

DOI: <https://doi.org/10.56936/18290825-4.v18.2024-4>

DYNAMICS OF THE LEVEL OF AMINO-TERMINAL FRAGMENT OF PRO-BRAIN NATRIURETIC PEPTIDE IN PATIENTS WITH ATRIAL SEPTAL DEFECT LIVING AT HIGH ALTITUDE AT DIFFERENT STAGES OF DEFECT CORRECTION

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Received 09.01.2024; Accepted for printing 10.11.2024

ABSTRACT

N-terminal pro b-type natriuretic peptide levels reflect cardiac overload in congenital heart disease.

The aim of the present study was to investigate N-terminal pro b-type natriuretic peptide during the stages of surgical correction of atrial septal defect in an older age group living in a lowland and highland area.

A retrospective analysis of operated patients from 2013 to 2021 was performed. The main group consisted of 30 patients with atrial septal defect living in the high mountainous area. The control group included 30 patients living in the plain area. A comparative analysis of the immediate results of N-terminal pro b-type natriuretic peptide at the stages of disease-modifying antirheumatic drug plasty was performed, which was the basis for performing this study. N-terminal pro b-type natriuretic peptide values in healthy people vary from 0 to 125 pg/mL (control group). At the preoperative stage N-terminal pro b-type natriuretic peptide values in patients living in the plain averaged 532.33 ± 257.31 pg/mL, which was significantly 6.48 times ($p < 0.001$) higher than in the control group. In highlanders with interatrial septal defect N-terminal pro b-type natriuretic peptide levels significantly exceeded the values of the control group amounted to 2743.67 ± 163.87 pg/mL ($p < 0.001$). Positive correlation between N-terminal pro b-type natriuretic peptide, tricuspid annular plane systolic excursion and systolic dysfunction of the left atrium was determined.

N-terminal pro b-type natriuretic peptide indices in highlanders are significantly higher than in lowlanders both before and at all stages of surgical correction. Preoperative N-terminal pro b-type natriuretic peptide level more than 2743.6 ± 163.87 pg/mL in patients with ventricular septal defect living in high mountainous areas, New York Heart Association class III - IV, left ventricular ejection fraction less than 50% leads to secondary surgical outcome development in early postoperative period. N-terminal pro b-type natriuretic peptide is an independent reliable marker of heart failure.

KEYWORDS: atrial septal defect, NT-proBNP, high altitude, tricuspid annular plane systolic excursion, left ventricular ejection fraction.

INTRODUCTION

The main risk factor for cardiovascular complications in the older age group is right ventricular insufficiency [Ro S *et al.*, 2023] due to initial high pulmo-

nary hypertension, affecting the severity of the initial condition of patients and the course of the early postoperative period [Baumgartner H *et al.*, 2021].

CITE THIS ARTICLE AS:

Abdramanov K.A., Kokoev E.B., Abdramanov A.K. *et al.* (2024). Dynamics of the level of amino-terminal fragment of pro-brain natriuretic peptide in patients with atrial septal defect living at high altitude at different stages of defect correction. The New Armenian Medical Journal, vol.18(4), 4-11; <https://doi.org/10.56936/18290825-4.v18.2024-4>

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Among various imaging methods for cardiac assessment, echocardiography remains the main method because of its availability, non-invasive nature and cost-effectiveness [Lang R et al., 2015; Hulshof H et al., 2019; Sanz J et al., 2019].

An assessment of pulmonary artery systolic pressure is used to monitor the course of the disease. Tricuspid annular plane systolic excursion determination is the most informative in assessment of right ventricular contractile function at values of pressure in the small circle of blood circulation exceeding the systemic circulation [Lopez L et al., 2011; Alison B et al., 2019].

The use of non-invasive biomarkers reflecting pathologic changes in pulmonary artery vessels and allowing to diagnose pulmonary hypertension has a high relevance in clinical practice as well [Gainitdinova V, Avdeev S, 2019; Goetze J et al., 2020]. Brain natriuretic peptide is the most applicable prognostic biomarker to control right ventricular failure and myocardial stress in left ventricular hypertrophy [Galiè N et al., 2016; Nakagawa Y et al., 2019].

In the literature there are data on prognostic value of N-terminal pro b-type natriuretic peptide (NT-proBNP) in patients with congenital heart disease, but to date there is no unified position on NT-proBNP levels characterizing the presence or absence of heart failure and the degree of its development [Saperova E, Vakhlova I, 2017].

A retrospective study conducted by Takatsuki S. et al. (2020) with inclusion of 88 patients with pulmonary hypertension, 39 of which were patients with congenital heart disease under 21 years of age, showed that increased concentrations of brain natriuretic peptide and NT-proBNP are clinically significant predictors of pulmonary hypertension progression and death. However, BNP correlates more closely with hemodynamic changes due to a shorter half-life, and NT-proBNP is a more clinically significant predictor of mortality [Takatsuki S et al., 2012].

In a retrospective study of 7571 patients, it was concluded that congenital heart disease patients with high NT-proBNP levels have an increased risk of mortality compared to patients with low NT-proBNP levels [Ziqiang G et al., 2022].

Saidova V. and others (2012) in a study of 90 children with congenital heart disease revealed a

correlation between the level of NT-pro-BNP and the severity of heart failure.

Studies of NT-pro-BNP in adult patients are mainly retrospective in nature. Thus, Vivan J. et. al. (2017) while examining 595 patients previously operated on for various congenital heart disease, concluded that patients with high NT-proBNP levels have an increased risk of cardiovascular complications.

In the available literature, we did not find information on the diagnostic and prognostic informativity of the level of natriuretic peptide in blood in highlanders with atrial septal defect. Therefore, the purpose of the study was set.

MATERIAL AND METHODS

The study was conducted in patients over 30 years old, operated in the Southern Regional Centre for Cardiovascular Surgery of the Ministry of Health of the Kyrgyz Republic from 2013 to 2021. The first group included 30 patients aged 30 to 66 years, 19 of them female and 11 males, living in a flat area. The second group consisted of 30 patients, of which: 25 females and 5 males, aged 30 to 63 years, living in a settled highland environment (from 1800-2500 m to 3500-4500 m) [Mirra-khimov M, Goldberg P, 1978].

All operations were performed under artificial circulation and pharmaco-cold cardioplegia from the midline sternotomy. Xenopericardium or autopericardium was used to close the defects.

Preoperative diagnostics included such general clinical examination methods as electrocardiography, echocardiography and chest radiography.

The data were analyzed using a statistical software package (Excel, Statistica 7). To identify the reliability of differences between quantitative features having normal distribution, the parametric Student's test with calculation of t and p value was used. To identify correlations between quantitative data or quantitative data and qualitative features, the nonparametric Spearman rank correlation method was used with calculation of correlation coefficients (r) and statistical significance criteria (p). Depending on the value of r, the severity of the relationship was evaluated: ≥ 0.7 - pronounced; 0.4 - 0.69 - moderate; ≤ 0.39 - weak. Differences in values were considered reliable at a probability level of more than 95% ($p < 0.05$).

The clinical status of patients was assessed according to the ninth edition of the New York Heart Association classification issued in 1994 by the Criteria Committee of the American Heart Association, New York Branch. The New York Heart Association functional classification provides a simple way to categorize the degree of heart failure. It assigns patients to one of four categories based on how limited they are during physical activity; limitations/symptoms relate to normal breathing and varying degrees of dyspnea and/or angina pectoris (the New York Heart Association classification issued in 1994), (Table 1).

In both groups there were no patients belonging to functional capacity I. There were 22 (93.3%) patients from group 1 and 10 (33.3%) patients from group 2 in functional capacity II. Functional capacity III included 8 (6.6%) patients from group 1 and 18 (60%) patients from group 2. Functional capacity IV consisted of 2 patients from group 2, which amounted to 6.6%. It should be noted that the main number of patients in group 1 were in functional capacity II, namely 93.3%. The majority of patients of functional capacity III were patients from group 2 – 60%. Two patients with aortic calcification IV underwent prolonged preoperative preparation with dopamine and diuretics.

When analyzing electrocardiography, the following cardiac rhythm disorders were initially revealed: ventricular extrasystoles in group 1 patients were diagnosed in 6 (20%) cases, and in group 2 patients 16 (53.3%), which exceeded the number of patients with ventricular extrasysto-

les 2.6 times more than in group 1 patients. Also the number of patients with atrial fibrillations in the second group 18 (60%), exceeded the number of atrial fibrillations detected in the first group 7 (23.3%) in 2.57 times.

Echocardiographic examination revealed that the majority of patients in the studied groups had functional insufficiency of the tricuspid valve of various degrees due to enlargement of the right heart compartments. Relative insufficiency of tricuspid valve of II degree was revealed in 18 patients both in the first and second group. In group 2, patients' relative insufficiency of tricuspid valve of III degree was diagnosed in 10 (33.3%) patients and in 1 (3.33%) case in group 1 patient. Total tricuspid valve insufficiency was revealed in 2 patients of group 2.

RESULTS AND DISCUSSION

Preoperative NT-proBNP levels in patients with atrial septal defect living in the plains area:

Preoperative levels of NT-proBNP in serum of the patients with atrial septal defect living on the plains ranged from 320.0 to 1050.0 *pg/ml*, and averaged 532.33 ± 257.31 *pg/ml*, which was significantly 6,48 times ($p < 0.001$) higher than the values of the control group.

Preoperative NT-proBNP levels in serum of the 2nd group of patients ranged from 2610 to 3053 *pg/mL*, and, on average, amounted to 2743.67 ± 163.87 *pg/mL*, which was 33.1 times significantly ($p < 0.001$) higher than the values of the control group.

TABLE 1

Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels

Steps	Functional Capacity	Objective Assessment
Class I.	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II.	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III.	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV.	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

TABLE 2

Correlations between preoperative NT- proBNP levels and clinical and instrumental data of the patients with atrial septal defect

Clinical and instrumental data	r	p
Age	0.81	0.000
Sex	0.07	0.05
Functional capacity, heart failure, (New York Heart Association)	0.93	0.000
Tricuspid annular plane systolic excursion	-0.09	0.61
Left ventricular ejection fraction (%)	-0.63	0.02
Systolic pressure in the pulmonary artery	0.08	0.66
Right ventricle	-0.11	0.05

To confirm the data available in the literature about clinical and diagnostic value of NT-proBNP in patients with cardiovascular disease, we performed correlation analysis between preoperative peptide level and preoperative clinical and instrumental data of patients. As clinical data of the patient we used the clinical class of heart failure NYHA, instrumental data – echocardiography (right ventricular dimensions, tricuspid annular plane systolic excursion, pulmonary artery systolic pressure and left ventricular ejection fraction). The results of correlation analysis are presented in table 2.

Correlation analysis revealed no correlation between NT-proBNP and sex; a moderate positive correlation between NT-proBNP and age, and a moderate negative correlation between NT-proBNP and left ventricular ejection fraction, and between NT-proBNP and tricuspid annular plane systolic excursion.

The postoperative period in this group of patients after atrial septal defect plastics was favorable, no complications were observed. Patients were extubated 4-6 hours after surgical correction. The average stay in the intensive care unit was 18.24 ± 2.22 hours. In the postoperative period the patients were treated according to the standards of cardiac surgery patients' management. On 10.54 ± 0.24 days the patients were discharged from the hospital in satisfactory condition.

In addition to determination of preoperative NT-proBNP levels in group 1 patients, the dynamics of changes in this index in the postoperative period was studied (Table 3).

On the 1st day after surgical intervention there is a significant ($p < 0.05$) increase in NT-proBNP level compared to preoperative values. On the 3rd day - the tendency to reliable ($p < 0.05$) increase of NT-proBNP level is preserved. On the 6th day there is a significant ($p < 0.05$) decrease of NT-proBNP level in comparison with the 3rd day. On the 10th day there is a tendency to significant ($p < 0.05$) decrease of NT-proBNP level, however NT-proBNP values do not reach initial values and remain significantly ($p < 0.05$) higher than initial ones.

Preoperative NT-proBNP levels in groups of patients with atrial septal defect living at high altitude: Preoperative NT-proBNP levels in serum of the 2nd group of patients ranged from 1550.0 to 3200.0 pg/mL, and, on the average, amounted to 2423.16 ± 522.88 pg/mL, which is 29.5 times significantly ($p < 0.001$) higher than the values of the control group.

The study group consisted of patients with increased right ventricular tricuspid annular plane systolic excursion and increased LV diastolic volume.

To study the clinical and diagnostic value of NT-proBNP in patients with atrial septal defect living in high altitude conditions, a correlation analysis was performed, the results of which are presented in table 4.

As in the previous group, there was no correlation between peptide and sex. A weak positive correlation was found between NT-proBNP level and age. A moderate negative correlation was found between peptide level and tricuspid annular plane systolic excursion, as well as left ventricular ejection fraction.

The study of NT-proBNP synthesis dynamics in the postoperative period in patients living in high altitude conditions revealed a significant ($p < 0.001$)

TABLE 3

Dynamics of changes in serum NT-proBNP levels in patients with atrial septal defect living in a lowland area

Research stages	NT-proBNP (pg/ml)
Before surgery	532.33 ± 257.31^1
1 st 24 hours after surgery	728.10 ± 132.82^1
3 rd 24 hours after surgery	1018.31 ± 155.03^1
6 th 24 hours after surgery	721.64 ± 136.55^1
10 th 24 hours after surgery	699.81 ± 52.96^1

Note: reliability of differences ($p < 0.05$)

TABLE 4

Correlations between preoperative NT- proBNP levels and clinical and instrumental data of patients with atrial septal defect

Clinical and instrumental indicators	r	p
Age	0.42	0.01
Sex	0.07	0.05
Functional capacity, heart failure (New York Heart Association)	0.01	0.95
Tricuspid annular plane systolic excursion	-0.41	0.02
Left ventricular ejection fraction (%)	-0.63	0.02
Systolic pressure in the pulmonary artery	0.08	0.66
Right ventricle	-0.11	0.05

TABLE 5

Dynamics of NT-proBNP level changes in the postoperative period in patients of group 2

Research stages	NT-proBNP (pg/ml)
Before surgery	2743.67±163.87
1 st 24 hours after surgery	6258.03±364.78 ²
3 rd 24 hours after surgery	8041.50±381.35 ¹
6 th 24 hours after surgery	5872.34±312.64 ²
10 th 24 hours after surgery	3888.75±245.76 ¹

Note: ¹ – reliability of differences ($p < 0.001$); ² – reliability of differences ($p < 0.05$).

TABLE 6

Comparative characterization of preoperative NT-proBNP levels, clinical and instrumental data, early postoperative period

Investigated indicator, units of measure	1 (n=30)	2 (n=30)
NT-proBNP, (pg/ml)	430.33±72.37	2743.6±163.87 ¹
Pulmonary artery systolic pressure (mmHg)	30.73±5.23	38.50±7.72 ¹
Right ventricle (cm)	2.75±0.37	3.11±0.24 ¹
Tricuspid annular plane systolic excursion	1.29±0.06	1.09±0.15 ¹
Heart rhythm disturbance	0	14 (46,6%)
Acute cardiovascular		
Insufficiency	0	10(33.3%)
Stay in the intensive care unit (hours)	18.24±2.22	49.0±6,67 ¹
Bed days (days)	10.54±0.24	17.62±1.54 ¹

Note: ¹ – reliability of differences between groups ($p < 0.05$).

increase in its level in the 1st day after surgery compared to the preoperative level. On the 3rd day there was a tendency to significant ($p < 0.001$) increase of NT-proBNP level in comparison with the 1st day after the operation. On the 6th day a significant ($p < 0.001$) decrease of NT-proBNP level started in comparison with the 3rd day, which lasted till the 10th day, including in comparison with the 6th day, when NT-proBNP level did not reach initial values

The postoperative period was complicated by cardiac rhythm disturbance, and inotropic therapy was required. The patients spent 49.0 ± 6.67 hours on average in the intensive care unit and were discharged from the hospital in satisfactory condition on the 20th-24th day. Dynamics of NT-proBNP level changes in the postoperative period in patients of the 2nd group is presented in table 5.

To determine the threshold value of NT-proBNP the course of early postoperative period in both groups of patients was analyzed (Table 6).

The studied groups were comparable in age and number. The presented data shows that the maximum average values of NT-pro BNP level are observed in group 2 patients.

Statistically significant differences between pulmonary artery systolic pressure, right ventricle, tricuspid annular plane systolic excursion were determined. In 14 patients in group 2 the early postoperative period was complicated by the development of cardiac rhythm disturbances (atrial fibrillation) and in 10 patients – acute cardiovascular insufficiency, which led to a significant increase in the duration of their stay in the intensive care unit and hospital.

When comparing the highest NT-pro BNP secretion, namely on the 3rd day after surgery in both groups the following parameters were obtained (Table 7).

Group 1 patients showed a weak positive association between NT-pro BNP and tricuspid annular plane systolic excursion and a weakly negative association with right ventricle.

In group 2 patients' positive correlation with pulmonary artery systolic pressure and negative strong correlation with tricuspid annular plane systolic excursion and weak correlation with right ventricle indices was revealed.

TABLE 7

Correlations between postoperative NT-proBNP levels and clinical and instrumental data of patients in group 1 and 2

Clinical and instrumental data	r	p
Patients in group 1		
Tricuspid annular plane systolic excursion	0.31	0.08
Left ventricular ejection fraction (%)	-0.22	0.24
Pulmonary artery systolic pressure	0.12	0.50
Right ventricle	-0.32	0.08
Patients in group 2		
Tricuspid annular plane systolic excursion	-0.67	0.00
Left ventricular ejection fraction (%)	-0.22	0.24
Pulmonary artery systolic pressure	0.54	0.00
Right ventricle	-0.32	0.08

Conducting a study on NT-proBNP threshold values in elderly patients with atrial septal defect was the lack of data in the literature on patients living in high altitude conditions, as well as ambiguity and contradictory literature data on the prognostic value of NT-proBNP in patients with cardiovascular diseases.

According to the data of our study, NT-proBNP indices in highlanders significantly exceeded the values in patients living in the plain. This is explained by the fact that patients of the 2nd group were diagnosed with heart rhythm disorders in the preoperative period: in 16 (53.3%) – ventricular extrasystoles and in 18 (60%) atrial fibrillation. According to the European Society of Cardiology, elevated NT-proBNP levels in Parkinson's Disease may be an indicator of underlying atrial disease [Baumgartner H et al., 2021].

Also, the elevated NT-proBNP values in highlanders were influenced by chronic hypoxia, which leads to high pulmonary artery systolic pressure, as a result of which pulmonary artery dilation and pulmonary valve insufficiency often develop, which subsequently leads to right ventricular insufficiency. The development of right ventricular heart failure reveals hypertrophy and dilatation of the right heart, as well as impaired systolic and diastolic function of the right ventricle [Maripov A et al. 2013].

At the first stages of the study, to clarify the significance of NT-proBNP in patients with atrial septal defect living in high altitude conditions, a correlation analysis between preoperative levels of the peptide and clinical and instrumental data of patients was performed, which allowed us to identify common trends in the studied groups

The positive correlation between NT-proBNP, tricuspid annular plane systolic excursion and pulmonary artery systolic pressure we found indicates that NT-proBNP is an independent reliable marker of heart failure.

According to the results of the study it should be noted that NT-proBNP in the postoperative period behaves as a marker of myocardial damage, i.e. its increase on the 1-3rd day after surgery occurs in response to cardiomyocyte damage during cardiac surgery [Mauritz G et al., 2011; Kozlov I, 2016].

According to studies by Mauritz G.J. et al (2011), NT-proBNP concentration ≥ 1256 pg/mL at the time of diagnosis is a predictor of poor prognosis.

Thus, the analysis of the results of the study of preoperative NT-proBNP levels in patients with atrial septal defect living in high altitude conditions allows us to draw the following conclusion:

CONCLUSION

N-terminal pro b-type natriuretic peptide values in highlanders were significantly higher than in patients living in the plain.

N-terminal pro b-type natriuretic peptide is a marker of heart failure, hemodynamic abnormalities and the development of cardiovascular complications in the early postoperative period.

Preoperative NT-proBNP level more than 2743.6 ± 163.87 pg/mL in patients with atrial septal defect living in high altitude, New York Heart Association class III - IV, left ventricular ejection fraction less than 50% leads to the development of cardiovascular complications in the early postoperative period.

To reduce the risk of cardiovascular complications development in the early postoperative period, patients with preoperative NT-proBNP concentration higher than 2743.6 ± 163.87 pg/mL should undergo preoperative preparation of patients to compensate for heart failure.

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CONTENTS

4. **ABDRAMANOV K.A., KOKOEV E.B., ABDAMANOV A.K., ARZIBAeva P.M., ALISHEROV R.T.**
DYNAMICS OF THE LEVEL OF AMINO-TERMINAL FRAGMENT OF PRO-BRAIN
NATRIURETIC PEPTIDE IN PATIENTS WITH ATRIAL SEPTAL DEFECT LIVING AT HIGH
ALTITUDE AT DIFFERENT STAGES OF DEFECT CORRECTION
12. **KIRAKOSYAN E.V., NAZARENKO T.A., TROFIMOV D.YU., PAVLOVICH S.V., SUKHIKH G.T.**
UNEXPLAINED INFERTILITY: CLINICAL CHARACTERISTICS OF COUPLES AND
EMBRYOLOGICAL FEATURES OF IN VITRO FERTILIZATION PROGRAMS
25. **HOVHANNISYAN A.H., BAGHDASARYAN E.G., BAGHDASARYAN A.G., HARUTYUNYAN L.G.,
GRIGORYAN S.V., KHAN S., PANDIT D., ASOYAN V.A.**
THE CHALLENGES OF TREATMENT OF PATIENT WITH VIRAL HEPATITIS C AND
BRUCELLOSIS:
31. **SADUAKAS A.Y., KURAKBAYEV K.K., ZHAKUBAYEV M.A., MATKERIMOV A.ZH., SHAMSHIYEV A.S.,
KHANSHI MEAD, ABILKHANOV Y.Y., MAKKAMOV R.O., ERKINBAYEV N.N., KOZHAMKUL A.ZH.**
OUTCOME COMPARISON OF CAROTID ENDARTERECTOMY AND CAROTID ARTERY
STENTING IN PATIENTS WITH EXTRACRANIAL CAROTID ARTERY STENOSIS: ONE-
HOSPITAL-BASED RETROSPECTIVE STUDY
37. **SAROYAN G.E., MANUKYAN R.R., OHAN G.G., TER-STEPANYAN M.M.**
GROUP B STREPTOCOCCUS IN PREGNANCY, EPIDEMIOLOGICAL PECULIARITIES OF
EARLY AND LATE ONSET STREPTOCOCCAL INFECTIONS IN NEWBORNS
46. **TUKESHOV S.K., BAYSEKEEV T.A., CHOI E.D., KULUSHOVA G.A., NAZIR M.I., JAXYMBAYEV N.B.,
TURKMENOV A.A.**
DIAGNOSTICS, SURGICAL TREATMENT, AND REHABILITATION OF PATIENTS WITH
COMPLEX FRACTURED HAND INJURIES
55. **YAVROYAN ZH.V., HAKOBYAN N.R., HOVHANNISYAN A.G., GEVORGYAN E.S.**
CISPLATIN AND DEXAMETHASONE SEPARATE AND COMBINED ACTION ON LIPID
PEROXIDATION IN NUCLEAR FRACTIONS OF RAT BRAIN AND KIDNEY CELLS
67. **SHOJAEI S., HANAFI M.G., SARKARIAN M., FAZELINEJAD Z.**
PROGNOSTIC FACTORS FOR ENLARGED PROSTATE IN HEALTHY MEN'S ADULTS: A
CROSS-SECTIONAL STUDY
73. **BAYKOV A.V., HOVHANNISYAN H.A.**
PRIORITIZING COMMUNICATION SKILLS IN THE ARMENIAN UNDERGRADUATE
MEDICAL EDUCATION SYSTEM
84. **KARDOONI M., NIKAKHLAGH S., SALMANZADEH S., MIRMOMENI G., SADEGH ZADEH DIMAN S.**
RISING INCIDENCE OF MUCORMYCOSIS IS A NEW PANIC CHALLENGE IN SOUTHWEST
OF IRAN DURING COVID-19 PANDEMIC: ASSOCIATED RISK FACTORS AND
PREVENTIVE MEASURES
91. **MASHARIPOVA A., NURGALIYEVA N., DERBISSALINA G., BLAŽEVIČIENE A.**
EVIDENCE-BASED PRACTICE IN PALLIATIVE CARE NURSING
98. **KARRAR ALSHARIF M.H., ELAMIN A.Y., ALMASAAD J.M., BAKHIT N.M., ALARIFI A., TAHA K.M.,
HASSAN W.A., ZUMRAWI E.**
USING CHATGPT TO CREATE ENGAGING PROBLEM-BASED LEARNING SCENARIOS IN
ANATOMY: A STEP-BY-STEP GUIDE
107. **MARDIYAN M.A., DUNAMALYAN R.A., SAKANYAN G.H., SARGSYAN A.V., SAHAKYAN A.A.,
MKRTCHYAN S.A., SHUKURYAN A.K., GALSTYAN H.G.**
INTERRELATIONS BETWEEN SITUATIONAL AND PERSONAL ANXIETY AND QUALITY
OF LIFE DOMAINS
114. **VARDANYAN G.R.**
HEALTH RISKS OF SHIFT WORK FOR SERVICEMEN: PREVENTION AND REDUCTION
STRATEGIES
122. **ANDRADE-ROCHA F.T., CARDONA MAYA W.D.**
THE STRONG NEGATIVE IMPACT OF VARICOCELE ON SPERM MORPHOLOGY AND
INFERTILITY: A CASE REPORT