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The role of laboratory test biomarkers in diagnosis, risk assessment, and monitoring of COVID-19 patients

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Abstract

Government officials, healthcare providers, and scientists continue their efforts to identify and find ways of treatment regarding the coronavirus infection (CoV), also known as Severe acute respiratory syndrome coronavirus 2. This is due to the fact that the COVID-19 infection is ongoing and there is a possibility of new infections or new waves of disease. In addition to this possibility, there is also the continuity of the COVID-19 infection (SARS-CoV-2). Researchers have a pressing need for adequate biomarkers that are associated with the progression of SARS-CoV-2 in order to stratify patients who are at high risk. Because the disease can spread so rapidly, patients need to be classified into risk groups as soon as possible after their diagnosis in order to make the most efficient use of available resources. In addition, new markers are required in order to identify patients who have a rapid progression of their disease, which can lead to death or a serious infection. It is essential to gain a comprehension of the viral pathogenetic mechanisms, as well as the cellular and organ damage, prior to the discovery of novel biomarkers. The clinical management, screening, and prevention of serious complications could all be improved with the use of reliable biomarkers. To effectively manage the COVID-19 pandemic, future prevention, prompt diagnosis, superior treatment, and precise detection are not only extremely important but also have the potential to assist in reducing the spread of the virus. According to the conventional medical consensus, biomarkers play a very important role in the prompt detection of the etiology, treatment, diagnosis, and prognosis of a disease. This work discusses emerging and known biomarkers for detecting SARS-CoV-2 diagnostics, prognosis, and treatment in order to assist the numerous innovations and investigations that are currently taking place.

Introduction

SARS-CoV-2 has been declared a pandemic by WHO. Humans and animals (alpacas and bats) are all infected by SARS-CoV. Many human SARS-CoV-2 are causing many respiratory infections—majorly mild illnesses like the common cold that might result in life-threatening and more severe infections (1). SARS-CoV-2 got its name from how they are seen under a microscope. CoV contains a genetic material core surrounded via an envelope with protein spikes; thus, it appears as a crown (2). SARS-CoV-2 are zoonotic, meaning the viruses are transmitted between humans and animals (3). Commonly, SARS-CoV-2 presents with respiratory symptoms. There might be no symptoms among some of the infected individuals, whereas individuals developing symptoms might show mild-moderate yet self-limiting disease with symptoms comparable to seasonal flu. Those clinical manifestations might be cough, fever, difficulties in breathing, shortness of breath, sore throat, and fatigue (4). Some patients show symptoms of more severity with a need for hospitalization, commonly with pneumonia. In a few instances, the illness might involve acute respiratory distress syndrome (ARDS), sepsis, and septic shock (4).

To stratify high-risk patients, scientists urgently need adequate biomarkers associated with the progression of SARS-CoV-2. To ensure optimum resource allocation, patients must be immediately classified into risk groups after diagnosis due to the quick spread of the disease. Also, new markers are required to recognize patients who experience quick disease progression, death, and serious infection. Understanding viral pathogenetic mechanisms and cellular and organ damage are critical to discovering novel biomarkers. Effective biomarkers could benefit clinical management, screening, and preventing serious complications. The presented study focuses on commonly used laboratory tests for inflammation and organ damage, such as ferritin, C-reactive protein (CRP), leucocyte count, procalcitonin, urea, estimated glomerular filtration rate (eGFR), D-dimer, alanine aminotransferase (ALAT) and troponin.

Pathogenesis of SARS-CoV-2

There are three stages for the disease's symptoms. Throughout the first stage (asymptomatic stage), the virus is attached to the Angiotensin-Converting Enzyme-2 (ACE 2) replicates and receptors. Swab testing may be used to identify the virus, with throat swabs being less accurate than nasal swabs. Throughout this stage of the disease, there is a limited innate immune response (5). The second phase, known as the respiratory infection, involves the virus moving down the respiratory system as the innate immune responses are activated. The upper respiratory tract will often be the only area of infection for affected people (5). Hypoxia and Acute Respiratory Distress Syndrome is the third stage (ARDS); it is where the virus can reach, infect and damage the alveoli in the lung. Also, interferons are released, signaling the close healthy cells to release antiviral peptides (6). A virus breakdown is caused by antiviral peptides. Furthermore, injured cell emit toxic compounds known as cytokines, damage-related molecules, and protein-related molecular patterns that stimulate phagocytosis by the innate immune system (7).

The signs are responded to through immune cells, which release further inflammatory signals, causing the fluid between the capillary and the alveolus to fill (a zone accountable for gas exchanges). Furthermore, neutrophils reach the infection site while the virus destroys the healthy pneumocytes. As a result, the alveolar surfactant level drops. Furthermore, phagocytic cells emit inflammatory mediators such as IL2, IL6, IL10, TNF, G-CSF, and MCP1 (3,8).

Cytokine storm is the body's hyperactive immune response. It affects the alveoli's gas exchange, resulting in ARDS and hypoxemia. The protein-rich fluid may enter the circulation in highly serious infections, leading to multiorgan failure and SIRS (systemic inflammatory response syndrome) (9) **(Figure 1).**

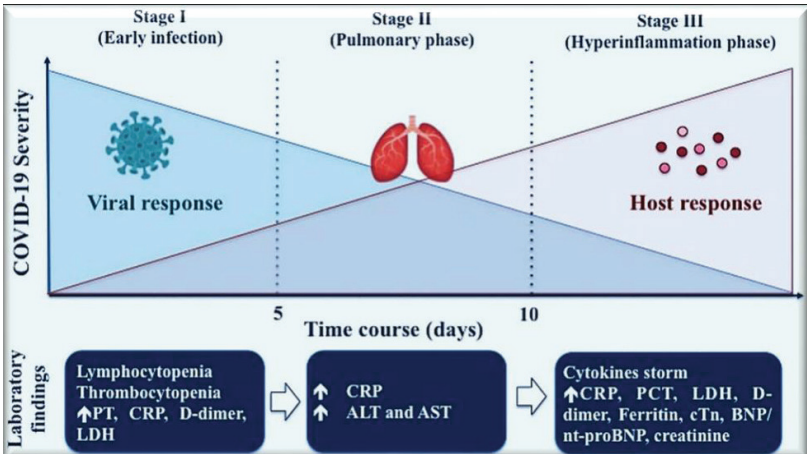

Figure 1: Biochemical biomarkers alterations in COVID-19

COVID-19 infection and severe progression markers

Patients with severe illnesses were found to have a sequence of biochemical, hematological, inflammatory, and immune biomarker defects, which justifies their inclusion in risk prediction models **(Table 1)** (10).

Table 1: Summary of laboratuary changes in patients experiencing fata or severe COVID-19

Hematologic	Biochemical	Coagulation	Inflammatory biomarkers
↑ WBC count	↓ Albumin	↑ Prothrombin time	↑ Erythrocyte sedimentation rate
↑ Neutrophil count	↑ Alanine aminotransferase	↑ D-dimer	↑ CRP
↓ Lymphocyte count	↑ Aspartate aminotransferase		↑ Serum ferritin
↓ Platelet count	↑ Total bilirubin		↑ PCT
↓ Eosinophil count	↑ Blood urea nitrogen		↑ IL-6
↓ Hemoglobin	↑ Creatinine		↑ IL-8
	↑ Creatine kinase		↑ IL-10
	↑ Lactate dehydrogenase		
	↑ Myoglobin		
	↑ Creatine kinase-MB		
	↑ Cardiac troponin I		

CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; WBC, white blood cell.

Hematologic biomarkers utilized for stratifying patients experiencing SARS-CoV-2 lymphocyte count, white blood cell count (WBC count), neutrophil-lymphocyte ratio (NLR), neutrophil count, eosinophil counts, and platelet counts. A study conducted by Qin et al., analyzed markers associated with the immune responses' dysregulation in a group of 450 COVID-19 eusured patients, indicating that severe situations tend to have low lymphocyte-, high leukocyte-counts, and high NLR, also low percentage values of eosinophils, monocytes, and basophils in comparison to mild cases (11). Also, in a meta-analysis of 21 studies involving 3,377 COVID-19 positive patients, Henry et al. found that patients with fatal and severe diseases had significantly higher WBCs and lowered platelet and lymphocyte counts than survivors of the non-severe disease (10). In SARS-CoV-2 patients, both (suppressor and helper T cells) were lower than normal, with lower helper T cell levels Linked to severe situations. The fraction of naïve helper T cells notably grew in severe instances, whereas memory helper T cells reportedly decreased. Patients with SARS-CoV-2 also exhibit low levels of regulatory T cells, which, in extreme cases, were damaged (11). To suppress the viral infection, killer lymphocytes such as natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) were required. Cytotoxic lymphocyte functional fatigue is correlated with disease progression. In SARS-CoV-2 patients, the overall number of T cells, NK cells, and B cells has been markedly reduced (11,12).

A study by Xue et al. indicated that a reduction in the specific T lymphocyte subsets had been related to severe illness and in-hospital death. Low counts of T lymphocyte subsets; the cluster of differentiation 3 T-cell (CD3 + T-cell) (less than 200/μL), lymphocyte (less than 500/μL), cluster of differentiation 8 T-cell (CD8+ T-cell) (less than 100/μL), cluster of differentiation 4 T-cell (CD4+ T-cell) (less than 100/μL), and B-cell (less than 50/μL) were related to high risks of in-hospital death caused by COVID-19. In addition, warning values for predicting in-hospital deaths of lymphocytes, CD 3+ T-cells, CD 4+ T-cells, CD 8+ T-cells, and B-cells have been $559\mu L^{-1}$, $235\mu L^{-1}$, $104\mu L^{-1}$, $85\mu L^{-1}$ and $82\mu L^{-1}$, respectively[12]. In research that involved 32 SARS-CoV-2 patients, reduced eosinophil count has been reported in 66%. A study by Liu *etal.*, indicated low eosinophil values during the initial hospitalizations, which returned to normal before discharges, specifying that an increase in eosinophils might indicate a clinical improvement of SARS-CoV-2 (13).

The neutrophil-lymphocyte ratio (NLR), calculated via the neutrophils count/lymphocytes count ratio, is one of the inflammatory markers predicting the death probability in patients with different cardiovascular diseases. Regarding patients experiencing COVID-19, NLR was reported as an independent risk factor for severe disease. A total of 50 (75.8%) patients with a progression of the disease throughout hospitalization had an NLR ≥2.973, indicating the severity of SARS-CoV-2 (14). Platelet count was used as a possible biomarker for patients experiencing SARS-CoV-2 because it is a cheap, easily available, and simple biomarker independent of the disease's severity and mortality risks in the ICU. The number of platelets is considerably decreased in SARS-CoV-2 patients and has been low in nonsurvivor patients compared to the survivors, and might serve as one of the indicators of clinical disease worsening throughout hospitalization. Furthermore, damaged lung tissue and pulmonary endothelial cells might activate platelets in the lungs, leading to aggregating and forming of micro-thrombi, thus increasing the platelets' consumption (15). In severe disease, WBC shows lymphocytopenia, impacting $CD\ 4^+$ and $CD\ 8^+$ cells, along with a reduction in eosinophils and monocytes and an increase in NLR and neutrophils. Those simple parameters might be utilized for critically ill patients' identification and early diagnosis (10,16,17).

Biochemical biomarkers

In fatal or severe SARS-CoV-2 patients, the major laboratory changes have been explored recently in the meta-analysis, involving 3 large types of research comparing nonsurvivors with survivors. A considerable rise in creatine kinase (CK) and total bilirubin, along with serum ferritin, counts of the WBCs, and IL6, has

been registered in no survivors compared with the survivors. Also, assuming a strong relation between SARS-CoV-2 and thrombo-embolism and somewhat myocardial injury, cardiac markers and D-dimer is vital in SARS-CoV-2 monitoring(16), Also used as usfull tools disfuncion in muscles such as heart muscles in which the injury or dysfunction in these organs cause increase in CK level , However, Several studies was shown that CK amd D dimer have been increased in patients with fatal SARS-CoV-2 infection . At presentation, nonsurvivors had considerably high levels of cardiac troponin WMD: 32.70 ng/L), which is possible because of cardiac injury and viral myocarditis from the progression of the disease to MOF. Regarding MOF, a significant increase in liver enzymes (AST and ALT) is associated with critical variations in renal function tests (creatinine, blood urea nitrogen) and coagulation markers (10).

In this regards *Chenn et al.*, identified in a group of 799 patients (161 recovered and 113 nonsurvivors) significantly high concentrations of AST, ALT, creatinine, cardiac troponin I, Lactate dehydrogenase (LDH), D-dimer and N-terminal pro-brain natriuretic peptide in nonsurvivors in comparison with the Cured patients. Concerning prospective research of 179 patients with SARS-CoV-2 pneumonia (21 no survivors), cardiac troponin I more than 0.05 ng/mL has been recognized between the 4 risk factors predictive of mortality (more than 64 years old, pre-existing concurrent cardiovascular or cerebrovascular illnesses, T cells less than 75 cell/ μL) (17). In addition, hypoalbuminemia has been indicated in 55% of hospitalized patients with SARS-CoV-2 and is related to the severity of the disease. Also, hypoalbuminemia is one of the mortality's independent predictors. Low pre-albumin levels were indicated in patients with severe SARS-CoV-2, assuming reduced hepatic synthesis. Regarding inflammation, hypoalbuminemia might also reflect albumin extravasation due to the increase in capillary permeability. Other factors that might explain the identified hypoalbuminemia in severe SARS-CoV-2 are increased malnutrition and catabolism (18). Furthermore, the correlation between SARS-CoV-2 severity and renal dysfunction was analyzed. Serum renal function indexes such as urea nitrogen, uric acid, cystatin C, creatinine, and estimated glomerular filtration rate (eGFR) have been evaluated. The levels of cystatin C and serum creatinine were high, while the serum eGFR levels were low in severe patients compared to the ones with mild disease. Urea nitrogen, uric acid, and cystatin C did not differ between patients with severe and mild disease. According to the results, 11 (37.9%) cases of renal disfunction were present in Acute ill patient upon entry, compared to 5 (4.0%) cases in mild patients (19).

Coagulation biomarkers

Hypercoagulation which is linked to SARS-CoV-2. In both retrospective and prospective studies, patients with severe SARS-CoV-2 had increased levels of coagulation proteins than non-severe cases. The major abnormal coagulopathy biomarkers identified were increased D-dimer levels, reduced platelet counts, and a slightly prolonged prothrombin time (20). Patients with D-dimer levels above 1,000 ng/mL (standard range 250 ng/mL) had an 18-fold higher mortality risk in one study from Wuhan, China (21). One large retrospective study (n = 380) showed that Prothrombin time (PT), D-dimer, and fibrin degradation products (FDP) have been considerably high in critically-ill patients in comparison to the ones with severe and mild disease, and their levels are positive correlation with the severity of the disease (22). The presence of disseminated intravascular coagulation is suggested by thrombocytopenia, elevated D-dimer, and increased prothrombin time (DIC). Nonetheless, the biomarker levels reported in SARS-CoV-2 are not representative of those seen in other conditions that cause DIC, such as sepsis. SARS-CoV-2 -induced DIC has significantly higher D-Dimer levels and lower platelet counts than sepsis-induced DIC (20).

Patients with SARS-CoV-2 are at higher risk of venous thromboembolism (VTE). Comorbidities and the potential of endothelial cell activations/damages because of the virus binding to the ACE 2 receptor collectively raise VTE risks. Prompt pharmacological thrombo-prophylaxis with heparin of low molecular weight has been suggested (23). In brief, considerable coagulation abnormalities have been identified in patients experiencing SARS-CoV-2 compared to healthy controls, while they were positively correlated with the severity of the disease. Monitoring coagulation parameters might be extremely important for the early identification of severe cases.

Clinical utility of the D-dimer

An increase in D-dimer occurs physiologically in neonates, older adults, and pregnant women. Increase in pathological situations associated with thrombosis, such as cerebrovascular accident (CVA), deep vein thrombosis (DVT), pulmonary thromboembolism (PET), and disseminated intravascular coagulation (DIC). Numerous other situations not related to thrombosis in which this biomarker is increased hemorrhage, cancer, respiratory distress syndrome, hemolysis, kidney disease, liver disease, congestive heart failure, infection, recent surgery, trauma, burns, rheumatoid arthritis, and in hospitalized patients (2).

In the laboratory it is mainly used for the diagnosis and monitoring of DIC and to rule out venous thromboembolic disease (VTE) in patients with intermediate or low clinical probability. For the latter case, the methodology must have high sensitivity (SS) and negative predictive value (NPV). That is why it is important to find out what needs we have in our work center to select the most appropriate one (23).

D-dimer and SARS-CoV-2

Approximately 15% of patients infected with the SARS-CoV-2 virus evolve with a severity that requires hospitalization. In a large percentage of these patients, coagulopathy characterized by hypercoagulability is observed, with a risk of venous and/or arterial thrombotic phenomena, alteration of coagulation tests, and, rarely, bleeding. D-dimer is a marker of the severity of this coagulopathy (24).

In the laboratory, the method used should be quantitative and reportable to the countable range since very high results are observed in severe patients. As described in other pathologies, in the course of infection, the values are not comparable between the different methodologies used. It is postulated that the disproportionate increase in D-dimer in SARS-CoV-2 infection is the result of systemic activation of coagulation, with fibrin formation and lysis of it (intra-vascular source) and direct lysis of pulmonary interalveolar fibrin due to urokinase, produced by alveolar and endothelial epithelial cells (extravascular source) (25).

Upon admission to hospitalization, to have a baseline value and make an initial estimate of the patient's risk, an initial D-dimer value greater than or equal to 4 times the upper normal value would indicate a worse prognosis.

During hospitalization, if the value of admission is less than 2 times the upper limit of normal, no further determinations would be necessary unless clinical deterioration. If the initial value is greater than 2 but less than 6 times the upper limit of normal, it is suggested to use the dimer D together with other parameters of the laboratory (ferritin, PCR, LDH, etc.) and the patient's clinic to predict the possible deterioration of the picture or the search for thrombosis, measuring it every 24 or 48 h. 6 If the value of admission is greater than 6 times the upper limit of normal, monitoring is suggested according to clinical evolution, since an abrupt increase in D-dimer without an increase in other inflammatory markers (CRP, ferritin) could indicate the presence of thrombosis. 15 For patients hospitalized in Critical Care, monitoring is recommended every 24-48 hours. The Argentine Society of Hematology also suggests for these patients evaluate the development of severe coagulopathy as a prognostic factor every 24 hours by calculating ISTH CIS/CID scores (25).

Procalcitonin and COVID-19

The viral particles enter by endocytosis, binding through their S protein (spike) to the ACE 2 receptor of the host cell (26,27). It is a positive polarity RNA virus that deposits its material into the cytoplasm of the host cell. The cytoplasm is where the enzymes needed for the creation of cellular components and the replication of the host cell's genetic material are found. The viral particles that will be discharged from the infected cell are formed as a result of the replicated RNA joining with the nucleocapsid and putting together with the structural proteins. The innate immune response is the first to respond: through toll-like receptors (TLRs), it recognizes PAMPs (pathogen-associated molecular patterns) – in this case, viral RNA – and de-chains the signaling cascade for immune response (28-30). The INF will regulate viral replication, and the NK cells (natural killers) will destroy infected cells. Then, macrophages and dendritic cells will present viral debris on their surface to activate T and B lymphocytes in triggering the adaptive immune response (31,32). Thus, T lymphocytes (CD4+) or helpers will stimulate more macrophages, NK, T lymphocytes (CD8+), or cytotoxic (26,33).

Laboratory methodology

procalcitonin is a very stable molecule in vitro, so it is easy to use pre-analytically, and its determination in clinical practice is expedited. It can be measured in serum or plasma and is stable for 24 h at 4 - 8ºC and 3 months at -20ºC. For procalcitonin dosing, there are different tests, semi-quantitative and quantitative methods,

Inflammatory biomarkers

Severe respiratory viral infections were related to cytokine storm, including an increase in the proinflammatory cytokines' production IL-6, TNF-α, MCP-1, and IL-1β. The release of such cytokines increases pulmonary edema, vascular permeability, multiple organ dysfunctions, and acute respiratory distress syndrome. [24] C-reactive protein (CRP) marker has been considerably increased in the infection's initial phases for patients experiencing severe SARS-CoV-2 before indicating critical results with clotting time. CRP was related to the development of the disease and is one of the early predictors of severe SARS-CoV-2. Also, authors indicated via correlation analyses that CRP ($R = 0.620$, $p < 0.010$), granulocyte/lymphocyte ratio ($R = 0.49$, $p < 0.010$), ESR ($R = 0.55$, $p < 0.010$) have

been associated positively with CT severity scores (25).

In research on patients experiencing SARS-CoV-2 pneumonia, high plasma levels of IL-7, IL-2, GSCF, IL-10, TNF-α, and MCP-1 were related to cardiac injury, acute respiratory distress syndrome, and secondary infections requiring ICU admission (26) Considerably high increase was identified for serum ferritin and IL-6 in survivors vs. nonsurvivors (760.2 ng/mL and WMD: 4.6 pg/mL, respectively) in comparison to non-severe vs. severe form (408.3 ng/mL and WMD: 1.7 pg/mL, respectively). Thus, we suggested that two parameters be utilized to monitor prognosis in SARS-CoV-2 patients over the hospitalization course (10).

These rises, along with a rise in CRP, point to the emergence of patients with the disease's severe form of a systemic inflammatory response syndrome (SIRS) picture. Additionally, the excessive rise of inflammatory cytokines like IL-6, which might cause a cytokine storm, might be one of the drivers behind ARDS and acute lung injury, resulting in other tissue damage progressing and MOF (27). One of the recent researches suggested that a progressive increase in the levels of procalcitonin (PCT) might predict a worse prognosis. Overall, 38 patients with serially-measured PCT values have been included in this paper, of whom 32 have been discharged from the hospital, and six died. Concerning 32 discharged patients, abnormal and high-normal levels of the PCT were reduced throughout recovery. For the six cases of death, however, the levels of serum PCT were subjected to an

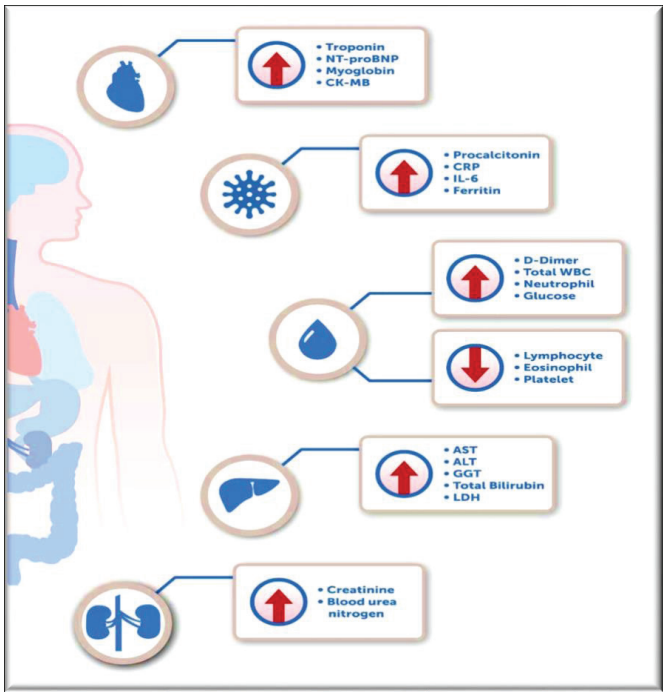

Figure 3: How COVID-19 Impacts Certain Biomarkers in Patients

increase when the disease worsened. The results show that serial measurements might predict the prognoses of SARS-CoV-2 patients (**Figure 3**) (28,33).

Treatment

Symptomatic treatment, such as preserving the airway, respiration, blood circulation, and oxygen supply (ventilation, if necessary, partial pressure of Oxygen (PO_2) less than 55%), correction of electrolyte imbalance, controlling fever (antipyretic drugs such as Paracetamol), and supporting other affected vital organs, is thought to be the best way to manage patients with various degrees of infection. Extracorporeal membrane oxygenation (ECMO) was applied to address the respiratory failure issue, yet its advantages remain under consideration. In addition, personal hygiene with diet and a healthy lifestyle were suggested for enhancing immunity. Centers for Disease Control and Prevention (CDC) states that the ones suspecting that they are carrying the virus must wear a face mask. Supportive treatments might be effective in the ones with mild symptoms at the infection's early stage (29,32).

According to a WHO report, there is no specific treatment for SARS-CoV-2 as of May 2020. Protection is the preferred solution for this pandemic because no curative treatment has been discovered. However, researchers are working on more effective drugs, and many vaccines are now available to the public.

Clinical studies have examined several medications to discover the most efficient and secure cure for this deadly infection. Drugs that counteract the effects of Cytokine Storm include tocilizumab (IL-6 blocking) and anakinra (IL-1 blockage). Clinical studies are also being conducted for antiviral and anti-HIV medications such as Remidisivr, Lopinavir/ Ritonavir, and Favilavir. Remdesivir has been suggested as a viable treatment option for hospitalized individuals with severe SARS-CoV-2 (30,31).

Conclusions

Finally, we have provided in this work a comprehensive review regarding the biomarkers linked to severe disease in patients experiencing SARS CoV 2. Hematological, inflammatory, biochemical, and coagulation biomarkers are among them. D-dimer and procalcitonin are useful biomarkers in the follow-up of patients diagnosed with COVID-19. In certain patients with SARS-CoV-2 infection, D-dimer shows a disproportionate increase due to systemic coagulation activation, fibrine formation, lysis (intravascular source), and lysis. We looked at various biomarkers with changed levels that might help guide clinical

decision-making in patients experiencing SARS CoV 2. A few biomarkers were predictive, meaning they might be assessed early in the course of a disease and might indicate whether a patient has a bad or good prognosis. They aid in the early identification of patients with a more severe disease course and must be triaged to more aggressive therapies.

In contrast, others might be spared from the harsher treatments and their debilitating side effects. Other biomarkers could be prospectively utilized for monitoring because they might be utilized in serial measurements to determine if a patient is responding to a specific therapy or if a different treatment course is required. Other biomarkers, like IL6 for tocilizumab, are predictive because they might help us identify patients who may respond to specific therapies. To validate the relevance and association of the present findings, prospective studies with sizable cohorts, precisely defined illness severity, repeated assessments, and defined sample collection schedules are necessary.

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Research concept and design: **ODS, SKI, RGR**
Data analysis and interpretation: **RGR, HAH, ODS**
Collection and/or assembly of data: **ODS, SKI, RGR, HAH**
Writing the article: **SKI, RGR, HAH**
Critical revision of the article: **ODS, HAH**
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