# HYPER-COAGULATION AND THE USED OF ANTICOAGULANT FOR PATIENT WITH COVID-19

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***ABSTRACT***

*Coronavirus SARS-CoV-2 (COVID-19) infection has become a global infection with high mortality and morbidity rate. The pathophysiology of COVID-19 has not yet clear but associated with increasing proinflammatory cytokines and chemokines that leads to cytokine storm. Cytokine storm leads to increasing coagulation that defined by increasing D-dimer, Prothrombin Time (PT), and activated partial thromboplastin time (aPTT). The use of anticoagulant in patient with COVID-19 decrease the mortality rate and become one of the recommended therapy.*

***Keyword****: COVID-19, Hyper-coagulation, Anticoagulant*

**ABSTRAK**

Virus korona SARS-CoV-2 (COVID-19) telah menjadi infeksi global dengan angka mortalitas dan morbiditas yang tinggi. Patofisiologi dari COVID-19 ini masih belum jelas dan dikaitkan dengan peningkatan sitokin dan kemokin inflamasi yang menyebabkan badai sitokin. Badai sitokin ini menyebabkan peningkatan koagulasi dan ditandai dengan peningkatan D-dimer, *Prothrombin Time* (PT), dan *activated partial thromboplastin time* (aPTT). Pemberian antikoagulan pada pasien COVID-19 terbukti dapat mengurangi angka mortalitas sehingga menjadi salah satu terapi yang dianjurkan.

**Kata Kunci***: COVID-19, Hyper-coagulation, Anticoagulan*

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## INTRODUCTION

Coronaviruses (CoVs) are enveloped RNA viruses with club-like spikes, exceptionally large RNA genome, and has different replication strategy compare to other viruses as its characters. Coronaviruses affects to mammals and poultry including humans and cause many types of sign and symptoms. Types of coronaviruses that have caused endemic to humans are *Severe Acute Respiratory Syndrome coronavirus* (SARS-CoV) and

*Middle Eastern Respiratory Syndrome Coronavirus* (MERS-CoV).[1]

Coronaviruses SARS-CoV-2 is the caused of COVID-19, which has become a global infection with high mortality and morbidity rates. In Indonesia, the first finding happened on March 2, 2020 and increase continuously while spreading throughout Indonesia with mortality rate around 6,7% of all positive cases.[2]

COVID-19 could be associated with higher mortality rate in patient with comorbidity as hypertension, diabetes, coronary heart disease, tumour, chronic obstructive pulmonary disease, chronic kidney disease, tuberculosis, asthma, and hepatitis B.[3-5]

**Table 1 : Reported outcomes among COVID-19 patients of all ages, by hospitalization status, underlying health condition, and risk factor for severe outcome from respiratory infection — United States, February 12–March 28, 2020.[5]**

| Underlying health condition/Risk factor for severe outcomes from respiratory infection (no., % with condition) | No. (%) | | | |
|---|---|---|---|---|
| | Not hospitalized | Hospitalized, non-ICU | ICU admission | Hospitalization status unknown |
| **Total with case report form (N = 74,439)** | **12,217** | **5,285** | **1,069** | **55,868** |
| **Missing or unknown status for all conditions (67,277)** | **7,074** | **4,248** | **612** | **55,343** |
| **Total with completed information (7,162)** | **5,143** | **1,037** | **457** | **525** |
| One or more conditions (2,692, 37.6%) | 1,388 (27) | 732 (71) | 358 (78) | 214 (41) |
| Diabetes mellitus (784, 10.9%) | 331 (6) | 251 (24) | 148 (32) | 54 (10) |
| Chronic lung disease* (656, 9.2%) | 363 (7) | 152 (15) | 94 (21) | 47 (9) |
| Cardiovascular disease (647, 9.0%) | 239 (5) | 242 (23) | 132 (29) | 34 (6) |
| Immunocompromised condition (264, 3.7%) | 141 (3) | 63 (6) | 41 (9) | 19 (4) |
| Chronic renal disease (213, 3.0%) | 51 (1) | 95 (9) | 56 (12) | 11 (2) |
| Pregnancy (143, 2.0%) | 72 (1) | 31 (3) | 4 (1) | 36 (7) |
| Neurologic disorder, neurodevelopmental, intellectual disability (52, 0.7%)† | 17 (0.3) | 25 (2) | 7 (2) | 3 (1) |
| Chronic liver disease (41, 0.6%) | 24 (1) | 9 (1) | 7 (2) | 1 (0.2) |
| Other chronic disease (1,182, 16.5%)§ | 583 (11) | 359 (35) | 170 (37) | 70 (13) |
| Former smoker (165, 2.3%) | 80 (2) | 45 (4) | 33 (7) | 7 (1) |
| Current smoker (96, 1.3%) | 61 (1) | 22 (2) | 5 (1) | 8 (2) |
| None of the above conditions¶ (4,470, 62.4%) | 3,755 (73) | 305 (29) | 99 (22) | 311 (59) |

US CDC shown that some underlying disease are more at risk to Intensive Care Unit (ICU) admission as diabetes mellitus, cardiovascular disease, chronic lung disease, and chronic kidney disease.[3]

Patient with COVID-19 frequently show symptoms as fever, cough, sore throat, myalgia, diarrhoea, and severe pneumonia with tachypnoea (≥30 breaths per min), oxygen saturation ≤93% at rest, or PaO2/FiO2 ratio <300 mm Hg) with complication that can be associated with higher mortality rate including pneumonia, septic, and Acute Respiratory Distress Syndrome (ARDS).[4-9]

**Pathophysiology of COVID-19**

Pathophysiology of COVID-19 related ARDS has similarities to other pneumonia. There is overproduction of early response proinflammatory cytokines including tumour necrosis factor (TNF), interleukin (IL)-6, and IL-1β that resulted in cytokine storm. Cytokine storm related to

the risk of vascular hyperpermeability, multiorgan failure, and eventually death.[10]

**Cytokine Storm Mechanism in COVID-19**

In-vitro cells study shown that at early stage of COVID-19 there is delayed release of cytokines and chemokines in respiratory epithelial cells, dendritic cells, and macrophages. Later, the cells secrete low levels of antiviral factors interferons (IFNs) and high levels of proinflammatory cytokines (IL-6, IL-1β, and tumour necrosis factor (TNF) and chemokines (C-C motif chemokine ligand (CCL)-2, CCL-3, and CCl-5). Coronavirus infected airway epithelial cells, THP-1 cells (monocyte cell), human peripheral blood monocyte-derived macrophages, and dendritic cells that resulted in delayed but elevated levels of proinflammatory cytokines and chemokines.[11-13]

Patient with severe symptoms had significantly higher serum cytokines and chemokines levels than patient with mild to moderate symptom. This phenomenon are prompt by substantial number of neutrophils and monocytes in lung tissues and peripheral blood and lead to lung pathology.[14,15]

Patient with COVID-19 shown increasing levels cytokines as IL-1β, IFN-γ , IP-10, and monocyte chemoattractant protein 1 (MCP-1).[4] This cytokines trigger the reaction of T-helper type 1 (TH1) cells.[16] There is also increasing numbers of cytokines as IL-4 and IL-10 which inhibit the inflammatory response that secreted from TH2 cells. The serum levels of cytokines IL-2 and IL-6 in patient with COVID-19 influence the severity of the disease with higher levels mean more critically ill patients.[7] Some study also shown elevated serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF- α in patient with COVID-19 that treated in ICU compared to the one in general unit. The increasing cytokines are positively correlated with disease severity.[4]

More than 70% of COVID-19 related pneumonia patients required mechanical ventilation and around 70% suffered ARDS.[17] In patient with ARDS there are significantly increasing serum levels of cytokine that positively correlated with development and progression of the disease.[18] Increasing cytokine that cause cytokine storm also play a role that determined multiple organs failure. [19]

Several therapeutic approaches have been used to deal with cytokine storms in COVID-19 including IFN-λ, corticosteroids, Intravenous Immunoglobulin (IVIG), IL-1 antagonists, IL-6 antagonists, TNF blockers, IFN-αβ, chloroquine, and so on.[13]

**Hyper-coagulation in COVID-19**

Infection triggers a responses that lead to coagulation. Coagulation itself limits the invasiveness of the pathogen.[20] Coagulation pathway leads to overproduction of proinflammatory cytokines. Thrombin promotes clot formation by activating platelets and converting fibrinogen to fibrin. Thrombin also stimulates inflammation through proteinase-activated receptors (PARs). Thrombin production is managed by negative feedback loops and anticoagulants such as antithrombin III, tissue factor pathway inhibitor, and the protein C system.[21] These three anticoagulant mechanism impaired during the inflammation then imbalance of thrombin production and consumption occurs. [10]

The imbalance between procoagulant and anticoagulant induced the development of micro-thrombosis, disseminated intravascular coagulation (DIC), and multiorgan failure.[22] In patient with COVID-19, coagulopathy defined as increasing prothrombin time (PT) > 3 seconds, increasing activated partial thromboplastin time (aPTT) > 5 seconds, and increasing D-dimer > 1.0 mcg/mL as main indicator. Patient COVID-19 with severe pneumonia and associated with increasing mortality shown an elevated D-dimer, increased PT, and elevation in IL-6. [23] Increased IL-6 levels itself correlated with increased fibrinogen levels which increase fibrin and further clot promotion.[24]

**Anticoagulant in Patient with COVID-19**

Anticoagulant such as heparin decrease the mortality rate. Patient COVID-19 patient in Wuhan with Sepsis Induces Coagulopathy (SIC) score ≥ 4 or increased D-dimer more than 6 fold considered as more severe.[22,25] Low molecular weight heparin (LMWH) therapy for at least 7 days show decrease mortality by 20% from 52,4% to 32,8%.[25] In New York, the anticoagulant therapy affect to the mortality of patient COVID-19 with 22.5% with median survival of 21 days compared with mortality rate of 22.8% with median survival of 14 days in patient without anticoagulant therapy.[26]

**Table 2. ISTH SIC scoring system[10]**

| Item | Score | Range |
|---|---|---|
| Platelet count (×10$^9$/L) | 1 | 100-150 |
| | 2 | <100 |
| PT-INR | 1 | 1.2-1.4 |
| | 2 | >1.4 |
| SOFA score | 1 | 1 |
| | 2 | ≥2 |
| Total score for SIC | ≥4 | |

ARDS considered one of many complication of COVID-19 with highest mortality rate. This lung coagulopathy are established by localized tissue factor-mediated thrombin generation and decreased bronchoalveolar plasminogen activator-mediated fibrinolysis.[28,29] Treatment using LMWH within 7 days onset of ARDS reduce the mortality up to 35% % and the risk of 28 days mortality by around 37%.[30]

Treatment with systemic anticoagulant also shown significantly increased PT, aPTT, lactate dehydrogenase, ferritin, C reactive protein, and D-dimer compared to those who did not receive the treatment. The mortality of patient also associated with the duration of the anticoagulant treatment[26]. Low molecular heparin considered as a potential and effective anticoagulant in COVID-19 patient with hyper-coagulation.

However, Heparin administration itself come with complication as bleeding events. Major bleeding define as 1) decreasing Haemoglobin (Hb) < 7 g/dL and required blood cell transfusion, 2) given minimal two units red blood cell transfusion within 2 days or 3) diagnose for internal bleeding including intracranial haemorrhage, hematemesis, melena, peptic ulcer with haemorrhage, colon, rectal, or anal haemorrhage, haematuria, ocular haemorrhage, and acute haemorrhagic gastritis. Among patient with anticoagulant therapy 3% individuals had bleeding event compared with 1,9% patient with bleeding event without anticoagulant therapy.[26]

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