Editorial

iMedPub Journals
http://www.imedpub.com

Biomarkers Journal
ISSN 2472-1646

2020
Vol. 7 No. 1:1

DOI: 10.36648/2472-1646.7.1.70

The Role of Blood Biomarkers to Indicate the Clinical Severity of COVID-19 Prognosis

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Received: August 26, 2020; **Accepted:** September 09, 2020; **Published:** September 16, 2020

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Citation: Bag SS. The Role of Blood Biomarkers to Indicate the Clinical Severity of COVID-19 Prognosis. Biomark J. Vol. 7 No. 1: 1.

Editorial

COVID-19 is a highly contagious disease in humans caused by the infection of the SARS-CoV-2 virus. The present crisis of the COVID-19 pandemic is life-threatening and affects every society from all spheres of life. The rate of infection is increasing, though with a lower death rate compared to MERS-CoV and SARS-CoV. The number of deceased patients has reached 668,910, with total infections counting to 17,106,007 as of 31st July 2020. Till the date, there is no medicine or vaccine to prevent or cure the disease, COVID-19. The clinical management followed at COVID Care Centers and designated COVID hospitals are the only avenue for treatment. Fortunately, the recovery rate around the globe is quite promising and optimistic. Under the existing clinical management and manifestations, the symptomatic COVID-19 cases are stratified under three categories: mild, moderate, and severe. However, scientists and doctors across the globe believe that it would be more specific to interpret the disease conditions based on biomarkers from blood samples of the patients for objective evaluation of disease progression [1,2]. As a result, categorizing patients into mild, moderate, and severe will be more defined [1,3].

To understand the biomarkers that are important for the distinctive identification of COVID-19 prognosis and severity, we must understand the immune response generated against the SARS-CoV-2 infection. The SARS-CoV-2 virus enters the host cells by establishing interaction between the spiked glycoproteins (S proteins) present on the viral outer surface with angiotensin-converting enzyme 2 (hACE2 protein) on the epithelial cells. After getting entry into the host cell, the virion un coats envelop and releases the genomic RNA (gRNA) [4]. The gRNA gets immediately recognized by the pattern recognition receptors like Toll-Like Receptors (TLR3, TLR7/8). As a result, a cascade of immune response pathways is generated, leading to an increase in the pro-inflammatory cytokine (IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP-10, MCP-1, CCL3, and TNFα) population. These "cytokine storm" attracts neutrophils, lymphocytes, and macrophages to the site of infection [5]. This situation creates stress conditions in the body and activates the hypothalamus-pituitary-adrenal axis (HPA axis), which leads to the secretion of cortisol. With an increase in the level of cortisol in the serum, they initially force migration of lymphocytes out of the peripheral circulation system and ultimately cause mass destruction of the lymphocytes through apoptosis [5]. This phenomenon leads to a condition of lymphocytopenia in COVID-19 severe cases. **Figure 1** portrays a generalized understanding.

Apart from lymphocytopenia, severe and critical conditions of COVID-19 patients have also resulted from a severe lung injury, cardiovascular injury, and severe liver impairment. The cascade of pro-inflammatory cytokine response causes severe vasculitic damage. These damages result in acute edema, ARDS, and cardiovascular damage (ischemia, deep vein thrombosis, pulmonary thromboembolism, myocardial injury) [6]. Recent studies suggest that SARS-CoV-2 infects the liver by attaching to the ACE2 receptors of cholangiocytes in bile duct leading to liver impairment [7]. All the diseases mentioned above are crucial and specific towards predicting COVID-19 patient mortality. Therefore, it is of utmost importance to conduct a thorough study of the related biomarkers to understand the severity of COVID-19 patients. However, the present laboratory biomarkers such as D-Dimer or prothrombin time/activated partial thromboplastin time (PT/aPTT) are not sufficient to understand the disease prognosis. A recent report suggests that the detection of biomarkers such as ILs, D-Dimer, lactate dehydrogenase (LDH), and transaminases along with the routine clinical reports are crucial for understanding the severity of COVID-19 disease [8]. As it is always impossible to carry out expensive tests for the detection of cytokines, the examination of some associated biochemical markers such as Ferritin and C-reactive protein CRP can predict the infection and severity of disease prognosis are also proposed. According to a recent report on the novel SARS-CoV-2 treatment program [9], the COVID-19 patients were categorized into mild, moderate, severe, and critical. The altered levels in some significant hematological biomarkers, such as White Blood

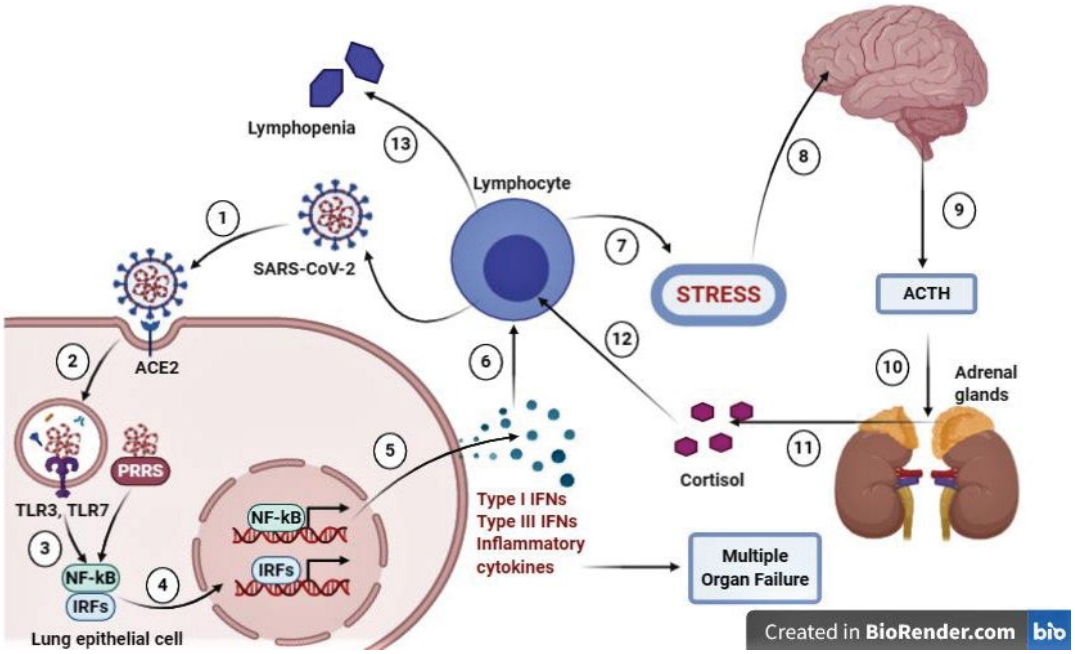

Figure 1 A generalized diagram showing the pathway causing Lymphocytopenia and Multiple Organ Failure due to SARS-CoV-2 infection.

Cells (WBC), lymphocytes, and biochemical biomarkers, like CRP, LDH, Creatine Kinase (CK), and troponin are also associated with disease severity indicating a critical condition of COVID-19 patients. The detection of specific biomarkers like homocysteine (Hcy) and angiotensin II is advised to predict the possible cardiovascular risk and lung damage, respectively, associated with COVID-19 patients.

The hematological biomarkers which have been proposed for study and stratification of COVID-19 patients are WBC, lymphocyte count, eosinophil, neutrophils, thrombocyte, platelet, T cell, and B cell count, Natural Killer T cell count, monocytes/basophil and Neutrophil-Lymphocyte Ratio (NLR). Various clinical studies have reported that blood tests conducted on COVID-19 patients developing lymphopenia have shown abnormal fall in their lymphocyte eosinophil, platelet, monocyte/basophil count associated with an increased level of WBC/Neutrophil. Abrupt and abnormal fall in lymphocyte count has directly caused the depreciation of T cell and B cell population. COVID-19 patients developing severe conditions showed a fall in helper T cell, and suppressor T cell counts. In critical cases, the level of helper T cells and regulatory T cells are found to be lowest to negligible. Further, the populations of naive T cells are found to increase with a significant fall of memory T cell level. A drastic decrease in NK cells count, and cytotoxic T lymphocytes (which are programmed to fight/control viral infections) are also associated with disease progression [10-12]. A general and comparative study of the various biomarkers related to COVID-19 severity is presented in **Figure 2**.

Fatality in COVID-19 cases often results from Multi-Organ Failures (MOF) such as ARDS, liver damage, and cardiovascular dystrophy. Therefore, the biochemical markers, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total

Biomarkers	Patient Condition	
	Mild	Severe
Haematological Biomarkers		
WBC count Neutrophil count	Normal to slightly elevated	↑
Lymphocyte count Eosinophil count Platelet count Monocyte count Basophil count	Normal to slightly low	↓
Thrombocyte count T cell count B cell count NK T cell count	Normal	↓
Biochemical Biomarkers		
ALT AST SGPT/SGOT Total bilirubin	Normal to slightly elevated	↑
Blood urea nitrogen CK LDH Glucose Myoglobin CK-MB Cardiac troponin 1 Creatinine	Normal	↑
Inflammatory Biomarkers		
CRP Procalcitonin Ferritin TNF-α INF-γ CMP-1 IL-(2/6/7)	Normal	↑
IL-(1/8/10)	Normal	Normal
Coagulation Biomarkers		
D-dimer PT aPTT FDP	Normal	↑
Significant Novel Biomarkers		
Hcy Angiotensin II NLR	Normal	↑
Angiotensin(1-7/1-9) Alamandine	Normal	↓

Figure 2 Biomarkers relevant to COVID-19 prognosis

bilirubin, blood urea nitrogen, SGPT/SGOT, CK, LDH, myoglobin, cardiac troponin I, and creatinine should be regularly monitored in COVID-19 patients to predict the possibility of MOF. Recent clinical studies with COVID-19 patients have reported a significant rise in ALT, AST, creatinine, LDH, cardiac troponin 1, and N-terminal pro-brain natriuretic peptide, and D-dimer in MOF related non-survivors [13]. This indicates severe lung and liver damage as the primary reason for fatality. Some other clinical studies have reported an elevated level of cardiac troponin I in fatal COVID-19 cases. The sudden and abnormal elevation in cardiac troponin levels is associated with viral myocarditis and cardiac injury [9,14].

Vasculitic damage associated with COVID-19 causes severe parenchymal lesions in vital organs of the body. This condition, if not detected early, often results in MOF. Vasculitic damage is mostly resulted from the cytokine storm. Therefore, the study of inflammatory biomarkers such as IL-6, IL-2, IL-7, tumor necrosis factor (TNF)-a, interferon-c inducible protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP) 1-a, granulocyte-colony stimulating factor(G-CSF), CRP, Procalcitonin (PCT), and ferritin, is crucial for early detection of COVID-19 severity [15-17]. Some recent clinical studies have reported a correlation of the elevated level of inflammatory cytokine IL-6 with COVID-19 fatality. Thus, patients with higher IL-6 developed ARDS with further deterioration in conditions resulting from tissue damage and MOF [18]. Reports from another study showed an abrupt increase in CRP, IL-6, and serum ferritin levels associated with the death of COVID-19 patients [14].

It has been observed form various clinical studies that abnormality detected in coagulation parameters often results in poor disease prognosis and ultimately leads to fatality. The non-surviving COVID-19 patients have been tested to have higher levels of plasma D-Dimers, fibrin degradation products (FDP), increased prothrombin time (PT), and activated Partial Thromboplastin Times (aPTT) [19]. Another study reported that coagulopathy and disseminated intravascular coagulation (DIC) confirmed from elevated D-Dimer in serum resulted in increased mortality rates amongst COVID-19 patients [20].

Through this article, we have tried to attract clinicians and medical practitioners' attention to the importance of various biomarkers categorized as hematological, biochemical, inflammatory, and coagulation. The biomarkers are expected to play a crucial role in the better and early assessment of clinical severity associated with COVID-19 patients. Under the present situation, complete caregiving and clinical management (need for ICU or artificial ventilation) depend on symptom presentation. Therefore, we believe that monitoring the alterations in biomarkers such as lymphocyte count, levels of CRP, D-dimer, ferritin, cardiac troponin, and IL-6 will help in fast prediction and clinical decision making for COVID-19 treatment planning in severe cases.

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