Journal of Research in Pharmacy

Research Article

www.jrespharm.com

Assessing Thromboembolic Complications and In-Hospital Mortality and Clinical Factors Affecting Thromboembolic Complications in COVID-19 stage 3-5 ICU cases

Wan Nur Maisarah Wan Rosli [1,2], Tharmini Ravi [3,4], Long Chiau Ming [5], Hanis Hanum Zulkifly [1,2] *

1 Faculty of Pharmacy, Universiti Teknologi MARA, Kampus Puncak Alam, Selangor, Malaysia.
2 Cardiology Therapeutics Research Group, Universiti Teknologi MARA, Puncak Alam, Malaysia.
3 Hospital Sungai Buloh, Sungai Buloh, Selangor, Malaysia.
4 Clinical Research Center, Hospital Sungai Buloh, Sungai Buloh, Selangor, Malaysia.
5 School of Medical and Life Sciences, Sunway University, Sunway City, Malaysia.
* Corresponding Author. E-mail: hanish2984@uitm.edu.my (H.H.Z.).

Received: 24 August 2023 / Revised: December 2023 / Accepted: 21 March 2024

ABSTRACT: **Background:** Thromboembolic (TE) complications are associated with the severity of the infection and are no less of a disease that contributes to the fatality of critically ill patients infected with COVID-19. **Objective:** This study aimed to investigate the prevalence of TE complications, in-hospital mortality, and risk factors among ICU patients (stage 3, 4, 5) infected with COVID-19. **Methodology:** In this retrospective single-center cross-sectional study, 106 severe patients referred to intensive care units (ICUs) due to COVID-19 between February 2021 and December 2022 were included. All patients received a thromboprophylaxis agent. **Results:** Mean (SD) age 49.81(13.27), 50.9% were male, 68.9% Malays, mean (SD) (2-12) days of ICU admission with the most coexisting comorbidities being hypertension (44.3%), diabetes mellitus (33%), and obesity (60.3%). Of 106 patients, 51 (41.9%) developed pulmonary embolism (PE) and 27.5% died despite adequate thromboprophylaxis. In total, 51 (41.9%) developed TE event during their ICU admission. Significantly higher proportions of COVID-19 patients who developed complications of PE (77.8% vs 42%; p = 0.006) died. D-dimer, fibrinogen, white cell count (WCC), and troponin were significantly greater among those with TE events. Demographics, co-morbidities, other laboratory parameters and were similar in COVID-19 patients with and without TE events. **Conclusion:** There is a high incidence of TE complications and in-hospital mortality in critically ill patients with COVID-19. A high level of D-dimer, fibrinogen, white cell count, and troponin were associated with in-hospital TE events. It is apparent that routine chemical thromboprophylaxis may not be sufficient to prevent TE complications in patients with severe COVID-19.

KEYWORDS: COVID-19; thromboembolic complications; venous thromboembolism; prevalence of pulmonary embolism; deep vein thrombosis; laboratory findings.

1. INTRODUCTION

Since the WHO declared the sudden outbreak of COVID-19 infection a global health crisis in February 2020, more than 6.58 million people have died and 629 million have been infected by the coronavirus SARS-CoV-2 [1]. Its main mechanism to infect cells is through the spike protein, which is needed for binding to the angiotensin-converting-enzyme 2 (ACE2) receptors in the upper respiratory system [2]. Some people with an infection may be asymptomatic carriers, whereas others may have severe symptoms such as fever, cough, shortness of breath and can even get worse and turn into acute respiratory distress syndrome (ARDS) [2]. Even though pulmonary manifestations are the most well-known complications of COVID-19 that led to a high death rate in ICU patients with COVID-19, thromboembolic (TE) complications are also linked to the severity of the infection and are no less a disease that contributes to the fatality of critically ill patients [3].

How to cite this article: Wan Nur Maisarah Wan Rosli, Ravi, T., Long, C. M., Hanis Hanum Zulkifli. Assessing Thromboembolic Complications and In-Hospital Mortality and Clinical Factors Affecting Thromboembolic Complications in COVID-19 stage 3-5 ICU cases. J Res Pharm. 2023; 28(4): 1244-1252.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.805

Journal of Research in Pharmacy
Research Article

TE complications are complex with multifactorial etiology [4]. It can be divided into venous thromboembolism (VTE) and arterial thromboembolism (ATE). VTE is further subdivided into deep vein thrombosis (DVT) and pulmonary embolism (PE) [5].

TE complications in hospitalized COVID-19 patients have been said to be correlated with coagulation abnormalities [6]. It can be seen that patients in a hypercoagulable state are associated with the increased blood levels of D-dimer, prolonged PT, thrombocytopenia, and high fibrinogen levels [7, 8]. These conditions have been linked with a poor prognosis, which may lead to a higher chance of mortality. Numerous potential risk factors for this complication have been identified including immobilization, prolonged mechanical ventilation, and central venous catheter in terms of those admitted to ICU [9]. Therefore, patients in the ICU setting are at a greater risk to manifest from just COVID-19 infection to a more serious TE event. Moreover, a study with a cohort of 40 patients in ICU departments in German, reported half of ICU COVID-19 patients (n=23; 57.5%) were observed to have TE complications [10].

Nevertheless, the amount of research that has been conducted on the TE complications among COVID-19 patients, specifically focusing on those who were admitted to the ICU, is still insufficient. Limited research on this issue is dissatisfying to multiple sectors, especially the health care sector, which is responsible for enhancing the overall quality of life in society with a hindrance for them to formulate appropriate interventions for the disease. In response to this issue, our study proposed to investigate the prevalence of TE complications, in-hospital mortality, and the intricate clinical factors influencing TE in COVID-19 patients at stages 3-5 in the intensive care unit (ICU). While previous research has initiated the exploration of the coagulopathy associated with severe COVID-19, our study addresses a critical gap in the literature by focusing specifically on stage 3-5 ICU patients. This is a demographic that represents some of the most severely ill patients and, as our data indicates, is at a particularly high risk of developing TE complications despite current prophylaxis strategies. This is highlighted by our finding that 41.9% of our patient cohort developed TE events during their ICU admission, with a significant association between these events and increased mortality. Moreover, our study moves beyond prevalence data and delves into the potential predictors and risk factors for TE complications in this specific patient population. We identified specific laboratory markers, including D-dimer, fibrinogen, white cell count, and troponin levels, that were significantly elevated in patients who developed in-hospital TE events.

2. RESULTS

A total of 153 patients were screened with 47 patients excluded from the study due to incomplete clinical records and diagnosis of COVID-19 by rapid test kit antigen (RTK). This made only 106 patients with confirmed COVID-19 by a positive RT-PCR admitted to ICU department of Hospital Sungai Buloh between period of February 2021 to December 2022 were included based on the inclusion and exclusion criteria.

2.1. Demographic Characteristics and Laboratory Findings

Patient demographic characteristics and laboratory findings are shown in **Table 1**. The average age of the cohort was 49.81 ± 13.27 years with 54 (50.9%) of patients were male. Majority of patients were Malay (73 [68.9%]) followed by Chinese (18 [17%]), Indian (6 [5.7%]) and others. A total of 69/106 (65%) patients had one or more coexisting comorbid conditions. The most common coexisting comorbidities were hypertension (47 [44.3%]), diabetes mellitus (35 [33%]), and obesity (38 [60.3%]). Only 6 (5.7%) of these patients were recorded as smokers in the EMR.

Analyses of the coagulation parameters revealed no significant differences between the groups except for d-dimer, fibrinogen, WCC and troponin. Compared to the patients without TE outcome, patients' presence with TE had abnormally elevated D-dimer levels on baseline, which was significantly higher (1.20 [1.66] vs 0.41 [0.47], $p < 0.01$). Critically ill COVID-19 patients with TE events were also more likely to have high level of fibrinogen (681 [184] vs 548 [221], $p = 0.002$), WCC (15.26 [5.34] vs 9.6 [3.38], $p < 0.01$), and troponin (56.09 [21.78] vs 12.8 [30.95], $p < 0.01$) than without the TE complications, as illustrated in **Table 1**.

When compared to non-TE groups, patients with clinical outcomes had a longer ICU stay (12.02 [8.16] days vs. 9.56 [11.56] days, $p = 0.212$); nonetheless, there were no statistically significant differences between groups. Mechanical ventilation was shown to be received by patients with TE complications more frequently than without TE complications, although these differences were insignificant. All patients were given adequate thromboprophylaxis, with 51.9% of patients received the most common dose of low molecular weight heparin (LMWH) enoxaparin 40 mg once daily (11). Meanwhile, one or more continued therapeutic

anticoagulation agents were given at the time of ICU admission to patients with TE complications, as the most common one being enoxaparin 60 mg bid (12). Gender, age, race, and other variables revealed no statistically significant differences between the TE and non-TE groups.

Table 1. Demographic characteristics and laboratory findings among COVID-19 patients admitted to the ICU (n=106)

	All patients (n=106)	Thromboembolic outcome (n=51)	No Thromboembolic Outcome (N=55)	p value
Age, years (mean, [SD])	49.81 ± 13. 27	50.8 ± 12.31	48.89 ± 14.16	0.461
Male gender, n (%)	54 (50.9)	25 (49)	29 (52.7)	0.703
Race, n (%)				
Malay	73 (68.9)	40 (78.4)	33 (60)	0.076
Chinese	18 (17)	5 (9.8)	13 (23.6)	
Indian	6 (5.7)	1 (2)	5 (9.1)	
Others	9 (8.5)	5 (9.8)	4 (7.3)	
Comorbidities, n (%)				
Hypertension	47 (44.3)	25 (49)	22 (40)	0.350
Ischemic Heart Disease				0.570
STEMI	4 (3.8)	2 (3.9)	2 (3.6)	
UA	1 (0.9)	1 (2)	0 (0)	
CABG	1 (0.9)	0 (0)	1 (1.8)	
Asthma	11 (10.4)	5 (9.8)	6 (10.9)	0.852
Diabetes mellitus	35 (33)	16 (31.4)	19 (34.5)	0.729
Cancer	2 (1.9)	1 (2)	1 (1.8)	0.957
Social history, n (%)				
Obesity	38 (35.8)	20 (62.5)	18 (58.1)	0.719
Smoking status (n=6)	6 (5.7)	5 (9.8)	1 (1.8)	0.075
Laboratory findings				
D dimer (mg/ml), median [IQR]	0.61 [0.78]	1.20 [1.66]	0.41 [0.17]	<0.001 1
Fibrinogen (g/ml), median [IQR]	633.5 [226]	681 [184]	548 [221]	0.002
INR, mean [SD]	1.16 ± 1.24	1.28 ± 1.78	1.04 ± 0.10	0.340
White Cell Count x 109, mean [SD]	12.32 ± 5.25	15.26 ± 5.34	9.6 ± 3.38	<0.001
CRP (0.0-1mg/dl), median [IQR]	8.15 [7.15]	7.4 [9.1]	8.8 [11.7]	0.200
Lymphocytes, mean [SD]	0.9 ± 0.6	0.9 ± 0.44	0.91 ± 0.72	0.968
APTT ratio, mean [SD]	36.41 ± 10.78	34.95 ± 8.07	37.72 ± 12.68	0.186

1

Troponin (pg/ml), median [IQR]	43.5 [43.94]	56.09 [21.78]	12.8 [30.95]	<0.001
Ferritin (ng/ml), median [IQR]	1196.5 [1092]	1358 [1066]	946 [11.56]	0.702
Length of ICU stay, mean [SD]	10.74 ± 10.1	12.02 ± 8.16	9.56 ± 11.56	0.212
Mechanical ventilation, n (%)	84 (79.2)	41 (80.4)	43 (78.2)	0.779

Abbreviation: STEMI, ST-elevation myocardial infarction; UA, unstable angina; CABG, coronary artery bypass graft; INR, international normalized ratio; CRP, C-reactive protein; APTT ratio; activated partial thromboplastin time ratio. $p<0.05$ is considered significant.

2.2 Clinical Outcomes

Thromboembolic complications were identified in 51 patients (41.2%). All of them were diagnosed with PE by computed tomography pulmonary angiography (CTPA). 25 (49%) of them were male and 26 (51%) were female. All the patients with PE also received mechanical ventilation (Table 2).

Table 2. Medications received by the ICU COVID-19 patients on admission and in the wards

All patients (n=106)	N	%
Medications on admission		
Antihypertensive	33	31.1
Antidiabetics	31	29.2
Antiplatelet	21	19.8
Asthma medications	19	17.9
Medications in the wards		
Clexane Dose		
20 mg OD	36	34
40 mg OD	55	51.9
20 mg BD	1	0.9
40 mg BD	24	22.6
60 mg BD	47	44.3
Fondaparinux Dose		
2.5 mg OD	12	11.3
7.5 mg OD	25	23.6
Heparin Dose		
5000 u BD	14	13.2
Methylprednisolone	82	77.4
Dexamethasone	48	45.3
Favipiravir	11	10.4
Tocilizumab	5	4.7

2.3. Death Outcomes

Significantly higher proportions ($p = 0.006$) of patients with PE complications remained alive (72.5%) compared to non-survivors (27.5%).

3. DISCUSSION

3.1 Prevalence of thromboembolism in critically ill COVID-19 patients

In this study, we investigate the prevalence of thromboembolic (TE) complications, in-hospital mortality, and risk factors among critically ill COVID-19 patients. Our findings found a high prevalence of TE complications in COVID-19 patients who were admitted to the ICU and low mortality rate (for patients

with TE). The highest proportion of were PE and high level of D-dimer, fibrinogen, WCC and troponin has been associated to the TE complications.

In this small cohort of ICU patients with severe COVID-19, we reported an overall high proportion of TE complications, essentially pulmonary embolism (n = 51, 48.1%). These accounts for almost half of the general ICU population despite thromboprophylaxis that were routinely given during admission. Previous studies reported the similar observations on PE being the highest proportion of TE complications in critically ill COVID-19 patients [9, 13]. Moreover, much higher PE incidence compared to other form of TE complications was described among inpatients with bigger study cohort [13]. Patients in both studies were also given anticoagulant prophylaxis. This can be seen that hospitalised patients with severe COVID-19 are at high risk of VTE, even with the use of pharmacological prophylaxis in all of them. To add up, the result of our study also was insignificant between the prophylactic anticoagulant with TE and non-TE outcome in the patients ($p = 0.543$ and $p = 0.089$).

3.2 Risk factor of Thrombosis in ICU patients with COVID-19

Most of the patients presented with TE complications had a mean age of 50.8 years with underlying comorbidities such as hypertension, diabetes mellitus and obesity being the common coexisting medical conditions. In contrast, research had shown that the majority of patients who have encountered TE were older patients, ranging from mean age of 55 to 62.2 years old [14-19]. Their results indicate that older people above 55 years old with severe COVID-19 infection had a significantly higher probability of TE compared to younger patients [14-19]. This explains the insignificant age data in this study ($P = 0.461$). Hypertension and diabetes had been observed to have the highest prevalence rates of the studied population with the outcomes [14, 16, 19]. It is worth noting that approximately half of the patients who had TE were associated with hypertension [17]. Nonetheless, our study reported no significant differences between coexisting disease with TE group and non-TE group respectively ($p = 0.35, 0.729, 0.719$).

We also found that the proportion of female patients presented with PE was slightly higher than male patients (25 [49%] vs 26 [51%]). Nevertheless, there is a small disparity in the percentages with only 2% gap between male and female, explains that both genders were in critical state to get TE complications. We also found that patients who developed TE had more extended ICU stay (12.02 days vs 9.56 days, $p=0.212$) compared to patients without TE complications. However, there were no statistically significant differences between the groups. This finding is inconsistent to what had been observed in ICU in United States with 3531 patients where TE group had a longer ICU length of stay (12.2 days vs 8.8 days) and days on ventilator (2.4 days vs 1.1 days) than non-TE group [20].

In terms of laboratory values, we found markedly elevated markers of coagulation and inflammation in D-dimer, fibrinogen, CRP, WCC, troponin and ferritin; however only D-dimer, fibrinogen, WCC, and troponin were found to be differed significantly between patients with and without TE complications. The result of our study showed that there was a marked difference in the D-dimer level between the two groups which was beyond the usual range of 0-0.05 mg/L ($p < 0.001$). The high concentration of D-dimer in the TE population is consistent with that reported by Hippensteel et al. but appears to be lower than the majority of previous studies, particularly when compared to Nahum et al., who reported a fourfold increase in D-dimer levels among ICU patients [9, 14-16]. Since D-dimer is a protein fragment produced when fibrin is degraded, an elevated level of D-dimer can be used to indicate the presence of excessive coagulation activation and breakdown of clot that is due to either hypofibrinolysis or hyperfibrinolysis [10, 21]. This provides insight into the high baseline D-dimer value as a valuable primary predictor of TE risk in COVID-19 patients, as both conditions were responsible for their hypercoagulable state. A few studies have investigated the association between baseline D-dimer levels with increased risk of TE incidence [21, 22]. Similar to data reported previously, we identified D-dimer as an independent risk factor for the development of TE in COVID-19 ICU patients [3, 10, 15].

This study demonstrated an independent association between severe derangements of fibrinogen and elevated thromboelastography (TEG) maximum amplitude (MA), a measure of clot strength among hypercoagulable patients [23]. As patients with TE outcomes in our study presented with higher fibrinogen levels than those without TE ($p = 0.002$) and hypercoagulability has been noted to be common especially in severe COVID-19, this suggest that high fibrinogen level can be used as a hypercoagulability marker in those patients. Consistently, previous data have shown that elevated plasma fibrinogen is associated with excessive inflammation and may predict disease severity in ICU COVID-19 patients [24, 25]. Monitoring of

Journal of Research in Pharmacy
Research Article

fibrinogen level may represent a more practical method for the identification of patients at risk for COVID-19 related hypercoagulability. In addition, our findings also shown an association between high level of WCC and troponin and TE outcome ($p < 0.001$). Since there is correlation between the laboratory values of D-dimer, fibrinogen, WCC and troponin with TE outcome in severely ill patients infected with COVID-19, these findings can serve as key predictors in determining the complications.

3.3 Prevalence of mortality among COVID-19 patients admitted to the ICU with thromboembolism

Fourteen (27.5%) of 51 patients with TE outcomes had died and 37 (72.5%) remained alive. This is consistent with reports from Netherlands, United Kingdom, and the USA in which the mortality rate of ICU admission among patients admitted with COVID-19 ranged from 9-25% [13, 26-29]. Since our study population was small compared to previous studies, it most likely resulted in a slightly higher mortality rate. Anticoagulant treatments were initiated for all patients suffering with TE complications.

4. LIMITATION

There are several limitations in this study. Firstly, this study was a single-center, retrospective study with the biases inherent of this type of study and therefore needs to be further validated in a prospective study. Secondly, being an observational dataset, no definite conclusions can be taken in regard to the ideal risk factors of thromboembolic complications for critically ill COVID-19 patients should be as it is impossible to be sure that the results were accurate due to many factors that may influenced the results. Thirdly, time constraints when collecting the data resulted in small study cohort that causes no variation to the types of TE outcome found in this study. Due to the small study population screening and the chance of encountering another form of TE is limited, therefore, results need to be confirmed on a larger sample size of COVID patients with different severity clusters. Lastly, as this is not an interventional study, the center relied on its own screening methods for the detection of thromboembolic complications, without a systematic screening of patients for TE events.

5. CONCLUSION

There is a high incidence of TE complications and in-hospital mortality in critically ill patients with COVID-19 attributed to the SARS-CoV-2 infection-induced systemic hypercoagulability. A high level of D-dimer, fibrinogen, white cell count, and troponin were shown to be associated with in-hospital TE events. It is apparent that routine chemical thromboprophylaxis may not be sufficient to prevent TE complications in patients with severe COVID-19. Therefore, we recommend that ICU-admitted COVID-19 patients with these characteristics receive higher anticoagulant prophylaxis doses to prevent the occurrence of TE events and in-hospital mortality. Future research should be conducted and focus on optimal diagnostic and prophylactic strategies to prevent VTE and potentially improve survival.

6. MATERIALS AND METHODS

6.1. Study and selection of patients

We retrospectively performed a single-center cross-sectional study at the intensive care unit (ICU) department of Hospital Sungai Buloh, Selangor. Critically ill patients with laboratory-confirmed COVID-19 were screened through electronic medical record (EMR) and entered the database. We included adult patients (age > 18 years old) of stage 3, 4 and 5 (Supplementary Info) COVID-19 who received ICU care from the period of February 2021 until December 2022. Only patients with complete clinical records and received thromboprophylaxis agent were included. The flow of research is depicted in **Figure 1**.

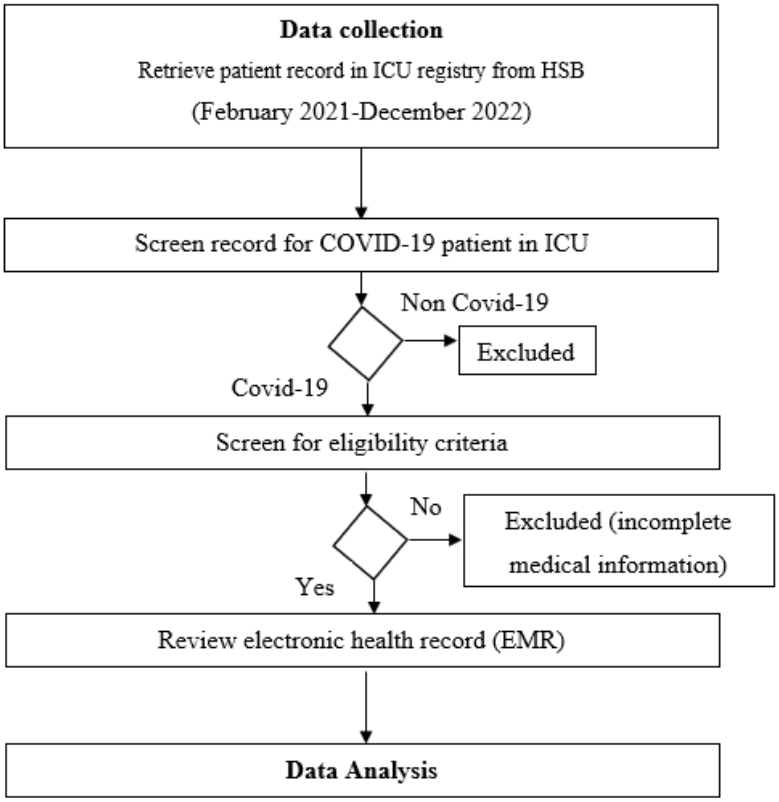

Figure 1. Flow of methods

Data that was collected include sex, age, nationality, race, body weight, height, date of hospital admission and discharge, date of ICU admission and discharge or death, obesity, smoking, alcohol intake, chronic disease history (hypertension, diabetes, ischemic heart disease, heart failure, stroke, PE, DVT, atrial fibrillation, asthma, chronic obstructive pulmonary disease (COPD), malignancy and kidney disease), the outcome of TE events, and medications that were given during hospital stay. The laboratory values such as PCR test, white cell counts (WCC), lymphocytes, fibrinogen, troponin, international normalized ration (INR), C-reactive protein (CRP), ferritin, activated partial thromboplastin time (APTT) ratio and D-dimer were also included.

6.2. Statistical Analysis

All data analysis was performed using Statistical Package for the Social Science (SPSS) for Windows version 28. For descriptive data, we expressed categorical variables as numbers and percentages and as mean with standard deviations or median with interquartile ranges (IQR) for continuous variables. Qualitative data were analyzed using the independent sample T-test for parametric data and Mann–Whitney U test for nonparametric data, while the categorical variables were compared using the Chi-square test. The tests were employed to compare differences between baseline variables with TE outcomes and non-TE outcomes. $p \leq 0.05$ was considered statistically significant.

6.3. Ethical approval

Ethical approval for this study was obtained from the institutional ethical approval Medical Research Ethics Committee (MREC) with reference number REC (PH)/UG/051/2023.

Acknowledgements: None

Conflict of interest statement: None

Ethical approval: Ethical approval for this study was obtained from the Faculty Ethics Review Committee (FERC) and Medical Research Ethics Committee (MREC) with reference number REC (PH)/UG/051/2023.

REFERENCES

[1] Medicine JHU. Covid-19 Johns Hopkins Coronavirus Resource Center 2022 [Available from: http://coronavirus.jhu.edu/].
[2] Ciotti M, Ciccozzi M, Terrinoni A, Jiang W-C, Wang C-B, Bernardini S. The COVID-19 pandemic. Crit Rev Clin Lab Sci. 2020;57(6):365-88. https://doi.org/10.1080/10408363.2020.1783198
[3] Russell L, Weihe S, Madsen EK, Hvas CL, Leistner JW, Michelsen J, et al. Thromboembolic and bleeding events in ICU patients with COVID-19: A nationwide, observational study. Acta Anaesthesiol Scand. 2023;67(1):76-85.
[4] Vaqar S, Graber M. Thromboembolic Event. 2019. https://doi.org/10.1111/aas.14157
[5] Ashorobi D, Ameer MA, Fernandez R. Thrombosis. StatPearls [Internet]. 2022.
[6] Boonyawat K, Chantrathammachart P, Numthavaj P, Nanthatanti N, Phusanti S, Phuphuakrat A, et al. Incidence of thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Thromb J. 2020;18(1):1-12. https://doi.org/10.1186/s12959-020-00248-5
[7] Cuker A, Peyvandi F. COVID-19: Hypercoagulability. UpToDate Ed: Post TW Waltham, Massachusetts Cuker A Peyvandi F COVID-19: Hypercoagulability In UpToDate Post TW Waltham, Massachusetts Search in. 2021. https://doi.org/10.1097%2FSHK.0000000000001660
[8] Gomez-Mesa JE, Galindo-Coral S, Montes MC, Martin AJM. Thrombosis and Coagulopathy in COVID-19. Curr Probl Cardiol. 2021;46(3):100742. https://doi.org/10.1016/j.cpcardiol.2020.100742
[9] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98. https://doi.org/10.1007/s00134-020-06062-x
[10] Kruse JM, Magomedov A, Kurreck A, Münch FH, Koerner R, Kamhieh-Milz J, et al. Thromboembolic complications in critically ill COVID-19 patients are associated with impaired fibrinolysis. Crit Care. 2020;24(1):1-10. https://doi.org/10.1186/s13054-020-03401-8
[11] Health Mo. Clinical Management of Confirmed COVID-19 Case in Adult [-]. -: -; 2020 [updated 3/11; cited 2020 3/11]. -; -: [Prophylaxis dose of anticoagulant]. Available from: https://covidlawlab.org/wp-content/uploads/2021/02/Malaysia_2020.11.03_Guidelines_Clinical-Management-of-Confirmed-COVID-19-Case-in-Adult_EN.pdf.
[12] Malaysia MoH. Prevention and Treatment of Venous Thromboembolism 2013. Available from: https://www.moh.gov.my/moh/attachments/9005.pdf.
[13] Klok F, Kruip M, Van der Meer N, Arbous M, Gommers D, Kant K, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7. https://doi.org/10.1016/j.thromres.2020.04.013
[14] Nahum J, Morichau-Beauchant T, Daviaud F, Echegut P, Fichet J, Maillet J-M, et al. Venous thrombosis among critically ill patients with coronavirus disease 2019 (COVID-19). JAMA Netw Open. 2020;3(5):e2010478-e. https://doi.org/10.1001%2Fjamanetworkopen.2020.10478
[15] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-4. https://doi.org/10.1111/jth.14830
[16] Hippensteel JA, Burnham EL, Jolley SE. Prevalence of venous thromboembolism in critically ill patients with COVID-19. Br J Haematol. 2020;190(3):e134. https://doi.org/10.1111/bjh.16908
[17] Bellmunt-Montoya S, Riera C, Gil D, Rodríguez M, García-Reyes M, Martínez-Carnovale L, et al. COVID-19 infection in critically ill patients carries a high risk of venous thrombo-embolism. Eur J Vasc Endovasc Surg. 2021;61(4):628-34. https://doi.org/10.1016/j.ejvs.2020.12.015
[18] Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation. 2020;142(2):184-6. https://doi.org/10.1161/circulationaha.120.047430
[19] Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324-9. https://doi.org/10.1111/jth.14859
[20] Lee Y, Jehangir Q, Li P, Gudimella D, Mahale P, Lin C-H, et al. Venous thromboembolism in COVID-19 patients and prediction model: a multicenter cohort study. BMC Infect Dis. 2022;22(1):1-14. https://doi.org/10.1186/s12879-022-07421-3

[21] Hansen E-S, Rinde FB, Edvardsen MS, Hindberg K, Latysheva N, Aukrust P, et al. Elevated plasma D-dimer levels are associated with risk of future incident venous thromboembolism. Thromb Res. 2021;208:121-6. https://doi.org/10.1016/j.thromres.2021.10.020
[22] Evensen LH, Folsom AR, Pankow JS, Hansen JB, Allison MA, Cushman M, et al. Hemostatic factors, inflammatory markers, and risk of incident venous thromboembolism: The Multi-Ethnic Study of Atherosclerosis. J Thromb Haemost. 2021;19(7):1718-28. https://doi.org/10.1111%2Fjth.15315
[23] Yuriditsky E, Horowitz JM, Merchan C, Ahuja T, Brosnahan SB, McVoy L, et al. Thromboelastography profiles of critically ill patients with coronavirus disease 2019. Crit Care Med. 2020. https://doi.org/10.1097%2FCCM.0000000000004471
[24] Sui J, Noubouossie DF, Gandotra S, Cao L. Elevated plasma fibrinogen is associated with excessive inflammation and disease severity in COVID-19 patients. Front Cell Infect Microbiol. 2021;11:734005. https://doi.org/10.3389/fcimb.2021.734005
[25] Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virол. 2020;92(7):791-6. https://doi.org/10.1002/jmv.25770
[26] Klok F, Kruip M, Van der Meer N, Arbous M, Gommers D, Kant K, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res. 2020;191:148-50. https://doi.org/10.1016/j.thromres.2020.04.041
[27] Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MC, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995-2002. https://doi.org/10.1111/jth.14888
[28] Thomas W, Varley J, Johnston A, Symington E, Robinson M, Sheares K, et al. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. Thromb Res. 2020;191:76-7. https://doi.org/10.1016%2Fj.thromres.2020.04.028
[29] Maatman TK, Jalali F, Feizpour C, Anthony Douglas I, McGuire SP, Kinnaman G, et al. Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe coronavirus disease 2019. Crit Care Med. 2020. https://doi.org/10.1097/ccm.0000000000004466