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## ORIGINAL ARTICLE

# Hematological Parameters of Patients Positive for Coronavirus With and Without Comorbidities

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## SUMMARY

***Background:*** **The causative agent of the coronavirus disease (COVID-19) is a virus from the SARS-CoV-2 group of viruses that cause severe acute respiratory syndrome. The aim of the study was to examine the differences in hematological analyses of patients suffering from COVID-19 with and without comorbidities, to determine the degree of the clinical picture based on the MEWS scale and to examine the persistence of inflammatory parameters with the severity of the clinical picture.**
***Methods:*** **The research is a cross-sectional retrospective study, conducted in the laboratory diagnostics service of Tesanj General Hospital. It included 211 respondents positive for the coronavirus in the Tesanj General Hospital. The degree of severity of the clinical picture was determined on the basis of the MEWS scale.**
***Results:*** **A total of 211 patients positive for coronavirus participated in the study, of which 61.1% (129) were male and 38.9% (82) were female. Based on the results, a statistically significant difference was found in the ratio of hematological parameters in subjects with and without comorbidities ($p < 0.05$). A strong positive correlation was found between the ratio of SE and D-dimer in subjects and the degree of severity of the clinical picture.**
***Conclusions:*** **A statistically significant difference was recorded in the ratio of hematological parameters (lymphocytes, granulocytes, erythrocytes, hematocrit, and APTT) in subjects with and without comorbidities in all three of the observed groups ($p < 0.05$), while there were no statistically significant differences in other hematological parameters ($p > 0.05$).**
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**KEYWORDS**

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## INTRODUCTION

The causative agent of the coronavirus disease (COVID-19) is a virus from the SARS-CoV-2 group of viruses that cause severe acute respiratory syndrome. According to data from the World Health Organization, as of March 3, 2024, over 774 million confirmed cases and more than seven million deaths have been reported globally [1]. Symptoms of the disease are most similar to the flu´s: dry cough, fever, and fatigue. The clinical picture often manifested itself from milder forms of the disease to very complicated conditions that ended in

death [2]. Certain studies have proven that there are other symptoms, too, such as dyspnea, headache, muscle pain, nausea, and vomiting [3]. X-ray of the lungs, ultrasound, CT of the lungs, and numerous laboratory tests are used to establish the diagnosis of COVID-19 [4]. Laboratory test results help to diagnose tissue and organ damage associated with infection, identify infected patients with a lower risk of severe disease, identify patients who are likely to have a worse prognosis (e.g. need for mechanical ventilation or intensive care, death), and monitor the course of the disease [5]. Lymphopenia is a common finding in patients with COVID-19 infection and is believed to represent an immune response to the virus [6]. Thus, in one study, it is stated that lymphopenia was registered in 63% of the respondents [7]. One meta-analysis showed that 35% - 75% of patients develop lymphopenia, more often in severe forms of the disease [8]. Studies conducted on patients with COVID-19 from Singapore also report absolute lymphopenia [7], which is predictive of admission to the intensive care unit [8]. Another feature of coronavirus infection is pronounced coagulopathy [9]. Coagulopathy is most often manifested as a prothrombotic condition with an increased incidence of venous and arterial thrombosis [10]. Research has shown that patients often develop a more severe form of the disease, disseminated intravascular coagulation (DIC), with activation of the fibrinolytic pathway and consumption of platelets and clotting factors [11]. Elevated D-dimer in infected patients is associated with an unfavorable prognosis of the disease. In addition, high values of prothrombin time (PT) and activated partial thromboplastin time (APTT) and increased concentration of fibrinogen were found in affected patients [11]. D-dimer is a valid laboratory biomarker widely used as part of the diagnostic workup of patients with suspected venous thromboembolism or disseminated intravascular coagulation (DIC) and predicts poor outcomes and thromboembolic events [12]. Changes in D-dimer concentration are seen in most patients who are hospitalized with COVID-19 [13].

Patients suffering from COVID-19 can be classified into 4 categories, taking into account the modified early warning score (MEWS):

1) mild or asymptomatic disease of COVID-19
2) medium-severe stable disease of COVID-19 (MEWS $< 3$)
3) severe unstable but non-critical illness of COVID-19 (MEWS 3 - 4)
4) severe critical disease of COVID-19 (MEWS $\geq 5$) [14].

The condition of patients infected with COVID-19 becomes more difficult if the patient has comorbidities (such as hypertension, obesity, coagulation disorders, and diabetes mellitus). Diabetes mellitus is the second most common comorbidity, right after arterial hypertension in patients with COVID-19 [15]. It has been shown that people with diabetes have a higher chance of suffering from a more severe form of infection with this virus, because hyperglycemia can modulate inflammatory and immune responses by interacting with other risk factors [16]. This means that a person with diabetes is more susceptible to infection with COVID-19 due to weak immunity, and people infected with COVID-19 may develop hyperglycemia due to the use of steroid drugs [17]. The latest research indicates that the presence of systemic arterial hypertension in people with COVID-19 can lead to an unfavorable outcome, including an increased risk of death [7]. Studies investigating this connection in patients found that hypertension is the most common chronic disease in people infected with the new coronavirus [18]. People with systemic arterial hypertension have endothelial dysfunction, which is manifested as an imbalance between vasodilators and vasoconstrictor substances that directly affect vascular function. This is considered a major feature of the vascular system in hypertensive individuals. In connection with the aging process, hypertension results in progressive stiffening and loss of elasticity of large arteries, which is crucial in the pathogenesis of cardiovascular complications associated with COVID-19 [19]. Guided by the available literature data, the main goal of the study was to determine the difference in the value of the basic hematological parameters of patients suffering from COVID-19 with and without comorbidities, to determine the degree of the clinical picture based on the MEWS scale, and to examine the correlation of inflammatory markers with the severity of clinical images.

## MATERIALS AND METHODS

The research is a cross-sectional retrospective study, conducted in the laboratory diagnostics service of Tesanj General Hospital. It included 211 respondents positive for the coronavirus in the area of Tesanj municipality and neighboring municipalities, who were hospitalized in the COVID department of the general hospital. The respondents were divided into three age groups. The first group were aged 18 - 40 years, the second group were aged 41 - 64 years, and the third group were older than 65 years. In subjects positive for coronavirus, the following hematological parameters were monitored: CBC (number of leukocytes, erythrocytes, platelets, and hematological indices), DBC, sedimentation (SE) first hour, and D-dimer and coagulation factors (PT, INR, APTT). The degree of severity of the clinical picture was determined on the basis of the MEWS scale. Blood was taken on the father-in-law, by puncture of the cubital vein. The analysis of hematological parameters was performed on the following device: MINDRAY BC 3200 (Bio-medical Electronics Co., Ltd., Taiwan). The parameters performed by the device were: WBC, Lymph, Mid, Gran, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT, MPV, and a histogram for WBC, RBC, and PLT. The analysis cycle is fully automatic. The sample volume required is 15 mL of whole blood and 20 mL of diluted sample. Temperature for

working environment is 15°C - 35°C, humidity is 30% - 85%. The principle and method are electrical impedance for cell counting and the cyanide-free method for Hgb. D-dimer analysis was performed on the VIDAS-PC device (bioMerieux S.A. France). It is an automated bench-top immunoanalyzer that contains five independent sections with six tests. The device is based on enzyme-linked fluorescent assay (ELFA) technology. It is ideal for low to medium throughput of up to eighty tests per hour. It has a wide menu of over a hundred parameters available in a single test format for routine, specialized, or emergency testing; one patient – one test. Coagulation factors were measured on a semi-automated STart Max Stago machine (Diagnostica Stago S.A.S-9, France). The semi-automated instrument has calibration menus and a large color touch screen using standardized "Max Generation" graphics. The device has the ability to archive patient results with the addition of quality control, a series of reagents, and modern connectivity (on LIS and/or STA Coag Expert, with a USB port and the possibility of connecting a manual barcode reader).
Sedimentation was done by the Westergren method; it is a manual method where 3.8% Na Citrate 0.4 mL and 1.6 mL of whole blood were used. In this way, a mixture of Na citrate and blood is obtained in a ratio of 1:4, then the resulting mixture is drawn into a dry Westergren pipette, and the reading is taken after one hour [20].

**Statistical analysis**

The sample size is 211 subjects of both sexes. All data are stored in anonymized databases in accordance with data protection laws. The results of the examined hematological parameters were processed using descriptive statistics with 95% confidence intervals by using SPSS version 21.0. Differences in the characteristics of the subjects (gender, age, degree of pneumonia) were tested using the chi-squared test. The correlation between hematological parameters and the degree of pneumonia in COVID-19 patients, as well as comorbidities, was analyzed using the Pearson correlation rank.

## RESULTS

A total of 211 subjects positive for the coronavirus took part in the study, out of which 61.1% were male and 38.9% were female. The subjects were divided into three age groups, all tested parameters were analyzed for each age category, and the obtained results are presented in Table 1.
Out of the total number of respondents, 61.1% were male and 38.9% were female. The first group of respondents was the smallest, 5.2% of the total sample, dominated by male respondents with a 73% share, and no comorbidities were recorded among them, while among female respondents from this group, we have comorbidities present. The second age group was the most numerous (41 - 64 years old); it made up 58.3% of the total number of respondents, with the dominance of the male gender within the group at 57.7%. In 66.2% of the male respondents from this group, comorbidity was present, and in female respondents, comorbidity was recorded in 80.7% of the female respondents. The third age group made up 34.5% of the total sample. Within this group, men made up 64.9% and women 35.1%. In male respondents of this group, comorbidity was recorded in 90% of the respondents, and in women from the same age group, comorbidity was present in 92.6% of the respondents (Table 1). Lower values of lymphocytes (M = 13.6 and M = 16.7, respectively) and higher values of granulocytes (M = 81.8, and M = 77.4, respectively) were found in the first and third groups of subjects with comorbidities. In the first and third groups of respondents without comorbidities, higher PT values were determined (M = 14.4 and M = 14.9, respectively). Higher INR values were observed in all groups of subjects without comorbidities (M = 1.3, M = 4.2, and M = 1.3), as well as in the second and third groups of subjects with comorbidities (M = 2.2 and M = 1.5, respectively) (Table 2). Tables 3a and 3b show the statistical significance of the hematological parameters of subjects II and III groups with and without comorbidities. In the second group of subjects, higher results of hematological parameters were found in subjects without comorbidities for all parameters except for the value of platelets, which was higher in subjects of this group with comorbidities, but not statistically significant, while a statistically significant difference was found for MCH and MCV. In the third group of subjects, a statistically significant value was determined for lymphocytes, granulocytes, PT, APTT, and INR. Values of lymphocytes and PT were higher in subjects without comorbidities, and other values were higher in subjects with comorbidities (Table 3a and 3b). Out of the total number of respondents, 47.4% of the men and 26.1% of the women had a mild clinical picture. 1.9% of the male and 4.3% of the female respondents had a moderately-severe clinical picture with diagnosed pneumonia. Severe, unstable clinical picture, subjects with diagnosed pneumonia who are on oxygen therapy, was found in 11.8% of the male and 8.5% of the female subjects (Table 4). A strong positive correlation was found between the ratio of SE and D-dimer in subjects and the severity of the clinical picture (Table 5).

## DISCUSSION

In total, 211 subjects positive for the coronavirus took part in the study, out of which 61.1% were male and 38.9% were female. Most respondents were in the age category between 41 and 64 years, a total of 58.3% of the respondents, and they also had the highest percentage of comorbidities, 22.3% of the male and 19.9% of the female respondents. In a study examining the hematological parameters of people positive for the coronavirus, the authors state that the average age of the patients

**Table 1. Display of patients by age category.**

| Presence of comorbidities in relation to gender and age | | Age | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 18 - 40 years | | 41 - 64 years | | Over 65 years | | Total | |
| | | n | % | n | % | n | % | n | % |
| Male | No comorbidities | 8 | 3.8 | 24 | 11.3 | 5 | 2.4 | 37 | 17.5 |
| | Comorbidity | 0 | 0.0 | 47 | 22.3 | 45 | 21.3 | 92 | 43.6 |
| | Total | 8 | 3.8 | 71 | 33.6 | 50 | 23.7 | 129 | 61.1 |
| Female | No comorbidities | 2 | 0.9 | 10 | 4.7 | 2 | 0.9 | 14 | 6.6 |
| | Comorbidity | 1 | 0.5 | 42 | 19.9 | 25 | 11.8 | 68 | 32.2 |
| | Total | 3 | 1.4 | 52 | 24.6 | 27 | 12.8 | 82 | 38.9 |
| Total | No comorbidities | 10 | 4.7 | 34 | 16.1 | 7 | 3.3 | 51 | 24.2 |
| | Comorbidity | 1 | 0.5 | 89 | 42.2 | 70 | 33.2 | 160 | 75.8 |
| | Total | 11 | 5.2 | 123 | 58.3 | 77 | 36.5 | 211 | 100.0 |

**Table 2. Hematological parameters by age category in relation to comorbidity.**

| Hematological analyses of subjects with and without comorbidities | | Mean value of hematological analyses of subjects with and without comorbidities | | | | | |
|---|---|---|---|---|---|---|---|
| | | No | Yes | No | Yes | No | Yes |
| | | Grupa I | Grupa I | Grupa II | Grupa II | Grupa III | Grupa III |
| WBC | (4.0 - 10.0) x $10^9$/L | 5.8 | 4.1 | 6.3 | 6.8 | 6.9 | 7.2 |
| Lymph | (20 - 40)% | 29.6 | 13.6 | 20.1 | 20.3 | 24.5 | 16.7 |
| Mid | (3.0 - 15.0)% | 8.1 | 4.6 | 6.1 | 6.5 | 7.6 | 6.0 |
| Gran | (50.0 - 70.0)% | 56.2 | 81.8 | 73.8 | 72.5 | 67.9 | 77.4 |
| Hgb | (110 - 160) g/L | 153.7 | 141.0 | 139.5 | 134.9 | 134.1 | 130.6 |
| RBC | (3.50 - 5.50) x $10^{12}$/L | 4.9 | 4.3 | 4.4 | 4.4 | 4.3 | 4.3 |
| HCT | (37.0 - 54.0)% | 43.4 | 39.0 | 39.7 | 39.0 | 38.6 | 37.5 |
| MCV | (80 - 100) fL | 87.8 | 90.9 | 89.5 | 87.4 | 90.1 | 88.4 |
| MCH | (27 - 34) pg | 31.1 | 32.7 | 31.4 | 30.6 | 31.2 | 30.7 |
| MCHC | (320 - 360) g/L | 354.0 | 361.0 | 351.0 | 349.5 | 347.1 | 347.6 |
| PLT | (150 - 500) x $10^9$/L | 217.8 | 164.0 | 190.6 | 244.0 | 192.3 | 197.9 |
| PV | (0.9 - 14.0) s | 14.4 | 12.4 | 12.4 | 12.9 | 14.9 | 12.7 |
| APTT<br>INR | (26“ - 39“) s<br>(0.96 - 1.18) s | 29.0<br>1.3 | 28.0<br>1.1 | 27.1<br>4.2 | 26.1<br>2.2 | 29.7<br>1.3 | 25.6<br>1.5 |
| D dimer | (< 500) ng/mL | 585.3 | 494.0 | 1,377.5 | 1,359.7 | 1,494.6 | 1,945.0 |

was 54 years, and 68.3% were men. The results showed that there is a significantly higher age of patients with moderate and severe disease compared to the group of asymptomatic patients, with a statistically significant difference, and that the presence of comorbidities increases with increasing severity of the disease [21]. In relation to age and the presence of comorbidities, it was shown that there is a slight increase in the number of granulocytes and D-dimer, except in the subjects of the first group with comorbidities present, where D-dimer did not show a tendency to increase in value. This research showed that the examined hematological parameters did not change significantly in subjects with and without comorbidities, only in the second group was a significant difference recorded for MCV and MCH, whose values were higher in subjects of this group without comorbidities, which speaks of the preservation of the hematopoietic process. In the third group of subjects, a statistically significant value was determined for lymphocytes, granulocytes, PT, APTT, and INR. Higher

**Table 3a. Statistical significance of hematological parameters of the second group of subjects with and without comorbidities.**

| Anova test | Sum of squares | df | F | p |
|---|---|---|---|---|
| WBC x $10^9$/L | 5.998 | 1 | 0.542 | 0.463 |
| Lymph % | 0.646 | 1 | 0.005 | 0.942 |
| Mid % | 4.871 | 1 | 1.152 | 0.285 |
| Gran % | 42.726 | 1 | 0.263 | 0.609 |
| RBC x $10^{12}$/L | 0.017 | 1 | 0.095 | 0.759 |
| HCT % | 42.476 | 1 | 3.041 | 0.084 |
| MCV fL | 106.366 | 1 | 3.880 | 0.051 (0.049) |
| MCH pg | 15.221 | 1 | 3.634 | 0.059 (0.050) |
| MCHC g/L | 54.624 | 1 | 0.735 | 0.393 |
| PLT x $10^9$/L | 27,040.725 | 1 | 2.975 | 0.087 |
| PV | 4.064 | 1 | 0.371 | 0.544 |
| APTT | 23.465 | 1 | 1.415 | 0.237 |
| INR | 0.026 | 1 | 0.206 | 0.651 |
| D-dimer | 6,869.857 | 1 | 0.002 | 0.961 |

**Table 3b. Statistical significance of hematological parameters of the third group of subjects with and without comorbidities.**

| Anova test | Sum of squares | df | F | p |
|---|---|---|---|---|
| WBC x $10^9$/L | 0.556 | 1 | 0.050 | 0.823 |
| Lymph % | 341.854 | 1 | 4.445 | 0.038 |
| Mid % | 14.674 | 1 | 3.587 | 0.062 |
| Gran % | 498.180 | 1 | 5.312 | 0.024 |
| RBC x $10^{12}$/L | 0.002 | 1 | 0.006 | 0.937 |
| HCT % | 7.780 | 1 | 0.254 | 0.616 |
| MCV fL | 22.185 | 1 | 0.508 | 0.478 |
| MCH pg | 1.965 | 1 | 0.270 | 0.605 |
| MCHC g/L | 1.778 | 1 | 0.015 | 0.901 |
| PLT x $10^9$/L | 402.921 | 1 | 0.064 | 0.801 |
| PV s | 29.573 | 1 | 8.841 | 0.004 |
| APTT s | 95.337 | 1 | 4.427 | 0.039 |
| INR | 0.427 | 1 | 10.820 | 0.002 |
| D-dimer ng/mL | 1,283,372.273 | 1 | 0.454 | 0.503 |

values of lymphocytes and PT were found in subjects without comorbidities, and other values were higher in subjects with comorbidities. Other studies by the authors also report low lymphocyte counts in patients requiring intensive care as well as in those with a fatal outcome [22-24]. Possible mechanisms for reduced lymphocyte numbers include inhibition of lymphocytes by metabolites, such as lactic acid, and apoptosis due to inflammatory cytokines [25]. The authors proved that the infection with COVID-19 causes a worsening of the inflammatory response, which then worsens the suppressed function of the immune system and is manifested by a decrease in lymphocytes and an increase in granulocytes, especially in severe cases [26]. All results are correlated with the results of our study. D-dimer values are an important indicator of disease progression. In our research, there was no statistically significant difference by age group and in relation to comorbidity ($p > 0.05$), but the recorded values of D-dimer were significantly above the upper reference value for this parameter. The results we obtained follow the results cited by Guan et al. (2020), which indicate a correlation between high D-dimer values and the severity of the disease in patients with COVID-19 [27], as well as the results cited for D-dimer by Tang et al. (2020), reporting that patients with a severe clinical picture have approximate-

**Table 4. Degree of severity of the clinical picture.**

| Degree of severity of the clinical picture (MEWS scale) | Gender | | | |
|---|---|---|---|---|
| | Male | | Female | |
| | n | % | n | % |
| Mild without pneumonia | 100 | 47.4 | 55 | 26.1 |
| Medium-severe pneumonia | 4 | 1.9 | 9 | 4.3 |
| Severe, unstable oxygen therapy | 25 | 11.8 | 18 | 8.5 |
| Total | 129 | 61.1 | 82 | 38.9 |

**Table 5. Correlation of inflammatory parameters with the degree of clinical picture.**

| Correlation of inflammatory parameters with the degree of clinical picture (Se, D-dimer) | Se | D-dimer |
|---|---|---|
| Severity of the clinical picture | 0.103 * | 0.302 ** |
| Se | 1 | 0.043 |
| D-dimer | | 1 |

*** positive correlation, ** strong positive correlation (p > 0.001).**

ly 3.5 times higher D-dimer levels compared to patients with a mild or moderate clinical picture [11]. Their results were confirmed by Wang et al., who reported approximately 2.5 and up to 5 times higher D-dimer values in patients with severe clinical course of COVID-19 compared to patients with mild or moderate clinical course [28,29]. Both Wang and Tanaka state that the D-dimer values in patients with severe clinical picture of COVID-19 show about four- and nine-times lower D-dimer levels, respectively, compared to the D-dimer levels of deceased patients [11,31]. Our study showed that the level of D-dimer in those infected with the COVID-19 virus, who have a milder clinical picture, is significantly lower than the D-dimer value in subjects with a more severe clinical picture, which agrees with the results seen by Lippi and Favaloro [30], but also Yao et al. (2020), Bilaloglu et al. (2020), and Petrilli [31-33]. All of them state that higher D-dimer values are positively correlated with a poor outcome of the disease, while patients with low D-dimer levels have a greater chance of a faster recovery and less chance of developing a more severe form of the disease [33]. When it comes to the severity of the clinical picture of the respondents included in our research from the total number of respondents, 155 of them had a mild clinical picture, out of which 47.4% were male and 26.1% were female respondents; 1.9% of the male and 4.3% of the female respondents had a moderately severe clinical picture with diagnosed pneumonia; and a severe unstable clinical picture in subjects diagnosed with pneumonia who are on oxygen therapy was found in 11.8% of the male and 8.5% of the female subjects. A strong positive correlation was found between the ratio of Se and D-dimer in subjects and the degree of severity of the clinical picture. Other studies of patients with COVID-19 infection also record increased values of CRP and sedimentation, and this is an indicator of the severity of the clinical picture, and elevated D dimer levels are the cause of inflammatory processes and the severity of disease progression and may be a sign of acute lung failure [34]. Therefore, the severity of disease progression is accompanied by increased levels of D-dimer, which coincides with our research. Research by the Faculty of Medicine of the University of Belgrade and the Institute for Blood Transfusion of Serbia, Belgrade, which report increased values of CRP $\geq$ 81 mg/L and D-dimer $\geq$ 760 ng/mL, indicate a serious condition of patients with COVID-19 infection, which can also predict hospitalization mortality of these patients [35]. These data correlate with our research, where the highest CRP values were found in subjects with a severe clinical picture.

## CONCLUSION

A statistically significant difference was found in the ratio of hematological parameters (lymphocytes, granulocytes, erythrocytes, hematocrit, and APTT) in subjects with and without comorbidities in all three of the observed groups ($p < 0.05$), while there were no statistically significant differences in the other hematological pa-

rameters ($p > 0.05$). Lymphocytes showed lower values in the first and third groups of subjects, and granulocytes showed higher values in the same groups of subjects without comorbidities. The values of erythrocytes and hematocrit showed lower values in all groups of subjects without comorbidities, while PT showed higher values in the first and third groups of subjects without comorbidities.

The largest number of subjects had a mild clinical picture, a total of 155 subjects; medium-severe clinical picture was found in 13 subjects and severe clinical picture, subjects with diagnosed pneumonia who are on oxygen therapy, was found in 43 subjects.

A strong positive correlation was found between the ratio of Se and D-dimer in subjects and the degree of severity of the clinical picture.

**Declaration of Interest:**

The authors declare that they have no conflicting interests or other interests that could be perceived as influencing the results and/or discussion presented in this study.

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