords: forensic medical examination, thymic-lymphatic dysgenesis, thymus hyperplasia, thymic-lymphatic status, sudden infant death syndrome.

Introduction

In a number of countries, sudden infant death syndrome (SIDS) occupies a leading position in the structure of child mortality. The prevalence of SIDS in the world is 0.2-1.5 cases per 1000 children. Sudden death in children (without sudden cardiac death syndrome) accounts for 5-10% of all child deaths, which is about 1.3-4.0 per 100,000 population [1]. Thus, the average mortality rate from SIDS per 1000 births is: in Japan - 0.25, the Netherlands - 0.3, Russia - 0.4, Great Britain - 2.3, Germany - 1.6, Austria - 1.0, Italy - 0.5, the USA - 2.8, in Russia - 0.43 per 1000 children [2]. In Kazakhstan, the infant mortality rate in 2021 was 8.41, but the data on deaths of children from SIDS were not allocated to a separate category [3].Thymic-lymphatic status (Latin: Status Thymico-Lymphancus) is a condition of the body characterized by pathological hyperplasia of the thymus gland or in combination with generalized hyperplasia of the entire lymphoid tissue, including lymph nodes, palatine tonsils, spleen, as well as atrophic changes in the adrenal glands, causing sudden death from influences whose strength is inadequate to a fatal outcome [4]. Thymic-lymphatic status was the background of the underlying disease, contributing to the development of sudden death syndrome [5,6]. Timely verification of this condition is an urgent issue of medical practice, and therefore the presented case of sudden death of a child as a result of thymico-lymphatic dysgenesis is of particular interest to the medical community.

Case presentation

The sudden death of a two-year-old child was recorded in a private kindergarten. Upon examination of the incident, no signs of violent death were found. During the examination of the child's corpse by a forensic medical expert, only small-point hemorrhages of dark red color were found on the mucous membrane of the upper eyelid of the right eye, bodily injuries (bruises, abrasions, wounds) were not found.

An external examination of the corpse during the forensic medical examination confirmed the complete absence of traces of any injections, rashes, swellings, scabs, ulceration, congenital or acquired anatomical defects or individual characteristics on the child's body. All bones of the child's skeleton are intact, without pathological mobility and deformation.

An internal forensic examination of the corpse confirmed the absence of damage to the bones of the cranial vault and congenital pathologies: all brain structures are pathology-free and age-appropriate. Autopsy of internal organs revealed thymomegaly (dimensions 11.8 x 6.9 x 5.6 cm, weight 41 grams) and splenomegaly (dimensions 12.0 x 7.2x3.8 cm, weight 54.5grams), other organs without features, macroscopically no pathology was found.

Materials from the brain, heart, liver, kidneys, lungs, spleen, adrenal glands, thymus and pancreas were seized for laboratory studies. The fixation of the material was carried out in a 100% formalin solution, alcohol wiring

was used, followed by the manufacture of paraffin blocks with staining of the obtained micropreparations with hematoxylin-eosin and the conclusion of micropreparations in a Bio Mount HM medium. Microscopic studies were performed using a Leica DM500 microscope with a magnification of 100x.

Microscopy of the thymus shows large lobules, the stroma between the lobules is wide and loose, there is no separation of layers, the ratio of layers is 3:1 with a sharp predominance of the cortical layer over the cerebral one, the Hassall's bodies are small, small, with pronounced dystrophic changes, arranged randomly with varying degrees of calcification (Figure 1). These signs made it possible to diagnose hyperplasia of the cortical layer of the thymus with pronounced dystrophic changes in the Hassall's bodies.
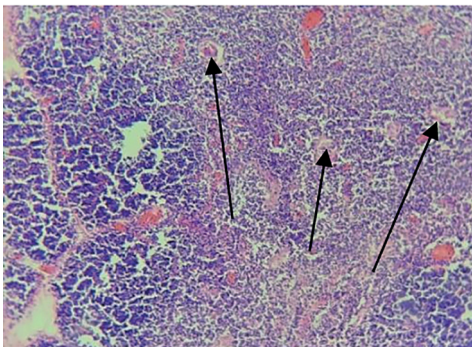
Figure 1 - Thymus: pronounced dystrophic changes in Hassall's bodies

A forensic histological examination of the adrenal glands revealed: the boundary between the cortical and cerebral substance is weakly expressed, the cerebral layer is sharply reduced, additional lobules are noted in the cortical layer (Figure 2), almost all cells are filled with vacuoles, the vessels are thin, full-blooded. The obtained microscopic data allowed us to verify: nodular hyperplasia of the adrenal cortex (the presence of additional adrenal lobules) and hypoplasia of the adrenal medulla (Figure 3), as well as large-focal adrenal delipidization and plethora of adrenal vessels.
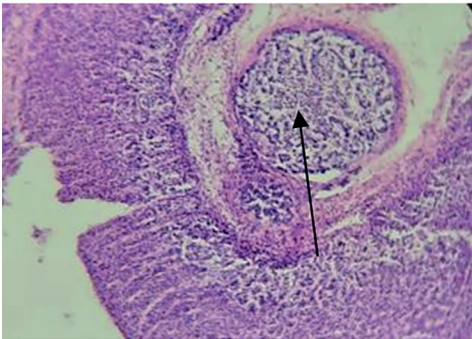
Figure 2 - Adrenal gland: accessory lobule
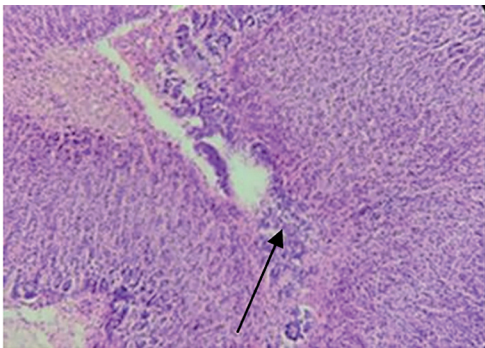
Figure 3 - Adrenal gland: adrenal medulla hypoplasia

The analysis of the microscopic picture of the spleen revealed a sharp hyperplasia of the red pulp, a mass of small and large lymphoid follicles without formed enzymatic centers with a large number of lymphoid cells and thin vessels, weak blood filling, which indicates hyperplasia of the red pulp of the spleen and its weak blood filling, reduction of lymphoid follicles of the spleen.

Microscopy of the brain revealed a significant expansion of the perivascular and pericellular spaces due to edema. The neurocytes are swollen, with clear and pale nuclei. The soft meninges are loose, with pronounced edema. The vessels are thin, full-blooded. The revealed morphological changes are signs of pronounced edema and fullness of the brain and soft meninges, as well as focal vasculitis in the soft meninges.

In the heart: cardiomyocytes of normal size, granular, with clear nuclei, there are areas of cardiomyocyte discomplexation, edematous stroma, thin intramural vessels, weak blood filling and sometimes spasmodic. The revealed structural changes indicate granular dystrophy and focal discomplexation of cardiomyocytes with stroma edema, as well as anemia and focal spasm of intramural vessels.

In the lungs: the pleura is loose, full-blooded, the interalveolar septa are thin and full-blooded, in places with diffuse lymphoid infiltration, the septa in some areas are torn apart, forming small voids. The lumen of the alveoli in many areas is filled with edematous fluid. The bronchi are scalloped in shape, the epithelium is desquamated into the lumen. The vessels are thin, full-blooded, and lymphoid infiltration is noted around some vessels. The detected pathomorphological changes indicate focal interstitial pneumonia, acute focal emphysema and focal protein edema of the lungs, focal bronchospasm and pulmonary vascular fullness.

In the liver: the capsule is thin, the beam-radial structure of the lobules is preserved. Hepatocytes with granular cytoplasm, nuclei are clearly visible in all cells. The inter-girder spaces are moderately expanded, due to edema. The portal tracts are thin. The vessels are thin, full-blooded. All this confirms the presence of granular liver dystrophy with fullness of its vessels.

In the kidneys: the capsule is loose and full-blooded, the glomeruli are rounded, full-blooded. The epithelium of the tubules is high and cloudy, with vacuolated cytoplasm, the nuclei are clearly visible. The stroma is loose, the vessels are thin and full-blooded. Vacuole dystrophy of the kidneys and fullness of the renal vessels have been identified. Morphological changes in the studied organs are characteristic of "acute death".

Based on the external and internal examination of the child's corpse and the morphological data obtained, a forensic medical diagnosis was made:

1. Thymic-lymphatic dysgenesis R94.7 (macroscopically: thymomegaly, splenomegaly, adrenal hypoplasia. microscopically: nodular hyperplasia of the adrenal cortex (the presence of additional adrenal lobules), hypoplasia of the adrenal medulla, large-focal delipidization of the adrenal glands; hyperplasia of the cortical layer of the thymus, pronounced dystrophic changes in the Hassall bodies; hyperplasia of the red pulp of the spleen).

2. Acute adrenal insufficiency.

3. Acute focal interstitial pneumonia.

During the examination of the child's corpse, morphological signs of acute focal interstitial pneumonia were found, which are causally related to the onset of death.

Discussion

All cases of sudden death of children without signs of violent death are usually a matter of concern for forensic medical experts [7-9]. According to R. W. Byard, all autopsies of SVSD should undergo a structured examination aimed at identifying the main causes of sudden death [10]. The mechanisms leading to sudden and unexpected death seem complex and multifactorial and require the coordination of several overlapping factors in order for death to occur [11, 12]. In this case, a thorough full autopsy was performed in accordance with the Rules of organization and production of forensic medical examination in the Republic of Kazakhstan, due to the lack of other macroscopic, histological and toxicological data, the authors assumed that the cause of death of the child was thymic-lymphatic dysgenesis complicated by acute adrenal insufficiency. Autopsy showed that the thymus was enlarged, of a soft elastic consistency, pinkish-gray in color with a slightly pronounced lobulation, weighing 41.0 grams and measuring 11.8 x 6.9 x 5.6 cm. Usually, the mass of the thymus at birth is 12-15 grams, during puberty - 30-40 grams, at the age of 60 – 10-15 grams [13]. Histologically, no changes, signs of thymoma or other diseases of the thymus were found in the thymus. Consequently, an increase in the mass and size of the histologically preserved thymus determines the true hyperplasia of the thymus [4, 8, 14].

Such data prompted the authors to discuss the theory of the so-called "thymic death", expressed at the end of the XIX century by a number of authors who testified that hyperplastic thymus can lead to tracheal obstruction and sudden death of infants and described "thymus death" as a systemic disease accompanied by an increase in all lymphoid tissues, which can lead to sudden death from heart disease-vascular collapse [15]. The theory of "thymicus-lymphaticus status", confirmed by more than 800 publications, has dominated for 30 years in cases of sudden infant death [12]. Later, a theory was developed (1942, Pende) of "constitutional hyperthymic syndrome" or "Pende syndrome", a condition characterized by an increase in the volume and activity of the thymus from birth, macrosomia and poor development of the genitals during puberty [16]. However, some scientists have insisted that since the thymus is affected within a few days after the disease, it reaches large sizes only if the patient dies suddenly [1, 17].

In 1931, The Lancet magazine published an editorial entitled "The End of the status of Lymphaticus", supporting Greenwood's theory, as a result of which the status of "thymic-lymphatic" was included in the list of "historical medical errors" in 2000 [15]. According to the opinion of N. Rackham, the corpses studied earlier to determine the "normal" size of the thymus belonged to poor people who usually died from severe chronic diseases (e.g. tuberculosis, infectious diseases) or malnutrition that cause stress-related thymus involution: therefore, they simply underestimated the size and weight of the "normal" thymus gland. Consequently, in infants and young people who died suddenly, it was mistakenly believed that they had an enlarged thymus gland [18]. However, later the theory of "thymic death" was revived due to a number of studies: a link was found between mortality associated with cardiovascular diseases and higher thymus weight [19, 20] and patients with atrioventricular node tumors, Langerhans islet hyperplasia, multicystic ovaries, adrenal heterotopia, right kidney clear cell adenomatosis and hyperplasia were described thymus, which indicates a unique genetic defect [21]. In 2017, Zou et al. autopsies of adult corpses from 1984 to 2014 were analyzed and found that thymus hyperplasia significantly increases the risk of sudden unexpected death in young people, both men and women, mainly from cardiovascular diseases [22].

Researchers have proved that the thymus is a link between the immune and endocrine systems, however, its full physiological role is still not fully understood [23]. An analysis of the literature has shown that massive thymus hyperplasia, a rare variant of true thymus hyperplasia, is extremely rare during the first two decades of life and can clinically cause compression of the mediastinum or acute and recurrent pulmonary infection [24]. Thymus hyperplasia in adults has been widely studied for a fairly long period, namely, the diagnosis of thymus hyperplasia is based on microscopic signs [19].

According to previous studies, in the period from 1975 to 2020, only 10 cases of this pathology were registered in children aged < 1 year of life, while the prevalence of males among them (70%) was noted, nine out of ten children had initial symptoms or signs associated with the respiratory system, and Respiratory distress was observed in six patients, and surgical thymectomy was successfully performed in all patients without any postoperative complications [9, 24]. However, when detecting thymus hyperplasia, it is necessary to remember about the possibility of a secondary process against the background of various diseases, as well as neoplasms [10, 14]. According to some studies, persons with thymic-lymphatic dysgenesis are characterized by biological instability, as a result of which sudden death may occur from the effects of some, even minor, factors [25]. The presented case allowed the authors to prepare the basis for increased attention to the thymus in subsequent cases of sudden death. Whether there is a link between sudden death and thymus hypertrophy, and if so, how, is a matter for further investigation.

References

1. Vincent A, Chu NT, Shah A, Avanthika C, Jhaveri S, Singh K, Limaye OM, Boddu H. Sudden Infant Death Syndrome: Risk Factors and Newer Risk Reduction Strategies. *Cureus*. 2023; 15(6): e40572. https://doi.org/10.7759/cureus.40572.
2. Gras-Le Guen C, Franco P, Plancoulaine S. Editorial: Sudden infant death syndrome: Moving forward. *Front. Pediatr*. 2022; 10: 972430. https://doi.org/10.3389/fped.2022.972430.
3. Mussabekova S, Stoyan A. The case of determining the species, gender, age and race of the skull with congenital multiple developmental anomalies. *J CLIN MED KAZ*. 2022; 19(1): 80-4. https://doi.org/10.23950/jcmk/11682.
4. Khan MA, Anjum F. Thymic Hyperplasia. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing*. 2023.
5. Grassi S, Pinchi V, Campuzano O, Oliva A, Brugada R. Editorial: Genetics of sudden unexplained death in children and young adults: state of the art, testing and implications for translational research, public health and forensic pathology. *Front. Med*. 2023; 10: 1309179. https://doi.org/10.3389/fmed.2023.1309179.
6. Karataeva LA. Sindrom vnezapnoj smerti i ego sovremennye aspekty [in Russian]. *Medicus*. 2020; 3(33): 68-70.
7. Zakharov MV, Fedulova MV, Pigolkin YuI. Sudden death in school-aged children at physical exercise: forensic diagnosis. *Sudebno-Meditsinskaya Ekspertisa*. 2021; 64(4): 64–67. https://doi.org/10.17116/sudmed20216404164.
8. Claes L, Dendooven A, van Heerden J. Challenges in diagnosing ectopic thymus tissue in children. *BMJ Case Rep*. 2019;12(9):e228807. https://doi.org/10.1136/bcr-2018-228807.
9. Varga I, Bódi I, Mešťanová V, Kováč M, Klein M. Association between histological alterations in the thymus and sudden infant death syndrome. *J Forensic Leg Med*. 2018; 55: 8-13. https://doi.org/10.1016/j.jflm.2018.02.007.
10. Byard RW. Thymic changes and sudden infant death syndrome (SIDS). *J Forensic Leg Med*. 2019; 61: 141. https://doi.org/10.1016/j.jflm.2018.09.004.
11. Avanesjan HA, Berlaj MV, Kopylov AV, Korobkeev AA, Karpov SM. Sudebno-medicinskaja diagnostika morfologicheskih izmenenij pri sindrome vnezapnoj detskoj smerti [in Russian]. *Medicinskij vestnik Severnogo Kavkaza*. 2018; 13(4): 667-671.
12. Qu D, Preuss V, Hagemeie L. Radomsky L, Beushausen K, Keil J, et al. Age-related cytokine imbalance in the thymus in sudden infant death syndrome (SIDS). *Pediatr Res*. 2023. https://doi.org/10.1038/s41390-023-02809-6.
13. Tolstova EM, Zajceva OV. Fiziologija i patologija timusa v detskom vozraste [in Russian]. *Pediatrija. Zhurnal im. G. N. Speranskogo*. 2018; 97 (6): 166-172.
14. Guleria P, Jain D. Thymic lesions of the paediatric age group: a comprehensive review of non-neoplastic and neoplastic etiologies. *Mediastinum*. 2019; 3: 24. https://doi.org/10.21037/med.2019.05.04.
15. Borisenko NS, Popugajlo MV. Timiko-limfaticheskij status kak istoricheskij fenomen v medicine [in Russian]. *Vestnik UGMU*. 2023; 2: 62-72.
16. Weis CA, Märkl B, Schuster T, Vollert K, Ströbel P, Marx A. True thymic hyperplasia: Differential diagnosis of thymic mass lesions in neonates and children. *Pathologe*. 2017; 38(4): 286-293. https://doi.org/10.1007/s00292-017-0283-z.
17. Mlika M, Yaiche R, Fourti A, Braham E, Houcin Y, Marghli A, Mezni F. Thymic hyperplasia: A study of 46 cases. *Ann Pathol*. 2021; 41(6): 544-548. https://doi.org/10.1016/j.annpat.2021.01.003.
18. Benevento M, Nicolì S, Ferorelli D. Sudden cardiac death and thymic hyperplasia in adults: myth or reality? A case report. *Egypt J Forensic Sci*. 2023; 13: 37. https://doi.org/10.1186/s41935-023-00357-y.
19. Tsuda T, Fitzgerald KK, Temple J. Sudden cardiac death in children and young adults without structural heart disease: a comprehensive review. *Rev. Cardiovasc. Med*. 2020; 21(2): 205-216. https://doi.org/10.31083/j.rcm.2020.02.55.
20. Serfilippi LM, Quance JL. Pathology in Practice. J Am Vet Med Assoc. 2018; 253(2): 173-176. https://doi.org/10.2460/javma.253.2.173.
21. Chen C, Zhang C, Deng Y, Du S, Wang H, Li D. Thymic hypoplasia induced by copy number variations contributed to explaining sudden infant death based on forensic autopsies. *Forensic Sci Int*. 2022; 336: 111323. https://doi.org/10.1016/j.forsciint.2022.111323.
22. Zou L, Zhang Y, Zhu R. Thymic Hypertrophy and Sudden Unexpected Death in Adults – A Retrospective Study Of 56 Autopsy Cases. *International Journal of Human Anatomy*. 2017; 1(1): 9-20. https://doi.org/10.14302/issn.2577-2279.ijha-17-1538.
23. Bhalla P, Su DM, van Oers NSC. Thymus Functionality Needs More Than a Few TECs. *Front Immunol*. 2022; 13: 864777. https://doi.org/10.3389/fimmu.2022.864777.
24. Yang M, Zeng L, Ji Y, Xiang B, Xu ZC. Massive true thymic hyperplasia in a 3-month-old infant: case report and literature review. *Turk J Pediatr*. 2021; 63(4): 721-726. https://doi.org/10.24953/turkjped.2021.04.022.
25. Jiao J, Yu J, Chen C, Chen T, Zheng T, He L, Zeng Q. Thoracoscopic approach for massive thymic hyperplasia in an infant: Case report and literature review. *Front Pediatr*. 2023; 11: 1144384. https://doi.org/10.3389/fped.2023.1144384.

CONTENTS