The Challenging Anticoagulant Therapy in Patient with COVID-19-Associated Coagulopathy

Raissa Virgy Rianda[1], Mohammad Subkhan[2,3], Aditya Doni Pradana[4], Fahrun Nisa'i Fatimah[5], Rama Azalix Rianda[6], Muhammad P. Airlangga[2,7], Muhammad Miftahussurur[8,9]

[1] Department of Child Health, Faculty of Medicine Universitas Airlangga-Dr. Soetomo Hospital, Surabaya, Indonesia.
[2] Siti Khodijah Hospital, Sidoarjo, Indonesia.
[3] Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, Universitas Muhammadiyah Surabaya, Surabaya, Indonesia.
[4] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[5] Department of Cardiology and Vascular Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia.
[6] Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[7] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Muhammadiyah Surabaya, Surabaya, Indonesia.
[8] Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine Universitas Airlangga-Dr. Soetomo Teaching Hospital, Surabaya, Indonesia.
[9] Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia.

Corresponding Author:
Muhammad Miftahussurur, MD., PhD. Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya. Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya 60131, Indonesia. Email: muhammad-m@fk.unair.ac.id.

ABSTRAK

COVID-19 menjadi penyakit infeksius yang meluas di seluruh dunia di akhir tahun 2019. Saat ini Indonesia menduduki angka kematian tertinggi di Asia, sekitar 4-5 persen. Menariknya, koagulopati terkait COVID-19 yang ditandai dengan meningkatnya faktor prokoagulan termasuk fibrinogen dan D-Dimer, yang berhubungan dengan tingginya mortalitas dan prognosis yang buruk. Kami melaporkan kasus laki-laki usia 30 tahun datang ke rumah sakit dengan keluhan muntah, demam yang memburuk, dan sesak, dengan diagnosis COVID-19 terkait koagulopati. Tujuh hari setelah masuk, dia mengalami perburukan kondisi dengan penurunan saturasi oksigen yang signifikan, dan parameter koagulasi meningkat dengan tinggi dicurigai adanya emboli paru. Pasien mendapat terapi azithromycin, isoprinosine, lopinavir, dam fondaparinux dengan dosis tromboprofilaksis sejak awal masuk. Peningkatan dosis fondaparinux berperan pada saat perburukan klinis yang kemudian diikuti dengan perbaikan klinis dan penurunan kadar D-dimer. Terapi antikoagulan, terutama dengan fondaparinux, menunjukkan prognosis yang lebih baik pada pasien dengan D-Dimer yang meningkat tinggi. Fondaparinux perlu dipantau secara tepat untuk mencegah perdarahan dan efek samping. Pasien keluar dari rumah sakit dalam kondisi yang lebih baik dan tingkat D-Dimer normal. Tidak ada kejadian perdarahan atau efek samping utama yang ditemukan dalam kasus ini. Keputusan untuk meningkatkan dosis antikoagulan dapat dinilai secara individu, dengan mempertimbangkan risiko, manfaat, dan yang terpenting adalah temuan klinis.

Kata kunci: *COVID-19, koagulopati, antikoagulan, trombosis.*

ABSTRACT

COVID-19 became a widespread infectious disease in late 2019. Indonesia currently has the highest COVID-19 mortality rate in Asia, between 4-5 percent. Interestingly, COVID-19-associated coagulopathy characterized by an increase of several procoagulant factor levels, including fibrinogen and D-dimer, that has been associated with higher mortality and unfavorable outcomes. We report a case of a 30-year-old male admitted to the hospital with a profuse vomiting and worsening fever, cough and shortness of breath, and was diagnosed with COVID-19-associated coagulopathy. Seven days after admission, he became deteriorated with significant reduction of oxygen saturation and his coagulation parameter levels were increased with highly suspicion of pulmonary embolism. He was treated with azithromycin, isoprinosine, lopinavir, and fondaparinux with thromboprophylaxis dosage since admission. The role of increased fondaparinux dosage at the time of clinical deterioration was then followed by clinical improvement and reduced D-dimer level. Anticoagulant therapy, mainly with fondaparinux, showed a better prognosis in patients with markedly elevated D-Dimer. Fondaparinux needs to be monitored appropriately to prevent bleeding and adverse. The patient was discharged from the hospital in an improved condition and normal D-Dimer levels. There were no bleeding event nor other major side effects that had been found. The decision for increasing dose of anticoagulant may be determined on individual basis, considering risks, benefits, and also the most important is clinical findings.

Keywords*: COVID-19, coagulopathy, anticoagulation, thrombosis.*

INTRODUCTION

The coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which had been declared a pandemic by the World Health Organization.[1] As of August 2020, the global death toll from COVID-19 has reached 725.330, with more than 19 million confirmed cases. Indonesia has 123.503 confirmed cases, with 5.658 deaths and 79.306 recoveries. According to WHO, East Java province had contributed the highest case in Indonesia with 24.992 confirmed cases (20.2%) followed by DKI Jakarta, and Central Java province.[2] Coagulation abnormalities have been found in COVID-19 infection, characterized by an increase of several procoagulant factor levels, including fibrinogen and D-dimer. COVID-19-associated coagulopathy has been associated with higher mortality and unfavorable outcomes.[1] Recent studies show that the D-dimer level frequently increases in 36% to 43% COVID-19 patients. Compared to mild cases, D-dimer in severe COVID-19 has a higher predictive value for the patient's outcome and worsening condition.[3,4] We reported a case of COVID-19 with clinically significant coagulopathy and deterioration which was treated with fondaparinux as thromboprophylaxis during the first week of hospitalization, which was later converted to therapeutic anticoagulant dose in spite of the current clinical guideline not recommending it solely based on clinical findings. This issue remains controversial since guidelines do not recommend the decision to increase anticoagulant dose only based on clinical findings. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 infection in this case was confirmed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay.

CASE ILLUSTRATION

A 30–year-old Javanese male was admitted to hospital because of nausea and profuse vomiting for three days and was getting worse 6 hours before admission. He reported syncope after few episodes of profuse vomiting. There was no history of eating either spicy or sour food before vomiting. The patient denied any complaints of painful swallowing, fever, cough, and shortness of breath. There was no history of previous illnesses such as diabetes mellitus or hypertension, but he was a heavy smoker. He stayed with his mother in Surabaya, East Java, family members denied any complaint and remained healthy but local transmission of COVID-19 has been recorded in his residential area. There was no known COVID-19 contact, and he has not recently traveled.

Our initial examination revealed a weak general condition, but the patient remained alert. Vital signs were stable: blood pressure, 110/70 mmHg; body temperature, 36.5°C; heart rate, 85 times per minute; respiratory rate was 20 times per minute, and oxygen saturation was 99% in room air. Cardiac examination revealed unremarkable results. Lung auscultation was bilaterally clear. Abdominal physical examination results were unremarkable. During admission, there was no sign and symptoms of dehydration, vital signs were normal, capillary refill time was normal, and skin turgor was normal. His blood laboratory results are summarized in (**Table 1**) but had notably high NLR of 4.4 when he first arrived to the hospital. The 12-lead electrocardiogram showed normal sinus rhythm.

The next day, the patient developed a fever and cough. The body temperature rose to 38°C and his chest x-ray showed atypical pneumonia (**Figure 1**). Rapid diagnostic test using IgM and IgG as screening test was non-reactive, and other lab results showed fibrinogen was 342.7 mg/dL (normal range 180-350 mg/dL), CRP, D-dimer, Procalcitonin increased respectively 2.14 mg/dL (normal range <0.3 mg/dL), 0.51µg/mL (normal range <0.5 µg/mL) and 0.1 ng/mL (normal range <0.05 ng/mL). He had no prolonged activated partial thromboplastin time (a PTT) of 24.8 s and plasma prothrombin time (PPT) of 11.5 s. The reverse transcription polymerase chain reaction (RT-PCR) SARS-CoV-PCR nasopharyngeal swab result was confirmed positive COVID-19 (Standard M nCoV Real-Time Detection Kit, SD

Table 1. Clinical laboratory results.

Laboratory Characteristic	On admission	Day-7	Discharge	Normal limits
Haemoglobin (g/dL)	15.9	10.6	11.2	13-18
Red Blood Cell (10^6/uL)	5.44	3.75	3.89	4.5-5.5
Haematocrit (%)	44.5	32.8	34.3	40-50
White Blood Cell (10^3/uL)	6.29	13.75	7.37	4-11
Neutrophil %	75.8	88.0	73.0	50-70
Lymphocyte %	16.4	9.5	19.0	20-40
NLR	4.62	9.26	3.84	
Platelet count (10^3/uL)	216	413	529	150-400
Blood Glucose (mg/dL)	187	-	-	<200
Creatinine (mg/dL)	0.9	-	-	0.7-1.2
BUN (mg/dL)	22.0	-	-	7-20
Ureum (mg/dL)	47.1	-	-	17-43
Bilirubin Direct (mg/dL)	0.38	-	-	<0.2
Bilirubin Total (mg/dL)	1.12	-	-	0.1-1.2
Alkaline Phosphatase (U/L)	83	-	-	<50
Alanine Transferase (U/L)	161	-	-	<50
Sodium (mmol/L)	135	-	-	136-145
Potassium (mmol/L)	4.0	-	-	3.5-5.1
Chloride (mmol/L)	98	-	-	98-107
D-dimer (µg/mL)	0.51	2.52	0.39	<0.5
Fibrinogen (mg/dL)	342.7	596.4	-	180-350
Procalcitonin (ng/mL)	0.10	-	-	<0.05
CRP (mg/L)	2.14	-	-	<0.3

Table 2. Blood gas analysis obtained in day-9 hospitalization.

Parameters	Results	Normal limits
pH	7.43	7.35 - 7.45
PCO2	37	35-45 mmHg
PO2	60	90 – 100 mmHg
BE	0.1	-2 - +2 mmol/L
tCO2	25.2	mmol/L
HCO3	24.1	22-26 mmol/L
SO2	90%	≥ 95 %
FiO2	1.00	

Biosensor,Inc, Suwon, South Korea).

The patient was treated with Azithromycin orally 500 mg/day for five days, and Isoprinosine orally in doses of 500 mg every 8 hours. The patient had been well until five days of treatment. On the sixth day of hospitalization, the patient's clinical condition rapidly deteriorated. He underwent shortness of breath abruptly, and the respiratory rate became 28 times per minute, oxygen saturation declined to 83% in room air. Lung auscultation revealed rhonchi symmetrically all over his chest and diminished vesicular sounds. At the hospital, he underwent an evaluation chest x-ray examination (**Figure 1**). Blood gas analysis revealed mild hypoxemia with pO_2 60 mmHg, pH 7.43, pCO_2 37 mmHg **(Table 2)**. He was planned to be referred for mechanical ventilation, but all hospital in the adjacent area had limited capacity. Later, the patient was put on a non-rebreathing mask with 10 L/min flow (**Figure 2**). The oxygen saturation was slowly increased to 94%. The

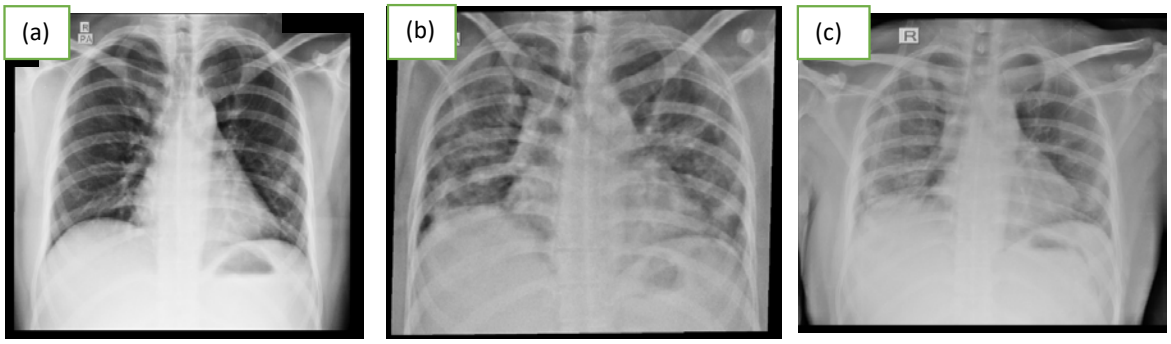

Figure 1. Chest x-ray imaging of the patient. **(a)** chest x-ray at the first admission to the hospital revealed atypical pneumonia **(b)** chest x-ray evaluation images on day 16 demonstrated infiltrates pneumonia in both lungs which was worse than the ones at the first visit **(c)** Chest x-ray re-evaluation image on the day 24 of hospitalization showed improvement which was no infiltrate in lungs.

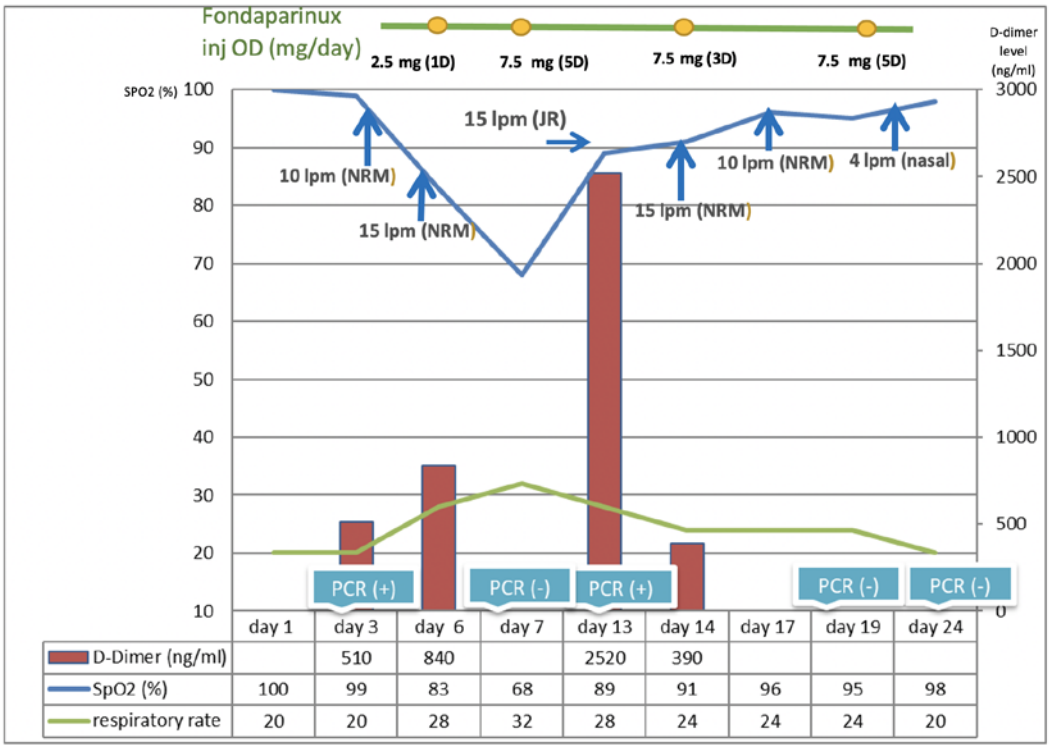

Figure 2. Summary of clinical patient's course of the present case. NRM: non-rebreathing mask. JR: Jackson Rees.

fibrinogen became 596.4 mg/dL, and the D-Dimer level was 0.84 µg/L (normal range <0.5 µg/mL). Fondaparinux at a dose of 2.5 mg was administered subcutaneously for three days as thromboprophylaxis, and a combination of Lopinavir/Ritonavir was given orally every 12 hours. On the next day, his general condition was deteriorating, and respiratory rate was 32 times per minute, oxygen saturation declined to 64%, the patient was put on Jackson Rees with 100% oxygen at a flow rate up to 15 L/min. The oxygen saturation was increased to 91%. The dosage of anticoagulant (Fondaparinux) was increased to 7.5 mg subcutaneously for five days.

On the fourteenth day of hospitalization, the patient's condition gradually improved. Lung auscultation revealed diminished rhonchi all over his chest. The patient began to wear a non-rebreathing oxygen mask with 15 L/min flow, and oxygen saturation was 96%, respiratory rate was 24 times per minute. However, D-Dimer was still increased, 2.52 µg/mL (normal range <0.5 µg/mL), therefore Fondaparinux injection was still given in the same dose of 7.5 mg/day for the next three days, but lopinavir/ritonavir was stopped. D-Dimer was decreased significantly to 0.39 µg/mL (normal range <0.5 µg/mL), and the patient clinical condition markedly improved. On the nineteenth day, respiratory rate was 24 per minute with O2 nasal 4 L/min, and Fondaparinux was given 7.5 mg/day for five days. The patient was discharged from the hospital after 24 days of hospitalization without complaint according to WHO criteria, lung auscultation revealed vesicular sounds symmetrically and the last chest x-ray was taken (**Figure 1**). There was no bleeding and no other adverse events after fondaparinux usage in patient.

DISCUSSION

Case definition of COVID-19 guidelines based on symptoms, laboratory results showed decrease in lymphocytes and white blood cells, chest radiography showing new pulmonary infiltrates, and no improvement in symptoms after 3 days of antibiotics treatment.[5] The confirmation of diagnosis is based on the positive result of RT-PCR on a nasal swab.[6] The most commonly reported symptoms are fever (83%), cough (82%), shortness of breath (31%), myalgia (11%) or fatigue (9%).[5,7] whereas forms with digestive symptoms were anorexia, nausea, diarrhea, abdominal pain or initially non-febrile may be at the forefront.[6] In our patient, digestive symptoms were presented in first day of admission and then followed by respiratory symptoms. Confirmation of COVID-19 diagnosis is based on positive RT-PCR nasal swab result.

Coagulopathy is one of the most significant factor for poor outcome in COVID-19.[8,9] Several putative mechanisms had been suggested, including inflammation-induced hypercoagulability, hypoxia-mediated endothelial dysfunction, and focal-to-extensive microvascular thrombosis.[10,11] Thrombosis incidence in severe COVID-19 cases is triggered by hypoxia through the increase of blood viscosity and hypoxia-induced transcription factor-dependent signaling pathway.[12] Our case reported symptoms of COVID-19-associated coagulopathy during the first two days of hospitalization. Laboratory results revealed a marked increase of D-dimer, CRP, and Fibrinogen. Coagulopathy, which is defined as spontaneous prolongation of prothrombin time by more than 3 seconds or activated partial thromboplastin time (aPTT) by more than 5 seconds, was reported as an independent predictor of thrombotic complications. Hematologic abnormalities noted in COVID-19 coagulopathy include: decreased platelet counts, decreased fibrinogen levels, elevated PT/INR, and elevated D-dimer.[13]

D-dimer is one of the markers that thought to be beneficial for COVID-19 management. Recent studies stated that anticoagulant therapy, especially with low molecular weight heparin (LMWH) and Fondaparinux, appears to give a better outcome in severe COVID-19 patients that meet sepsis-induced coagulopathy criteria or with significantly elevated D-dimer.[9] According to ISTH ad interim guideline, thromboprophylaxis with LMWH or fondaparinux prophylactic dosage should be given to all hospitalized COVID-19 patients with no contraindications (high bleeding risk, active bleeding, platelets <25,000/uL).[14] Fondaparinux is more preferred than unfractionated heparin (UFH) in terms of

bleeding risk and clinical efficacy. A previous study also showed that fondaparinux had anti-inflammatory properties, bringing extra benefit for COVID infection where there is a marked increase of pro-inflammatory cytokines.[15] Several cost-effectiveness analysis studies also show superior efficacy of Fondaparinux compared to other anticoagulants as thrombophrophylaxis.[16,17] Besides the satisfactory clinical result in terms of reduction in thromboembolism and mortality, Fondaparinux should not be used in patients with severe renal impairment.[15] However, if COVID-19 patients are at risks of venous thromboembolism, pulmonary embolism, and renal insufficiency, UFH might act as an alternative anticoagulant.[18]

In our patient, the SIC score was normal which according to the dosage guideline, Fondaparinux should only used in thromboprophylaxis dosage. However, we decided to increase the fondaparinux dose to 7.5 mg/day empirically although it was not recommended by ISTH solely based on the patient's clinical condition (deteriorating pulmonary status with high suspicion of PE), D-dimer level on Day 6, and no contraindication was found in the patient. The physician used recommendations from the ESC/ERS PE guidelines, that highlight the importance of induction or step-up approaches of anticoagulation therapy in all patients suspected for pulmonary embolism (PE) with high or intermediate clinical probability without delay. We used the treatment dosage until the patient was discharged on day 24 from our hospital. We also observed clinical improvement on Day 13 after being given a treatment dosage of Fondaparinux for seven days. This increased dosage therapy was based on a recent consensus as long as no contraindications were found, and closed monitoring was performed due to bleeding risk.[19] According to the IMPROVE bleeding risk score, our patients receive 1 point (low risk of major bleeding) for each component for a maximum score of 30,5. The score is stratified into low (<7 points) and high (≥ 7 points) bleeding risk.[20]

Previous studies reported that the COVID-19 mortality rate was estimated to be 4.3% to 14.6%.[1,21] A recent study that included 449 patients severe COVID-19, in which 99 patients were treated with heparin at prophylactic dosage, showed that anticoagulant therapy was reported to be associated with a better outcome in correlation to mortality rate (40.0% versus 64.2%, P = 0.029).[9] Another study also reported that patients with increased D-dimer levels (6 times the upper limit of normal) treated heparin showcased lower mortality rates.[4] Fibrinogen count is also recommended by ISTH guidance for disseminated intravascular coagulation (DIC) in addition to platelet count, PT, and D-dimers.[14]

Several case reports suggested thrombolysis agents such as tissue plasminogen activator (tPA) in pulmonary embolism cases with refractory hypoxia, where improvement of perfusion / diffuse ratio (P / F) was reported.[22] DIC reported increasing mortality rate, where 71.4% of patients with DIC did not survive during infection compared to one patient (0.6%) who survived. Researchers also noted that there was a significant increase of D-dimer level and PT, and decreased fibrinogen level in non-survivors at day 10 and 14 of treatment.[9]

CONCLUSION

The increasing dose of anticoagulant from thromboprophylaxis to an empirical therapeutic dosage of anticoagulant solely based on clinical condition, D-dimer level, and no contraindication is considered safe and effective anticoagulant treatment for COVID-19-associated coagulopathy. No bleeding risk nor other major side effects have been found in this case.

ACKNOWLEDGMENTS

We thank the healthcare workers at the COVID ward at the Siti Khodijah Hospital, for their assistance in the clinical management of this case. The COVID-19 management team who is working hard day and night after wearing cumbersome personal protective equipment. We declare no conflict of interest.

REFERENCES

1. 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;395:1054–62. https://doi.org/10.1016/S0140-

6736(20)30566-3.
2. WHO. Coronavirus disease situation report. World Health Organization. vol. 19. 2020.
3. Lippi G. D-dimer is associated with severity of Coronavirus disease 2019: A pooled D-dimer is associated with severity of Coronavirus disease 2019: A pooled analysis. 2020:2019–21. https://doi.org/10.1055/s-0040-1709650.
4. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID19 coagulopathy in Caucasian patients. Br J Haematol. 2020. https://doi.org/10.1111/bjh.16749.
5. Adhikari SP, Meng S, Wu Y, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. 2020:1–12.
6. Mezalek ZT, Khibri H, Ammouri W, et al. COVID-19 associated coagulopathy and thrombotic complications 2020. https://doi.org/10.1177/1076029620948137.
7. Ozma MA, Maroufi P, Khodadadi E. Clinical manifestation, diagnosis, prevention and control of SARS-CoV-2 (COVID-19) during the outbreak period 2020;2.
8. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46:1089–98. https://doi.org/10.1007/s00134-020-06062-x.
9. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020:1094–9. https://doi.org/10.1111/jth.14817.
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;2019:1–9. https://doi.org/10.1016/S2665-9913(20)30121-1.
11. García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. Front Immunol. 2020;11:4–8. https://doi.org/10.3389/fimmu.2020.01441.
12. Suresh M V, Balijepalli S, Zhang B, et al. Hypoxia-inducible factor (HIF)-1α promotes inflammation and injury following aspiration-induced lung injury in mice. Shock. 2019;52.
13. 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;18:844–7. https://doi.org/10.1111/jth.14768.
14. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020:1023–6. https://doi.org/10.1111/jth.14810.
15. Turpie AGG. Selective factor Xa inhibition with fondaparinux: From concept to clinical benefit. Eur Hear Journal. 2008;10 (Suppl):1–7. https://doi.org/10.1093/eurheartj/sun003.
16. Bjorvatn A, Kristiansen F. Fondaparinux sodium compared with enoxaparin sodium: a cost-effectiveness analysis. Am J Cardiovasc Drugs. 2005;5:121–30. https://doi.org/10.2165/00129784-200505020-00006.
17. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med. 2002;162:1833–40. https://doi.org/10.1001/archinte.162.16.1833.
18. British Thoracic Society. BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19. Br Thorac Soc. 2020;2:7.
19. Ramacciotti E, Macedo AS, Biagioni RB, et al. Evidence-based practical guidance for the antithrombotic management in patients with Coronavirus disease (COVID-19) in 2020. Clin Appl Thromb. 2020;26. https://doi.org/10.1177/1076029620936350.
20. AlHajri L, Gebran N. The use of low molecular weight heparin for venous thromboembolism prophylaxis in medical patients: How much are we adherent to the guidelines? Open J Intern Med. 2015;5:81–91. https://doi.org/10.4236/ojim.2015.54012.
21. Bi X, Su Z, Yan H, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial fibrinogen to albumin ratio and platelet count prediction of severe illness due to COVID-19 based on an analysis of initial fibrinogen to albumin ratio and platelet count. Platelets. 2020;31:674–9. https://doi.org/10.1080/09537104.2020.1760230.
22. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series 2020:1–4. https://doi.org/10.1111/jth.14828.