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Biomarkers for The Recognition of SARS-CoV2-Virus and in the Prediction of COVID-19 Infection Severity

Yasmin Anum Mohd Yusof [1], Mainul Haque [2] *

The outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection since December 2019 has provided clinicians with a battery of laboratory tests and imaging tools to back up in the speedy pin-pointing of high-risk COVID-19 victims, enabling them to make the most optimized treatments for COVID-19 patients lowering the mortality rates. The biochemical tests include inflammatory markers, hematological parameters, liver and kidney functions.

COVID-19 disease was initially discovered in Wuhan, China, in a conglomeration among inhabitants of the state who presented with unusual symptoms of pneumonia in December 2019. Nevertheless, in late January 2020, it was dyed-in-the-wool as a case of infection caused by the SARV-CoV-2 virus. The World Health Organization (WHO) designated the illness as COVID-19 and declared it a pandemic on 11 March 2020 (WHO, 2020). Since then, the disease has spread globally, altering people's lifestyles as they grapple and cope with the disease. "Globally, as of 4:14pm CET, 29 December 2021, there have been 281,808,270 confirmed cases of COVID-19, including 5,411,759 deaths, reported to WHO. As of 27 December 2021, a total of 8,687,201,202 vaccine doses have been administered" (WHO, 2021).

[1]Unit of Biochemistry, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, 57000 Kuala Lumpur, Malaysia. Email: yasmin.anum@upnm.edu.my.

[2]Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), 57000 Kuala Lumpur, Malaysia. Email: runurono@gmail.com.

***Corerspondence Authors**

The massive outbreak of COVID-19 has blazed a trail to the introduction of a battery of biochemical and hematological parameters to monitor the progression of the disease (Udugama *et al*., 2020). The treatment outcome and prognostic indicators among patients infected with the COVID-19 virus became important issues (Wiersinga *et al*., 2020). They include inflammatory markers C reactive protein (CRP), Interleukin-6 (IL-6), Interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-α), hemostatic system profile such as D-dimer, platelets, activated Partial Thromboplastin Time (aPTT), and serum biochemical tests for liver and kidney functions (Letelier *et al*., 2021). In severely infected patients, the SARV-CoV-2 virus induces lung inflammation that leads to a cytokine storm accompanied by an elevation of inflammatory biological indicators such as C-reactive protein (CRP), IL-6, IL-10, and TNF-α (Costela-Ruiz *et al*., 2020; Melo *et al*., 2021). Excessive inflammation is highly associated with causing more severe ailment and even death among COVID-19 infected cases (Roberts *et al*., 2021).

CRP is labeled as an acute-phase protein that is raised during the early inflammation phase of the disease (Jain *et al*., 2011) and interestingly bring into being to be preeminent among the majority of patients with COVID-19 infection (Yang *et al*., 2020; Ali *et al*., 2021). Nonetheless, CRP elevation is seldom seen in viral diseases (Jeon *et al*., 2017). In the current COVID-19 pandemic, inflammation caused by the virus's infection may be the primary reason for CRP elevation, which further activates the complement system of the macrophages and promotes uncontrolled inflammatory responses (Noris *et al*., 2020; Luan *et al*., 2021). This wild initiation of complement persuaded by the SARS-CoV-2 in the pulmonary tree and additional vital organs act as a foremost protagonist in acute and chronic

inflammation, endothelial cell dysfunction, thrombus formation, and intravascular coagulation, and eventually leads to several organ calamities and bereavement (Noris *et al*., 2020; Luan *et al*., 2021). In the early stage of inflammation, cytokines, for instance, IL-6, TNF-α stimulate the hepatocyte to produce CRP. The cytokine storm elicited among grave COVID-19 victims correlates highly with CRP elevation (Luan *et al*., 2021; Stringer *et al*., 2021).

Research conducted by Stringer *et al*. observed that a cut-off of CRP values >40 mg/L was associated with mortality among the UK cohorts from several hospitals, which gave clinicians guidelines for proper treatment decisions and advanced care planning (Stringer *et al*., 2021). Those COVID-19 infected patients who passed away, the median CRP level was 86 mg/L (48 mg/L- 173.5 mg/L), equated to 53 mg/L (16 mg/L-109 mg/L) among patients who recovered from the SARS-CoV-2. One more research conducted among one hundred forty COVID-19 cases with moderate to severe bronchopneumonia requiring oxygen supplementation admitted in a hospital in Wuhan, China, found that patients with low oxygen saturation (SpO2 ≤ 90%) had significantly higher levels of CRP (median 76.5 mg/L) than patients with high oxygen saturation (SpO2>90%) (median 12.7 mg/L), demonstrating that appalling cases with extreme lung involvement have raised levels of CRP (Xie *et al*., 2020a). Wang also found a similar correlation whereby CRP levels in the initial phase of COVID-19 were definitely interrelated with severe pulmonary pathology (Wang *et al*., 2020).

D-dimer is a fibrin breakdown compound produced by plasmin-induced fibrinolysis and is used as a biomarker for thrombotic disorder (Favresse *et al*., 2018; Riley *et al*., 2016). A marked elevation of D-dimer (≥1.5 -2.0 ug/ml) is an precise decipher of hospital mortality in patients with COVID-19 (Poudel *et al*., 2021; Yao *et al*., 2020). D-dimer elevation was detected in 75% of patients admitted to a hospital in Wuhan, China (184/248). The increase was significantly interrelated to the lethality of the illness as determined by clinical staging and chest CT staging (Yao *et al*., 2020). Many researches have made known that COVID-19 inclines patients to thrombosis in both arteries and veins, suggesting that measuring D-dimer can be a good prognosticator of thrombosis (Poudel *et al*., 2020; Yao *et al*., 2020; Cui *et al*., 2020).

COVID-19-associated coagulopathy can be classified into 3 stages: stage 1 shows a raised D-dimer, stage 2 shows an eminent D-dimer along with somewhat protracted PT/INR and aPTT, and trivial thrombocytopenia and stage 3 shows life-threatening COVID-19 infection and laboratory-based research findings shows the disease progressing towards classic disseminated intravascular coagulation (DIC) (Thachil *et al*., 2020). D-dimer is a routine measurement upon admission in some hospitals to foresee the mortality of patients with COVID-19. Its increased levels are also closely linked with inflammatory indicators such as CRP, IL-6, and TNF-α (Yu *et al*., 2020). A meta-analysis study by Zhan *et al*. showed that the prognostic relevance of D-dimer in predicting the severity, mortality, and venous thromboembolism in COVID-19 patients was shown to be 77%, 75%, and 90%, respectively (Zhan *et al*., 2021).

Hematological changes are common among COVID-19 patients, including reduced lymphocyte and platelet counts and prolonged aPTT (Xu *et al*., 2020). Additionally, it has been revealed that lymphopenia can represent a critical laboratory finding and possess a predictive analytical value. Neutrophil/lymphocyte (NLR) ratio and peak platelet/lymphocyte ratio (PLR) also bear the possibility to represent analytical value in determining severe cases (Terpos *et al*., 2020). Similarly, multiple studies reported that lower lymphocytes ($p<0.001$), platelets ($p<0.001$), and higher white blood cells ($p<0.001$), neutrophils ($p<0.001$), NLR ($p<0.001$), PLR ($p<0.001$), and Lymphocyte-Monocyte ratio ($p=0.011$) found in COVID-19 cases were statistically significantly different than healthy controls (Khalid *et al*., 2021; Waris *et al*., 2021). The reduced number of lymphocytes is in parallel with the SARS-CoV-2 illness severity and intensification of mortality (Waris *et al*., 2021; Tavakolpour *et al*., 2020). It was further explained that the T lymphocytes are essential for eradicating infectious viral particles (Tavakolpour *et al*., 2020; Härter *et al*., 2020).

Research conducted among 1099 patients from 31 territories in China exhibited that 82.1% of patients had lymphopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia (Guan *et al*., 2020). A meta-analysis of 7,613 SARS-CoV-19 cases, as published from April 2020, reported thrombocytopaenia among patients with severe disease compared to those with non-severe disease, with the deceased having a considerably lower platelet count than the recovered cases (Jiang *et al*., 2020). Platelets work together as the crow flies with viruses via several receptors, together with Toll-like receptors, triggering inflammatory and immunological responses, engulfing and aggregating the viruses, thereby suppressing their infections (Seyoum *et al*., 2018; Li *et al*., 2020a; Wool and Miller, 2021). Thrombocytopenia in SARS-CoV-2 patients (Li *et al*., 2020b) could be instigated by platelet activation that is followed by elimination by the reticuloendothelial system; amplified endothelial damage promotes platelet elimination process; development of platelet autoantibody that consequently leads to

platelet removal by spleen/liver; and poor function of marrow/megakaryocyte (Wool and Miller, 2021).

As a result of COVID-19 complications, organ failure poses further challenges among clinicians in treating patients infected with the COVID-19 (Shang *et al*., 2020; Wiersinga *et al*., 2020). Liver failure can be detected by simple, inexpensive biochemical tests such as Urea nitrogen, liver enzymes, and kidney metabolites (Lala *et al*., 2021; Sharma and Nagalli, 2021). A meta-analysis of 24 pieces of research with confirmed COVID-19 patients by Sharma *et al*. proposes that acute liver injury and raised up liver enzymes such as ALT and AST were significantly associated with severity of SARS-CoV-2 (Sharma *et al*., 2021). A meta-analysis of 29 pieces of research with confirmed corona viral infected cases by Singh *et al*. suggests that comorbid chronic kidney disease (CKD) (overall prevalence of 9.7%) and acute kidney injury (AKI) (overall prevalence 11.6%) were significantly associated with COVID-19 disease severity (Singh *et al*., 2021).

Nonetheless, there are quite a lot of diagnostics systems accessible for uncovering coronavirus disease 2019 infection. These approaches are not cheap enough, particularly for low-middle income countries (LMICs), and they also have hands-on problems and issues (Mariappan *et al*., 2021). Thereby, a compact, low-priced, and cost-effective method that will precisely spot the COVID-19 viral infection and assess disease progression is an urgent need, especially for the marginalized communities around the globe (Mariappan *et al*., 2021; Gupta *et al*., 2020). Finally, this paper suggests combining COVID-19 clinical and laboratory data and associating the disease's natural course of progression might be of great help to clinicians (Xie *et al*., 2020b). Multiple diagnostic parameters should be monitored rather than a single value (Samprathi and Jayashree, 2021). National and international COVID-19 management guidelines should be tailored to the specific needs of each patient, and healthcare settings are critically essential (Samprathi and Jayashree, 2021).

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CONFLICTS OF INTEREST

The authors declare they have no relevant conflicts of interest.

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