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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.[1] Numerous recent studies revealed remarkable relationship between COVID-19 with coagulopathy and thrombotic complications.[2–4] 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.[5,6]

Patients having aforementioned risk factors are prone to clinical deterioration observed in first-to-second phase transition and progression into severe phase.[5] Severe disease (Table 2) is a crucial factor to coagulopathy and thus, mortality rate, as ensuing visceral thrombosis constituted to most life-threatening complications.[6–8] COVID-19-associated coagulopathies (CACs) manifestations encompasses both systemic (sepsis-induced coagulopathy [SIC] and disseminated intravascular coagulopathy [DIC]) and local (venous thromboembolism [VTE]) responses.[9]

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.[10] Hyperinflammation caused by aberrant immune response holds a central role in CAC pathogenesis. Viral invasion generates tissure 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

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Table 1 Symptomatology in COVID-19[6]

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[6]

Mild	Symptomatic patients fulfilling case definition	Exclude viral pneumonia or hypoxia
Moderate	Clinical signs of non-severe pneumonia	Imaging may assist in evaluating pulmonary complications
Severe	Clinical signs of pneumonia	Imaging may assist in evaluating pulmonary complications
Critical	Acute respiratory distress syndrome, sepsis, septic shock	

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 endotheliopathy 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]

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.[24] 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 studies[32–35] 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] -31×10^9/L) and mortality (WMD -48×10^9/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 392×10^9/L in severe vs 301×10^9/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.[12] 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.[21] 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,[44–46] that is higher than 3-fold of the upper limit of normal (ULN).

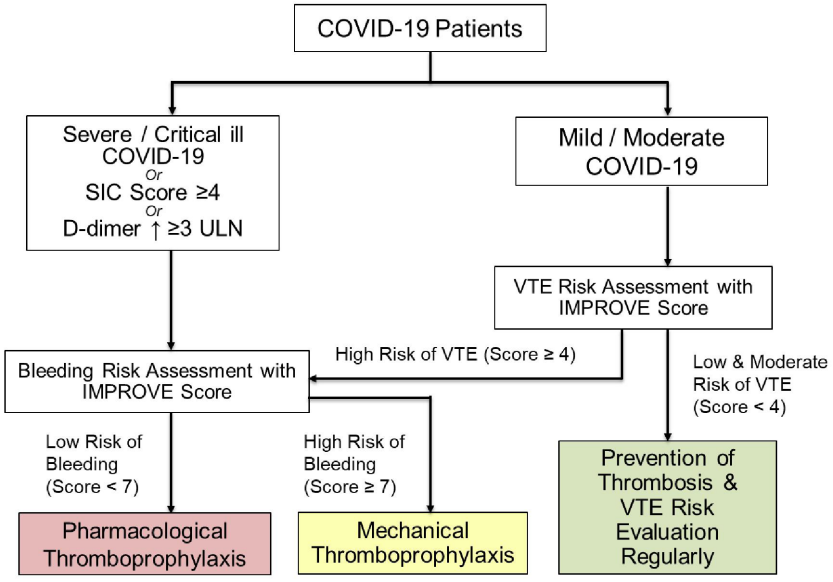

Figure 1 Proposed flowchart of anticoagulant prophylaxis in COVID-19 patients (IMPROVE: International Medical Prevention Registry on Venous Thromboembolism, SIC: sepsis-induced coagulopathy, ULN: upper limit of normal, VTE: venous thromboembolism)

Table 3 **ISTH SIC score**[51]

Parameter	Score 1	Score 2
Platelet count (× 10^9/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)

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.[52] 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).[53] 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.[55] Prophylactic dose of LMWH is the recommended first-line pharmacological agent[6,52,56] while unfractionated heparin (UFH) is recommended[52] 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.[58] Abnormal PT and activated partial thromboplastin time (APTT) are not regarded as contraindication in

Table 4 IMPROVE bleeding RAM[54]

Risk Factors	Points
Moderate renal failure (GFR 30-59 mL/min/m^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^2)	2.5
Hepatic failure (INR >1.5)	2.5
Age ≥85 years old	3.5
Platelet <50 × 10^9/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[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[58]

Drugs	Prophylaxis	Treatment
Enoxaparin	40 mg/24 hour SC in BMI >40 kg/m^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 (if GFR <30 mL/min or AKI)	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.[56] Non-heparin anticoagulants are recommended in the setting of profound thrombocytopenia or possible heparin-induced thrombocytopenia (HIT).[59] 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.[52] Detailed dosing for each anticoagulant as stated by Indonesian 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.[6,52,60,61]

Mild and moderate cases, particularly those with fever or gastrointestinal symptoms, require prompt adequate rehydration to prevent dehydration.[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.[47]

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.[47] Nevertheless, negative finding in clinical risk score and D-dimer allows for limited utility in VTE exclusion.[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.[47,48,52,61,62] 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.[48]

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.[48,52,61] 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.[48,52] Bodyweight adjustment for LMWH therapeutic dose (Table 6) and substitution of the anticoagulant agent to UFH in severe renal impairment are recommended.[52] 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.[52,61] 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.[52]

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

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