Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 May 05; 10(A):817-823.
https://doi.org/10.3889/oamjms.2022.8937
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Pathophysiology*

Assessment of the Level of Protein C in Hospitalized Iraqi Patients with COVID-19 and its Correlation with Hematological and Inflammatory Markers

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Edited by: https://publons.com/researcher/391987/mirko-spiroski/
Citation: Al-Mamoori HS, Ahmed MH, Al-Nafie TYS, Al-Attar Z. Assessment of the Level of Protein C in Hospitalized Iraqi Patients with COVID-19 and its Correlation with Hematological and Inflammatory Markers. Open Access Maced J Med Sci. 2022 May 05; 10(A):817-823. https://doi.org/10.3889/oamjms.2022.8937
Keywords: COVID-19; Protein C; D-Dimer; Coagulopathy
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Received: 08-Feb-2022
Revised: 28-Feb-2022
Accepted: 06-Mar-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: COVID-19 coagulopathy manifests by elevation of certain marker of active coagulation as fibrinogen and this increment associated with increased markers of inflammations.

AIM: To measure protein C (PC) level in hospitalized patients with COVID-19 and to find a possible correlation with hematological and inflammatory markers.

PATIENTS AND METHODS: Seventy-five hospitalized Iraqi adult patients with COVID-19 were included in a descriptive cross-sectional research. PC, D-dimer, and erythrocyte sedimentation rate (ESR) blood samples were collected, and further information was received from patient's records. Statistical analysis was conducted using SPSS version 23 and Microsoft Office Excel 2019.

RESULTS: Mean age of 75 patients included in the study was 60.13 ± 14.65 years. Sixty-two (62.7%) of patients exhibited neutrophilia, whereas 41 had lymphopenia (54.7%). High ratio of neutrophil/lymphocyte (N/L) was seen in 66 (88.0%), eosinopenia was seen in 46 (61.3%), high lactate dehydrogenase level was seen 68 (90.7%), serum ferritin was high in 66 (88.0%), and high level of C-reactive protein was seen in 68 (90.7%), increased ESR was seen in 69 (92.0%) and high level of D-dimer was seen in 56 (74.7%), while low level of PC was seen in 12 (16.0%) patients. PC had significant negative correlation with prothrombin and partial thromboplastin time but no significant correlation with hematological and inflammatory parameters.

CONCLUSION: COVID-19 coagulopathy is common in majority of patients which include significant changes in WBCs counts, inflammatory markers, PC, and D-dimer levels. Such changes may have a great impact on morbidity and mortality and thus need to be monitored throughout treatment and convalescence.

Introduction

Coronavirus illness (COVID-19) began in Wuhan, China, as a cluster of unidentified pneumonia patients. The new coronavirus, 2019-nCoV, was isolated from airway epithelial cells. The most prevalent symptoms associated with COVID-19 were fever, coughing, headache, expectoration, muscle aches or fatigue, frequent bowel movements, and hemoptysis, as well as aberrant features on chest computerized tomography [1], [2], [3], [4], [5]. These signs and symptoms are associated with raised inflammatory respone in the form of adult respiratory syndrome , sepsis, coagulapoathy and high mortality [6].

Coagulation abnormalities have been seen in up to 50% of individuals with severe COVID-19 symptoms. A high D-dimer level is associated with the most substantial alteration in coagulation indices in patients with severe COVID-19, and rising levels may be utilized as a prognostic indicator, predicting a poor outcome [7], [8].

Recent research on COVID-19 patients have shown that the predominant pulmonary pathological symptoms are widespread alveolar damage and acute respiratory distress syndrome (ARDS) [9]. While some COVID-19 patients had cardiovascular problems, including venous thromboembolic illness [10], [11] and ischemic disorders of the arterial system, such as stroke [12].

The virus is directed specifically toward endothelial cells expressing ACE-2.

They stimulate the immune system's inherent defenses, promote tissue permeability, initiate inflammation, and may contribute to the disease's severity. Endothelium dysfunction may result in systemic harm, including coagulopathy, renal problems, pulmonary embolism (PE), and sepsis [13]. Viral infection results in the secretion of pro-inflammatory cytokines by stimulating the innate immune system's inflammatory responses. Platelets are activated as a result of this inflammation and heightened immunological response, and natural anticoagulant mechanisms such as protein C

(PC) and protein S are downregulated [14]. Endothelial dysfunction has been identified as a risk factor for developing coagulopathy in COVID-19; certain markers can be used for evaluation of the severity of inflammation as D-dimer, fibrinogen, erythrocyte sedimentation rate (ESR), CRP, and factor VIII.

Along with the aforementioned complications, COVID-19-associated coagulopathy is induced by other pathways, including higher von Willebrand factor release from damaged endothelium, TLRs, and complement activation [15], [16]. The PC system is crucial for blood coagulation control because it modulates the activity of factor Va (FVa) and VIIIa (FVIIIa), which serve as cofactors for factor X and prothrombin activation, respectively [17], [18]. On the endothelial cells membrane, it is triggered effectively by thrombin coupled to the membrane protein thrombomodulin.

Activated PC (APC) and protein S inhibit coagulation by degrading FVa and FVIIIa on negatively charged phospholipid membranes [9]. Since the PC system is involved in the modulation of severe systemic inflammations such as sepsis, and ARDS through its anticoagulant and anti-inflammatory properties, we sought to determine the level of this protein and its correlation with other prognostic markers in patients with COVID-19, which may aid in classifying patients according to the severity and assisting in critical care patient management [19], [20].

The purpose of this research is to determine PC amount in hospitalized patients with COVID-19 and to see if there is any link with hematological or inflammatory indicators.

Patients and Methods

A descriptive cross-sectional study had been directed on a total of 75 samples of hospitalized Iraqi adult patients with COVID-19 admitted to the following centers: the 35 patients from Al-Imamein Al-Kadhimein Medical city, 10 patients from Dar Al-Salam Hospital, and 30 patients from Ibn Al-khatib Infectious Diseases Hospital, the samples were collected between November 22, 2020 and January 4, 2021. All patients included in this study were diagnosed with COVID-19 patients with positive PCR and randomly collected regarding age and sex. Verbal consent was taken from all patients.

Inclusion criteria

Hospitalized adult patients with COVID-19 proved by positive PCR.

Exclusion criteria

Pregnant ladies, patients with a history of D.M, history of chronic renal failure, history of malignant diseases, history of other inflammatory conditions, and patients on oral anticoagulants.

Methods

Peripheral venous blood sample (from the antecubital fossa) was withdrawn from all applicants under the aseptic technique, 4 mL of whole blood were aspirated and separated into three tubes: 1.8 mL poured into K2-EDTA tube for ESR and 2 mL separated into two sodium citrate tubes, gently mixed, addressed with patients ID and moved to the Teaching Laboratory in the Al-Imamein Al-Kadhimyein for investigation within less than 6 h after sample collection. For D-dimer measurements, 2 ml of venous blood samples were taken from the patients with COVID-19 in Sodium Citrate 9 NaCl tubes, gently mixed and plasma was obtained after centrifugation for 15 min at 2500 g. STA Compact Max2 Coagulation analyzer was used to analyze blood samples from Ibn Alkhatib Infectious Diseases Hospital provided from patient's files.

For the determination of PC activity in plasma, 2 ml of venous blood samples were taken from the patients with COVID-19 in Sodium Citrate 9NC tubes, gently mixed and then moved to a private laboratory in Baghdad for investigation within less than 6 h. For PC measurements, plasma was obtained after centrifugation for 15 min at 2500 g. Then, for deep freezing, placed the samples in Eppendorf tubes in deep freezing reached (< −20 – < −30), until PC assay was done by STA® - Deficient PC Kit using the Stago (STart Max), Diagnostica, USA.

Statistical analysis

The Statistical package for the Social Sciences 23 and Microsoft Office Excel 2019 were used to gather, summarize, analyze, and display data. Qualitative (categorical) variables were presented as numbers and percentages, whereas quantitative (numeric) variables were evaluated for normality distribution using the Shapiro–Wilk test and then expressed as mean (an index of central tendency) and standard deviation (an index of dispersion) for normally distributed numeric variables, and median (an index of central tendency) for non-normally distributed numeric variables (an index of dispersion).

Pearson correlation is used to measure the correlation between any two numeric variables, with the findings given as the correlation coefficient (r) and degree of significance (P). $p \leq 0.05$ were deemed significant. A $p \leq 0.01$ was deemed significant.

Results

This current cross-sectional study involved 75 Iraqi patients with COVID-19, 25 (33.3 %) were female and 50 (66.6 %) were male, the male-to-female ratio was 2:1. The mean age of the registered patients was 60.13 ± 14.65 years and it ranged from 24 to 90 years (Table 1).

Table 1: Comparison of age between male and female patients with coronavirus disease-19

Age (years)	Total (*n* = 70)	Male (*n* = 50)	Female (*n* = 25)	p*
Mean ± SD	60.13 ± 14.65	58.64 ± 15.47	63.12 ± 12.61	0.214
Range	24–90	24–88	37–90	

*Unpaired *t*-test. SD: Standard deviation, *n*: Number of cases.

Regarding hematological parameters, the mean hemoglobin level was 13.06 ± 2.3. The proportion of anemic subjects was 26 (34.7%), and the proportion of normal hemoglobin was 46 (61.3%), while the proportion of patients with polycythemia was 3 (4%) (Table 2).

Table 2: Frequency distribution of complete blood count parameters in patients with coronavirus disease-19

Parameter	Results
Hb (g/dl) (reference range: Men: 13–17, women: 12–15)	
Mean ± SD	13.06 ± 2.3
Median	13.2
Range	6.7–19.4
Anemia, *n* (%)	26 (34.7)
Normal, *n* (%)	46 (61.3)
Polycythemia, *n* (%)	3 (4.0)
Neutrophils (× 10^9/l) (reference range 2–7)	
Mean ± SD	9.46 ± 5.48
Median	8.6
Range	2.3–27.2
Neutropenia, *n* (%)	0 (0.0)
Normal, *n* (%)	28 (37.3)
Neutrophilia, *n* (%)	47 (62.7)
Lymphocytes (× 10^9/l) (reference range: 1–3)	
Mean ± SD	1.07 ± 0.72
Median	0.9
Range	0.2–3.2
Lymphopenia, *n* (%)	41 (54.7)
Normal, *n* (%)	32 (42.7)
Lymphophilia, *n* (%)	2 (2.6)
Neutrophils/lymphocytes ratio (reference range: 1–3)	
Mean ± SD	12.86 ± 10.3
Median	9.0
Range	0.97–49
Low, *n* (%)	1 (1.3)
Normal, *n* (%)	8 (10.7)
High, *n* (%)	66 (88.0)
Eosinophils (× 10^9/l) (reference range: 0.02–0.5)	
Mean ± SD	0.04 ± 0.11
Median	0.0
Range	0.0–0.76
Eosinopenia, *n* (%)	46 (61.3)
Normal, *n* (%)	28 (37.3)
Eosinophilia, *n* (%)	1 (1.3)
Platelets (× 10^9/l) (reference range: 150–410)	
Mean ± SD	276.67 ± 119.59
Median	259
Range	23–668
Thrombocytopenia, *n* (%)	10 (13.3)
Normal, *n* (%)	56 (74.7)
Thrombocytosis, *n* (%)	9 (12.0)

Hb: Hemoglobin, SD: Standard deviation, *n*: Number of cases.

The mean hemoglobin level was greater in men than women, 13.55 versus 12.07 g/dl, in a highly significant manner (p = 0.008). In addition, serum ferritin was higher in men in comparison with women, 656.50 versus 489.85 ng/ml, in a significant manner (p = 0.026) (Table 3).

The mean of the neutrophil count was 9.46 ± 5.48 ×10^9/L and 47 (62.7%) patients had neutrophilia. The mean of lymphocyte count was 1.07 ± 0.72 ×10^9/L and lymphopenia was seen in 41 (54.7%), the mean of N/L ratio was 12.86 ± 10.3 and a high ratio was seen in 66 (88.0 %). The mean of eosinophil count was 0.04 ± 0.11 ×10^9/L, and the low count was seen in 46 (61.3 %).

Table 3: Comparison of complete blood count parameters between males and female patients with coronavirus disease-19

Parameter	Female (*n* = 25), *n* (%)	Male (*n* = 50), *n* (%)	p
Hb (g/dl) (reference range: Men: 13–17, women: 12–15)			
Anemia	10 (40.0)	16 (32.0)	0.662* (NS)
Normal	13 (52.0)	33 (66.0)	
Polycythemia	2 (8.0)	1 (2.0)	
Neutrophils (× 10^9/l) (reference range: 2–7)			
Neutropenia	0	0	0.615* (NS)
Normal	8 (32.0)	20 (40.0)	
Neutrophilia	17 (68.0)	30 (60.0)	
Lymphocytes (× 10^9/l) (reference range: 1–3)			
Lymphopenia	13 (52.0)	28 (56.0)	0.922* (NS)
Normal	12 (48.0)	20 (40.0)	
Lymphophilia	0	2 (4.0)	
Neutrophils/lymphocytes ratio (reference range: 1–3)			
Low	0	1 (2.0)	0.930* (NS)
Normal	2 (8.0)	5 (10.0)	
High	23 (92.0)	44 (88.0)	
Eosinophils (× 10^9/l) (reference range: 0.02–0.5)			
Eosinopenia	14 (56.0)	32 (64.0)	0.906* (NS)
Normal	10 (40.0)	18 (36.0)	
Eosinophilia	1 (4.0)	0	
Platelets (× 10^9/l) (reference range: 150–410)			
Thrombocytopenia	4 (16.0)	6 (12.0)	0.469* (NS)
Normal	16 (64.0)	40 (80.0)	
Thrombocytosis	5 (20.0)	4 (8.0)	

*Yates Chi square test. Hb: Hemoglobin, *n*: Number of cases, NS: Non-significant.

In concern to inflammatory markers, the median level of ESR was 52.00 mm/hr and increased ESR was seen in 69 (92.0 %), the median level of lactate dehydrogenase (LDH)was 417.00 IU/L, and elevated LDH level was seen 68 (90.7 %). Serum ferritin median level was 600.00 ng/ml and abnormal level was seen in 66 (88.0 %), while the median level of CRP was 52.0 mg/L and it was at an extreme level in 68 (90.7 %) patients (Table 4).

Table 4: Frequency distribution of inflammatory parameters in patients with coronavirus disease-19

Parameter	Results
ESR (mm/h) (reference range: For men: 17–50 years≤10, 51–60 years≤12, 61–70 years≤14, > 70 years≤30, for women: 17–50 years≤12, 51–60 years≤19, 61–70 years≤20, > 70 years≤35)	
Mean ± SD	53.84 ± 26.66
Median	52.0
Range	5–140
Normal, *n* (%)	6 (8.0)
High, *n* (%)	69 (92.0)
CPR (mg/l) (reference range: < 10)	
Mean ± SD	74.74 ± 71.57
Median	52.0
Range	2.3–290.01
Normal, *n* (%)	7 (9.3)
High, *n* (%)	68 (90.7)
Serum ferritin (ng/ml) (reference range: For men: 15–300, for women: 15–200)	
Mean ± SD	658.59 ± 396.68
Median	600
Range	10.3–1650
Low, *n* (%)	1 (1.3)
Normal, *n* (%)	8 (10.7)
High, *n* (%)	66 (88.0)
LDH (U/l), (reference range: 120–246)	
Mean ± SD	481.75 ± 215.81
Median	417
Range	140–912
Low, *n* (%)	0 (0.0)
Normal, *n* (%)	7 (9.3)
High, *n* (%)	68 (90.7)

ESR: Erythrocyte's sedimentation rate, CPR: C-reactive protein, LDH: Lactate dehydrogenase, SD: Standard deviation, *n*: Number of cases.

Considering the markers of coagulation, the median level of D-dimer was 1.45 μg/ml, the elevated

Table 5: Frequency distribution of coagulation parameters in patients with coronavirus disease-19

Parameter	Results
PT (s) (reference range: 11–16)	
Mean ± SD	14.23 ± 2.25
Median	13.7
Range	11–20
Low, *n* (%)	0 (0.0)
Normal, *n* (%)	63 (84.0)
High, *n* (%)	12 (16.0)
APTT (s) (reference range: 26–40)	
Mean ± SD	30.12 ± 5.45
Median	30
Range	19.9–41.3
Low, *n* (%)	15 (20.0)
Normal, *n* (%)	58 (77.3)
High, *n* (%)	2 (2.7)
D-dimer (mg/ml) (reference range: < 0.5)	
Mean ± SD	2.63 ± 3.34
Median	1.45
Range	0.1–16
Normal, *n* (%)	19 (25.3)
High, *n* (%)	56 (74.7)
PC (%) (reference range: 70–140)	
Mean ± SD	75.29 ± 16.73
Median	76
Range	22–110
Low, *n* (%)	12 (16.0)
Normal, *n* (%)	63 (84.0)
High, *n* (%)	0 (0.0)

APTT: Activated partial thromboplastin clotting, PT: Prothrombin time, PC: Protein C, SD: Standard deviation, *n*: Number of cases.

level was seen in 56 (74.7 %), median PT was 13.75 s, activated partial thromboplastin time (APTT) was 30.0 s and the median level of PC was 76 %, and the low PC level was seen in 12 (16.0 %) and the normal level was seen in 63(84.0 %), no patients with a high PC level are seen (Table 5).

While the correlation of the PC level was negatively significant with PT, and highly significant with APTT, there was no significant correlation found with hematological, inflammatory, and other coagulation markers (Table 6, Figures 1 and 2).

Table 6: Correlation of protein C with other parameters

Parameter	PC	
	r	p
Age (years)	0.081	0.488
Hb (g/dl)	−0.066	0.575
Neutrophils (× 10^9/l)	−0.080	0.493
Lymphocytes (× 10^9/l)	−0.086	0.462
Neutrophils/lymphocytes ratio	0.090	0.444
Eosinophils (× 10^9/l)	0.135	0.250
Platelets (× 10^9/l)	0.096	0.411
ESR (mm/h)	−0.122	0.295
CPR (mg/l)	0.098	0.402
Serum ferritin (ng/ml)	−0.014	0.907
LDH (U/l)	0.045	0.700
PT (s)	−0.276	0.016
APTT (s)	−0.567	<0.001
D-dimer (mg/ml)	0.047	0.687

Hb: Hemoglobin, ESR: Erythrocyte's sedimentation rate, CPR: C-reactive protein, LDH: Lactate dehydrogenase, APTT: Activated partial thromboplastin clotting, PT: Prothrombin time, PC: Protein C.

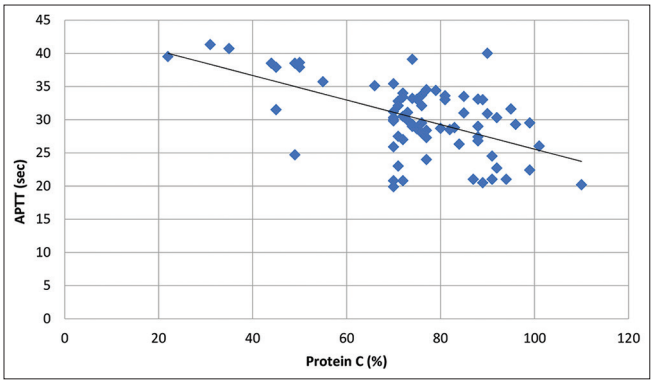

Figure 1: Correlation of protein C with activated partial thromboplastin time

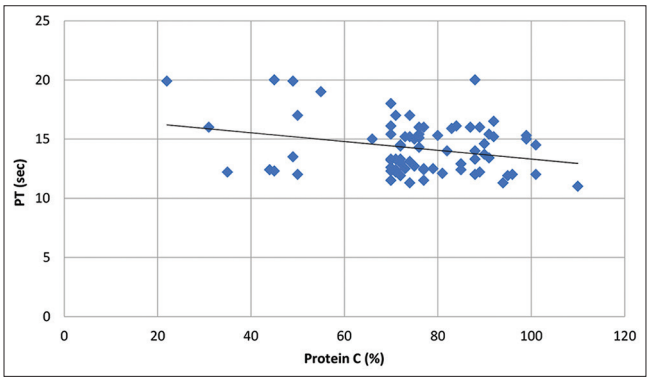

Figure 2: Correlation of protein C with activated prothrombin time

Discussion

Coronavirus disease (COVID-19) is a respiratory infection that manifests itself in various ways. Although some individuals exhibit minimal or minor symptoms, others develop more significant problems requiring specialist therapy in critical intensive care units [11]. Unusual hematological findings may be associated with coagulopathy, as low platelet counts, APTT levels, and increased prothrombin time (PT), as well as higher fibrin degradation product and D-dimer values, which all are related with a poor result and higher mortality in COVID-19 patients [20], [21]. Individuals infected with SARS-CoV2 had a comparable increased risk for developing disseminated intravascular coagulation (DIC) [13], and since PC works as a natural anticoagulant, its low level may give rise to these findings. In the current study of hospitalized patients with COVID-19, most of the adult patients were old, with a mean age of 60.13 ± 14.65 years; this was similar to many other studies [14], [15], and this was expected since the increasing age is one of the risk factors for developing a more severe disease requiring hospitalization. The male/female ratio was 2/1.

Regarding hematological parameters, the mean hemoglobin concentration was 13.06 ± 2.3g/dl and. The low hemoglobin level was seen in 26 (34.7%) and the number of normal hemoglobin was 46 (61.3%), while the proportion of patients with polycythemia were 3 (4.0%), this result was in agreement with many other studies from Iran, Singapore, Wuhan, Spain, and Italy [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26].

Anemia in COVID-19 patients might be related to the increased level of hepcidin as a response to inflammatory markers, which in turn leads to the increased level of ferritin and abnormal utilization of the serum iron leading to anemia [41].

While the mean neutrophil count in this study was 9.46 ± 5.48 $\times 10^9$/L and the range was 2.3–27.2. Normal neutrophil count was reported in (37.3%) of patients, while (62.7 %) of the patients had neutrophilia. This is agreed with other studies [16], [24].

Regarding lymphocytosis, which was found in 2.6% and agreed with other studies in Malaysia and India and this might be associated with a milder disease [25], [26] [27].

Lymphopenia was also a finding in 54.7%, and it might be due to an abnormal immune response to the virus and the associated inflammatory process, and it might be caused by the direct lymphocyte's inhibition by the direct infection and lactic acidosis damaging the cells [28], [29], [30], [31].

Regarding inflammatory markers the ESR, serum ferritin, CRP, and LDH, there were elevation in 92.0%, 90.7%, 88.0%, and 90.7% of the patients similar studies had the same findings [25], [32], [33], [34].

In the review of coagulation parameters, the APTT was lower than the reference range in 15 patients (20%) similar finding was observed in a study done by Hui Long, but at a lower frequency [35], this shortened level might be related to the increased level of procoagulant in the patients' plasma which might be a sign of early DIC or could reflect the high level of FVIII which act as acute phase reactant protein. Furthermore, in regard to D-dimer level, it was elevated in 74.7% of the patients similar studies had the same findings [25], [34], [35].

In severe COVID-19, increased D-dimer levels reflect higher fibrin deposition (microthrombosis) rather than enhanced fibrin breakdown (fibrinolysis), and the cumulative effects of increased fibrin deposition and hypofibrinolysis/fibrinolysis shutdown lead to microcirculation thrombosis, eventually leading to lung and kidney failure, as well as neurologic disorders [36]. The median PC level was below the normal range; Tabatabai, Ali, *et al*. obtained a similar result [37]. In our research, we observed a normal level of PC in 84% of patients and a reduction in 16% of them, which is consistent with the findings of Calderon-Lopez M.T [38]. Since the PC is found on the surface of endothelial cells. APC is a potent inhibitor of the coagulation system, primarily in microcirculation, when combined with PS. The APC inhibits inflammation and apoptosis and maintains the integrity of the endothelium and epithelial barriers [39], [40]. As a result, the APC is engaged in a large number of the pathologic events seen in COVID-19. PC deficiency has been linked to DIC and a poor outcome in sepsis. Reduced PC levels were one of many indicators used in a recent investigation to differentiate the pre-DIC condition in septic patients [40]. Furthermore, since PC and APC have short half-lives and are linked with enhanced coagulation pathway activation, this might result in PC shortage and the establishment of a hypercoagulable state [40]. As a result, the decrease in admission PC levels seen in such individuals is most likely attributable to increased intake and may be indicative of DIC rather than decreased liver production.

The majority of patients exhibited a high neutrophil count, a low lymphocyte count, an elevated neutrophil-to-lymphocyte ratio, and a low eosinophil count. Inflammatory markers (S. ferritin, LDH, CRP, and ESR) were elevated. PC levels were low in some individuals with COVID-19, although D-dimer levels were increased in the majority of patients.

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