JoCASS
Çukurova Anestezi ve Cerrahi Bilimler Dergisi
2018 Adana

THE RELATIONSHIP BETWEEN COVID-19 RELATED COAGULOPATHY WITH ORGAN DAMAGE AND PROGNOSIS

Özge Özden[1], Demet Laflı Tunay[2]

1 *Department of Anesthesiology and Reanimation, Adana City Training and Research Hospital, Adana, Türkiye*
2 *Department of Anesthesiology and Reanimation, Faculty of Medicine, Balcalı Hospital, Cukurova University, Adana, Türkiye*

Abstract

Aim: Coagulopathy and thromboembolic complications are frequently seen in COVID-19. We aimed to evaluate the relationship of coagulopathy with organ dysfunction and mortality in COVID-19.

Methods: COVID-19 patients requiring intensive care for treatment and follow-up were retrospectively analyzed. In the definition of coagulopathy, the International Society on Thrombosis and Hemostasis (ISTH) overt disseminated intravascular coagulation (DIC) scoring system was used. Patients were divided into three groups according to the ISTH scores as follows; patients with no coagulopathy (ISTH score <2), patients with non-evident abnormal coagulation (ISTH score = 2), and patients with evident abnormal coagulation (ISTH score > 2) and mechanical ventilation requirement, acute kidney injury (AKI), acute hepatic injury (AHI) and mortality rates were compared between these groups.

Results: One hundred fifty-five critically ill adult patients with COVID-19 were included in the study. An abnormal coagulation profile developed in 94 (60.6%) patients; of those, 56 (36.1%) patients had non-evident abnormal coagulation, and 38 (24.5%) had evident abnormal coagulation. While there was a significant difference between the groups regarding coagulopathy and development of AKI, requirement for mechanical ventilation, and mortality, no significant difference was found in AHI and length of stay in the intensive care unit. Both mortality and development of AKI increased in correlation with the severity of coagulopathy. ISTH score and development of AKI and AHI were risk factors for both mortality and mechanical ventilation requirement.

Conclusions: COVID-19-related coagulopathy, as determined by the ISTH overt DIC scoring system, is a predictor of organ damage and mortality.

Keywords: *Coagulopathy, Coronavirus disease 2019 (COVID-19), critical illness, mortality, organ damage.*

Corresponding Author: Demet Laflı Tunay, e-mail: dlafli@yahoo.com

Received: 13.09.2022, Accepted: 16.10.2022, Available Online Date: 31.12.2022

Cite this article as: Ozden Ö, Laflı Tunay D. The Relationship Between COVID-19 Related Coagulopathy with Organ Damage and Prognosis. J Cukurova Anesth Surg. 2022;5(3):342-50.

doi: 10.36516/jocass.1174534

Introduction

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a remaining global epidemic. The spectrum of clinical manifestations is broad and varies from asymptomatic to severe respiratory failure in different individuals.[1] Although most severe patients initially present with single-organ failures, such as respiratory failure, the disease later progresses to a systemic involvement manner, and multi-organ dysfunction may occur. Organ dysfunction is a common and mortal complication in COVID-19.[2] Many mechanisms such as inflammatory response (cytokine storm), shock, and disseminated intravascular coagulation (DIC) may contribute to organ dysfunction in COVID-19. Coagulopathy is one of the most important prognostic factors for these patients' outcomes.[3] There is increasing evidence that coagulopathy and thrombosis are common complications, particularly in COVID-19 patients who do not survive.[2,4] Although the hypercoagulable state associated with COVID-19 has been termed by some as disseminated intravascular coagulation (DIC)-like state, it differs from DIC in terms of some clinical and laboratory findings. COVID-19-associated coagulopathy (CAC) usually exhibits coagulation abnormalities with elevated fibrinogen and D-dimer levels, mild thrombocytopenia, and thrombosis in arterial and venous systems.[5] Unlike the classical DIC pattern resulting from bacterial sepsis or trauma, activated partial thromboplastin time (aPTT) and/or prothrombin time (PT) prolongation is minimal in COVID-19.[6] Therefore, finding effective hematology and coagulation parameters and predicting prognosis in patients with COVID-19 is a priority. The International Society on Thrombosis and Hemostasis (ISTH) overt DIC scoring systems[7] can be used to establish a risk classification and manage coagulopathy in COVID-19 patients at admission. In this study, we retrospectively analyzed the effects of COVID-19 associated coagulopathy on the requirement for mechanical ventilation, acute kidney injury (AKI), acute hepatic injury (AHI), and mortality in COVID-19 patients treated in the intensive care unit.

Materials and Methods

The study was registered at the Adana City Training and Research Hospital Clinical Research Ethics Committee on 27 January 2022 and approved with the approval number of 1758. In this study, COVID-19 patients requiring intensive care for treatment and follow-up, who were hospitalized in the Republic of Turkey Ministry of Health Adana City Training and Research Hospital between October 1, 2020 - October 1, 2021, were retrospectively analyzed. Since the study was retrospective, informed consent was not obtained from the subjects. Exclusion criteria included a history of liver disease or failure, chronic kidney disease or failure, known hematological disease or coagulation disorder, glomerular filtration rate (GFR) <90 mL min^{-1} at admission to the hospital, missing data on hematological, biochemical, and coagulation parameters. Patients' data on COVID-19-related symptoms, signs, and laboratory parameters were obtained from electronic medical records. Demographic characteristics of patients (age, gender, etc.), parameters of blood tests (e.g., complete blood count, kidney and liver function tests, coagulation parameters, blood gas analysis), additional diseases including hypertension, diabetes, cerebrovascular disease, malignancy, coronary artery disease (CAD), presence of chronic obstructive pulmonary disease (COPD), Acute Physiology and Chronic Health Assessment (APACHE) II score calculated within the first 24 h after hospital admission, Glasgow Coma Scale (GCS) score were recorded for all patients. ISTH overt DIC scoring systems were used to define coagulopathy.[7] Coagulopathy was graded by dividing the patients into three groups: patients with ISTH score <2 with no coagulopathy (Group non-coagulopathy), patients with

ISTH score=2 with non-evident abnormal coagulation (Group NEAC), and patients with ISTH score>2 with evident abnormal coagulation (Group EAC). The requirement for mechanical ventilation, AKI, AHI, and mortality rates were compared between these three groups. Kidney Disease: Improving Global Outcomes (KDIGO)[8] definition and staging system was used for AKI diagnosis. Acute hepatic injury was defined as the alanine aminotransferase (ALT) level exceeding twice the upper limits of normal (ALT > 80 U/L) according to Schiff's liver diseases.[9] The primary outcomes were to compare the requirement for mechanical ventilation, the development of AKI and AHI between the groups, and secondary outcomes included length of stay in the intensive care unit and mortality.

Statistical analysis

Statistical analysis of the study was performed using SPSS version 23. Demographic data were given as mean, standard deviation, and number and percentage. The normal distribution for continuous variables was checked with the Kolmogorov–Smirnov test. Statistical differences between groups were evaluated using Fisher's exact and ANOVA tests. Variables were expressed as mean ± SD, and survival analysis was performed using the Kaplan-Meier test. Logistic regression analysis was applied for the relationship of risk factors with mortality and mechanical ventilation. The statistical significance value was accepted as $p<0.05$.

Table 1. Demographics and baseline characteristics of COVID-19 patients

		Group non-coagulopathy (n=61)	Group NEAC (n=56)	Group EAC (n = 38)	p-value
Gender	Male	39(%63.9)	34(%60.7)	16(%42.1)	
	Female	22(%36.1)	22(%39.2)	22(%57.9)	
Age		56.13±17.02	54.79±20.34	56.21±18.01	0.906
Comorbidities		30(%49.2)	22(%39.3)	21(%55.3)	0.291
GCS		14.26±2.02	13.30±3.31	12.84±3.60	0.050
APACHE II score		13.02±4.75	15.39±3.07	14.89±6.56	0.126
Hospitalization Day		13.26±11.18	14.39±12.54	18.92±15.85	0.099
Mortality		12(%19.17)	22(%39.3)	20(%52.6)	0.002*
Acute Kidney Injury	Total	10(%16.4)	17(%30.4)	17(%44.7)	0.009*
	Stage 1	1(%1.6)	3(%5.4)	4(%10.5)	0.153
	Stage 2	6(%9.8)	7(%12.5)	10(%26.3)	0.067
	Stage 3	3(%4.9)	7(%12.5)	3(%7.9)	0.337
Mechanical Ventilation	Total	39(%63.9)	44(%78.6)	33(%86.8)	0.027*
	Invasive	16(%26.2)	26(%46.4)	23(%60.5)	0.002*
	Noninvasive	23(%37.7)	18(%32.1)	10(%26.3)	0.502
Acute Hepatic Injury		24(%39.3)	24(%42.9)	21(%55.3)	0.291

*Data are shown as the number and percentages of patients n(%) or mean±SD; *p<0.05 compared to groups; NEAC: non-evident abnormal coagulation; EAC: evident abnormal coagulation; GCS: Glasgow coma scale; APACHE: Acute Physiology and Chronic Health Assessment*

Table 2. Laboratory parameters of COVID-19 patients on admission.

	Group non-coagulopathy (n=61)	Group NEAC (n=56)	Group EAC (n = 38)	p-value
PCT (µg L-1)	0.78±3.27	1.72±7.89	1.83±3.87	0.552
CRP (mg L^{-1})	83.42±66.56	106.78±99.12	147.57±106.72	0.003*
WBC (10^3 μL^{-1})	10.23±4.98	11.08±4.19	14.07±14.29	0.068
Hb (g dL^{-1})	12.76±2.01	11.95±2.13	11.52±1.78	0.008*
Neutrophil (10^3 μL^{-1})	9.00±4.50	9.87±4.02	10.70±6.48	0.241
Lymphocyte (10^3 μL^{-1})	0.61±0.68	0.60±0.48	0.66±0.50	0.881
Monocyte (10^3 μL^{-1})	0.58±0.70	0.51±0.45	0.49±0.35	0.686
PLT (10^3 μL^{-1})	233.39±85.72	244.30±94.36	256.82±127.35	0.526
Albumin (g L^{-1})	31.36±4.30	29.52±4.61	28.32±3.43	0.002*
Bilirubin (mg dL^{-1})	0.55±0.23	0.80±0.51	0.89±0.64	0.001*
ALT (U L^{-1})	36.79±22.94	34.79±28.97	37.53±29.46	0.871
AST (U L^{-1})	41.51±21.55	42.95±22.59	49.97±33.49	0.250
BUN (mg dL^{-1})	39.70±15.91	34.59±17.31	43.24±20.28	0.058
Creatinine (mg/dl)	0.63±0.18	0.54±0.18	0.64±0.18	0.009*
GFR (mL min^{-1} 1.7^{-1})	108.44±17.50	116.86±23.92	108.34±16.38	0.042
PT (sec)	13.92±10.39	12.87±2.68	14.42±2.96	0.525
aPTT (sec)	24.65±8.13	24.21±7.12	26.09±9.14	0.524
INR	1.03±0.10	1.41±2.70	1.20±0.27	0.464
D-Dimer (µg L^{-1})	572.00±231.59	1718.75±511.05	8913.42±13055.46	0.000*
Fibrinogen (mg dL^{-1})	560.35±187.43	500.95±193.27	551.01±178.19	0.202
PH	7.44±0.06	7.43±0.07	7.42±0.07	0.159
PO2 (mmHg)	72.96±24.82	73.98±28.54	79.34±39.71	0.574
PCO2 (mmHg)	38.88±9.73	39.70±13.58	39.46±15.66	0.939

*Data are shown as mean±SD or number of patients (n); *p<0.05 compared to groups; PCT: procalcitonin, CRP: C-reaction protein; WBC: white blood cell; Hb: Hemoglobin; PLT: Platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; GFR: glomerular filtration rate; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: International Normalized Ratio*

Results

This retrospective study recruited two hundred thirty-one COVID-19 patients requiring intensive care for treatment and follow-up. Seventy-six patients who did not fulfill the inclusion criteria were excluded from the study.

So, the data of 155 adult patients admitted to the intensive care unit with the diagnosis of COVID-19 were analyzed. 61 (39.8%) patients had no abnormal coagulation profile (group non-coagulopathy), while 94 (60.6%) had coagulopathy according to the ISTH overt DIC scoring system. Of the patients with coagulopathy, 56 (36.1%) had non-evident abnormal coagulation (group NEAC), and 38 (24.5%) had evident abnormal coagulation (group EAC).

The mean age of the patients was 55.66±18.41 years. The number of males was higher in both groups with non-coagulopathy and non-evident abnormal coagulation [39 (63.9%) and 34 (60.7%), respectively].

Approximately half of the patients (47%) had at least one comorbidity (Table 1).

While there was a significant difference between the groups regarding the development of AKI, requirement for mechanical ventilation, and mortality, there was no sig-

nificant difference in AHI and length of stay in the intensive care unit. The death occurred in the intensive care unit in 54 patients; 12 (19.7%) of those were in the group non-coagulopathy, 22 (39.3%) were in the group NEAC, and 20 (52.6%) were in the group EAC (Figure 1). The development of AKI and mechanical ventilation requirements were statistically significantly higher in subjects with abnormal coagulation than in subjects with non-coagulopathy ($p<0.009$ and $p<0.027$, respectively). AKI developed in 44 patients; 10 (16.4%) of them were in the group non-coagulopathy, 17 (30.4%) were in the group NEAC, and 17 (44.7%) were in the group EAC. Mechanical ventilation was required in 116 patients; 39 of them (63.9%) were in the group non-coagulopathy, 44 (78.6%) were in the group NEAC, and 33 (86.8%) were in the group EAC. It was observed that the development of AKI, the requirement for mechanical ventilation, and mortality increased in correlation with the severity of coagulopathy. Although there was no significant difference in the length of stay in the intensive care unit ($p<0.099$), it was observed that the length of hospital stay was longer in patients with evident abnormal coagulation (18.92±15.85) (Table 1).

There were significant differences between the groups in the laboratory findings of the patients in the levels of CRP, hemoglobin, albumin, total bilirubin, and D-dimer. CRP was significantly higher in groups with abnormal coagulation than in patients with non-coagulopathy ($p<0.003$). Hemoglobin and albumin were significantly lower in the group EAC than in the other groups ($p<0.008$ and $p<0.002$, respectively). D-dimer was significantly higher in patients with abnormal coagulation than with non-coagulopathy ($p<0.000$). It was also observed that D-dimer increased in correlation with the severity of coagulopathy (Table 2). ISTH score and development of AKI and AHI were risk factors associated with mortality and mechanical ventilation requirement.

At the same time, the APACHE score ($p<0.000$) was a risk factor associated with mortality, and the elevation of AST ($p<0.001$) and ALT ($p<0.022$) were risk factors significantly associated with the requirement for mechanical ventilation (Table 3).

Table 3. Risk factors associated with mortality and mechanical ventilation

	Mortality		Mechanical Ventilation	
Variable	OR (%95 CI)	p-value	OR (%95 CI)	p-value
Age	1.03 (1.01, 1.05)	0.020*	0.99 (0.97, 1.01)	0.462
ISTH Score	1.54 (1.18, 2.01)	0.001*	1.51 (1.12, 2.04)	0.006*
AKI	23.25 (9.29, 58.18)	0.000*	22.38 (2.96, 168.90)	0.003*
AHI	5.36 (2.60, 11.03)	0.000*	8.36 (3.05, 22.92)	0.000*
Comorbidity	1.89 (0.97, 3.69)	0.061	0.60 (0.29, 1.26)	0.180
AST	1.01 (0.99, 1.02)	0.302	1.03 (1.01, 1.05)	0.001*
ALT	0.99 (0.98, 1.07)	0.290	1.02 (1.00, 1.04)	0.022*
Creatinine	1.18 (0.20, 6.96)	0.851	0.48 (0.07, 3.35)	0.462
APACHE II score	1.11 (1.05, 1.18)	0.000*	1.01 (0.95, 1.06)	0.734

*Data are shown as odds ratio(range of values); *p<0.05 for risk factors of mortality or indication of mechanical ventilation; OR: odds ratio; CI: confidence interval; ISTH: International Society on Thrombosis and Hemostasis; AKI: Acute Kidney Injury; AHI: Acute Hepatic Injury; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APACHE: Acute Physiology and Chronic Health Assessment.*

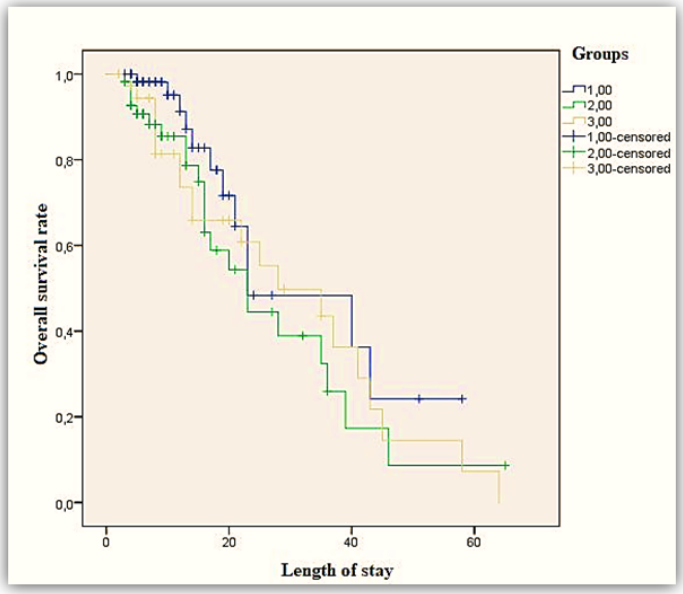

Figure 1. Illustrated survival rates of non-coagulopathy patients, non-evident abnormal coagulation patients, and evident abnormal coagulation patients during hospitalization.
Group 1: non-coagulopathy;
Group 2: non-evident abnormal coagulation;
Group 3: evident abnormal coagulation.

Discussion

Our study showed that as the severity of coagulopathy increased in critically ill COVID-19 patients, AKI and mortality rates gradually raised. It was also shown that the ISTH score was significantly associated with the requirement for mechanical ventilation (OR 1.51, 95% CI 1.12-2.04 P=0.006) and mortality (OR 1.54, 95% CI 1.18-2.01 P=0.001). All results suggested that ISTH overt DIC scoring systems may be used to establish a risk stratification and manage coagulopathy in COVID-19 patients.

COVID-19 is a disease caused by SARS-CoV-2 and may affect multiple organ systems. SARS-CoV-2 causes lung inflammation that progresses to a cytokine storm in severe cases. Alveolar and interstitial inflammation is observed in the lungs of COVID-19 patients.[10] In COVID-19 patients, the immune system is overactivated, numerous inflammatory mediators are released, and activation of platelets occurs.[11] Severe pulmonary inflammation can damage pulmonary vascularity and trigger pulmonary thrombosis in the early stages of the disease.[12] Processes of inflammation and coagulation are the primary defense mechanisms of the body. Both increase in correlation with disease severity and harm the patient.[13]

Unlike classical DIC and sepsis-induced coagulopathy (SIC), patients with COVID-19 have some different abnormal coagulation characteristics. Fibrinolysis is generally suppressed in DIC and SIC, leading to fibrin deposition in the microcirculation and ultimately to organ damage.[14] In these coagulation disorders, the two most helpful laboratory parameters used in estimating SIC are a decrease in platelet count and a prolongation of PT. Additionally, abnormal increases in D-dimer are not expected because fibrinolysis is suppressed in DIC. Patients with COVID-19 pneumonia usually have abnormal coagulation parameters, elevated fibrinogen and D-dimer levels, and mild thrombocytopenia. In COVID-19, D-dimer levels are disproportionately elevated compared to abnormalities seen in other coagulation parameters. This process may be explained by the up-regulation of local fibrinolysis in the alveoli by urokinase-type plasminogen activator (u-PA) released from alveolar macrophages.[15] Tang et al.[4], in a study examining abnormal coagulation parameters, identified markedly elevated D-dimers as one of the predictors of mortality. In an analysis of laboratory-confirmed clinical cases with COVID-19 from more than

550 hospitals in China, which includes data on 1099 patients, D-dimer ≥ 0.5 mg L^{-1} was recorded in 260/560 (46.4%) patients, disease in patients tested if not severe, only 43% had D-dimer elevated, and approximately 60% had severe disease.[3] Similarly, in a large epidemiological study conducted in China, it was observed that D-dimer increased during disease progression in approximately 50% of patients with COVID-19, and this rate increased to approximately 100% in patients who died.[16] Huang et al.[17] reported that in patients who needed intensive care support, D-dimer levels [median D-dimer level of 2.4 mg L^{-1} (0.6-14.4)] at admission were higher compared with those who did not require intensive care support [median D-dimer level of 0.5 mg L^{-1} (0.3–0.8), p = 0.0042]. Our study shows that D-dimer levels reach abnormal levels as the severity of coagulopathy increases. Transiently increased D-dimer levels may be used as an indication of the need for more aggressive treatment and intensive care.

Consumptive coagulopathy seen in SIC and DIC is not seen in the early stage of COVID-19. Spiezia et al.[18] affirmed that patients with COVID-19 and acute respiratory failure present with severe hypercoagulation rather than hypocoagulation (i.e., consumptive coagulopathy). The same study identified that PT and APTT were within the normal range in most patients at presentation, as hypercoagulation occurs in the early stages of COVID-19. Several studies have reported that patients with COVID-19 are in a hypercoagulable state, manifested by decreased PT and aPTT and elevated D-dimer levels.[3,19] In our study, PT was lower in patients with non-evident and evident abnormal coagulation than in patients with non-coagulopathy, which was interpreted in favor of hypercoagulation.

Acute kidney injury (AKI) occurs in 0.5-9% of patients with COVID-19 and is a major complication of COVID-19. AKI develops in 10-30% of critically ill patients.[20] SARS-CoV-2 binds to the ACE2 receptor in the kidney and causes deregulation of the angiotensin mechanism. In COVID-19, this results in hypoxia and hypotension via hypercoagulation and microangiopathy, leading to acute kidney injury.[21] Although AKI development is considered a predictor of disease severity and an unfavorable prognostic factor for survival, few studies have reported a significant relationship between AKI and mortality during the COVID-19 pandemic.[22] In our study, the development of AKI was seen as a risk factor associated with mortality (OR 23,25, %95 CI 9,29-58,18 P=0.000).

Liver dysfunction is more common in severe COVID-19 patients, and patients with liver dysfunction are also at risk of developing severe illness.[23,24] In some studies, the simultaneous increase in ALT and D-dimer was noted in most patients indicating that liver injury may be induced, at least in part, by potential intrahepatic microvascular thrombosis.[25] Although there was no significant difference in our study, it is seen that the development of AHI is higher, especially in patients with evident abnormal coagulopathy.

Conclusion

COVID-19 associated abnormal coagulation is initially localized in the lung, but later systemic involvement may progress to CAC and SIC/DIC. Although the abnormal coagulation state associated with COVID-19 has some similarities to DIC, including a marked increase in D-dimer and mild thrombocytopenia, and meets the criteria for probable DIC in the ISTH scoring system, coagulation parameters like high fibrinogen and factor VIII activity are unlike from DIC.[26] Therefore, just like in DIC, the diagnosis of coagulopathy is made clinically in COVID-19 patients. There is no single test or combination of pathognomonic tests for DIC and CAC. However, the ISTH scoring system, which has high sensitivity and specificity based on expert opinion, may be used in COVID-19 as a guide in preventing, diagnosing, and treating coagulopathy.

In our study, the primary determinant of ISTH was a significant increase in D-dimer levels. In the light of these data, we suggest that patients with a 2 to 5-fold increase in D-dimer levels for COVID-19 associated coagulopathy should be evaluated for intensive care and aggressive treatment, already in the lack of other severe symptoms.

Author contributions
All authors read and approved the final manuscript. Concepts 1,2, Design 1,2, Definition of intellectual content 1,2, Literature search 1,2, Clinical studies 1, Experimental studies 1, Data acquisition 1,2 Data analysis 1,2, Statistical analysis 2, Manuscript preparation 1, Manuscript editing 1,2, Manuscript review 1, Guarantor 2.

Conflict of interest
The authors declare that they have no conflict of interest.

Funding
Authors declared no financial support.

Ethical approval
The study's ethical approval was given by the Adana City Training and Research Hospital Clinical Research Ethics Committee on 27 January 2022 and approved with the approval number of 1758.

References

1. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus. 2020;18(3):167-9. https://doi.org/10.2450/2020.0083-20
2. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368. https://doi.org/10.1136/bmj.m1091
3. Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. https://doi.org/10.1056/NEJMoa2002032
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7.
5. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7(6):e438-e40. https://doi.org/10.1016/S2352-3026(20)30145-9
6. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020;58(7):1116-20. https://doi.org/10.1515/cclm-2020-0188
7. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. Journal of thrombosis and haemostasis. J Thromb Haemost. 2019;17(11):1989-94. https://doi.org/10.1111/jth.14578
8. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1-138. https://doi.org/10.1038/kisup.2012.1
9. Schiff ER, Maddrey WC, Reddy KR. Schiff's Diseases of the Liver: John Wiley & Sons; 2017. https://doi.org/10.1002/9781119251316
10. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol. 2020;2(7):e437-e45. https://doi.org/10.1016/S2665-9913(20)30121-1
11. Lefrançais E, Ortiz-Muñoz G, Caudrillier A, et al. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature. 2017;544(7648):105-9. https://doi.org/10.1038/nature21706
12. Thachil J, Cushman M, Srivastava A. A proposal for staging COVID-19 coagulopathy. Res Pract Thromb Haemost. 2020;4(5):731-6. https://doi.org/10.1002/rth2.12372
13. Iba T, Levy J. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost. 2018;16(2):231-41. https://doi.org/10.1111/jth.13911
14. Iba T, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Anesthesiology. 2020;132(5):1238-45. https://doi.org/10.1097/ALN.0000000000003122
15. Gralinski LE, Bankhead III A, Jeng S, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. MBio. 2013;4(4):e00271-13. https://doi.org/10.1128/mBio.00271-13
16. 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. The lancet. 2020;395(10229):1054-62.

https://doi.org/10.1016/S0140-6736(20)30566-3
17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
18. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020;120(06):998-1000. https://doi.org/10.1055/s-0040-1710018
19. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. https://doi.org/10.1016/S0140-6736(20)30211-7
20. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81. https://doi.org/10.1016/S2213-2600(20)30079-5
21. Batlle D, Soler MJ, Sparks MA, et al. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. J Am Soc Nephrol. 2020;31(7):1380-3. https://doi.org/10.1681/ASN.2020040419
22. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829-38. https://doi.org/10.1681/ASN.2020040419
23. Mao R, Qiu Y, He J-S, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(7):667-78. https://doi.org/10.1016/S2468-1253(20)30126-6
24. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. J Hepatol. 2020;73(3):566-74. https://doi.org/10.1016/j.jhep.2020.04.006
25. Tsutsumi T, Saito M, Nagai H, et al. Association of coagulopathy with liver dysfunction in patients with COVID-19. Hepatol Res. 2021;51(2):227-32. https://doi.org/10.1111/hepr.13577
26. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020 Jul;18(7):1738-1742. https://doi.org/10.1111/jth.14850