Hematological Profiles of Patients Referred to Intensive Care Unit Due to COVID-19 in Southern Saudi Arabia

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a pandemic infection that emerged in December 2019 leading to an outbreak worldwide. We aimed to investigate the hematological parameters and coagulation profiles specifically for the referral of coronavirus disease 2019 (COVID-19) patients to intensive care unit (ICU) due to the severity of illness to determine a pathognomonic association of infection severity and the hematological markers. The pathognomonic markers could assist physicians in better management of the infection to reduce mortality and morbidity. Thirty patients infected with COVID-19 who were receiving treatment during November and October 2020, in the ICU at Asir Central Hospital, Asir Region, Saudi Arabia, were recruited. The age of patients ranged between 30 and 90 years old. COVID-19 patients in the ICU displayed a statistical reduction in red blood cells (RBCs), hemoglobin (HBG), and hematocrit (HCT). Leukocytosis, neutrophilia, thrombocytopenia, and lymphocytopenia were significant in ICU COVID-19 patients. Hematological parameters and coagulation profiles may be used as signs to predict the severity of the coronavirus infection. COVID-19 cases in the ICU showed a dramatic change in hematological parameters and coagulation profiles, indicating that the virus may interfere with hemoglobin, platelet, and immune cell functions through either inhibition or stimulation, leading to severe complications.

KEYWORDS: Intensive Care Units; SARS-CoV-2; Hematological Parameters; Coagulation Profiles.

1. INTRODUCTION

The severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) are two global viral infectious diseases that are part of the coronavirus family (CoV) [1]. These pathogens were associated with an outbreak originating in Guangdong Province in southern China and a patient who died in Jeddah, Saudi Arabia, respectively [2,3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel third member of the CoV family whose outbreak has led to an ongoing worldwide pandemic that emerged in December 2019. The first affected patients were connected to the Huanan South China Seafood Market in Wuhan, Hubei Province, China, who developed pneumonia-like symptoms of an unknown origin [4]. The novel SARS-CoV-2 presented with symptoms such as cough, fever, headache, sore throat, fatigue, shortness of breath, and myalgia [5]. The virus was transmitted via the inhalation or ingestion of viral droplets from infected persons through either direct contact with contaminated surfaces or the respiratory droplets from infected patients' sneezing, coughing, and/or physical contact. Hands contaminated with the virus could transmit the infection by touching the eyes, nose, and mouth [6]. Unfortunately, the virus also has some specific attributes; the virus is highly infectious, asymptomatic-infected patients may spread the virus, and the infection can be remarkably severe and require admission to infectious disease clinics or referral to the intensive care unit (ICU) [7]. Particularly ill cases of coronavirus disease 2019 (COVID-19) were determined to affect several organs, and critically ill patients showed to require immediate intervention for infection management [8]. Recent studies demonstrated a significant variation of blood parameters and coagulation profiles associated with severe cases of COVID-19. This includes an increase in leukocytes, neutrophils, neutrophil to lymphocyte ratio, activated partial thromboplastin time, and D-dimer [9,10]. Additionally, lymphopenia among COVID-19 was illustrated as the common significant marker [10].

Currently, several methods are used to confirm the diagnosis of COVID-19, including real-time reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) tests for SARS-CoV-2 [6]. However, the costs of the tests as well as social, logistics, and analytical issues contribute to making a SARS-CoV-2 diagnosis in clinical

practice challenging. Therefore, suggestive parameters of routine tests for SARS-CoV-2 diagnosis confirmation are needed [6]. Laboratory blood tests play an essential role in the early diagnosis of diseases as these tests provide information to physicians regarding the possible reason for the illness and its severity [11]. Blood tests such as complete blood count (CBC) and coagulation profiles are inexpensive and performed routinely in the diagnostic labs. A person's general health can be evaluated with the use of CBC, which is commonly ordered by physicians [12]. A CBC presents information about several values, such as the amount of hemoglobin, red blood cells (RBCs), RBC indices, white blood cells (WBCs), and platelets, while coagulation tests provide information on the clotting function [13].

The present study aimed to compare the hematological parameters of COVID-19-positive patients admitted to ICU with healthy individuals to investigate the possible variations in screening blood tests such as CBC and the coagulation profile. This investigation may provide associated signs between the severity of the disease and blood test results.

2. METHODS

2.1. STUDY DESIGN AND PARTICIPANT

This retrospective study included the results of 30 patients infected with COVID-19 who were receiving treatment during months of November and October 2020 in the ICU at Asir Central Hospital, Asir Region, Saudi Arabia, which were compared with selected healthy individuals. The age of patients ranged between 30 and 90 years old. Ethical approval {REC - No: (REC-11-1O-2020)} for this study was obtained from the Regional Committee for Research Ethics, Directorate Health Affairs - Asir Region, Ministry of Health, Saudi Arabia.

2.2. SAMPLE PREPARATION AND MEASUREMENT

Blood samples were collected from selected healthy participants via a vein puncture and placed in ethylenediaminetetraacetic acid (EDTA) and trisodium citrate tubes for several hematological tests. For coagulation studies, plasma was collected by centrifugation at 900 rpm for 15 minutes at room temperature. The hematological parameters were analyzed at Asir Central Hospital, Asir Region, Saudi Arabia, using an automated hematology analyzer (Sysmex XN550), and coagulation profiles were assessed with an automated coagulation analyzer (Stago Satellite).

2.3. COVID-19 DATA COLLECTION

We obtained patients' data exclusively from the Laboratory Information System (LIS), which provided information on the age, gender, ethnicity, and results of each patient.

2.4. STATISTICAL ANALYSIS

For statistical analysis, GraphPad Prism was used for analyses (GraphPad Prism version 9.00 for Mac, GraphPad Software, San Diego, CA). A Mann–Whitney U test was used to compare COVID-19 patients with normal healthy individuals. To evaluate the degree of association between two variables, Spearman's correlation was used. P values were considered to be significant when they were less than 0.05.

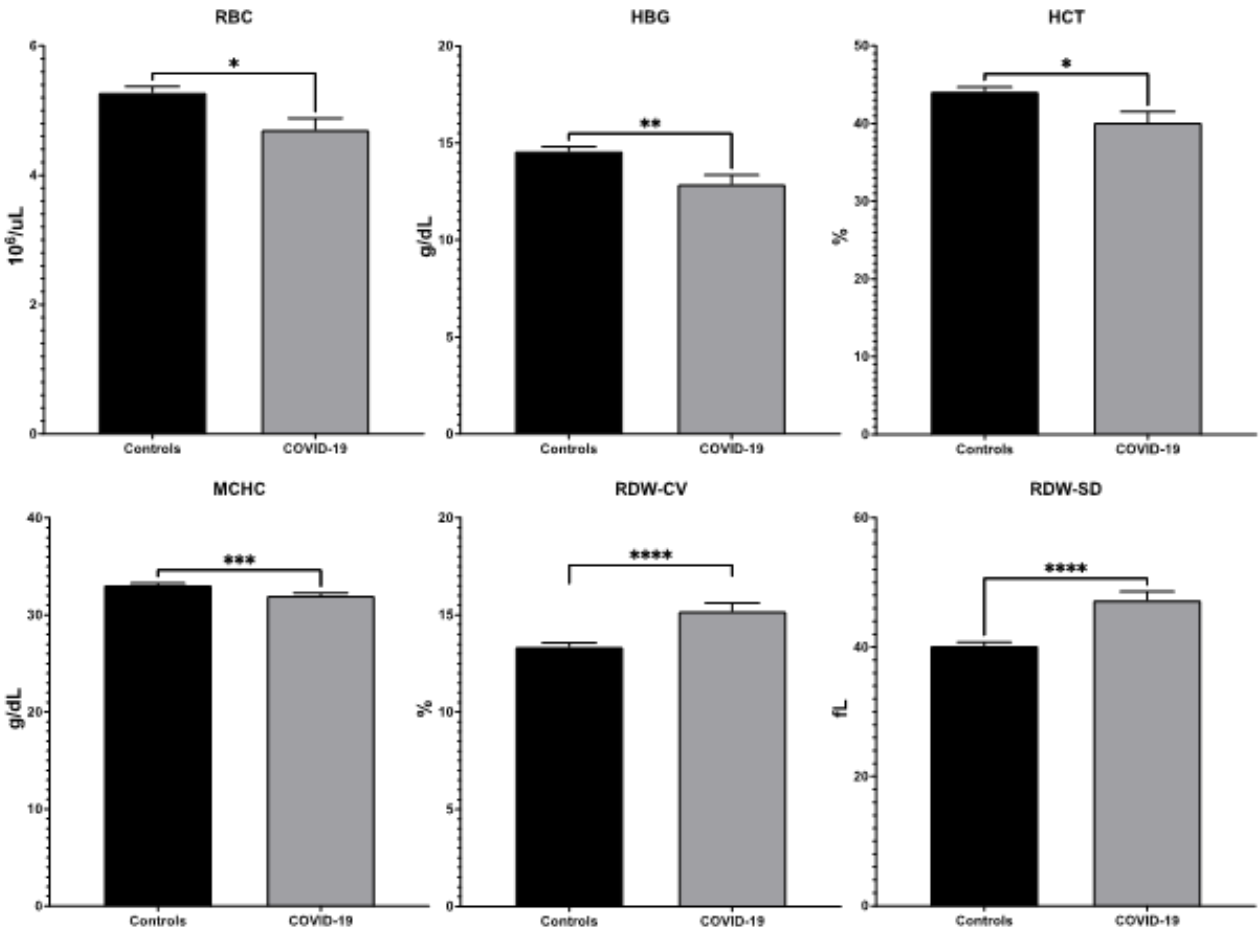
3. RESULTS

This retrospective study investigated RBCs with their indices, hemoglobin (HBG), and hematocrit (HCT); CBC reports of patients diagnosed with SARS-CoV-2 admitted to ICU were obtained from the central hospital. The Mann–Whitney U test was used to examine the statistical differences between the SARS-CoV-2 patients and healthy individuals.

The results from 30 patients displayed a significant reduction of RBCs (M = 4.875; P value = 0.0165; U = 388), HBG (M = 13.4; P value = 0.0063; U = 372), and HCT (M = 41.05; P value = 0.0281; U = 415.5) compared with the healthy group (Figure 1). The RBCs, HBG, and HCT of the healthy group were as follows, respectively: M = 5.390; P value = 0.0165; U = 388; M = 14.60; P value = 0.0063; U = 372; and M = 44.40; P value = 0.0281; U = 415.5.

Red cell indices such as mean cell volume (MCV) and mean cell hemoglobin (MCH) displayed no significant differences (Table 1). However, the mean cell hemoglobin concentration (MCHC) value (M = 32.30; P value = 0.0009; U = 326) was significantly lower in the patient group compared with the healthy controls (M = 33.25; P value = 0.0009; U = 326) (Figure 1). Besides, ICU patients diagnosed with SARS-CoV-2 tended to have a higher RBC distribution width RDW-CV and RDW-SD (M = 14.45; P value < 0.0001; U = 267; and M = 45.95; P value < 0.0001; U = 197.5, respectively) compared with healthy controls (M = 13.15; P value < 0.0001; U = 267; and M = 39.20; P value < 0.0001; U = 197.5, respectively) as shown in Figure 1.

Figure 1: Comparison of ICU COVID-19 patients' RBC, HBG, HCT, RBC distribution width (RDW-CV) and (RDW-SD) with those of healthy controls. The unpaired, two-tailed Mann–Whitney U test's P value's significance is illustrated in the graph. P < 0.05 was considered significant.



To examine WBCs and the differential of SARS-CoV-2 ICU patients, a CBC was analyzed using the Mann–Whitney U test. As shown in Figure 2, leukocytosis (WBC: M = 9.775; P value < 0.0001; U = 261) and neutrophilia (neutrophil (NEUT) %: M = 87.40; P value < 0.0001; U = 61) were more significantly evident in the infected group than the control group (WBC: M = 6.130; P value < 0.0001; U = 261; NEUT %: M = 48.65; P value < 0.0001; U = 61). However, a significant reduction was observed in lymphocyte (LYMPH) % (M = 7.300; P value < 0.0001; U = 96), monocyte (MONO) (M = 4.100; P value < 0.0001; U = 193), eosinophil (EO) (M = 0.05000; P value < 0.0001; U = 170.5), and basophil (BASO) (M = 0.2000; P value < 0.0001; U = 136) compared with healthy individuals. The median, P value, and Mann–Whitney U results for the control group were as follows: WBC (M = 6.130; P value < 0.0001; U = 261), NEUT % (M = 48.65; P value < 0.0001; u = 61), LYMPH % (M = 39.50; P value < 0.0001; U = 96), MONO % (M = 7.950; P value < 0.0001; U = 193), EO % (M = 2.000; P value < 0.0001; U = 170.5), and BASO % (M = 0.6500; P value < 0.0001; U = 136).

We hypothesize that platelet counts and the coagulation profile might be affected by the SARS-CoV-2 infection. To confirm this hypothesis, we analyzed the platelet counts and coagulation profile, including the patients' prothrombin time (PT), international normalized ratio (INR), activated partial prothrombin time (APTT), and APTT ratios, and compared them with the control group using the Mann–Whitney U test. Other platelet parameters were also examined, including platelet hematocrit, mean platelet volume (MPV), and platelet distribution width (PDW).

Figure 2: Comparison of ICU COVID-19 patients' WBCs and differential counts with those of healthy controls. The unpaired, two-tailed Mann–Whitney U test's P value's significance is illustrated in the graph. P < 0.05 was considered significant.

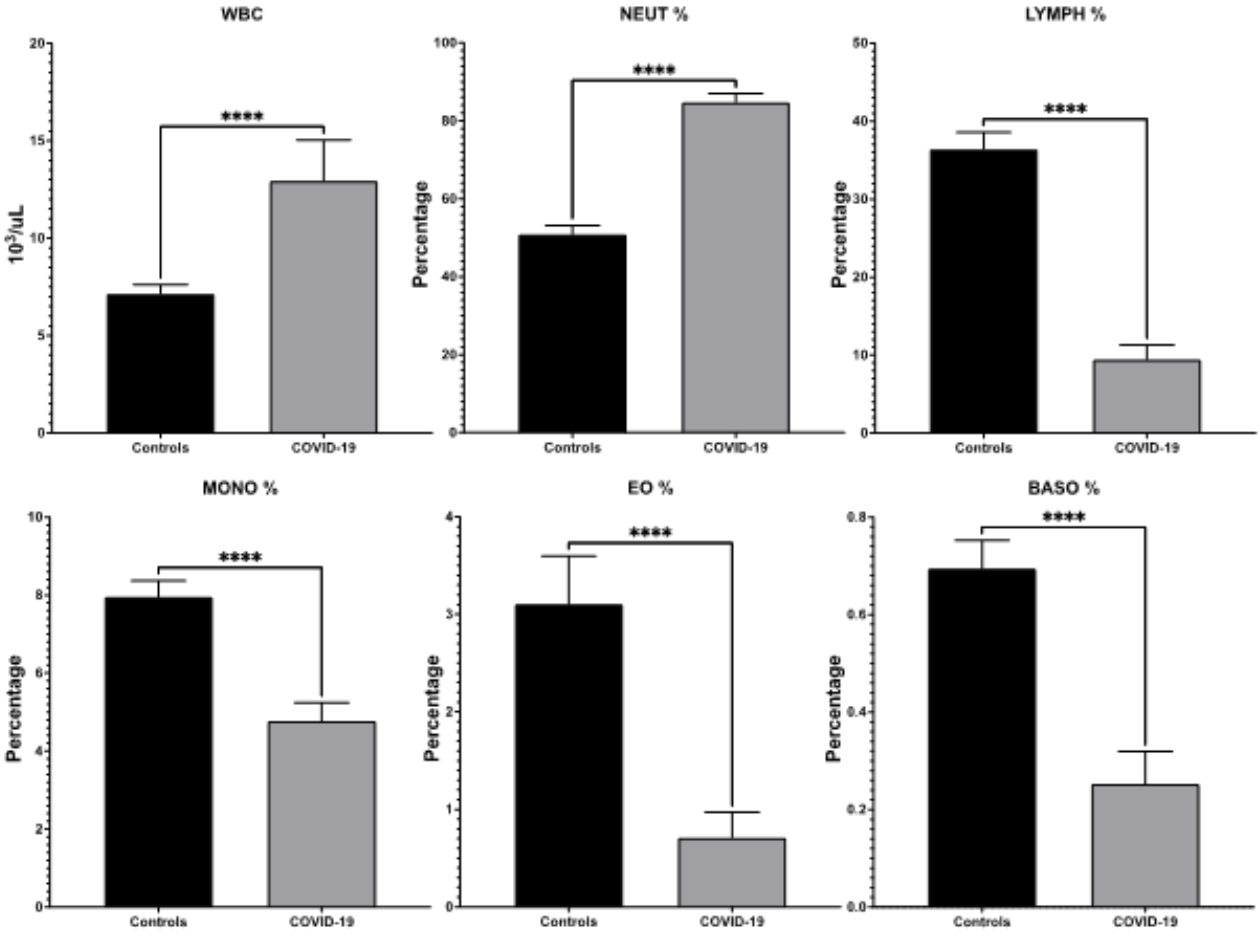
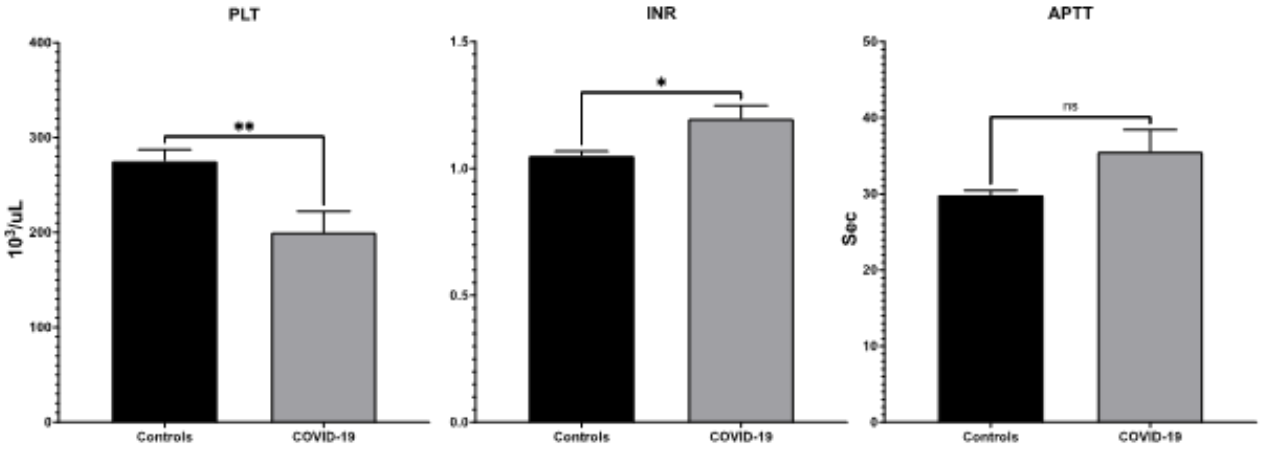


Figure 3 indicates that the platelet (PLT) counts of patients diagnosed with SARS-CoV-2 admitted to the ICU were significantly lower than those of the control group (PLT: M = 179.5; P value = 0.0035; U = 356.5; and PLT: M = 282.0; P value = 0.0035; U = 356.5, respectively). In addition, INR presented a notable increase (INR: M = 1.108; P value = 0.0380; U = 241) compared with the INR of healthy individuals (INR: M = 1.024; P value = 0.0380; U = 241). In contrast, APTT did not vary significantly. Other hematological parameters, including PDW, MPV, platelet hematocrit, and APTT ratio, were statistically analyzed and are shown in Table 1. However, no statistical differences (P > 0.05) were observed between the two groups.

Table 1: Comparison of ICU COVID-19 patients' hematological parameters with those of healthy controls.

Hematological parameter	Median		U-statistic	P value
	Control (n = 40)	COVID-19 (n = 30)		
MCV (fL)	84.40	85.30	473.5	0.1347
MCH (pg)	27.90	27.60	555	0.5973
PDW (fL)	12.20	13.35	352.5	0.0773
MPV (fL)	10.45	10.75	365	0.1116
Platelet hematocrit (%)	0.2900	0.2600	407.5	0.3185
APTT ratio	0.9000	0.9000	308.5	0.3652

Figure 3: Comparison of ICU COVID-19 patients' platelet counts (PLT) and coagulation profiles with those of healthy controls. The unpaired, two-tailed Mann–Whitney U test's P value's significance is illustrated in the graph. P < 0.05 was considered significant.



4. DISCUSSION

The COVID-19 pandemic that originated in Wuhan, China, in 2019, has created a clinical and economic crisis for most if not all countries worldwide [14]. Both mortality and morbidity rates due to the virus are high and were predicted to increase dramatically due to the fast spread [15]. Thus, the early diagnosis of infection is crucial and may lead to quick medical care to save the patient's life. However, the process for diagnosing COVID-19 is costly and prolonged. It relies on the results of real-time RT-PCR or viral gene sequencing [15]. The aim of the present study was to investigate the hematological changes of patients diagnosed with COVID-19 admitted to the ICU to identify predictable, simple, rapid, and low-cost markers to determine the severity of the infection.

Regardless of anemia diagnosis, our findings revealed a reduction in RBCs, HBG, and HCT among ICU COVID-19 patients. The finding is consistent with a previous report that showed that anemia is common among hospitalized COVID-19 patients not admitted to the ICU [16]. Anemia may result because COVID-19 is a chronic inflammation, and the laboratory findings of most cases have indicated normal or high serum ferritin with reduced transferrin saturation as a consequence of iron retention [16]. Furthermore, the SARS-CoV-2 protein may attack hemoglobin, specifically the heme molecule, causing iron release and making porphyrin available for binding. As a result of the high binding between the virus and porphyrin, heme synthesis could be inhibited [17]. Thus, this may contribute to the persistent breathing difficulties in patients diagnosed with COVID-19. Red cell indices involving MCV and MCH were not changed, although MCHC seemed to decrease in COVID-19 patients, which may have been due to a lack of iron absorption resulting from the overproduction of interleukin (IL)-6, which blocks iron absorption via hepcidin.

Patients diagnosed with SARS-CoV-2 were shown to present with either an increase or decrease in WBCs [14]. The reduction of lymphocyte counts was pronounced in most positive cases of SARS-CoV-2 [14], which is perhaps due to the impact of the COVID-19 virus on T lymphocytes, especially CD4+ and CD8+ T [18]. The immune cells from our study unveiled significant leukocytosis and lymphocytopenia. Leukocytosis tends to be more prominent in severe cases than less severe reports, which is consistent with our results. WBC increases have yet to be determined but could occur due to pneumonia or as a result of drug use, such as steroids [14].

Neutrophils are the most abundant type of immune cells and are the first line of immune defense. Concerning WBC differentials, an early study reported that neutrophilia and lymphocytopenia were significantly observed in severe cases. Severe cases also showed a lower percentage of monocyte, eosinophil, and basophil counts [19]. An increase in neutrophil count occurred in COVID-19 patients suffering from severe respiratory symptoms, but this was described as a poor outcome and suggested as an indicator of the severity of the cases [20]. Our findings indicated a statistical increase in the absolute and percentage of neutrophil counts among ICU patients, suggesting the severity of respiratory symptoms is consistent with the previous report [19]. Furthermore, the percentages and absolute counts of eosinophils and basophils also showed a significant reduction among infected patients, consistent with the earlier study [19]. A reduction in the percentage of monocyte was also determined, but not in absolute monocytes [19]. The median of absolute monocytes in our data showed a higher value in patients than in control group, but the difference was not statistically significant.

Some of the SARS-CoV-2 patients developed serious complications, including coagulation abnormalities [21]. The findings of the present study revealed a statistical alteration in the platelet counts and INR of SARS-CoV-2 patients. COVID-19

was shown to cause thrombocytopenia through different proposed mechanisms, including ineffective hematopoiesis triggered by coronaviruses, injury of endothelial cells elicited by the use of mechanical ventilation, and the presence of SARS-CoV-2 infection leading to the exposure of the subendothelium matrix, thereby allowing platelet–collagen binding that in turn triggers platelet activation and ineffective thrombopoiesis due to lung deformation as platelet releases may occur mainly in the lungs [22]. Consequently, endothelial damage may also increase INR results of ICU-admitted SARS-CoV-2 patients, as the release of tissue factors from the subendothelium matrix activates the extrinsic pathway and leads to factor VII activation.

COVID-19 has become a public health emergency of international concern. The effect of infection varies, as it can be asymptomatic or may lead to severe respiratory complications. Therefore, searching for clinical biomarkers is highly recommended to monitor the severity of the disease, although restricted procedures and government regulations due to the pandemic limit the ability to closely monitor daily hematological testing for ICU patients. Our results support the unique impact of COVID-19 on the hematological markers, particularly in severe cases. Therefore, hematological testing could contribute to investigating the severity of the disease. The introduction of the vaccine may reduce the severity of the infection; however, monitoring vaccinated patients' hematological and coagulation profiles is required, specifically for susceptible individuals. Our findings may further support the need for hematological testing to predict the severity of COVID-19, encouraging early medical intervention to reduce clinical complications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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