

## DIFFERENCES BETWEEN BIOCHEMICAL, HEMATOLOGICAL AND COAGULATION PARAMETERS AMONG PATIENTS WITH MILD AND SEVERE COVID-19

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**Abstract: Introduction:** COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 and causes a series of respiratory symptoms. Considering the appearance and development of symptoms, the course of COVID-19 can go from mild to severe. Depending on the course of COVID-19, the laboratory parameters change a lot, trying to defend the organism against the foreign pathogen and all the changes it causes. Therefore, the aim of this study is to observe the differences between biochemical, hematological and coagulation parameters depending on the disease stage of COVID-19 patients. **Material and methods:** We conducted cross-sectional study which included 160 COVID-19 patients from Sarajevo, Bosnia and Herzegovina. Biochemical, hematological and coagulation analyzes were performed. **Results:** COVID-19 patients with a severe clinical course have higher average values of fibrinogen ( $6.53 \pm 4.47$ ,  $p < 0.001$ ), D-dimer ( $6.89 \pm 7.81$ ,  $p < 0.001$ ), APTT ( $32.05 \pm 5.96$ ,  $p = 0.002$ ), eosinophil ( $0.66 \pm 0.09$ ,  $p = 0.002$ ) and CRP ( $93.42 \pm 75.86$ ,  $p = 0.023$ ), and lower values of lymphocytes ( $1.04 \pm 0.98$ ,  $p < 0.001$ ), monocytes ( $0.45 \pm 0.3$ ,  $p < 0.001$ ), compared to COVID-19 patients with a mild clinical course. COVID-19 patients with a severe clinical course had higher average values of neutrophils ( $10.12 \pm 5.80$ ,  $p = 0.002$ ) and lower values of reactive lymphocytes ( $0.02 \pm 0.03$ ,  $p < 0.001$ ) compared to

COVID-19 patients with a mild clinical course. **Conclusion:** Biochemical, hematological and coagulation parameters can be a sensitive and specific biomarker for distinction of mild and severe COVID-19.

**Keywords:** COVID-19, laboratory parameters, clinical course.

### INTRODUCTION

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 and causes a series of respiratory symptoms. All symptoms, depending on the severity of the disease, are accompanied by different reactions of our body (1). Increased coagulability is one of the basic mechanisms of the disease and the main cause of death of severe COVID-19 patients. Severe COVID-19 patients may have prothrombotic complications of the disease, such as venous thrombosis and pulmonary embolism. A more frequent occurrence of cardiovascular and thromboembolic complications and death has also been proven (2). Standard diagnostics of the SARS-CoV-2 virus is based on the detection of its nucleic acid by the rt-PCR method or the detection of its spike glycoprotein by various rapid tests (3). The development of the disease, a physician can monitor the course of the disease with various general and specific laboratory tests and imaging techniques. Basic laboratory tests that can be used

to monitor the course of the disease are complete blood count, C-reactive protein and D-dimer, which can be used to identify the development of secondary, bacterial infection and thrombosis (4).

During the automatic processing of samples from patients with the confirmed presence of the SARS CoV-2 virus, the concentration of C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), liver enzymes, total bilirubin (BIL), creatinine, high-sensitivity cardiac troponin T (hs-TnT) is mostly increasing. Previous research has observed a significant higher value of CRP in COVID-19. A steady increase in C-reactive protein in COVID-19 positive patients is noted during the period of hospitalization, with higher values measured in patients placed in the intensive care unit (5). Thus, this observation of its values confirms the usefulness of C-reactive protein as an early inflammatory biomarker, and studies have proven that CRP is associated with progression and predicting the severe clinical course of COVID-19.

The hematological abnormalities that most often accompany SARS CoV-2 positive patients upon admission to the hospital are: lymphocytopenia, to the greatest extent, followed by thrombocytopenia and leukopenia. These hematological changes are more pronounced in patients with a severe clinical course compared to patients with a mild clinical course. One of the salient features of SARS-CoV-2 infection is lymphopenia (6). Fibrinogen and D-dimer were generally high in 80-100% of patients immediately upon admission to the hospital. In patients placed in the intensive care unit, higher D-dimer levels were recorded after admission and after 14 days of hospitalization, where its value was more than 20 times higher than in patients not placed in that unit. APTT and PT/INR were slightly high (7). Therefore, the aim of this study is to observe the differences between biochemical, hematological and coagulation parameters depending on the disease stage of COVID-19 patients.

## MATERIAL AND METHODS

This cross-sectional study included 160 subjects positive for SARS CoV-2, who were divided into two groups: mild and severe COVID-19 patients. Study was conducted at the "JU Dom zdravlja KS" and at the Faculty of Health Studies, University in Sarajevo in Sarajevo, Bosnia and Herzegovina in the period from February to April in 2021. Venous blood of COVID-19 patients was used as material. Blood samples were obtained by venipuncture from in a tube with EDTA anticoagulant. Then peripheral blood smears were prepared and stained with May Grunwald Giemsa staining using the Pappenheim method. A sufficient amount

of blood, 5-10 mL of blood, plasma or serum was taken to perform all required tests. Advia 2120i, Siemens hematology analyzer was used to obtain a complete and differential blood count of the patients, Dimension EXL 200, Siemens for C-reactive protein and Sysmex CA 660, Siemens for coagulation tests (APTT, INR, fibrinogen and D-dimer). The number of reactive lymphocytes was obtained by examining a peripheral blood smear from a blood sample collected from an EDTA tube.

This study was approved by Ethics Committee of "JU Dom zdravlja KS" and Ethics Committee of Faculty of Health Studies, University of Sarajevo.

The statistical analysis of the collected data were performed using the statistical package IBM Statistics SPSS version 23.0, where Microsoft Office programs were used to prepare and display the results. Data were analyzed using Mann-Whitney U test, Chi-squared test and Spearman's rank correlation coefficient. Statistical significance was assumed at  $p < 0,05$ .

## RESULTS

Of the total number of patients ( $n = 160$ ), the number of male respondents was 89 (56%), while 71 (44%) were female, aged between 18-87 years. The group of patients with mild COVID-19 consisted of 60, while the group with severe COVID-19 consisted of 100 patients.

According to the Mann-Whitney U test, a statistically significant difference in the average values of fibrinogen, D-dimer, APTT, CRP, and the average number of neutrophils, lymphocytes, monocytes, eosinophils, and reactive lymphocytes was shown. COVID-19 patients with a severe clinical course have higher average values of fibrinogen ( $p < 0.001$ ), D-dimer ( $p < 0.001$ ), APTT ( $p = 0.002$ ), eosinophil ( $p = 0.002$ ) and CRP ( $p = 0.023$ ), and lower values of lymphocytes ( $p < 0.001$ ), monocytes ( $p < 0.001$ ), compared to COVID-19 patients with a mild clinical course. COVID-19 patients with a severe clinical course had higher average values of neutrophils ( $p = 0.002$ ) and lower values of reactive lymphocytes ( $p < 0.001$ ) compared to COVID-19 patients with a mild clinical course.

According to the Chi-squared test, an association between leukopenia, normal values of leukocytes, and leukocytosis was shown ( $p = 0.027$ ), whereby a significant number of COVID-19 patients had leukocytosis.

According to Spearman's correlation coefficient ( $\rho$ ), there were numerous positive and negative correlations between the examined parameters. Some of them are expected due to the direct mutual dependence of the parameters, e.g. significant positive correlation between INR and APTT and D-dimer. The inflam-

**Table 1.** Differences in the values of hematological, coagulation, and inflammatory parameters between COVID-19 patients with a severe (n = 100) and COVID-19 patients with a mild (n = 60) clinical course

|                                   | Patient group | Mean    | Std. Deviation | Mean Rank | Sum of ranks | Mann-Whitney U | p-value |
|-----------------------------------|---------------|---------|----------------|-----------|--------------|----------------|---------|
| INR                               | Mild          | 1.172   | 0.5436         | 83.35     | 5001.00      | 2829.000       | 0.534   |
|                                   | Severe        | 1.078   | 0.0245         | 78.79     | 7879.00      |                |         |
| Fibrinogen (g/l)                  | Mild          | 4.802   | 1.0479         | 61.65     | 3699.00      | 1869.000       | < 0.001 |
|                                   | Severe        | 6.536   | 4.4744         | 91.81     | 9181.00      |                |         |
| D-dimer (mg/l)                    | Mild          | 2.5857  | 2.06999        | 62.23     | 3733.50      | 1903.500       | < 0.001 |
|                                   | Severe        | 6.8987  | 7.81699        | 91.47     | 9146.50      |                |         |
| APTT (sec)                        | Mild          | 29.668  | 5.8051         | 65.78     | 3947.00      | 2117.000       | 0.002   |
|                                   | Severe        | 32.054  | 5.9610         | 89.33     | 8933.00      |                |         |
| WBC (x10 <sup>9</sup> /l)         | Mild          | 11.7348 | 6.50023        | 88.88     | 5332.50      | 2947.500       | 0.077   |
|                                   | Severe        | 10.7989 | 8.47225        | 75.48     | 7474.50      |                |         |
| Neutrophils (x10 <sup>9</sup> /l) | Mild          | 7.746   | 5.8171         | 71.68     | 5712.00      | 2118.000       | 0.002   |
|                                   | Severe        | 10.123  | 5.8068         | 95.20     | 7168.00      |                |         |
| Lymphocytes (x10 <sup>9</sup> /l) | Mild          | 1.795   | 3.9917         | 92.12     | 9212.00      | 1838000        | < 0.001 |
|                                   | Severe        | 1.042   | 0.9812         | 61.13     | 3668.00      |                |         |
| Monocytes (x10 <sup>9</sup> /l)   | Mild          | 1.7132  | 6.50559        | 98.20     | 9819.50      | 1230.500       | < 0.001 |
|                                   | Severe        | 0.4505  | 0.30208        | 51.01     | 3060.50      |                |         |
| Eosinophils (x10 <sup>9</sup> /l) | Mild          | 0.0544  | 0.17793        | 68.68     | 4120.50      | 2290.500       | 0.012   |
|                                   | Severe        | 0.661   | 0.09731        | 87.60     | 8759.50      |                |         |
| Basophils (x10 <sup>9</sup> /l)   | Mild          | 0.0573  | 0.05909        | 72.97     | 4378.00      | 2548.000       | 0.110   |
|                                   | Severe        | 0.1185  | 0.38517        | 85.02     | 8502.00      |                |         |
| RBC (x10 <sup>9</sup> /l)         | Mild          | 4.477   | 0.60980        | 83.79     | 5027.50      | 2802.500       | 0.486   |
|                                   | Severe        | 4.3646  | 0.74618        | 78.53     | 7852.50      |                |         |
| Hgb (g/l)                         | Mild          | 135.663 | 20.4663        | 84.22     | 5053.00      | 2777.000       | 0.432   |
|                                   | Severe        | 131.846 | 21.1496        | 78.27     | 7827.00      |                |         |
| Hct (%)                           | Mild          | 40.071  | 6.0091         | 84.73     | 5083.50      | 2746.500       | 0.372   |
|                                   | Severe        | 38.521  | 6.4362         | 77.97     | 7796.50      |                |         |
| MCV (fl)                          | Mild          | 89.555  | 6.1867         | 84.39     | 5063.50      | 2766.500       | 0.411   |
|                                   | Severe        | 88.861  | 5.9762         | 78.17     | 7816.50      |                |         |
| Thrombocytes (x10 <sup>9</sup> )  | Mild          | 214.92  | 104.698        | 82.00     | 4920.00      | 2910.000       | 0.751   |
|                                   | Severe        | 207.93  | 108.137        | 79.60     | 7960.00      |                |         |
| MPV (fl)                          | Mild          | 7.4788  | 1.49805        | 79.75     | 4785.00      | 2955.000       | 0.874   |
|                                   | Severe        | 7.7312  | 2.04058        | 80.95     | 8095.00      |                |         |
| CRP (mg/l)                        | Mild          | 64.278  | 49.9850        | 69.73     | 4148.00      | 2354.000       | 0.023   |
|                                   | Severe        | 93.426  | 75.8690        | 86.96     | 8696.00      |                |         |
| Reactive lymphocytes              | Mild          | 0.1005  | 0.03451        | 125.94    | 7556.50      | 273.500        | < 0.001 |
|                                   | Severe        | 0.0290  | 0.03189        | 53.24     | 5323.50      |                |         |

Abbreviations: **INR** – international normalized ratio, **APTT** – activated partial thromboplastin time, **WBC** – white blood cells, **RBC** – red blood cells, **Hgb** – hemoglobin, **Hct** – hematocrit, **MCV** – mean corpuscular volume, **MPV** – mean platelet volume, **CRP** – C-reactive protein.

**Table 2.** Differences between leukocyte count in mild and severe COVID-19 patients

|   | Mild COVID-19<br>N (%) | Severe COVID-19<br>N (%) | Chi-squared | p-value      |
|---|------------------------|--------------------------|-------------|--------------|
| Leukopenia<br>< 4*10 <sup>9</sup> /l    | 3 (1.88)               | 10 (6.25)                | 7.193       | <b>0.027</b> |
| Normal value<br>4–10*10 <sup>9</sup> /l | 20 (12.5)              | 50 (31.25)               |             |              |
| Leukocytosis<br>> 10*10 <sup>9</sup> /l | 37 (23.13)             | 40 (25)                  |             |              |

**Table 3.** Correlations between the tested parameters of the total number of patients (n = 160)

|                         | INR                           | Fibrinogen<br>(g/l)           | D-dimer<br>(mg/l)             | APTT<br>(sec)                 | CRP<br>(mg/l)                 |
|-------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Fibrinogen<br>(g/l)     | -,103<br>,195                 |                               |                               |                               |                               |
| D-dimer<br>(mg/l)       | <b>226**</b><br><b>,004</b>   | ,076<br>,338                  |                               |                               |                               |
| APTT<br>(sec)           | <b>,238**</b><br><b>0,002</b> | ,058<br>,467                  | ,005<br>,955                  |                               |                               |
| CRP<br>(mg/l)           | ,078<br>,327                  | <b>,247**</b><br><b>,002</b>  | ,084<br>,289                  | <b>,185*</b><br><b>,019</b>   |                               |
| Reactive<br>lymphocytes | ,084<br>,292                  | <b>-,279**</b><br><b>,000</b> | <b>-,221**</b><br><b>,005</b> | <b>-,193**</b><br><b>,014</b> | <b>-,253**</b><br><b>,001</b> |

Abbreviations: **INR** – international normalized ratio, **APTT** – activated partial thromboplastin time, **CRP** – C-reactive protein.

matory parameter CRP has a significant positive correlation with fibrinogen ( $\rho = 0.247$ ,  $p = 0.002$ ) and APTT ( $\rho = 0.185$ ,  $p = 0.019$ ). Reactive lymphocytes show significant negative correlations with fibrinogen ( $\rho = -0.279$ ,  $p < 0.001$ ), D-dimer ( $\rho = -0.221$ ,  $p = 0.005$ ), APTT ( $\rho = -0.193$ ,  $p = 0.014$ ) and CRP. ( $\rho = -0.253$ ,  $p = 0.001$ ).

## DISCUSSION

In our study, we proved that the examined biochemical, hematological and coagulation parameters of COVID-19 patients affect the severity of the clinical course, and that, by monitoring the other parameters, we can assess the severity of the disease course and react therapeutically in a timely manner. Given that the total examined population (n = 160) was divided into two groups, when monitoring the parameters of these two groups and comparing the values in the group of patients with a severe and mild clinical course, significant differences were observed in the average values of fibrinogen, D-dimer, APTT -a, CRP and the average number of neutrophils, lymphocytes, monocytes, eosinophils and reactive lymphocytes. Higher average values of fibrinogen ( $p < 0.001$ ), D-dimer ( $p < 0.001$ ), aPTT ( $p = 0.002$ ), lymphocytes ( $p < 0.001$ ), monocytes ( $p < 0.001$ ), eosinophils ( $p = 0.002$ ) and CRP ( $p$

$= 0.023$ ) compared to COVID-19 patients with a mild clinical course. On the other hand, COVID-19 patients with a severe clinical course had lower average values of neutrophils ( $p = 0.002$ ) and reactive lymphocytes ( $p < 0.001$ ) compared to COVID-19 patients with a mild clinical course.

Khourssaji M et al. in their research highlighted significant changes in biochemical and hemostasis parameters in COVID-19 positive subjects. They state that at the admission of patients, an elevated level of CRP was one of the most common results, increased in as many as 100% of respondents. Long-term follow-up of these parameters revealed that CRP levels were significantly different ( $p < 0.05$ ) between intensive care patients and non-intensive care patients at least 14 days after admission. A continuous increase in CRP values was even observed for ICU patients during the first two weeks. Fibrinogen and D-dimer were elevated in more than 83% (1.3 times) and 100% (2.7 times) of patients with COVID-19 at admission. In ICU patients, higher D-dimer levels after admission was recorded until the fourteenth day of hospitalization, where it was 25 times higher than in the non-ICU population (8). Guan WJ et al. showed that CRP was elevated in 56.4% of patients with mild and in 81.5% of COVID patients with severe disease (9). Elevated values of APTT and fibrinogen were associated with mortality in patients

with moderately severe COVID-19 showed Jamil SW et al. in their study (10). Meta-analysis of 13 studies in 1,807 COVID-19 patients showed that the serum D-dimer concentrations in patients with severe forms of the disease were significantly higher than those in patients with milder forms. D-dimer concentrations might be helpful to rapidly identify COVID-19 patients with high risk of pulmonary complications and venous thromboembolism, facilitating the early initiation of effective therapies (11). Our presented values follow the results of these studies and we notice significantly higher values of fibrinogen, APTT and D-dimer in severe COVID-19 patients.

It has been proven that low platelet values in COVID-19 patients are associated with the severity of the clinical picture, leading to coagulopathy. Lippi G et al. proved the association of lower platelet values with worse prognosis and death of patients (12). Our results showed that thrombocytes were lower in severe patients, but their MPV was higher in that patients.

Rostami-Far Z et al. showed in their study that erythrocytes, hemoglobin and hematocrit were significantly decreased in severe COVID-19 patients (13). Yuan et al. showed that severe and critical COVID-19 patients had significantly lower values of hemoglobin and erythrocytes (14) and all these results follow our findings.

The association between leukopenia, normal values of leukocytes and leukocytosis was not shown in the study by Layla KN et al., while they compared these values among mild, moderate and severe COVID-19 patients (15), while in our study this association was statistically significant. Neutrophilia, which was shown in our study in severe COVID-19 patients, is a characteristic of a severe form of the disease and a poor prognosis (16, 17), which is explained by the fact that neutrophilia is associated with hyperinflammatory and cytokine events, which characterizes the mechanism of the development of the COVID-19 infection. Activation of neutrophils and release of contents from granules represent one of the more active cellular mechanisms as a result of the immune response, but their significance in virus destruction has not been proven (18). The most important

parameter of the blood count is the decreased number of lymphocytes, which is observed in more than 80% of patients with severe clinical course. A changed number of lymphocytes and their subtypes has been described in many viral infections, and it is assumed that the mechanisms of viral infections and changes in lymphocyte subtypes are related. It is assumed that binding of the virus and damage to the immune system leads to a reduced number of lymphocytes. Also, a reduced number of lymphocytes can also interfere with their migration into the lung parenchyma (19). In our study, lymphopenia was present in severe COVID-19 patients, which follows the results of other studies (20-22), which confirms the fact that lymphopenia is one of the main laboratory parameters for monitoring the prognosis of COVID-19.

This study has some limitations. First of all, our study included smaller number of patients compared to other studies and data come only from one institution and one region in Bosnia and Herzegovina, it is single-center study.

## CONCLUSION

In our study, we showed that a mild clinical course is characterized by higher values of INR, WBC, lymphocytes, monocytes, RBC, Hgb, Hct, MCV, platelets and reactive lymphocytes. A severe clinical course is accompanied by higher values of fibrinogen, D-dimer, APTT, neutrophils, eosinophils, basophils, MPV and CRP.

Ethics approval: This study was approved by Ethics Committee of "JU Dom zdravlja KS" (04-7-72/21(02-3-614/11)) and Ethics Committee of Faculty of Health Studies, University of Sarajevo (01-06-5847-3/20).

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## Sažetak

RAZLIKE BIOHEMIJSKIH, HEMATOLOŠKIH I KOAGULACIONIH PARAMETARA  
MEĐU PACIJENTIMA SA BLAGOM I TEŠKIM OBLICIMA COVID-19

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**Uvod:** COVID-19 je infektivna bolest uzrokovana teškim akutnim respiratornim sindromom koronavirus 2 i uzrokuje niz respiratornih simptoma. S obzirom na pojavu i razvoj simptoma, tok COVID-19 može ići od blagog do teškog. Zavisno od toka COVID-19, laboratorijski parametri se dosta menjaju, pokušavajući odbraniti organizam od stranog patogena i svih promena koje on uzrokuje. Stoga je cilj ovog istraživanja uočiti razliku između biohemijskih, hematoloških i koagulacijskih parametara u zavisnosti od stadijuma bolesti kod pacijenata obolelih od COVID-19. **Materijal i metode:** Proveli smo presečnu studiju koja je obuhvatila 160 pacijenata obolelih od COVID-19 iz Sarajeva, Bosna i Hercegovina. Urađene su biohemijske, hematološke i koagulacijske analize. **Rezultati:** COVID-19 pacijenti sa težom kliničkom slikom imaju više prosečne vrednosti fibrino-

gena ( $6,53 \pm 4,47$ ,  $p < 0,001$ ), D-dimera ( $6,89 \pm 7,81$ ,  $p < 0,001$ ), APTT ( $32,05 \pm 5,96$ ,  $p = 0,002$ ), eozinofila ( $0,66 \pm 0,09$ ,  $p = 0,002$ ) i CRP ( $93,42 \pm 75,86$ ,  $p = 0,023$ ), te niže vrednosti limfocita ( $1,04 \pm 0,98$ ,  $p < 0,001$ ), monocita ( $0,45 \pm 0,3$ ,  $p < 0,001$ ), u poređenju sa COVID-19 pacijentima sa blažom kliničkom slikom. COVID-19 pacijenti sa težom kliničkom slikom imali su više prosečne vrednosti neutrofila ( $10,12 \pm 5,8$ ,  $p = 0,002$ ) i niže vrednosti reaktivnih limfocita ( $0,02 \pm 0,03$ ,  $p < 0,001$ ) za razliku od COVID-19 pacijenata sa blažom kliničkom slikom. **Zaključak:** Biohemijski, hematološki i koagulacijski parametri mogu biti osetljivi i specifični biomarkeri za razlikovanje blagog i teškog oblika COVID-19 ili blage i teške kliničke slike COVID-19

**Ključne reči:** COVID-19, laboratorijski parametri, klinička slika.

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