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Article

Hematological Parameters in Patients with Covid-19: Age and Gender Aspects

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Absract: During the pandemic of COVID-19, the availability of robust laboratory data for patient triage is of paramount importance. This study aimed to investigate the hematological profile of patients with COVID-19 at an early stage of the disease who were admitted to the hospital. We used the retrospective analysis of hemograms of 332 patients with COVID-19 to calculate the average values of white blood cell variables, the neutrophil-lymphocyte ratio (NLR)1, and the systemic immune-inflammation index (SII). At the stage of hospital admission, the most typical change in the blood picture of patients with COVID-19 was a decrease in the absolute count of lymphocytes and eosinophils, especially in patients with severe and extremely severe disease. High absolute neutrophil counts frequently occurred in severe and critically ill patients, too. The majority of patients had a high level of NLR and SII. As a whole, high neutrophil count and lymphocytopenia were common among males, and a pronounced age-dependent increase in cases of neutrophilia and eosinopenia was observed for females. The clinical value of individual hematological parameters and/or their combination varies significantly depending on the gender and age of patients, which predetermines a differentiated approach to build a robust scale for diagnosis and disease progression assessment.

Keywords: COVID-19, Age and gender aspects, Hematological parameters, Neutrophil-to-lymphocyte ratio, Systemic immune-inflammation index

1. Introduction

The pandemic of the new coronavirus infection (COVİD-19) is still “an extraordinary event” because its intricate pathophysiology remains not completely understood. Daily update of COVİD-19 new cases and deaths has indicated significant geographic variability in morbidity and mortality rates across continents, countries, and regions, suggesting that the biological, behavioral, and socio-economic determinants of health shape response to disease [1]. COVİD-19 is caused by SARS CoV-2 (severe acute respiratory syndrome coronavirus type 2), an enveloped positive-sense single-stranded RNA virus belonging to the family of Coronaviridae, the genus Coronavirus. The entry point of the virus into body cell is the angiotensin-converting enzyme 2 (ACE 2), whose polymorphism and tissue expression pattern is responsible for the clinical heterogeneity of the disease [2].

According to the WHO, COVID-19 is characterized by an unpredictable risk of disease progression from asymptomatic or mild to severe and critical illness, requiring treatment in an intensive care unit (ICU). The lack of robust clinical and laboratory markers for the triage and appropriate disease management of people with COVID-19 increases the risk of a complicated course and adverse outcomes [3]. Cohort studies have documented that more than a quarter of patients, mostly males, were readmitted within 3–6 months, and about 6−9% of them died from complications associated directly or indirectly with COVID-19 [4,5]. Thus, the identification of specific laboratory parameters suitable for diagnosis and disease progression control seems to be extremely required [6,7]. The laboratory findings represent “fingerprints” of disease and must be consistent with the concepts of SMART or SMARTER (S: specific and sensitive, M: measurable, A: available and affordable, R: relevant, T: timely, E: evaluate, and R: re-evaluate) [8,9].

Implementation of the costly and time-consuming laboratory testing strategy recommended by WHO during the COVID-19 pandemic has been significantly (frequently) restricted by laboratory capacities such as equipment, reagents, and trained staff [3,6]. In this context, the complete blood count as the most common laboratory test in clinical utility practice is important. By applying machine learning-based approaches, several combinations of parameters in blood tests have already been suggested for the clinical

management of COVID-19 patients [7,10,11]. However, for accurate interpretation of blood test results, population-based research is mandatory due to the high individual (age, sex, and premorbidity) and population (ethnic and racial) variability of blood findings [12,13]. All of the above has determined the purpose of our research – study the hematological profile of patients with COVID-19 at the stage of diagnosis and hospital admission.

2. Materials and Methods

A single-center retrospective cohort study of COVID-19 hematological features was performed based on the health records of 332 patients with COVID-19 admitted to the Infectious Diseases Department of the Baku City Central Customs Hospital for the period June-August 2020. Based on WHO guidelines, the case was defined as confirmed by positive results of the PCR test for SARS-CoV-2 (78% of patients) and considered as suspected if patients had specific clinical and radiological symptoms.

The patient cohort was classified by gender and age with 10-year intervals (21–30, 31–40, 41–50, 51–60, 61–70, and >70 years old) or into two large groups younger than 50 and over 50, depending on research objectives. The mean age of the hospitalized patients was 53 ± 14.7 years old (2–84) for males and 50 ± 14.7 years old (5–92) for females. The smallest group of patients included patients under the age of 30 (7.5%) and older than 71 (6.6%), while the largest group comprised patients between 51 and 70 years old (49.1%). Since the number of patients under the age of 20 was small, their data were excluded from the research.

Upon hospital admission, 93% of males and 89.9% of females were diagnosed clinically and/or radiologically (CT) with bilateral pneumonia and had typical diffuse lung ground-glass opacities with different lesion areas. Severe and critical illness in male patients accounted for about one-third of total cases in the age groups of 21–30 (33%), 41–50 (28.6%), and older than 71 years (28.6%). There were few severe cases in females, predominantly in old age (11.1% of cases in the age group of 61–70 years and 14.3% in the group older than 71 years versus 3.8% in the group of 31–50 years). Of the total number of patients, 28 were admitted to the ICU with 19 (67.9%) males and 9 females, whose mean age was 55 ± 13.3 and 63.6 ± 13.5 years, respectively.

The white blood cell absolute count and subpopulation distribution were performed on the SYSMEX XT-4000i hematology analyzer (Sysmex Corporation, Japan). To assess the systemic inflammatory response, the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune inflammation index (SII, defined as platelet counts x neutrophil counts/lymphocyte counts) were calculated. The data were compared for age and gender. For statistical analysis, we used the Statistical Package for Social Sciences (SPSS) 26.0. Descriptive statistics included the measure of central tendency (median, upper, and lower quartile) for continuous variables and the measure of absolute frequency for categorical data. A comparative analysis was performed using either the Mann-Whitney U-test or Fisher's exact test.

3. Results

3.1. White Blood Cells

3.1.1. Leucocytes

Upon admission to the hospital for inpatient treatment, 28.3% of patients with COVID-19 had a high WBC count, which was not associated with the severity of the disease. However, in the ICU, leukocytosis was observed in 82.1% of patients. High WBC counts were found more frequently in male patients (36.9%). Among females, leukocytosis was observed in 20.7% of cases, mainly in the age group over 50 years (Table 1). Low WBC count occurred only in 10.4% of total cases, mainly in females aged 31–50 years old and males aged 61–70 years old.

Table 1. Distribution of hematological parameters depending on demographics of patients with COVID-19 (data are presented as the median (Me), Q1 and Q3 are the lower and upper quartiles, respectively. The Mann-Whitney U-test was used for the comparison of continuous variables, and Fisher's exact test to compare the proportions of the nominal variable).

Characteristics	**Gender**		**Significance level**
Age groups	**Female**	**Male**	
Leucocytes (N 4–8.8 × 10^3 uL)			
Frequency of leukocytosis			
21–50 years old	11.50%	38.10%	**φ = 3.77, $p < 0,01$**
>50 years old	26.40%	35.10%	φ = 1.28, $p > 0.05$

Table 1. *cont.*

Significance level	**φ = 2.51, $p < 0.01$**	φ = 0.381, $p > 0.05$	
WBC absolute count of Me (Q1; Q3)			
21−50 years old	5.45 [4.33;7.31]	6.95 [5.07;9.96]	**$p < 0.001$**
>50 years old	6.73 [5.48;9.13]	6.44 [5.11;10.71]	$p > 0.05$
Significance level	**$p < 0.01$**	$p > 0.05$	
Neutrophils (N 1.8–7.7 × 10^3 uL)			
Frequency of absolute neutrophilosis			
21−50 years old	7.70%	31.70%	**φ = 3.743, $p < 0.01$**
>50 years old	23.10%	31.90%	φ = 1.340, $p > 0.05$
Significance level	**φ = 2.858, $p < 0.01$**	φ = 0.025, $p > 0.05$	
Neutrophil absolute count Me (Q1; Q3)			
21−50 years old	3.19 [2.6;4.48]	4.69 [3.30;8.65]	**$p < 0.001$**
>50 years old	4.47 [3.38;6.68]	4.47 [3.38;6.68]	$p < 0.05$
Significance level	**$p < 0.001$**	$p > 0.05$	
Lymphocytes (N 1.0–4.5 × 10^3 uL)			
Frequency of absolute lymphocytopenia (%)			
21−50 years old	20.50%	41.30%	**φ = 2.692, $p < 0.01$**
>50 years old	29.70%	52.10%	**φ = 3.128, $p < 0.01$**
Significance level	φ = 1.38, p>0.05	φ = 1.333, p>0.05	
Lymphocyte absolute count Me (Q1; Q3)			
21−50 years old	1.42 [1.02;2.04]	1.12 [0.8;1.69]	**$p < 0.01$**
>50 years old	1.39 [0.97;1.78]	0.995 [0.80;1.41]	**$p < 0.001$**
Significance level	$p > 0.05$	$p > 0.05$	
Eosinophils (N 0.02–0.5 × 10^3 uL)			
Frequency of absolute eosinopenia			
21-50 years old	34.60%	74.60%	**φ = 4.882, $p < 0.01$**
>50 years old	50.50%	53.20%	φ = 0.367, $p > 0.05$
Significance level	**φ = 2.093, $p < 0.05$**	**φ = 2.764, $p < 0.01$**	
Eosinophils absolute count Me (Q1; Q3)			
21-50 years old	0.04 [0.01;0.09]	0.01 [0.0;0.01]	**$p < 0.01$**
>50 years old	0.01 [0;0.05]	0.01 [0;0.05]	$p > 0.05$
Significance level	**$p < 0.02$**	$p > 0.05$	

3.1.2. Neutrophils

High absolute neutrophil count (ANC) was registered in 84.2% of men and 77.8% of women admitted to the ICU as an indicator of critical illness. Among patients with mild or moderate symptoms, it occurred in 24.6% of males and 12.5% of females.

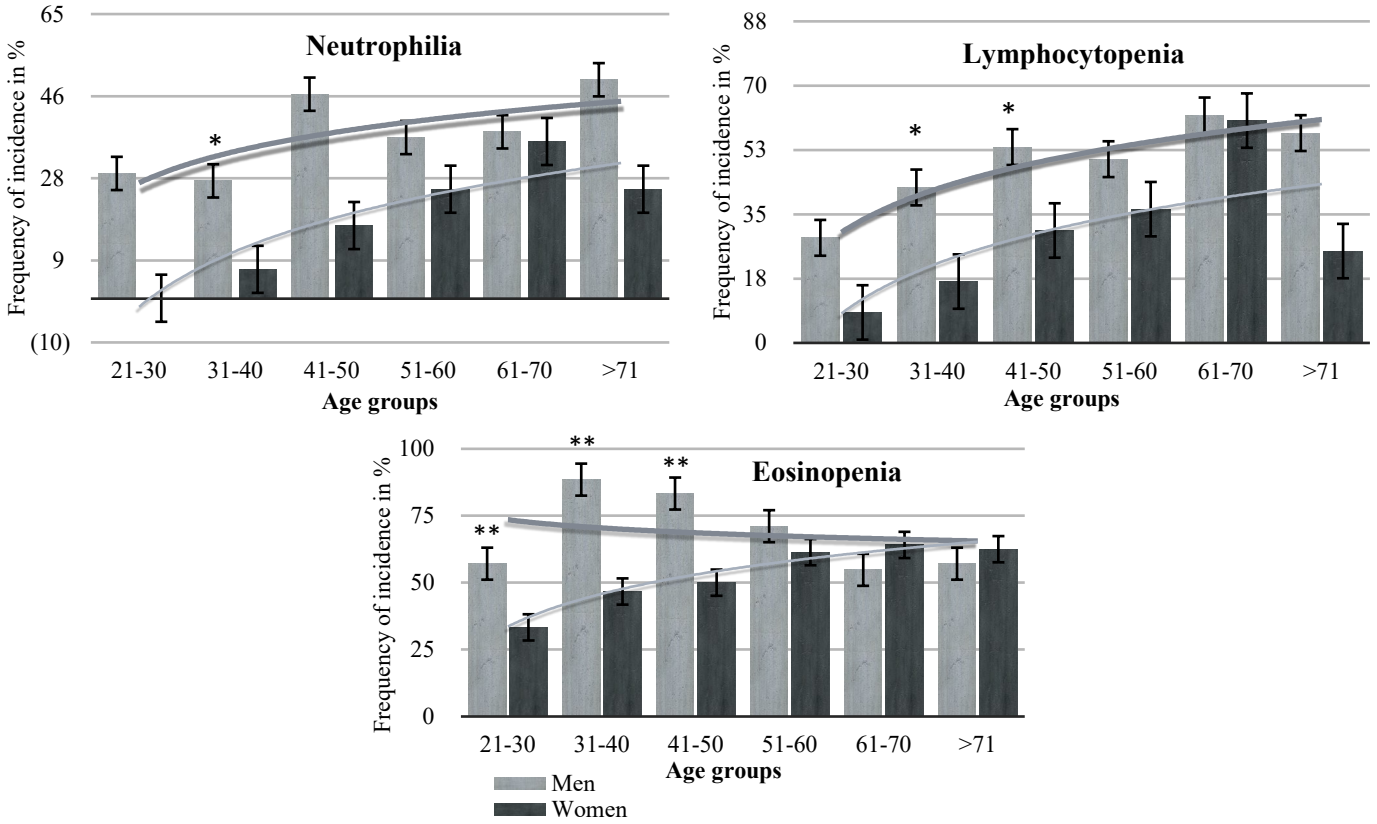

Fig. 1. Gender and age-dependent frequency of incidence of low relative blood neutrophil, lymphocyte, and eosinophil counts in patients with COVID-19. A logarithmic trend has been shown. The significance levels of $p < 0.05$, and $p < 0.01$ are shown by *, and **, respectively.

In general, high ANC was more frequently registered among males aged 41−50 years old and older than 71 years old (Fig. 1). In females, neutrophilia was often seen after 50 years (Table 1). Low ANC was not a typical blood feature for COVID-19. It was revealed only in a few cases and was equally common for males under 50 years old and females over 50 years old (6.3% and 6.6%, respectively). High ANC in combination with low absolute lymphocyte count and/or with absolute eosinopenia was a distinctive blood picture associated with the severity of COVID-19 in males and females younger than 50 years old. No such association was found in patients older than 50 years old. In ICU patients, the combination of high neutrophil count with absolute eosinopenia was found in 68.4% of males and 44.4% of females. High ANC and absolute lymphocytopenia were much less common in females (22.2%) than in males (68.4%).

3.1.3. Lymphocytes

High absolute lymphocyte count was observed in only 1 patient, while relative lymphocytosis was more frequently registered, preferably in females below 50 years old (14.1%) compared to 1.6% of males in the same age group ($p < 0.01$). Low lymphocyte count (LLC), both absolute (34.7% of total cases) and relative (42.6% of total cases), was the most statistically significant laboratory manifestation of a novel coronavirus infection. Both age and gender sufficiently affected the frequency of lymphocytopenia (Table 1, Fig. 1). Absolute LLC among males occurred in 47.8% of the males and 25% of the females ($p < 0.01$) (Absolute LLC among males occurred in 47.8% of cases versus 25% of cases among female ($p<0.01$)). The age-dependent trend to the gradual increase of LLC frequency was typical for males (Fig. 1). Absolute LLC (0.82 [0.51; 0.94] X 109/l) was registered in 83.3% of the males admitted to the ICU, while two-thirds of the females with critical illness had a normal level of lymphocytes in the blood (1.09 [0.86; 1.76] X109/L) at $p < 0.05$.

3.1.4. Eosinophils

Upon hospital admission, more than half of the patients had low absolute and/or relative eosinophil count (LEC). Gender- and age-related trends in the frequency of eosinopenia were revealed (Table 1, Fig. 1). LEC was the common blood count abnormality in about 80% of the males who were 30–50 years old but not for older ones. Otherwise, the frequency of LEC tends to increase

among females after 50 years old (Table 1, Fig. 1). Absolute eosinopenia occurred in 88.9% of the males and 55.6% of the females admitted to the ICU, regardless of age. In combination with a high neutrophil count, the LEC had prognostic value in critically ill patients.

3.2. Hematological Indices

Different integral hematological indices were analyzed for a comprehensive disease severity assessment. It was revealed that an increase in the neutrophil-lymphocytic ratio (NLR) and systemic immune inflammation index (SII) was associated with the severity of illness (Table 2).

Table 2. Systemic immune inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) and their gender and age-dependent prevalence in patients with COVID-19. (Data are presented as the median (Me), and Q1 and Q3 are the lower and upper quartiles, respectively. The Mann-Whitney U-test was used for the comparison of continuous variables, and Fisher's exact test - to compare the proportions of the nominal variables).

Characteristics	**Gender**		**Significance Level**
	Female	**Male**	
SII (N < 600)			
Frequency			
21−50 years old	41%	55.60%	**φ=1.73, $p < 0.05$**
> 50 years old	60.40%	61.70%	φ = 0.184, $p > 0.05$
Significance level	**φ = 2.527, $p < 0.01$**	φ = 0.762, $p > 0.05$	
Mean value of the index			
21−50 years old	505.55 [323.29;839.47]	640.12 [349.02;219.18]	**$p < 0.01$**
> 50 years old	730.25 [472.27;144.51]	1020.66 [437.8;2578.60]	$p > 0.05$
Significance level	**$p < 0.01$**	$p > 0.05$	
NLR (N < 3)			
Frequency			
21−50 years old	30.80%	52.40%	**φ = 2.609, $p < 0.01$**
> 50 years old	56%	67%	φ = 0.184, $p > 0.05$
Significance level	**φ = 3.331, $p < 0.01$**	φ = 1.544, $p > 0.05$	
Mean value			
21−50 years old	2.23[1.68;3.47]	3.18 [2.28;9.8]	**$p < 0.02$**
> 50 years old	3.46[2.32;6.33]	4.61 [2.35;1.68]	$p < 0.05$
Significance level	**$p < 0.01$**	$p > 0.05$	

The NLR value in severe and critically ill patients was higher than in patients with mild or moderate disease (12 [8.2;14.1] vs. 2.8 [1.9;5.4], $p < 0.001$). Basically, up to the age of 50 years old, a high NLR prevailed in males, but no gender differences were found in the patients over 50 years old. The age-dependent increase in NLR was noticeable among females (Table 2). The highest SII was detected in severe and critically ill patients with 2820.7 [1251.5;4694.9] compared to 632,7 [360,5;1288,4] in patients with moderate disease, $p < 0,001$. Age-dependent gender differences in inflammatory response were apparent. Under 50 years, high SII value was more common in male patients (55.6%, 640.1 [349;2193.2]) than in female patients (41%, 505.6 [323.3;839.5]). Gender differences in the value and frequency of SII were gradually reduced for patients over 50 years old due to a significant increase in this indicator among females (Table 2).

4. Discussion

The single-center retrospective study of the hematological profile of patients with COVID-19 revealed two main trends: (1) sexual dimorphism in peripheral blood response to coronavirus infection and (2) age-related hematological changes. Amidst hospitalized patients, females slightly outnumbered males in all age groups up to 60 years old. However, severe illness was more common for males without significant association with age. About a quarter of severe cases were observed in males aged 41 to 50 years old and older than 70. This gender distribution profile was consistent with the demography of outbreaks in many other countries: prevalence of females in overall cases of disease incidence, but a strong tendency towards severe disease in males [14]. Gender bias in COVID-19 susceptibility may be physiologically associated with sex hormone and immune system interplay. The specific gender-dependent pattern of expression of sex hormone receptors by immune cells suggests the direct involvement of gonadal steroids in the regulation/modulation of the immune response [15]. It is also assumed that incomplete inactivation and/or spontaneous reactivation of the second X chromosome in females (incomplete dosage compensation) may be associated with excessive activity of immune response genes and cause sexual dimorphism in susceptibility to infectious, inflammatory, and autoimmune diseases [16]. In general, the activity and expression pattern of genes responsible for immunological surveillance has a strong age aspect. Aging is accompanied by immune system remodeling (immune-senescence) and pro-inflammatory phenotype development [17]. Most of the factors affecting the susceptibility and host response to coronavirus infection include smoking, obesity, hypertension, diabetes, and cardiovascular diseases which are recognized as a common pathogenetic feature in a chronic low-grade inflammatory process and an acute phase reaction (cytokine storm) under COVID-19.

In our studies, high NLR and SII values highlight the ongoing active inflammatory processes and correlate with patients' severity. However, the question of whether this is due to viral load or exacerbation of chronic diseases remains open. In any case, these are “alarming” indicators that require special attention to the patient, regardless of their immediate status. It is reasonable to assume that the high level of these proinflammatory biomarkers is evidence of the exaggerated systemic inflammatory response, which probably requires specific therapeutic approaches and can serve as a marker of their effectiveness [18]. Lymphocytes are key players against viral infections. The result of this study showed that 25% of females and 47.8% of males diagnosed with COVID-19 had low circulating lymphocytes. Many clinical studies have shown the presence of lymphocytopenia among COVID-19 patients. It is also argued that the absolute lymphocyte count has a strong prognostic value [19,20].

In general, age-related and accidental involution of the thymus results in a decreased absolute number of T-lymphocytes. It is also believed that gonadotropin-releasing and sexual hormones facilitate thymic atrophy, and testosterone inhibits T-lymphocytes' development [21]. Thus, the age-dependent gender difference in the frequency of lymphocytopenia may be explained by the aging of the adaptive immunity in males (Fig. 1). Interesting thing is the changes in the absolute and relative counts of eosinophils in patients with COVID-19. Recent advances in the understanding of eosinophil biology highlight their crucial effector, homeostatic, and immunomodulatory functions. Through expression of pattern recognition receptors such as Toll-like receptors TLR 3 and TLR 7 and the ability to immediately release and synthesize de novo a wide range of regulatory and cytotoxic molecules (chemokines, cytokines, leukotrienes, growth factors, RNases, and so on), the eosinophils are involved in all stages of immune response development from the virus- associated molecular pattern recognition to modulation/regulation of the activity of other immunocompetent cells and direct cytotoxicity [22]. On the other hand, excess eosinophils activity may lead to massive tissue destruction through both cytotoxic granule exocytosis and the release of extracellular DNA trap (ETosis) [23].

The results of this study indicate the obvious involvement of eosinophils in the pathogenesis of coronavirus infection, as their decrease to nadir has been detected in the majority of patients with confirmed or suspected COVID-19 [24]. Moreover, persistent eosinopenia is considered a predictor of poor prognosis [7]. There were age-and gender-dependent changes in the frequency of eosinopenia. Eosinophilia or eosinopenia prevailed in blood parameters in the majority of male patients of all age groups up to 60 years old with a tendency to decrease its frequency. In contrast, in females, eosinopenia incidence began to increase over 50 years old which may be associated with a physiological (age-related) decline in the production of estrogens that actively control the processes of migration, adhesion, and degranulation of eosinophils. Thus, the study of the hematological profile of patients with COVID-19 revealed an age-dependent tendency to increase the frequency of lymphocytopenia in males, and eosinopenia in females. The pro-inflammatory phenotype was the main feature of male patients regardless of age and females over 50 years old. It is still required to discuss the results on how they can be interpreted from the perspective of previous studies and in terms of the working hypotheses. The findings and their implications must be discussed in the broadest context possible in future research.

5. Conclusions

The findings of this study indicate that the diagnostic and prognostic value of individual hematological findings and/or their combination varies significantly depending on the gender and age of the patient and predetermines a differentiated approach in the

development and validation of health screening tests and scales. It is worth noting that sexual dimorphism of the white blood cell distribution may reflect the difference in immune response underlying the susceptibility to the virus, disease progression risks, and responsiveness to therapy that should take into consideration for therapy decision-making. On the whole, the results of the study indicate the prognostic value of routine hematological variables in the control of disease progression and prediction of outcomes.

Author Contributions: U. Hashimova and I. Afandiyev have conceptualized research and have made substantive contributions to the final review and editing of the manuscript. A. Akhmadov and M. Abdullayeva have been responsible for data collection and participated in drafting the article. Kh. Safikhanova and A. Gaisina have performed formal analysis and data curation, and have contributed to the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Review Board (IRB) of Abdulla Garayev Institute of Physiology, Ministry of Science and Education of the Republic of Azerbaijan, and the protocols used in the study were approved by the Committee of Human Subjects Protection, the Central Hospital of Medical Service Department, Azerbaijan State Customs Committee, Baku, Azerbaijan.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: "Not applicable"

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