Introduction

COVID-19 is a new type of pneumonia that began it spreads since December 2019, for the first time in Wuhan, China, caused by beta-coronavirus, Severe Acute Respiratory System Coronavirus 2 (SARS-CoV-2). Beta-coronaviruses also previously caused SARS and Middle East Respiratory Syndrome Corona Virus (MERS-CoV) that became outbreaks in 2003 and 2012, respectively.1
The clinical features of COVID-19 are divided into asymptomatic, mild symptoms (fever, cough, and fatigue), and severe symptoms (acute respiratory distress syndrome, metabolic acidosis, sepsis, and coagulopathy including disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE)). Organ dysfunction and coagulopathy were associated with high mortality in COVID-19 patients, 11.0% and 14.6%, respectively. Patients with severe COVID-19 infection are at high risk for developing VTE because they usually became immobilized and in a state of acute inflammation that leading to hypercoagulation. On the other hand, DIC is one of the most common complications of sepsis that usually happen in severe pneumonia case. In this systematic review, we will evaluate current articles related to coagulopathy and COVID-19.

Search Strategies

A comprehensive search of literature was conducted in the PubMed (NIH) and EMBASE databases (January 2019 to March 2020) using keyword combinations of the medical subject headings (MeSH) of ‘coagulopathy’, ‘disseminated intravascular coagulation’, ‘consumeptive coagulopathy’, ‘COVID-19’, ‘coronavirus disease 2019’, and ‘SARS-CoV-2’. Relevant reference lists were also manually searched.

Problems of COVID-19 Patients with Coagulopathy

Zhou et al. found risk factors of mortality in COVID-19 patients are older age, high Sequential Organ Failure Assessment (SOFA) score, and D-dimer greater than 1 μg/mL on admission (81% of non-survivor had D-dimer levels of > 1 μg/mL on admission). They also found that D-dimer levels and prothrombin time (PT) were associated with death. Patients with a high level of D-dimer and sepsis associated with 28-day mortality in the emergency department. Tang et al. also revealed that non-survivors had higher D-dimer and fibrinogen degradation product (FDP) levels, longer PT and activated partial thromboplastin time (APTT) than survivors on admission, so conventional coagulation tests in COVID-19 was associated with prognosis.

Mechanism of Coagulopathy in COVID-19

DIC is most commonly found in death with COVID-19. Sepsis-induced DIC is associated with organ dysfunction as in the patient with viral infection as in COVID-19 infection. In sepsis, the system of blood coagulation is shifted toward the hypercoagulable state which is acute inflammatory mediator induced tissue factor expression in CD14+ monocyte and endothelial cells. Antithrombin also decreased in sepsis because of consumption by the formation of thrombin-antithrombin complexes and degradation by proteases that released from activated neutrophil, so free thrombin circulated and activate platelet and fibrinolysis pathway, but the level of fibrinolytic activity is too low to counteract the systemic deposition of fibrin clots in SIRS. High level of plasminogen activator inhibitor-1 (PAI-1) that originates from endothelial cells also has a big role in predicting multiple organ dysfunction in sepsis-induced DIC. D-dimer and FDP is elevated in all patients who were died in the late stages of COVID-19. Risk of VTE also higher in severe COVID-19 because of immobility and long-term bed rest. On the other hand, severe COVID-19 cause hypoxia that increased risk of thrombosis because of increased blood viscosity and hypoxia-inducible transcription factor-dependent signaling pathways.

Diagnosis of Coagulopathy in COVID-19

The earlier phase of sepsis-induced DIC can be detected using International Society on Thrombosis and Hemostasis new scoring system, named “sepsis-induced coagulopathy” (SIC) (Figure 1). Tang et al. started to use this scoring when the patients classified as severe COVID-19 that define by meeting any one of these: respiratory rate ≥ 30 breaths/minute, arterial oxygen
saturation ≤ 93% at rest, and PaO2/FiO2 ≤ 300 mmHg.\textsuperscript{13} Beside SIC, D-dimer and PT also measure at the time the patient classified as severe COVID-19. In the previous study, they used ISTH diagnostic criteria for DIC (Figure 2) and found that 71.4% non-survivor and 0.6% survivor matched in ≥ 5 points or the grade of overt-DIC.\textsuperscript{16} DIC was detected in median time of 4 days after admission to hospital.\textsuperscript{8} Platelet count may not be sensitive to detect coagulopathy in COVID-19, due to the reactively increased thrombopoietin following pulmonary inflammation.\textsuperscript{17} ISTH recommended to measure fibrinogen level besides of D-dimer, PT, and platelet count in the guidance of DIC, this recommendation can be used in COVID-19 infection.\textsuperscript{18} Tang et al. found that D-dimer and PT level increased, and fibrinogen level decreased at days 10 and 14 in non-survivors.\textsuperscript{8} Other researcher noted that for early identification of severe COVID-19 cases, monitoring the level of D-dimer and FDP can be helpful as their levels higher in severe COVID-19 infections than in milder forms.\textsuperscript{10}

![Figure 1. International Society on Thrombosis and Hemostasis (ISTH) diagnostic algorithm for the diagnosis of overt DIC\textsuperscript{16} cited from Taylor J, et al. Thromb Haemost. 2001;86(5):1327–30.]

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (x10\textsuperscript{9}/L)</td>
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<td>100-150</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&lt;100</td>
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<tr>
<td>PT-INR</td>
<td>1</td>
<td>1.2-1.4</td>
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<td>SOFA score</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Total score for SIC</td>
<td>≥ 4</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of Coagulopathy in COVID-19

In Tang and colleagues’ study that included 449 patients with severe COVID-19 infection, 99 of them were treated with heparin, mainly low molecular weight heparin (LMWH) for 7 days at prophylactic doses. The result was no difference in 28-day mortality between patients who received LMWH and those who did not. So, if there isn’t any contraindication (active bleeding and platelet count less than 25x10^9/L), prophylactic doses LMWH should be given in all patient including non-critical patients who required hospital admission for COVID-19 infection. In those with SIC score ≥ 4 and D-dimer > six-fold of the upper limit of normal, anticoagulant therapy (LMWH) associated with decreased mortality.13 Besides that, LMWH also has other benefits such as against VTE in critically ill patients and its anti-inflammatory properties in COVID-19 infection where pro-inflammatory cytokines raised.19–21 All immobilized and severely ill patients with COVID-19 should receive thromboprophylaxis unless there is any contraindication (for CrCl > 30: LMWH or Fondaparinux subcutaneous (s.c) according to the license, for CrCl < 30 or acute kidney injury (AKI): unfractionated heparin 5000 unit s.c twice daily or three times daily or dose-reduced LMWH). ISTH has an algorithm to manage coagulopathy in COVID-19 based on simple laboratory markers (D-dimer, PT, platelet count, and fibrinogen). (Figure 2)18

Liu et al. suggest the use of anticoagulant in the early sign of elevated D-dimer in COVID-19 patients, they found that Dipyridamole (DIP), an antiplatelet, has the effectiveness to prevent hypercoagulability if given early in severe COVID-19 infection. It also has other benefits in COVID-19 infection such as broad spectrum of antiviral,22 anti-inflammatory effect,23 and anti-fibrotic effect.24 DIP prevent the increased of D-dimer levels and increased platelet and leukocyte count.22 Recent data showed data immune-thrombosis played a big role other than DIC.25 In order to that modulation of inflammation could make a difference. Steroid and anti IL-6 could give several benefits in particular conditions.26–28 By giving tocilizumab, anti IL-6 blocker for instance could improve inflammation parameters.29 Several parameters D-Dimer and CRP had been proved as several severity markers in COVID-19.30 These showed interaction between inflammation and thrombosis. Responses of inflammation to COVID-19 also influence by gut microbiota.31 By modulating angiotensin-converting enzyme 2 may give benefit.32 Others part also should concomitantly be controlled for instances the cardiovascular risk factors which also played extensive roles in COVID-19.33,34 People have these cardiovascular risk factors should continue their medications35–37, because in some particular conditions could give benefits to survival of COVID-19 when got infected.

* The list of markers is given in the decreasing order of importance
** Performing fibrinogen assays may not be feasible in many laboratories but monitoring the levels can be helpful after patient admission
*** Although a specific cut-off cannot be defined, a 3 to 4 folds increase in D-dimer values may be considered significant

Conclusion
Coagulopathy plays a big role in determine the prognosis of COVID-19 patients, DIC mostly appeared in died patients. D-dimer levels and FDP can be used to evaluate prognosis. In the guidance for DIC, D-dimer level, PT, platelet count, and fibrinogen measurement are recommended by ISTH and can be used in COVID-19 patients. LMWH in prophylactic doses should be given in all patient including non-critical patients who required hospital admission for COVID-19 infection if they didn’t have any contraindications. Treatment with LMWH gave some benefits in COVID-19 patients, especially reduced mortality in patients with SIC score ≥ 4 and D-dimer levels >six-fold of the upper limit of normal.

Authorship contributions
Concept: A.K; Design: S.W.; Data Collection or Processing: S.W., A.K.; Analysis or Interpretation: S.W., A.K.; Literature search: S.W., A.K., Writing: S.W, A.K.

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