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

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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).

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 SARS-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

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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 deciper 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 thrombocytopenia 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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