Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

Efficacy of Bivalirudin for Therapeutic Anticoagulation in COVID-19 Patients Requiring ECMO Support

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Objectives: The Coronavirus Disease 2019 (COVID-19) pandemic has been associated with cases of refractory acute respiratory distress syndrome (ARDS) sometimes requiring support with extracorporeal membrane oxygenation (ECMO). Bivalirudin can be used for anticoagulation in patients on ECMO support, but its efficacy and safety in patients with COVID-19 is unknown. The authors set out to compare the pharmacologic characteristics and dosing requirements of bivalirudin in patients requiring ECMO support for ARDS due to COVID-19 versus ARDS from other etiologies.
Design and Setting: This retrospective case-control study was performed at Indiana University Health Methodist Hospital in Indianapolis, Indiana.
Participants: Patients were included if they were on venovenous ECMO support between June 2019 and June 2020, and divided into two groups: ARDS secondary to COVID-19 and those with ARDS from another etiology (Non-COVID).
Interventions: Patient demographics, such as age, sex, weight, chronic comorbid conditions, baseline antiplatelet and anticoagulant use, antiplatelet use during ECMO, and need for renal replacement therapy were collected, and compared between groups. Time to activated partial thromboplastin time (aPTT) goal, percentage of time at aPTT goal, bivalirudin rates, total bivalirudin requirements, total duration on bivalirudin, total duration on ECMO, mortality, and complications associated with ECMO were collected and compared between groups.
Measurements and Main Results: A total of 42 patients met inclusion criteria (n = 19 COVID-19, n = 23 non-COVID). However, percentages of aPTTs at goal were maintained more consistently in patients with COVID-19 versus non-COVID (86% *v* 74%: $p < 0.01$). Higher median (IQR) daily rates (3.1 μg/kg/min [2.3-5.2] *v* 2.4 μg/kg/min [1.7-3.3]: $p = 0.05$) and higher median (IQR) maximum rates of bivalirudin (5 μg/kg/min [3.7-7.5] *v* 3.8 μg/kg/min [2.5-5]: $p = 0.03$) were required in the COVID-19 group versus the non-COVID group. Time to goal aPTT was similar between groups. There were no differences in complications associated with anticoagulation, as demonstrated by similar rates of bleeding and thrombosis between both groups.
Conclusions: Patients on ECMO with ARDS from COVID-19 require more bivalirudin overall and higher rates of bivalirudin to maintain goal aPTTs compared with patients without COVID-19. However, COVID-19 patients more consistently maintain goal aPTT. Future randomized trials are needed to support efficacy and safety of bivalirudin for anticoagulation of COVID-19 patients on ECMO.

Keywords: anticoagulation; ECMO; COVID-19; Respiratory Failure; Bivalirudin; thrombosis

Abbreviations: SARS CoV-2, Severe Acute Respiratory Distress Syndrome due to novel Coronoavirus; COVID 19, Coronavirus Disease 2019; ARDS, Acute Respiratory Distress Syndrome

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THE CORONAVIRUS 2019 (COVID-19) pandemic has been associated with severe acute Respiratory Syndrome due to novel Coronavirus (SARs-CoV-2) pneumonia, and subsequent development of severe acute respiratory distress syndrome (ARDS), at times refractory to standard mechanical ventilation. Rescue therapy with extracorporeal membrane oxygenation (ECMO) often is considered for severe SARs-CoV-2 pneumonia with ARDS. Support of COVID-19 patients with ECMO presents many clinical challenges. COVID-19 infection has been associated with an increased prothrombotic state, resulting in increased incidences of arterial and venous thrombi.[1] This unique physiologic state, occurring in patients infected with COVID-19, combined with the intrinsically prothrombotic nature of ECMO, make the use of systemic anticoagulation in this patient population imperative.[2]

Unfractionated heparin is the most used anticoagulant in the United States for ECMO, due to physician familiarity, availability, cost-effectiveness, and ease of reversal. Despite its popularity, heparin comes with its own challenges. Heparin requires binding to antithrombin to exert its anticoagulant effect. In patients with low antithrombin levels, this leads to heparin resistance, need for antithrombin III supplementation, and the potential for thrombosis. Heparin also binds to plasma proteins, including acute phase reactants, which leads to fluctuations in activated partial thromboplastin time (aPTT) values and coagulation status.[3] Bivalirudin, a direct thrombin inhibitor, recently has been gaining popularity. Bivalirudin, unlike heparin, inhibits both free-circulating and fibrin-bound thrombin. Bivalirudin is a renally cleared agent with a short half-life, which allows for rapid attainment of steady state, rate titration, and cessation of anticoagulant effects when necessary. Bivalirudin does not rely on antithrombin III to exert its anticoagulant effect, removing need for costly supplementation, and negates the risk for the development of heparin resistance and heparin-induced thrombocytopenia.[4] Bivalirudin is the primary anticoagulant used at the authors' institution for all ECMO patients due to its indirect reduction of costly antithrombin III supplementation and the ability to maintain aPTTs in goal range more consistently than with heparin.[5,6] Bivalirudin has been used for anticoagulation for all COVID-19 patients placed on ECMO support at the authors' institution. Given the novel nature of both this disease and its associated coagulopathy, the authors set out to collect observational data regarding pharmacologic properties, drug dosing and requirements, and associated outcomes in patients with COVID-19, using anticoagulation with bivalirudin while on ECMO. The authors hypothesized that given the prothrombotic findings seen in COVID-19 patients, they would require higher dosing regimens of bivalirudin to achieve goal anticoagulation.

Methods

Adult patients 18 years of age and older who were hospitalized at IU Health Methodist Hospital (Indianapolis, IN), requiring venovenous ECMO between June 17, 2019 and June 17, 2020, were identified through electronic medical records. The Indiana University Institutional Review Board approved the conduct of this study and deemed it exempt (IRB Study Number 2006253636). Informed consent was waived, and deidentified data were analyzed.

Patients were supported using either the Cardiohelp (Maquet) or Centrimag (Abbot) extracorporeal systems. Decision to cannulate for ECMO was determined by a multidisciplinary team of intensivists and cardiovascular surgeons. This decision was multifactorial but primarily dictated by the presence of presumed reversible hypoxic or hypercarbic respiratory failure refractory to traditional management. Secondary factors considered on a case-by-case basis included age, comorbidities, and presence of other organ system failures. Patients were excluded from this study if they required venoarterial ECMO or other ventricular support devices. Patients also were excluded if venovenous ECMO was used in the immediate postoperative period after lung transplantation or for respiratory failure secondary to trauma. Bivalirudin was dosed in all patients by in-house pharmacists who were monitoring values 24 hours a day at the authors' institution.

Age, sex, weight in kilograms (kg), chronic comorbid conditions, need for renal replacement therapy after initiation on ECMO, use of antiplatelet agents or therapeutic anticoagulation before cannulation, antiplatelet use during ECMO, as well as in-hospital and on-ECMO mortality, were recorded. Comorbidities collected included obesity, cardiovascular disease, chronic respiratory disease, chronic kidney disease, and diabetes mellitus. Obesity was defined as body mass index greater than 30 kg/m^2. History of cardiovascular disease was defined as hypertension, coronary artery disease, or congestive heart failure. Chronic kidney disease was defined as abnormalities of kidney function, present for longer than three months, documented by a reduction of glomerular filtration rate <60 mL/min/1.73 m^2. Chronic respiratory disease history included chronic obstructive pulmonary disease, asthma, or chronic respiratory failure requiring supplemental oxygen use.

The authors' primary outcomes of total daily bivalirudin requirement and highest daily rate of bivalirudin infusion (both in μg/kg/min) were obtained via manual chart review. The authors' secondary outcomes of incidences of bleeding and thrombotic events, as well as the proportion of aPTT measurements within the defined goal range for the individual patient, also were collected. Bleeding events were defined as acute blood loss requiring acute transfusion, and thrombotic events were defined as deep venous thromboses diagnosed on ultrasound evaluation. Specific bleeding events subsequently were categorized as intracranial bleeding as diagnosed on cross-sectional imaging, and gastrointestinal bleeding as diagnosed on bedside examination or endoscopic evaluation. Transfusions were performed according to providers' judgment, with usual criteria being a hemoglobin less than 7 g/dL or an acute blood loss with associated hemodynamic changes. Cessation of bivalirudin also was provider-directed, with no

Table 1
Bivalirudin Dosing and Adjustment Protocol for Patients on ECMO

Measured aPTT (s)	Dosing Adjustment Protocol
<45	Increase infusion rate by 40%
45-59	Increase infusion rate by 20%
60-80	No change to infusion rate
81-110	Decrease infusion rate by 20%
>110	Hold infusion for one hour, and then restart with previous rate decreased by 40%

Abbreviation: aPTT, activated partial thromboplastin time.

defined protocol but generally only performed in the setting of acute bleeding. Ultrasounds were performed routinely on all patients successfully decannulated from ECMO. Total cost of bivalirudin also was calculated for each patient. The goal aPTT ranges used in this analysis were consistent with the pre-COVID-19 targets at this center, which was 60-to-80 seconds. The authors' institutional protocol for bivalirudin dosing while on ECMO is defined in Table 1.

Baseline variables with normal distributions were described as mean and standard deviation, and as median and interquartile ranges for data with skewed distribution. Continuous variables were compared using Mann-Whitney U test, and categorical measures through Pearson χ^2 test or Fisher exact test. All p values of <0.05 were defined as statistically significant. All analyses were performed using SPSS Statistics 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY).

Results

Forty-two patients requiring venovenous ECMO for ARDS were included for analysis (n = 42), 19 patients in the COVID-19 group and 23 patients in the non-COVID group. Among patients in the non-COVID-19 group, bacterial pneumonia and viral influenza were the most common causes of respiratory failure, each accounting for 30.4% of cases, as displayed in Table 2. Demographic, clinical, and complication data are shown in Table 3. The groups were well-matched with regard to age, sex, comorbidities, and utilization of renal replacement therapy. However, patients in the COVID-19 group were noted to have higher baseline weight (98.0 kg *v* 87.1 kg, p = 0.04) compared with the non-COVID-19 group, but had no differences in rate of obesity (74% *v* 52%, p = 0.21). There was also no difference noted in rate of aspirin use before cannulation

Table 2
Causes of Respiratory Failure Requiring ECMO Support for Patients in the Non-COVID Group (n = 23)

	n (%)
Bacterial pneumonia	7 (30.4)
Viral influenza	7 (30.4)
Aspiration	6 (26.1)
Asthma exacerbation	2 (8.7)
Unknown	1 (4.3)

Table 3
Demographic, Clinical, and Complication Data for Patients on Therapeutic Bivalirudin Anticoagulation During ECMO Support

Demographic	Non-COVID (n = 23)	COVID(n = 19)	p Value
Age (y), median (IQR)	48 (28-52)	40 (33-49)	0.75
Females, n (%)	11 (48)	6 (32)	0.29
Weight (kg), median (IQR)	87.1 (68.2-99.8)	98.0 (87.2-110.1)	0.04
Obese, n (%)	12 (52)	14 (74)	0.21
Hx. diabetes mellitus, n (%)	2 (9)	5 (26)	0.21
Hx. chronic kidney disease, n (%)	3 (13)	0 (0)	0.24
Hx. cardiovascular disease	10 (44)	5 (26)	0.34
Hx. chronic respiratory disease	10 (44)	3 (16)	0.09
Prior aspirin use	3 (13)	2 (11)	1.00
Aspirin while on ECMO	3 (13)	1 (5)	0.61
Prior anticoagulation use	2 (9)	0 (0)	0.49
In-hospital mortality	5 (22)	3 (16)	0.71
Mortality on ECMO	3 (13)	3 (16)	1.00
Renal replacement therapy after ECMO initiation, n (%)	6 (26)	2 (11)	0.20
Clinical			
Total time on ECMO (h), median (IQR)	167 (136-351)	263 (165-525)	0.16
Total time on bivalirudin (h), median (IQR)	136 (79-260)	255 (160-502)	0.03
Time to goal aPTT (h), median (IQR)	16.4 (5.7-26.5)	12.1 (7.79-16.4)	0.87
Percentage of aPTT measurements in goal (%), median (IQR)	74.0 (59.5-81.8)	86.0 (80.1-90)	<0.01
Median daily bivalirudin rate (μg/kg/min), Median (IQR)	2.4 (1.7-3.3)	3.1 (2.3-5.2)	0.05
Highest daily rate (μg/kg/min), median (IQR)	3.8 (2.5-5)	5 (3.7-7.5)	0.03
Total cost of bivalirudin (US dollars)	12,507 (3,411-19,329)	28,425 (13,075-46,617)	0.01
ICU length of stay (d), median (IQR)	20 (8-28.5)	29 (16.8-36.25)	0.04
	24 (13-38.5)	29.5 (26-35.3)	0.17

(*continued*)

Table 3 (*continued*)

Demographic	Non-COVID (n = 23)	COVID(n = 19)	p Value
Hospital length of stay (d), median (IQR)			
Complications			
Bleeding, n (%)	6 (26)	4 (21)	0.70
Intracranial or intraocular bleeding, n (%)	0 (0)	0 (0)	1.00
Gastrointestinal bleeding, n (%)	5 (22)	3 (16)	0.63
Deep venous thrombosis, n (%)	9 (39)	11 (58)	0.23

Abbreviations: aPTT, activated partial thromboplastin time; COVID-19, Coronavirus 2019; ECMO, extracorporeal membrane oxygenation; Hx. history of:ICU, intensive care unit; IQR, interquartile range.

nor while on ECMO (13% *v* 11%, p = 1.00 and 13% *v* 11%, p = 0.61, respectively). No patients in either group were on other antiplatelet agents before cannulation or while on ECMO. Therapeutic anticoagulation use before cannulation also was not statistically different (9% *v* 0%, p = 0.49). Finally, there also was no significant difference with in-hospital mortality between the groups (22% *v* 16%, p = 0.71) or mortality while patients were on ECMO (13% *v* 16%, p = 1.00).

Clinical data for these patients showed similar total time on ECMO but longer total time spent on bivalirudin in the COVID group (255 hours *v* 136 hours, p = 0.03). Maintenance of goal therapeutic aPTT, described as a percentage of time within goal range, was achieved more often in the COVID group (86% *v* 74%, p < 0.01). Patients in the COVID-19 group were found to have higher median daily bivalirudin requirements (3.1 μg/kg/min *v* 2.4 μg/kg/min, p = 0.05), as well as higher maximum rates (5 μg/kg/min *v* 3.8 μg/kg/min, p = 0.025). This also corresponded to a higher overall cost of bivalirudin in the COVID-19 group ($28,425 *v* $12,507, p = 0.01). Patients in the COVID-19 group also were found to have longer intensive care unit (ICU) length of stay (29 days *v* 20 days, p = 0.04) but there was no difference in their overall hospital length of stay (29.5 days *v* 24 days, p = 0.17). There were no differences between groups in the incidence of bleeding events (26.1% *v* 21.1%, p = 0.7) or thrombotic events (39.1% *v* 57.9%, p = 0.23) after initiation of ECMO and systemic anticoagulation with bivalirudin.

Discussion

This was the first known study to assess the pharmacologic characteristics and dosing requirements of bivalirudin in patients requiring ECMO support for COVID-19. In this report, patients on ECMO for ARDS secondary to COVID-19 were more consistently able to maintain aPTTs within goal and were found to require higher median and maximum bivalirudin rates without increased incidences of bleeding or thrombosis.

While heparin remains the most used anticoagulant for patients on ECMO in the United States, bivalirudin use is increasing. Although previously being used primarily in patients with heparin sensitivities,[7] it is becoming an increasingly common first-line anticoagulant. More evidence is coming to light and supporting this shift, finding that it may be associated with decreased circuit-related thrombotic events, as well as decreased blood product transfusion.[8,9] Its use in COVID-19 patients also has been described in several case studies,[4,10] but never has been compared directly between COVID-19 patients and those with other etiologies of respiratory failure before the authors' investigation.

The patients in this study were well-matched except for weight. Bivalirudin employs weight-based dosing using total body weight, which is supported as the most accurate guide for achieving aPTT goals.[11] Though the overall weight was higher in the COVID-19 patients, the rate of obesity was not different between the groups. The patients spent similar times on ECMO, though the large interquartile ranges in both groups spoke to the variability of individual patient ECMO runs. There was a significantly higher total time spent on bivalirudin in the COVID group as compared with the non-COVID patients. In reviewing the data, this seemed to be due primarily to two patients in the non-COVID group who spent prolonged times off bivalirudin during their course due to significant hemorrhage that was difficult to control. There were no other confounders that the authors believed would have contributed to the difference in the ability to maintain their desired levels of anticoagulation in these patients.

A possible physiologic explanation for aPTTs being more consistent in the COVID-19 group is that there were more heterogeneous pathologies making up the non-COVID group. This heterogeneity may have led to variable effects on both the pharmacokinetics of bivalirudin, as well as underlying coagulation disturbances of the disease processes themselves. There also was heightened awareness among providers of the prothrombotic nature of COVID-19 infection, which may have driven more stringent scrutiny of aPTT trends and rate titrations.

There were several hypotheses that may explain the higher bivalirudin rate requirement in the COVID-19 group; the first being the development of bivalirudin resistance in this patient population. In non-COVID patients, direct thrombin inhibitor resistance was speculated to be due to elevated factor VIII and fibrinogen, as well as large clot burden.[12,13] Hypercoagulability has been documented in COVID-19 patients,[14,15] but specific correlation with overall dosing of anticoagulants has not been explored. Patients with COVID-19 have been found to have markedly elevated fibrinogen and factor VIII levels.[11] Heparin resistance has been demonstrated in COVID-19 patients, and likely was due to increased factor VIII and fibrinogen.[16] When heparin resistance is present, aPTTs are typically seen as a poor marker and other assays, such as anti-Xa monitoring, are used. This increased factor VIII and fibrinogen in COVID-19 patients also potentially could have contributed to the higher rates of bivalirudin use in the COVID-19 group; however, alternative assays to monitor anticoagulation for direct thrombin inhibitors, such as dilute thrombin time and ecarin thrombin time, were not readily available.[12]

Second, COVID-19 patients also have been shown to have an increased incidence of microthrombi.[17,18] Because bivalirudin binds to both free and clot-bound thrombin, the increase in microthrombi may have resulted in increased binding sites and an increased concentration necessary for saturation.[19] Further support for this theory is that the patients in the COVID-19 group often required very high bivalirudin rates up front but did not remain at these rates throughout treatment with bivalirudin.

In comparing the clinical courses of these patients, COVID-19 patients were found to have longer ICU durations but similar overall hospital lengths of stay. The ICU duration may have been skewed by several variables, including time needed for mechanical ventilation both before and after cannulation of ECMO, as well as bed availability for patients transfer once stable enough to leave the ICU. The latter was particularly notable during the COVID-19 pandemic, with high hospital censuses limiting patient movement. The similar hospital lengths of stay, however, suggested that the differing ICU courses were not as impactful on overall admission duration.

Notably, there were no significant differences in the rates of bleeding or thrombosis in either group. Although this did suggest that bivalirudin was safe in these COVID-19 patients at the higher doses they were given, the small number of events in each group also limited more substantial conclusions and may be a target for further research.

There were several strengths of this analysis, the first of which included the institutional utilization of bidirectional infusion pump technology, which allowed the investigators to more accurately calculate maximum and total bivalirudin infusion rates. In addition, the use of a 24-hour clinical pharmacist-driven bivalirudin-dosing service allowed for rapid protocolized bivalirudin rate adjustment. The primary weaknesses of this analysis were the size and single-center nature of the authors' study population. This led to essential limitations in the statistical and clinical conclusions that can be drawn, as well as the generalizability of the findings. Finally, given the retrospective nature of the data collection, it often was difficult to determine when bivalirudin may have been temporarily held for procedures or minor bleeding. Although this could have influenced the overall amount of bivalirudin each patient received, it was unlikely to significantly change the results comparing the two groups because the documentation issue occurred in both the COVID and non-COVID groups.

COVID-19 and its associated coagulopathy have been explored extensively in recent literature. In this small retrospective review of patients requiring venovenous ECMO support, those with respiratory failure secondary to COVID-19 infection required higher median daily and maximum bivalirudin rates, as compared with patients without COVID-19, to sustain goal aPTT values. Despite these higher rates, the aPTT values were more consistent in the COVID-19 group and there were no increases in bleeding or thrombotic complications. Further prospective analyses are needed to draw definitive conclusions regarding anticoagulation requirements in COVID-19 patients on venovenous ECMO support.

Conflict of Interest

None.

References

1 Wu C, Chen X, Cai Y, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934.

2 Edmunds LH, Colman RW. Thrombin during cardiopulmonary bypass. Ann Thorac Surg 2006;82:2315–22.

3 Wong JJM, Lam JCM, Mok YH, Lee JH. Anticoagulation in extracorporeal membrane oxygenation. J Emerg Crit Care Med 2018:2; Available at: https://jeccm.amegroups.com/article/view/4078; Acessed July 2, 2021.

4 Seelhammer TG, Rowse P, Yalamuri S. Bivalirudin for maintenance anticoagulation during venovenous extracorporeal membrane oxygenation for COVID-19. J Cardiothorac Vasc Anesth 2021;35:1149–53.

5 Sheehan C, Jegerski M. Cost Analysis of bivalirudin versus unfractionated heparin and antithrombin as anticoagulation for extracorporeal membrane oxygenation. In: Extracorporeal Life Support Organization Annual Meeting, Philadelphia, PA Philadelphia, PA, September 2013.

6 Sheehan C, Layne T, Roe D, et al. Bivalirudin versus unfractionated heparin for anticoagulation during extracorporeal membrane oxygenation. In: Extracorporeal Life Support Organization Annual Meeting, Ann Arbor, MI Ann Arbor, MI, September 2014.

7 Brogan TV, Lequier L, Lorusso R, MacLaren G, Peek G. Extracorporeal Life Support: The ELSO Red Book. (1 ed.) Extracorporeal Life Support Organization. 2017. https://www.elso.org/Publications/RedBook5thEdition.aspx.

8 Rivosecchi RM, Arakelians AR, Ryan J, et al. Comparison of anticoagulation strategies in patients requiring venovenous extracorporeal membrane oxygenation: Heparin versus bivalirudin. Crit Care Med 2021;49:1129–36.

9 Machado DS, Garvan C, Philip J, et al. Bivalirudin may reduce the need for red blood cell transfusion in pediatric cardiac patients on extracorporeal membrane oxygenation. ASAIO J 2021;67:688–96.

10 Bissell BD, Gabbard T, Sheridan EA, et al. Evaluation of bivalirudin as the primary anticoagulant in patients receiving extracorporeal membrane oxygenation for SARS-CoV-2–associated acute respiratory failure [e-pub ahead of print]. Ann Pharmacother 2021;10.1177/10600280211036151. Accessed July 29, 2021.

11 Tsu LV, Dager WE. Comparison of bivalirudin dosing strategies using total, adjusted, and ideal body weights in obese patients with heparin-induced thrombocytopenia. Pharmacotherapy 2012;32:20–6.

12 Cardinale M, Ha M, Liu MH, Reardon DP. Direct thrombin inhibitor resistance and possible mechanisms. Hosp Pharm 2016;51:922–7.

13 Berlioz B, Kaseer HS, Sanghavi DK, Guru PK. Bivalirudin resistance in a patient on veno-venous extracorporeal membrane oxygenation with a therapeutic response to argatroban. BMJ Case Reports CP 2020;13:e232262.

14 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;58:1116–20.

15 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;120:998–1000.

16 Tabatabai A, Rabin J, Menaker J, 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:e01236.

17 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;18:1738–42.

18 Lin J, Yan H, Chen H, et al. COVID-19 and coagulation dysfunction in adults: A systematic review and meta-analysis. J Med Virol 2021;93:934–44.

19 Chen W, Pan JY. Anatomical and pathological observation and analysis of SARS and COVID-19: Microthrombosis is the main cause of death. Bio Proced Online 2021;23:4.