Position paper from the Indonesian Society of Thrombosis and Hemostasis (InaSTH), Semarang chapter: Management of coagulopathy in COVID-19

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ABSTRACT

A newly emerging pandemic of coronavirus disease 2019 caused by severe acute respiratory coronavirus 2 is responsible for significant morbidity and mortality worldwide. The ongoing substantial research endeavor to comprehend its associated coagulopathy requires proportional progress on guidance establishment. Current review of evidence and statements on management of coagulopathy and thrombotic complications related to this novel disease is expected to be a precursory formulation for prospective guideline development.

Keywords: Coronavirus disease 2019, SARS-CoV-2, coagulopathy, venous thromboembolism, management

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INTRODUCTION

Severe acute respiratory coronavirus 2 (SARS-CoV-2) is a pathogenic virus of a new infectious disease termed coronavirus disease 2019 (COVID-19) which spreads rapidly leading to a pandemic status declaration by World Health Organization (WHO) within three months of its first identification. Numerous recent studies revealed remarkable relationship between COVID-19 with coagulopathy and thrombotic complications. These findings emphasize the importance of developing management approach to mitigate associated risks and establish an adequate standard care. The Indonesian Society of Thrombosis and Haemostasis (InaSTH), Semarang chapter, compiled an evidence-based clinical practice guideline for the prevention and treatment of coagulopathy and venous thromboembolism in COVID-19. Management of coagulopathy and thrombotic complications will ultimately modify the course of disease, overall prognosis, and reduce mortality.

COVID-19 CLINICAL CLASSIFICATION

Dynamic interplay between viral load and immune-mediated inflammation across the disease course designates three distinct phases of COVID-19 viz: viremia, acute (pneumonia), and severe or recovery phase. Vast array of symptomatology occurring in the first two phases has multisystemic involvement with respiratory system being the most pronounced (Table 1). The absence of severe disease risk factors (i.e. advanced age, underlying noncommunicable diseases, smoking) along with immunocompetence may prevent severe disease progression.

Patients having aforementioned risk factors are prone to clinical deterioration observed in first-to-second phase transition and progression into severe phase. Severe disease (Table 2) is a crucial factor to coagulopathy and thus, mortality rate, as ensuing visceral thrombosis constituted to most life-threatening complications. COVID-19-associated coagulopathies (CACs) manifestations encompasses both systemic (sepsis-induced coagulopathy [SIC] and disseminated intravascular coagulopathy [DIC]) and local (venous thromboembolism [VTE]) responses.

PROPOSED PATHOGENESIS OF COAGULOPATHY

Applying Virchow’s triad by broadly dividing CAC pathomechanisms into three (blood hypercoagulability, endothelial dysfunction, altered blood flow) major components offers a more comprehensive construct for subsequent explanation. Hyperinflammation caused by aberrant immune response holds a central role in CAC pathogenesis. Viral invasion generates tissue injury which in turn induces ineffective and exaggerated innate, mucosal, and adaptive immune responses in severe cases. Significantly disproportionate tissue injury and high cytokine levels exceeding observed...
evidence of inflammation supports the hypothesis of counterproductive pathological inflammation culminating in cytokine storm or cytokine release syndrome. Collectively, presenting inadvertent proinflammatory changes, regardless of the viral intrinsic property, seem to contribute in coagulation activation which degree corresponds to disease severity.11–14

Endothelial cells and its surrounding pericytes are among the major potential targets of SARS-CoV-2 owing to their abundance and ubiquitous characteristics. Resulting endothelial dysfunction may be inflicted directly as the virus gains access to its cellular tropism via receptors and indirectly by cellular activation secondary to inflammation, while pericyte alterations appear to involve only the latter mechanism. It is postulated that endothelioapathy promotes microvasculopathy with following impaired perfusion.15–17

Blood flow of the entire length of vasculature network is affected, hence generating distinct manifestations according to the site of injury. In addition to hypercoagulable state and endothelial injury, low blood flow is also attributed to hypoxemia-induced vasoconstriction and stasis. Microthrombosis is evident especially in lungs and might be systemic (SIC and/or DIC) in critically ill. The occurrence of macrothrombosis in venous (deep vein thrombosis, pulmonary embolism) and arterial system display distinguishing increments of associated clotting factor level, namely thrombin and ultralarge von Willebrand factor multimers, respectively.18,19

### Table 1 Symptomatology in COVID-19

| Common       | Non-specific | Uncommon | Population-specific |
|--------------|--------------|----------|---------------------|
| Fever        | Sore throat  | Anosmia  | Elders and immunosuppressed individuals: absence of fever, reduced alertness, reduced mobility, loss of appetite, delirium |
| Cough        | Nasal congestion | Ageusia | |
| Fatigue      | Headache     |          | |
| Anorexia     | Diarrhoea    |          | |
| Shortness of breath | Nausea, vomiting |          | |
| Myalgia      |              |          | |

### Table 2 Highlights of World Health Organization disease severity classification

|         | Mild                  | Moderate                | Severe                  | Critical                      |
|---------|-----------------------|-------------------------|-------------------------|-------------------------------|
| Case    | Symptomatic patients fulfilling case definition | Exclude viral pneumonia or hypoxia | Imaging may assist in evaluating pulmonary complications | Acute respiratory distress syndrome, sepsis, septic shock |
| Definition |                       |                         |                         |                               |

### COAGULATION PARAMETERS IN COVID-19

D-dimer is a biomarker of fibrinolysis and fibrin turnover commonly utilized in ruling out VTE and establishing DIC, however the lack of standard reference renders reported value to be the sole means of clinical consideration.20 Elevation of this parameter was related to disease severity in scoping review and pooled analysis, although a contradictive result in a nationwide retrospective study led to its omission from developed clinical risk score to predict critical illness.21–23 Increased risk of VTE was also reported in retrospective studies despite varying disease severity and hospitalization status.24–26 Cut-off value of <1.0 µg/ml yielded respective negative predictive value of 90% and 98% for VTE and pulmonary embolism (PE), whereas positive predictive value of VTE for ≥1.0 µg/ml and ≥3 µg/ml cut-off D-dimer levels was 44% and 67%, respectively.27 An evidence from a systematic review found significant association between D-dimer level and COVID-19 mortality risk.27 Optimum cut-off >2.0 µg/ml of D-dimer level on admission to predict mortality needs further confirmatory studies.28

Prothrombin time (PT) represents a universal coagulation test incorporated in DIC score system and VTE management. Quantitative measure of prolonged PT in number of seconds surpassing upper normal limit (10–12 s) or mathematical correction into international normalized ratio (INR) assists in inter-laboratory result reporting standardization.29 Significance of PT difference based on intensive care unit (ICU) admission status was variable in two studies;30,31 contrarily, other studies32–35 indicated PT prolongation on admission and follow-up as disease severity and mortality predictor. Standardized INR value was also found to correlate with disease severity.36,37

Two prominent possible patterns of laboratory data contrasting CAC from other coagulopathy differential diseases are elevation of platelet count and fibrinogen.38 A meta-analysis investigating thrombocytopenia in severe COVID-19 infection concluded low platelet count as an indicator of disease severity (weighted mean difference [WMD] −31 × 10⁹/L) and mortality (WMD −48 × 10⁹/L).39 On the other hand, one single-center case series, which took dynamic platelet changes into account, proposed peak platelet during treatment (average platelet peak 392 × 10⁹/L in severe vs 301 × 10⁹/L in non-severe cases) as an influencing factor in severe cases.40 A plausible explanation for this phenomenon is the active production of platelet from abundant extramedullary megakaryocytes.42 Evidence
pertaining fibrinogen level was less rigorously sought for, but some studies pointed to its association with disease severity both at admission and late in the course of hospitalization.33,36,41–43

All the parameters are listed in order of importance and strength of evidence available. Considering these evidence altogether, we remarked the noteworthy part of timing in laboratory parameters evaluation. A growing body of evidence on laboratory data guides clinical decision-making strategy in COVID-19 management timeline. We recommend periodical evaluation of these parameters for monitoring purpose whenever clinically indicated.

MANAGEMENT OF COAGULOPATHY IN COVID-19

Combination of coagulation parameter patterns exhibited in CAC, particularly moderate thrombocytopenia and elevated fibrinogen level, underpin the postulated distinction of COVID-19 associated DIC from conventional coagulopathy entities judging by its thrombotic tendency. Notwithstanding the evidence of frequent VTE during hospitalization (up to 49%), further analysis revealed that it was mostly contributed by ICU admissions.24 The inherent link of COVID-19 severity and CAC gives a solid basis for initial risk stratification in management algorithm (Figure 1). The use of ≥4 cut-off value for SIC score (Table 3) by International Society on Thrombosis and Haemostasis (ISTH) was validated to screen for potential candidates of pharmacological anticoagulant therapy at expectedly earlier phase preceding overt DIC.44 We propose using the lowest cut-off of D-dimer values among available evidence,34–44 that is higher than 3-fold of the upper limit of normal (ULN).

Assessment of VTE and bleeding risk is imperative in acutely ill and all COVID-19 patients likewise.47,48 Given the multitude of VTE and bleeding risk assessment models (RAMs) available, two preliminary VTE RAM candidates (Padua and IMPROVE) for medical patients and IMPROVE bleeding RAM (Table 4) are chosen because these are most extensively studied and externally validated for VTE.49 IMPROVE VTE RAM (Table 5) is opted for its better performance at reducing pharmacological thromboprophylaxis in medical inpatients.50

Patient clinical conditions, comorbidities, the use of concomitant medications that may affect coagulation status, and invasive procedure plans should be considered in CAC management.51 All hospitalized non-pregnant severe and critically ill COVID-19 patients with low risk of bleeding are recommended to undergo pharmacological prophylaxis unless contraindication exists (e.g. high risk of bleeding, active bleeding, profound thrombocytopenia).52 Mild-moderate COVID-19 medical patients should be assessed for VTE and bleeding risks regardless of hospitalization status (Figure 1).52

Pharmacological profile of low molecular weight heparin (LMWH) extends beyond its role as a potent anticoagulant agent to antiinflammatory effect which would potentially confer additional benefit in severe and critical cases.53 Prophylactic dose of LMWH is the recommended first-line pharmacological agent,54,55 while unfractionated heparin (UFH) is recommended in patients with severe renal impairment (creatinine clearance rate <30 mL/min).

LMWH elimination through kidney excretion poses concern on kidney function evaluation and requires close monitoring accordingly.56 Abnormal PT and activated partial thromboplastin time (APTT) are not regarded as contraindication in

Figure 1 Proposed flowchart of anticoagulant prophylaxis in COVID-19 patients (IMPROVE: International Medical Prevention Registry on Venous Thromboembolism, SIC: sepsis-induced coagulopathy, ULN: upper limit of normal, VTE: venous thromboembolism)

Table 3 ISTH SIC score51

| Parameter | Score 1 | Score 2 |
|-----------|---------|---------|
| Platelet count (× 10⁹/L) | ≥100, <150 | <100 |
| PT ratio | >1.2, ≤1.4 | >1.4 |
| SOFA score | 1 | ≥ 2 |

PT: prothrombin time, SOFA: sequential organ failure assessment (SOFA score is the sum of respiratory, cardiovascular, hepatic, and renal SOFA)
Table 4  IMPROVE bleeding RAM\textsuperscript{54}

| Risk Factors                                         | Points |
|------------------------------------------------------|--------|
| Moderate renal failure (GFR 30-59 mL/min/m\textsuperscript{2}) | 1      |
| Male                                                 | 1      |
| Age 40-84 years old                                  | 1.5    |
| Current cancer                                       | 2      |
| Rheumatic disease                                    | 2      |
| Central venous catheter                              | 2      |
| ICU/CCU admission                                    | 2.5    |
| Severe renal failure (GFR <30 mL/min/m\textsuperscript{2}) | 2.5    |
| Hepatic failure (INR >1.5)                           | 2.5    |
| Age ≥85 years old                                    | 3.5    |
| Platelet <50 × 10\textsuperscript{9}/L               | 4      |
| History of bleeding within 3 months                  | 4      |
| Active gastrointestinal ulcer                        | 4.5    |

The score is interpreted as low (<7) and high (≥7) risk of bleeding (CCU: cardiac care unit, GFR: glomerular filtration rate, ICU: intensive care unit, INR: international normalized ratio).

Table 5  IMPROVE associative VTE RAM\textsuperscript{57}

| Risk Factors | Points |
|--------------|--------|
| Previous VTE | 3      |
| Known thrombophilia | 2    |
| Lower-limb paralysis | 2    |
| Current cancer | 2      |
| Immobilization ≥7 days | 1    |
| ICU/CCU admission | 1      |
| Age >60 years old | 1      |

The score is interpreted as low (0-1), moderate (2-3), and high (≥4) risk of VTE (CCU: cardiac care unit, ICU: intensive care unit, VTE: venous thromboembolism).

Table 6  Anticoagulant doses for CAC prophylaxis and treatment\textsuperscript{48}

| Drugs                  | Prophylaxis | Treatment                              |
|------------------------|-------------|----------------------------------------|
| Enoxaparin             | 40 mg/24 hour SC in BMI >40 kg/m\textsuperscript{2}; 40 mg/12 hour SC | 1 mg/kgBW/12 hour SC or 1.5 mg/kgBW/24 hour SC |
| Nadroparin             | 2850 IU/24 hour SC | 86 IU/kgBW/12 hour SC or 171 IU/kgBW/24 hour SC |
| Fondaparinux           | 2.5 mg/24 hour SC | BW <50 kg: 5 mg/24 hour BW 50-100 kg: 7.5 mg/24 hour BW >100 kg: 10 mg/24 hour SC |
| Unfractionated heparin | 5000 IU/12 hour SC or in obese patients: 5000 IU/8 hour SC | 80 IU/kgBW given IV bolus followed with 18 IU/kgBW/hour IV continuous with normogram |

AKI: acute kidney injury, BMI: body mass index, BW: body weight, GFR: glomerular filtration rate, IV: intravenous, SC: subcutaneous.

CAC treatment.\textsuperscript{56} Non-heparin anticoagulants are recommended in the setting of profound thrombocytopenia or possible heparin-induced thrombocytopenia (HIT).\textsuperscript{29} Direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA) are generally not preferred for thromboprophylaxis during acute phases due to potential drug-drug interactions and comorbidities.\textsuperscript{52,53} Detailed dosing for each anticoagulant as stated by Indonesain Society of Thrombosis and Hemostasis (InaSTH) national guidance on VTE is presented in Table 6.

Severe and critical COVID-19 patients at an increased risk of bleeding are recommended to use mechanical thromboprophylaxis such as intermittent pneumatic compression (IPC) and graduated compression stockings (GCS) until major bleeding risk factors dissipate. IPC device is applied by trained medical staff with or without adjunctive GCS application initially guided by trained medical staff to warrant proper standardization. We do not propose combined pharmacological and mechanical means of thromboprophylaxis technique due to less robust effect of mechanical thromboprophylaxis and therefore, recommend on resuming pharmacological thromboprophylaxis as early as possible.\textsuperscript{6,52,60,61}

Mild and moderate cases, particularly those with fever or gastrointestinal symptoms, require prompt adequate rehydration to prevent dehydration.\textsuperscript{52} Patients with mild-moderate COVID-19 who have an acute illness and a high risk of VTE should be further evaluated for bleeding risk and managed appropriately. Patients who have an otherwise low risk of VTE, whether they are in self-isolation or case confirmation delay, should maintain proper hydration status and regular mobilization.\textsuperscript{67}

DIAGNOSIS AND MANAGEMENT OF VTE IN COVID-19

High index of suspicion should be maintained in typical clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE), hypoxemia out of proportion to respiratory compromise, or acute right ventricular dysfunction as these clues merit further investigations. Such findings are exceptionally practical provided that routine assessment of clinical criteria may be challenging because of infection transmission risk and acute clinical deterioration, besides underlying CAC which obscures D-dimer result interpretation.\textsuperscript{67} Nevertheless, negative finding in clinical risk score and D-dimer allows for limited utility in VTE exclusion.\textsuperscript{62}

Confirmatory imaging studies for DVT and PE are restricted to different sets of criteria with high suspicion on bedside clinical examination as the minimum common ground.\textsuperscript{65,66,60,62} Weighing risk and benefit for imaging exploration is of utmost priority when facing personnel exposure risk and
finite resource availability. Integrating pragmatic point-of-care bedside imaging (i.e. ultrasonography or echocardiography) and standard-of-care imaging (i.e. Doppler ultrasonography, computed tomography pulmonary angiography) under protective conditions could be the ideal approach whenever deemed feasible.

Firstline choice of LMWH for treatment of VTE in CAC is preferred over the usual recommendation of DOAC for acute symptomatic VTE since concurrent administration of drugs affecting P-glycoprotein or cytochrome P450 enzymes and frequent gastrointestinal and renal comorbidities are common in critical setting. Empiric parenteral anticoagulant therapy using therapeutic LMWH dose or dose escalation (i.e. from prophylactic to therapeutic dose) in the absence of contraindication should be considered in suspected cases even when diagnosis establishment is impossible. Bodyweight adjustment for LMWH therapeutic dose (Table 6) and substitution of the anticoagulant agent to UFH in severe renal impairment are recommended. Whilst PE confirmation requirement to determine systemic thrombolytic therapy commencement remains controversial, it is agreed that hypotension or hemodynamic deterioration with supporting echocardiographic finding warrants rescue systemic thrombolytic therapy given there is no high risk of bleeding. Advanced PE treatment modalities like extracorporeal membrane oxygenation (ECMO) in conjunction with surgical embolectomy or catheter-directed treatment is recommended for critical cases with refractory circulatory collapse or cardiac arrest.

PERSPECTIVES AND CONCLUDING REMARKS

In this perspective manuscript, we reviewed data from coagulation abnormalities that occur in association with COVID-19 and thrombosis complications likely to arise. This peer group guidance helps clinicians to engage with multidisciplinary COVID-19 patient care in both non-ICU and ICU settings. Our considerations are to provide patients with severe or critically ill COVID-19 patients and sepsis-induced coagulopathy with appropriate thromboprophylaxis while stratifying them who present with mild to moderate disease in more selected cases whom anticoagulant may be indicated. The risk must always be evaluated regularly and adjusted along the disease course while balancing between the risks of thrombosis and bleeding associated with the decision to start anticoagulation.

AUTHOR CONTRIBUTIONS

Concept and design: E.A.P., B.S., and D.S.; literature research: R.M.N., D.R., S. M.L.T., and C.S.; editing: R.M.N. and D.R.

CONFLICT OF INTERESTS

The authors have nothing to disclose.

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REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) pandemic [Internet]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Helms J, Tacquard C, Severac E, 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. Available from: link.springer.com/10.1007/s00134-020-06062-x
3. Klok FA, Kruip MIHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145. Available from: /pmc/articles/PMC7146714/?report=abstract
4. Wichmann D, Sperhake J-P, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med. 2020; Available from: /pmc/articles/PMC7240772/?report=abstract
5. Cao W, Li T. COVID-19: towards understanding of pathogenesis. Cell Res. 2020;30(5):367–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7186532/
6. World Health Organization. Clinical management of COVID-19: Interim guidance. 2020. WHO/2019-nCoV/clinical/2020.5
7. Xiong M, Liang X, Wei YD. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Br J Haematol. 2020;189(6):1050–2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7264726/
8. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020; Available from: /pmc/articles/PMC7177098/?report=abstract
9. Khan IH, Savarimuthu S, Leung MST, Harky A. The need to manage the risk of thromboembolism in COVID-19 patients. J Vasc Surg. 2020; Available from: /pmc/articles/PMC7224653/?report=abstract
10. Byrnes JR, Wolberg AS. New findings on venous thrombogenesis. Hemostasis. 2017;37(1):25–35. Available from: /pmc/articles/PMC5680619/?report=abstract
11. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: Current State of the Science. Immunity. 2020;52(6):910. Available from: /pmc/articles/PMC7200337/?report=abstract
12. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020;50(1):54–67. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7220959/

13. Lingswaran M, Goyal T, Ghosh R, Suri S, Mitra P, Misra S, et al. Inflammation, immunity and immuno-nigenetics in COVID-19: A narrative review. Indian J Clin Biochem. 2020;1:1. Available from: /pmc/articles/PMC7275846/report=abstract

14. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033–40. Available from: /pmc/articles/PMC7223827/report=abstract

15. Huertas A, Montani D, Savale L, Pichon J, Tu L, Parent F, et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? Eur Respir J. 2020; Available from: http://www.ncbi.nlm.nih.gov/pmc/pmid/32554538

16. Cardot-Leccia N, Hubiche T, Dellamonica J, Burel-Vandenbos F, Passeron T. Pericyte alteration sheds light on micro-vascularopathy in COVID-19 infection. Intensive Care Med. 2020;1:1. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7291173/

17. Tibibrica E, De Lorenzo A. Importance of the evaluation of systemic microvascular flow and reactive; pin critically ill patients with coronavirus disease 2019 — COVID-19. Microvasc Res. 2020;131:104028. Available from: /pmc/articles/PMC7288018/report=abstract

18. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. Crit Care Med. 2020;

19. Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med. 2020;1:1. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7225398/

20. Johnson ED, Schell JG, Rodgers GM. The D-dimer assay. Am J Hematol. 2019;94(9):833–9. Available from: /pmc/articles/PMC7286786/report=abstract

21. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk and suspected pulmonary embolism. Rosell A. D-dimer in patients infected with COVID-19 and suspected pulmonary embolism. Eur Respir J. 2020; Available from: https://pubmed.ncbi.nlm.nih.gov/32350161/

22. Iba T, Levy JH, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. Crit Care Med. 2020;

23. 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.

24. Fargyny H, Townsend L, Ni Cheallaghaí B, Bergin C, MacManus MC, Sweeney M, et al. COVID-19 and hypercoagu- lopathy in Caucasian patients. Br J Haematol. 2020; Available from: /pmc/articles/PMC7264579/report=abstract

25. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, et al. D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. Biomed Res Int. 2020; Available from: /pmc/articles/PMC7301188/report=abstract

26. Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med. 2020;1:1. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7225398/

27. Li D, Yang J, Wang X, Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9. Available from: /pmc/articles/PMC7042881/report=abstract

28. Zou Y, Guo H, Zhang Z, Liu Y, Wang J, et al. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. Biosci Trends. 2020; Available from: https://pubmed.ncbi.nlm.nih.gov/32305616/

29. Li D, Yang J, Wang X, Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9. Available from: /pmc/articles/PMC7042881/report=abstract

30. 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.

31. Fargyny H, Townsend L, Ni Cheallaghaí B, Bergin C, MacManus MC, Sweeney M, et al. COVID-19 and hypercoagu- lopathy in Caucasian patients. Br J Haematol. 2020; Available from: /pmc/articles/PMC7264579/report=abstract

32. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, et al. D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. Biomed Res Int. 2020; Available from: /pmc/articles/PMC7301188/report=abstract

33. Zou Y, Guo H, Zhang Z, Liu Y, Wang J, et al. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. Biosci Trends. 2020; Available from: https://pubmed.ncbi.nlm.nih.gov/32305616/

34. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03077-0

35. Li D, Yang J, Wang X, Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9. Available from: /pmc/articles/PMC7042881/report=abstract

36. Zou Y, Guo H, Zhang Z, Liu Y, Wang J, et al. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. Biosci Trends. 2020; Available from: https://pubmed.ncbi.nlm.nih.gov/32305616/

37. Shahriarirad R, Khodamoradi Z, Erfani A, Hosseinipour H, Ramijkar B, Emami Y, et al. Epidemiological and clinical features of 2019 novel coronavirus diseases (COVID-19) in the South of Iran. BMC Infect Dis. 2020;20:427. Available from: https://doi.org/10.1186/s12879-020-05128-x

38. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03077-0

39. Li D, Yang J, Wang X, Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9. Available from: /pmc/articles/PMC7042881/report=abstract

40. Qu R, Ling Y, Zhang Y, Wei L, Chen X, Li X, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with Coronavirus Disease-19. J Med Virol. 2020;25767. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25767

41. Bi X, Su Z, Yan H, Du J, Wang J, Chen L, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count. Platelets. 2020;1–6.

42. Specieza I, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19 Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thromb Haemost. 2020;120(6):998–1000.

43. 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 Virol. 2020;

44. 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;18(5). Available from: https://pubmed.ncbi.nlm.nih.gov/32220112/

45. Rico-Mesa JS, Rosas D, Ahmadian-Tehrani A, White A, Anderson AS, Chilton R. The role of anticoagulation in COVID-19-induced hypercoagulability. Curr Cardiol Rep. 2020;22(7):53. Available from: http://link.springer.com/10.1007/s11886-020-01328-8
46. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9(1):727–32. Available from: pmc/articles/PMC7103533/report=abstract

47. Bikdeli B, Madhavan MV, Jimenez D, Chuchu T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(23):2950–73. Available from: https://pubmed.ncbi.nlm.nih.gov/32311448/

48. Spyropoulos AC, Levy JH, Agno J, Connors JM, Hunt BJ, Iba T, et al. Scientific and standardization committee communication: Clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(5):1023–6. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14810

49. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv. 2018;2(22):3198–225. Available from: pmc/articles/PMC6258910/report=abstract

50. Raifzadeh R, Turgeon RD, Batterink J, Su V, Lau A. Characterization of venous thromboembolism risk in medical inpatients using different clinical risk assessment models. Can J Hosp Pharm. 2016;69(6):454–9. Available from: pmc/articles/PMC5242277/report=abstract

51. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(23):2950–73. Available from: https://pubmed.ncbi.nlm.nih.gov/32311448/

52. Zhai Z, Li C, Chen Y, Gerotziafas G, Zhang Z, Wan J, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17(11):1989–94. Available from: https://pubmed.ncbi.nlm.nih.gov/31410983/

53. Shi C, Wang C, Wang H, Yang C, Cai FEI, Zeng F, et al. The potential of low molecular weight heparin to mitigate cytokine storm in severe covid-19 patients: a retrospective clinical study. medRxiv. 2020:2020.03.28.20046144. Available from: http://medrxiv.org/content/early/2020/03/28/20046144.abstract

54. Decousus H, Tapson VF, Bergmann JF, Chong BH, Froehlich JB, Kakkar AK, et al. Factors at admission associated with bleeding risk in medical patients: Findings from the improve investigators. Chest. 2011;139(1):69–79. Available from: https://pubmed.ncbi.nlm.nih.gov/20453069/