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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

CLINICAL, DIAGNOSTIC AND PREDICTIVE VALUE OF CYTOKINES IN RESPIRATORY DISEASES IN CHILDREN

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Branch of science: Medicine
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Baku -2024

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11.01.2024

GENERAL DESCRIPTION OF THE WORK

Relevance of the research. Taking into account the high prevalence and recurrence of acute respiratory diseases (ARD) among children and the high risk of development of severe forms, preparation of the effective treatment and prevention remains one of the urgent problems of modern pediatrics[1]. According to the data of epidemiological studies, up to 10 billion ARDs are registered in the world every year[2], about 2.2 million people lose their lives, and 3/4 of them are pneumonias [3]. 80% of cases of morbidity in children are ARDs, which mainly occur in early and preschool age [4].

The respiratory infections can weaken the functional activity of the immune system in children, and cause the inflammatory process to be prolonged and aggravated [5]. In recent years, the etiology of acute respiratory infections has been significantly expanded due to the identification of new viruses. The genetic structures of viruses are constantly changing, and as a result of this change, new types of viruses are formed, as a result of which the child's immune response to them varies. So, in recent years, a new viral agent has been discovered in the world: SARS-CoV-2.

It turned out that SARS-CoV-2 can cause many diseases in humans, from a mild form of acute respiratory infection to a severe acute

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respiratory syndrome, accompanied by symptoms of damage to other organs and systems [6]. Scientific studies have shown that children are also at risk of being infected with coronavirus, but compared to adults, the disease is asymptomatic or mild in them[7].

According to many researchers, children are a potential source of the spread of the COVID-19 infection, and the asymptomatic, mild course of the disease in them leads to the assessment of the epidemiological importance of the child population in the spread of the new coronavirus infection[8, 9]. However, little is known about the biological characteristics of this uncommon infection in children, and further research is needed.

It is known that cytokines play an important role in the pathogenesis of inflammatory diseases of the respiratory tract. Disruption of production and reception of cytokines during inflammatory diseases leads to immunological defects in the defense against infection, enhances the damaging effect of microorganisms and their toxins on lung tissue [10]. From this point of view, the study of endogenous factors that play a role in the pathogenesis of acute respiratory diseases - the state of immunity and the immunoregulatory system, the interaction of the cytokine system is of great scientific and experimental importance.

Thus, the relevance of the above-mentioned problems and the assessment of cytokines during respiratory diseases in children can play

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an important role in the early diagnosis and prediction of these diseases.

Object and subject of the research: 89 children (54.3%) of studied were diagnosed with ARD, 75 children (45.7%) were diagnosed with pneumonia of COVID-19 (PCR positive) were the object of study. The clinical, diagnostic and prognostic significance of the cytokines we determined in the blood serum of patients was studied as the subject of the research.

The aim of the research: Study of the clinical, diagnostic and predictive significance of proinflammatory cytokines in respiratory tract diseases in children.

The tasks of the research:

1. To determinate the level of pro-inflammatory cytokines (IL-1β, IL-6, IL-18, IL-21 and γ-INF) in blood serum in diseases of the respiratory tract in children.
2. The clarifying the clinical features of the disease depending on the severity of the disease in children with COVID-19 (PCR positive) pneumonia.
3. Determination and assessment of clinical significance of biomarkers -ferritin, fibrinogen, D – dimer in serum of patients with COVID-19 (PCR positive) pneumonia.
4. Determination of the level of vitamin D in children with respiratory diseases.
5. To prepare a logistic mathematical model that predicts the severity of COVID-19 disease.

Research methods. Examination methods include anamnestic data, epidemiological (learned from the history of the disease and parents), clinical data. At the same time, instrumental and laboratory examinations were performed, general and biochemical blood analysis, concentration of cytokines in blood serum was studied, ferritin, fibrinogen, D-dimer and vitamin D levels were determined and analyzed. A typical diagnosis of COVID-19 was established by polymerase chain reaction (PCR) of a nasopharyngeal swab according to protocol.

The main provisions of the defense are:

- The imbalance in the expression of pro-inflammatory cytokines in the pathogenesis of acute respiratory diseases indicates the activity

of the inflammatory process.

- During the course of COVID-19, the disease manifests itself clinically with symptoms of damage to the respiratory tract (respiratory syndrome), and these symptoms are important in determining the diagnosis and prognosis.
- A low level of vitamin D in the blood serum in children with respiratory tract diseases is considered one of the essential factors for exacerbation of the disease.

- The prognostic mathematical program "UCA-2022" (Complications of COVID-19 in Children) prepared on the basis of clinical and laboratory risk factors allows to determine the risk of complications of the disease with individual high sensitivity and specificity.

The scientific novelty of the research work:

- The characteristic features of cytokines in complex form in children's respiratory tract diseases were studied, and the clinical-diagnostic and prognostic significance of the changes detected in their level was determined.

- Clinical and laboratory indicators studied in children with COVID-19 (PCR positive) pneumonia were important in early diagnosis of complications of the disease.

- The impact of vitamin D on the clinical signs of respiratory diseases in children was studied.

- For the first time, the effectiveness and feasibility of the "UCA-2022" mathematical model, which allows predicting the severity of the COVID-19 disease based on statistical studies, has been proven

Theoretical and practical importance of the research work: Investigating the diagnostic and prognostic significance of cytokines in inflammatory diseases of the respiratory tract in children will be considered as an additional diagnostic criterion and will create a basis for the improvement of appropriate treatment measures.

The importance of coronavirus in the etiological structure of acute respiratory infections was clarified and its clinical characteristics were studied. The prognostic mathematical program "UCA-2022" developed on the basis of the indicators important during COVID-19 can be applied to predict the severity of the disease.

The approval of the research work: Dissertation work discussion: 08.10.2021 at the International Scientific-Practical Conference dedicated to Tamerlan Aliyev's 100th anniversary "Actual Problems of Medicine-2021" (Baku, 2021), 23.11.2021 at the XXIV Republican Scientific Conference of Doctoral Students and Young Researchers dedicated to the 880 th anniversary of Nizami Ganjavi (Baku, 2021), 10.11.2021 at the International Scientific and Practical Conference on "Modern medicine: new approaches and current research" (Moscow, 2021), 04.03.2021 at the "Pediatric Otolaryngology Module 1" scientific-practical conference organized by the Ministry of Health of the Republic of Azerbaijan and ISIM (Baku, 2021), 26.12.2021 organized by the Ministry of Health of the Republic of Azerbaijan and ISIM "Role of Laboratory Diagnostics in Clinical Medicine. Traditions and Innovations" at the scientific-practical conference (Baku, 2021), May 21-25, 2022, at the İnternational scientific-practical conference dedicated to "270 years of Shusha" on the topic "Current problems of medicine-2022" (Baku, 2022), 11-13.10.2022 XII İnternational scientific-practical congress on "Actual problems of pediatrics" (Baku, 2022), at the İnternational scientific-practical congress on "Innovations in Pediatrics and Neonatology" dedicated to the 100th anniversary of Heydar Aliyev on 06.05.2023 (Baku, 2023) , reported at the 41st National Congress of the Azerbaijan Association of Pediatricians dedicated to the 100th anniversary of Heydar Aliyev on 24.06.2023 (Baku, 2023).

The application in practice: The results of the research are applied in the Educational Therapeutic Clinic of AMU, in the practical work of the Children's Infectious Diseases Hospital of Narimanov Medical Center Public Legal Entity, and in the teaching process of the II Department of Pediatric Diseases.

The name of the institution where the research study was perfomed: Dissertation work was performed at the Educational-Therapeutic Clinic of Azerbaijan Medical University and Children's Infectious Diseases Hospital of Narimanov Medical Center Public Legal Entity.

Published scientific works: 25 scientific works have been published on the subject of the dissertation, 16 of them are articles and 9 are theses.

The volume and structure of the dissertation work: The dissertation consists of 161 pages of computer text (200.700 characters), introduction (10.000 characters), literature review (50.900 characters), chapter of materials and methods (14.600 characters), 3 chapters of personal research (82.100 characters), conclusion, results, practical recommendations (43.100 characters) and a bibliography including 245 sources (14 of them Azerbaijani , 231 foreign). The dissertation work is illustrated with 27 tables, 2 pictures and 21 graphs.

MATERIALS AND METHODS OF RESEARCH

164 children between the ages of 1 month and 17 years with moderate and severe course were involved in the study. For comparison, 35 patient formed the control group of practical healthy children.

According to the purpose of the study, patients were divided into two groups: group I included 89 (54.3%) patients diagnosed with ARD, group II included 75 (45.7%) patients diagnosed with COVID-19 (PCR positive) pneumonia. Group I, in turn, was divided into two subgroups: subgroup I with ARD – 53 (59.6%), subgroup II 36 (40.4%) consisted of patients diagnosed with other upper respiratory tract diseases (bronchitis, laryngotracheitis, laryngitis et al.). Subgroup II is conventionally denoted as ARD+.

COVID-19 (PCR positive) patients were divided according to the degree of severity into the group of moderately severe - 49 (65.3%) and severe - 21 (34.7%) patients.

During the study, patients with bronchial asthma, autoimmune diseases, cystic fibrosis, primary and acquired immune deficiency, asymptomatic, mild course during COVID-19 (PCR positive), typical multisystem inflammatory syndrome (MIS-C) were excluded.

When diagnosing the patients included in the study, the International Classification of Diseases (ICD-10) was used. When diagnosing the patients with COVID-19, the recommendation of WHO and Methodical guidance on (COVID-19) management which was approved by the decision of the Scientific and Medical Council of the Ministry of Health of the Republic of Azerbaijan dated 2020 (protocol No. 9) was used.

When comparing the examined children by gender, there were 91 (55.5%) boys, 73 (44.5%) girls in the patient group, 17 (48.6%) boys and 18 (51.4%) girls in the control group. During the examination, there were no significant gender differences among children.

By gender distribution in the study groups: 54 (60.7%) boys, 35 (39.3%) girls diagnosed with ARD, 37 (49.3%) boys, 38 (50.7%) girls diagnosed with COVID-19.

The average age of children in the main group was 3.9±0.3, and in the control group it was 4.1±0.7.

In order to compare the clinical characteristics of the disease of the children included in the study according to their age, the children were divided into groups of <1 year, 1-3 years, and >3 years: 26 children under 1 year (15.9%), 71 - under 1-3 years (43, 3%), the older age group consisted of 67 children (40.9%).

When dividing the patients studied by area: 63 people (84.0%) of the COVID-19 patients were from the city, 12 people (16.0%) were from the district, 73 people (82.0%) of the AR-patients were from the city, 16 people (18, 0%) were from the district.

During the analysis of obstetric and gynecological anamnesis, it was found that 85 (51.8%) of patients included in the study were born mainly from primary pregnancy, 78 (47.6%) from repeated pregnancy, 96 (58.5%) from Caesarean section, and 68 (41.5%) from physiological birth. Pathological pregnancy was recorded in 17 (10.4%) of patients, consanguineous marriage was recorded in 13 (7.9%) of patients. 93 children (56.7%) were fed artificially, 68 children (41.5%) were fed breast milk, and 3 children (1.8%) were fed mixed food.

According to the information given by the parents, 93 (56.7%) of the children received preventive vaccinations on time according to the schedule, 53 (32.3%) were partially vaccinated, and 18 (11.0%) were not vaccinated and 18 (11.0%) did not receive vaccinations.

The laboratory tests used for the study were conducted in the Scientific Research Laboratory of the Department of Biological Chemistry of AMU, in the Central Laboratory of the Educational Therapeutic Clinic of AMU and in the Scientific-Research Immunology Laboratory of AMU.

The concentration of IL-1ß, IL-6 and IL-18 cytokines in blood

serum was determined by the "IFA-Best" test system manufactured by the company "Vektor-Best" (Russian Federation), and the concentration of IL-21 and γ-IFN cytokines by "Invitrogen" (by Thermo Fisher Scientific, USA, Medispec 6000 (Microplate Reader RT-6000 device) company, using mono- and polyclonal antibodies against the indicated cytokines using a solid-phase immunoenzymatic method using the sandwich principle.

The concentration of fibrinogen was determined in the "Steelex" device and the reagent kit of the "Steelext" company was used. The concentration of D-dimer in the blood serum was determined by the enzyme immunoassay (IFA) method, using the Wondfo device and the reagent kit of the "Wondfo Bio-Tech" company. The concentration of 25 (OH) D3 was determined using the reagent kit of the company "Pishgaman" (made in Germany), the concentration of ferritin was determined using the reagent kit of the company "Alkor Bio" (made in Russia), by the enzyme immunoassay (IFA) method, on the "Stat Fax 4700" device.

Statistical studies were carried out in "MS EXCEL-2019" and "IBM Statistics SPSS-26" programs using variation, discriminant, correlation, dispersion, regression and ROC-analysis methods. Logistic regression analysis was performed by Wald's backward method.

A special "UCA-2022" online calculator was developed based on the formula obtained in the logistic regression model and is available for free use on the Internet at https: //amu.edu.az/page /1327/elm.

RESULTS OF PERSONAL RESEARCH

In the first stage of the study, clinical and laboratory indicators of patients diagnosed with ARD were examined. The clinical picture of the disease was typical for the studied pathology. The patients were examined during the acute period of the disease.

The following clinical signs were observed in patients with ARD, in the acute period of the disease: fever and catarrhal symptoms, cough, rhinorrhea, etc.

In patients included in ARD- subgroup, temperature – 35 (66%) (37.9±0.10° C), cough – 24 (45.3%), dyspnea – 2 (3, 8%), rhinorrhea

– 36 (67.9%), loss of appetite – 32 (60.4%), pallor of mucous membranes - 49 (92.5%), hyperemia of throat –41 (77,4%) cases were detected. SPO2 – 96.5±0.2%, pulse – 125.4±1.6/min., RR – 32.5±0.9/min. were registered. During the percussion of the lungs, a clear percussive sound was heard in the patients, and harsh breathing was heard during auscultation.

In patients included in the ARD+ subgroup, the following were identified: temperature - 21 (58.3%) cases (37.6±0.20 C), cough - 35 (97.2%) ($p < 0.001$), dyspnea – 7 (19.4%) ($p=0.017$), rhinorrhea – 21 (58.3%), hyperemia of throat –27 (75,0%), pallor of the mucous membranes – 32 (88.9%), loss of appetite – 12 (33.3%) ($p=0.013$) cases. SpO2 – 95.9±0.3%, pulse – 125.6±3.2/min, RR – 32.0±1.4/min were registered. Expiratory dyspnea and the participation of auxiliary muscles in breathing were observed during accompanying bronchoobstructive syndrome in some patients, including the KRX+ subgroup. The cough was spasmodic, with difficult expectoration.

On percussion of the lungs in patients, the presence of a clear percussive sound or a box sound, dry whistling and single dry crackles were heard on the background of stiff breathing during auscultation.

X-ray of the chest showed the enlargement of the lung roots and the strengthening of the lung pattern in both subgroups. A general analysis of blood in both subgroups revealed relatively leukocytosis, a slight increase in the level of CRP and ESR, and eosinophilia in children with a tendency to allergies.

During the study, the frequency of clinical features of patients with ARD was compared between different age groups. When comparing clinical signs between age groups, no noticeable differences were observed, the most common symptoms were fever, cough, rhinorrhea.

In the next stage of our research, a comparative analysis of cytokines (IL-1β, IL-6, IL-18 in 30 children, IL-21 and γ-INF in 56 children) was performed in patient diagnosed by ARD.

In ARD, the mean value of IL-1β increased by 1.9 times compared to the value of the control group and was 1.05±0.25 pg/ml on average, and 0.55±0.21 pg/ml - in the control group ($p = 0.938$). The level of IL-6 increased 1.6 times to 2.56 ± 0.37 pg/ml, while in the control

group this indicator was 1.63 ± 0.46 pg/ml (p=0.044), the level of IL-18 was 186.5±24.5 pg/ml, while in the control group it was 231.9±21.9 pg/ml (p=0.185). The level of IL-21 increased 2.6 times compared to the control group and reached 26.92±2.8 pg/ml, in the control group it was 10.34±4.2 pg/ml (p<0.001), level of γ-INF increased 1.4 times and was 4.74±0.60 pg/ml (p=0,681), while in the control group it was 3.32±0.44 pg/ml.

When comparing the level of cytokines depending on the clinical course of the disease, these indicators differed in ARD- and ARD+ subgroups. Thus, the average concentration of IL-1β was 1.17 pg/ml in the ARD- subgroup (median 0.50 pg/ml, 0.00-2.35 in Q_1 and Q_3 quartiles), 0.91 pg/ml in the ARD+ subgroup (median 0.00 pg/ml, 0.00-1.90 in Q_1 and Q_3 quartiles). In the ARD- subgroup, the level of IL-1β increased by 2.1 times compared to the control group, and in the ARD+ subgroup by 1.7 times. The average level of IL-6 in the ARD- subgroup was 1.79 pg/ml (median1.40 pg/ml, 0.95-2.65 in Q_1 and Q_3 quartiles), and in the ARD+ subgroup was 3.44 pg/ml (median 2.95 pg/ml, 1.00-6.10 in Q_1 and Q_3 quartiles). In the ARD- subgroup, the level of IL-6 was 1.1 times higher than that of the control group, and in the ARD+ subgroup, it was 2.1 times higher than that of the control group (p=0,024).The level of IL-18 in the ARD and ARD+ subgroups was at the lower limit of their mean indicators of the control group, on average 162.3 pg/ml (median 159.8 pg/ml, 47.4–247.4 in Q_1 and Q_3 quartiles) and 214.2 pg/ml (median 199.4 pg/ml, 98.2-366.4 in Q_1 and Q_3), respectively. The concentration of IL-21 increased by 2.3-fold (p<0,001), and 3.2-fold (p<0,001) in the ARD and ARD+ subgroups compared to the control group, on average 23.3 pg/ml (median 18.4 pg/ml, 13.9- 25.1 in Q_1 and Q_3 quartiles), 33.1 pg/ml (median 24.8 pg/ml, 10.6-42.9 in Q_1 and Q_3 quartiles). Serum γ-IFN levels in the ARD-subgroup averaged 6.40 pg/ml (median 5.80 pg/ml, 2.20–10.10 in Q_1 and Q_3 quartiles), compared with the control group 1.9 times increased (p=0.030). In the ARD+ subgroup, it was 1.95 pg/ml (median 1.20 pg/ml, 0.70-2.60 in Q_1 and Q_3 quartiles) and was 1.7 times less than the control group (p=0.018).

Based on the ROC analysis, it is determined that the area of the ROC curve of IL-1β in ARD patients compared to the control group is

0.440±0.107; 95% CI: upper and lower limits - 0.230-0.649; p=0.575; area of ROC curve of IL-6 is 0.667±0.105; 95% CI: upper and lower limits - 0.462 - 0.873: p=0.119; area of ROC curve of IL-18 is 0.596 ±0.107; 95% CI: upper and lower limits - 0.389 - 0.807: p=0.360; area of ROC curve of IL-21 is 0.567±0.086; 95% CI: upper and lower limits - 0.398- 0.736: p=0.393 was determined. The area of the ROC curve of the γ-INF indicator is 0.185±0.056; 95% CI: upper and lower limits - 0.075- 0.294: p<0.001 was statistically significant.

Thus, it shows that pro-inflammatory cytokines, which affect the pathogenesis and course of inflammatory diseases, play a role in inflammatory reactions by affecting the proliferation and differentiation of immune system cells, especially T-lymphocytes and their subpopulations that perform different functions, B-lymphocytes. The detected change in the level of cytokines in the blood serum of children with ARD is one of the components of the immune response that eliminates the activity of the pathogen and can be considered as clinical and diagnostic criteria of the inflammatory process.

The level of vitamin D in patients with acute respiratory disease was less in both subgroups (2.2 and 2.3 times) than in the control group (46.4±3.0), 21.5±1.5 ng/ml (14,2-28.7 ng/ml), 20.1±1.2 ng/ml (11.32-24.1 ng/ml), respectively.

We evaluated the correlative relationships between the patient's condition and main clinical indicators in the patients examined during ARD. Negative correlation was observed between patient condition and age in AR-patients ρ=-0.356, p<0.001; vit. D: ρ=-0.444, p=0.050; a significant positive correlation was observed between patient condition and temperature: ρ=+0.348, p<0.001; pulse: ρ=+0.323, p=0.008; loss of appetite: ρ=+0.330, p=0.002; CRP: ρ=+0.236, p=0.044. Significant negative correlation between dyspnea and SPO2: ρ=-0,332, p=0,002 and positive correlation between dyspnea and cough: ρ=+0.239, p=0.024 were revealed; positive relationship between temperature and heart tones: p=+0.229, p=0.033; pulse: ρ=+0.303, p=0.014; negative relationship between SPO2 and temperature: ρ=-0.303, p=0.005; negative correlation between SPO2 and pulse: ρ=-0.249, p=0.046; RR: ρ=-0.263, p=0.034; dyspnea: ρ=-0.332, p=0.002 was observed.

In the first stage of the study, clinical and laboratory indicators of patients diagnosed with COVID-19 (PCR positive) pneumonia were examined.

When comparing the clinical symptoms in children with COVID-19 (PCR positive) pneumonia, the main leading symptoms were fever and cough. In addition to the clinical signs characteristic of pneumonia, patients have various clinical symptoms characteristic of a severe course. İntoxication, toxic symptoms, lethargy, muscle hypotonia, cyanosis, etc. has been observed.

X-ray examination of the lungs revealed unilateral and bilateral pneumonia in patients. Among physical symptoms, shortening of the percussive sound, wet crackles with small bubbles and dry crackles on the background of hard breathing were observed.

The following clinical signs were observed in the patients with COVID-19 (PCR positive): in moderately severe course Sp02 – 97.7±0.2%, pulse – 109.5±2.41/min, RR – 30.0±1.51/min. were registered. Fever (37.5±0.10C) – in 45 (91.8%) patients, cough – in 48 (98%) patients, dyspnea – in 3 (6.1%), loss of appetite – in 46 (93.9%), muscle pain – in 6 (12.2%), headache – in 3 (6.1%), loss of sense of smell and taste – in 2 (4.1%), vomiting – in 5 (10.2%), diarrhea – in 1 (2.0 %) were detected.

In patients with a severe clinical course, $Sp0_2$ - 92.5±0.7% ($p<0.001$), pulse – 117.8±5.0/min ($p=0.020$), RR – 31.4±1.6/min was recorded. Fever in 21 (80.8%) cases (38.1±0.1°C), cough – 26 (100%), dyspnea – 10 (38.5%) ($p<0.001$), loss of appetite 26 (100,0%), muscle pain – 7 (26.9%), headache – 4 (15.4%), loss of sense of smell and taste – 3 (11.5%), vomiting – 9 (34.6%) ($p= 0.010$), diarrhea – 6 (23.1%) ($p=0.003$), lethargy – 21 (80.0%)($p<0.001$), cyanosis – 8 (30.8%) ($p<0.001$), muscle hypotonia was observed in – 16 (61.5%) ($p<0.001$) cases.

According to the statistical analysis of some data in COVID-19 (PCR positive) pneumonia patients, the frequency of occurrence of coronavirus varied between age groups. In our study, comparing clinical signs between age groups, the most common symptoms were fever and cough. Muscle pain, headache, loss of sense of smell and taste

were observed in older age groups, lethargy, cyanosis, muscle hypotonia mainly in <1 age groups.

The analysis of hematological indicators of blood in COVID-19 (PCR positive) patients showed different changes during the acute period of the disease. In the peripheral blood analysis, the changes in leukocyte, monocytosis, lymphocytosis, tendency to thrombocytopenia, and a slight increase in the level of CRP and ESR were observed.

In the next stage of the study, significantly increase in the amount of cytokines in blood serum was found in patients with COVID-19 (PCR positive) compared to the indicators of the control group.

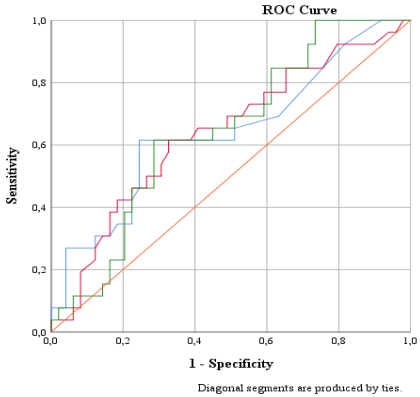
The concentration of IL-1β in the blood serum increased 3.3 times compared to the corresponding indicators in the control group, on average 1.84±0.39 pg/ml ($p=0.013$), the level of IL-6 increased 2.4 times and was 3.97±0.36 pg/ml on average ($p=0.001$). The level of IL-18 in the COVID-19 group increased by 1.8 times compared to the corresponding indicator of the control group, and was calculated on average 421.5±20.6 pg/ml ($p<0.001$).

In the study, the ROC curve of the studied cytokine indicators was constructed in the patients with COVID-19 (PCR positive) pneumonia compared to the control group. It was determined that the area of the ROC curve of IL-1β was 0.704±0.085; 95% CI: upper and lower limits - 0.537–0.870, respectively; $p=0.013$. IL-1β can be evaluated as an indicator with higher specificity and sensitivity. The area of the ROC curve of IL-6 was 0.775±0.066; 95% CI: upper and lower limits - 0.645-0.905; $p=0.001$; the area of the ROC curve of the IL-18 indicator is 0.846 ±0.047; 95% CI: upper and lower limits - 0.754–0.939, respectively; $p<0.001$ can be considered as a diagnostically significant indicator.

In children with COVID-19 (PCR positive), the level of pro-inflammatory cytokines in the blood serum was determined to be significantly higher than the control limits, depending on the severity. Thus, compared to the control group the concentration of IL-1β in patients with COVID-19 (PCR positive) was 2.3 times higher in moderately severe course ($p=0,042$), 5.4 times higher in severe course ($p=0.006$), IL-6 was 2.2 times higher in moderately severe course ($p=0,004$), 2.9 times in severe course ($p<0,001$), IL-18 increased 1.7 times higher in

moderately severe (p<0,001) and 2 times in severe course (p<0,001). The mean value of IL-1β level was 2.97 pg/ml in patients with severe course (median 1.20 pg/ml, 0.05-5.00 in Q_1 and Q_3 quartiles), in patients with moderately course was 1.24 pg/ml (median 0.10 pg/ml, 0.05-1.00 in Q_1 and Q_3 quartiles). The highest level of IL-6 was recorded at 4.79 pg/ml during severe (median 4.45 pg/ml, 1.80-6.90 in Q_1 and Q_3 quartiles) and in moderately severe course it was 3.54 (median 2.70 pg/ml, 1.40-5.30 in Q_1 and Q_3 quartiles). The concentration of IL-18 in the blood serum was 469.2 pg/ml during the severe course of the disease (median 468.0 pg/ml, 317.2-513.5 in Q_1 and Q_3 quartiles), and 396.1 pg/ml during the moderately severe course of the disease (median 372.5 pg/ml, 253.3-480.2 in Q_1 and Q_3 quartiles).

ROC analysis of cytokine indicators in different severity levels was performed in COVID-19 (PCR positive) patients (graph 1).



Indicators	Area	Standart error	p- statistical sign.	95% Cİ	
				Upper Bound	Lower bound
IL-1β	0,641	0,070	0,045 *	0,505	0,778
IL-6	0,639	0,068	0,048 *	0,506	0,773
IL-18	0,644	0,065	0,041 *	0,518	0,771

Graph 1. Indicators of ROC-analysis in diagnosing disease severity in COVID-19 (PCR positive) patients.

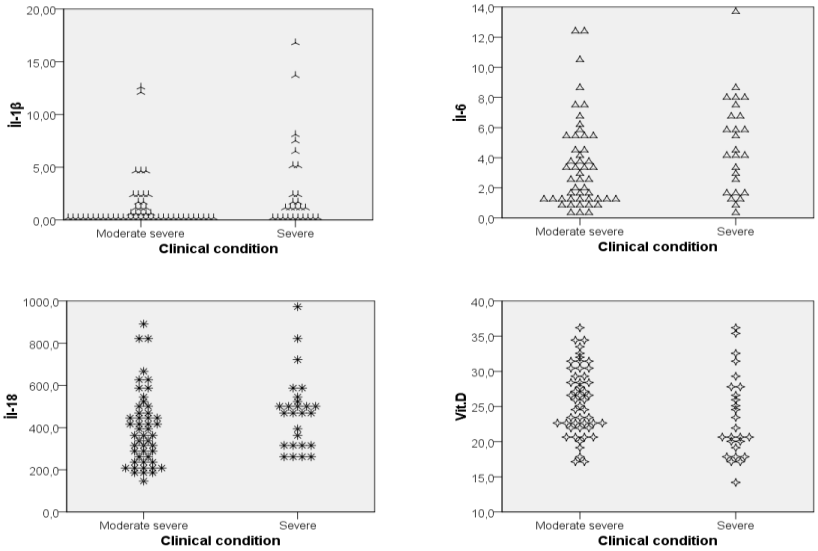
According to our calculations, the mentioned cytokines have high specificity and sensitivity and can be independent markers in the early diagnosis of COVID-19.

It is clear from the study that the level of cytokines in children with COVID-19 (PCR positive) pneumonia affects the formation of the immune response during inflammation. Prominent changes in the studied parameters were found in children with COVID-19 (PCR positive) with severe course compared to moderate course. It is characterized by the immaturity of the immune system, their low functional activity and suppressor orientation of the immune response formation mechanisms in patients with a severe course.

In COVID-19 (PCR positive) patients, correlational relations between both clinical symptoms and cytokine indicators were determined. A significant positive correlation was observed between IL-1β and IL-18: $\rho=+0.297$, $p=0.010$; a significant positive correlation was observed between IL-6 and IL-18: $\rho=+0.341$, $p=0.003$. Between the patient's clinical condition and cytokines: with IL-1β: $\rho=+0.234$, $p=0.043$; with IL-6: $\rho=+0.230$, $p=0.047$; with IL-18: $\rho= +0.238$, $p=0.040$ significantly positive correlation was found (graph 2).

We evaluated the correlation some clinical signs in the examined COVID-19 (PCR positive) patients: during COVID-19 (PCR positive), there is a negative relationship between the patient's condition and SPO2: $p=-0.713$, $p<0.001$; pulse: $\rho=+0.280$, $p=0.019$; temperature: $\rho=+0.389$, $p=0.001$; dyspnea: $\rho=+0.407$, $p<0.001$; vomiting: $\rho=+0.298$, $p=0.009$; diarrhea: $\rho=+0.344$, $p=0.003$; $p=+0.446$, $p<0.001$, there was a significant positive correlation between the course of pregnancy, that is, in the acute period of the disease, the increase in clinical indicators with the worsening of the patient's condition leads to the worsening of the disease. There was an inverse relationship between vitamin D and the patient's condition $p=-0.227$, $p=0.051$. Significant negative correlations were observed between SpO2 and dyspnea: $\rho=-0.459$, $p<0.001$; vomiting: $\rho=-0.233$, $p=0.045$; diarrhea: $\rho=-0.357$, $p=0.002$; glucose: $\rho=-0.409$,$p=0.038$, there were significant positive relationships with RBC: $\rho=+0.426$, $p<0001$; HGB: $\rho=+0.372$, $p<0.001$; HCT: $\rho=+0.312$, $p=0.008$. There are positive relationships

between muscle pain, headache, loss of sense of smell and taste, hyperemia of yawning and age: ρ=+0.598, p<0.001; ρ=+0.406, p<0.001; ρ=+0.397, p<0.001; ρ=+0.402, p<0001. There were significant positive correlations between loss of sense of smell and taste and muscle pain: ρ=+0.584, p<0.001; headache: ρ=+0.701, p<0.001; CRP: ρ=+0.261, p=0.031.



Graph 2. Correlations between cytokines, vitamin D and severity of disease in COVID-19 (PCR positive) pneumonia patients.

In the next stage of the study, the comparative characteristics of clinical data and cytokines in ARDs and COVID-19 (PCR positive) patients were analysed.

During COVID-19, intoxication, digestive disorders, auscultative changes in the lungs, weakened breathing, loss of sense of smell and taste, muscle aches, headaches, etc. are observed, and during ARDs, the syndrome of damage to upper respiratory tract at various levels, catarrhal symptoms, rhinitis were more pronounced. In both compari-

son groups, fever (88.0%, 62.9%), cough (98.7%, 66.3 %) were generally noted.

The level of cytokines in COVID-19 (PCR positive) patients was found to be significantly different compared to the corresponding indicators in patients diagnosed by ARD. The level of IL-1β in patients with COVID-19 (PCR positive) compared to the patients with ARD increased by 1.8 times ($p<0.001$), IL-6 by 1.6 times ($p=0.025$), and IL-18 by 2.3 times ($p<0.001$) (table 1).

Table 1. Comparison of cytokine levels in ARD and COVID-19 (PCR positive) pneumonia patients

		N	M	±m	Min	Max	Pu
IL-1β	COVID-19	75	1,84	0,39	0,02	16,8	< 0,001*
	ARD	30	1,05	0,25	0,0	3,8	
IL-6	COVID-19	75	3,97	0,36	0,2	13,7	0,025*
	ARD	30	2,56	0,37	0,3	7,2	
IL-18	COVID-19	75	421,5	20,6	146,5	973	< 0,001*
	ARD	30	186,5	24,5	11,9	432,3	

Note: The indicators of PU - groups were evaluated by the U-Mann-Whitney criterion for the statistical integrity of the difference.

* - "0" hypothesis is rejected

Thus, the data described above confirm that cytokines play a role in the pathogenesis of inflammatory diseases, affect the development and course of the disease, and the formation of complications.

All this proves the importance of deeper study of cytokines in respiratory diseases, use of the obtained results for diagnostic purposes and development of adequate treatment measures.

During the hyperinflammatory reaction, which is the main cause of the severity of the disease of COVID-19, an increase in the level of inflammatory biomarkers in the blood, including a number of laboratory indicators, is observed.

Biomarkers play a crucial role in early detection, diagnosis, monitoring and treatment of patients. From this point of view, the next

stage of our research was the determination of the amount of biomarkers in the blood serum of COVID-19 (PCR positive) patients.

As a result of our research, it was determined that the average indicators of ferritin in blood serum of COVID-19 (PCR positive) patients increased by 3.1 times compared to the corresponding indicators of the control group, 221.5±18.7 ng/ml, in the control group this indicator was 71.9±2.8 ng/ml ($p<0.001$).

The ROC curve of the ferritin index in the COVID-19 (PCR positive) patients compared to the control group was constructed. The area of the ROC curve of the ferritin indicator was calculated 0.963±0.019; 95% CI: upper and lower limits - 0.926±0.999; $p<0.001$. The sum of the specificity and sensitivity of ferritin covers its diagnostic value.

Depending on the severity of COVID-19 (PCR positive) patients, the concentration of ferritin was significantly elevated compared to the indicators of the control group. Thus, in the acute period of the disease, the concentration of ferritin in the blood serum of patients with a moderately severe course was 196.6±16.8 ng/ml ($p<0.001$), and in the severe course, this indicator was 268.6±42.6 ng/ml ($p<0.001$). ROC analysis of ferritin index was performed in COVID-19 (PCR positive) patients depending on severity. The area of the ROC curve of ferritin is 0.570±0.072; 95% CI: upper and lower limits - 0.428-0.712: $p=0.319$ is calculated, but we could not evaluate it as a statistically significant, diagnostic indicator.

In the next stage of the study, the level of fibrinogen and D dimer in 57 patients with COVID-19 (PCR positive) was analysed. Analysis of the level of fibrinogen in patients with COVID-19 (PCR positive) showed that its level increased by 1.4 times compared to the control group and was 341.7± 11.3 g/l, while in the control group this indicator was 244,2± 10.9 g/l ($p<0,001$).

ROC analysis of the fibrinogen index was performed in comparison with the control group. Fibrinogen index ROC curve area was 0.816±0.046; 95% CI: upper and lower limits - 0.727–0.906, respectively; $p<0.001$ indicates statistical significance.

Depending on the severity of the disease, the concentration of fibrinogen in the blood serum increased to 327.3 ±12.0 g/l ($p<0.001$) in the moderate course, and 368.8 ±22.9 g/l ($p<0.001$) in the severe

course, compared to the control group. The area of the ROC curve of the fibrinogen indicator depending on the degree of severity in COVID-19 (PCR positive) patients is 0.602 ±0.074; 95% CI: upper and lower limits - 0.458± 0.746: p=0.148 was calculated but not statistically significant.

In COVID-19 (PCR positive) patients, the D-dimer level in blood serum increased 2.0 times during the acute period of the disease and was 1209.7±312,7 μg/ml. Depending on the severity of the disease, the average level of D-dimer was 1037.6±378.4 μg/ml in moderately severe course and 1504.7±553.8 μg/ml in severe course. The concentration of D-dimer in the blood serum increased by 1.7 times compared to the reference indicators in moderately severe course, and by 2.5 times in severe course. However, no statistical difference was obtained.

In COVID-19 (PCR positive) patients, positive correlations were established between biomarkers and clinical signs of the patient: ferritin with RR: ρ=+0.273, p=0.045: dyspnea: ρ=+0.251, p=0.030; muscle pain: ρ=+0.328, p=0.004: loss of smell and taste: ρ=+0.294, p=0.011. There is a negative correlation between fibrinogen and SPO2: p=-0.290, p=0.012; and significant positive correlations between fibrinogen and temperature: ρ=+0.343, p=0.003; dyspnea: ρ=+0.297, p=0.010; headache: ρ=+0.308, p=0.007. Direct correlation relationships between D-dimer and ESR, fibrinogen; ρ=+0.272, p=0.041; ρ=+0.660, p<0.001 were recorded.

In the next stage of our research, the level of vitamin D in 95 examined patients was compared with the corresponding indicators of 15 control groups.

When evaluating the role of vitamin D in blood serum, the concentration of the 25 (OH) D form was considered an adequate indicator.

To study the level of vitamin D, serum samples of patients were routinely taken during the acute phase of the disease. 25 (OH) vitamin D blood levels were assessed based on the following criteria: normal above 30-70 ng/ml, mild deficiency between 20-29 ng/ml, severe deficiency 10-19 ng/ml, and deficit below 10 ng/ml has been accepted.

According to the amount of vitamin D in children's blood serum,

patients were grouped into 3 groups. The analysis of the indicators of vitamin D in the groups showed that in the control group, the normal amount of vitamin D was found in 14 (93.3%) children, and mild deficiency was found in 1 (6.7%) child. In the group of patients, 16 (21.3%) children had normal, 58 (61.1%) had severe deficiency, and 21 (22.1%) had deficit.

During our study, the evaluation of the level of vitamin D in blood serum showed that its level in the main group was significantly lower compared to the corresponding indicators of the control group.

Thus, the level of vitamin D in the blood serum was 1.9 times or 47.8% lower on average in the patient group compared to the control group (table 2).

Table 2. Level of vitamin D in the blood serum of examined children

		N	M	±m	Min	Max	Pu
D vitamin ng/ml	Main	95	24,2	0,6	11,32	36,3	<0,001*
	Control	15	46,4	3,0	23,3	64,2	

Note: The indicators of PU - groups were evaluated by the U-Mann-Whitney criterion for the statistical integrity of the difference.

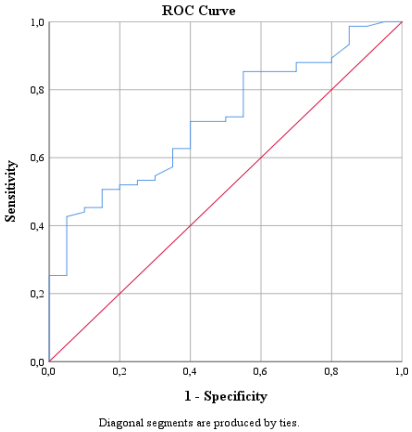
* - "0" hypothesis is rejected

At the next stage of the study, we evaluated the level of vitamin D in the studied patient groups. In the course of COVID-19, its amount was 25.1 ng/ml (median 24.8, Q_1 and Q_3 quartiles 20.6-29.2) compared with the indicators of the control group, and ARD was 20.8 ng/ml (median 21.0, Q_1 and Q_3 quartiles 18.3-23.8) ($p<0.001$).

In the study, the ROC curve of the indicator of vitamin D in ARD and COVID-19 (PCR positive) patients was compared to the control group. The area of the ROC curve of vitamin D is 0.712±0.059; 95% CI: upper and lower limits - 0.597-0.826; p=0.004 indicates that it has high specificity and informativeness (Graph 3).

The level of vitamin D in blood serum was analysed according to the degree of severity in patients with COVID-19 (PCR positive) and it was determined that compared to the indicators of the control

group, it was 25.9±0.7 ng/ml (p<0.001) in moderately severe course, and 23.5±1.2 ng/ml - in severe course (p<0.001), while its minimum amount was 14.2 ng/ml, which is considered a deficiency of vitamin D.



Indicators	Area	Standart Error	p- statistical sign.	95% CI	
				Upper bound	Lower bound
D vit. ng/ml	0,712	0,059	0,004*	0,597	0,826

Graph 3. Integral indicator of ROC-specific and sensitivity of vitamin D in cases of ARD and COVID-19 (PCR positive) pneumonia.

ROC analysis was performed in the next stage of the research to study the diagnostic value of vitamin D in the severity of the disease in patients with COVID-19 (PCR positive). The area of the ROC curve of vitamin D is 00,363±0,072; 95%. CI: upper and lower limits -0,222-0,503: p=0,051- the hypothesis“0” can be conditionally denied.

Serum vitamin D levels were analysed among different age groups. Low levels of vitamin D were recorded mainly in the older age group. Thus, 70.0% deficiency and 28.3% deficit of vitamin D in >3 years old, 40.9% deficiency and 13.6% deficit in <1 age group; in the

1-3 age group, 53.8% deficiency and 7.7% deficit were recorded.

In our study, negative correlations were observed between vitamin D and the patient's clinical symptoms: between the level of vitamin D and muscle pain; ρ=-0.412, p<0.001; loss of sense of smell and taste: ρ=-0.338, p=0.003; headache: ρ=-0.259, p=0.025, which may be due to increased sensitivity to VDR receptors in nociceptors (pain sensitive receptors), neurotransmitters during vitamin D deficiency. Dyspnea with vitamin D; ρ=-0.366, p<0.001; ferritin: ρ=-0.417, p<0.001 had an significantly negative correlation.

In our study between vitamin D levels during COVID-19 and ARD and the clinical condition of the disease (respectively: ρ=-0.227, p=0.051 and ρ=-0.444, p=0.050) and the age of the patients (respectively: ρ=-0.557, p<0.001 and ρ=-0.489, p=0.029) have been found.

Thus, when analysing the results of our study, a deficiency of vitamin D was found in children. The serum vitamin D levels of children in the control group correspond to the average values of the norm. The insufficient level of vitamin D in the blood serum is considered the one of the necessary indicators that affect the development and exacerbation of inflammatory diseases of the respiratory tract in sick children.

In the final stage of our study, Logistic regression analysis was performed to determine the effect of the levels of prognostically sensitive and informative clinical and laboratory indicators that are statistically significantly different from each other on the probability of infection with COVID-19 in children.

The logistic regression model of our study made it possible to determine that the patient's condition is severe with a sensitivity of 92.3±5.2% and a specificity of 98.0±2.0%.

The logistic regression model was characterized by the following formula:

The severity of disease= 334,288 – 3,541 x SpO_2 + 14,486 x Vomiting + 6,665 x The course of pregnancy + 1,339 x WBC + 1,130 x IL-1β + 0,024 x IL-18 – 1,062 x vitamin D.

The overall prognostic value was 96.0±2.3%. For this purpose, the

regression equation posted on the official website of the Azerbaijan Medical University at the electronic address https: //amu.edu.az/page/1327/elm was placed in open use for all researchers and conditions for proposals were created (picture).

Factors	Grading
Vomiting (no / yes)	No
Pathological course of the pregnancy (no / yes)	No
SpO2 (80 - 100%)	98
WBC (0 - 25 g/l)	8,1
Il-1β (0 - 25 pg/ml)	0,7
Il-18 (1 - 1000 pg/ml)	177
Vit.D (1 - 100 ng/ml)	29,8
Expected complication of COVİD-19	*No*

Picture. An example from the UCA-2022 program.

The "UCA-2022" program was prepared on the basis of clinical and laboratory indicators in COVID-19 (PCR positive) patients and can be an additional assessment criterion in pediatric practice to predict the severity of the disease.

RESULTS

1. In children with acute respiratory diseases (ARD), compared to the control group, IL-1β level in blood serum increased by 1.9 times, IL-6 level - by 1.6 times ($p=0.044$), IL-21 level - by 2.6 times ($p<0.001$), the level of γ-INF increased 1.4 times respectively [3, 4, 5, 6, 7, 10, 23, 24]

2. In children with COVID-19 (PCR positive) pneumonia, the level of IL-1β increased by 3.3 times ($p=0.013$), IL-6 increased by 2.4 times ($p=0.001$), IL-18 increased by 1.8 times ($p<0.001$) [12, 14, 15, 18, 21, 22, 23, 24].

3. The frequency of clinical symptoms in patients with COVID-19 (PCR positive) pneumonia, depending on the severity of the disease, was as follows: fever in moderate and severe course was 91.8% and 80.8%, respectively; cough - 98,0% and 100%; loss of appetite 93.9%, 100.0%, muscle pain - 12.2% and 26.9%; headache – 6.1% and 15.4%; loss of smell and taste - 4.1% and 11.5% of cases; dyspnea - 6.1% and 38.5% ($p<0.001$), vomiting 10.2% and 34.6% ($p=0.010$), diarrhea 2.0% and 23.1% ($p=0.003$) and only in severe course, lethargy was observed in 80.8% ($p<0,001$), cyanosis in 30.8% ($p<0,001$), muscle hypotonia in 61.5% ($p<0,001$) of cases. At the same time, between the clinical condition of the patient and cytokines: with IL-1β $\rho=+0.234$, $p=0.043$; with IL-6: $\rho=+0.230$, $p=0.047$; with IL-18: $\rho=+0.238$, $p=0.040$ significantly positive correlations were found [12, 14, 19, 22, 23].

4. Biomarkers in children with COVID-19 (PCR positive) pneumonia: the level of ferritin compared to the control group increased by 3.1 times ($p<0.001$), fibrinogen increased by 1.4 times ($p<0.001$) and D-dimer increased above the upper limits of the norm by 2.0 times [14, 16, 22].

5. In children, the level of vitamin D in respiratory tract diseases was 1.9 times or 47.8% less compared to the indicators of the control group, on average 24.2 ±0.6 ng/ml (minimum and maximum indicators 11,32-36.3 ng/ml) ($p<0.001$) [9, 13, 14, 17, 20].

6. Based on the results of our research conducted during COVID-19, the main risk factors were determined and based on this, the Logistic regression model that allows predicting the severity of the disease with 92.3% sensitivity and 98.0% specificity (RR = 96.0%):

$$\textit{The severity of disease} = 334{,}288 - 3{,}541 \times SpO_2 + 14{,}486 \times \textit{Vomiting} + 6{,}665 \times \textit{The course of pregnancy} + 1{,}339 \times WBC + 1{,}130 \times \textit{IL-1}\beta + 0{,}024 \times \textit{IL-18} - 1{,}062 \times \textit{vitamin D}.$$

"UCA-2022" program was prepared based on this formula [14, 19, 22].

PRACTICAL RECOMMENDATIONS

1. It is recommended to determine pro-inflammatory cytokines IL-1β, IL-6, IL-18, IL-21, γ-INF and vitamin D in the blood serum as an additional diagnostic criterion in children with ARD, especially during COVID-19 disease.
2. In patients with COVID-19 (PCR positive) pneumonia , it is recommended to carry out screening diagnostics, to study ferritin, fibrinogen, D-dimer.
3. It is recommended to use the program "UCA-2022" (https: //amu.edu.az/page/1327/elm), which allows predicting the severity of the disease during COVID-19 in children.

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List of abbreviations

ARD	– acute respiratory diseases
COVID-19	– coronavirus disease -2019
SARS-CoV-2	– Severe Acute Respiratory Syndrome Coronavirus -2
WHO	– World Health Organization
PCR	– polymerase chain reaction
Cİ	– confidence interval
IL	– interleykin
INF	– interferon
RR	– respiratory rate
SpO2	– blood oxygen saturation
Th	– T helper cells
VDR	– vitamin D receptors

The defence will be held on " 14 " " February" 2024, at 14.00 at the meeting of the Dissertation council ED 2.27 of Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University

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Electronic versions of dissertation and abstract are available on the official website of the Azerbaijan Medical University (www.amu.edu.az).

Abstract was sent to the required addresses on date "11" January 2024

Signed for print: 28.12.2023
Paper format: 60 x 84 1/16
Volume: 38.700 characters
Number of hard copies: 30