Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(11) 1–11

DOI: 10.1177/03000605211059939
journals.sagepub.com/home/imr
SAGE

Coagulation profile and correlation between D-dimer, inflammatory markers, and COVID-19 severity in an Indonesian national referral hospital

Lugyanti Sukrisman[1] and Robert Sinto[2]

Abstract

Background: Coagulopathy and inflammation are associated with coronavirus disease 2019 (COVID-19) severity. This study assessed D-dimer concentration and its correlation with inflammatory markers and COVID-19 severity.

Methods: This was a retrospective cross-sectional study involving 194 COVID-19 cases, with the severity of infection graded in accordance with the World Health Organization (WHO) guidelines. We measured D-dimer, C-reactive protein (CRP), and ferritin on admission and determined the cutoff values for D-dimer and CRP and evaluated the correlation between D-dimer and CRP and ferritin.

Results: Median D-dimer, CRP, and ferritin concentrations were 2240 μg/L, 73.2 mg/L, and 1173.8 μg/mL, respectively. The highest median D-dimer value was seen in mild and moderate acute respiratory distress syndrome (ARDS). The highest ferritin concentration was seen in severe ARDS. There was a significant correlation between D-dimer value and CRP ($r = 0.327$), but no significant correlation between D-dimer and ferritin ($r = 0.101$). The area under the receiver operating characteristic curve (AUC) for the combination of CRP $\geq$72.65 mg/L and D-dimer $\geq$1250 μg/L as a marker of COVID-19 severity was 0.722 (95% confidence interval (CI): 0.615–0.781).

[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia

[2]Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia

Corresponding author:
Lugyanti Sukrisman, Division of Hematology and Medical Oncology, Department of Internal Medicine, Universitas Indonesia/Cipto Mangunkusumo National Hospital, Jl. Pangeran Diponegoro no. 71, Jakarta 10430, Indonesia.
Email: lugyanti@gmail.com

Conclusion: The combination of CRP ≥72.65 mg/L and D-dimer ≥1250 μg/L can be used as marker of COVID-19 severity, with moderate accuracy.

Keywords
Coronavirus disease 2019, D-dimer, ferritin, inflammation, severity, C-reactive protein, acute respiratory distress syndrome, correlation

Date received: 21 April 2021; accepted: 27 October 2021

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel *ß-coronavirus* widely known as sudden acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1,2] On 11 March 2020, the World Health Organization (WHO) declared this disease a global pandemic.[3] As of 1 September 2020, global COVID-19 mortality was 3.34% and had reached 4.2% in Indonesia.[4]

Coagulopathy occurs in 50% of the patients who die because of COVID-19.[2] Coagulopathy can take the form of pulmonary intravascular coagulopathy, venous thromboembolism, and disseminated intravascular coagulation (DIC).[5,6] Zhang et al reported that D-dimer value ≥2000 μg/L at hospital admission was a mortality predictor in COVID-19 patients.[7] The International Society on Thrombosis and Haemostasis (ISTH) suggested monitoring the coagulation parameters, D-dimer, prothrombin time (PT), and fibrinogen, in COVID-19 patients.[8]

Massive increases in the levels of proinflammatory cytokines (cytokine storm), such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), indicate severe inflammation and coagulopathy, which could worsen outcomes in COVID-19 patients.[9–11] This inflammatory cascade is seen in the incremental increases of inflammatory markers, such as C-reactive protein (CRP).[12]

Ferritin is another acute phase-protein that increases in infection or inflammation.[13,14] A meta-analysis revealed that higher ferritin levels were seen in COVID-19 death cases compared with survivors and in COVID-19 patients with thrombotic complications.[15]

Many studies have shown that coagulopathy and inflammatory markers are important and related to COVID-19 severity.[2,5–7] However, limited numbers of studies have evaluated coagulation profiles, especially D-dimer, regarding the severity of COVID-19 infection and its correlation with inflammatory markers. Thus, we aimed to evaluate D-dimer, CRP, and serum ferritin values, and to determine the correlations between these markers and disease severity in COVID-19 patients in Rumah Sakit Cipto Mangunkusumo (RSCM; Cipto Mangunkusumo National Hospital), Jakarta.

Method

This was a retrospective cross-sectional study, conducted at RSCM, Jakarta from May 2020 to November 2020. The inclusion criteria were patients with COVID-19 confirmed by positive SARS-CoV-2 polymerase chain reaction (PCR) testing who were admitted from 28 May 2020. The exclusion criteria were: (1) patients receiving anticoagulant therapy before contracting

COVID-19; and (2) patients undergoing routine blood transfusion and/or those who had already received blood transfusion at the time of treatment.

All data were extracted from electronic medical records. We recorded the following patients' demographic data: age, sex, and comorbidities. The severity of COVID-19 infection was determined in accordance with the WHO guidelines (Supplementary Table 1).[16] D-dimer, CRP, and ferritin laboratory testing was performed in the Clinical Pathology Laboratory of RSCM on the day of hospital admission. D-dimer value was determined using a Sysmex 5100 analyzer (Siemens Healthcare Diagnostics, Marburg, Germany), while CRP and ferritin were determined using a Cobas analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

The Faculty of Medicine Universitas Indonesia Ethics Committee approved this study (No. KET-1139/UN2.F1/ETIK/PPM.00.02/2020). Verbal informed consent was obtained from all patients for blood testing, including D-dimer, CRP, and ferritin.

The sample size for this study was based on the sample size for a correlation study, with an estimated $\alpha = 0.05$, $\beta = 0.20$, and correlation coefficient = 0.2. The calculated required sample size was 194 patients. The data were analyzed using Statistical Package for the Social Sciences (SPSS) 23 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented as median and interquartile range (IQR), while categorical variables were presented as frequencies. D-dimer, CRP, and ferritin values were described at various degrees of COVID-19 severity. The cut-off point for D-dimer value as a marker of COVID-19 disease severity was determined using receiver operating characteristics (ROC) curve analysis. The correlations between D-dimer, CRP, and ferritin were analyzed using Spearman's test. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17]

Results

There were 194 patients with COVID-19 enrolled in this study. The patients' baseline characteristics are shown in Table 1. The patients' age ranged from 37 to 63 years (median: 53 years), and 62.4% were men. The most common COVID-19 severity was critical disease (43.8%), followed by moderate disease (33%). Moderate acute respiratory distress syndrome (ARDS) and septic shock (10.8% for both) dominated the critical disease category, and 89.7% of the patients had at least one comorbidity. The most prominent comorbidity was hypertension (39.2%), followed by renal disease (35.1%), and diabetes mellitus (30.9%).

The overall D-dimer value ranged from 890 μg/L to 5640 μg/L, with a median value of 2240 μg/L (Table 1). Table 2 and Figure 1 show the D-dimer values according to each COVID-19 disease severity category. D-dimer values in patients with severe COVID-19 disease were three-fold higher than those in patients with mild COVID-19 disease (median 1870 μg/L vs 630 μg/L, respectively). Patients with mild ARDS had the highest D-dimer values (median: 5725 μg/L), followed by the moderate ARDS group (median: 4680 μg/L), and septic shock group (median: 3740 μg/L). In comparison, patients with mild COVID-19 disease had the lowest D-dimer values (median: 630 μg/L). D-dimer values in the mild ARDS group were significantly higher than those in the mild COVID-19 disease group (median: 5725 μg/L vs 630 μg/L, respectively; $p = 0.002$) and moderate COVID-19 disease group (median: 5725 μg/L vs 1660 μg/L, respectively; $p = 0.007$) (Figure 1, Appendix 1).

Table 1. The patients' baseline characteristics.

Variable	Result
Number of patients (N)	194
Age (years), median (IQR)	53 (37–63)
Sex (n,%)	
• Male	121 (62.4)
Female	73 (37.6)
COVID-19 severity (n, %)	
• Mild	39 (20.1)
• Moderate	64 (33.0)
• Severe	6 (3.1)
• Critical (Mild ARDS)	19 (9.8)
• Critical (Moderate ARDS)	21 (10.8)
• Critical (Severe ARDS)	14 (7.2)
• Critical (Sepsis)	10 (5.2)
• Critical (Septic shock)	21 (10.8)
Comorbidities (n, %)	
• No comorbidity	20 (10.3)
• Hypertension	76 (39.2)
• Diabetes Mellitus	60 (30.9)
• Renal Disease	68 (35.1)
• Liver Disorder (Increased transaminase level)	25 (12.9)
• Hepatitis B	4 (2.1)
• Hepatitis C	4 (2.1)
• Lung tuberculosis	21 (10.8)
• HIV/AIDS	7 (3.6)
• Autoimmune Disease	5 (2.6)
• Congestive Heart Failure	27 (13.9)
• Coronary Heart Disease	25 (12.9)
• Chronic Obstructive Pulmonary Disease (COPD)	1 (0.5)
• Cerebrovascular Disease	15 (7.7)
• Malignancy	22 (11.3)
Coagulation profiles, median (IQR)	
• D-dimer value (μg/L)	2240 (890.0–5640.0)
Inflammatory markers, median (IQR)	
• CRP (mg/L)	73.2 (22.65–144.25)
• Ferritin (μg/mL)	1173.8 (431.37–3160.74)

IQR, interquartile range; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CRP, C-reactive protein.

The median CRP value was 73.2 mg/L (IQR: 22.65–144.25 mg/L). CRP (normal value: <0.5 mg/L) increased with COVID-19 severity (Table 3, Figure 2a), with the highest median value of 107.4 mg/L (IQR: 30.65–243.35 mg/L), in septic shock. Moreover, the median serum ferritin level was 1173.8 μg/mL (IQR: 431.37–3160.74 ng/mL). Ferritin (normal value: 20.0–500.0 μg/mL) also increased with COVID-19 severity, with the highest median value of 2971.03 μg/mL (IQR: 966.24–3248.06 μg/mL) in severe ARDS (Table 3, Figure 2b). There was no significant difference between CRP and ferritin values between the groups.

Table 2. D-dimer values according to COVID-19 severity.

Variable, median (IQR)	Mild COVID-19	Moderate COVID-19	Severe COVID-19	Mild ARDS	Moderate ARDS	Severe ARDS	Sepsis	Septic shock
D-dimer (μg/L)	630 (330–3060)	1660 (907.5–3465.0)	1870 (925–18,645)	5725 (1805–21,230)	4680 (1750–5960)	2370 (880–12,100)	2150 (780–5450)	3740 (1402.5–9715.0)

COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; IQR, interquartile range.

An analysis of the correlation between D-dimer and the inflammatory markers, CRP and ferritin, (Table 4) revealed a significant but weak correlation between D-dimer and CRP ($r = 0.327$, $p < 0.001$) and no significant correlation between D-dimer and ferritin ($r = 0.101$).

The area under the curve (AUC) for the CRP value as a marker of COVID-19 severity was 0.652 (95% confidence interval (CI): 0.573–0.730). In comparison, the AUC for D-dimer value as a marker of COVID-19 severity was 0.698 (95% CI: 0.615–0.781). ROC curve analysis provided a CRP cut-off value of $\geq$72.65 mg/L, with 60% sensitivity and 66% specificity, and a cut-off for D-dimer of $\geq$1250 μg/L, with 83% sensitivity and 53% specificity. The AUC for the combination of CRP and D-dimer was 0.722 (95% CI: 0.615–0.781) (Figure 3).

Discussion

The clinical spectrum of COVID-19 illness varies and ranges from asymptomatic or mild illness to severe, life-threatening infection.[18] COVID-19 patients may also have variable laboratory findings. In the early stages of infection, D-dimer and fibrinogen levels are abnormally high, reflecting excessive inflammation and hypercoagulability.[19,20] Furthermore, uncontrolled inflammation combined with hypoxia and the direct cytotoxic effects of the virus on endothelial cells may contribute to thromboembolic complications.[21]

In the present study, the median overall D-dimer value was 2240 μg/L. Zhang et al reported that D-dimer value $\geq$2000 μg/L at hospital admission was a predictor of mortality in COVID-19 patients.[7] A retrospective case study involving 1000 COVID-19 patients in New York City suggested that age and comorbidities, such as renal disease, were associated with death. Moreover, sex and hypertension are considered risk factors for severe COVID-19

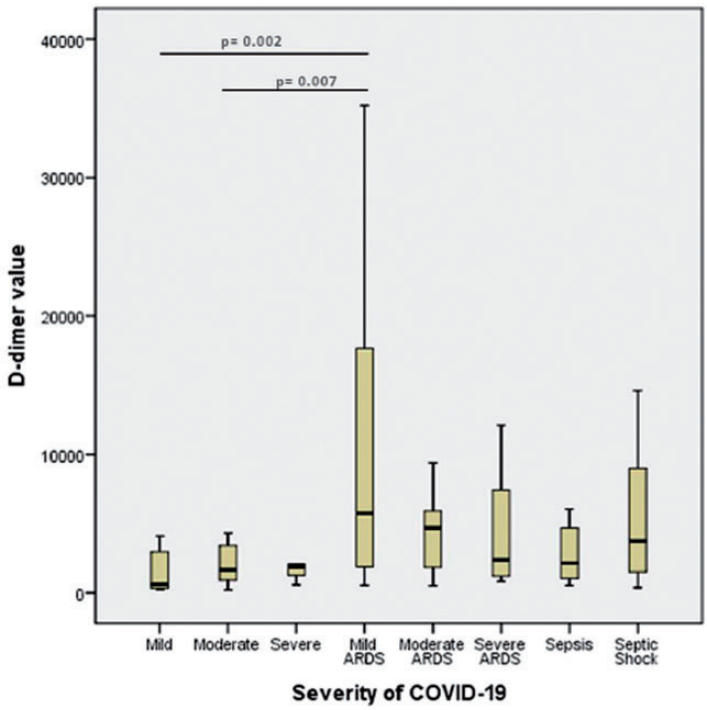

Figure 1. D-dimer values in the different groups of coronavirus disease 2019 (COVID-19) severity.

requiring intubation or resulting in death.[22] Approximately 89% of our subjects had comorbidities, such as hypertension, diabetes, renal disease, congestive heart failure, coronary artery disease, and malignancy, that may increase the D-dimer level independent of COVID-19. These comorbidities could have contributed to the higher D-dimer values in mild ARDS (median: 5725 μg/L) and moderate ARDS (median: 4680 μg/L) patients with COVID-19. In addition, D-dimer values in patients with severe COVID-19 disease were three-fold higher than those in patients with mild disease (median 1870 μg/L vs 630 μg/L, respectively). This finding is similar to that from a pooled analysis by Lippi and Favaloro.[23] In the present study, we identified that the AUC for D-dimer reached almost 0.7 (AUC: 0.698), with a cut-off value of 1250 μg/L.

The physiological inflammatory process begins immediately after tissue injury. One of the systemic manifestations of this inflammatory process is an increase in acute-phase proteins, such as CRP and ferritin.[24] CRP, which is produced by the liver, increases in infection, inflammation, and cardiovascular diseases.[25] A meta-analysis by Huang et al elucidated that elevated CRP levels were associated with severe COVID-19 disease and the need for intensive care unit (ICU) admission.[26] The association between CRP and mortality is inconclusive.[25,27,28] Liu et al suggested that a CRP cut-off value of >41.8 mg/L predicted more severe complications in COVID-19 patients.[29] In the present study, the AUC of CRP was <0.7, with a cut-off value of 72.65 mg/L. This cut-off is similar to the cut-off (>75 mg/L) suggested by the RECOVERY Collaborative Group

Table 3. C-reactive protein and ferritin values according to COVID-19 severity.

Variable, median (IQR)	Mild COVID-19	Moderate COVID-19	Severe COVID-19	Mild ARDS	Moderate ARDS	Severe ARDS	Sepsis	Septic shock
CRP (mg/L)	25.20 (8.50–64.05)	80.70 (24.25–148.40)	62.60 (8.35–91.35)	95.20 (56.22–143.87)	79.6 (9.8–221.2)	93.4 (25.8–182.7)	47.0 (9.4–372.2)	107.40 (30.65–243.35)
Ferritin (μg/mL)	681.00 (261.04–2781.42)	1434.20 (433.66–3748.45)	1989.70 (490.85–4567.40)	772.90 (192.35–4072.48)	1522.9 (526.8–4090.0)	2971.00 (966.24–3248.06)	1214.50 (514.11–3311.21)	758.30 (432.99–2432.24)

COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; IQR, interquartile range; CRP, C-reactive protein.

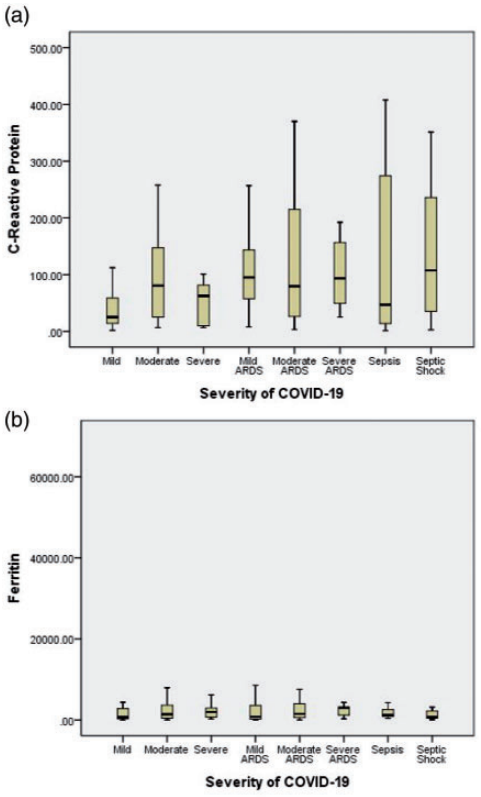

Figure 2. Inflammatory marker values in the different groups of coronavirus disease 2019 (COVID-19) severity: (a) C-reactive protein; (b) ferritin.

to initiate tocilizumab treatment in hospitalized severe COVID-19 patients; confirming the consistency of our cut-off value.[30] The lowest CRP levels were documented in mild COVID-19 disease (median: 25.2 mg/L). With severe disease, septic shock was clearly associated with the highest CRP levels (median: 107.4 mg/L). Unfortunately, CRP value did not increase proportionally with COVID-19 severity, as seen in sepsis, with a median CRP value of 47 mg/L.

While ferritin levels correlate with inflammatory activity, in a previous study, elevated ferritin in COVID-19 patients was reported in elderly patients and in those

Table 4. Correlation between D-dimer, CRP, and ferritin values in COVID-19 patients.

Variable	r	p value	Remarks
D-dimer and CRP	0.327	<0.001	Weak correlation
D-dimer and ferritin	0.101	0.284	Moderate correlation

CRP, C-reactive protein; COVID-19, coronavirus disease 2019.

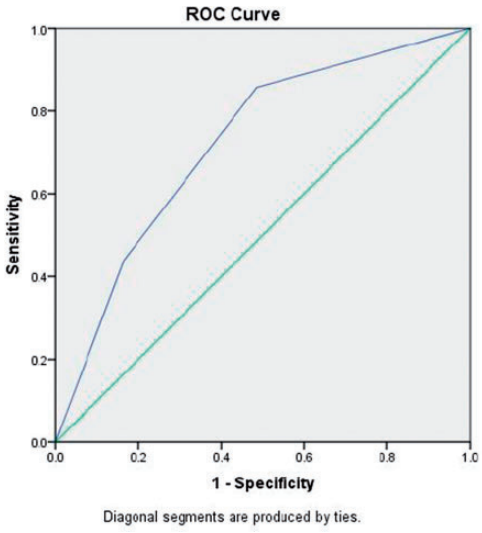

Figure 3. ROC curve for the combination of CRP and D-dimer to predict COVID-19 severity ROC, receiver operating characteristic; CRP, C-reactive protein; COVID-19, coronavirus disease 2019.

with hypertension, diabetes, cancer, and thromboembolic events.[15,31] Despite these findings, iron parameters, such as ferritin, were not mentioned in the most recent guidelines for COVID-19.[16,32] Interestingly, in 2014, Kell and Pretorius reported that high ferritin levels were associated not only with inflammation, but also resulted from cellular damage, especially when the value reached >600 µg/mL, implying a relationship between ferritin levels and organ damage.[33] Qin et al revealed that greater proportions of COVID-19 patients with severe illness and death had high ferritin levels.[34] The median ferritin value in our study was 1173.8 µg/mL. The lowest ferritin level was seen in mild COVID-19 disease (median: 681 µg/mL), while severe ARDS was associated with the highest ferritin level (median: 5725 µg/L).[15]

We observed a significant positive correlation between D-dimer and CRP ($r = 0.327j$; $p < 0.001$). Siemes et al reported similar results in patients with pulmonary embolism.[35] A significant positive correlation between D-dimer and CRP was also seen in COVID-19 patients.[36] However, we failed to detect a correlation between D-dimer and serum ferritin. These findings suggest that hyperinflammation during the immune response to COVID-19 activates coagulation pathways.[37]

There are limitations in this study that must be acknowledged. First, this was a single-center study that was performed in an Indonesian national referral hospital in Jakarta. Therefore, the patients may have had more complex conditions or comorbidities than those in the general population. Furthermore, additional studies are needed in wider populations. Second, we did not evaluate comorbid diseases, such as malignancy or thrombophilia, which could potentially have influenced higher D-dimer levels in COVID-19 patients with mild ARDS. Third, the sample size for patients with severe COVID-19 disease was small, which may have affected statistically significant differences.

Conclusion

Our data confirmed that COVID-19 patients showed sharp increases in

D-dimer values, as a marker of coagulation dysfunction, and those of serum inflammatory biomarkers (CRP and ferritin). The combination of CRP $\geq$72.65 mg/L and D-dimer $\geq$1250 µg/L can be used as a marker of COVID-19 severity, with moderate accuracy.

Acknowledgement

The authors thank Sayang Rahmadini, MD, for help in collecting the data and creating the figures.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Lugyanti Sukrisman https://orcid.org/0000-0003-4498-7735

Supplemental material

Supplemental material for this article is available online.

References

1. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. *Mil Med Res* 2020; 7: 11.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062.
3. Cucinotta D and Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed* 2020; 91: 157–160.
4. Indonesia COVID-19-Task Force [Internet]. 2020. Available from: https: //setkab.go.id/en/covid-19-task-force-indonesias-recovery-rate-higher-than-that-of-global-average-2/ (2020, accessed 1 September 2020).
5. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; 18: 844–847.
6. McGonagle D, O'Donnell JS, Sharif K, et al. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020; 2: e437–e445.
7. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020; 18: 1324–1329.
8. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020; 18: 1023–1026.
9. Pedersen SF and Ho YC. SARS-CoV-2: a storm is raging. *J Clin Invest* 2020; 130: 2202–2205.
10. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. *J Thromb Haemost* 2020; 18: 786–787.
11. Yuen KS, Ye ZW, Fung SY, et al. SARS-CoV-2 and COVID-19: The most important research questions. *Cell Biosci* 2020; 10: 40.
12. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; 46: 846–848.
13. Kernan KF and Carcillo JA. Hyperferritinemia and inflammation. *Int Immunol* 2017; 29: 401–409.
14. Halstead ES, Rajasekaran S, Fitzgerald JC, et al. Hyperferritinemic sepsis: an opportunity for earlier diagnosis and intervention? *Front Pediatr* 2016; 4: 77.
15. Cheng L, Li H, Li L, et al. Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Clin Lab Anal* 2020; 34: e23618. Available from: https: //onlinelibrary.wiley.com/doi/10.1002/jcla.23618
16. World Health Organization. Clinical management of COVID-19: living guidance.

WHO, 2021. Available from: https://apps.who.int/iris/rest/bitstreams/1328457/retrieve (2020, accessed 1 September 2020).
17. Von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
18. Li Y, Shi J, Xia J, et al. Asymptomatic and symptomatic patients with non-severe coronavirus disease (COVID-19) have similar clinical features and virological courses: a retrospective single center study. *Front Microbiol* 2020; 11: 1570.
19. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; 26: 1017–1032.
20. Orsi FA, De Paula EV, De Oliveira Santos F, et al. Guidance on diagnosis, prevention and treatment of thromboembolic complications in COVID-19: a position paper of the Brazilian Society of Thrombosis and Hemostasis and the Thrombosis and Hemostasis Committee of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy. *Hematol Transfus Cell Ther* 2020; 42: 300–308.
21. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120–128.
22. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ* 2020; 369: m1996.
23. Lippi G and Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost* 2020; 120: 876–878.
24. Lino K, Guimarães GMC, Alves LS, et al. Serum ferritin at admission in hospitalized COVID-19 patients as a predictor of mortality. *Braz J Infect Dis* 2021; 25: 101569.
25. Sproston NR and Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol* 2018; 9: 754.
26. Huang I, Pranata R, Lim MA, et al. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis* 2020; 14: 175346662093717.
27. Ryoo SM, Han KS, Ahn S, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: a multicenter prospective registry-based observational study. *Sci Rep* 2019; 9: 6579.
28. Koozi H, Lengquist M and Frigyesi A. C-reactive protein as a prognostic factor in intensive care admissions for sepsis: a Swedish multicenter study. *J Crit Care* 2020; 56: 73–79.
29. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol* 2020; 127: 104370.
30. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; 397: 1637–1645.
31. Taneri PE, Gómez-Ochoa SA, Llanaj E, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *Eur J Epidemiol* 2020; 35: 763–773.
32. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020; 46: 854–887.
33. Kell DB and Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics* 2014; 6: 748–773.
34. Qin L, Li X, Shi J, et al. Gendered effects on inflammation reaction and outcome of COVID-19 patients in Wuhan. *J Med Virol* 2020; 92: 2684–2692.
35. Siemes C, Berendes P, Van Der Straaten F, et al. The value of D-Dimer in patients with increased C-reactive protein suspected of pulmonary embolism. *Blood* 2009; 114: 5056.
36. Qi X, Kong H, Ding W, et al. Abnormal coagulation function of patients with COVID-19 is significantly related to hypocalcemia and severe inflammation. *Front Med (Lausanne)* 2021; 8: 638194.
37. Jose RJ and Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020; 8: e46–e47.

Appendix 1. Significance of D-dimer value comparisons (p values) between the COVID-19 disease severity groups

	Mild COVID-19	Moderate COVID-19	Severe COVID-19	Mild ARDS	Moderate ARDS	Severe ARDS	Sepsis	Septic shock
Mild COVID-19		1.000	1.000	0.002*	1.000	1.000	1.000	1.000
Moderate COVID-19	1.000		1.000	0.007*	1.000	1.000	1.000	1.000
Severe COVID-19	1.000	1.000		1.000	1.000	1.000	1.000	1.000
Mild ARDS	0.002*	0.007*	1.000		0.917	1.000	1.000	1.000
Moderate ARDS	1.000	1.000	1.000	0.917		1.000	1.000	1.000
Severe ARDS	1.000	1.000	1.000	1.000	1.000		1.000	1.000
Sepsis	1.000	1.000	1.000	1.000	1.000	1.000		1.000
Septic shock	1.000	1.000	1.000	1.000	1.000	1.000	1.000	

*p-value <0.05.

COVID-19, coronavirus disease 2019; ARDS, acute respiratory disease syndrome.