Biomarkers during COVID-19

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As the COVID-19 (Coronavirus disease 19) pandemic spreads worldwide, the massive numbers of COVID-19 patients have created a considerable healthcare burden for every country. The clinical spectrum of SARS-CoV-2 infection is broad, ranging from asymptomatic to mild, moderate, severe, and critical. Most COVID-19 patients present with no or mild symptoms, but nearly one-fifth of all patients develop severe or life-threatening complications. In addition to localized respiratory manifestations, severe COVID-19 cases also show extra-pulmonary complications or induce multiorgan failure. Identifying, triaging, and treating patients at risk early is essential and urgent. Biomarkers are measurable biochemical substances used to recognize and indicate disease severity or response to therapeutic interventions. The information they provide is objective and suitable for delivering healthcare providers with a means of stratifying disease state in COVID-19 patients.

Keywords: COVID-19 ; SARS-CoV-2 ; biomarker ; cytokine storm ; point-of-care testing

1. Immunological and Inflammatory Response to SARS-CoV-2 Infection

As the SARS-CoV-2 virus enters host cells, binding to the angiotensin-converting enzyme 2 (ACE-2) receptor, viral replication in the cytoplasm releases many virions, causing local infection of neighboring cells and a viremia-induced systemic immune response [1]. Both innate and adaptive immune responses are therefore activated. Meanwhile, the SARS-CoV-2 also induces the secretion of soluble serum and urine ACE2, further releasing a vast quantity of cytokines and causing a systemic inflammatory response [2]. Excessive cytokines stimulate and recruit immune cells, causing dysregulated, overcompensating host responses leading toward “cytokine storm syndrome” [3][4]. This dysregulated immune response is a life-threatening, urgent-care condition that may be progressively characterized by persistent fever, nonspecific muscle pain, hemodynamic instability, disseminated intravascular coagulation (DIC), multiorgan failure, and, in the absence of suitable treatment, death [5].

1.1. Cytokines

The rapid deterioration of severely affected COVID patients may be attributable to an over-reacting immune system. This response may evolve from multiple pathways, including, but not limited to, NF-κB signaling, the JAK/STAT pathway, the NLRP3 pathway, and granulocyte macrophage-colony stimulating factor (GM-CSF) activation pathways [5][6]. While SARS-CoV-2 virus infects epithelial cells, the above immune pathways are activated, and several pro-inflammatory cytokines are released, including interleukin 1β, (IL-1β), IL-2, IL-6, IL-7, IL-8, IL-10, IL-17, TNF-α, and interferons (INFs) [3][4][5]. Elevated cytokine levels result in the recruitment of immune cells such as macrophages, T cells, and neutrophils to the infected area. Meanwhile, released serum cytokines such as interleukin-6 (IL-6), lead to increased synthesis of prototypic acute phase reactants, such as C-reactive protein (CRP), from the liver and into the bloodstream. Eventually, all of these dysregulated immune responses elicit various sequelae, such as the destabilization of endothelial cell-to-cell interactions, the destruction of the capillary and vascular barrier, tissue damage, and multiple organ failure, which may eventually result in the death of the infected individual [3][7].

The relationship between interleukin-6 and COVID-19 severity has been investigated by many studies [8][9][10]. Interleukin-6 (IL-6), a cytokine secreted by stimulated monocytes and macrophages, mediates a broad range of biological reactions [11]. Plasma IL-6 increases only 1 h after bodily insult and peaks after about 3–6 h [12][13]. Measurably increased IL-6 levels have been noted following trauma, stress, and infection [11]. A multifunctional cytokine that transmits cell signals and regulates immune cells, IL-6 has a strong proinflammatory effect associated with multiple biological functions and plays an important role in inflammation, tumor growth, and hematological diseases [14][15]. IL-6 triggers multiple immune responses by forming a positive feedback loop that eventually results in a cytokine storm, and elevated serum IL-6 may indicate disease severity and prognosis. Among COVID-19 patients admitted to the hospital, IL-6 was higher in the non-survival group than in the survival group [16][17]. Many studies have recognized IL-6 as a pivotal marker for implying the prognosis and severity of various diseases [18][19][20][21]. In addition, serum IL-6 may be useful for monitoring treatment response and

evaluating the efficacy of medications such as tocilizumab, an IL-6 receptor blockade used for treating severe COVID-19 infections [10][22].

1.2. C-Reactive Protein, Procalcitonin and Ferritin

As serum cytokines such as IL-6 and TNF-α are released, they further stimulate several downstream immune pathways, increasing the production of acute-phase reactants such as C-reactive protein (CRP) and procalcitonin (PCT). CRP is a non-specific acute-phase protein induced by IL-6 in the liver and a sensitive biomarker of inflammation, infection, and tissue damage [23].

CRP level is usually low in the bloodstream. Following acute inflammatory reactions, serum CRP increases significantly within 12–24 h, with a 20–72 h plateau and a subsequent return to baseline levels in 3–7 days [24][25][26]. As most CRP components are synthesized in the liver, liver failure would hinder the production of CRP [27]. COVID-19 patients with higher serum CRP are prone to evolve to severe disease states [28]. Among these COVID-19 patients, higher circulating CRP is associated with a higher rate of adverse events, such as venous thromboembolism events, acute kidney injury, and higher in-hospital mortality [29].

Procalcitonin (PCT), the precursor of calcitonin, is a glycoprotein consisting of a 116-amino acid, which is typically synthesized and released by thyroid parafollicular C cell [30][31]. Procalcitonin increases within four hours of response to infection or acute injury as an acute inflammatory marker, peaks at 6 h with a plateau at 8–24 h, and a return to baseline levels in 2–3 days [26]. Increased serum PCT level is associated with a high risk of bacterial infections and sepsis rather than viral infections, and PCT has previously been used to distinguish between bacterial and viral infections [32]. However, elevated PCT levels are correlated with the severity of SARS-CoV-2 infection [33][34][35]. Compared to moderate COVID-19 patients with abnormal image findings and clinical symptoms only, severe cases demonstrated a four to eight times higher procalcitonin level during severe or critical SARS-CoV-2 infection, respectively [35]. PCT levels appear to be useful as a disease severity predictor and may further imply concomitant bacterial infections. Co-infection rates were higher during severe SARS-CoV-2 infection and were accompanied by raised PCT levels [35]. For this reason, gradually increasing serum PCT levels may indicate a poorer prognosis.

Ferritin, an acute-phase protein, may interfere with iron metabolism [36]. Iron parameters, such as ferritin and transferrin, are not yet considered standard biomarkers for monitoring COVID-19 disease progression because the relationship between iron metabolism and COVID-19 remains unclear [37]. Some studies have claimed that elevated ferritin is a risk factor for COVID-19 severity [38][39][40].

2. Hematological Abnormality

SARS-CoV-2 infection alters the hematopoietic system and hemostasis, causing hematological abnormality and coagulopathy.

Lymphocytopenia, a hallmark of COVID-19, may be considered a crucial laboratory finding in terms of being a prognostic predictor. The degree of lymphopenia is correlated with the severity of the disease, while absolute lymphocyte counts (ALC) lower than 1000/mm^3 indicate a poor prognosis [41]. The pathological mechanism of lymphopenia during severe COVID-19 disease states remains unclear, but the current evidence has led to multiple hypothesized mechanisms: (1) because SARS-CoV-2 is known to affect tissues (lung, heart, gastrointestinal tract) and induce ACE2 expression in the process, and because lymphocytes express ACE2 receptor on their surface [42], SARS-CoV-2 may directly infect lymphocytes and induce lysis or apoptosis; (2) the cytokine storm, a significantly increased cytokine response provoked by SARS-CoV-2 infection, attributes significant elevation of interleukins (primarily IL-6, IL-2, IL-7, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, MCP-1, and MIP1-a) and raised tumor necrosis factor (TNF)-α, which leads to lymphocyte apoptosis [43][44][45]; (3) coexisting lactic acidosis may interfere with lymphocyte proliferation [46]; and, (4) increased cytokines may also contribute to lymphoid organ atrophy (including the spleen) and further hinder lymphocyte turnover [47].

From an adaptive immunity perspective, SARS-CoV-2 infection influences total lymphocyte count and balance. This hematological presentation, the result of an increase in circulating pro-inflammatory cytokines, is most impactful in patients with severe COVID-19 infection, who have shown significant reductions in the absolute number of CD4+, CD8+, B, and natural killer (NK) cells [48][49]. Additionally, decreased numbers of other mononuclear leukocytes, such as monocytes, eosinophils, and basophils, have also been documented [50], and may provide a strong predictive value for in-hospital mortality, organ injury, and severe respiratory injury and complications [51].

Eosinopenia seems to have a significant role in COVID-19 diagnosis and prognosis, as significantly reduced eosinophils were found in severe cases [52][53]. Eosinophils are primarily responsible for allergic reactions and anti-parasitic infections [54]. Previous animal studies have demonstrated an antiviral effect of eosinophils in various respiratory infections [55][56]. Persistent eosinopenia was associated with higher mortality, but an increased eosinophil count was associated with disease improvement [57][58]. Interestingly, asthmatic patients with higher eosinophil counts have lower hospitalization rates and are less likely to succumb to severe disease. Patients with pre-existing conditions associated with eosinophilia, such as asthma or allergic rhinitis, may be more protected from severe SARS-CoV-2 infection [52].

Neutrophilia in COVID-19 patients may be also be used as a predictive marker for disease severity. Following SARS-CoV-2 infection, the increased emergence of immature neutrophils in the blood has been directly correlated with the severity of COVID-19 [59][60]. The recruitment of neutrophils from the circulation into tissues occurs in most organs, especially in highly vascularized areas such as the lungs and kidneys [61]. This influx of neutrophils somehow damages neighboring vessels and parenchyma. Neutrophils are provoked to release neutrophil extracellular traps (NETs) upon facing threat signals. NETs immobilize and limit pathogens and facilitate their killing by antimicrobial agents. However, excessive formation or impaired removal would endanger the host [62]. The dysregulated NET formation may contribute to direct vascular injury and indirectly induce autoimmune vasculitis by forming autoantibodies [63]. Histopathological evidence suggests that NET-induced immune-thrombosis is associated with thrombotic events and organ damage in severe COVID-19 infections [64].

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been recognized as essential independent predictive factors for identifying at-risk COVID-19 patients [65][66]. Elevated NLR or PLR indicate that patient health is deteriorating and that they require increased oxygen, and that they are at higher risk of developing acute respiratory distress syndrome (ARDS) [67]. The unique hematological manifestations of SARS-CoV-2 infections may indicate the possible utility of a prognostic test base on hematological responses. Continuous assessment of lymphocyte count dynamics may provide valuable information for predicting patient prognoses. At the point of symptom onset, patients presenting lower lymphocyte percentages have been associated with increased disease severity over time [68].

3. Organ Damage Indicator

3.1. Acute COVID–19 Cardiovascular Syndrome

A host of cardiovascular complications and involvements, called “acute COVID-19 cardiovascular syndrome”, occur during SARS-CoV-2 infection [69]. Acute coronary syndrome, myocardial injury, decompensated heart failure, stress-induced cardiomyopathy, pericardial effusion, viral myocarditis, or arrhythmia may be induced by various pathogenic routes following COVID-19 infection. Among patients with pre-existing cardiovascular comorbidities, cardiovascular diseases become more compromised or decompensated during COVID-19 infection. Systemic inflammatory response, thromboembolic events, and direct viral invasion compromise the cardiovascular system in COVID-19 patients, as do particular medication side-effects and hospital-acquired infections [69][70].

3.2. Cardiac Troponin

Myocardial injury is associated with poorer prognosis and outcome [69]. Cardiac troponins, consisting of troponin T, troponin I, and troponin C, are sensitive and specific for myocardial injury, and will appear elevated 4–10 h after acute myocardial ischemia [71]. They have been correlated with poor prognosis in cases involving pulmonary embolism or ischemic heart disease [70]. Cardiac complications have been more prevalent among COVID-19 cases compared to cases of SARS (severe acute respiratory syndrome). Epidemiological evidence indicates that 12% to 20% of hospitalized patients with COVID-19 have cardiac injuries, as implied by raised cardiac troponin levels [69][72]. For this reason, cardiac troponin may be useful as a potential prognostic marker to estimate patient outcome and mortality risk.

3.3. Brain Type NPs and N-Terminal Pro-BNP

Plasma natriuretic peptides (NPs), such as BNP (brain type NPs) and N-terminal pro-BNP (NT-proBNP), are commonly examined to evaluate acute heart failure (HF) patients [73]. Elevated NT-proBNP levels are associated with higher in-hospital mortality rates in COVID-19 cases [74] and provide more predictive value in combination with cardiac troponin [75]. However, although higher serum brain natriuretic peptide levels have been associated with cardiogenic pulmonary edema in COVID-19 patients with ARDS, some may have high levels of brain natriuretic peptide without significant ventricular dysfunction [76]. These cardiac biomarkers should be carefully considered when evaluating heart failure, as there are multiple mechanisms of cardiac injury. A point-of-care cardiac ultrasound should be considered to assess heart function to tailor treatment [76].

3.4. COVID 19-Associated Acute Renal Injury

In addition to the pulmonary manifestations associated with COVID-19, acute kidney injury (AKI) is a common complication during SARS-CoV-2 infection. Several pathogeneses injure renal tissues: local or systemic inflammatory responses and reactions, endothelial injury, coagulation-induced thromboembolic event, and renin–angiotensin system activation [77]. According to Kidney Disease Improving Global Outcomes (KDIGO), guidelines, which provides the consensus definition of AKI, previous studies have reported that nearly 30–50% of hospitalized patients with COVID-19 develop some form of AKI [78][79][80]. Near half of all patients in intensive care units (ICU) with acute kidney injury require renal replacement therapy [79][80], and in-hospital mortality is higher among patients with acute kidney injury [77]. The clinical manifestations of renal function deterioration range from mild proteinuria/hematuria to a drop in glomerular filtration rate (GFR), increased serum creatinine, or evolution to chronic kidney disease [77]. Notably, patients with pre-existing chronic kidney disease are vulnerable to severe clinical presentations and higher mortality [81]. For these reasons, deteriorated renal function or pre-existing renal disease during COVID-19 infection may indicate a poorer prognosis.

3.5. Markers for Other End-Organ Injury

Lactate dehydrogenase, an enzyme ubiquitously present in all human tissue, can be used as an indicator of gluconeogenesis and DNA metabolism [82]. Inflammatory responses and thromboembolic events hinder microcirculatory function and compromise oxygen delivery, increasing the likelihood of gluconeogenesis and DNA metabolism. Higher serum LDH might, therefore, be used to indicate COVID-19 disease severity and predict mortality risk [83][84][85].

Furthermore, higher serum lactate level is frequently considered an indicator of organ hypoperfusion or tissue hypoxia and is associated with more severe COVID-19 conditions. Higher serum lactate level is associated with poor prognosis and higher mortality [86][87].

3.6. Multisystem Inflammatory Syndrome

Multisystem inflammatory syndrome (MIS) is a rare but severe condition associated with post-COVID-19 infection in which various body parts become inflamed. MIS may involve the heart, lungs, kidneys, brain, skin, eyes, and/or the gastrointestinal organs. The presence of the symptoms in people <21 years old (or ≤19 years old per the World Health Organization definition is defined as MIS-children (MIS-C), and the presence of symptoms in people >21 years old is defined as MIS-adult (MIS-A). MIS-C is more common than MIS-A [88][89]. MIS shares similar clinical features with Kawasaki disease, an acute pediatric medium-vessel vasculitis. Symptoms, which include fever, elevated inflammatory markers, and multiple organ dysfunction, develop during or after SARS-CoV-2 infection [90].

Additional MIS-associated abnormalities include leukopenia/lymphopenia, elevated serum D-dimer, PCT, creatine kinase, and IL-6. Moreover, children with severe complications may have higher CRP, procalcitonin, or troponin levels and lower lymphocyte/platelet count [91][92]. The biomarkers listed in **Table 1** may help establish the relationship between diagnostic criteria and clinical presentations [89][92].

Table 1. Diagnostic criteria for multisystem inflammatory syndrome in children (MIS-C) [89][93].

World Health Organization	Centers for Disease Control and Prevention (United States) *
• Children and adolescents **0–19 years** of age with **fever > 3 days** AND • **Two** of the following: ◆ Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet). ◆ Hypotension or shock.AND ◆ Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP), ◆ Evidence of coagulopathy (by PT, PTT, elevated d-Dimers). ◆Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain). • Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. AND • No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes. AND • Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.	• An individual **aged <21 years** presenting with fever >38.0 °C for ≥24 h • Laboratory evidence of inflammation, **> 1 finding** ◆An elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin • Evidence of clinically severe illness requiring hospitalization, with **>2 organ involvement** ◆Cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND • No alternative plausible diagnoses. AND • Positive for current or recent SARS-CoV-2 infection ◆Confirmed by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the *4 weeks prior to the onset of symptoms*.

* (1) Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C. (2) Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

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