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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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, expectation, 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 response in the form of adult respiratory syndrome, sepsis, coagulopathy 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-Kadhimyeyin 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 ≤ 0.05 were deemed significant. A p ≤ 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 = 75) | Male (n = 50) | Female (n = 25) |
|------------|----------------|--------------|-----------------|
| Mean ± SD  | 60.13 ± 14.65  | 58.64 ± 15.47| 63.12 ± 12.61   |
| 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 |
|-----------|---------|
| Mean ± SD | 9.46 ± 5.48 |
| Median    | 9.0 |
| Range     | 0.97–49 |
| Low, n (%)| 1 (1.3) |
| Normal, n (%) | 68 (88.0) |
| High, n (%)| 8 (10.7) |
| Neutrophils (× 10^9/L) (reference range: 2–7) | Mean ± SD 1.07 ± 0.72 |
| Median    | 0.9 |
| Range     | 0.2–3.2 |
| Neutrophilia, n (%) | 41 (54.7) |
| Normal, n (%) | 32 (42.7) |
| Lymphopenia, n (%) | 5 (6.7) |
| 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 (%) | 68 (88.0) |
| High, n (%)| 8 (10.7) |

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 ×10^11/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 %).

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 66 (88.0 %). The mean of ferritin level was 417.00 IU/L, and the low level was seen in 70 (93.3 %). The mean of CRP was 52.0 mg/L, and the high level was seen in 68 (90.7 %) (Table 4).

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

| Parameter | Results |
|-----------|---------|
| 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     | 23–290.01 |
| Normal, n (%) | 7 (9.3) |
| High, n (%)| 68 (90.7) |

The mean ferritin level was 1.45 μg/ml, the elevated ESR, C-reactive protein, and lactate dehydrogenase were all significantly higher in male patients than in female patients.
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 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 |
| Low, n (%) | 19 (25.3) |
| Normal, 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) |

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 ± 2.3 g/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 ×10⁹/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.

References

1. Griffin JH, Lyden P. COVID-19 hypothesis: Activated protein C for therapy of virus-induced pathologic thromboinflammation. Res Pract Thromb Haemost. 2020;4(4):506-9. https://doi.org/10.1002/rth2.12362 PMid:32548551
2. Al Otair H, AlSaleh K, AlQahtany FS, Al Ayed K, Al Ammar H, Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Griffin JH, Lyden P. COVID-19: Coagulopathy, risk of disseminated intravascular coagulation (DIC), and a poor outcome in septic patients. J Intern Med. 2021;289(2):207-22. https://doi.org/10.1111/joim.12972 PMid:34512966
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. N Engl J Med. 2020;382(8):727-33. https://doi.org/10.1056/nejmoa2001017 PMid:31978945
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. https://doi.org/10.1001/jama.2020.1585 PMid:32031570
5. Liu L, Lei X, Xiao X, Yang J, Li J, Ji M. Epidemiological and clinical characteristics of patients with coronavirus disease-2019 in Shiyian city, China. Front Cell Infect Microbiol. 2020;10:284. https://doi.org/10.3389/fcimb.2020.00284 PMid:32574282
6. Miesbach W, Makris M. COVID-19: Coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149. https://doi.org/10.1177/1076029620938149 PMid:32677459
7. Vajari MK, Shirin M, Pourbagheri-Sigaroodi A, Alkbari ME, Abolghasemi H, Bashash D. COVID-19-related coagulopathy: A review of pathophysiology and pharmaceutical management. Cell Biol Int. 2021;45(9):1832-50. https://doi.org/10.1002/cbin.11623 PMid:33945651
8. Liu Q, Wang RS, Qu GQ, Wang YY, Liu P, Zhu YZ, et al. Gross examination report of a COVID-19 death autopsy. Fa Yi Xue Za Zhi. 2020;36(1):21-3. https://doi.org/10.12116/j.issn.1004-5619.2020.01.005 PMid:32198987
9. Dahlbäck B, Villoutreix BO. Regulation of blood coagulation by the protein C anticoagulant pathway: Novel insights into structure-function relationships and molecular recognition. Arterioscler Thromb Vasc Biol. 2005;25(7):1311-20. https://doi.org/10.1161/01.atv.0000168421.13467.82 PMid:15860736
10. Bashash D, Hosseini-Baharanchi FS, Rezaie-Tavirani M, Safa M, Dilmaghani NA, Faranoush M, et al. The prognostic value of thrombocytopenia in COVID-19 patients: a systematic review and meta-analysis. Arch Acad Emerg Med. 2020;8(1):e75. PMid:33134971

11. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res. 2019;181:77-83. https://doi.org/10.1016/j.thromres.2019.07.013 PMid:31376066

12. Giannis D, Zogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362. https://doi.org/10.1016/j.jcv.2020.104362 PMid:32305883

13. Wang YD, Zhang SP, Wei QZ, Zhao MM, Mei H, Zhang ZL, et al. COVID-19 complicated with DIC: 2 cases report and literatures review. Zhonghua Xue Ye Xue Za Zhi. 2020;41(3):245-7. https://doi.org/10.3760/cma.j.issn.0253-2727.2020.0001 PMid:32133824

14. Stanne TM, Pedersen A, Gisslén M, Jern C. Low admission hematocrit and mortality in hospitalized patients with COVID-19. Thromb Res. 2021;204:13-15. https://doi.org/10.1016/j.thromres.2021.05.016 PMid:34102452

15. Franciscietti IM, Toomer K, Zhang Y, Jani J, Siddiqui Z, Brotman DJ, et al. Upregulation of pulmonary tissue factor, loss of thrombomodulin and immunothrombosis in SARS-CoV-2 infection. EClinicalMedicine. 2021;39:101069. https://doi.org/10.1016/j.eclinm.2021.101069 PMid:34377969

16. Fan BE, Chong VC, Chan SS, Lim GH, Lim KG, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95(6):E131-4. https://doi.org/10.1002/ajh.25774 PMid:32129508

17. Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of neutrophil-to-lymphocyte is associated with severe COVID-19. Epidemiol Infect. 2020;148:e139. https://doi.org/10.1017/s0950268820001557 PMid:32641174

18. Martin-Rojas RM, Pérez-Rus G, Delgado-Pinos VE, Domingo-González A, Regalado-Artamendi I, Alba-Urieltes N, et al. COVID-19 coagulopathy: An in-depth analysis of the coagulation system. Eur J Haematol. 2020;105(6):74-50. https://doi.org/10.1111/ejh.13501 PMid:32749010

19. Ruscitti P, Bruno F, Berardicurti O, Acanfora C, Pavlych V, Palumbo P, et al. Lung involvement in macrophage activation syndrome and severe COVID-19: Results from a cross-sectional study to assess clinical, laboratory and artificial intelligence-radiological differences. Ann Rheum Dis. 2020;79(9):1152-5. https://doi.org/10.1136/annrheumdis-2021-218048 PMid:32719039

20. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020;120(6):998-1000. https://doi.org/10.1055/s-0040-1710018 PMid:32316063

21. Lin S, Mao W, Zou Q, Lu S, Zheng S. Associations between hematological parameters and disease severity in patients with SARS-CoV-2 infection. J Clin Lab Anal. 2021;35(1):e23604. https://doi.org/10.1002/jcla.23604 PMid:33184946

22. Sayad B, Afshar ZM, Mansouri F, Rahimi Z. Leukocytosis and alteration of hemoglobin level in patients with severe COVID-19: Association of leukocytosis with mortality. Health Sci Rep. 2020;3(4):e194. https://doi.org/10.1002/hsr2.194 PMid:33083572

23. Urrechaga E, Zalba S, Otamendi I, Zabalegui MA, Galbete A, Ongay E, et al. Hemoglobin and anemia in COVID19 patients. Hematol Med Oncol 2020;5:1-4 https://doi.org/10.15761/hmo.1000217

24. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. Am J Respir Crit Care Med. 2020;211(13):1372-9. https://doi.org/10.1164/rccm.202003-0543oc PMid:32242738

25. Ish P, Malhotra N, Agrawal S, Gupta N. Relative lymphocytosis in COVID-19; a ray of hope. Adv Respir Dis. 2020;88(3):287-8. https://doi.org/10.5603/arm.a2020.0098 PMid:32706115

26. Kasinathan G, Sathar J. Haematological manifestations, mechanisms of thrombosis and anti-coagulation in COVID-19 disease: A review. Ann Med Surg (Lond). 2020;56:173-7. https://doi.org/10.1016/j.amsu.2020.06.035 PMid:32637095

27. Smolka A, Kowalewski M, Żekanowska E. Coronavirus disease 2019 (COVID-19): A short review on hematological manifestations. Pathogens. 2020;9(6):493. https://doi.org/10.3390/pathogens9060493 PMid:32575886

28. Lipi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020;506:145-8. https://doi.org/10.1016/j.cca.2020.03.022 PMid:32178975

29. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID19 patients. Ann Hematol. 2020;99(6):1205-8. https://doi.org/10.1007/s00277-020-04019-0 PMid:32296910

30. Agbuduwe C, Basu S. Haematological manifestations of COVID-19: From cytopenia to coagulopathy. Eur J Haematol. 2020;105(5):540-6. https://doi.org/10.1111/ejh.13491 PMid:32663356

31. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-8. https://doi.org/10.1093/cid/ciaa248 PMid:32161940

32. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta. 2020;507:167-73. https://doi.org/10.1016/j.cca.2020.04.027 PMid:32348783

33. Testa S, Paolotti O, Giorgi-Pierfranceschi M, Pan A. Switch from oral anticoagulants to parenteral heparin in SARS-CoV-2 hospitalized patients. Intern Emerg Med, 2020;15(5):751-3. https://doi.org/10.1007/s11739-020-02331-1 PMid:32290789

34. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, et al. D-Dimer and prothrombin time are the significant indicators of fatal cases of COVID-19 from Wuhan. A retrospective observational study. Thromb Haemost. 2020;2020:6159720. https://doi.org/10.1155/2020/6159720 PMid:32596339

35. Görlinger K, Levy JH. COVID-19-associated coagulopathy. Anesthesiology. 2021;134(3):366-8. https://doi.org/10.1097/
36. Tabatabai A, Rabin J, Menaker J, Madathil R, Galvagno S, Menne A, et al. Factor VIII and functional protein C activity in critically ill patients with coronavirus disease 2019: A case series. A A Pract. 2020;14(7):e01236. https://doi.org/10.1213/xaa.0000000000001236
PMid:32539272

37. Calderon-Lopez MT, Garcia-Leon N, Gomez-Arevalillo S, Martin-Serrano P, Matilla-Garcia A. Coronavirus disease 2019 and coagulopathy: Other prothrombotic coagulation factors. Blood Coagul Fibrinolysis. 2021;32(1):44-9. https://doi.org/10.1097/mbc.0000000000000996
PMid:33417336

38. Mazzeffi M, Chow JH, Amoroso A, Tanaka K. Revisiting the protein C pathway: An opportunity for adjunctive intervention in COVID-19? Anesth Analg. 2020;131(3):690-693. https://doi.org/10.1213/ane.0000000000005059
PMid:32541255

39. Faust SN, Levin M, Harrison OB, Goldin RD, Lockhart MS, Kondaveeti S, et al. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. N Engl J Med. 2001;345(6):408-16. https://doi.org/10.1056/nejm200108093450603
PMid:11496851

40. Chornenki NL, Dwivedi DJ, Kwong AC, Zamir N, Fox-Robichaud AE, Liaw PC, et al. Identification of hemostatic markers that define the pre-DIC state: A multi-center observational study. J Thromb Haemost. 2020;18(10):2524-31. https://doi.org/10.1111/jth.14973
PMid:32573898

41. Al-Attar Z, Jasim S, Hashim I, Badai S. Prevalence of anemia types among overweight and obese patients attending the obesity research and therapy unit at Al-Kindy college of medicine. Int Med J. 2020;24(3):435. https://doi.org/10.47723/kcmj.v13i2.98