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**Review Article**

# A Critical Review: Blood and Clinical Hematology Disorders in Covid-19

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**ABSTRACT**
Severe acute respiratory coronavirus 2 (SARS–CoV– 2) is a pathogen virus from the infectious Coronavirus disease which was reported first in Wuhan, Hubei Province, by the People's Republic of China to WHO on December 31st, 2019. Due to its rapid and global spread that infected about 2 million people with mortality rate of more than 150.000, it was declared a pandemic on March 12th, 2020. The opening speech of the WHO Director General on the media about COVID-19 was carried out on March 18th, 2020, and it was stated that the virus needs rapid and large scale tests. Therefore, Solidarity Test was chosen because it may help reduce 80% of the time that is needed in a research rather than random clinical check that requires longer time. Based on the data from several countries, it was found that COVID-19 is a systemic infection disease that brings significant effect to hematopoietic systems and hemostasis such as low ALC and high LDH which was found in many ICU patients. Lymphopenia is considered to be a cardinal laboratory finding with potentials of being a prognosis. Blood disorders in COVID-19 are divided are divided into two, namely malignant and non-malignant. However, this study mainly focused on non-malignant blood disorders.

**Keywords:** COVID-19, blood disorders, coagulopathy, laboratory, therapy

## INTRODUCTION

Severe acute respiratory coronavirus 2 (SARS-CoV-2) is a pathogen virus from the infectious, Coronavirus disease 2019 which was reported first in Wuhan, Hubei Province, by the People's Republic of China to WHO (World Health Organization) On December 31st, 2019. It was stated that there was a cluster of pneumonia cases of which the causes were not yet ascertained. The current assumption was that it is due to a new type of coronavirus which is called the SARS-CoV-2 caused Coronavirus disease 2019 (COVID-19). However, due to its rapid and global spread that infected more than 2 million people with a mortality rate that is more than 150,000, it was declared a pandemic by WHO on March 12th, 2020. [1,2]

The opening speech of the WHO Director General on the media about COVID-19 was carried out on March 18th 2020, and it was stated that the virus needs rapid and large scale tests. Therefore, Solidarity Test was chosen because it may help reduce 80% of the time that is needed in a research rather than random clinical check that requires longer time. The solidarity test uses simpler procedures, therefore hospital facilities could participate without any necessary documents. Furthermore, it was reported on April 21st, 2020 that 100 countries have come together to find an effective therapy as soon as possible through this test.[3]

Based on several clinical researches in the laboratories that was carried out on animals, the, following options of treatments maybe used presently: Remdesivir, Lopinavir/Ritonavir, Lopinavir/Ritonavir with Interferon beta-1a, and Chloroquine or Hydroxychloroquine.[3,4]

Out of those four treatments that have been used, only Remdesivir, Chloroquine and Hydroxychloroquine have shown positive results to COVID-19. Remdesivir that was initially used as an Ebola treatment test, was used on the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS). It produced a positive result and was believed to be able to give recovery effect to COVID-19. While Chloroquine and Hydroxychloroquine that were used to treat malaria and rheumatology, and based on the small studies in China and French, produced a

positive result to pneumonia cases that were caused by COVID-19. However, random sampling tests are still needed to support those studies.[3]

The conditions for patients to participate in the solidarity test are adults (age ≥18 years old) that are being treated in the hospital or have been hospitalized and tested positive to COVID-19 without contraindications. Furthermore, they need to have signed an approved letter to participate in the test with the possibility of risks and benefits of this research. After the examination, all participants were asked to fill in their identities and conditions online, where this data would later be included in a randomized study. Anonymous critical trial information was collected at the randomization stage such as the reports of deaths with or without study treatment (within days), receiving ventilation or intensive care by recording date, discharge date, deaths date and the cause of death while still in the hospital.[3]

The interim trial analysis was monitored by the Global Safety and Monitoring Committee, which is an independent expert group. Certain countries or groups of hospitals made collaborations in making further serial measurements or observations such as virology, blood or chemistry laboratory and lung imaging. it was also possible to add the disease status data to the routine medical databases although not as a core requirement.[3]

## HEMATOLOGY PARAMETER OF PATIENTS WITH COVID-19 INFECTION

Based on the data from several countries that reported to WHO, it was stated that COVID-19 is a systemic infection that brings significant effect to hematopoietic systems and hemostasis.[2] A study from the National Center for Infectious Disease in Singapore and case reports from Wuhan stated that majority of the patients that were hospitalized showed low ALC (Absolut Lymphocyte Count), and were mainly the ICU (intensive care unit) patients. While the numbers of hemoglobin, thrombocyte, and lactate dehydrogenase (LDH) showed normal value. However, the reports from Wuhan showed that the LDH tends to be higher. Therefore the study in Singapore makes the condition of lymphopenia as the parameter indication of supportive treatments for patients in ICU. It is also in accordance with the exact Fisher test that is used to differentiate laboratory index of ICU and non ICU patients which shows that for the ICU patients they had lymphopenia and high LDH. On that test, the ICU patients also had CD45 +, CD3 +, CD4+, CD8 +, CD19 + and CD16/56 + which were significantly lower. While for relatively non ICU patients, it showed normal LDH.[2]

Lymphopenia is considered to be a cardinal laboratory finding which has potentials of being a prognosis. Neutrophil/lymphocyte ratio and platelet/lymphocyte peak ratio are also considered as prognostic value and they could be used to determine the severity of COVID-19 cases. Besides that, inflammation index, LDH, C-reactive protein (CRP), and interleukin 6 (IL-6) and other biomarkers such as procalcitonin and ferritin serum could also be used as case identification and prognosis.[5,6]

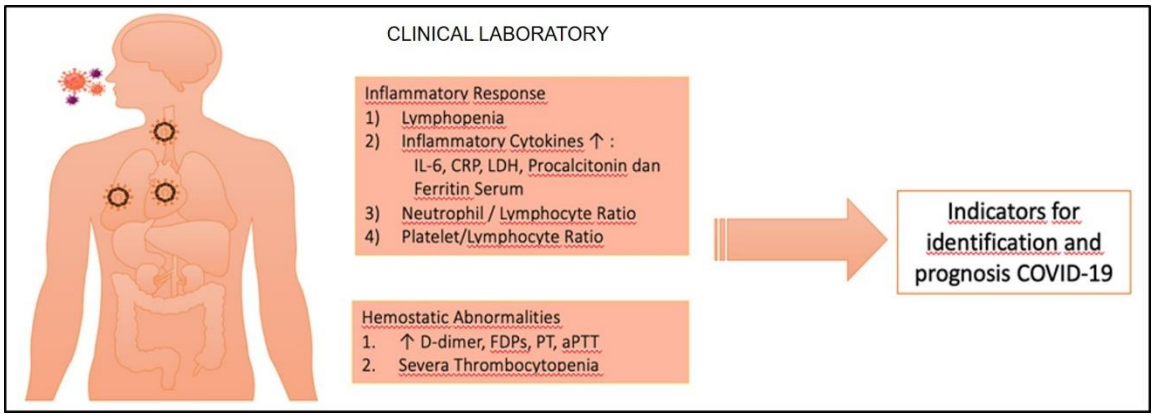


**Fig.1: Scheme of clincal laboratorium as indicators for COVID-19**

IL-6 = Interleukin 6; CRP = C-Reactive Protein; LDH = Lactate Dehydrogenase; FDPs = Fibrinogen Degradation Products; PT = Prothrombin Time; aPTT = activated Partial Thromboplastin Time.

Blood hyper-coagulation may occur among COVID-19 patients, and sometimes it is found that the D-Dimer level increase consistently. Abnormality coagulation that is shown on prothrombin time (PT) and activated partial

thromboplastin time (aPTT) level extension, fibrin degradation products and increases with severe thrombocytopenia that is life threatening is called disseminated intravascular coagulation (DIC).[5,6] These indicators can be seen in Figure 1.

## BLOOD DISORDERS AND GUIDANCE IN COVID-19

Blood disorders in COVID-19 are divided into two group, namely malignant and non-malignant. The malignant blood disorders consist of COVID-19 and Non-Hodgkin Lymphoma, adult/child Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Chronic Myeloid Leukemia, Chronic Lymphocytic Leukemia, Indolent Lymphomas, Hodgkin Lymphoma, Myeloproliferative Neoplasms, Myelodysplastic Syndrome, and Multiple Myeloma. While non-malignant blood disorders include, COVID-19 and Aplastic Anemia, coagulopathy, Immune Thrombocytopenic Purpura, Thrombotic Thrombocytopenia Purpura, Pulmonary Embolism, Sickle Cell Disease, and venous thromboembolism (VTE)/Anticoagulant.[7]

## COAGULOPATHY

A large number of recent data shows an association between SARS-CoV-2 infection with the hemostasis system and venous thromboembolic disease. A study conducted by Dohlnikoff et al., focused on the pathological features of COVID-19 patients in severe/critical cases.[8] The results obtained include exudative or proliferative diffuse alveolar damage, cytopathic effect of the virus on the alveolar epithelium, small fibrinous thrombus in the pulmonary arterioles in the damaged lung parenchymal area, activation of the coagulation cascade, and secondary infection. Furthermore, the pathology findings supported the concept of hyper-coagulative occurrence which indicates an increase in microthrombosis in the lungs of COVID-19 patients.

Coagulopathy is classified based on symptoms of mild, moderate, severe to critical illness which requires ventilator assistance and intensive care in the ICU. In coagulopathy, the laboratory findings used as a coagulation parameter, an indication of treatment and a predictor of mortality in the hospital were elevated D-dimer. An increase in D-dimer ≥ 2 to 3 times the normal value was used as an indication for hospital admission. Other coagulation tests in critically ill patients were PT and platelets.[1]

The International Society on Thrombosis and Hemostasis in the coagulopathy management algorithm for COVID-19 uses D-dimer, PT, platelet counts and Fibrinogen tests as indicators for the management of COVID-19 patients.[9] In coagulopathy, there was an increase in fibrinogen levels, and in correlation with a parallel increase in inflammatory markers such as CRP, moderate to severe thrombocytopenia, prolonged PT and aPTT, a marked increase in D-dimer and a drastic reduction in fibrinogen over 3 days. Meanwhile, in DIC from bacterial sepsis or trauma, it was found that the degree of aPTT increase was less than that of PT, mild thrombocytopenia and no microangiopathy.[10]

Coagulopathy therapy in COVID-19 involves treating the underlying condition.[11] Supportive therapy, including blood transfusions, need to be individualized, however only in conditions of active bleeding or at risk of bleeding complications.[12] In COVID-19–associated coagulopathy (CAC) or DIC patients that are actively bleeding, blood transfusion need to be carried out when the platelet count is below 50 x $10^9$ /L and, give 4 units of plasma when the INR (International Normalized Ratio) is above 1.8 and the fibrinogen concentrate (4 grams) or cryoprecipitate (10 units) when the fibrinogen level is below 1,5 gr/L. Furthermore, for patients with coagulopathy and bleeding due to hepatic dysfunction, Four-Factor Prothrombin Complex Concentrate (4F-PCC) instead of plasma should be considered. Anticoagulant therapy is not required in COVID-19 patients with CAC/DIC unless there is VTE or atrial fibrillation, and the efficacy of which is under study. Low molecular weight heparin (LMWH) prophylaxis is recommended for all COVID-19 patients that are hospitalized even though there are no coagulation disorders and no active bleeding. This is evidenced from the case data in China which shows that there is a decrease in mortality with LMWH or UFH (unfractionated heparin) prophylaxis.[10,11]

Increased levels of D-dimers are strongly associated with the mortality of COVID-19 patients. Treatment with prophylactic doses of LMWH is the only current treatment, especially in severe or critical conditions without contraindications such as active bleeding, platelets less than 25 x $10^9$ /L, renal impairment. severe, abnormal PT or aPTT). In a study conducted by Tang et al., in 449 COVID-19 patients with severe illness, 99 of them received heparin (LMWH) with prophylactic doses. Furthermore, heparin administration was associated with an improved prognosis and may prevent venous thromboembolism.[9]

All critically ill COVID-19 patients have a high risk of VTE. Therefore, to assess the risk of VTE in patients with mild or moderate COVID-19, it is recommended to use VTE by PADUA or IMPROVE

bleeding score.[11,13] The results of the study conducted by Klok et al., showed 31% incidence of thrombolytic complications in 184 ICU patients with severe COVID-19 infection.[14] Therefore, the prevention of thrombotic occurrence requires high dose thrombosis prophylaxis therapy and close monitoring.[15]

## THALASSEMIA

The clinical course about thalassemia with COVID-19 is no more an accepted literature. The chronic conditions in thalassemia patients, especially young adults, that could be associated with comorbidities such as heart failure, diabetes, and pulmonary hypertension which could lead to an increased risk of more severe COVID-19 disease in some patients. However, a small group of patients in northern Italy, where cases of infected thalassemia patients were lower than expected, may be due to self-isolation and awareness from the general public. During a pandemic, thalassemia patients need to have scheduled blood transfusions in a safe environment, because there is no evidence that the SARS-Cov-2 could be transmitted by blood donors. Furthermore, they need to be screened for respiratory symptoms and given personnel health care protective equipment. Iron chelation are also provided to thalassemia patients that are infected by Covid-19, both with or without the symptoms.[16]

There were some recommendations concerning the administration of low-dose glucocorticoid supplements in virus-infected thalassemia patients. However, it should be taken into account the possibility that corticosteroids could slow down the clearance of RNA viruses in the respiratory tract in SAR-CoV or MERS-CoV infection and may increase complications.[16]

## CONCLUSION

COVID-19 is a systemic infection that brings significant effect to hematopoietic systems and hemostasis and this virus has a significant impact on the hematopoietic and hemostasis systems. Laboratory findings on the hematopoietic system such as lymphopenia, neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio, LDH, CRP, IL-6, procalcitonin and serum ferritin, D-dimer, PT, aPTT, FDS, and severe thrombosiopenia have potentials of being a prognosis for COVID-19 patients. Blood disorders in COVID-19 are divided into two groups, namely malignant and non-malignant. However, this study mainly focused on non-malignant blood disorders, such as coagulopathy and thalassemia.

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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