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## AIMS AND SCOPE OF THE JOURNAL

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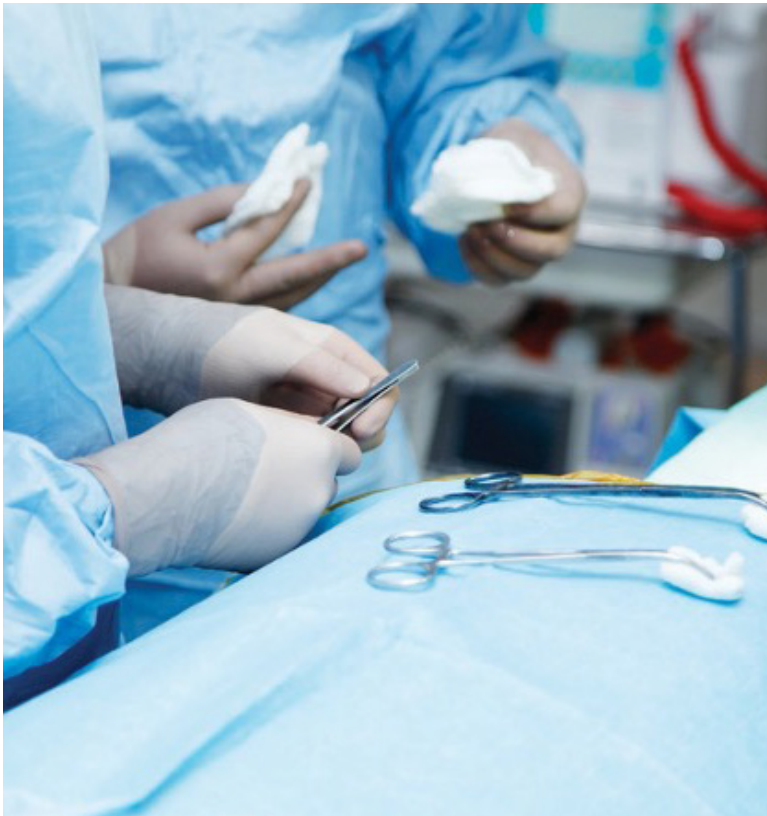
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## JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

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## SURGERY AND TRANSPLANTATION

The key activities of these departments of NSMC are reconstructive surgery, transplantation, innovative minimally invasive approaches, microsurgical correction, cell-based therapy of various surgical diseases.

New types of minimally invasive surgical technologies, video-endoscopic and microsurgical techniques, mini-thoracoscopic operations, chemoembolization of tumors were implemented that fundamentally change the approaches to the treatment of many surgical diseases and reduce the time of hospitalization of the patients.

# Study of Hygienic Hand Disinfection of Staff and Dental Students at the Medical University – Plovdiv

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## Abstract

**Introduction:** Transient microbial flora on the hands of medical personnel is a prerequisite for healthcare-associated infections. Unlike permanent this micro flora can be removed by washing and disinfection. The hands of the dental staff are factor number one in the transfer of microorganisms: from patient to patient as well as on objects from the dental environment.

The **aim** of the present study was to microbiologically examine hand washes of 5th year dental students and medical staff before starting work with a patient in order to evaluate the quality of hygienic disinfection performed.

**Methodology:** The hands of a total of 115 doctors and students from the Faculty of Dental Medicine of the Medical University of Plovdiv were wiped with a sterile swab after treatment with a disinfectant. Isolates were identified to species using Vitek MS and MALDI-TOF technology.

**Results:** Coagulase-negative staphylococci with a microbial number of  $10^3$ – $10^4$  were found to have the highest microbial count (70%). 9% of the samples with coagulase-negative staphylococci had microbial count  $\geq 10^5$ . The most common isolates detected were: *Staphylococcus hominis*, *Staphylococcus epidermidis* and *Micrococcus luteus*.

**Conclusion:** The presence of coagulase-negative staphylococci in a high microbial count, enterococci and representatives of *Bacillus simplex* is undesirable, especially in immunosuppressed patients. These results highlight the need to increase knowledge about hand disinfection and its actual application before working with a patient.

**Keywords:** hand disinfection, dental staff, students, microbial flora

## Exposure

Dental practice, as a branch of medical science, follows and implements the same rules and norms as medical practice. The hands of dental personnel are a means of transferring microorganisms from one object to another in the dental environment, between patients and from patients to personnel and vice versa [1, 2]. Microorganisms that fall on healthy and clean skin

gradually decrease and die in a few hours. With skin contamination this ability weakens [2, 3].

Back in 1938 bacteria isolated from the hands are divided into permanent (resident) and transient flora [4, 5]. Characteristic of the resident flora is that it is impossible to be removed after washing or disinfection, but only partially reduced [6]. Transient flora is most commonly associated with Healthcare-associated infections (HAIs).

Unlike permanent, this flora is superficial and can be removed by washing and disinfection [4]. This leads to the need for complete and effective decontamination and disinfection of hands to prevent the transmission of microorganisms, respectively infections. Contamination of the hands of the dental staff with microorganisms in the process of daily work occurs during direct contact with blood, oral secretions and other fluids from the patient, during indirect contact with the patient or with contaminated objects from the surrounding dental clinical environment [3–5]. Most microorganisms can survive for a long time in the absence of effective control measures [1]. Such a measure is properly performed hand disinfection, as ordinary soaps have minimal antibacterial activity and hygienic hand washing alone is not sufficient to remove transient flora.

Good dental practice requires that alcohol-based skin antiseptics be used firstly. They are active within 30 seconds



**Figure 1** – Steps in hand disinfection according to EN 1500

for liquid forms and one minute for gels. It is important they to be applied on dry hands following the six steps of disinfection (Fig. 1) [7].

This highlights the need for accurate training and precise application of the rules of hygienic hand disinfection by dental students as they have clinical work with patients starting from the third-year, second-semester till the end of their education and must be already trained and work according to the rules of disinfection.

A detailed introduction to the stages and means of surgical disinfection and hand hygiene are part of the training of dental students in Epidemiology of Infectious Diseases in the fourth year of education. It is necessary for both students and practicing dentists in their curricula, respectively in their postgraduate training, additional hours and courses on these issues to be included.

**Objective:** the hands of 5th-year dental students and dental staff to be microbiologically examined before starting work with a patient in order to evaluate the quality of the hygienic disinfection performed, the important problems from an epidemiological point of view to be outlined and recommendations to be prepared.

## Material and methods

In the period March–April 2019 with a sterile swab with Amies transport medium, the hands of a total of 115 dentists

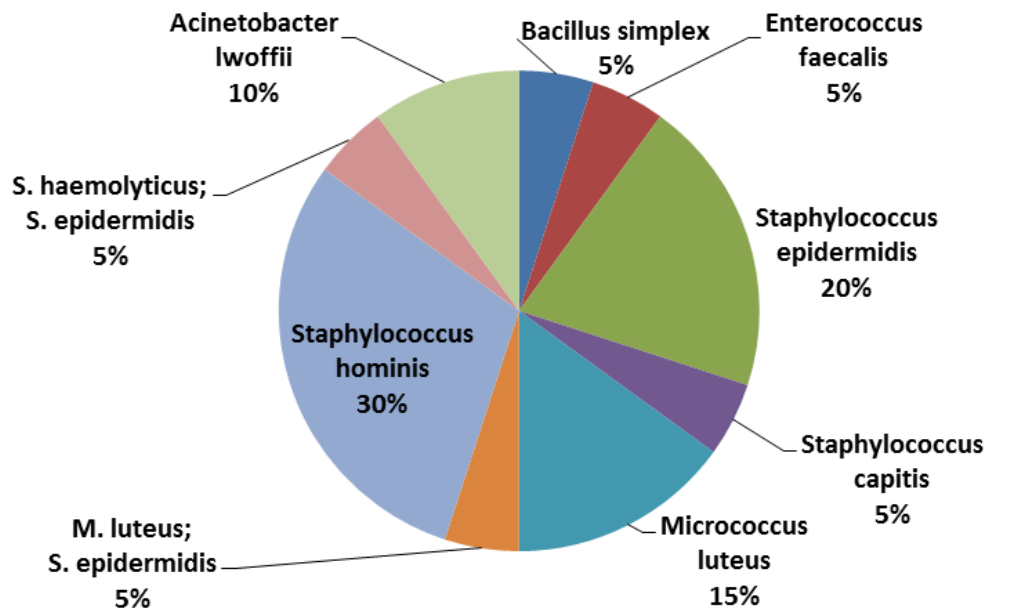


**Figure 2** – In red – areas that tend to be worst washed; in blue – areas that get moderately washed; in green – areas that usually get well washed according to data from the World Health Organization (WHO) during routine hand washing (1)

(dental staff and dental students) from the Faculty of Dentistry at MU-Plovdiv were examined before starting work with patients in the clinical halls. The purpose and the importance of the study were explained in details in the presence of the clinical practice assistants and the dental nurse in charge of the respective clinical room. A swab was taken from both their hands with a sterile tampon. The method of swabbing the hands with a sterile transport medium swab has the following advantages: the ability to swab a larger area, the skin folds of the palms and between the fingers. They are indicated as risky, "red zones", often missed during daily hygienic hand disinfection (Fig. 2) [1]. Before sampling everyone was asked to wash and disinfect their hands as usual. Samples were taken immediately after that (15–30 seconds) and transported to the Laboratory of microbiology, UMHAT, Plovdiv. They were inoculated on blood and Levine agar, and the results were reported on the 24th and 48th hours after cultivation at 37°C in a thermostat. Isolates were identified to species using a Vitek MS system (BioMérieux, France) and MALDI-TOF technology. The data were processed with statistical programs Excel, Microsoft 2020 and SPSS19.9, IBM.

## Results

Twenty (20) of the samples remained sterile. A total of 8 species of microorganisms were isolated from the remaining 95 (82.6%) samples (Fig. 3, see the next page). Coagulase-negative staphylococci with a microbial count of  $10^3$ – $10^4$  were found to have the largest relative share (70%). In 9% of the samples, the presence of coagulase-negative staphylococci with a microbial count  $\geq 10^5$  was demonstrated. The most common bacteria identified by Vitek MS and MALDI-TOF systems were: *Staphylococcus hominis* (30%), *Staphylococcus epidermidis* (30% – alone and in combination) and *Micrococcus luteus* (20% – alone and in combination), followed by *Acinetobacter lwoffii* (belonging to the normal human skin flora [8]), Gram positive spore-bearing rods *Bacillus simplex* – an environmental microorganism found in soil, but could be associated with human infections [9], as well as enterococci (*E. faecalis*), which are human intestinal commensals but could also provoke infections in humans [10]. Single coryneform bacteria, viridans group streptococci (which could not be identified to



**Figure 3** – Percentage distribution of microorganisms isolated from the hands of dentists

species due to low microbial counts – 2–5 colonies) were also detected.

## Discussion

The absence of "transient microflora" *S. aureus*, representatives of the order Enterobacteriales and *Pseudomonas aeruginosa* is a good indicator of the quality of hygienic hand disinfection with an alcohol-containing antiseptic. On the other hand the presence of *Enterococcus faecalis* and *Bacillus simplex* is undesirable as well as coagulase-negative staphylococci in a high microbial count. Recalling the method of the 6 steps of hand disinfection before performing the sampling probably contributed to such relatively good results (Fig. 1).

Evaluating the influence of the duration of rubbing with a disinfectant on the reduction of the number of bacteria on the hands of healthcare personnel and the quality of the performed hygienic hand disinfection, Pires et al. (Geneva, Switzerland) found an interesting result in 2017 [11]. The team conducted an experimental study – hand wiping was performed for 10, 15, 20, 30, 45 or 60 seconds, according to the WHO technique, using 3 ml of alcohol-based skin antiseptic, the hands were previously contaminated with *E. coli* ATCC 10536. A total of 32 medical specialists performed 123 trials. All of the above mentioned durations of hand rubbing resulted in a significant reduction in bacterial counts ( $P < 0.001$ ). The bacterial reduction achieved after 10, 15 or 20 seconds of hand rubbing was not significantly different from that obtained after 30 seconds. The mean bacterial reduction after 15 seconds of hand wiping was  $0.11 \log^{10}$  less (95% CI, -0.46 to 0.24) than after 30 seconds, indicating that it was not significantly less. This proves that if the 6 steps are strictly followed even a shorter duration of rubbing is acceptable.

The results we obtained are probably due to not strictly applying the 6 steps of hand disinfection from each person included in the study, especially in the so-called "red zones" that were emphasized as risky during sampling and do not depend on the time of rubbing (Fig. 2).

## Conclusion

Regardless of the fact that coagulase-negative staphylococci belong to normal skin flora, their presence in part of the samples in high microbial count is undesirable, especially in patients with immunosuppression, impaired or underdeveloped immune system (as cancer patients, newborns) and the presence of skin-mucosal lesions [12–17]. This refers also to the presence of *Bacillus simplex* and enterococci [9, 10].

The analysis of the foreign literature on the problem and the suboptimal results we obtained point us to the need to increase the knowledge and commitment of the dental staff and students in decontamination of hands before manipulations – a main component in the complex of the so-called standard precautions.

Good dental practice requires training and control of knowledge about decontamination, disinfection and the correct use of personal protective equipment which are key to the prevention of HAIs. Continuing postgraduate training for the prevention and control of HAIs should become mandatory as so far it has been rather optional and relies mainly on student training.

**Author Contributions:** Conceptualization – V.S, H.B., A.P.; methodology – A.P., V.S, H.B.; validation – A.P.; formal analysis – A.P., V.S.; resources and sample collection – V.S., H.B.; microbiological investigation – A.P.; data analysis – A.P.; writing – original draft preparation – A.P., V.S.; final writing, review and editing – A.P.; visualization and translation- A.P.; funding acquisition – H.B. All authors have read and agreed to the published version of the manuscript.

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# The Effect of Parental Presence on The Anxiety Level of Nurses During Intravenous Interventions in Children

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## Abstract

**Aim:** The present study employed an analytical, cross-sectional, and pretest-posttest design to assess the impact of parental presence on the anxiety levels of nurses during intravenous interventions in pediatric patients.

**Methods:** The research was conducted in a public hospital in Istanbul between 01 September and 30 December 2021. The population of the research consisted of nurses working in the pediatric clinic of the hospital (N = 70), and the sample consisted of 50 nurses who met the research criteria and agreed to participate in the research. Data were obtained through an information form and a state-trait anxiety inventory. Participants were first asked to fill out the information form and the trait anxiety inventory. The research was carried out in two phases with the same sample group. In the first phase, nurses were asked to fill out the state anxiety inventory immediately after intravenous interventions were administered to children while their parents were with their children. In the second phase, after a period of 15 days, a state anxiety inventory was applied to the nurses with the same sample group immediately after the intravenous interventions, without the participation of the family. The SPSS 26 package statistical program was used to evaluate the data.

**Result and Conclusion:** It was determined that the mean trait anxiety scores of the participants were at a medium level and that the mean state anxiety scores of the nurses were statistically significantly higher ( $p < 0.001$ ) in the interventions in which the parents were included in the process compared to the interventions in which the parents were not included in the process. Continuous in-service training can be recommended for pediatric nurses to adopt family-centered care.

**Keywords:** Intravenous procedure; child; nurses; anxiety.

## Introduction

The process of admission or hospitalization can elicit stress for both the child and their family, regardless of the child's age, when their health and overall well-being deteriorate. Within the hospital setting, children are subjected to several distressing procedures aimed at diagnosis and treatment, including vaccination, intravenous treatments, urine catheterization, and lumbar puncture. In the hospital setting, nurses commonly provide intravenous treatments as a routine practice [1, 2]. Children in hospitals undergo a variety of medical treatments. It is stated that inpatient

children get 6.3 unpleasant treatments on average per day [3]. These practices are important causes of anxiety and stress for children. Improper management of this procedure has the potential to result in pre-procedural anxiety, needle phobia, and subsequent healthcare avoidance behaviors [1]. Separation of a child from their parents during hospitalization also causes psychological distress, which is cause for concern. Several variables contribute to the experience of procedural pain, with one such variable being the influence of parents and their parenting habits. It is well acknowledged that there exists a correlation between



anxiety within the family unit and the anxiety levels shown by children [4].

Family-centered care is a care model in which healthcare professionals and families cooperate and best meet the needs and expectations of parents and children [2]. The implementation of nurse-supported family-centered care practices is crucial in the context of pediatric treatment. These practices aim to address various aspects, including anxiety reduction, effective communication, enhanced self-efficacy and care satisfaction, establishment of mutual trust, facilitation of treatment and care compliance, optimization of the healing process, and equipping parents with problem-solving skills through nurse intervention. It is stated that it has positive effects such as improving caregiving capacity, increasing professional satisfaction, and reducing ethical responsibilities [5, 6].

When children are subjected to invasive procedures, parents are often willing to stay with their children to reassure and comfort them. This is beneficial for both parents and healthcare personnel [1, 7]. Minimizing the physical (pain, insomnia, etc.) and psychological (fear of medical procedures, anxiety) problems of children and parents in the health care environment is among the goals of pediatric nurses. Previous studies have demonstrated the importance of parental presence in reducing the anxiety levels of family members during invasive procedures with pediatric patients, reducing anxiety and pain in children undergoing the procedure, and accelerating the healing process [6, 8–10]. However, for a variety of reasons, most healthcare professionals do not favor parental involvement in interventional procedures. There are several factors that contribute to healthcare professionals' reluctance to involve parents in interventional procedures. These include concerns about potential negative psychological effects on parents, ethical dilemmas, psychological pressure on healthcare workers, parents' reactions to the procedures, interference in the work environment, potential negative impact on patient care, infringement upon the privacy of other patients, and the potential exacerbation of a child's attention-seeking behaviors.

There are other factors, including the detrimental effect on technical expertise and the possibility of family members suing in the event of a malfunction [10, 11]. However, there are no studies that look at the anxiety nurses feel while giving children intravenous medication. It is known that the success rate of intravenous catheter insertion in pediatric patients is lower than in adult patients. The procedure's success might suffer as a result of the nurses' anxiety. The performance of the procedures becomes more challenging for both the medical staff and the kids, and the kids' anxiety increases as the success rate declines. Ensuring good communication with parents and healthcare personnel during invasive interventions and providing them with accurate information will significantly reduce these problems [11].

This research was conducted to evaluate the effect of parental presence on nurses' anxiety levels during intravenous interventions in children.

**Research questions:** In the research, "What are the trait anxiety levels of nurses?" and "How does the presence of parents during intravenous interventions affect the state anxiety levels of nurses?" and "Is there a relationship between the nurses' age and experience and their state anxiety levels?" were answered.

## Material and methods

### *Study Design*

This research was carried out in an analytical, cross-sectional, and pretest-posttest manner to evaluate the effect

of parental presence on the anxiety level of nurses during intravenous interventions in children.

### *Population and sample*

Data were collected with nurses working in the pediatric departments of a public hospital in Istanbul between 01 September and 30 December 2021. The population for the research consisted of 70 pediatric nurses. The number of participants to be included in the research was determined using the sampling formula with a known as population. The sample size was calculated as 50 pediatric nurses with the 80% confidence interval,  $p$  (probability of the event examined) as = 0.5, and  $\pm 5\%$  sampling error. Totally 50 pediatric nurses participated in the research. The universe has been reached by 71.42%.

The inclusion criteria for the study were having at least one year of experience in the pediatric clinic and volunteering to participate in the study.

### *Instrumentation*

Research data were collected using the Information Form and the State-Trait Anxiety Inventory.

1. Information Form: This form, prepared by the researchers, includes questions regarding the socio-demographic characteristics of the nurses and their profession.

2. The State-Trait Anxiety Inventory: Ner and Le Compte (1982) assessed the scale's reliability and validity developed by Spielberger et al. (1970). The State-Trait Inventory is a self-assessment questionnaire and has two separate scale forms consisting of 40 items. It was initially developed to investigate anxiety in adults, and later it was found to be suitable for high school students and people with psychiatric disorders and physical diseases. After ten years of trials, psychologists have concluded that this inventory can be applied to all youth and adults.

**Trait Anxiety (A-Trait):** Trait anxiety is the individual's tendency to become anxious. These people tend to perceive the situations they experience as constantly stressful and experience feelings of unhappiness and discontent as a result of perceiving a threatening element. Individuals who experience constant anxiety can be easily upset, become pessimistic, and experience state anxiety frequently.

**State Anxiety (A-State):** It is the fear that individuals feel about the stressful situations they are in, and physical changes such as sweating, turning pale, and trembling occur in the individual. State anxiety inventory level increases when stress increases, and decreases when stress disappears.

In the State-Trait Anxiety Inventory, both scales have four answer options, and the weight values of the options vary between 1-4. The State Anxiety Scale determines the fear individuals feel about stressful situations, and the answer options for each item are marked as (1) not at all, (2) a little, (3) a lot, and (4) completely. The trait anxiety scale determines the individual's tendency towards anxiety, and each answer option is marked as (1) not at all, (2) a little, (3) a lot, or (4) completely. There are two types of expressions in the scales, such as direct and reversed. The State Anxiety Scale has ten reversed statements, and the Trait Anxiety Scale has seven reversed statements. The scales consist of twenty statements, and the total scores obtained from each scale vary between 20 and 80. High scores indicate a high level of anxiety [12].

The State-Trait Anxiety Inventory's Turkish adaptation found that the reliability coefficients for the state anxiety scale and the trait anxiety scale were both between 0.83 and 0.92. In this study, the pre-test was found to be 0.79 for the state anxiety scale, the post-test was 0.89 for the state anxiety scale, and 0.83

for the trait anxiety scale, and both scales together were found to be 0.87.

### Collection of data

In the hospital where the research was conducted, intravenous procedures are performed by nurses. The intervention room in the area was used for interventions on the cephalic or basilic vein. During intravenous interventions, the parent is not present with the child in the hospital routine, and the procedure is performed together with another healthcare professional. Nurses and the parents of the children who would undergo the procedures were informed about the study, and their written consents were obtained. The nurses who made up the sample were asked to fill out the introductory information form and the trait anxiety inventory. The research was carried out in two phases with nurses who would apply intravenous catheters to children. In the first phase, the nurses in the sample group were asked to fill out the State Anxiety Inventory within 15 minutes after the intravenous interventions were applied to the children while the parents were with their children. In the group where parents were included, parents were positioned within the child's view and held their children's arms during the procedure. In the second phase, after a period of 15 days, the same sample group had invasive interventions performed without the participation of the family; the child's arm was held by another healthcare professional; and after the procedure, the nurses filled out the State Anxiety Inventory within 15 minutes.

### Data analysis

The SPSS 26 package statistical program was used to evaluate the data. Frequency, percentage, mean, and standard deviation findings in the descriptive characteristics of the nurses were presented. The mean, standard deviation, maximum, and minimum values of the State-Trait Anxiety Inventory were stated, and normality distributions were examined with the Kolmogorov-Smirnov test ( $p > 0.05$ ). An independent sample t test was used to compare independent variables with two categories with dependent variables, and a one-way ANOVA was used to compare independent variables with more than two categories with dependent variables. A dependent sample t test was used to compare repeated measurements of the State Anxiety Scale. The relationship between quantitative data was examined with Pearson correlation analysis. The data was tested with a 5% margin of error.

### Ethical considerations

Before conducting the research, the necessary approvals were obtained from the Non-Interventional Research Ethics Committee of Biruni University (Date: May 21, 2021/Protocol Number: 2021/51-20) and the hospital where the research was conducted. An informed consent form was presented to the participants before the research, and they were included in the study after they approved the form. Participants were informed that they could withdraw from the research at any time.

## Results

It was observed that 68% of the participants were women, 78% had a bachelor's degree, 42% had income less than their expenses, 62% were single, and 26% had children. 54% of the nurses stated that they worked in the pediatric emergency department; 62% of them stated that they worked in the unit willingly; and 82% of them were not satisfied with their financial income. 80% of the participants stated that they did not participate in communication programs in nursing. It was determined that the average working time as a nurse was

6.30±6.94 years, and the average working time in the pediatric ward was 3.96±3.55 years. The average working time as a nurse was 6.30±6.94 years, the average working time in the pediatric ward was 3.96±3.55 years, and the average monthly working time in the ward was 211.64±32.59 hours (Table 1).

Table 1

The distribution of nurses' descriptive features (N:50)

Variables		Mean ±SD	Min-Max
Age (years)		28.94±6.37	22-48
Duration of working in the profession (years)		6.30±6.94	1-30
Working time in children's service (years)		3.96±3.55	1-16
		<b>n</b>	<b>%</b>
Gender	Male	16	32.0
	Female	34	68.0
Education Status	High School	6	12.0
	Bachelor's degree	39	78.0
	Postgraduate (Master of Science and/or doctorate)	5	10.0
Income status	Income less than expenses	21	42.0
	Income equals expenses	19	38.0
	Income more than expenses	10	20.0
Marital Status	Single	31	62.0
	Married	19	38.0
Do you have children?	Yes	13	26.0
	No	37	74.0
Unit/ward/department that is worked	Child emergency	27	54.0
	Pediatric clinic	23	46.0
Voluntary employment in the service	Yes	31	62.0
	No	19	38.0
Satisfaction with the profession's financial income	Yes	9	18.0
	No	41	82.0
Participation in nursing communication programs	Yes	10	20.0
	No	40	80.0

Of the nurses; 58% stated that they experienced stress during intravenous interventions, 36% said that when intravenous interventions failed, they waited for the patient to rest and tried again, 46% were affected by the attitude of the patient's relatives during the intervention, 46% were hesitant to try again when they were intervened during intravenous interventions, and 96% stated that he thought that patients' relatives interfered with his initiatives in his professional life.

When they thought that they were guided by their parents during intravenous interventions, 52% stated that they warned their parents not to interfere with my interventions, 94% stated that they considered it disrespectful for patients' relatives to intervene during intravenous interventions, and 42% stated that they considered changing the department they worked in because of the patient's relatives but gave up such a decision (Table 2).

When the nurses' mean scores on the State-Trait Anxiety Scale are examined, the mean score on the Trait Anxiety Scale is 42.70±7.36. When a parent is with the children during the procedure, the mean State Anxiety Scale score is 52.32±6.66. The mean State Anxiety Scale score when the child was not with a parent was 33.028.18. The suitability of the data for a normal distribution was examined with the Kolmogorov-Smirnov test, and it was found that it conformed to a normal distribution ( $p > 0.05$ ).

Table 2

Distribution of nurses' opinions regarding the procedure (N:50)

Variables		n	%
Stress during intravenous interventions	Yes	29	58.0
	No	21	42.0
Attitude in case of failure of intravenous interventions	I try until I succeed	9	18.0
	I continue until the patient starts to feel uncomfortable.	8	16.0
	I wait for the patient to rest, then I try it.	18	36.0
	I receive assistance from other health professionals	15	30.0
Being affected by the attitude of the patient's relatives during the intervention	Yes	23	46.0
	Partially	21	42.0
	No	6	12.0
If your intravenous intervention is interfered during the procedure, would you be hesitant to try again?	No, I focus on my work	27	54.0
	Yes, I hesitate	23	46.0
Have you ever considered that the relatives of your patients can obstruct your professional efforts?	Yes	48	96.0
	No	2	4.0
How do you react when you think that you are being manipulated by the parents during your intravenous interventions?	I take the parents out of the room	15	30.0
	I warn parents not to interfere with my attempts	26	52.0
	I ignore the parents	5	10.0
	I apply intravenous interventions in cooperation with parents	4	8.0
Would you consider it disrespectful if patients' relatives interfere during your intravenous interventions?	Yes, totally disrespectful	47	94.0
	No, I don't see it as disrespect	3	6.0
Have you ever thought about changing the department you work in because of patient relatives?	Yes, I changed my department	8	16.0
	I thought about it but gave up on such a decision.	21	42.0
	I'm thinking of changing it now	14	28.0
	No, I never had that thought	7	14.0

Table 3

Distribution of nurses' State-Trait Anxiety Scale mean scores (N:50)

Parameter	Number of Items	Mean ±SD	Min	Max	p**
Trait Anxiety Scale	20	42.70±7.36	29 (20)*	59 (80)*	0.200
State Anxiety Scale (With parent presence)	20	52.32±6.66	33 (20)*	71 (80)*	0.200
State Anxiety Scale (When parent is not present)	20	33.02±8.18	20 (20)*	55 (80)*	0.200

SD: Standard Deviation;

Min: Minimum;

Maks: Maksimum

\* The smallest and largest values that can be taken from the scale,

\*\* Kolmogorov-Smirnov normality test (p&gt;0,05)

Table 4

Comparison of State Anxiety Scale mean scores in the presence and absence of a parent during the procedure

Parameter	Mean ±SD	t	P
State Anxiety Scale (With parent presence)	52.32±6.65	13.232	0.000
State Anxiety Scale (When parent is not present)	33.02±8.17		

SD: Standard Deviation;

t: Dependent Sample t Test

When the mean scores of the State Anxiety Scale measured in the presence and absence of a parent with the children during the procedure were compared, it was seen that there was a significant difference. Accordingly, the nurses' state anxiety scale mean score was significantly lower when a parent was not with the children during the procedure (p<0.001).

Table 5

The relationship between age, working hours, working years in the pediatric ward, monthly working hours and the State-Trait Anxiety Scale

Parameter		Trait Anxiety Scale	State Anxiety Scale (With parent presence)	State Anxiety Scale (When parent is not present)
Age	r	-0,112	-0,009	-0,055
	p	0,440	0,952	0,705
Working time in the profession (years)	r	-0,080	0,029	-0,072
	p	0,579	0,840	0,621
Working time in the child clinic (years)	r	-0,079	-0,075	-0,046
	p	0,588	0,607	0,753
Monthly working time (hours)	r	0,001	0,101	0,054
	p	0,995	0,485	0,711

r: Analysis of Pearson Correlation

When the relationship between age, working time, working time in the pediatric ward, monthly working time, and the State-Trait Anxiety Scale was examined, it was seen that there was no significant relationship (p>0.05).

## Discussion

Parents are the most significant source of support for children during hospitalizations and painful procedures. The absence of trusted individuals in the hospital environment can reduce a child's tolerance to pain during procedures. Anxiety and fear are the most critical emotional reactions accompanying pain. Studies have shown a direct relationship between anxiety and pain, with each intensifying the severity of the other [6,13]. In the study, when examining nurses' mean scores according to the State-Trait Anxiety Inventory, the mean score of the Trait Anxiety Scale was found to be 42.70±7.36 (Table 3). Similar to study, conducted by Ocaktan et al., (2002) found the average trait anxiety score among healthcare workers to be 44.8±5.9 [14]. Results can be explained by both the stressful nature of the nursing profession and the fact that the research was conducted during the pandemic period.

In all nursing interventions, there is an interaction between

the nurse and the patient, and in invasive procedures, factors can positively or negatively affect the relationship between the nurse, the patient, and their families. Especially during invasive procedures involving painful applications, both the patients and nurses can be affected. Managing interactions during painful and discomforting procedures that may result in failure or frequent repetitions can be challenging. In such cases, patients' or their families' reactions can be a stressor for nurses, affecting them as well [15]. In present study, the mean score of the State Anxiety Scale during procedures when parents were present was  $52.32 \pm 6.66$ , and it was  $33.02 \pm 8.18$  when parents were not present. When comparing the mean scores of the State Anxiety Scale during procedures with and without the presence of parents, it was significantly lower when parents were not present ( $p < 0.001$ ) (Table 4). However, studies investigating family involvement in healthcare settings have concluded that parents should be present with their children as painful procedures increase [16,17].

There are studies showing that parents' presence during invasive procedures reduces the anxiety levels of both parents and children, speeds up the recovery process, and reduces pain [6,13,18-21]. Pani et al. (2016) reported that the presence of parents during the first dental examination of children aged 6-8 reduced anxiety levels, and Sağlık & Çağlar (2019) indicated that involving parents during invasive procedures in emergency departments reduced children's anxiety levels [6,21]. Studies in the literature support that families' presence during intravenous procedures is also supported by nurses working in pediatric clinics [5,10,22]. Davidson et al. (2017) found that family-centered care minimized anxiety for patients and parents and positively affected the recovery process [8]. In the study conducted by Khajeh et al. (2017) noted that healthcare workers did not include the family in the patient's treatment and care process, adversely affecting both the family and the child [23].

In addition to studies showing that parents' presence reduces children's anxiety levels, there are also studies indicating no difference in anxiety levels between children with and without parents present [24-27]. In a study conducted by Tantikul and Theeranate in 2014 with 72 families with children under the age of 4, parents who were with the child during IV interventions, parents who wanted to be with the child but were not allowed to be with the child and parents who did not want to be with the child were studied in 3 groups. As a result of the study, it was observed that there was no significant difference between the groups in terms of anxiety and pain levels [27]. In another study, the pain level was examined in two groups: those who were with their parents and those who were with healthcare personnel during intravenous access and it was concluded that the presence of parents had the least effect on the pain level [26].

In addition to these studies, in a study conducted by Boztepe (2012), 62.8% of nurses stated that parents should not be present with their children during painful procedures. As for the reasons for this; nurses stated that the disadvantages of parents being with their children were that 77.1% of them increased the stress of the child, 60% of them increased the stress of healthcare professionals, 60% of them made the procedure difficult, and 48.5% of them prolonged the duration of the procedure [28]. Similarly, in a study conducted by Karadaş and Şenturan in 2021, 62.9% of nurses reported that 62.9% experienced stress when patients and their relatives were with them during invasive

interventions; 51.3% were afraid of making mistakes during the interventions, and 25.4% were afraid to re-enter the patient's room when the intervention was performed [15]. However, it should not be forgotten that family-centered care practices are recommended.

During one of the painful procedures, inserting an intravenous catheter, nurses also experience anxiety alongside the anxiety experienced by children and their families. More than half of the nurses (58%) experienced stress during intravenous interventions; nearly half (46%) were affected by the attitudes of the patient's relatives, (46%) were hesitant to try again when intervened, almost all (96%) thought their interventions were interfered with by the patient's relatives, and (94%) considered it disrespectful (Table 2). A study indicated that while nurses supported parents' active participation in care, they believed that the parents' constant presence during the hospital process could cause some problems [17]. According to Krinstensson-Hallström (2000), it was determined that pediatric nurses supported family-centered care but did not always include parents in the practice [29]. In another study stated that nurses advocated the necessity of family-centered care but faced various challenges in care and treatment due to systemic and physical conditions [18, 30]. Kuo et al. (2012) found that these challenges as staff and time shortages, communication difficulties, role confusion, fear of role loss, high workload, and difficulty in ensuring collaboration between nurses and parents [31]. However, there are studies emphasizing the importance of family-centered care. In the study conducted by Yildiz and Temuçin, cooperation with the family in treatment and care, convenience in the implementation of care, more efficient and effective use of time and resources were stated as the benefits of family-centered care for nurses [32]. In another study, nurses identified the advantages of parents being with their children during invasive procedures as increased child compliance with the procedure (90.0%) and calming the child (65%) [28].

There are many studies showing that family-centered care reduces anxiety levels for both the child and the family during invasive procedures. Providing information about the procedure to parents and children and explaining it in a language they understand will reduce such interventions. Developing individualized approaches to reduce the concerns and strengthen coping strategies of children and their parents is crucial. Healthcare workers should use strategies to understand each child and family's issues, ask questions to get to know them, listen, and explain. These strategies are vital for strengthening the communication between the child, family, and nurse [33]. A review of the literature shows that education and communication support provided to children and families about the procedure and including the family in the child's care reduces parental stress and anxiety levels [34-36]. In another study Jaber et al. (2020) found that anxiety levels decreased and satisfaction levels increased among parents who participated in educational sessions in the clinic [37].

To adopt family-centered care, it should be emphasized to nurses starting from their education process, and they should be encouraged to implement it in clinical settings. Factors that increase nurses' state anxiety scores should also be identified. Additionally, informing parents about their behavior and attitudes while being present with their children is essential for raising awareness and understanding among children and parents.

## Limitations

This study was limited in that the pediatric nurses who participated worked in the pediatric units of hospitals in Istanbul. Therefore, the findings of this study may have limited application to other pediatric nurses working in other hospitals, regions, or countries. Conducting the research during the pandemic period may have affected the trait and state anxiety score averages. Changes in the children and families in the patient group of this study may have affected the results.

## Recommendations

The presence of parents with their children during intravenous catheterization increases the anxiety of nurses. This anxiety may affect the success of the procedure. Therefore, the necessary service education programs should be organized for nurses to identify the causes of anxiety and to adopt family-centered care in reducing this anxiety. Conducting studies with larger sample groups where the children in the intervention and control groups have similar characteristics during intravenous catheterization will help to ensure the generalizability of the findings.

## Conclusion

This study determined that nurses experience anxiety during invasive procedures, feel that patient relatives interfere with them during these procedures, are affected by this behavior, prefer to warn the patient relatives after the intervention, perceive this behavior as disrespectful, and are hesitant to attempt again when interfered with during invasive procedures.

It was also found that nurses have high levels of trait anxiety, and their state anxiety levels are higher when a parent is present during an invasive procedure compared to when a parent is not present. Although nurses experience more stress when parents are present during invasive procedures, pediatric nurses should support family-centered care by ensuring that parents are present with their children during intravenous catheter insertion, as this reduces the anxiety levels of both children and parents. Identifying and reducing nurses' anxiety levels will contribute to their professional development by enabling them to exhibit positive attitudes towards the child, themselves, and the family. Continuous in-service training is recommended to help pediatric nurses adopt family-centered care.

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# Soluble and Cellular Inflammatory Predictive Markers Associated with Recurrent Pregnancy Loss Among Kazakhstani Women: a Pilot Study

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## Abstract

**Background:** Recurrent pregnancy loss (RPL) is a common complication of pregnancy globally, characterized by multiple miscarriages but with poorly explained etiologies. Insofar as a state of low-grade inflammation (LGI) accompanies RPL, this study explores the link between RPL and markers of LGI among Kazakhstani women.

**Methods:** The retrospective study was conducted on 112 Kazakh women, comprising 64 with a confirmed diagnosis of RPL and 48 women with two or more uncomplicated pregnancies serving as controls. Statistical analysis was performed on SPSS 29 software.

**Results:** All tested blood analytes, including CRP, glucose, cholesterol, LDL-cholesterol, Hemoglobin, and RBC counts, were negatively associated with RPL. The only exception was neutrophil values having a positive association with RPL despite a lack of significant correlation between groups.

**Conclusion:** The study shows a marginal association between the LGI biomarkers considered and the overall risk factors of RPL in Kazakh women, which is in apparent contradiction with earlier studies. The absence of parallel studies in Central Asian countries hampers the analysis of study trends in related communities. Future case-control studies with more sample sizes are needed to explore the RPL biomarkers in depth.

**Keywords:** recurrent pregnancy loss, low grade inflammation, recurrent miscarriages, RPL markers, Kazakhstan.

## Introduction

Miscarriage, defined as the spontaneous loss of a pregnancy before it reaches the viability stage, is a common complication of pregnancy, with 23 million

miscarriages occurring every year globally, which translates to 44 pregnancies lost every minute [1]. Repetitive miscarriages, also designated as recurrent pregnancy loss (RPL), vary in frequency according to

the definition of RPL adopted by different international societies. While the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) characterize RPL as two or more miscarriages [2, 3], the Royal College of Obstetricians and Gynaecologists (RCOG) requires three or more failed pregnancies [4]. This translated to RPL prevalence of 2–4% among child-bearing women depending on the definition adopted [5]. Broadly speaking, RPL is classified into primary, secondary, and tertiary categories. The causes of RPL are multifactorial and include genetic (2–5%), anatomic (10–15%), endocrine causes (17–20%), autoimmune (20%), infections (0.5–5%), and environmental [6] factors. Despite identifying these and related RPL risk factors, 50–70% of all cases remain idiopathic [7], thus necessitating the search for additional causative factors of RPL.

Several well-controlled studies have reported on genetic risk factors for RPL but with varied outcomes. We recently reported on the association of the human forkhead Box P3 (*FOXP3*) gene and Human Leukocyte Antigen (HLA) class II genes with idiopathic RPL [8, 9]. It was also shown that a regulated inflammatory response is needed for a successful pregnancy [10]. While chronic low-grade inflammation (LGI) remains largely asymptomatic with a protracted progression, it plays a major role in various chronic disorders. These include cardiovascular and metabolic diseases, neurodegenerative conditions, cancer [11], and various pregnancy complications, including pregnancy loss [12].

It was suggested that LGI is a main contributor to the etiology of RPL [13, 14], highlighted by the suggested association of neutrophil activation, marked by elevated neutrophil counts and neutrophil-to-lymphocyte ratio (NLR), in women with a history of multiple miscarriages [14]. However, the precise cutoff values for these and related parameters remain uncertain necessitating further exploration. While no significant difference in CRP levels allegedly exists between women with RPL and the control group, serum CRP values were higher in RPL patients when serum CRP levels were evaluated in the context of *CRP* gene polymorphisms, as observed in women carrying the rs2794520 T allele [15]. This prompted the speculation that variation in the CRP may influence the risk of repeated miscarriages without affecting CRP levels *per se*. Other inflammation markers, such as neutrophil and lymphocyte counts and NLR, were higher in women with RPL in early pregnancy [10]. Nevertheless, there was no difference between the two observed groups in platelet, and WBC counts and hemoglobin (Hgb) levels [15].

A Turkish study established that unexplained infertility is positively correlated with TGs, LDL-cholesterol, total cholesterol, and CRP, in addition to baseline LGI biomarkers [16]. This research investigates the predictive potential of CBC parameters, CRP, and cholesterol levels as potential contributors to RPL. While studies on the association of LGI biomarkers with altered risk of RPL were reported for Asian, European, and USA subjects, no comparable investigations were done on Kazakhstani women. The present study aims to examine the association between RPL and the presence of LGI in the analysis of CBC parameters, CRP, cholesterol levels, etc. Due to the limited number of studies on this topic, this work will help enhance understanding of the RPL from the perspective of inflammation among women from Kazakhstan.

## Material and methods

### *Study Design and Study Settings*

This was a retrospective case-control study involving 112 Kazakhstani women and was conducted from September 2022 to January 2024. These consisted of 64 women with confirmed RPL diagnosis (Cases) and 48 multiparous women serving as Control. RPL definition per the ESHRE guidelines was used [3], with the inclusion criteria considered: women older than 18 with two or more pregnancy losses of unknown etiology with the same partner. The exclusion criteria for the case group included one or more spontaneous miscarriages, older age (> 40 years) at first pregnancy, and/or presence of female genital anatomical abnormalities. Women were also excluded if they reported prior or current autoimmune disorders, liver dysfunction, or managed ovarian hyperstimulation or artificial insemination (ART). Inclusion criteria for the control group were two or more successful pregnancies and deliveries, negative somatic diseases, or the receipt of infertility drug treatment throughout pregnancy.

### *Study Instrument*

A questionnaire in Kazakh and Russian languages was provided depending on the participants' preferences and included sociodemographic and clinical data such as biochemical tests, CBC workups, as well as smoking and drinking habits, and was completed during patients' routine check-ups with a gynecologist. In addition to the questionnaire, available medical data of patients were also taken after an informed consent form was taken from each eligible woman for the inclusion criteria.

### *Study Variables*

Independent variables included sociodemographic characteristics (age, ethnicity, education), and gynecological data such as menarche, menstrual dysfunction, surgeries, infections and illnesses, vaginal swab, and PAP smears. Pregnancy history, including the number of gestations and parity, and clinical and habitual data (smoking and alcohol consumption) were independent variables. Body mass index (BMI) on the height (m) and weight (kg) of study participants was calculated as kg/m<sup>2</sup>. Chronic illnesses (hypertension, diabetes, thyroid function, and venous thrombosis), and laboratory data (blood Hemoglobin levels, RBC, and WBC, neutrophils, lymphocytes, monocytes, platelet counts), and other analytes including erythrocyte sedimentation rate (ESR), CRP, HDL-cholesterol (HDL-c) and LDL-cholesterol (LDL-c), and other vitamins C, D, and B12. The number of spontaneous miscarriages has been considered a dependent variable.

### *Statistical Analysis*

Statistical analysis was done using SPSS v. 29 (IBM, Armonk, NY). The analysis included the calculation of mean and standard deviation to give a comparative description of each normally distributed variable between case and control groups. For the continuous variables student t-test and categorical variables, a chi-square test was performed. Estimation of the student t-test was performed for the parametric values, while for the non-parametric values Mann-Whitney “U” test was used.

## Results

Table 1 displays sociodemographic characteristics and clinical profiles of RPL cases and control women. Age ( $p = 0.579$ ), BMI ( $p = 0.496$ ), and ethnic origin ( $p = 0.648$ ) were



not statistically significantly different between the two groups. Most of the study subjects were Kazakh (> 95%), and the remainder were Russians and other ethnicities. The number of live births ( $p < 0.001$ ) were significantly lower, and the number of miscarriages ( $p < 0.001$ ) were significantly higher in the case group compared to the control group.

**Table 1**

Sociodemographic characteristics and clinical profiles of RPL cases and control women

Variables	RPL cases (n = 64)	Control (n = 48)	P <sup>3</sup>
Age (years) <sup>1</sup>	33.3 ± 5.9	32.7 ± 5.5	0.579
BMI (kg/m <sup>2</sup> ) <sup>1</sup>	24.2 ± 4.2	23.7 ± 2.6	0.496
Ethnic origin <sup>1</sup> :			0.648
Kazakh	50 (94.3)	42 (95.5)	
Russian	2 (3.8)	2 (4.5)	
Others	1 (1.9)	0 (0.0)	
Oral contraceptive <sup>2</sup> :			0.507
Barrier	2 (3.1)	3 (6.3)	
Hormonal	4 (6.3)	5 (10.4)	
Irregular menses <sup>2</sup>	0 (0.0)	1 (2.1)	1.000
Aspirin intake <sup>2</sup>	6 (9.4)	2 (4.3)	0.463
Progesterone treatment <sup>2</sup>	14 (21.9)	3 (17.6)	1.000
LMW heparin <sup>2</sup>	6 (9.4)	0 (0.0)	0.334
Vitamin B supplements <sup>2</sup>	3 (4.7)	7 (14.6)	0.096
Abnormal Pap smear <sup>2</sup>	7 (10.9)	2 (4.2)	0.296
Smoking <sup>2</sup>	0 (0.0)	4 (8.3)	0.031
Alcohol <sup>2</sup>	0 (0.0)	3 (6.3)	0.076
Pregnancy outcome <sup>1</sup> :			0.169
Gestation	4.44 ± 1.76	4.00 ± 1.50	
Live births	0.37 ± 0.55	3.52 ± 1.13	<0.001
Still births	0.22 ± 0.45	0.00 ± 0.00	0.001
Miscarriages	3.83 ± 1.54	0.00 ± 0.00	<0.001
Ectopic	0.11 ± 0.44	0.29 ± 0.87	0.159
Artificial (IVF)	0.33 ± 0.92	0.27 ± 0.68	0.692

1. Mean ± SD

2. Number (percent total)

3. Student t-test (continuous variables), chi-square test (categorical variables)

**Table 2**

The biochemical and haematological characteristics of the study participants

Laboratory variables	RPL cases (n = 64)	Control (n = 48)	P <sup>1</sup>
Glucose <sup>2</sup>	3.9 ± 0.34	4.4 ± 0.50	<0.001
ESR <sup>3</sup>	10.11 (2.00 – 40.00)	4.00 (1.00 – 34.00)	0.068
CRP <sup>3</sup>	1.47 (0.10 – 4.60)	1.90 (0.88 – 2.54)	0.006
Albumin <sup>2</sup>	55.17 ± 8.82	43.35 ± 4.23	<0.001
TSH <sup>3</sup>	2.10 (0.87 – 3.54)	1.44 (0.27 – 3.99)	<0.001
TG (mmol/L) <sup>3</sup>	1.81 (1.00 – 3.80)	1.01 (0.50 – 3.28)	<0.001
Cholesterol (mmol/L) <sup>3</sup>	3.20 (1.80 – 9.90)	4.20 (2.30 – 7.30)	<0.001
HDL-cholesterol (mmol/L) <sup>3</sup>	1.42 (0.80 – 2.20)	1.35 (0.84 – 2.40)	0.062
LDL-cholesterol <sup>3</sup>	1.19 (1.00 – 3.20)	1.83 (1.10 – 3.82)	<0.001
Hemoglobin <sup>3</sup>	11.14 (8.6 – 13.7)	12.17 (8.5 – 15.5)	<0.001
RBC count <sup>2</sup>	3.09 ± 0.70	4.42 ± 0.57	<0.001
WBC count <sup>2</sup>	7.4 ± 3.38	6.42 ± 1.92	0.074
Neutrophils <sup>2</sup>	65.16 ± 11.99	63.41 ± 7.09	0.384
Platelet count <sup>2</sup>	257.54 ± 97.57	275.87 ± 78.72	0.299
Lymphocytes <sup>2</sup>	35.70 ± 11.23	29.86 ± 7.35	0.003

1. Student t-test for parametric, Mann-Whitney U-test for non-parametric

2. Mean ± SD

3. Median (range)

The biochemical and haematological characteristics of the study participants are represented in Table 2. HDL-c, WBC count, neutrophils, platelet count, and lymphocytes were not significantly different between Case and Control groups. RPL cases had significantly lower glucose (3.9 ± 0.34 vs. 4.4 ± 0.50 mmol/L) and cholesterol (3.20 (1.80 – 9.90) vs. 4.20 (2.30–7.30) mmol/L) levels compared with control women. TSH (2.10 (0.87 – 3.54) IU/ml) and TG (1.81 (1.00 – 3.80) mmol/L) values, were also higher in RPL cases compared to healthy participants. Similarly, LDL-c, Hemoglobin and RBC counts were significantly different between the two groups ( $p < 0.001$ ), with the case group (1.19 (1.00 – 3.20) mmol/L, 11.14 (8.6 – 13.7) g/dL, 3.09 ± 0.70 respectively) being lower compared to control women (1.83 (1.10 – 3.82) mmol/L, 12.17 (8.5 – 15.5) g/dL, 4.42 ± 0.57). CRP levels were not markedly altered (1.47 (0.10 – 4.60)) in some cases, while ESR values were greatly increased (10.11 (2.00 – 40.00)). Furthermore, albumin was significantly elevated in RPL cases ( $p < 0.001$ ) than in controls.

Table 3 illustrates haematological and biochemical indices for the RPL cases and control group. There is a significantly higher TG / Glucose and TG / HDL and HDL / LDL ratios in RPL cases than in control group ( $p < 0.001$ ). In contrast, CRP / Albumin ( $p$  adj = 0.002), NLR ( $p$  adj = 0.004), and Platelet /

**Table 3**

Haematological and biochemical indices for the RPL cases and control group

Index	RPL Cases	Controls	Z score	P	P <sub>adj</sub>
TG / Glucose	0.46 (0.23 – 0.92)	0.24 (0.11 – 0.70)	2.992	<0.001	<0.001
CRP / Albumin	0.025 (0.00 – 0.01)	0.043 (0.02 – 0.06)	-2.411	0.016	0.002
TG / HDL	1.28 (0.56 – 2.55)	0.98 (0.33 – 3.55)	1.958	0.011	<0.001
HDL / LDL	1.17 (0.47 – 1.80)	0.67 (0.24 – 2.18)	2.411	<0.001	<0.001
Neutrophil / Lymphocytes	1.88 (0.66 – 5.00)	2.12 (0.97 – 5.54)	-2.237	0.025	0.004
Platelet / Lymphocytes	7.43 (2.62 – 20.09)	8.94 (3.13 – 27.86)	-2.761	0.006	0.001

/ Lymphocytes (PLR) ( $p$  adj = 0.001) ratios were significantly lower in RPL cases than in control women (Table 3).

## Discussion

Many women worldwide experience repeated miscarriages, making it a significant global health concern [1], with half of its etiology remains poorly defined [6]. Recent consensus has been on linking RPL with a state of LGI [17]. This study furthers the understanding of the causes and risk factors of RPL in Kazakhstan, as no similar research has been done on women of specific geographical regions of Central Asia.

Results of this study demonstrate that glucose and cholesterol levels greatly vary ( $p$ -value < 0.001) between the two groups, prompting the speculation of altered metabolism in the etiology of RPL [18]. This was reminiscent of a prospective study on US women, which established hypercholesterolemia as a risk marker of RPL [19]. Despite RPL's association with inflammation being confirmed by many publications, according to Verit [16] and Yang [20], our results show unexpectedly decreased cholesterol levels in patients with RPL. The data obtained present a weak association of cholesterol with LGI and,

accordingly, RPL, suggesting that it cannot be a reliable source of biomarkers in diagnosing RPL.

The findings of altered HDL-c and LDL-c values in RPL appear contradictory to previous studies [16, 20], as we reported a higher median of HDL-c and decreased LDL-c in RPL patients. These diverges might be linked to diets, smoking, or medication intake that alters HDL-c and LDL-c values [21, 22]. Noteworthy, the RPL subjects' blood parameters specifically lowered Hemoglobin levels and RBC counts and increased TSH and TG values despite those parameters falling in the considered normal reference range [22–25]. Our study showed for the first time a significant range between groups for TSH in disagreement with TSH values established for Palestinian women, which are critical for normal embryonic and fetal development and overall healthy thyroid function, with negligible variations in RPL patients and control group [26].

The lack of differences in CRP values disagreed with studies done in the Netherlands [27] and Sweden [28], in which RPL women established significantly higher median CRP levels compared to healthy women. Despite previous studies evidencing elevated levels of CRP during normal pregnancy, and growing substantially in RPL cases [28] this study distinguishes by showing a weak association between CRP levels and RPL. However, consensus with this study was found in a study done in Turkey [15], claiming that there is no difference in CRP levels between groups. This study demonstrated opposite connotations probably due to the investigated study subjects' ethnic differences, because of the range in dietary patterns [29] and environmental exposures [30]. Also, as suggested by Guvey et al., (2021) the problem will be linked to some specific CRP genes that can cause RPL without increasing CRP values itself, because of this, there is a need to do a DNA test on CRP genes for further subsequent researches.

In a study done in China by Jiang et al., (2021) positive correlation was found between increased neutrophils, NLR, and RPL diagnosis, which was in line with our study [14]. In our study despite having negligible results ( $p=0.384$ ) between the two investigated groups neutrophil values' mean was higher in RPL cases. However, NLR failed to show the same results being increased in the control group. This prompts neutrophils' importance in the diagnosis of RPL.

Study strengths and limitations. This retrospective study was the first to examine to association of RPL and LGI based on specific blood parameters among Kazakh women by contributing valuable knowledge to the healthcare of Central Asia which is considered an under-represented population. This study expands, even more, the growing body of evidence in this explored link between RPL and LGI because it focuses on a new population and gives a chance to build up even more applicable associations for more clinical interventions to emerge. This study's findings will help to better understand the pathogenesis of RPL and other related disorders. Also will aid in emerging new clinical therapies as insightful information on cholesterol, CRP, neutrophil values, and other blood parameters was shown.

This study was limited by a lack of sample size and scarcity of the information available in Central Asia to make comparisons for a comprehensive understanding of the RPL. Furthermore, the retrospective nature of the study which relies on previously collected data and raises the possibility of bias in data selection as well as other confounding variables might also affect the results of this study. The study considered CBC test results only but for more understanding of the RPL, specifically one of the important biomarkers CRP and its gene polymorphisms, DNA test results should be included in future studies.

## Conclusion

This study examined Kazakh women's CBC blood parameters to assess the hypothesis stating that LGI is one of the contributing factors of RPL. However, the finding of this study established a weak association between inflammation markers such as cholesterol (including LDL-c and HDL-c), CRP, RBC, TSH, and RPL diagnosis, except for neutrophils which is in line with prior studies. Finally, well-designed clinical studies with a larger sample size are needed to gain a more comprehensive understanding of RPL and to identify new RPL biomarkers.

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**Ethical Considerations:** This study received approval from the Nazarbayev University Institutional Research Ethics Committee (NU-IREC) on 29/09/2022, #599/05092022. All study participants were informed about the study aims, methods, and potential risks and benefits. A consent form was introduced and taken from all study subjects of this research study.

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# Study of Anxiety Among Older People in Kazakhstan and Factors Affecting This Indicator

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## Abstract

**Aim:** The purpose of this research was to study of anxiety among older people in Kazakhstan and factors affecting this indicator.

**Methods:** A cross-sectional survey was conducted with 221 randomly selected elderly people from different regions of Kazakhstan. The survey covered questions of socio-demographic type and also used the GAD-7 (Generalized Anxiety Disorder-7).

**Results:** The majority of participants showed low levels of anxiety on the test. Nevertheless, a significant proportion of older adults experienced mild and moderate anxiety, accounting for 33% and 23.1%, respectively. The analysis showed that age (OR = 0,852, 95% CI: 0,779-0,931,  $p < 0,001$ ), gender (OR = 8,167, 95% CI: 3,232-20,642,  $p < 0,001$ ), level of education (OR=9,928, CI 95%: 3,760 - 26,212,  $p < 0,001$ ) and living conditions (OR=0,167, 95% CI: 0,060-0,467,  $p = 0,001$ ) have a statistically significant impact on the anxiety level of this population group.

**Conclusion:** The results of the analysis confirm the importance of developing and implementing a set of measures aimed at improving the quality of life of older people, taking into account the individual characteristics and needs of each person. The following measures can be suggested to improve the quality of life of older persons: organize social activity and community involvement programs through clubs and activities; establish accessible health and social service centers where older persons can receive qualified care; use technology, such as mobile applications and smart devices, to facilitate daily life, including telemedicine and home-based services.

**Keywords:** anxiety, older people, risk factors.

## Introduction

Aging is an inevitable process that occurs in all people. It is a natural stage of life during which various physical, psychological and social changes occur. Aging can be described as a gradual and irreversible decline in physical and mental abilities [1]. According to the World Health Organization (WHO), the proportion of people over the age of 65 in the world population is as high as 20%, with approximately 70% of them living in developing countries [2]. Older adults experience a gradual decline in organ function, leading to multiple chronic diseases such as cardiovascular disease (e.g., hypertension, coronary heart disease), skeletal diseases (e.g., arthritis, osteoporosis), and mental disorders (e.g., anxiety and depression) [3].

Although anxiety can occur at any age, it is particularly prevalent among older adults and has a greater impact on them. Older people are more likely to experience stress and anxiety due to loss or decline in self-esteem, decreased activity and stimulation, loss of close friends and relatives, loss of physical independence, chronic illness, changes in daily life or environment, fear of death and lack of social support [4]. More than 40 million adults in the United States suffer from anxiety disorders, which is a serious problem. In older adults, anxiety symptoms are common, especially in those with chronic diseases. The prevalence of anxiety symptoms in older adults is 15-52%, and anxiety disorders occur in 3-15% of adults. Anxiety in older adults can manifest with a variety of physical and

psychological symptoms such as insomnia, behavioral changes, sensory, urinary, cardiovascular, and gastrointestinal disorders. Anxiety is characterized by excessive worry and unrealistic fears about ordinary events. These symptoms can be present almost every day for long periods of time. Undetected and untreated anxiety can lead to decreased quality of life, increased disability, greater demand for medical care, and even increased mortality. Therefore, it is important to detect and treat anxiety in a timely manner to prevent such negative consequences [5].

In assessing anxiety levels, the use of the GAD-7 scale, Generalized Anxiety Disorder Screening, has shown high reliability and validity. It helps to identify potential cases of generalized anxiety disorder and to assess the severity of symptoms [6]. In their study, Shrestha S. et al. investigated the psychometric properties of common anxiety and worry assessment techniques among African American and Caucasian older adults living in low-income communities. The GAD-7 showed high convergent, discriminant, and predictive validity [7]. Researchers in Pakistan adapted the GAD-7 scale for use in primary health care settings. Principal component analysis confirmed the univariate structure of the scale explaining 64.8% of the variation. The total score showed a negative correlation with positive affect and life satisfaction, and a positive correlation with negative affect, indicating high validity. Cronbach's alpha was 0.92 and the split-half reliability was 0.82, confirming the high reliability of the instrument. Thus, the GAD-7 is an effective and concise tool for the diagnosis of anxiety disorders in primary care [8].

Older people may experience a gradual deterioration in their quality of life as they age. Quality of life can be described as a harmonious combination of the pleasures people enjoy in their daily lives, taking into account physical, psychological and social well-being. Improved well-being, the ability to carry out daily tasks and maintaining independence are all key components of a good quality of life for older people. Help and support for older people is therefore aimed at achieving this goal [9]. According to the Statistics Agency of the Republic of Kazakhstan, as of 2023, about 7.7% of the country's population is over 65 years of age, and this figure is expected to grow. Older people in Kazakhstan also face many stressors, including loneliness, financial difficulties and chronic diseases. However, there remains a significant gap in the scientific literature in understanding the specifics of anxiety among this group, as well as the factors contributing to its development. There are no accurate data on the prevalence of anxiety disorders among older people in Kazakhstan, and the factors that cause them remain poorly understood.

The study of anxiety among older adults represents an important field of research aimed at improving their quality of life, social adaptation and psychological well-being. Analyzing this phenomenon contributes to the development of effective strategies for the prevention and treatment of anxiety, which ultimately contributes to the comfort and satisfaction of older adults. In addition, the study of anxiety among this population allows the creation of support and adaptation programs that contribute to improving their lives, as well as the development of effective methods of psychological assistance for those who suffer from anxiety manifestations.

## Materials and methods

A cross-sectional study was conducted with voluntary participation of 221 older people from different regions

of Kazakhstan, including Southern, Northern, Western, Eastern and Central Kazakhstan. In some cases, relatives (close relatives) of older people helped them to complete the questionnaire. In the future, it is planned to conduct larger-scale studies involving a larger number of participants. The research design is a cross-sectional study.

Inclusion criteria:

- elderly people (60–74 years old);
- voluntary participation in the study;
- capable persons.

Exclusion criteria:

- refusal to participate in the study;
- presence of mental illness;
- people under 60 years of age and over 74 years of age.

The online platform Google Forms was used to conduct the survey. The link to the survey was distributed via social media. Participants were selected randomly, and the principle of 'Recommendations and Chains' was also applied: participants could recommend other suitable candidates to take part in the survey.

The survey covered questions of socio-demographic type and also used the GAD-7 Anxiety questionnaire.

The GAD-7 Anxiety Questionnaire is a widely used instrument with high reliability and validity, making it an effective tool for identifying and assessing the level of generalized anxiety disorder in people. The GAD-7 is a validated tool for diagnosing generalized anxiety disorder. The tool consists of only 7 questions, making it quick and easy to use. This is especially important for older adults who may have difficulty sustaining attention for long periods of time or become fatigued by long questionnaires. The questions in the GAD-7 are formulated in simple and clear language, which makes it easier for older people to complete them, and also facilitates interpretation of the results for both professionals and patients. The questions assess the frequency and degree of worry about various anxiety symptoms over the past two weeks. The results of the questionnaire help to assess the presence and degree of anxiety disorder in an individual. The GAD-7 anxiety severity score is calculated by assigning scores of 0, 1, 2, and 3 to the response categories 'not at all', 'some days', 'more than half of the days', and 'almost every day' respectively. The total GAD-7 score for the seven items ranges from 0 to 21. (Table 1) The interpretation of the results is as follows: 0–4 points – minimal anxiety; 5–9 points – mild anxiety; 10–14 points – moderate anxiety; 15–21 points – severe anxiety. Informed consent was obtained from the

**Table 1** GAD-7 Anxiety questionnaire

In the past two weeks, how often have you been bothered by any of the following prob-blems?	Not at all	For a few days	More than half the days	Almost every day
1. Feeling nervous, anx-ious or worried	0	1	2	3
2. Inability to stop or control anxiety	0	1	2	3
3. Too much anxiety about all sorts of things	0	1	2	3
4. Inability to relax	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Easily irritated or be-come irritable	0	1	2	3
7. A feeling of dread, as if something terrible might happen	0	1	2	3

study participants before conducting the study. Protection of personal data and confidentiality was guaranteed by the researchers. Descriptive statistics was used to analyse the data. Multinomial logistic regression analysis was conducted to determine the risk factors of anxiety in elderly people. Statistical analysis was performed using SPSS version 20.0 software (IBM Ireland Product Distribution Limited, Ireland). The level of statistical significance was set at  $p < 0.05$ .

## Results

A total of 221 elderly people participated in the study. The median age was 67 years [Q1-Q3=63–71 years]. Table 2 presents the socio-demographic characteristics of the study participants. The majority (63.8%) of them were women. More than half (58.4%) of the respondents had secondary specialised education. 74.7% of the elderly were married at the time of the study. The participants mostly lived with their family members and were retired. The results of the test are presented in Table 3. The median score obtained by participants when taking the GAD-7 Anxiety questionnaire was 5 points [Q1-

Q3=1–7 points]. The majority of participants showed low levels of anxiety on the test. Nevertheless, a significant proportion of older adults experienced mild and moderate anxiety, accounting for 33% and 23.1%, respectively. It is comforting to note that no severe anxiety was found among the respondents. Table 4 shows multinomial logistic regression using moderate anxiety as the control group. The results revealed that age, gender, education level and living conditions of the elderly were statistically significant influencing factors. A decrease in the probability of minimal anxiety compared to moderate anxiety (OR = 0.868, 95% CI: 0.798-0.948,  $p = 0.001$ ) and a decrease in the probability of mild anxiety compared to moderate anxiety (OR = 0.852, 95% CI: 0.779-0.931,  $p < 0.001$ ) was associated with increasing age. Men were significantly more likely to have minimal anxiety compared to moderate anxiety (OR = 8.167, 95% CI: 3.232–20.642,  $p < 0.001$ ). Compared to low anxiety, people with high levels of education were 9.928 times more likely to experience moderate anxiety (95% CI: 3.760 - 26.212,  $p < 0.001$ ). People living with family were 0.167 times less likely to develop moderate anxiety compared to mild anxiety (95% CI: 0.060–0.467,  $p = 0.001$ ).

## Discussion

The results of our study revealed that the majority of participants showed low levels of anxiety. Nevertheless, a part of the elderly people had insignificant or moderate levels of anxiety. The analysis showed that age, gender, level of education and living conditions have a statistically significant impact on the anxiety level of this population group. There is a higher predisposition to moderate anxiety among older adults with a high level of education compared to those with a lower level of education. This may be due to greater awareness of health and social changes that can cause stress and anxiety. In Kazakhstan, there are cultural and social stereotypes that influence the manifestation of anxiety in men. In traditional societies, men are most often associated with strength and resilience, which may lead to minimizing the expression of their feelings and anxiety. At the same time, living in a family environment reduces the likelihood of developing moderate anxiety among the Kazakh population. This may be due to the support and stability that family provides, which is especially important in line with Kazakhstan's cultural traditions, where family values play a key role.

A study by Chinese scientists found that anxiety is a common problem among the elderly, with 30.11% of patients showing symptoms related to anxiety. However, anxiety levels varied according to multiple factors including gender, education level, occupation, place of residence, marital status and income. Interestingly, age had no effect on the development of anxiety disorders. Multiple regression analysis revealed that

**Table 2** Characterisation of respondents

Variabes		n (%)
gender	male	80 (36,2)
	female	141 (63,8)
education	higher	92 (41,6)
	specialised secondary	129 (58,4)
marital status	married	165 (74,7)
	divorced	9 (4,1)
	widow/widower	47 (21,3)
living conditions	with the family	187 (84,6)
	alone	34 (15,4)
occupancy	work	19 (8,6)
	retiree	202 (91,4)

**Table 3** Interpretation of the results of the GAD-7 Anxiety questionnaire

Score	The severity of the anxiety	n (%)
0–4 score	minimal anxiety	97 (43,9)
5–9 score	mild anxiety	73 (33,0)
10–14 score	moderate anxiety	51 (23,1)
15–21 score	severe anxiety	-

**Table 4** Multinomial logistic regression

Variables		Minimal anxiety VS moderate anxiety				Mild anxiety VS moderate anxiety			
		Odds ratio	Standard error	p	95%CI	Odds ratio	Standard error	p	95%CI
age		0,868	0,043	0,001	0,798-0,948	0,852	0,046	0,000	0,779-0,931
gender	male	8,167	0,473	0,000	3,232-20,642	0,992	0,564	0,988	0,328-2,997
	female								
education	higher	1,415	0,448	0,439	0,588-3,404	9,928	0,495	0,000	3,760-26,212
	specialised secondary								
living conditions	with the family	4,551	0,821	0,065	0,911-22,734	0,167	0,525	0,001	0,060-0,467
	alone								

patients with depression, loneliness, and cognitive impairment, as well as women living in rural areas or living alone, were at increased risk of developing anxiety disorders [10]. Our study also found that a significant proportion of elderly individuals experience varying degrees of anxiety. Mild anxiety was diagnosed in 33% of the participants, while moderate anxiety was observed in 23.1% of them. In addition, factors such as age, gender, level of education and living conditions were found to have a statistically significant effect on the level of anxiety in older adults. Gender differences in the perception and expression of emotions affect anxiety levels, with women being more likely to suffer from anxiety disorders, which may be related to culture, family and social roles. Women working in low-paid and unstable jobs may experience higher levels of anxiety due to financial hardship. In addition, socioeconomic factors such as income and employment levels may also interact with gender and education to create anxiety problems. Thus, in order to better understand anxiety in Kazakhstan, it is important to consider the complex interaction of gender, education and socioeconomic factors, which will allow for the development of more effective strategies to support the mental health of the population.

During a study by Canadian scientists, 16.4 per cent of respondents reported experiencing chronic anxiety symptoms. Women were found to be more likely to experience these symptoms [11]. During our study, it was revealed that 23.1 per cent of the studied elderly individuals have moderate anxiety. It was found out that the gender factor influences the level of anxiety conditions.

Socio-demographic risk factors for anxiety in older adults may include aspects such as age, gender, education level, marital status, social relations, financial status, and others. Some of these factors may increase the risk of developing anxiety disorders in older adults [12]. With age, the risk of anxiety disorders in older adults may increase due to physical and cognitive changes associated with aging. Women tend to be more prone to anxiety disorders than men. This may be due to differences in hormones, social expectations, and stressful situations that women face. People with lower levels of education may be more at risk for developing anxiety disorders, as they may have fewer resources to cope with stress and other life challenges [13]. Older people who live alone or have lost loved ones may be more at risk of anxiety disorders due to lack of social support and isolation. Older people with limited socialisation and social connections may be more at risk of anxiety disorders. Lack of social support and low self-esteem can also contribute to the development of anxiety disorders. People with low income or financial difficulties may be more at risk for anxiety disorders because they may experience increased levels of stress due to financial problems. Older adults with chronic illnesses or limited mobility may be more at risk for anxiety disorders because of physical and emotional difficulties related to their health conditions [14]. Older adults may experience problems with memory and cognitive function, which can cause anxiety and restlessness [15]. To cope with anxiety in older people, it is important to seek the help of professionals such as doctors, psychologists or social workers who can offer support and treatment and help find solutions to the problems causing the anxiety [16].

Anxiety, according to scientific research, is an emotional and behavioural state characterised by feelings of worry, fear and anxiety. It can be a normal response to stressful situations or a symptom of anxiety disorders such as generalised anxiety

disorder, sociophobia, panic attacks, etc. [17]. Anxiety can be caused by a variety of factors including genetic, biological, psychological and social factors. Studies show that anxiety is associated with brain dysfunction, particularly in areas responsible for processing emotions, such as the limbic system and prefrontal cortex [18].

Anxiety prevention in older adults may include the following: physical activity, balanced nutrition, social interaction, fun and hobbies, meditation and relaxation, healthy sleep, and professional help. Physical activity, including regular exercise such as walking, yoga or aerobics, helps to improve mood and reduce anxiety levels [19]. A balanced diet that includes plenty of fruit, vegetables, whole-grain foods and healthy fats helps to maintain physical and emotional well-being. Social interaction, such as participation in communities, clubs or interest groups, can help older people feel accepted and supported, which in turn reduces anxiety levels. Engaging in recreational activities and hobbies can also bring happiness and fulfilment, thereby reducing anxiety. Practicing meditation, breathing exercises or other relaxation techniques can help in reducing stress and anxiety. Improving sleep patterns, including observing proper rest and wake-up times, also helps to reduce anxiety. If anxiety is significantly affecting quality of life, seeing a psychologist or psychiatrist for professional help and support is appropriate [20].

Understanding the causes and consequences of anxiety among older people provides an opportunity to create more effective approaches to support and therapy, thereby improving the quality of life of this age group. Anxiety can have adverse effects on the physical and mental well-being of older people, including weakening of the immune system, increased risk of cardiovascular problems and other somatic diseases. Therefore, it is crucial to develop prevention and treatment methods for anxiety disorders to improve health outcomes in this population. Anxiety can lead to social isolation and restricted activity in older adults, which in turn can exacerbate anxiety symptoms and reduce quality of life. Consequently, studying this phenomenon is important for developing strategies to prevent social isolation and promote activity. Anxiety in older people can lead to increased costs of health care and social services, placing an additional financial burden on the health care system and society as a whole. Therefore, the study and prevention of anxiety is key to reducing these costs [21].

Kazakhstan, like many other countries, faces the problem of population ageing. The increasing proportion of older people in the total population leads to an increase in the incidence of anxiety and other mental disorders among older people. The unstable economic situation and low level of pension provision can cause anxiety and worry among older persons, especially if they are dependent on pensions and social benefits. Many older people have little understanding of mental health problems and how to deal with them. In addition, limited access to qualified health care can exacerbate anxiety. In order to solve the problem of anxiety in older people in Kazakhstan, it is necessary to develop comprehensive measures aimed at improving social support, ensuring access to medical care, increasing the level of pension provision and conducting awareness-raising work among the population.

In the context of existing research, the following directions should be emphasized for future research on anxiety levels in older adults: studying the impact of social connections, loneliness and support from family and friends, various methods of psychotherapy, regular physical exercise,



chronic diseases, culture, region, evaluating the effectiveness of digital technologies (e.g., mobile applications, telemedicine), various forms of leisure activities, polypharmacotherapy. All this will allow us to further explore the problem of anxiety emergence in the elderly. The problem of anxiety in the elderly requires intervention at the government level, as this population often faces isolation, loss of loved ones and deteriorating health, which significantly affects their psycho-emotional state. Consequently, comprehensive measures are needed to improve the quality of life of the older generation and reduce anxiety levels. To realize the reduction of anxiety level in the elderly in practice:

1. To develop at the state level free hotlines and support groups for older people where they could get counseling and assistance.

2. Upgrading the skills of health care providers and social services on aging and mental health so that they can at the outpatient level in a timely and correctly identify and treat anxiety disorders.

3. Providing activities and courses that encourage older people to be socially active and interact with the community (e.g. hobby clubs), which requires developing accessible and diverse programs, engaging volunteers and active participants, and conducting information campaigns to raise awareness of opportunities.

4. Facilitating the process of getting help from psychiatrists and psychologists, including telemedicine. Telemedicine allows older people to receive care from home. Conduct seminars and trainings for older people and their families on the use of technology for telemedicine consultations. It is equally important to create accessible information materials (booklets, websites) about mental health and opportunities for help, including contact information of specialists. The use of technology to monitor the mental state of older people will allow timely response to their needs.

5. Increasing awareness of mental health issues among older adults and their families through information about available resources and support.

All of these measures will help to create a supportive environment for older adults, reduce anxiety and improve their overall psycho-emotional well-being.

Our study had some limitations. Firstly, as this was a cross-sectional study, the causality between compared variables cannot be established. Secondly, the surveyed population in this study was relatively small. Also unknown and unmeasured confounders may exist, and the results should be interpreted with caution. Despite these limitations, it is the first study in Kazakhstan where we analyzed anxiety among older people using the valid instruments as GAD-7 scale.

## Conclusion

Multinomial logistic analysis revealed the main correlations between these factors and the level of anxiety in the subjects. The results of the analysis confirm the importance of developing and implementing a set of measures aimed at improving the quality of life of older people, taking into account the individual characteristics and needs of each person, for the realization of which the following specific steps can be proposed:

1. Conduct focus groups and in-depth interviews with older adults to understand their experiences and perceptions of anxiety, which will help supplement quantitative data with qualitative information.

2. Based on the findings, create programs to reduce anxiety such as support groups, stress management courses, and psycho-emotional counseling.

3. Organize trainings for social workers, psychologists, and physicians on working with older adults, including anxiety and stress management techniques.

4. Establish a monitoring system to evaluate the effectiveness of intervention programs and conduct regular measurements of anxiety levels among the elderly to track changes over time.

5. Conduct information campaigns to raise awareness about anxiety among older adults, their needs, and the importance of mental health in the community.

6. Develop an online platform to share expertise and resources among professionals working with older adults, which can help to better understand and support this population.

Thus, the study of anxiety among elderly residents of Kazakhstan requires intervention at the government level and showed that risk factors such as age, gender, level of education and living conditions play a significant role in the development of anxiety disorders in this population group.

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# Predictors of All-cause Mortality among Hospitalized HIV Patients in Kazakhstan: a Retrospective Study

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## Abstract

**Aim:** This paper examines the predictors of all-cause mortality among hospitalized HIV-positive patients in Kazakhstan.

**Material and methods:** The study uses baseline data from patient hospital discharge records derived from the Unified Electronic Healthcare System of Kazakhstan (UNEHS) between 2014 and 2019. Artificial intelligence technology was utilized to extract data from the discharge records. Patients were included based on their first hospitalization, and they were subsequently monitored until their discharge or occurrence of death.

**Results:** The study revealed that females had a 2.06-fold higher risk of all-cause mortality compared to males. After adjustments in the Cox proportional hazard model, age, intravenous drug use (IDU), and anemia were observed as independent predictors of mortality within the patient cohort.

**Conclusions:** Findings of this study emphasize the need to enhance efforts to prevent late HIV diagnosis by improving access to testing and treatment for those affected, and to strengthen potential for developing risk factors reduction strategies.

**Keywords:** HIV, predictors of mortality, all-cause mortality, comorbidity, regression analysis.

## Introduction

Human Immunodeficiency Virus (HIV), which is responsible for Acquired Immune Deficiency Syndrome (AIDS), is a threatening communicable zoonotic infection with profound social consequences [1]. An estimated 38 million people are living with HIV, with 1.7 million new HIV infections, and 690,000 deaths associated with AIDS [2]. Although HIV infection is preventable, significant HIV transmission continues across the world.

Despite recent improvements in health care as a result of government policy reforms, Kazakhstani health care facilities still face challenges in treating blood-borne infections such as HIV/AIDS, tuberculosis and other similar diseases [3]. According to UNAIDS (2019), the number of new HIV infections in Kazakhstan has increased by 39% since 2010 [4]. It was also forecasted that the prevalence of HIV infection in Kazakhstan will double from 2021 by 2030 [5]. Given

the rising incidence of newly contracted HIV cases and predicted prevalence of the disease in the future, it is essential to accurately assess the current situation and the real magnitude of the HIV epidemic in Kazakhstan. This evaluation is necessary to implement public health procedures that can effectively prevent and control the anticipated spread of HIV infection.

When focusing on data collection from HIV patients, it becomes imperative to trace the relationship between mortality and associated factors of patients, which predominantly stem studies conducted in developed nations, leaving a significant data gap in developing countries. Especially, demographic, behavioral, clinical, and laboratory data obtained at hospital admission engage significant attention as independent predictors of adverse outcomes, given their accessibility and potential for developing strategies for risk factor reduction that may have an impact on mortality rates. Consequently, despite existing research

on demographic determinants and the impact of concurrent illnesses on HIV mortality, this research represents the first effort to highlight the significance of clinical and laboratory data sourced from patients within the Unified National Electronic Health System (UNEHS) system to establish their association with mortality rates in Kazakhstan.

Hence, the objective of this retrospective cohort study is to discern predictors of mortality in patients with HIV admitted to tertiary care hospitals between 2014 and 2019, utilizing comprehensive patient-level clinical data.

## Methodology

### *Study design*

This retrospective study utilized hospital admission data from HIV-positive individuals between January 1, 2014, and December 31, 2019, obtained from the UNEHS database in Kazakhstan. A total of 152 medical discharges were analyzed with the assistance of a custom-designed data mining application using artificial intelligence. To eliminate risk of inaccurate data, the information extracted by the AI application underwent additional manual verification. The dataset included information on demographic characteristics, clinical findings upon admission, laboratory test results (general blood testing and biochemical blood testing), comorbidities, behavioral factors, and outcomes. Age was categorized into four categories: <18 years, 18–34 years, 35–50 years, and >50 years. Ethnicity was categorized into Kazakhs, Russians, and others (including 11 ethnicities). Laboratory data, including, but not limited to, hemoglobin, red blood cells (RBC), leukocytes (WBC), platelets (PLT), erythrocyte sedimentation rate (ESR), bilirubin, albumen, urea, creatinine, and cholesterol were gathered within the first day of admission. Quantitative variables were analyzed using interval scales, whereas qualitative variables were categorized as binary (yes/no).

Additionally, to evaluate all-cause mortality, we incorporated data on deaths occurring outside the hospital for the same 152 patients up to the conclusion of 2023, with any additional observations beyond these parameters excluded from the analysis. Duplicate entries were eliminated by employing the unique population registry ID (RPN ID) utilized in the UNEHS registry, confirming that every patient was included in the analysis once.

### *Study population*

The cohort consisted of patients recognized according to the following ICD-11 (The International Classification of Diseases, 11th revision) codes: B20.0 (HIV disease resulting in mycobacterial infection), B20.1 (HIV disease resulting in other bacterial infections), B20.3 (HIV disease resulting in other viral infections), B20.8 (HIV disease resulting in other infectious and parasitic diseases), and B20.9 (HIV disease resulting in unspecified infectious or parasitic disease). Patients were included based on their first hospitalization, and they were subsequently monitored until their discharge or occurrence of death.

### *Statistical analysis*

Statistical analysis, data cleaning and data management were conducted using Stata SE 18.0 version. Data analysis (percentage for categorical variables and mean  $\pm$  standard deviation (SD) or median (interquartile range – IQR) for continuous variables) were performed to describe the

characteristics of the research population. The cohort was categorized into two groups as alive and dead patients. Two-sided t-tests for parametric and Mann-Whitney U tests for non-parametric data were implemented for comparison of means. Pearson's chi-square and Fisher's exact tests were used to compare proportions.

For all-cause mortality risk assessment of hospitalized HIV patients, the Cox proportional hazard regression analysis was performed to evaluate unadjusted (univariable) and adjusted (multivariable) hazard functions. The potential confounders introduced in the multivariable-adjusted model were derived from data availability in the cohort and theoretical considerations based on the statistical significance of unadjusted analysis. These are the models of multivariate Cox regression analysis: Model 1: age, gender, ethnicity, intravenous drug use (IDU); Model 2: in addition to variables from model 1 contained laboratory data as ESR and anemia; Model 3: in addition to variables from model 2 contained bilirubin and creatinine. The Kaplan-Meier survival function with log-rank test for statistical significance was used to estimate survival probabilities among hospitalized HIV patients.

Proportional hazards assumptions were tested using Schoenfeld residuals, Akaike's (AIC) and Schwarz's Bayesian (BIC) information criteria. Magnitude of hazard ratios (HR) and the width of their 95% confidence intervals (CI) were evaluated to determine the statistical and clinical significance of the associations. P-value are two-sided and reported as significant at <0.05 for all analyses.

## Results

Table 1 illustrates the socio-demographic, clinical, laboratorial, and behavioral characteristics along with immunology data, comorbidities, and outcomes by death in the hospitalized HIV cohort. The cohort included 152 patients diagnosed with HIV in their first hospital admissions over a 6-year period (2014–2019). There were 77 alive patients (50.7%) and 75 deceased patients (49.3%). 67.1% of the cohort (n = 102) were women (p = 0.041). The median age of hospitalized HIV patients was 31 years (IQR 12–39; p < 0.0001). 67 people (44.1%) of the cohort were young, aged <18 years. Nearly half (45.3%) of the cohort within the age range of 35–44 years experienced death. The majority of HIV-infected patients (47.0%) were ethnic Kazakhs (n = 71).

The mean heart rate for cohort was observed to be 97.8 $\pm$ 15.7 bpm (p = 0.039). Upon admission, non-survivors had lower levels of hemoglobin, lymphocytes, and monocytes count, alongside elevated erythrocyte sedimentation rate (ESR). Moreover, the deceased patients had significantly abnormal urea parameter. Regarding albumin and cholesterol levels, deceased individuals had lower values compared to alive patients. A comparable pattern was witnessed for CD4 cells. The cohort analysis displayed a median CD4+ T lymphocyte count of 540 cells/mm<sup>3</sup> (IQR 220–844), while the median CD4 cells count in deceased patients was almost 5 times lower (p < 0.0001).

More non-survivors had tachycardia, cholecystitis, unspecified operations, cachexia, and meningitis. Nearly 55% of deceased patients (n = 41) had viral hepatitis C (p = 0.001). No significant results were identified for diffuse liver change, cirrhosis, oral candidiasis, viral hepatitis B, and anemia. Concerning behavioral factors, 44.0% (n = 33) of deceased patients reported alcohol abuse, 35 (46.7%) reported intravenous

Table 1

## Demographic data

Characteristic	Total (n=152)	Alive (n=77)	Dead (n=75)	P value
Age, year (median [IQR])	31 [12–39]	12 [11–14]	38 [32–44]	p < 0.0001
< 18	67 (44.1)	61 (79.2)	6 (8.00)	
18–34	25 (16.5)	6 (7.80)	19 (25.3)	
35–44	41 (27.0)	7 (9.10)	34 (45.3)	
45–50	12 (7.90)	1 (1.30)	11 (14.7)	
> 50	7 (4.50)	2 (2.60)	5 (6.70)	
Gender, n (%)				0.041
Male,	50 (32.9)	33 (42.9)	17 (22.7)	
Female,	102 (67.1)	44 (57.1)	58 (77.3)	0.001
Ethnicity, n (%)				
Kazakh	71 (47.0)	43 (55.8)	28 (37.8)	
Russian	46 (30.5)	20 (26.0)	26 (35.1)	
Other	35 (22.5)	14 (18.2)	20 (27.1)	
Clinical findings at admission				
Heart rate bpm (mean ± SD)	97.8±15.7	93.2±15.6	99.1±15.6	0.039
General blood analysis				
Haemoglobin g/L (median [IQR])	115 [94.0–126]	122 [115–129]	98.0 [81.0–115]	p < 0.0001
RBC × 10 <sup>12</sup> /L (mean ± SD)	3.65±0.82	3.84±0.68	3.44±0.93	0.002
WBC × 10 <sup>9</sup> /L (median [IQR])	6.30 [4.50–8.90]	6.10 [4.60–7.80]	7.00 [4.40–10.4]	0.169
PLT × 10 <sup>2</sup> /L (mean ± SD)	266±117	301±92.7	219±130	0.142
Lymphocytes % (median [IQR])	27.0 [13.0–43.0]	35.0 [24.0–45.0]	18.0 [9.00–30.0]	0.004
Neutrophils % (median [IQR])	56.5 [45.0–74.0]	36.3 [34.5–37.8]	38.0 [32.0–57.0]	0.039
NLR (median [IQR])	1.90 [1.00–4.20]	1.60 [1.00–2.67]	4.49 [1.14–9.86]	0.030
Monocytes % (median [IQR])	8.00 [4.10–10.0]	10.0 [7.00–11.0]	5.00 [3.00–7.50]	p < 0.0001
Eosinophils % (median [IQR])	2.00 [1.00–2.00]	2.00 [1.00–2.00]	2.00 [1.00–5.00]	0.034
ESR mm/hour (median [IQR])	33.0 [15.0–54.0]	20.0 [9.50–32.5]	52.0 [35.0–64.0]	p < 0.0001
Blood chemistry				
Bilirubin µmol/L (median [IQR])	10.7 [7.00–15.7]	9.40 [6.75–13.2]	12.0 [7.20–17.9]	0.141
Total protein g/L (median [IQR])	68.3 [61.6–74.0]	69.1 [65.5–73.8]	67.4 [58.0–74.0]	0.051
Albumin g/L (mean ± SD)	40.3±9.19	41.7±6.30	35.8±14.7	p < 0.0001
Urea µmol/L (median [IQR])	4.10 [3.30–5.74]	3.82 [2.90–4.50]	5.00 [3.56–8.64]	p < 0.0001
Creatinine µmol/L (median [IQR])	61.0 [45.5–85.0]	56.0 [45.0–64.0]	79.2 [49.5–120]	0.062
Cholesterol µmol/L (mean ± SD)	3.65±1.20	3.86±0.96	3.20±1.51	0.0122
Triglyceride µmol/L (median [IQR])	1.10 [0.80–1.82]	1.10 [0.78–1.57]	1.45 [0.99–2.44]	0.135
Immunology				
CD4 cells/mm <sup>3</sup> (median [IQR])	540 [220–844]	664 [483–911]	118 [45.0–504]	p < 0.0001
CD8 cells/mm <sup>3</sup> (median [IQR])	640 [466–856]	652 [534–1021]	639 [377–856]	0.637
CD3 cells/mm <sup>3</sup> (median [IQR])	1618 [934–2226]	2103 [1610–2387]	934 [758–1320]	0.157
PTI % (mean ± SD)	80.4±22.9	112±15.1	76.3±20.5	0.766
Fibrinogen g/L (median [IQR])	3.40 [3.10–4.68]	4.80 [2.50–7.10]	3.40 [3.10–4.64]	0.511
Comorbidities				
Tachycardia, n (%)	54 (35.5)	19 (24.7)	35 (46.7)	p < 0.0001
Diffuse liver change, n (%)	69 (45.4)	35 (45.5)	34 (45.3)	0.046
Cirrhosis, n (%)	11 (7.24)	4 (5.19)	7 (9.33)	0.279
Cholecystitis, n (%)	37 (24.3)	16 (20.8)	21 (28.6)	p < 0.0001
Pancreatitis, n (%)	37 (24.3)	13 (16.8)	24 (32.0)	0.007
Oral candidiasis, n (%)	31 (20.4)	17 (22.1)	14 (18.7)	0.857
Hepatitis C, n (%)	63 (41.5)	22 (28.6)	41 (54.7)	0.001
Hepatitis B, n (%)	17 (11.2)	7 (9.09)	10 (13.3)	0.322
Any surgery, n (%)	22 (14.6)	3 (3.95)	19 (25.3)	0.002
Cachexia, n (%)	48 (31.6)	9 (11.7)	39 (52.0)	p < 0.0001
Meningitis, n (%)	11 (7.24)	2 (2.60)	9 (12.0)	0.002
Anemia	106 (70.2)	52 (67.5)	54 (73.0)	0.249
Behavioural factors				
Alcohol abuse, n (%)	40 (26.3)	7 (9.09)	33 (44.0)	p < 0.0001
IDU, n (%)	39 (25.7)	4 (5.19)	35 (46.7)	p < 0.0001
Smoking, n (%)	47 (30.9)	10 (13.0)	37 (49.3)	p < 0.0001
Outcomes				
Hospital stay duration, day median [IQR]	11 (8–19)	11 (9–16)	10 (5–32)	0.100
Years of illness, years median [IQR]	8 (2–10)	9 (4–10)	2 (0–5)	p < 0.0001

ESR – Erythrocytes sedimentation rate; IDU – Intravenous drug abuse; NLR – Neutrophils-to-lymphocytes ratio; PLT – platelets; PTI – Prothrombin index; RBC – Red blood cells; WBC – White blood cell.

Table 2

The association between demographic, clinical, laboratory, behavioral related variable and risk of all-cause mortality using unadjusted Cox proportional hazard model

Characteristics	Number of observations / number of deaths	Unadjusted HR [95% CI]	P value
Age+5	152 / 75	1.42 [1.30; 1.55]	<0.0001
Gender			
Male		ref	
Female	102 / 58	2.06 [1.11; 3.80]	0.021
Ethnicity			
Kazakhs		ref	
Russians	46 / 26	1.36 [0.74; 2.49]	0.088
Others	34 / 20	1.71 [0.92; 3.17]	0.324
Tachycardia	54 / 35	2.23 [1.35; 3.68]	0.002
Diffuse liver change	69 / 34	0.83 [0.50; 1.38]	0.470
Cirrhosis	11 / 7	2.89 [1.37; 6.09]	0.005
Cholecystitis	37 / 21	1.19 [0.68; 2.09]	0.544
Pancreatitis	37 / 24	1.72 [1.01; 2.93]	0.044
Oral candidiasis	31 / 14	1.34 [0.75; 2.40]	0.327
Non-hepatitis C		ref	
Hepatitis C	63 / 41	3.66 [2.14; 6.26]	<0.0001
Hepatitis B	17 / 10	2.63 [1.42; 4.86]	0.002
Any surgery	22 / 19	3.90 [2.23; 6.81]	<0.0001
Non-cachexia		ref	
Cachexia	48 / 39	5.65 [3.35; 9.54]	<0.0001
Meningitis	11 / 9	1.53 [0.66; 3.56]	0.321
Anaemia	106 / 54	2.52 [1.28; 4.98]	0.008
Non-alcohol abuse		ref	
Alcohol abuse	40 / 33	3.11 [1.87; 5.16]	<0.0001
Non-IDU		ref	
IDU	39 / 35	5.70 [3.41; 9.51]	<0.0001
Non-smoking		ref	
Smoking	47 / 37	3.30 [1.99; 5.49]	<0.0001
Haemoglobin <sup>10</sup>	146 / 75	1.52 [1.37; 1.69]	<0.0001
WBC	150 / 73	1.03 [0.99; 1.06]	0.143
PLT <sup>50</sup>	122 / 70	1.46 [1.25; 1.71]	<0.0001
Lymphocytes	134 / 75	0.97 [0.95; 0.99]	0.002
Neutrophils <sup>5</sup>	102 / 36	1.17 [1.05; 1.30]	0.004
NLR <sup>2</sup>	102 / 57	1.15 [1.08; 1.22]	<0.0001
Monocytes	135 / 60	1.00 [0.99; 1.02]	0.611
Eosinophils	112 / 66	1.11 [1.03; 1.19]	0.004
ESR <sup>10</sup>	149 / 73	1.42 [1.26; 1.60]	<0.0001
Bilirubin	140 / 72	1.01 [1.00; 1.01]	0.011
Total protein	138 / 72	0.99 [0.97; 1.02]	0.470
Albumin	55 / 42	0.89 [0.81; 0.96]	0.004
Urea <sup>5</sup>	136 / 72	1.49 [1.21; 1.84]	<0.0001
Creatinine <sup>20</sup>	107 / 45	1.05 [1.02; 1.09]	0.005
Cholesterol <sup>2</sup>	84 / 57	4.67 [1.95; 11.16]	0.001
Triglyceride	55 / 41	1.97 [1.00; 3.87]	0.050
CD4 <sup>100</sup>	87 / 63	1.84 [1.38; 2.47]	<0.0001
Hospital stay duration	152 / 75	1.00 [1.00; 1.01]	0.447
Years of illness	109 / 40	0.89 [0.81; 0.97]	0.009

ESR – Erythrocytes sedimentation rate; IDU – intravenous drug abuse; NLR – Neutrophils-to-lymphocytes ratio; PLT – platelets; WBC – White blood cell.

drug use (IDU) and 37 (49.3%) dead patients smoked ( $p < 0.0001$ ). The median duration of the disease from first diagnosis to death was 8 years. (IQR 2–10;  $p < 0.0001$ ), with deceased patients having a significantly shorter length of illness.

Table 2 shows the association of socio-demographic, clinical, laboratorial, and behavioral characteristics along with

immunology data, comorbidities, and outcomes with all-cause mortality in the unadjusted Cox proportional regression analysis. Every 5-year increment in age was linked to a 42% increase in the hazard of death (Undj. HR 1.42; 95% CI 1.30–1.55;  $p < 0.0001$ ). Moreover, females had a 2.06-fold increased risk of experiencing death in comparison to males (95% CI 1.11–3.80;  $p = 0.021$ ). Patients with tachycardia had 2.23-fold higher hazard of death (95% CI 1.35–3.68;  $p = 0.002$ ). Similarly, hospitalized HIV-positive patients with viral hepatitis B, cirrhosis, and anemia had high hazard ratios of 2.63 (95% CI 1.42–4.86;  $p = 0.002$ ), 2.89 (95% CI 1.37–6.09;  $p = 0.005$ ), and 2.52 (95% CI 1.28–4.98;  $p = 0.008$ ), respectively. Whereas people coinfecting with diffuse liver change, cholecystitis, pancreatitis, and oral candidiasis showed non-significant results. Each decrement in hemoglobin for 10 g/L was associated with a 52% unadjusted greater risk of all-cause mortality (Undj. HR 1.52; 95% CI 1.37–1.69;  $p < 0.0001$ ). Oppositely, increase of neutrophils by 5% raised risk of all-cause mortality by 17% (Undj. HR = 1.17; 95% CI 1.05–1.30;  $p = 0.004$ ). Every 2 increment in neutrophil-to-lymphocyte ratio (NLR) was associated with 15% greater hazard of death (Undj. HR 1.15; 95% CI 1.08–1.22;  $p < 0.0001$ ). Moreover, with each additional increase of 10 mm/hour in ESR, the risk of all-cause mortality was raised by 42% (Undj. HR 1.42; 95% CI 1.26–1.60;  $p < 0.0001$ ). Elevated by 5  $\mu\text{mol/L}$  urea (Undj. HR 1.49; 95% CI 1.21–1.84;  $p < 0.0001$ ) and reduced by 100 cells/mm<sup>3</sup> CD4 (Undj. HR 1.84; 95% CI 1.38–2.47;  $p < 0.0001$ ) also increase hazard of death. Furthermore, each decrement in cholesterol for 2  $\mu\text{mol/L}$  was associated with almost 5-fold increase hazard of death (Undj. HR 4.67; 95% CI 1.95–11.16;  $p < 0.0001$ ). With each 20  $\mu\text{mol/L}$  increase in creatinine, there was corresponding 5% rise in the hazard of death (Undj. HR 1.05; 95% CI 1.02–1.09;  $p = 0.005$ ).

In Kaplan-Meier survival analysis, patients diagnosed with viral hepatitis C had almost 4 times lower probability of survival (Undj. HR = 3.66; 95% CI 2.14–6.26;  $p < 0.0001$ ), compared with patients without viral hepatitis C (Figure 1).

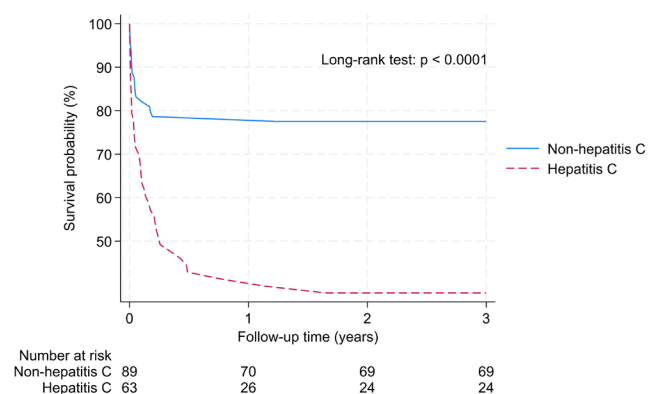
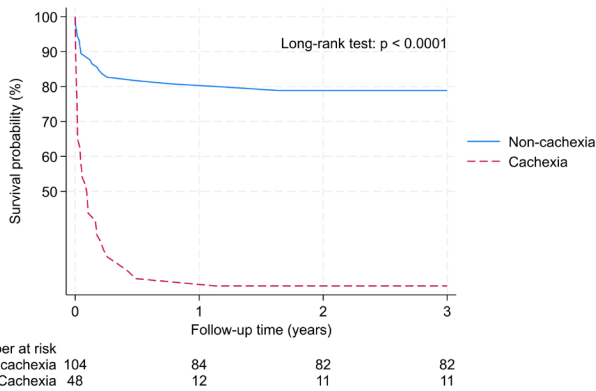
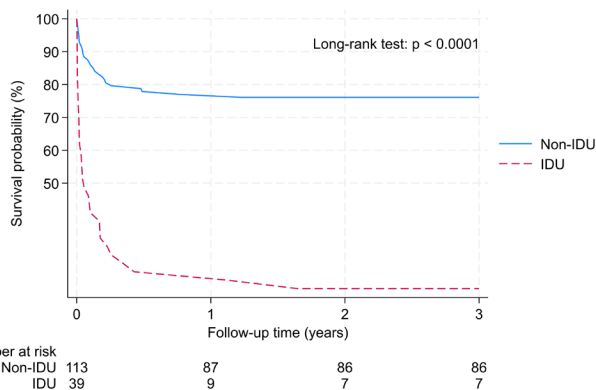


Figure 1 – Kaplan-Meier survival analysis among HIV-positive patients adjusted for viral hepatitis C

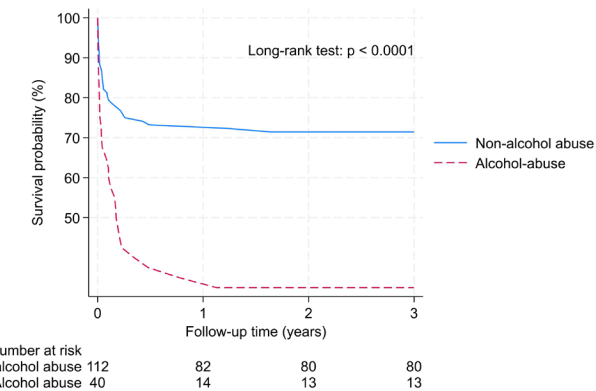
Patients with cachexia had almost 6 times higher hazard of death (Undj. HR = 5.65; 95% CI 3.35–9.54;  $p < 0.0001$ ) in comparison to those patients without cachexia (Figure 2). Figure 3 shows that individuals with IDU had a 5.7-fold higher risk of dying than those who did not report IDU (Undj. HR = 5.70; 95% CI 3.41–9.51;  $p < 0.0001$ ). Finally, patients with such behavioral characteristics as alcohol abuse and smoking showed 3 times decreased survival probability (Undj. HR = 3.11; 95% CI 1.87–5.16;  $p < 0.0001$ , and Undj. HR = 3.30; 95% CI 1.99–5.49;



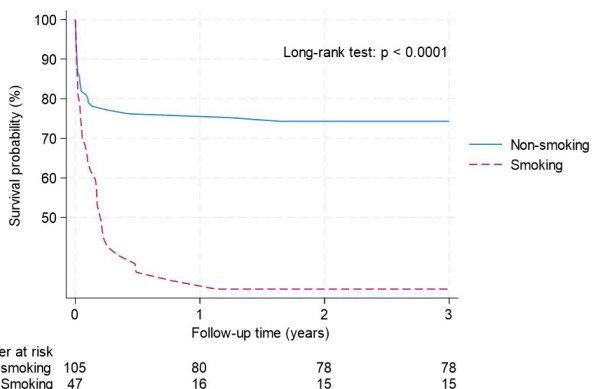
**Figure 2** – Kaplan-Meier survival analysis among HIV-positive patients adjusted for cachexia



**Figure 3** – Kaplan-Meier survival analysis among HIV-positive patients adjusted for intravenous drug use (IDU)



**Figure 4** – Kaplan-Meier survival analysis among HIV-positive patients adjusted for alcohol abuse



**Figure 5** – Kaplan-Meier survival analysis among HIV-positive patients adjusted for smoking

$p < 0.0001$ , respectively) when compared with HIV patients without those habits (Figure 4 and Figure 5).

Following adjustments in the Cox proportional hazard regression model (as shown in Table 3), age+5 (Model 3: HR 1.35; 95% CI 1.17–1.57;  $p < 0.0001$ ), IDU (Model 3: HR 1.90; 95% CI 1.83–10.23;  $p = 0.001$ ), and anemia (Model 3: HR 2.50; 95% CI 1.63–13.36;  $p = 0.004$ ) remained as independent predictors of all-cause mortality across Models 1, 2, and 3. The greatest risk of death was associated with the IDU.

**Table 3**

The association between demographic, clinical, laboratory, behavioral related variable and risk of all-cause mortality using adjusted Cox proportional hazard model

Cova-riates	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value	Model 3 HR (95% CI)	P value
Age <sup>+5</sup>	1.37 [1.24–1.51]	< 0.0001	1.37 [1.21–1.55]	< 0.0001	1.28 [1.10–1.50]	0.002
Gender						
Female						
Male	1.41 [0.68–2.89]	0.352	0.87 [0.41–1.86]	0.715	0.83 [0.30–2.26]	0.714
Ethnicity						
Kazakhs						
Russians	1.15 [0.65–2.53]	0.663	1.19 [0.61–2.31]	0.617	0.94 [0.43–2.07]	0.882
Others	1.28 [0.65–2.54]	0.469	1.53 [0.75–3.11]	0.239	1.48 [0.63–3.51]	0.371
IDU	2.43 [1.40–4.24]	0.002	3.30 [1.84–5.91]	< 0.0001	4.80 [1.85–10.52]	< 0.0001
Anemia	-	-	4.03 [1.88–8.64]	< 0.0001	4.41 [1.85–10.52]	0.001
ESR	-	-	1.00 [0.99–1.02]	0.467	1.01 [0.99–1.03]	0.316
Bilirubin	-	-	-	-	1.01 [1.00–1.02]	0.008
Creatinine	-	-	-	-	1.00 [0.99–1.00]	0.268

ESR – erythrocytes sedimentation rate; IDU – intravenous drug abuse.

## Discussion

This retrospective study was intended to provide an evaluation of all-cause mortality among HIV-positive patients and related risk factors in the population of Kazakhstan on the basis of the UNEHS data between 2014 and 2019. Previous studies have demonstrated a relationship between advancing age and heightened susceptibility to HIV-related mortality [6]. This trend aligns with the findings of this research, where older age was identified as an independent predictor of HIV-associated mortality. The increase in mortality risk with age could be attributed to various factors including limited access to effective antiretroviral therapy and other obstacles encountered by older individuals such as chronic illnesses, cognitive and psychological comorbidities, and deterioration in physical condition [7]. In this research, common HIV coinfections included tachycardia, pancreatitis, viral hepatitis C, and cachexia were identified as significant determinants of all-cause mortality using unadjusted Cox hazard regression analysis.

In studies from the USA and China, HIV-positive males comprise the majority of the patient cohort [8, 9]. In these countries, male HIV mortality exceeds that of females due to their involvement in high-risk behaviors that lead to increased transmission of the disease [10]. However, the larger proportion

of participants in this research was females (67.1%), resulting in divergent outcomes where females exhibit a twofold higher hazard of all-cause mortality as compared with males. This outcome could potentially be due to the limited sample size in this study.

In addition to laboratory observations, the neutrophil-to-lymphocyte ratio (NLR) was calculated, which is considered to demonstrate the balance between innate and adaptive immune responses and serves as a dependable marker of inflammation. Due to insufficient data on neutrophil count, its number was recalculated based on available data from lymphocytes, monocytes, and eosinophils counts which collectively constitute the total leukocytes count in the blood. In this research, the NLR was observed to be above 4 (IQR 1.14–9.86) for non-survivors. According to previous studies, there is a linear relationship between increased NLR values and heightened risk of death [11]. Therefore, high NLR value may be related to an increased risk of developing AIDS, as well as other non-AIDS-defining infections, including oncological and cardiovascular diseases in HIV-positive people [12].

In the research, non-survivors had elevated levels of alcohol and smoking abuse. This agrees with the results of former studies [13, 14]. Given that the study population of this research is predominantly female, it is notable that tobacco use among women rose from 4.5% to 10.1% between 2014 and 2019 [15]. This behavior should be addressed early in the beginning of treatment, and approaches for dealing with this problem should be discussed with the patient. Notably, smoking has been linked to heightened risks of chronic lung disease, cardiovascular disease, and cancer development in HIV-infected patients [16].

This study revealed that deceased patients had a shorter duration of illness from the onset of the disease to experiencing death compared to survivors. This could be attributed to delayed diagnosis of HIV, which reduces life expectancy [17]. Unfortunately, approximately half of HIV patients worldwide are diagnosed in later stage of the disease, as defined by a CD4+ T-cell count below 350 cells/mm<sup>3</sup> or with advanced HIV infection (AHP) with a CD4+ T-cell count below 200 cells/mm<sup>3</sup> [18]. In this research, non-surviving patients had a median CD4 count of 118 cells/mm<sup>3</sup> (IQR 45.0–504;  $p < 0.0001$ ), indicating the possibility for late diagnosis among the deceased cohort. Moreover, diagnosing the disease in more advanced stages or at terminal phases may stem from inadequate population testing coverage among HIV-positive individuals in Kazakhstan. This is a result of patients failing to attend check-ups due to social or psychological aspects, and the HIV-related stigma. This draws attention to the importance of early diagnosis, monitoring, and prioritizing patients to prevent adverse outcomes.

Alongside age, intravenous drug abuse (IDU) was observed as an independent predictor of all-cause mortality in both univariate and multivariate Cox proportional hazard analysis. Given that existing evidence suggests HIV transmission primarily through IDU, these findings have important implications for prevention and policy change [19]. It is imperative that the Kazakh government and international non-governmental organizations (NGOs) prioritize addressing structural barriers that restrain intravenous drug users from accessing HIV treatment. Policy reforms are essential to curb high arrest rates and discrimination against drug users. Failure to address these obstacles will likely perpetuate low utilization of needle exchange programs, HIV testing, and uptake of HIV services among drug users [20].

According to the World Health Organization (WHO), mild to moderate anemia is defined as hemoglobin levels  $< 13.0$  g/dL in males and  $< 12.00$  g/dL in females. Anemia was identified in this study based on hemoglobin levels from a general blood test. Given that anemia is one of the most frequent blood disorders among people with HIV infection, it was included in the multivariate Cox regression analysis [21]. In line with previous studies, anemia was identified as an independent predictor of all-cause mortality in HIV-positive patients in this research [22]. Thus, regular hematological screening and treatment are crucial for HIV-positive patients to potentially slow down the progression of HIV infection and its associated hematological complications.

In this study, HIV-infected patients exhibited elevated erythrocyte sedimentation rate (ESR) levels, which aligns with previous research demonstrating significantly higher ESR in HIV-positive patients compared to controls [23]. This elevation in ESR is typical of infectious and inflammatory conditions such as HIV. Therefore, ESR was included as a parameter in the multivariate Cox hazard model analysis. Although it was not identified as an independent predictor of all-cause mortality in HIV-infected individuals which may be explained by the limited sample size of the study. Similarly, bilirubin and creatinine, both recognized as indicators of renal function, did not show significant findings in the adjusted Cox hazard ration models. They were included in the model because, in addition to aging, various risk factors such as the viral infection itself, antiretroviral therapy, HIV-related opportunistic illnesses (diabetes mellitus and heart disease), and co-infection (such as viral hepatitis C, viral hepatitis B, and tuberculosis) significantly influence the development of kidney disease in the HIV-positive patients [24].

This study also has limitations that should be mentioned. First, as was noted earlier, the research is limited by the small sample size and missing data on some variables. In addition, the AI application developed to extract patient data from their hospital discharges may have made errors. Considering the human factor during the manual re-evaluation of the extracted information is also essential. Second, the lack of comprehensive HIV epidemiological data may introduce bias in this study. Data are incomplete on other social aspects of patients, such as employment status, additional comorbidities, and medication usage, which are significant factors in assessing the mortality of HIV patients. Finally, the majority of the patients were women, so the results may not be generalized to men.

Despite these limitations, to the best of our knowledge, this research represents the first analysis of hospitalized patients with HIV that looks beyond epidemiological data and focuses on laboratory and clinical observations. An additional unique feature of the study is its adaptation of artificial intelligence to extract specific data from hospital records of HIV patients.

## Conclusions

In conclusion, the study revealed a mortality rate of 49.3% among HIV patients from all causes of death. Poor outcomes were linked to many abnormal clinical and laboratory findings upon admission. Age, intravenous drug use (IDU), and anemia were identified as independent predictors of all-cause mortality. These findings provide valuable insights for healthcare practitioners in assessing mortality risk factors. Future research with larger cohorts is warranted to validate these results.



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# Investigation of Microbiological Effects of Atmospheric Pressure Cold Plasma on Hand Disinfection

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## Abstract

**Aim:** Atmospheric pressure cold plasma is the fourth state of matter obtained at low temperature with atmospheric pressure, which has antimicrobial, anti-inflammatory, sterilization, disinfection and surface modification enhancing properties. The aim of this study is to investigate the effectiveness of plasma activated medium (PAM) obtained from atmospheric pressure cold plasma on hand disinfection.

**Methods and Materials:** The study was carried out on 15 individuals aged between 18 and 65 with healthy hand structures (no wounds, no pathology). Of the 15 individuals, 5 were selected as cleaning staff, 5 as office stuff, and 5 as academics. Samples were first taken from individuals using swap for bacterial identification. Afterwards, they were asked to wash their hands for 5 minutes in 250 ml PAM. At the end of the period, samples were taken from the individuals in the same way for bacterial identification using swap. The effectiveness of PAM in terms of hand disinfection was determined by comparing these two samples.

**Results:** As a result of our study, it was found that bacterial colonies decreased in 3 of the samples taken from the hands of 5 cleaning personnel, remained stable in 2, a decrease in bacterial colonies in 4 of 5 office stuff, remained constant in 1, a decrease in bacterial colonies in 3 of 5 academicians, and remained stable in 2 of them. *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus megaterium*, *Staphylococcus capitis*, *Streptococcus mitis*, *Staphylococcus warneri* bacteria were identified on the hands of individuals.

**Conclusion:** As a result of our study, it was found that PAM, which has no side effects in the literature, could be an effective tool for hand disinfection.

**Keywords:** Plasma, Hand disinfection, Microbiological Efficacy, Plasma activated environment.

## Introduction

Materials in the universe are found in four states: solid, liquid, gas, and plasma. The history of plasma dates back to the 300s BC. At that time, Aristotle proposed that there were three states in the universe (solid, liquid, and gas) but that fire (plasma) was a different state. In 1929, Nobel laureate Irving Langmuir

first named fire (plasma) as plasma. Its current meaning was first used by British chemist Sir William Crooke [1–4].

Plasma is the fourth state of matter that contains electrons, ultraviolet photons, positive and negative ions, neutral atoms, and neutral particles. Plasma is a state of matter that we frequently encounter in

nature, industry, and healthcare. Lightning, flames, fluorescent lamps, welding machines, and plasma pens in beauty centers are some of the best examples. Plasma is formed when gas is passed through direct or alternating current. During formation, depending on the type of gas, reactive species and free radicals emerge [1, 3–6].

Plasma has a wide range of medical applications. There are two main methods of obtaining plasma in medical use. The first is dielectric barrier discharge, which was first introduced by Siemens in 1857. It is obtained by passing gas between the high-voltage electrode made of dielectric material and the ground electrode. The second method is the plasma jet obtained by passing gas between electrodes. If the plasma jet is obtained under atmospheric pressure and the gas temperature is lower than 1000 K, it is called atmospheric pressure cold plasma jet. [6–10].

Plasma jet can be used directly or indirectly. Indirectly, the substance obtained by applying plasma to water, 0.9% NaCl solution, phosphate-buffered saline, and organic matter solutions is called a plasma-activated media (PAM) [11, 12].

In the medical field, plasma's anti-cancer, anti-inflammatory, antimicrobial, sterilization, and disinfection effectiveness is a heavily researched topic. Plasma exhibits antimicrobial activity by damaging the DNA and membrane of microorganisms. This feature was first discovered by Laroussi et al. in 1996. In later years, it was shown to affect many microorganisms such as bacteria, viruses, and fungi [4, 5, 13–16].

The aim of this study is to investigate the microbiological effectiveness of PAM produced from atmospheric pressure cold plasma jet, which has no side effects, on hand disinfection.

## Materials and methods

### Population sample and Ethical permissions

The study was conducted on 15 healthy individuals aged between 18–65 years with no injuries about hand, surgical interventions or pathologies. The individuals were divided into three separate groups according to their occupations. The first group consisted of academicians (n=5), the second group consisted of office staff (n=5) and the third group consisted of cleaning staff (n=5). The study was carried out with the decision of the local ethics committee of İzmir Bakırçay University dated 28.09.2022 and numbered 718. The study was carried out in accordance with the Declaration of Helsinki.

### Statistical analysis

Visualization of the data used in the study and obtaining the percentages were made using Microsoft Office 365 Excel and Powerpoint (2023, USA) programs.

### Study design

Firstly, a system was created for the plasma jet. The system was obtained using an oscilloscope, high voltage power supply, computer, optical emission spectrometry, ground electrode, high voltage electrode, plasma pen, flowmeter, argon gas, argon gas cylinder, and flow control valve. The obtained plasma jet was applied to distilled water in a petri dish for 15 minutes and PAM was obtained (Figure 1). To perform the optical emission analysis of cold argon plasma obtained at atmospheric pressure, Thunder Optics brand SMA-E model and optical emission spectrometer with a wavelength measurement range of 350–920 nm were used. In order to obtain high resolution results during plasma

formation, the fiber optic cable was placed at a distance of 1 cm to see the center of the plasma jet. After converting the results from the spectrometer device into a graphic form, the emission line graph was obtained. NIST Atomic Spectra Database was used to define emission lines.

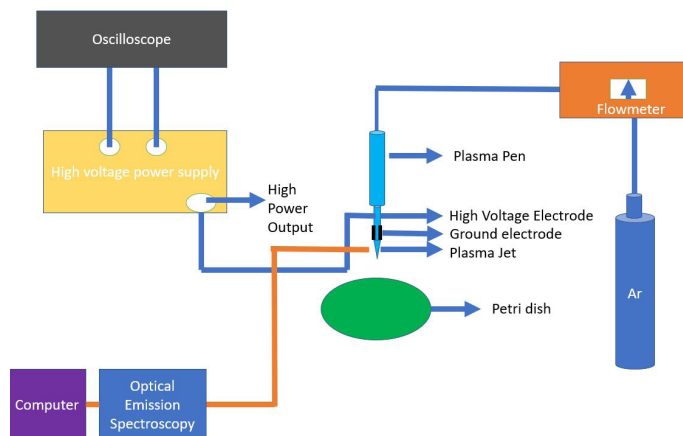


Figure 1 – Plasma assembly

After obtaining PAM, samples were taken from individuals using a swab for microbiological identity. Later, individuals were asked to wash their hands in a container for 5 minutes. After washing, samples were taken again from individuals' hands for bacterial identification.

Samples were inoculated onto 10 µL of 5% sheep blood agar, Eosin Methylene Blue (EMB) agar, and chocolate agar using a loop, and incubated at 37°C for 24–48 hours. Conventional methods and the Phoenix™ fully automated system (Becton Diagnostics, USA) were used for the identification of microorganisms that grew on the culture media.

## Results

*Staphylococcus epidermidis*, *Staphylococcus warneri*, *Staphylococcus capitis* bacteria were identified in the group of academicians involved in the study. *Staphylococcus epidermidis*, *Staphylococcus capitis*, *Streptococcus mitis*, *Staphylococcus warneri* were identified in the tong office staff group. *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus megaterium* bacteria were identified in the cleaning staff group. It was found that the bacterial colonies decreased in 3 of the samples taken from the 5 cleaning personnel in the study, remained stable in 2 of them, bacterial colonies decreased in 4 of the 5 office staff, remained stable in 1, a decrease in the bacterial colonies in 3 of the 5 academicians, and remained stable in 2 of them (Figure 2).

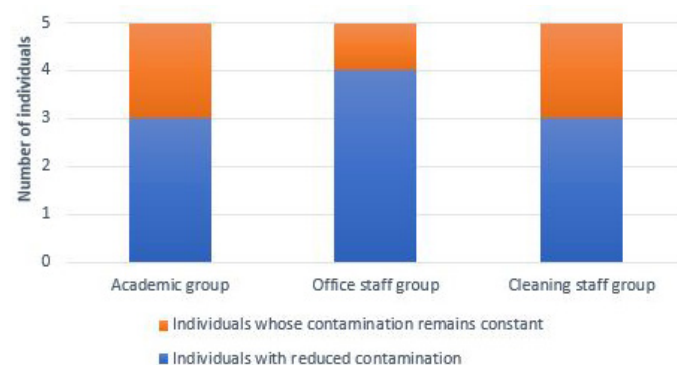


Figure 2 – Contamination rate

The bacterial colony counts obtained from the first and second samplings are shown in Table 1. It was observed that the colony count was higher in the cleaning staff group and the decrease due to PAM was the highest there.

**Table 1** Number of bacterial colonies obtained as a result of the first and second sampling

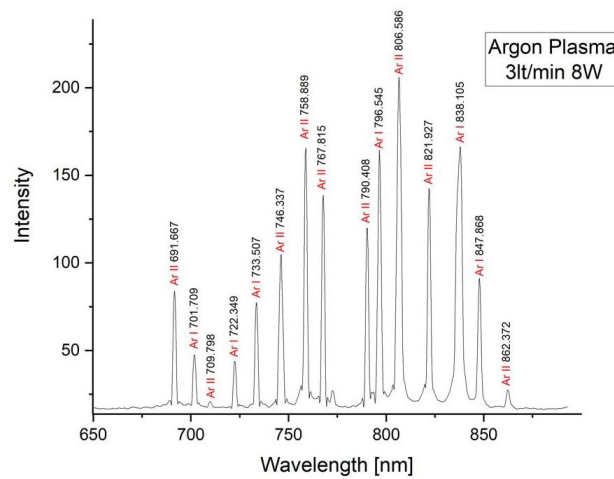
Samples	Reproducing Bacteria	Number of Colonies
CS 1-1	Staphylococcus aureus	50
CS 1-2	Staphylococcus aureus	50
CS 2-1	Staphylococcus epidermidis	1.000
CS 2-2	Staphylococcus epidermidis	35
CS 3-1	Bacillus megaterium	10.000
CS 3-2	Bacillus megaterium	1.000
CS 4-1	Staphylococcus epidermidis	50.000
CS 4-2	Staphylococcus epidermidis	200
CS 5-1	Bacillus megaterium	10.000
CS 5-2	Bacillus megaterium	10.000
OS 1-1	Staphylococcus epidermidis	300
OS 1-2	Staphylococcus epidermidis	50
OS 2-1	Staphylococcus capitis	20
OS 2-2	Staphylococcus capitis	20
OS 3-1	Staphylococcus epidermidis	20
	Streptococcus mitis	20
	Staphylococcus epidermidis	4
OS 3-2	Streptococcus mitis	1
OS 4-1	Staphylococcus warneri	60
OS 4-2	Staphylococcus warneri	6
OS 5-1	Staphylococcus epidermidis	10
OS 5-2	No reproduction	0
A 1-1	Staphylococcus epidermidis	100
A 1-2	Staphylococcus epidermidis	100
A 2-1	Staphylococcus warneri	15
A 2-2	Staphylococcus warneri	15
A 3-1	Staphylococcus capitis	15
A 3-2	Staphylococcus capitis	3
A 4-1	Staphylococcus epidermidis	200
A 4-2	Staphylococcus epidermidis	100
A 5-1	Staphylococcus epidermidis	10
A 5-2	Staphylococcus epidermidis	2

CS: Cleaning staff, OS: Office staff, A: Academician

The maximum decrease in colony count was observed in the individual of group CS 4-1 (the colony count was found to be 50,000 before PAM and 200 after PAM) (Figure 3).



**Figure 3** – Blood agar image of maximum colony reduction



**Figure 4** – Atmospheric pressure cold plasma jet spectrometer values

The spectrometer values obtained as a result of atmospheric pressure cold plasma produced from argon gas are shown in Figure 3. In the figure, the emission lines of argon at different wavelengths are shown and Argon I and II. degrees of ionization were determined.

## Discussion

In this study investigating the effectiveness of PAM obtained from cold plasma on hand disinfection, it was found that microbial contamination associated with PAM decreased in the hands of 3 out of 5 cleaning personnel, 4 out of 5 desk officers, and 3 out of 5 academics.

In this study, the effectiveness of PAM obtained from cold plasma on hand disinfection was investigated. Reactive species, UV radiation, free radicals, ionized gases in cold plasma at atmospheric pressure cause damage to the DNA and cytoplasm of bacteria, viruses and fungi, resulting in antimicrobial activity [5, 15]. It has been reported in the literature that atmospheric pressure cold plasma exhibits antimicrobial, anticancer, and anti-inflammatory activity, while having minimal effect on healthy tissues in individuals, and this effect can be ignored. In short, there are no side effects of atmospheric pressure cold plasma [15, 17–19].

Daeschlein et al. [20] reported that cold plasma showed antimicrobial activity against Escherichia coli, Candida albicans, Pseudomonas aeruginosa, Lancefield, Klebsiella, Staphylococcus aureus, Proteus, Acinetobacter spp., Stenotrophomonas spp., Enterococcus faecalis, and Staphylococcus epidermidis. The study also revealed that cold plasma could be an alternative to antiseptics. In another study, Daeschlein et al. [21] reported that antifungal activity was observed without resistance against Candida albicans, Trichophyton interdigitale, Microsporum canis, and Trichophyton rubrum. Isbary et al. [22] reported a high clinical improvement in patients with herpes zoster and varicella zoster viruses within 2 days after plasma treatment in their study.

Hand hygiene is critical for preventing the transmission of microorganisms and disease. Studies on hand hygiene date back to 1822. In 1822, a French pharmacist suggested that a solution of chlorinated lime could be used for disinfection. In 1843, Holmes stated that the hands of healthcare workers had a significant effect on the spread of puerperal fever. Three years later, Semmelweis stated that handwashing of healthcare workers could reduce sepsis and mortality and prevent puerperal fever.

Different solutions and substances are used for hand hygiene, such as soap, hexachlorophene, alcohol, and chlorhexidine [23–25].

Hand hygiene is critical in preventing hospital-acquired infections, fecal-oral transmission, reducing microorganism contact, and preventing infections [26]. Hospital infections have emerged as an important health problem especially in the last 30 years [27]. The use of antiseptic solutions for hand hygiene dates back to the 19th century. From the 19th century to the present, different antiseptic solutions have been preferred for hand hygiene. Chlorinated lime solutions, alcohol-based solutions, chlorhexidine-containing solutions, phenol-containing solutions, and iodine-containing solutions have been used as antiseptic solutions [28]. However, these solutions have different disadvantages as well as advantages [23–25].

The antimicrobial activity of atmospheric pressure cold plasma has been tested in the literature using jets. It was found that PAM, which had no side effects, showed antimicrobial activity. We believe that this study, which is original in this respect, will guide the future studies.

## Limitations

Is there a solution for hand hygiene that has no side effects? This study, which started with the hypothesis, was planned with a small sample; Due to the high cost in the production process of PAM, the number of samples was limited, which is the limitation of the study.

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# Modern Approaches to Diagnosing Cognitive Impairments in Patients with Multiple Sclerosis

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## Abstract

Multiple sclerosis in patients can cause not only motor, sensory, cerebellar and autonomic dysfunctions, but also cognitive and psychoemotional disorders such as difficulty with learning and recalling information, problems focusing on tasks and maintaining attention, slowed ability to process information, depression, anxiety. Cognitive impairment can appear at any stage of the disease and can be observed in more than half of patients. Patients with multiple sclerosis may not fully recognize or underestimate their complaints of psycho-emotional disturbances, fatigue or pain. For this reason, doctors should rely on the results of neuropsychological tests. Like all symptoms of multiple sclerosis, cognitive impairment is highly variable and significantly affects patients' work habits, social interactions and quality of life. Therefore, the assessment of cognitive functions in patients with multiple sclerosis is of undoubted interest.

**Keywords:** multiple sclerosis, cognitive dysfunction, social cognition, neuropsychological tests.

## Introduction

Multiple sclerosis (MS) is indeed a chronic disease characterized by demyelination of nerve fibers in the Central nervous system (CNS), which includes the brain and spinal cord [1]. Cognitive impairments is a common features of MS, although it can vary widely in severity and manifestation from person to person [1]. In addition, to date, multiple sclerosis is an incurable disease [2]. According to recent data, more than 2.3 million people worldwide have a history of the disease, and it is most commonly diagnosed between the ages of 20 and 50, with more cases in women [3]. In addition, people of Northern Europe and people of European descent have the highest risk of developing the disease [3]. In Central Asian countries, the overall prevalence is 10.1 per 100,000 population, with Caucasians having a much higher prevalence of 16.8 per 100,000 compared to Asians – 4.9 per 100,000 [4].

Absolutely, multiple sclerosis is a multifaceted disease that can affect various functions of the central

nervous system (CNS), leading to a wide range of symptoms beyond the typical motor and sensory dysfunctions [5]. Here's a breakdown of some of the cognitive and psychoemotional impairments that can occur in individuals with MS: difficulty with learning and recalling information, problems focusing on tasks and maintaining attention, slowed ability to process information, depression, anxiety [5].

The understanding and recognition of cognitive impairments in multiple sclerosis (MS) have evolved significantly over time. Thus cognitive impairments in MS were first described by Charcot and his colleagues in the mid-1800s [6]. However, these cognitive symptoms were often overshadowed by the more prominent motor and sensory deficits associated with the disease. For much of the 20th century, cognitive aspects of MS received relatively little attention in clinical practice and research [6].

It wasn't until the late 20th century, particularly in the last decade of that century, that there was a resurgence



of interest in cognitive impairments in MS [6]. This renewed focus was driven by advancements in neuropsychological testing methodologies, which allowed for more specific and sensitive assessment of cognitive functions in individuals with MS [6].

Specific and sensitive batteries of neuropsychological tests have been developed to assess various cognitive domains affected by MS. These tests can identify qualitative (types of cognitive deficits) and quantitative (severity of deficits) characteristics of cognitive impairment in MS patients [6].

With the advent of advanced neuroimaging techniques such as MRI (Magnetic Resonance Imaging), researchers have been able to correlate cognitive impairments with the neurological manifestations of MS. MRI can reveal the presence and location of lesions in the brain and spinal cord, which can help explain specific cognitive deficits observed in patients [6]. While cognitive impairments in MS were initially overlooked, advances in neuropsychological testing and neuroimaging have allowed for a more nuanced understanding of these deficits. This has led to increased awareness, research, and clinical attention towards managing cognitive aspects of MS alongside its other neurological manifestations [6].

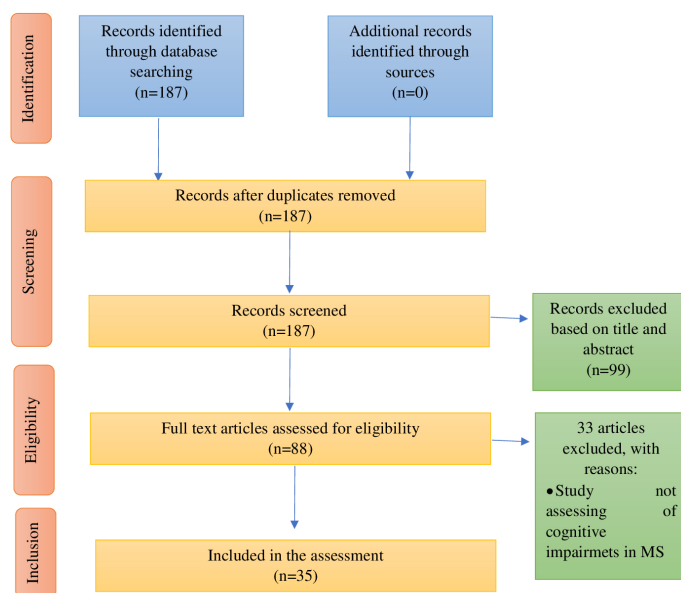
Cognitive impairment is indeed a common feature of multiple sclerosis (MS), and it can occur at any stage of the disease, from the early stages to more advanced phases. The prevalence rates of cognitive impairment in MS vary widely across studies but generally range from 42% to 70% [6, 7]. Cognitive symptoms in multiple sclerosis (MS) can often be subtle and less noticeable compared to more visible sensorimotor symptoms [6].

The assessment of cognitive impairment in patients with multiple sclerosis (MS) can be challenging due to several factors, including the underestimation or lack of awareness of symptoms by the patients themselves [6]. While acknowledging the importance of patient-reported symptoms and experiences, objective cognitive tests play a crucial role in the accurate assessment and management of cognitive impairment in MS. They provide reliable data that can guide clinical decision-making and facilitate interventions aimed at improving cognitive function and quality of life for individuals living with MS [6]. Given the variability and impact of cognitive impairment in MS, it is essential for healthcare providers to assess cognitive function routinely and consider its implications for treatment planning and support. Addressing cognitive deficits early and comprehensively can help improve overall outcomes and enhance the quality of life for individuals living with MS [6].

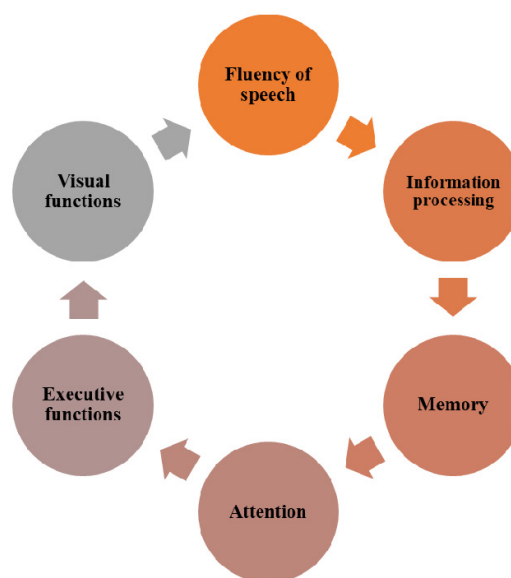
**The present review aims** to study cognitive impairment in patients with multiple sclerosis. A systematic search of English-language studies was conducted in the Web of Science, Scopus and The Cochrane Library from January 2008 to June 2024, which resulted in 187 matches. After checking the titles and annotations, we identified 88 potentially acceptable articles, of which 35 were included in this review. Figure 1 shows a detailed algorithm for selecting studies for this literature review.

## Specific profile of cognitive impairment in patients with MS

In MS cognitive impairments can vary widely, but several domains are commonly affected. The most frequently observed cognitive impairments include: difficulties in processing information quickly and efficiently, memory deficits, visual-spatial skills (Figure 2). In patients with MS, attention processes



**Figure 1** – Flow diagram of the of the literature search



**Figure 2** – The main cognitive functions impaired in patients with multiple sclerosis

are disrupted, in particular selective and sustained attention, although focused attention is preserved for a long time. Also, patients in this category have problems with information processing. Some of the first studies on MS showed that MS patients take much longer to analyze information than healthy patients. One of the first signs of cognitive impairment is manifested by a change in the speed of information processing. An important observed cognitive impairment in patients with MS is memory impairment. Thus, problems with long-term memory are most common. Although visual-spatial impairments have received less attention, there are reports that a quarter of MS patients suffer from them. These changes are manifested in patients by deficits in pattern integration and dislocation and an inability to follow an object. In recent years, there has been increasing recognition and study of cognitive impairments beyond the traditional domains in MS, including social cognition, decision-making, and moral judgment [6].

The pathophysiology of cognitive deficit development in multiple sclerosis is a complex multifactorial process and is

associated with lesions of the basal ganglia, thalamus, cerebellum and brainstem. In addition, white matter lesions and atrophy are known to contribute significantly to cognitive dysfunction in MS patients. However, the exact mechanisms leading to cognitive impairment in MS are not fully understood. Although it is known that in MS there are foci of inflammatory demyelination and neuronal damage in both white and gray matter associated with infiltration of activated lymphocytes. Over time, the incidence of external focal inflammation decreases and begins to be dominated by progressive axonal and neuronal loss, as well as diffuse glial dysfunction and lymphocyte organization in ectopic follicle-like structures. On the other hand, there is evidence that cognitive impairment may be associated with both structural damage and functional abnormalities of neuronal networks in the brain [5, 6].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), provides a structured framework for diagnosing cognitive disorders and categorizes cognitive impairment across several domains: ability to sustain attention and process information quickly, encoding, storage, and retrieval of information, speech, cognitive flexibility, perceptual-motor/visual-spatial abilities social cognition [8]. Cognitive impairment of various etiologies is categorized in this guideline into "severe" and "mild" severity, with cognitive disorders in MS categorized in the "mild cognitive impairment" subsection [8].

Despite the fact that the results of various neuropsychological tests should be 1–2 points below the normative values in "mild" MS, neither the currently available international literature nor the DSM-5-TR Guidelines specify in their recommendations any standardized, internationally recognized neuropsychological tests, as well as their thresholds for measuring cognitive impairment, which are necessary for accurate and timely determination of cognitive disorders in multiple sclerosis [8].

## **Neuropsychological batteries for assessing cognitive impairment in patients with multiple sclerosis**

There is a diverse array of neuropsychological tests utilized to assess cognitive impairment in patients with MS.

The Mini-Mental State Examination (MMSE) is a widely used screening tool to assess cognitive impairment in clinical and research settings. The MMSE is a valuable screening tool for assessing cognitive impairment, but for more comprehensive assessment of visual-spatial abilities, specific neuropsychological tests such as the Rey Complex Figure Test or other tests that involve more detailed visuospatial tasks may be utilized. These tests provide a more nuanced evaluation of visual-spatial abilities and their potential impairments in conditions like multiple sclerosis [9, 10]. However, the MMSE and the three-word memory test are currently considered insensitive for assessing cognitive impairment in multiple sclerosis because they do not take into account the specific neuropsychological profile of patients in this group [8].

Luria-Nebraska Neuropsychological Battery scale has 14 domains and assesses praxis, expressive and expressive speech, memory, visual-spatial gnosis, numeracy, intelligence [11]. This battery is highly informative, but has a number of limitations in the form of lack of standardization and difficulties in quantifying the results, contradictory data regarding the reliability of the test [8].

Paced Auditory Serial Addition Task (PASAT) provides valuable information about a person's cognitive abilities, particularly in tasks requiring rapid processing of auditory information, sustained attention, and manipulation of information in working memory. Its use helps clinicians and researchers assess cognitive function objectively and monitor changes over time in individuals with various neurological conditions, including MS. During the PASAT participants are indeed asked to listen to a series of single-digit numbers presented audibly at fixed intervals. To get the correct answer, patients must verbally respond before the next number appears [12]. The PASAT is recognized for several advantages that contribute to its reliability and suitability for clinical practice and research in assessing cognitive function. However, its use requires a trained professional, a device to play back the recording, and the test may be negatively perceived by the patient due to its complexity and the possibility of a learning effect cannot be ruled out [8].

The Symbol Digit Modalities Test (SDMT) provides valuable insights into processing speed, attention, and visual scanning abilities, making it a valuable tool in assessing cognitive impairment and monitoring cognitive function in clinical practice and research settings. Its standardized administration and reliable scoring enhance its utility for evaluating cognitive status across various populations [13, 14]. The SDMT test demonstrates high sensitivity and specificity not only in detecting cognitive impairment, but also demonstrates its dynamics over time or in response to treatment [13]. While the SDMT offers significant advantages in terms of reproducibility and correlation with MRI findings, its limited trainability should be considered when interpreting longitudinal changes in cognitive performance. Overall, it remains a valuable and widely used tool in the assessment of cognitive function, particularly in clinical neurology and research settings [8].

The Stroop Test is a classic neuropsychological test known for its ability to assess cognitive processes such as response inhibition, cognitive flexibility, and selective attention. The Stroop Color-Word Interference Test is a robust tool for assessing executive functions and cognitive flexibility through its structured administration of color naming, word reading, and interference conditions. Its ability to quantify interference effects provides valuable insights into cognitive processing abilities in both clinical and research settings [15, 16].

The two-minute Processing Speed Test (PST) screening test is designed to optimize the assessment of cognitive function in patients with MS. The advantage of this test is that the patient completes it independently using a tablet, and the high stability of the results, correlation with neuroimaging data [17–19].

The presence of cognitive disorders in patients with MS is possible by interviewing them using the Montreal Cognitive Assessment (MoCA), in which a score between 26 and 30 is considered normal (30 points is the maximum possible score) [20]. In patients with MS the Montreal Cognitive Assessment (MoCA) scale is often used to assess cognitive function and detect generalized cognitive impairment have highlighted the Montreal Cognitive Assessment (MoCA) scale's effectiveness in detecting cognitive impairment across various populations, including those with neurological conditions like MS [21]. However, it has been reported that lower scores than the initial threshold level are useful for optimal screening because they reduce false positives, increase the speed and accuracy of diagnosis of cognitive disorders. Adjusting the threshold value to 27 points on the MoCA scale in MS patients without subjective cognitive complaints appears to strike a better balance between sensitivity and specificity. This approach aims to optimize the

identification of cognitive impairment while minimizing the risk of overdiagnosis, thereby enhancing the clinical utility of the MoCA in MS management. As always, individualized assessment and interpretation of cognitive test results remain essential in clinical practice to ensure comprehensive care for MS patients [21]. Researchers have indeed highlighted the ongoing need for more robust studies to determine the optimal threshold on the Montreal Cognitive Assessment (MoCA) scale specifically for detecting cognitive impairment in patients with MS [21].

## Modern specific tests for the assessment of cognitive impairment in patients with MS

Three groups of validated tests are widely accepted for the assessment of cognitive impairment:

BRB-N (Brief repeatable battery of neuropsychological tests in multiple sclerosis), MACFIMS (Minimal assessment of cognitive functioning in multiple sclerosis) and BICAMS (Brief international cognitive assessment for MS) [8, 22–25].

The Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (BRB-N) is a comprehensive assessment tool designed to evaluate various cognitive domains commonly affected in multiple sclerosis (MS). While the BRB-N is a robust tool for assessing cognitive impairment in MS, its practical limitations, including time intensity and expertise required, necessitate careful consideration in its use within clinical practice settings. Addressing these challenges could enhance its utility in providing comprehensive cognitive evaluations for MS patients [8, 22].

MACFIMS (Minimal assessment of cognitive functioning in multiple sclerosis) is validated 90-minute battery that includes 7 tests assessing working memory, attention, visual-spatial gnosis, executive functions, visual and auditory memory. The tests used in this methodology have high reliability, but their widespread implementation is limited by the length of time it takes to administer them [23].

BICAMS (Brief International Cognitive Assessment for MS) – in 2012, a new battery of tests was proposed for routine use in clinical practice and research. The battery evaluates the speed characteristics of cognitive activity, auditory-verbal and visual memory. The testing time is no more than 15 minutes. This method allows predicting the daily activity of patients can be used as monitoring of cognitive functioning in patients receiving multiple sclerosis medications (PITRS) [24, 25]. This battery has recently been validated in the iBICAMS version for the iPad [26]. A recent study including 139 patients with MS showed that the electronic version of the iBICAMS neuropsychological test has high specificity, allows for clear and instantaneous integration of test results, automatic calculation, and digital data storage, which greatly facilitates the work of the researcher. However, the study had some limitations: highly disabled patients who could not perform the BVMT-R using the electronic tablet pen were not included [26]. Given the inherent advantages of automatic scoring, digital data storage, and standardized time, iBICAMS may become a standard in clinical practice [26].

The Multiple Screener represents an adaptation and refinement of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a well-established tool for assessing cognitive function in MS. The Multiple Screener represents a promising advancement in the assessment of cognitive impairment in MS, offering practical advantages such

as ease of administration, automated scoring, and consideration of psychological factors. Its implementation has the potential to enhance clinical management and research efforts aimed at improving outcomes for individuals living with MS-related cognitive challenges [27].

Assessing cognitive function in MS patients using smartphone learning games. The dreaMS smartphone application represents an innovative approach to monitoring multiple sclerosis (MS) activity and assessing cognitive function through the integration of cognitive games. The dreaMS smartphone application represents a promising tool for assessing cognitive function in MS patients through adaptive cognitive games. Its potential to complement traditional neuropsychological assessments and facilitate remote monitoring underscores its role in advancing personalized care and research in MS management. Continued research and development efforts will further refine its utility and impact in clinical practice [28].

The Virtual Brain (TVB) is an advanced open-source brain simulation platform designed to create personalized brain models using data on structural and functional connectivity. TVB represents a powerful tool in neuroscientific research, particularly in elucidating the complexities of cognitive impairment in MS through its modeling of brain connectivity. By linking structural and functional connectivity alterations to cognitive deficits, TVB contributes to a deeper understanding of MS pathology and opens avenues for personalized approaches to diagnosis and treatment [29]. However, despite advances in MRI technology and our understanding of brain connectivity in MS, the relationship between structural and functional connectivity and how these interact with disability and cognitive impairment remains a complex area of study.

## Cognitive phenotypes in patients with MS

In the context of multiple sclerosis (MS), cognitive impairment can manifest across a spectrum of severity and complexity. Researchers and clinicians often classify these cognitive presentations into different phenotypes based on the extent and domains of cognitive deficits observed [30]. The characterization of cognitive phenotypes in multiple sclerosis (MS) involves considering various demographic, clinical, and MRI features that may indicate different neural substrates of dysfunction at different stages of the disease [30]. Defined as a decrease of 1.5 standard deviations (SD) below the normative mean of the tests used. Significant Impairment: Defined as a decrease of 2 standard deviations or more below the normative mean. This level of impairment suggests more pronounced cognitive deficits that can significantly affect daily activities and quality of life. This level of impairment is considered mild and may indicate subtle cognitive changes that do not significantly impact daily functioning. Thus patients are categorized into cognitive phenotypes according to the severity of impairment (mild or significant) depending on the number of domains affected (one or more) [30].

## Prognostic value of serum biomarkers for early disease progression in MS

Neurofilaments are indeed emerging as promising biomarkers in the field of MS and other neurological conditions. Neurofilaments are structural proteins found in neurons, and their levels in the cerebrospinal fluid (CSF) or blood can serve as biomarkers for neuronal damage or inflammation in diseases

like MS. Effective therapy in MS aims to reduce the frequency and severity of relapses and to slow down the progression of the disease [31].

The idea of using genetic biomarkers associated with gray matter lesions to predict cognitive impairments in multiple sclerosis (MS) is an intriguing area of research. Gray matter lesions in MS are known to contribute to cognitive impairments. Identifying specific genes linked to these lesions can potentially provide insights into the underlying mechanisms of cognitive decline in MS. TLR9, CCL5, CXCL8, and PDGFRB are mentioned as genes that have been identified as potential biomarkers for cognitive impairments in MS. Each of these genes may play a role in inflammation, neuroprotection, or repair mechanisms within the CNS [32].

## Neuroimaging methods in the diagnosis of cognitive impairments in patients with MS

Routine MRI measures of brain volume did not show a significant correlation with cognitive impairment in the recent study, ongoing research continues to explore more nuanced imaging biomarkers and their associations with cognitive outcomes in MS. Integrating advanced imaging techniques and comprehensive cognitive assessments may enhance our understanding and clinical management of cognitive impairments in MS patients. Studies have consistently shown that higher T2 lesion loads are associated with greater physical disability in MS patients. This is because lesions in areas crucial for motor function can disrupt neural pathways, leading to motor impairments and disability [33].

Another study, which associates basal ganglia functional connectivity with both subjective and objective fatigue in MS, represents an important advancement in understanding the underlying mechanisms of fatigue in this disease. In addition, local basal ganglia functional connectivity during fatigue-inducing tasks may serve as a neurophysiological biomarker of cognitive impairment [34].

Meanwhile, atrophy of the cerebral white matter, corpus callosum, shell, and pallidum also showed significant correlation with the z-score of CogEval in secondary progressive multiple sclerosis (SPMS). Thus, the shell may be an important area of atrophy contributing to the impaired rate of cognitive impairment in MS, especially in the late stages of the disease after progression to SPMS [35].

Electroencephalography (EEG) has been used to investigate cognitive function and brain activity in patients with multiple sclerosis (MS), revealing various patterns that indicate dysfunction within the CNS. EEG is a valuable tool for investigating the neurophysiological changes associated with cognitive dysfunction in MS. The identified patterns of dysfunction, such as alpha rhythm alterations and paroxysmal activity, contribute to our understanding of how MS affects brain function and may inform future diagnostic and therapeutic strategies [36].

## Conclusion

Thus, cognitive impairment is a common and impactful symptom in patients with multiple sclerosis. Detecting cognitive deficits in patients with multiple sclerosis as early as possible is critical for several reasons, particularly because cognitive impairments can significantly impact daily functioning and quality of life, even in the absence of noticeable motor impairment. However, the validation and active integration of neuropsychological techniques into clinical practice for assessing cognitive deficits in multiple sclerosis remain important and ongoing areas of focus. While the development of a universal cognitive assessment test for MS presents challenges, its potential benefits in guiding treatment decisions, monitoring disease progression, and enhancing clinical care underscore the importance of ongoing research and innovation in neuropsychology and MS management.

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# Comparative Investigation of Mobile Portable Complex System Functional and Laboratory Diagnostics with Stationary Equipment

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## Abstract

**The aim** of the current study is to evaluate the effectiveness of mobile portable complex system functional and laboratory diagnostics in patients compared to stationary equipment. The scientific study examined the results of functional and laboratory diagnostics of 123 patients who were at JSC NSMC at the time of diagnosis and treatment. The study covered a 1-year period from January 2023 to December 2023. Patients were divided into two groups: 1 group – 63 patients, who were diagnosed using expert stationary equipment of NSMC; 2 group – 60 patients who were diagnosed using the mobile portable complex Health Examination System HES-7 (Konsung Technology; 2023).

**Results:** Laboratory diagnostics were performed in 63 (100%) patients of the 1st group and in 60 (100%) patients of 2nd group. The compared groups had the same characteristics, in particular, anaemia was detected in 4 (6.35%) patients of first group and in 5 (8.33%) patients of the second group. Mortality was not observed in the compared groups. According to all data obtained minor differences in diagnostic examination findings were found (1 to 6%). HES-7 demonstrated quite accurate functional analysis: electrocardiography, pulse oximetry, and spirometry.

**Conclusion:** The use of the digital mobile complex of functional and laboratory diagnostics Health Examination System HES-7 is safe and can be effectively used in primary health care settings by experienced nursing staff.

**Keywords:** mobile laboratory and functional diagnostics, health care, research.

## Introduction

Functional and laboratory analyses are the basis for diagnosing any disease. The rapid progress of diagnostics and its main success lies in the digital technological progress of small-sized medical equipment systems, which contributes to the spread of primary diagnosis of patient diseases. This technology makes possible to obtain primary results of diagnosing

patients' diseases in an optimal time frame and allow to define the need of emergency hospitalization.

## Objective

The aim of the scientific work is to evaluate the effectiveness of using mobile portable complex system of functional and laboratory diagnostics in medical

care. This study includes a series of diagnostic studies of patients with various diseases at JSC “NSMC” in Astana, the Republic of Kazakhstan.

## Materials and methods

We examined the results of diagnostics of 123 patients with diseases: diabetes mellitus, heart rhythm disturbances, angina pectoris, and chronic obstructive pulmonary disease (Table 1), diagnosed in the medical institution of NSMC. The study covered a 1-year period starting January 2023 and ending December 2023. Ethics approval was obtained from Local ethical committee of the National Scientific Medical Center (№085). Helsinki Declaration was followed at all stages of the study.

The patients were divided into two groups. The first group of patients underwent diagnostics on the expert stationary equipment (63 patients). The second group included 60 patients which analysis was taken with the mobile digital complex Health Examination System HES-7 (HES-7, Jiangsu Konsung Bio-medical Science and Technology Co, LTD). The HES-7 provide the digitalization of the entire diagnostic process on site location of the patient and the possibility of providing 21 remote medical services, performing wide range of high-quality primary laboratory and functional diagnostics within 15-30 minutes. The NES-7 complex includes compact laboratory diagnostic devices: blood, urine analysis, biochemical analyser (low- and high-density lipoproteins, total cholesterol, triglycerides, blood glucose, urea, creatinine, uric acid, AST, ALT, and albumin), immunofluorescent analyser for determining the level of C-reactive protein (CRP), procalcitonin (PCT), brain natriuretic hormone (NT-proBNP), glycosylated haemoglobin (HbA1c), Ferritin (Ferritin), Dimer (D-dimer), vitamin D (25- OH vitamin D), troponin/creatinine kinase/myoglobin (cTnI/CK-MB/MYO), thyroid hormone (T3, T4), thyroid-stimulating hormone (TSH), antibodies to Helicobacter (HP-Anti-H.pylori IgG), human chorionic gonadotropin (HCG). Functional diagnostics integrated into the monitor include electrocardiography (ECG), pulse oximeter, tonometer, thermometer, spirometer, electronic stethoscope, foetal Doppler. During the examination of patients, the “one-window” principle was applied to the HES-7 operating algorithm. All diagnostic procedures were carried out by nursing staff and included: electrocardiographic examination, pulse oximetry, thermometry, blood pressure measurement, spirometry, auscultation, biochemical blood test, general blood and urine analysis. All diagnostic procedures were combined by artificial intelligence into a single digital complex; diagnostic data is sent via the Internet to a medical information system; when deviations from the reference norm are determined, the complex signals the medical worker on a digital display the deviation from the health norm with a red indicator arrow. The results are transferred to the medical information system (MIS) DamuMed to the doctor via online for telemedicine consultations “doctor-doctor”, “doctor-nursing worker” for diagnostics, consultation in the process of treatment and rehabilitation by doctors.

Statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution of continuous variables. Continuous variables obtained from the analysis were reported as means ± standard deviations. Student's t-tests were used to compare normally distributed parameters, while Mann-Whitney U tests were used for non-normally

distributed variables. A significant P-value was considered to be less than 0.05.

## Results

Both groups of patients were comparable in age and weight at the time of initial diagnosis, and the number of concomitant anomalies (tab.1, 2). In the first group there were 19 patients with an association of heart rhythm disturbances

Table 1

Comparison of different equipment according to the time of initial diagnosis and hospital stay (1<sup>st</sup> group – expert stationary equipment; 2<sup>nd</sup> group – mobile equipment)

Indicator	1 Group (n=63)			2 Group (n=60)			“p” value
	mean	SD	range	mean	SD	range	
Diagnostic duration, min	39,13	3,12	3–70	15,61	3,58	3–18	0.049
Duration of hospital stay, days	10,4	3,54	5–22	9,11	3,16	5–17	0.310

“n” – the number of cases, «Mean» – the average value, «range» – the minimum and maximum value of the parameter, «SD» – the standard deviation.

Table 2

Comparison of patient groups by comorbidity, mortality and complications (1<sup>st</sup> group – expert stationary equipment; 2<sup>nd</sup> group – HES-7 compact mobile equipment)

Gender		
Groups	male	female
1 Group (n=63)	25 (39,68%)	38(60,32%)
2 Group (n=60)	23 (38,33%)	37 (61,67%)
Comorbidities		
Groups	abs	exists
1 Group (n=63)	42 (66,67%)	21(33,33%)
2 Group (n=60)	41 (68,33%)	19 (31,67%)
Mortality		
Groups	abs	
1 Group (n=63)	0 (0,0%)	
2 Group (n=60)	0 (0,0%)	
Anemia		
Groups	abs	exists
1 Group (n=63)	59 (93,65%)	4 (6,35%)
2 Group (n=60)	55 (91,67%)	5 (8,33%)
Deviations in leukoformula parameters		
Groups	abs	exists
1 Group (n=63)	58 (92,07%)	5 (7,93%)
2 Group (n=60)	56 (93,33%)	4 (6,67%)
Hyperglycemia		
Groups	abs	exists
1 Group (n=63)	52 (82,54%)	11 (17,46%)
2 Group (n=60)	50 (83,33%)	10 (16,67%)
Pathology of the cardiovascular system		
Groups	abs	exists
1 Group (n=63)	38 (60,32%)	25 (39,68%)
2 Group (n=60)	37 (61,67%)	23 (38,33%)
Respiratory diseases		
Groups	abs	exists
1 Group (n=63)	55 (87,31%)	8 (12,69%)
2 Group (n=60)	55 (91,66%)	5 (8,33%)

and arterial hypertension, 6 patients had angina pectoris and 11 other diseases, such as diabetes mellitus, anaemia, lungs and respiratory pathology. In the second group, 18 patients had cardiac arrhythmia and arterial hypertension, 5 had angina pectoris, 10 had diabetes, 5 had anaemia, whereas diseases of the lungs and respiratory system were recorded in 5 patients. The ratio of patients with primary functional and laboratory diagnostics were equal in the compared groups. Immediate diagnostic results are presented in table 1. A difference was revealed in the duration of primary diagnostics: the average duration of diagnostic examinations were 39.13 minutes (3–70 minutes) in the diagnostic group using stationary expert-class equipment and 16.61 minutes (3–18 minutes) in the diagnostic group using the “Diagnostic System health HES-7” with a significant difference ( $p < 0.05$ ).

There was no discrepancy in diagnostic data and no mortality were observed in the compared groups. Patients from both groups had comparative level of concomitant diseases (in group 1 – 21/63 (33.33%); in group 2 – 19/60 (31.67%).

The analysis of the 30 patients from the 2<sup>nd</sup> group were double checked with stationary equipment of the laboratory of NSMC. As a result, the difference in complete blood count did not reach the average of 3%; difference in biochemical tests consisted in 5% for creatinine, 3% – for urea, 2% – cholesterol, 2% – high-density and low-density lipoproteins, 1% – triglycerides, 6% for transaminases, 4% for albumin; the difference in urine testing was 5% (Tab. 3). HES-7 demonstrated quite accurate functional examination: electrocardiography, pulse oximetry, and spirometry assessed by comparison with similar hospital equipment.

Table 3

Comparison of patient groups by comorbidity, mortality and complications (1<sup>st</sup> group – expert stationary equipment; 2<sup>nd</sup> group – HES-7 compact mobile equipment)

Parameters	Automatic systems with internal and external quality assessment n=30, M±m	Mobile portable complex system n=30 M±m	“p” value
Hemoglobin (g/l)	127,1±3,9	129,5±3,2	0,63
White blood cells (*1012/l)	5,53±0,16	5,64±0,15	0,841
Red blood cells (*109/l)	4,22±0,18	4,41±0,12	0,151
Creatinine (mmol/l)	64,70±2,16	66,87±2,1	0,90
Urea (mmol/l)	3,74±0,29	3,92±0,31	0,28
LDL (mmol/l)	1,17±0,07	1,23±0,08	0,45
HDL (mmol/l)	0,73±0,04	0,78±0,04	0,61
Triglycerides (mmol/l)	1,24±30,09	1,27±0,10	0,3
ALT (mmol/l)	0,57±0,04	0,61±0,05	0,49
AST (mmol/l)	0,60±0,03	0,64±0,04	0,71
Albumin (g/l)	24,7±1,9	26,0±2,0	0,53
Protein in urine (g/l)	0,03±0,002	0,032±0,002	0,26
Urine pH (mmol/l)	6,0±0,46	6,2±0,47	0,51

Based on the laboratory studies, we can recommend the further use of the HES-7 health diagnostic system to determine the main parameters in small laboratories and primary care places that are not equipped with expensive automatic stations

and closed-type devices (particularly in rural healthcare). The HES-7 complex can be indispensable for providing medical care in emergency situations due to its mobility (small dimensions and weight of the kit within 8.5 kg).

In general, a reduction in the duration of diagnosis was observed using digital mobile diagnostic technologies; this is quite understandable in terms of the timing of obtaining diagnostic results and the accuracy of the results, which made it possible to ensure earlier hospitalization of the 2<sup>nd</sup> group compared to the 1<sup>st</sup> group. The average duration of hospitalization in patients who underwent diagnostic tests on stationary equipment did not differ significantly from the length of hospitalization performed on mobile digital equipment. There was no increase in the duration of hospitalization, nor an increase in the number of complications.

## Discussion

At the beginning of the XX century, functional and laboratory diagnostics underwent revolutionary changes. The main goal was to create diagnostic systems using specialized computer equipment [1]. Other opportunities also opened up and were implemented gradually: the creation of an electronic medical archive, the development of mathematical methods for analysing patient examination data, computer modelling of the operation of systems and organs, complex medical information systems integrated with the Internet, electronic accounting of medicines [2].

In this regard, the experience of using computer diagnostic systems in primary health care is noteworthy [3, 4]. A new model of medical care has been introduced, combining teleconsultations, digital solutions and mobile medical teams, which allows the provision of a wide range of health services by a multidisciplinary team of health workers. Since 2019, the Swedish government has implemented new public health policies aimed at promoting programs and continuously monitoring the availability of health care in remote rural areas with telemedicine [5]. The country has shifted the emphasis of medical care from hospitals to primary care and spends relatively little on inpatient care in hospitals, focusing instead on primary health care and long-term care [6]. The largest category of health care spending in Sweden is outpatient care (primary care, including home care), which accounted for just over one-third (34%) of all health care spending last year. This is the result of efforts over the past two decades to contain hospital costs while actively developing primary care [7].

With the development of science and cybernetics, mobile analysers of innovative designs of compact sizes have been evolved, capable of examining several analysis parameters in a short time with low reagent consumption and easy operation.

Investigating new diagnostic system at our hospital, we found accuracy, convenience and ease of use. The advantage of mobile laboratory equipment is the compactness and speed of obtaining diagnostic test results (3-18 minutes), the low cost of reagents compared to stationary expert equipment, the availability of mobile laboratory diagnostics reduces the morbidity and mortality of the population, where stationary diagnostics are not readily available. Because of the use of diagnostic studies using the digital mobile complex “Health Diagnostic System HES-7”, the “one window” principle was applied, allowing in one office, in a short time, to carry out functional and laboratory diagnostics of patients, make a diagnosis, and conduct a teleconsultation with a specialist. Using the mobile complex, primary functional



and laboratory diagnostics are carried out, the function of providing remote medical services is implemented, in which a specialist can provide telemedicine consultations “doctor-patient”, “doctor-nursing staff”, “doctor-doctor” at the level of consultation. Taking into account the possibility of portable diagnostics the system usage have economic benefits by reducing costs for patient way to the conventional laboratory. Doctors and medical professionals express positive feedback regarding the functionality and convenience of HES-7 system. The system is easy to integrate into clinical practice and provide convenient tools for effective diagnosis especially in primary care in remote areas.

The results of our research demonstrate that the use of mobile diagnostics in the treatment of patients is safe, simple and effective. Further improvement of cybernetics devices will make it possible in the nearest future to achieve advanced diagnostic results in shorter time. It will be possible to improve the timing of diagnosis, treatment and hospitalization of patients, placing emphasis on the outpatient health care sector. In mobile diagnostics of diseases, the principle of “one window” is applied to provide primary health care “here and now” in one office; from the point of view of the advantages of functional and laboratory diagnostics, there is no doubt. It is possible to adopt this approach as the “gold standard” in diagnosing diseases of primary health care patients, perhaps in the coming years, by equipping remote primary health care settlements with mobile diagnostics: in outpatient clinics, medical, paramedic and obstetric centers, pre-medical offices, where primary diagnostics would be carried out to provide primary medical care in remote settlements. The uniqueness of the HES-7 system is highlighted by the fact that existing analogues only consider the functional part of the diagnostic system. However, the laboratory part of a

diagnostic system analogue cannot be solved. The parameters of comparability, functional studies of ECG, pulse oximetry and spirometry assessed by comparison HES-7 with similar hospital equipment did not reveal any significant differences that may influence diagnostic results. The portable system meets quality standards and regulatory requirements, confirming its safety and efficacy in diagnostic procedures.

The benefits of this new approach are difficult to objectively assess due to the low prevalence of mobile diagnostic technologies. Therefore, this study provides evidence of the advantages of the mobile HES-7 portable complex and offers a new perspective on primary healthcare. Because minor discrepancies were observed between the portable device and traditional equipment, it can be inferred that this mobile device could be beneficial for doctors and other healthcare professionals, especially in remote areas where access to traditional diagnostic facilities is limited.

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# Efficacy of Cognitive-Behavioral Therapy in Optimizing Counseling Outcomes for Fast Remission of Social Anxiety with Panic Attacks

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## Abstract

**Aims:** The case study evaluates the efficacy of Cognitive Behavioral Therapy in optimizing counseling outcomes for social anxiety and panic attacks within an academic setting. Counseling sessions were conducted with a 23-year-old female client over a four-month period at T.S Government College.

**Method:** The study utilized a single case study design A-B-A. The client presented with symptoms of social anxiety and panic attacks, impacting various aspects of her life including academic performance, interpersonal relationships, social interactions and family dynamics.

**Results:** Cognitive Behavioral Therapy techniques including Cognitive Restructuring, Social Skills Training, Role Play and Role Reversal, and Systematic Desensitization through Gradual Exposure, were implemented over 8 sessions. Assessment tools including pre-post ratings, behavioral observations and therapy blueprints were utilized to assess the severity of social anxiety.

**Conclusion:** A significant decrease in the severity of social anxiety and panic attacks based on both subjective self-reporting and objective observations suggesting Cognitive Behavioral Therapy as an approach of counseling for individuals with social anxiety with panic attacks in educational setting.

**Keywords:** Cognitive Behavioral Therapy, case study, case report, social anxiety, panic attacks, cognitive restructuring, systematic desensitization, role play, role reversal, social skills training.

## Introduction

Social anxiety disorder (SAD) is one of the most prevalent mental health conditions characterized by excessive fear and discomfort in social situations, often leading to avoidance behaviors and significant impairment in daily functioning [1]. Social anxiety is the fear of social situations that involves interaction with other people. Panic attack is a sudden surge of overwhelming anxiety and fear leading to physiological and emotional changes along with fear of having additional panic attacks. Individuals with social anxiety disorder may experience intense anxiety, panic attacks, and distress when faced with social interactions, particularly in academic settings being one of the prominent areas where these challenges could manifest

profoundly [2, 3]. It causes impairment in individual's psychosocial functioning where an individual becomes stagnant and dependent on others [4]. The impact of social anxiety on academic performance, interpersonal relationships, and holistic well-being emphasizes the importance of effective therapeutic interventions [5].

To manage social anxiety and panic attacks with rapid outcomes, both pharmacological and psychological approaches have been developed. Studies comparing these treatments indicate that Cognitive Behavioral Therapy (CBT) is more effective than long-term pharmacological treatment. Cognitive Behavioral Therapy (CBT) has emerged one of the significant evidence-based therapeutic approach for managing social anxiety and panic attacks due to its

informed effectiveness focusing on cognitive restructuring, exposure techniques, and behavioral interventions [6]. CBT aims at identifying and modifying maladaptive thoughts, beliefs, and behaviors that could contribute to social anxiety symptoms, making it particularly suitable for addressing the cognitive and behavioral aspects of social anxiety disorder [7]. Despite the effectiveness and psychotherapeutic outcomes of CBT, there is a need for more research to evaluate its efficacy in specific contexts, such as academic or educational settings, where social anxiety can significantly impact academic performance, personal functioning, interpersonal relationships, and overall well-being. Understanding the effectiveness of CBT in optimizing counseling outcomes for social anxiety and panic attacks within educational environments is critical for informing evidence-based practices and improving mental health support for students.

This case study aims to evaluate the efficacy of Cognitive Behavioral Therapy in optimizing counseling outcomes for social anxiety and panic attacks within an academic setting. The study employs a single case study design using the A-B-A format to provide an in-depth analysis of the therapeutic process and counseling outcomes for a 23-year-old female client experiencing social anxiety and panic attacks. The chosen setting for this case study was T.S Government College, where counseling sessions were conducted over a four-month period. The client's experiences, challenges, and progress throughout the psychotherapeutic process were examined, focusing on the implementation of various CBT techniques such as Cognitive Restructuring, Social Skills Training, Role Play and Role Reversal, and Systematic Desensitization through Gradual Exposure, tailored to the client's specific needs and challenges. Specific techniques have been devised which base on CBT model. Majorly cognitive restructuring acted as to modify client's misinterpretations of physiological sensations to accurately perceiving them as usually bodily states. Secondly gradual exposure to feared avoiding situations either in imagination or in vivo performed a function of invalidation of the learned experiences of social anxiety and avoidance and individual becomes adapt to encounter them without being anxious or afraid of the situation. Moreover, homework assignments provided an opportunity to comprehend what clients have learned in counseling settings and modified their cognitive and behavioral patterns to gain control over their living. Cognitive Behavioral Therapy is the most thoroughly studied non-pharmacological approach to the counseling of social anxiety disorder and its efficacy seems to be prevalent in impaired quality of life as a consequence [8, 9].

The significance of this study specifically in the post-COVID pandemic era is profound, as it addresses a critical need for effective mental health interventions with the psychosocial aftermath of the pandemic [10]. The COVID-19 crisis has had a pervasive impact on global mental health, particularly exacerbating conditions of anxiety disorders, including social anxiety and panic attacks, due to prolonged social isolation, uncertainty, and disruptions to daily life, followed by unique challenges including remote learning, limited social interaction, and concerns about academic performance. This study's findings contribute to the growing literature body of evidence supporting the use of CBT as an effective intervention for social anxiety and panic attacks, especially in times of crisis. By demonstrating the effectiveness of CBT in reducing anxiety symptoms, this study reinforces the value of continued mental health support as society transitions into the post-COVID era [11]. As the world continues to deal with the long-term psychological impacts of

COVID-19, the findings offer valuable insights for mental health practitioners and policymakers for accessible, evidence-based therapies like CBT [12].

By exploring the client's experiences, coping strategies and progress throughout the counseling process and investigating the effectiveness of CBT in addressing social anxiety and panic attacks in an educational context, this study contributes to the growing body of literature on evidence-based interventions for mental health issues among college students. The findings have implications for counseling practices in academic settings and may inform the development of tailored psychological interventions to offer support to individuals with social anxiety in achieving better academic and social functioning. Overall, this case study aims at bridging the gap between research and practice in the importance of integrating empirically supported interventions like CBT into counseling services to strengthen outcomes for individuals struggling with social anxiety and panic attacks, particularly in educational environments where social interactions play a crucial role in personal and academic development as well as enhance mental health support and holistic wellbeing of individuals.

## Materials and methods

The participant in this case study was a 23-year-old female client with presenting problems of social anxiety and panic attacks. She sought counseling services due to the impact of these symptoms on her academic, interpersonal, social, and family functioning. A single case study design using the A-B-A model was utilized in this study. Presenting problems were assessed by establishing a baseline of pre-post treatment and evaluation for effectiveness of CBT. The A-B-A model involved three phases: baseline (A), intervention (B), and post-intervention (A). This design allowed for the assessment of the effects of the intervention by comparing baseline measures with post-intervention measures. The initial phase (Phase A – Baseline Assessment) involved the assessment of the client's social anxiety symptoms and panic attacks (severity, frequency and occurrences) through self-reported measures, behavioral observations, and psychotherapeutic/counseling interviews. This phase established baseline data against which the intervention's effectiveness could be measured. The intervention phase (Phase B) spanned over a four-month period and consisted of eight counseling sessions using Cognitive Behavioral Therapy (CBT) techniques. The techniques included: Cognitive restructuring which included identifying and challenging irrational thoughts related to social anxiety and panic attacks, Social Skills training involving teaching effective social interaction skills to reduce social anxiety, Role Play and Role Reversal which focused on practicing social scenarios and adopting different roles to address anxiety triggers, and Systematic Desensitization through Gradual Exposure which involved gradual exposure to anxiety-provoking situations to reduce fear and avoidance behaviors. Following the intervention phase comes the Post-Intervention Assessment (Phase A), the client's social anxiety symptoms and panic attacks (severity, frequency and occurrences) were reassessed using the same measures employed during the baseline assessment. This phase aimed at evaluating the effectiveness of CBT in managing social anxiety and panic attacks. Quantitative data obtained through a single-case experiment in sessions by establishing a baseline with assessment protocol for pre-post treatment for efficacy of CBT which were analyzed using statistical methods to assess changes in social anxiety severity and panic attacks.

Qualitative data from therapy blueprints and clinical observations were analyzed thematically to gain insights into the client's experiences and progress throughout the intervention. Ethical considerations were kept in by taking the client with informed consent by ensuring the privacy, confidentiality and professional ethical concerns. Ethical considerations were intact while dealing with the client in one-on-one session and session by session discussion with the supervisor and approved by Ethical Committee of the Institute of Clinical Psychology, University of Management and Technology, Lahore, against the ethical criteria based on The American Psychological Association, The British Psychological Society and The Pakistan Association of Clinical Psychologists.

## Assessment

A 23 years old female was self-referred client taken from T.S Government College presented with lacking self-confidence, feeling afraid of talking to boys and in a group. In physical symptom assessment, addition to palpitations, pounding heart, sweating and chilling hands, numb limbs, dry mouth and shortness of breath along with the fear of getting fainted, being unable to talk and getting embarrassed in front of people. Consequently, she avoided every possible interaction she can; avoid crowd situations and particularly class gatherings and going anywhere alone due to fear of being exposed and afraid. Her problem started when she was studying in a school grade 6 when two of her class fellows tried to get physical with her. About she told her mother and her mother talked to the school principal and then she felt so embarrassed because everyone knew and make fun of her. Later she had studied at girl's college where she felt the same experiences but start of co-education in bachelors with academic requirement of communication and speaking in gathering were perquisite brought her panic attack with severity. In her personal history, she responded that she had no hobby and she likes to spend time at her room alone watching television. From her family, she believed that she was the only girl who experiences this because her family members including her two sisters and four brothers were the opposite since their childhood. After her first panic attack in the crowd, she became fearful that she might have developed any coronary disease and might die of heart attack. For last couple of months she was having panic attacks on daily basis and she remained anxious all the time. Although at one point she had Valium and Xanax but she stopped using because she didn't want to depend on medication either. She approached counseling psychologist from the Institute of Clinical Psychology, University of the Management and Technology, Lahore. Standard psychological assessment modalities were incorporated including behavioral observation, counseling interview, and subjective rating of her presenting complaints, baseline chart, projective measures of Draw a Person Test (DAP) and through self-report measures through Student Problem Checklist scale and Self-Esteem Scale for adults (SES) [13–17]. Her behavioral observation in classroom setting, during sessions, interaction with her teachers and class fellows outside the class room indicated her social anxiety. And measures provided rich information about how she see herself, how she perceive others attitude towards herself and about her social relations the way she generally behave. She was a college student and a college student generally faces mental health problems so to assess those mental health problems Students Problem Checklist Scale was used.

Table 1

Client's Pre and Post scores on Student Problem Checklist Scale

Factors	M	SD	Range		Post-test score	Pre-test score
			Min	Max		
Sense of being dysfunctional	14.56	8.95	5.61	22	23.51	30
Loss of confidence	9.37	5.99	3.38	21	15.36	32
Lack of self-regulation	11.97	5.08	6.89	13	17.05	15
Anxiety Proneness	5.39	4.51	0.88	07	9.9	14
Factor Total	40.49	19.65	20.84	63	60.14	91

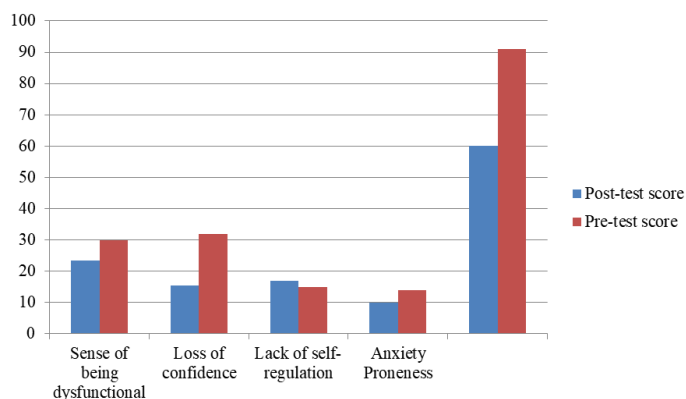


Figure 1 – Pre and Post score of Student Problem Checklist Scale of the client

Besides her social anxiety problem and generally feeling anxious and feared she seemed to have low self-esteem problem as well. In order to explore the experience and expressions of self-esteem of the client, Self-Esteem Scale was used.

Table 2

Client Pre and Post scores on Self-Esteem Scale for Adults (SES)

Factors	M	SD	Range		Pre-test score	Post-test score
			Min	Max		
Low self-esteem	16.31	6.87	9.44	23.12	26	15
Resilience	32.44	6.81	25.93	39.55	25	37
Withdrawal	14.86	6.77	8.09	21.63	25	13
Sociability	20.52	4.46	16.06	24.98	10	21
Self-confidence	25.36	5.37	19.99	30.73	20	28

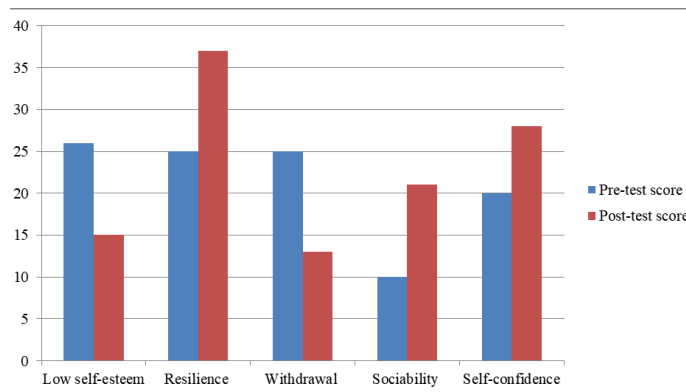


Figure 2 – Pre and Post score of Self-esteem Scale of Adults (SES) of the client

After the Pre and Post subjective ratings and Pre and Post ratings on self-report measures score indicated social anxiety, lack of self-confidence could be a result of sense of being

dysfunctional that leads towards her proneness of anxiety. In Eastern culture students are more sensitive to negative things and she had been experiencing negative reactions since a child and has been comparing that negative things with the positive things. That social withdrawal must have affected her self-confidence in her sociability cleared in before and after test scores.

Client was introduced with Cognitive Behavioral Therapy (CBT) and counseling was carried out over 4 months during which 8 therapeutic sessions were taken. The counseling techniques mainly comprised of rapport building for the prospective interventions, diaphragmatic breathing, and progressive muscle relaxation to manage her panic attacks, cognitive restructuring, Psychoeducation about her experiences, homework, behavioral experiment, and working on polarities to set the grounds for further techniques, incorporate social skills training, employ role play and role reversal, evokes behavioral rehearsal, and systematic desensitization with gradual exposure to feared situations and exercises to build self-esteem.

## Discussion/Therapeutic Outcome

In current study psychoeducation in initial sessions produced insight in client regarding psychological and physiological nature of her problems rather than merely relying on observed bodily symptoms. Cognitive Behavioral techniques not just helped client to challenge her thoughts and beliefs of her concerns, panic through evidence based Socratic inquiry but also, she was capable of recognizing a high occurrence of her Negative Automatic Thoughts (NATs) related to panic in relevance to her low occurrence of such events from virtually to reality [18–20]. Through behavioral techniques with integration of cognitive practice helped the client to systematically exposure of feared situation where she recovered from panic attacks by monitoring her progress, her thoughts and her behavior and consequently challenging and changing those to adept towards healthy pattern of thoughts and behaviors. Furthermore, reduction in her panic attacks alongside social avoidance was brought about through systematic desensitization. She structured herself a rating of anxiety first that provokes situations ranging from low to higher level of anxiety and then step by step she was being able to face situations where integration of homework, behavioral experiments, working on polarities, by the complementation of social skills from imagination of role play to role reversal to reality while it was conditioned with her relaxed state [21–25]. And at the end of the counseling sessions, she was able to deal her life without anyone’s guidance or assistance.

Decision of terminating therapy was taken after behavioral, cognitive and affective goals were discernibly achieved, and a means of maintaining changes already achieved and generally problem-solving skills acquired in counseling. By mutual decision of the client and counselor sessions were ended by reviewing the major events of the counseling experience, acknowledging the changes the client has made, and ending on a positive note. Reviewed through blueprint of how the problem was started, what kept the problem going, important lessons she learned in therapy and coping strategies she had learned which she will continue applying in her life [26].

Thus, it is suggested that CBT was not just only helpful in reducing presenting complaints of panic attacks and social anxiety but its outcome remained stable and consistent in a long run. In light of the above findings, it is proposed that mental health practitioners in Pakistan culture would even better results if the cognitive behavioral therapy techniques with clients facing mental health complaints apart from the clinical population. The findings of the current case study hold significant implications for educational counseling, particularly within college settings, where cultural phenomena intersect with challenges faced by adolescent girls who are dealing with social anxiety and panic attacks, influencing their coping mechanisms and adjustment processes. This study emphasized on the need of tailored counseling interventions to address the unique needs of diverse students struggling with the mental health issues.

## Limitations and Recommendations

One implication involves the development of counseling plans specifically designed to help young girls in managing and improving their academic and personal challenges related to social anxiety and panic attacks. These plans should be informed specifically considering the aftermath of impacts of the COVID-19 global pandemic on the youth by a deep understanding of both inter- and intra-cultural dynamics within

Table 3 Case Formulation of the client

Condi-tions	Past	Present	Future
Social	<ul style="list-style-type: none"> <li>• Role of parenting</li> <li>• Lack of social support</li> </ul>	<ul style="list-style-type: none"> <li>• Distant relationship with father</li> <li>• Intimacy vs. isolation</li> <li>• Social milieu</li> </ul>	<ul style="list-style-type: none"> <li>• Psycho education</li> <li>• Environment (new college &amp; internship)</li> <li>• Role of family</li> </ul>
Psycho-logical	<ul style="list-style-type: none"> <li>• Fear was developed when her male class fellows tried to get physical</li> <li>• Immature defense mechanism avoidance</li> <li>• Anal stage + autonomy vs. shame</li> </ul>	<ul style="list-style-type: none"> <li>• Anxiety become more prevalent when she joined co-education college</li> <li>• Introjections</li> <li>• Cognitions + behavior</li> <li>• Low self esteem</li> <li>• Conflict between ideal/real self</li> <li>• Fear of opposite gender</li> </ul>	<ul style="list-style-type: none"> <li>• Client’s personal motivation</li> <li>• Role of cognition, emotions and behavior</li> </ul>
Biolo-gical	<ul style="list-style-type: none"> <li>• Adolescence</li> <li>• Attachment</li> </ul>	<ul style="list-style-type: none"> <li>• Transition to Young adulthood</li> <li>• Temperament</li> </ul>	<ul style="list-style-type: none"> <li>• Attachment new roles / new responsibilities</li> </ul>

Factors	Individual Factors	Systemic Factors
	<ol style="list-style-type: none"> <li>1. Biological</li> <li>2. Behavioral</li> <li>3. Cognitive</li> <li>4. Psychodynamic</li> </ol>	<ol style="list-style-type: none"> <li>1. Family (dynamics and traditions)</li> <li>2. Academic/ occupational</li> <li>3. Social</li> <li>4. Cultural</li> </ol>
Predisposing factors	Avoidance	Financial difficulties
Precipitating factors	Temperament	Lack of social support Co-education
Perpetuating factors	Self esteem	Lack of social circle
Protective factors	Personal motivation	Supportive sister Role of friends New internship

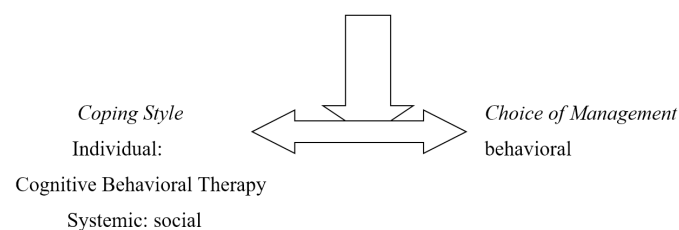


Figure 3 – Management for the client

the college setting, acknowledging the diverse backgrounds and challenging experiences of the student population [27-30]. Future research endeavors in this area should focus on exploring coping strategies integrated by individuals facing social anxiety and panic attacks. Specifically, there is a need to identify and differentiate between unhealthy coping strategies and positive coping mechanisms that promote resilience and well-being.

## Conclusion

This case study highlights the significant efficacy of Cognitive-Behavioral Therapy (CBT) in achieving rapid remission of social anxiety and panic attacks within educational setting. The client, a 23-year-old female, exhibited notable improvements across various domains of her life, including academic performance, interpersonal relationships, and social interactions. Through a carefully structured A-B-A design, the study demonstrates that CBT, incorporating techniques such as Cognitive Restructuring, Social Skills Training, Role Play and Role Reversal, and Systematic Desensitization, can markedly reduce the severity of social anxiety and its associated symptoms, as observed through both subjective self-reports and objective behavioral assessments, highlighting the effectiveness of CBT as a targeted therapeutic approach for individuals experiencing these challenges. This study emphasized the significance of culturally sensitive and tailored counseling interventions in an academic setting, particularly for female students navigating social anxiety and panic-attacks which impacted various aspects of their life including academic performance, interpersonal relationships, social interactions and family dynamics. This case study can potentially facilitate school/college's administration, mental health practitioners and families to pay attention towards the challenges youth experiences, how severe it can become if not dealt with, identification of the risks and protective factors and taking preventive measures and management of problems related that could be dealt effectively through Cognitive-Behavioral Therapy.

Moreover, the results suggest that CBT can be particularly beneficial within educational settings, where social anxiety and panic attacks, brought on by the COVID-19 pandemic, may

severely hinder academic performance, socialization and family functioning including abuse and trauma [31-33]. The therapeutic interventions implemented in this case not only provided relief from acute symptoms but also equipped the client with long-term coping strategies to manage anxiety-provoking situations, thereby fostering resilience and promoting psychological well-being. The takeaways from this study emphasize the importance of integrating CBT into counseling programs within academic institutions to address the mental health needs of students amplified in the aftermath of COVID-19 pandemic. The successful implications of CBT in this context supports its continued use and further research into its long-term efficacy across diverse populations and settings. Future studies might explore how CBT can be adapted and optimized for broader use in educational environments, ensuring that more individuals benefit from this evidence-based therapeutic approach in managing the ongoing psychological impact of the pandemic.

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# Respiratory Support for Patients with Chronic Respiratory Failure: the Necessity of a Long-Term Homecare Ventilation Program

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## Abstract

Severe respiratory failure, resulting from a wide range of acute and chronic diseases such as chronic obstructive pulmonary diseases, obstructive sleep apnoea, obesity hypoventilation syndrome (Pickwickian syndrome), COVID-19, bilateral pneumonitis, kyphoscoliosis, acute respiratory distress syndrome, amyotrophic lateral sclerosis, Guillain-Barré syndrome, and others, poses a significant challenge for healthcare systems worldwide. Treating severe respiratory failure often requires long-term or lifelong respiratory support, which places a heavy burden on both patients and healthcare systems. Despite the availability of free comprehensive care for patients with chronic kidney failure and heart failure, those requiring long-term respiratory support are often deprived of adequate medical and social assistance. This gap in care leads to frequent hospitalizations, disability, and premature death of patients with severe respiratory failure, further straining healthcare resources and increasing social tension. The solution of the problem is an organisation of ambulatory centre for homecare respiratory support for patients with severe chronic respiratory failure. Homecare respiratory support demonstrated worldwide cost-effectiveness by significantly enhancing patients clinical and social outcomes, restoring their work capacity, and reducing the need for hospitalizations. This article emphasizes the necessity of a comprehensive homecare respiratory support system and highlights how inadequate assistance can result in frequent hospitalizations, increased disability, and premature death, thereby imposing an additional strain on the healthcare system.

**Keywords:** homecare respiratory support, chronic respiratory failure, long-term homecare ventilation program.

## Introduction

Nowadays, homecare respiratory support for patients suffering from severe forms of chronic respiratory failure (CRF) is a major healthcare problem of Kazakhstan. CRF is a pathological condition that complicates the course of several different diseases, including chronic obstructive pulmonary disease (COPD), progressive neuromuscular diseases,

obstructive sleep apnoea syndrome, bilateral pneumonitis, acute respiratory distress syndrome, obesity hypoventilation syndrome, amyotrophic lateral sclerosis, Guillain-Barré syndrome. Treatment of severe CRF often requires highly specialized medical care, containing various options for respiratory support, in particular home respiratory support for a long period [1]. This poses a massive issue for healthcare. In turn,



## General morbidity in Kazakhstan

Diseases	Population 19 634 983			
	Absolute amount		Per 100 000 population	
	2021	2022	2021	2022
<b>Respiratory diseases</b>	<b>5 251 430</b>	<b>5 146 247</b>	<b>27 637.7</b>	<b>26 210</b>
Cardioscular diseases	3 216 233	3 313 861	16 926.7	16 877
Tumours	429 216	447 627	2 258.9	2 280

## Mortality (per 100 000 inhabitants)

	Diseases	Population 19 634 983	
		2021	2022
1	<b>Cardiovascular diseases</b>	<b>226.86</b>	<b>154.39</b>
2	<b>Tumours</b>	<b>73.7</b>	<b>68.76</b>
3	<b>Respiratory diseases</b>	<b>108.94</b>	<b>66.76</b>

**Respiratory diseases rank 1st in morbidity and 3rd in mortality after cardiovascular and oncological diseases**

Statistical collection 2021 and 2022..BUREAU OF NATIONAL STATISTICS, STRATEGIC PLANNING AND REFORM AGENCIES OF THE REPUBLIC OF KAZAKHSTAN

**Figure 1** – The general morbidity and mortality with the focus on respiratory diseases in Kazakhstan

home respiratory support leads to a significant improvement in the clinical status of patients, partial or complete restoration of working capacity.

## Current situation with respiratory diseases in Kazakhstan

The number of patients with chronic respiratory failure in the world is steadily growing and amounts to 328,000,000 people (5% of all patients with chronic lung diseases), and 936,000,000 of the working-age population suffers from sleep apnoea syndrome. Currently, in the Republic of Kazakhstan respiratory diseases rank 1st place in morbidity and 3rd in mortality after cardiovascular and oncological diseases (Fig. 1).

Unfortunately, there is no patient registry available in Kazakhstan. However, according to data from the Head of the Charity Fund "Omirge sen" (2023), currently, around 450 children require non-invasive ventilation within just one category of neuromuscular diseases. Out of these 450 children, approximately 100 are already receiving non-invasive ventilation. It has also been noted that there has been a significant increase in the number of patients requiring non-invasive ventilation, due to the increased availability of diagnostic equipment in the respiratory support center. Over the past three years, the frequency of diagnoses has increased tenfold. Currently, there is an increased identification of the need for ventilation among patients who were previously not considered as candidates for this treatment.

However, there is no system for providing homecare to patients in need of long-term respiratory support at the outpatient stage. The lack of a system of medical and social care for patients in need of long-term respiratory support creates a certain social tension and puts a significant burden on the healthcare system due to frequent hospitalizations, disability, and premature death of patients with severe chronic congestive respiratory failure. At the same time, for patients with chronic renal failure and heart failure, free medical care is provided in full. The social determinants or structural factors that influence the problem include high financial costs for the treatment of chronic respiratory failure, low quality of life of

patients with chronic respiratory failure with frequent and prolonged hospitalizations. In the case of patients with sleep apnoea, chronic fatigue syndrome results in a decrease of the labour productivity, memory loss, frequency of traffic accidents and industrial injuries. Chronic respiratory failure following any courses are characterised by early disability and high mortality of patients [2, 3].

## Worldwide experience of homecare respiratory support

Around the world, the number of centres for Homecare respiratory support is constantly growing. The number of respiratory support centres in sixteen European countries was 329 in 2001–2004. In France, the prevalence of external respiratory support centres was 33 per 100,000 people [4].

Respiratory support improves quality of life and survival. The experience of European countries demonstrated that patients using long-term respiratory support at the home with telemonitoring experienced a 36% reduction in urgent GP visits, exacerbations, and acute conditions, resulting in 33% cost savings [5]. The estimated overall prevalence of home mechanical ventilation use in South Korea was 9.3 per 100,000, with a prevalence of 6.3 per 100,000 among children (age < 15 y.o.) [5]. The most common primary diagnoses were neuromuscular diseases (42.0%) and lung and/or airway diseases (27.7%). The number of Non-invasive ventilation (NIV) users is constantly increasing worldwide. In France, the prevalence of home respiratory support use was 33 cases per 100,000 inhabitants in 2009. In Switzerland, it has increased 2.5 times since 2000 and reached 37.9 cases per 100,000 inhabitants in 2020.

Long-term Home-based use of non-invasive ventilation (NIV) costs £19,876 and results in an average quality-adjusted life year (QALY) of 2,391. Quality-adjusted life years (QALYs) is a measure that reflects the number of additional years of life gained by a patient as a result of preventive measures or treatment. It takes into account the quality of life during that period. The incremental cost of this strategy is cost-effectiveness =£11,318 per 1=QALY [6].

Long-term home-care NIV reduces the burden on medicine by lessening hospitalizations and the need for invasive

mechanical ventilation, as demonstrated by Davay Chandra et al. (2012). Their study revealed a substantial increase in NIV usage (462%) and a notable decrease (42%) in invasive ventilation use over a decade [7]. This shift towards NIV was associated with a decrease in hospitalizations, with the average length of stay dropping from 15 to 10.5 days, resulting in significant cost savings of \$158,443 per hospitalization [8]. Moreover, NIV usage is linked to a 44% reduction in the need for intubation and a 50% decrease in hospital mortality among COPD patients during exacerbations. It also helps prevent complications such as nosocomial pneumonia, reduces antibiotic usage, shortens Intensive care unit (ICU) stays, and lowers mortality rates, thereby significantly cutting healthcare expenses [9].

The effectiveness of home-care NIV is further supported by an analysis of 24 international home ventilation programs from 2005 to 2020. These programs served 35,413 users across 22 countries with a combined population of 546 million. The estimated prevalence of home ventilation ranged from approximately 7.3 to 47 per 100,000 population. Additionally, insights from developing nations suggest that a minimum budget of €168 per NMD patient annually can cover equipment costs, highlighting the cost-effectiveness of home ventilation in low to middle-income countries. Conversely, in high-income countries, a budget of approximately €1680 per patient per year is sufficient to cover the expenses of home lung ventilation [10].

Currently, in the Republic of Kazakhstan, there is no system in place to provide assistance to patients in need of prolonged respiratory support on an outpatient basis as part of medical care. Meanwhile, the number of patients with Chronic respiratory failure (CRF) is steadily increasing, consisting of 5% all over the world.

Additionally, a majority of studies support the notion that providing home non-invasive ventilation (NIV) for a specific group of COPD patients results in notable cost savings and improved outcomes. On average, each patient saved £8254 (Euro 11,720) annually. Hospital stays decreased from 78 to 25 days, admissions reduced from 5 to 2, and ICU days decreased from 25 to 4 [11]. Overall, domiciliary NIV was effective in reducing admissions and costs, emphasizing its importance in COPD management and securing financial for such services [12, 13].

A systematic review investigating the effects of CPAP therapy on OSA revealed that successful treatment significantly reduced the risk of near-miss incidents and road traffic accidents (RTAs). The studies utilized a before-and-after comparison method, with control groups made up the general population. Almost all studies reported a considerable reduction, and in some cases, a complete normalization, of RTA risk following effective treatment [14].

## **Tele-monitoring for homecare respiratory support**

Tele-monitoring can be used along with initiating long-term NIV (LTNIV), which has been proven to be worth the cost for certain conditions like CRF caused by NMDs and other restrictive lung diseases [15]. Initiation of home mechanical ventilation at home: a randomised controlled trial of efficacy, feasibility and costs [16].

Studies indicate that tele-monitoring can reduce healthcare usage such as emergency visits and hospital admissions, and is cost-effective for patients with ALS [17]. According to the early studies have explored the potential for tele-monitoring to detect

exacerbations of COPD in individuals using long-term NIV [13, 18].

The cost savings and improved clinical outcomes which are written above associated with using tele-monitoring for respiratory support in patients demonstrate its feasibility and effectiveness as a tool. Evidence from a group utilizing telemedicine showed an overall cost savings of \$54,843.61 USD (\$685.54 USD per patient per month) [19].

## **Project of Homecare Respiratory Support in Kazakhstan**

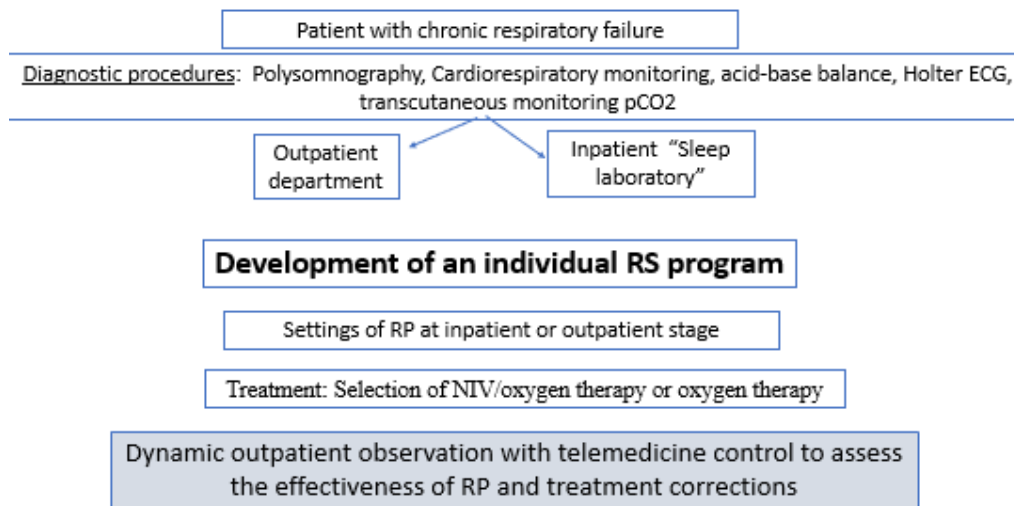
The planned project for the creation of a Centre for Homecare Respiratory Support will make possible to provide specialized medical care to patients suffering from severe CRF who require respiratory support on an outpatient basis with a 24-hour remote support service. Regular training will be provided for senior and mid-level medical professionals who provide long-term respiratory care in an outpatient setting.

The objectives of the project include the transfer of advanced international experience in the field of providing long-term respiratory support in outpatient settings, as well as professional training of senior and nursing staff, conducting training courses for doctors and nursing staff in the field of respiratory support, monitoring of outpatients on ventilation. The effectiveness of remote monitoring of respiratory support will also be assessed, clinical recommendations for the provision of long-term respiratory support in outpatient settings will be developed, and an optimal model of ambulatory centre for outpatient respiratory support will be created with its subsequent implementation in other regions of the country. The result of the project will be a significant improvement in the quality of life of patients, a reduction in the frequency and duration of hospitalizations, as well as a reduction in the social and financial burden on the healthcare system.

Based on our own clinical experience, as well as international experience in the use of various diagnostic options and respiratory support for patients with CRF, it is planned to purchase medical equipment, including consumables. Due to implement an action plan widely inform specialists of regional medical institutions and health authorities about the goals and objectives of the Homecare Respiratory Support Centre. To achieve this, it will be planned to hold several training conferences and seminars with the main subject experts at the regional and republican levels, and to use professional information portals and Internet resources. Information materials will be developed and created for doctors and patients, which will describe the principles of action, advantages, and clinical effects of the use of devices (invasive ventilation, non-invasive ventilation) of mechanical ventilation, as well as long-term oxygen therapy in patients with CRF. It is planned to establish professional contacts with clinic departments, pulmonologists, resuscitators, and family doctors to present our concept and identify patients in need of long-term respiratory support on an outpatient basis.

To obtain practical skills that are necessary to accompany patients receiving home respiratory support, it is planned to organize and conduct advanced training cycles for doctors and nursing staff with the involvement of leading domestic and foreign specialists. Currently, short-term courses of additional education are organized and conducted at our clinic. We have prepared short guides for doctors on sleep apnoea syndrome, non-invasive ventilation and bronchial drainage therapy. The next task necessary for the implementation of the Project is the selection of patients in need of long-term outpatient respiratory support. For this purpose, on a regular basis, consultations

## Algorithm of respiratory support



**Figure 2** – The algorithm of respiratory support for patients with chronic respiratory failure

with patients will be held at the outpatient centre of our clinic. Regular visits of Centre specialists to health care facilities in other regions of the country will be planned as well.

Based on the actual data obtained, action algorithms was developed for various situations that arise during remote monitoring of respiratory support carried out in an outpatient setting (Fig.2). It is planned that based on the results of two years of practical experience in the outpatient Respiratory Support Centre, a scientific assessment of the results of the treatment and diagnostic measures carried out and analysis of advanced international experience, we will develop clinical recommendations for the provision of long-term respiratory support in an outpatient setting.

In order to assess the medical and economic effect of long-term respiratory support in an outpatient setting, we plan to compare healthcare costs for patients receiving different types of respiratory support and those without it. Based on the results of the implementation and detailed critical analysis of the above tasks of our project, the optimal structure of the Centre for Outpatient Respiratory Support will be developed with a subsequent proposal to the Ministry of Health of Kazakhstan to open similar centres in other regions of the country.

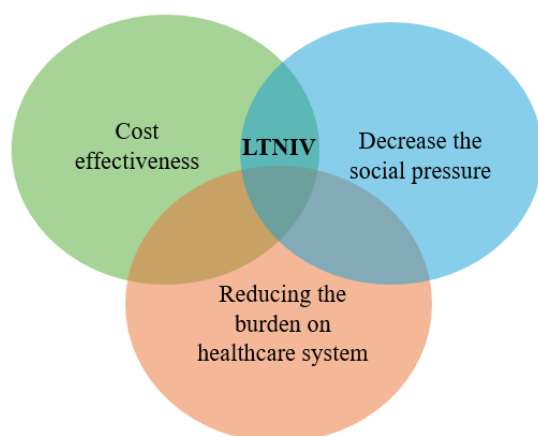
The important prospect of the project is the inclusion of long-term respiratory support in the State volume of free medical

care and further receipt of state subsidies to cover the costs of renting and maintaining artificial ventilation devices for patients with chronic respiratory failure in the Republic of Kazakhstan.

Successful implementation of homecare ventilation program will lead to a significant reduction in the financial burden of the state and society for the treatment of patients suffering from severe respiratory failure, improvement in the quality of life, reduction in the frequency and duration of hospitalizations (Fig. 3). Additionally, for patients with sleep apnoea, home respiratory support will lead to partial or full recovery of their working capacity, as well as a decrease in the frequency of road traffic accidents and industrial injuries.

Long-term home care non-invasive ventilation can alleviate social pressure by allowing patients to remain at home, which is often their preferred option. This choice for home care provides a comfortable and familiar environment for patients, leading to improved overall well-being and increased adherence to therapy.

In conclusion, homecare respiratory support can significantly improve clinical and social outcomes, reducing the need for hospitalizations of patients who suffer from severe chronic respiratory failure.



**Figure 3** – The interplay between cost-effectiveness, social tension, and the healthcare system culminates in the development of respiratory programs. LTNIV – long-term non-invasive ventilation

## Abbreviations

- ALS – Amyotrophic lateral sclerosis
- ARDS – Acute respiratory distress syndrome
- COPD – Chronic obstructive pulmonary disease
- CRF – Chronic respiratory failure
- CT – Computer tomography
- GP – General practitioner
- HRCT – High resolution computer tomography
- ICU – Intensive care unit
- LTNIV – Long-term non-invasive ventilation
- NIV – Non-invasive ventilation
- NMD – Neuromuscular disease
- OSA – Obstructive sleep apnoea
- QALY – Quality-adjusted life year
- RS – Respiratory support
- RTA – Road traffic accidents

**Author Contributions:** P.A., conceived of the presented idea. L.Z., and Zh.Z., worked on developing the theory. E.Ch.,

verified the analytical methods. A.B., supervised the findings of this work. All authors discussed the results and contributed to the final manuscript. The authors have read and agreed to the published version of the manuscript.

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