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Review Article

Diagnostic and Prognostic Blood Biomarkers in COVID-19

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Abstract:

Background: COVID-19 outbreak prompted the development of novel diagnostic and immediate treatment procedures. Protein biomarkers are helpful in the study of COVID-19 and SARS-related illness. Proteins linked to blood coagulation (D-dimer), cell damage (lactate dehydrogenase), and the inflammatory response, such as reactive protein (C), have previously been identified as possible COVID-19 severity or mortality predictions.

Objective: This study examined the applications of proteomics to COVID-19.

Methods: Narrative review.

Results and conclusion: This study showed that technologies such as artificial intelligence could be helpful for research into these diseases. In addition, the SPSelectin levels and the severity of COVID-19 infections were examined in this study. In a broad sample of patients, the efficacy of regular blood counts utilized in the diagnostic and prognostic value of COVID-19 and their independent biomarkers were retrospectively examined. This condition was diagnosed using low lymphocytes (LYM), white blood cells (WBC), CRP, and high ferritin levels. The results indicated that vascular inflammation and thrombosis appear to be critical drivers of poor clinical outcomes in COVID-19 patients. A significant decrease in the percentage of blood vessels with a cross-sectional area of 5.25-5 mm2 (BV5) on computed tomography (CT) of the chest in COVID-19 patients was expected to predict poor clinical outcomes in this investigation as a hypothesis.

Keywords: COVID-19, Biomarker, Prognostic, Diagnostic

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Background:

COVID-19 is a life-threatening disease with high transmission risk started in 2019 in Wuhan, China, and affected approximately 115 million people worldwide until March 4, 2021. The World Health Organization (WHO) has labeled the disease an epidemic, with an estimated 400,000 to 600,000 new cases every day and more than 2.5 million deaths (1). The disease's name was then changed to COVID-19 by the World Health Organization in February 2020 due to the disease's global spread (2). The virus originated in bats and transmitted to humans through animals in Wuhan, China, in December 2019 and then spread worldwide. COVID-19 outbreak due to severe acquired respiratory syndrome (coronavirus-2 (SARS-CoV-2)) continues to be a significant threat to public health worldwide (3). Many diagnostic and prognostic markers associated with Covid-19 disease include D-dimer, C-reactive protein (CRP), neutrophil count, leukocyte count, lymphocyte ratio, neutrophil to lymphocyte ratio, ferritin, and procalcitonin have been routinely tested (4,5). Patients may present with clinical symptoms of fever (above 37.3°C), cough, myalgia, sputum production, headache, hemoptysis, diarrhea, shortness of breath, and in some cases, acute respiratory distress syndrome (ARDS), acute heart injury, or secondary infection (6,7).

sP-Selectin is a 140 kDa molecule that mediates the interaction of endothelial cells, or platelets stimulated with white blood cells on the surface of arteries, which is also called the CD62 antigen platelet-activated foreign granule membrane protein (PADGEM) or granule membrane protein. When sP-Selectin combines with the PSGL-1 ligand, it releases platelets and mediates platelet adhesion to vascular endothelial cells (8,10). Common laboratory parameters are essential clinically in predicting the diagnosis and progression of the disease (9). Since the severity of COVID-19 disease varies considerably, the absence of symptoms is also vital in developing the disease. Currently, it is unclear whether all asymptomatic patients develop a detectable antibody titer, which is a sign of infection. Serum immunoglobulin conversion in response to COVID-19 occurs up to 12 days after the first diagnosis of symptoms (11, 12). The relationship between serum sPSelectin levels and COVID-19 infection has been evaluated in several studies. Venter et al. (2020) reported high serum sP-Selectin levels in COVID-19 patients by studying 30 patients and ten controls (13). Goshua et al. (2020) examined levels of markers involved in endothelial cells and platelet activation in COVID-19 infection and found that sP-Selectin levels were higher in patients receiving intensive care compared to patients who did not require special care (14). Lymphopenia is thought to be induced by the COVID-19 virus, either directly (by targeting the virus with ACE2 receptors) or indirectly (by suppressing lymphocyte production or shortening lymphocyte half-life) (15,16). This paper aimed to evaluate the role of different prognostic and diagnostic biomarkers in the pathogenesis of Covid-19 disease and investigate their levels depending on its severity.

Studied Biomarkers in COVID-19

C-reactive protein (CRP)

CRP is a plasma protein generated by the liver triggered by inflammatory mediators like IL-6. Despite its lack of specificity, this acute phase reactant is utilized as a biomarker to treat a variety of inflammatory disorders, and higher CRP levels are related to exacerbating disease severity (17). A published study indicated that CRP is one of the first biomarkers in blood plasma changing to indicate physiological effects. CRP will be the most effective biomarker to predict the progression of COVID-19 infection in the case of being accepted. This study also showed cases of infection revealing changes in serum amyloid A (SAA) instead of significant changes in CRP, which required further evaluation (18). Pathologically, CT scans can detect COVID-19-related lung lesions. Nevertheless, a study in China found that CT scores could not

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distinguish mild and severe cases. Compared with an erythrocyte sedimentation rate (ESR), CRP levels were significantly higher in the early stages of severe cases and proved to be a more sensitive biomarker in reflecting disease development (19).

Interleukin-6

Cytokine Release Syndrome (CRS) is a severe immune response with the high release of inflammatory mediators, underlying several pathological processes, including acute respiratory distress syndrome (ARDS) (20). According to studies, IL-6 levels as the most common cytokine released by active macrophages increase sharply in severe manifestations of COVID-19 (21). The results of six studies have represented that the average concentration of IL-6 in patients with COVID-19 is 2.9 times higher than in patients with the uncomplicated disease (22). Most patients require ICU admission and initiation into their ARDS, which even leads to death. Increased IL-6 was directly related to disease severity, and physicians could use this cytokine to detect severity and initiate oxygen therapy earlier, although different results made it difficult to determine IL-6 levels in the clinic.

Number of white blood cells

White blood cells (WBCs), known as leukocytes, are part of the blood generated by bone marrow and lymphatic tissue and divided into granulocytes and agranulocytes. Granulocytes include eosinophils, basophils, and neutrophils (NCs), while lymphocytes (LCs) and monocytes belong to the agranulocyte group.

An odd number of these cells may be a prognosis for underlying infection, so a white cell count (WCC) test can be done using a blood test.

However, the reliability of the WCC has not yet been established as a biomarker for COVID-19. Yang et al. (2020) found several differences in WCC between severe and non-severe COVID-19 patients (23). An increase in leukocytes and neutrophils, a decrease in lymphocytes along with a higher neutrophil to lymphocyte ratio (NLR), and a decline in monocytes, eosinophils, basophils are experienced in patients with severe COVID-19.

NLR is an unknown biomarker with a broad range of inflammatory conditions to reflect the severity of the disease. Nevertheless, comprehensive research is required to transparent the effectiveness of NLR as a biomarker. Yang et al. (2020) revealed that low blood lymphocyte count in critically ill patients indicates a poor prognosis. Since the virus can target lymphoid tissue and the mechanisms of IL-6, other causes of reduced LYM should be investigated. Similar to NLR, the clinical benefits of LYM as a COVID-19 biomarker are unclear (24).

Neutrophils

Patients requiring hospitalization in the ICU had a higher percentage and an absolute number of neutrophils (25).

Eosinophils

Low percentages of airway and serum eosinophil-derived eosinophils and serum eosinophils (EDN-1) could be a potential biological indicator of COVID pneumonia (24, 25). However, further studies are needed on the relationship of EDN-1 with clinical, radiographic, and physiological parameters (26).

Monocytes and basophils

Monocytes and basophils decrease similarly to lymphocytes and eosinophils (26).

Platelets

Both thrombocytopenia and thrombocytosis were observed; however, severe thrombocytopenia and bleeding are uncommon (27). Thrombocytopenia was related to other coagulation parameters and an increased risk of mortality (28).

Combined hematological markers

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These factors make it clear that severe COVID-19 disease is related to significant increases in leukocytes, neutrophils, infection biomarkers (such as CRP, PCT, and ferritin), cytokine levels (IL-2R, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF) -α), and decreased lymphocyte count.

IL-2R levels were negatively correlated with other cytokines and lymphocyte counts and predicted an increase in the ratio of IL-2R to lymphocytes distinguishing between severe and critical disease. This ratio is superior to other critical disease differentiation markers. This ratio decreases significantly in recovered patients but increases in critically ill patients, so it significantly correlates with disease outcome (29).

Zheng et al. (2020) developed a score based on the number of neutrophils, lymphocytes, and platelets, named "NLP score" in more than six intervals to predict the severity progression of the disease.

A high neutrophil-lymphocytes ratio (NLR) is a valuable alternative marker for diagnosing COVID-19 at admission. An increased NLR can also be used as a prognostic indicator to predict poor outcomes.

The lymphocyte to C-reactive protein (CRP) ratio (LCR) is a prognostic indicator, used in several types of cancer may also be helpful in this case. A meta-analysis of six studies concluded that increased NLR and decreased LCR were related to COVID-19 severity. Mainly, Low LCR was observed, in particular, to predict ICU acceptance and the need for invasive ventilation (30).

Inflammatory parameters

CRP and Procalcitonin (PCT)

Zhou et al. (2020) found that CRP, procalcitonin (PCT), and Lactate Dehydrogenase (LDH) increased in 60.7%, 5.5%, and 41% of patients, respectively (31). Decreases of >10 mg/L and >0.5 ng/ml for CRP and PCT predicted the poor outcome of the disease.

A retrospective study showed that a 26 mg/L CRP level could be an accurate indicator of severe disease progression. Lippi and Plebani's (2019) meta-analysis indicated that high PCT values were approximately five times more related to severe infection (32).

Cytokines

IL-6 is significantly increased in COVID-19 patients, and more than half of hospitalized patients have high levels of IL-6 (33). Higher baseline IL-6 levels are related to severity, bilateral Interstitial lung disease (ILD), and other acute inflammatory markers (34).

Many systematic studies and meta-analyses have identified IL-6 as an essential indicator of disease severity and predictor of mortality. Other proinflammatory cytokines (IL-1, IL-2, IL-8, IL-17, G-CSF, GMCSF, IP-10, MCP-1, CCL3, and TNF) are significantly raised in individuals with severe illness, and IL-6 is useful for evaluating therapy response. Another study found that COVID-19 patients with ARDS had lower cytokine levels than those with out-of-hospital septic shock, trauma, or cardiac arrest, which coincided with lowering leukocyte counts (35). These initial findings hesitate the existence of cytokine cascades and the benefits of anti-cytokine therapies.

Ferritin

Ferritin levels in COVID-19 patients have found conflicting results, and it is unclear whether this is an observer effect or an actual illness feature. Ferritin has been found to have a minor effect on predicting ICU admission, the need for ventilation, and mortality in two retrospective studies (36,37).

However, another study and a meta-analysis have shown the opposite result according to which Ferritin levels could predict severe disease and mortality (37,38).

Coagulation parameters

Coagulation in COVID-19 differs from normal diffuse intravascular coagulation in having high fibrinogen, prolonged normal or mild

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prothrombin time, relatively active thromboplastin time, and platelet counts greater than 100×103 per ml, but without significant bleeding (39).

Increased D-dimer levels are most commonly observed in patients with COVID-19, and levels >2.0 μg/ml at admission can predict mortality. Many meta-analyses have revealed the D-dimer levels have prognostic value and are related to disease severity and in-hospital mortality (40,41). D-dimer can be a primary marker to guide the management of COVID-19 patients.

Cardiac biomarkers

The use of cardiac biomarkers in diagnosis, triage, treatment, and prognosis has been examined. Increased cardiac biomarkers including LDH, creatine kinase (CK), creatine-kinase MB (Muscle Brain) activity (CK-MB), myoglobin (Mb), cardiac troponin I (cTnI), alpha hydroxybutyrate dehydrogenase (α-HBDH), aspartate aminotransferase (AST), and N-terminal (NT) -prohormone BNP (Brain Natriuretic Peptide) (NT-proBNP) have been observed in patients with COVID-19.

Meanwhile, LDH, CK, α-HBDH, and AST are not dedicated to the myocardium, and they can increase damage to the lungs, liver, and kidneys. On the other hand, CK-MB, cTnI, Mb, and NT-proBNP are more specific to myocardial damage and increase to varying degrees, especially in severe and critical diseases.

In addition, higher levels were associated with higher mortality, and a decrease in these biomarkers to predict mortality was much lower than in normal cardiovascular disease (42). Troponin and natriuretic peptides were investigated for risk classification, decision-making for echocardiography (ECG) and invasive therapy, and prognosis (43). Patients with myocardial damage showed reduced white blood cells, lymphocytes, and platelet counts when cardiac biomarkers were evaluated alongside other biomarkers (44). On the other hand, cardiovascular biomarkers should be utilized with caution because regular testing in all patients may be deceptive.

Biochemical parameters

Serum Albumin

Increased capillary permeability, blood circulation, volume distribution, and production of vascular endothelial growth and decreased protein synthesis and total serum albumin mass are all factors that contribute to hypoalbuminemia in critically ill patients. Although this component is widespread, the exact timing of hypoalbuminemia has yet to be investigated (45).

A similar trend was observed in COVID-19, and a meta-analysis containing studies showed that mean serum albumin of 3.50 g/dl and 4.05 g/dL at baseline were severe and non-severe in COVID-19 (45).

LDH

An increase in LDH levels is observed in around 40% of patients, related to a higher risk of ARDS, the need for intensive care, and mortality (46).

Biochemical parameters

Biochemical parameters were studied to predict disease severity. Positive glucose and protein levels were higher in the severe and critical groups compared to the moderate group, although urinary secreted blood and specific gravity were not related to disease severity (47).

Lactate dehydrogenase

The enzyme LDH in glucose metabolism converts pyruvate to lactate, and LDH secretion is stimulated by cell membrane necrosis, which is related to viral infection or lung damage, such as SARS-CoV-2 pneumonia.

According to studies, LDH levels are related to COVID-19 (48). A showed high levels of LDH in ICU patients compared to non-ICU patients (248 U/L vs. 151 U/L) (P = 0.002). Since high levels of LDH persisted in ICU patients

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throughout time (160 U/L vs. 218 U/L, p = 0.002), LDH could be a biomarker for predicting the severity of the disease.

A study of 1099 patients in several medical centers showed that the rate of tissue damage and inflammation was directly related to increased LDH levels (49).

Cardiac troponin

COVID-19 infection has been related to a more significant mortality rate in people with underlying cardiovascular disease. Several studies have studied high-sensitivity cardiac troponin I (hs-TnI) as a marker of disease progression and death. In a retrospective investigation of 191 COVID-19 patients in China, the risk of dying from hs-TnI remained unchanged at 80.1% (29). Another research of 416 hospitalized patients with COVID-19 found that 1 in 5 patients had a rise in hs-TnI (50).

Renal markers

According to Yan et al. (2019), chronic kidney disease is related to severe forms of COVID-19 infection (51). Studies have shown higher levels of renal biomarkers such as serum urea, creatinine, and glomerular filtration rate in severe cases (52). Laguna-Rangel et al. (2020) studied 701 patients and stated that increased creatinine levels at admission were related to disease severity due to significant abnormalities in the coagulation pathway (30). They also found that these patients needed more mechanical ventilation or intensive care and their urea levels showed a similar risk rate. Guan et al. (2020) revealed the potential role of urine analysis on serum markers of renal function (53).

Hemoglobin

Aziz et al. (2020) conducted a retrospective study in which anemia and altered iron homeostasis were common in patients with COVID-19. Primary anemia was associated with increased mortality, and a higher ferritin/transferrin ratio predicted the need for ICU admission and mechanical ventilation (45).

Conclusion

Covid-19 is a spectrum of heterogeneous diseases with a wide range of symptoms that change with age and the presence of comorbidities. Biomarkers are crucial in the early suspicion, diagnosis, monitoring, and recognition of problems, and patient care and resolution. Each of these factors can have significant implications for the healthcare system and office machinery, directly affecting patient care. At every level, clinical evaluation is critical, and biomarkers should be heavily incorporated into bedside decision-making.

Individual biomarkers may not provide as trustworthy information as biomarker panels, and cases such as cost must be considered. Physicians cannot integrate and analyze the massive amounts of data that are constantly being added to COVID-19 articles to extract practically meaningful information for the benefit of patients. As a result, national or regional guidelines are required to adapt current material to the needs of the local people.

The results of studies suggest that biomarker levels may change based on the severity of COVID-19 infection, which can be used as a supplement in clinical practice to guide treatment and admission to the ICU to improve prognosis and minimize mortality. Since we are still in the early stages of studying the pathology of this infectious disease, additional research is required around the world to better comprehend the reported changes.

Following a discussion of the clinical characteristics of COVID-19, the hematological and immunological characteristics of routine blood parameters in patients were examined. The results revealed that COVID-19 and disease progression threatened the older age and sex of males. Low LYM and WBC, high CRP, and ferritin effectively diagnose the disease, and their d-

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CWL and d-CFL biomarkers were the most critical risk factors. Various markers are being investigated for use in the diagnosis of COVID-19 and in predicting the outcome of infection. sP-Selectin levels were a valuable biomarker in this study, which can be used to aid in the diagnosis and prognosis of the requirement for intensive care treatment in patients.

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