REVIEW DERLEME

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A Narrative Review of the Evaluation of Biomarkers in COVID-19 Patients Indicating the Course of the Disease

COVID-19 Hastalarında Hastalığın Seyrini Gösteren Biyobelirteçlerin Değerlendirilmesine İlişkin Anlatısal Bir İnceleme

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ABSTRACT The global spread of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus has led to a widespread outbreak of coronavirus disease-2019 (COVID-19), resulting in a pandemic. Following the end of the pandemic, COVID-19 has transitioned into an endemic phase characterized by anticipated periodic surges. Therefore, the development of readily available prognostic biomarkers for COVID-19 patients continues to be a crucial field of study. Monitoring of blood biomarkers for patients with COVID-19 is a crucial component of patient care. Therefore, it is necessary to conduct hematological assessments such as leukocyte count, lymphocyte count, neutrophil count, neutrophil-lymphocyte ratio, and thrombocyte count. Additionally, inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and procalcitonin should be measured. Immunological indicators including interleukin-6 and tumor necrosis factor-α should also be evaluated. Furthermore, biochemical tests such as aspartate aminotransferase, alanine aminotransferase, urea, creatinine, and troponin levels should be assessed. Lastly, coagulation parameters such as D-dimer, fibrin degradation products, and fibrin levels should also be examined. The objective of this narrative review is to assess blood biomarkers that have the potential to be valuable in monitoring the progression and management of COVID-19. Studies published between 2020 and 2023 and scanned in PubMed, Ebsco and Google Scholar were used in the analysis. Keywords such as "COVID-19", "SARS-CoV2", "biomarkers" and "severe SARS-CoV-2 infection" were used to restrict the search.

Keywords: COVID-19; SARS-CoV-2; biomarkers

ÖZET Şiddetli akut solunum sendromu-koronavirüs-2 [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)] virüsünün küresel yayılımı, yaygın bir koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] salgınına yol açarak bir pandemiye yol açmıştır. Pandeminin sona ermesinin ardından, COVID-19, beklenen periyodik artışlarla karakterize edilen endemik bir aşamaya geçmiştir. Bu nedenle, COVID-19 hastaları için kolaylıkla bulunabilen prognostik biyobelirteçlerin geliştirilmesi önemli bir çalışma alanı olmaya devam etmektedir. COVID-19 hastalarına yönelik kan biyobelirteçlerinin izlenmesi hasta bakımının çok önemli bir parçasıdır. Bu nedenle lökosit sayısı, lenfosit sayısı, nötrofil sayısı, nötrofil-lenfosit oranı, trombosit sayısı gibi hematolojik değerlendirmeler; C-reaktif protein, eritrosit sedimantasyon hızı ve prokalsitonin gibi inflamatuar belirteçler; interlökin-6 ve tümör nekroz faktörü-α gibi immünolojik göstergeler değerlendirilmelidir. Ayrıca aspartat aminotransferaz, alanin aminotransferaz, üre, kreatinin ve troponin düzeyleri gibi biyokimyasal testler; D-dimer, fibrin bozunma ürünleri, fibrin düzeyleri gibi pıhtılaşma parametreleri incelenmelidir. Bu geleneksel derlemenin amacı, COVID-19 hastalığının ve tedavisinin monitörizasyonu için faydalanabilecek kan biyobelirteçlerini değerlendirmektir. Analizde 2020 ile 2023 yılları arasında yayımlanan ve PubMed, Ebsco ve Google Scholar'da taranan çalışmalar kullanılmıştır. Aramayı kısıtlayabilmek için "COVID-19", "SARS-CoV2", "biyobelirteçler" ve "şiddetli SARS-CoV2 enfeksiyonu" gibi anahtar kelimeler kullanılmıştır.

Anahtar Kelimeler: COVID-19; SARS-CoV-2; biyobelirteçler

The new coronavirus disease-2019 (COVID-19) pandemic is a virus outbreak emerging by November 2019 in Wuhan, China. This novel type of coronavirus named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was causing basically pneumonia and did not respond to conventional treat-

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ments. The transmission route of the virus was from person to person, and a global epidemic was declared by the World Health Organization on March 11, 2020. COVID-19 can infect cells through various mechanisms, the most common of which is via angiotensin-converting enzyme-2 (ACE-2) receptors.[1] Previous studies have found ACE-2 receptors to be expressed in various cell types, including Type 1 and Type 2 alveolar epithelial cells in the lungs, epithelial cells in the gastrointestinal tract, myocytes, vascular endothelial cells and hematopoietic stem cells.[2] Although the condition was initially thought to affect the respiratory system, with the increasing number of cases it was subsequently realized that COVID-19 is a systemic disease that affects multiple systems, including the cardiovascular system, gastrointestinal tract, nervous system, hematopoietic system and the immune system.[3] For this reason, molecular, serologic, and biochemical markers have gained importance for the diagnosis and follow-up of patients with COVID-19 and for evaluations of disease severity. The severity of the COVID-19 disease is determined by comparing the signs, symptoms, radiological, and biochemical indicators with the clinical aspects. This is done by creating four distinct groups.

Mild: Exhibiting minor symptoms without any indication of pneumonia.

Moderate: Common manifestation of chest symptoms accompanied by fever or signs of respiratory system involvement, along with radiographic evidence of pneumonia.

Severe: Presenting any of the three conditions; i) Breathing distress, with a breathing rate of 30 beats per minute or higher, ii) Oxygen saturation of 93% or less while at rest, iii) The arterial blood oxygen partial pressure or oxygen concentration should not exceed 300 mmHg. **Critical:** possessing one of the three specified conditions; i) Prevalence of shock, ii) Experiencing respiratory failure and needing assistance from mechanical ventilation, iii) Admission to the intensive care unit (ICU) due to multiple organ dysfunction.[4] Recognition and evaluation of COVID-19 individuals who are prone to progressing to a severe and critical stage, establishing suitable treatment protocols, and determining appropriate intensive care circumstances for high-risk patients helps enhance the disease's prognosis. Hence, the association between biochemical markers and the clinical progression of the disease has the great importance. The objective of this assessment is to assess blood biomarkers that could potentially signal the progression of the disease and the effectiveness of treatment. The analysis of the studies used for this narrative review, published from 2020 to 2023, have been indexed in PubMed (owned by the National Center for Biotechnology Information company in USA), Ebsco (owned by EBSCO Industries, Inc company in USA), and Google Scholar (owned by Google company in USA). The overall search has been limited with keywords "COVID-19", "SARS-CoV-2", "biomarkers", and "severe SARS-CoV-2 infection". Biomarkers for monitoring COVID-19 patients are given with Figure 1.

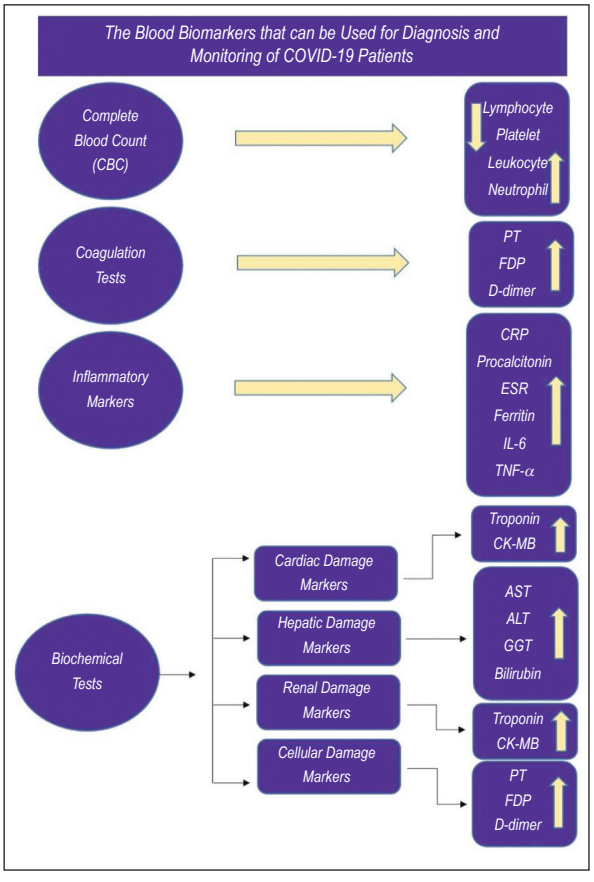

FIGURE 1: Biomarkers for monitoring COVID-19 patients.
CBC: Complete blood count; PT: Prothrombin time; FDPs: Fibrin degradation products; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor alpha; CK-MB: Creatine kinase-myocardial band; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyl transferase.

BLOOD BIOMARKERS IN COVID-19 PATIENTS

The routine tests ordered for the follow-up of COVID-19 patients and for the evaluation of possible risks include complete blood count (CBC), coagulation parameters [prothrombin time (PT), activated partial thromboplastin time (aPTT) and D-dimer] and inflammatory markers [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, procalcitonin]. In addition to these routine tests, an analysis of biochemical markers is appropriate and necessary for the evaluation of the functional activity of such vital organs as the heart, liver and kidneys, as the virus has the potential to severely affect these organs.[5]

CBC PARAMETERS

Lymphocytes

The absolute lymphocyte count in healthy human adults is 1000-4800/mm^3, and counts below 1000/mm^3 indicate lymphopenia.[6] Meta-analysis studies have reported lymphopenia to be a common finding, in which the lymphocyte count correlates with disease severity. In one study, the rate of lymphopenia was found to range between 40% and 91.6% in COVID-19 patients, independent of disease severity.[7] In a study investigating the effect of lymphopenia severity on disease course, a lymphocyte count of less than 500/mm^3 was considered severe and a level of 500-1000/mm^3 was considered moderate lymphopenia, with mortality rates in patients with severe lymphopenia being considerably higher than in those with moderate lymphopenia.[6]

In studies evaluating the subgroups of lymphocytes, aside from the total lymphocyte count, the number of natural killer cells, CD8+ T lymphocytes, CD4+ T lymphocytes and B lymphocytes are reported to be decreased and the lymphocyte count to be lower in patients requiring ICU admission than those who do not require ICU admission.[8,9]

One of the reasons for the frequent occurrence of lymphopenia in COVID-19 patients is the presence of ACE-2 receptors in the lymphocytes to which the virus attaches, while other factors frequently contributing to lymphopenia are the increased lymphocyte apoptosis associated with the increase in cytokines throughout the disease course [particularly interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)], the invasion of the spleen and thymus by the virus, and the suppression of lymphocyte proliferation by acidosis that frequently develops during the disease course.[10,11]

Leukocytes (white blood cell)

A significant increase in the total leukocyte count has been determined in COVID-19 patients with a mild disease course, in contrast to the significant decrease in the total leukocyte count observed in those with a severe disease course. Leukocyte count can thus be considered a crucial parameter for the determination of disease prognosis.[12] It has also been found that the morphological characteristics of leukocytes are affected by coronavirus, and that morphological abnormalities may develop in patients with a severe disease course and in non-survivors.[13]

Neutrophils

Neutrophils account for 50-70% of all leukocytes, and studies have found that the number and percentage of neutrophils are often increased and associated with mortality in COVID-19 patients requiring ICU admission. The neutrophil-to-lymphocyte ratio has been reported to be correlated with disease severity and mortality, and thus may be used to predict disease course.[12,14]

It has further been reported that an increased neutrophil count plays a significant role in the physiopathology of acute respiratory distress syndrome (ARDS) and cytokine storm development, and neutrophil count may also be increased in cases of secondary bacterial infection. It is thus necessary to monitor the neutrophil counts of patients to identify any potential secondary bacterial infections.[15]

Monocyte/Macrophages

Studies investigating monocyte counts in COVID-19 patients have reported slightly increased monocyte counts or levels close to the normal reference ranges, but decreased percentages of monocytes among the leukocytes. In addition, monocyte percentages have been found to be significantly higher in patients requiring ICU admission than those who do not require

ICU admission.[16] In a flow-cytometric study, the monocyte morphology was reported to be notably impaired, and the percentage of monocytes with impaired morphology was higher in ICU patients.[17] In a postmortem study of the tissues of non-survivors of COVID-19, an intense accumulation of monocytes and macrophages in the lung and kidney tissues was observed, and the accumulation of these cells was found to play a role in the physiopathology of ARDS and acute renal failure.[18]

Eosinophils-Basophils

There are studies in literature reporting decreased eosinophil and basophil counts in COVID-19 patients that are particularly remarkable in those requiring ICU admission, although another study reported eosinophil counts to be within normal ranges or slightly elevated in such cases, and found decrease eosinophil counts to be unrelated to disease course.[16,19,20]

Platelets

A platelet counts below <150,000 mm^3 in the blood is defined as thrombocytopenia, and is a common finding in COVID-19 patients that has been associated with poor prognosis. Patients with a severe disease course are more likely to develop thrombocytopenia than those with a milder disease.[21] A meta-analysis study investigating the prevalence of thrombocytopenia in COVID-19 patients found that the majority of studies reported a greater prevalence of thrombocytopenia among COVID-19 patients with a severe disease course than in those with a mild disease course.[22]

It is believed that the direct effect of the virus on hematopoietic stem cells in the bone marrow, the autoimmune-mediated destruction of the platelets and the consumption of thrombocytopenia as a result of microthrombus formation associated with organ damage may be responsible for the physiopathology of thrombocytopenia occurring in COVID-19 patients.[23]

Erythrocytes and Hemoglobin

No significant changes in erythrocyte counts have been reported in COVID-19 patients, although there are studies reporting slightly decreased hemoglobin levels.[2,24]

The red cell distribution width (RDW) test quantifies the degree of heterogeneity in erythrocytes size or volume as a component of a CBC. There are studies indicating that patients with a severe clinical course of COVID-19 disease are more prone to have high RDW levels. Additionally, these patients face an increased risk of developing acute renal failure. As a result, RDW can serve as an indicator for assessing the severity of COVID-19 and the potential renal impairment associated with this condition.[25]

Coagulation Tests

SARS-CoV-2 infection triggers an immune-hemostatic response, and both systems are closely related to each other and are required to limit inflammation and ensure a robust immune response. Stimulation of the coagulation cascade results in thrombotic complications, while an escalation of the inflammatory response causes tissue damage and thus leads to acute lung damage, impairment in respiratory function, ARDS, disseminated intravascular coagulation, multiple organ failure, and ultimately, death. Coagulopathy caused by COVID-19 can cause thrombosis in both the venous and arterial systems, and can lead to multiple organ failure, characterized by high D-dimer and fibrinogen levels and prolonged PT. The monitorization of coagulation markers is thus important in COVID-19 patients.[26] The relationships of biochemical markers used to monitor COVID-19 patients with disease severity and mortality are shown in Table 1.

APTT

The aPTT is generally observed to be normal in COVID-19 patients, with a prolonged aPTT observed in only 6% of patients. Moreover, no correlation has been identified between aPTT and prognosis in COVID-19 patients, meaning that aPTT cannot be considered a reliable test for the diagnosis and follow-up of COVID-19 patients.[27,28]

PT

PT is normal or close to normal in the majority of COVID-19 patients, with prolonged PT reported in only 5% of cases, although a considerably prolonged PT has been reported in severe COVID-19 patients requiring ICU admission.[29] In addition, conspicuously prolonged PTs have been recorded over the

TABLE 1: The relationships of biochemical markers used to monitor COVID-19 patients with disease severity and mortality.[53]

	A significant relationship between disease severity and biomarker (47 studies, totaling 7,388 patients)	A significant relationship between mortality and biomarker (28 studies, totaling 9,664 patients)
Platelet count	+	+
D-dimer	+	+
PT	+	+
aPTT	-	-
Fibrinogen	+	-
CRP	+	+
IL-6	+	+
Ferritin	+	+
Troponin	+	+
LDH	+	+

"+": Significant relationship exists (p<0.05); "-": No significant relationship (p>0.05); PT: Prothrombin time; aPTT: Activated partial thromboplastin time; CRP: C-reactive protein; IL-6: Interleukin-6; LDH: Lactate dehydrogenase.

course of the disease in approximately 48% of patients who did not survive COVID-19. Based on these findings, the use of PT for the follow-up of the disease course and the clinical assessment of the patients can be considered, particularly in those with a severe disease course. Progressive prolongation of PT can be regarded as an indicator of imminent mortality.[28]

FIBRINOGEN

Fibrinogen levels may be elevated in some patients with COVID-19, although no correlation has been found with increased mortality. Conversely, a decline in fibrinogen levels has been identified in 29% of COVID-19 non-survivors, although this phenomenon seems to occur very late in the disease course, and so it is inadvisable to use fibrinogen levels as an early prognostic indicator for COVID-19.[27]

FIBRIN DEGRADATION PRODUCTS (FDPS)

While normal levels of fibrin degradation products (FDPs) are frequently observed in mild or early-stage COVID-19 patients, studies have reported significantly elevated levels in fatal cases. An increase in FDP levels can serve as a prognostic marker based on studies that have reported an inverse relationship between FDP levels and survival.[28,30]

D-DIMER

D-dimer is a prognostic marker that is frequently used in the follow-up of thrombotic disorders. Under normal physiological conditions, D-dimer levels typically range from 0.0 to 0.5 µg/mL, while values exceeding 1 µg/mL are indicative of an elevated risk of thrombosis-related complications.[31] Elevated D-dimer levels are commonly encountered in COVID-19 patients, and there have been studies reporting higher D-dimer levels in patients with a severe disease course, and an inverse relationship with survival. In COVID-19 patients, a D-dimer level equal to or greater than 2.0 µg/mL has been linked to increased mortality, meaning that monitoring D-dimer levels is of prognostic value and essential for appropriate patient management, with further value in identifying patients who may benefit from anticoagulation therapy.[28-32]

PLATELET COUNT

Platelet count is one of the coagulation tests. It is already been covered in the CBC subsection.

INFLAMMATORY MARKERS

Taking advantage of inflammatory markers is essential in the follow-up of COVID-19 patients, in that studies to date have demonstrated their relationship with disease progression and mortality. Proinflammatory cytokines such as IL-6 and TNF-α, and procalcitonin, ferritin, CRP and ESR can be utilized as markers of inflammation. While proinflammatory marker measurements are not commonly used in routine clinical practice, ferritin, CRP and ESR are frequently utilized as indicators of inflammation.[33]

CRP

CRP-one of the non-specific acute-phase proteins, is synthesized in the liver through IL-6, and has a normal value of below 1 mg/dL in healthy people. Studies of COVID-19 patients have often reported increased CRP levels, with slight elevations in the initial stages of the disease.[32] During this stage of the illness, CRP levels rise due to the increased activity of angiotensin II on the AT1 receptor, which occurs as a result of the interaction between SARS-CoV-2 and ACE-2.[34]

It has been suggested that CRP could be used to monitor disease course as the levels correlate with disease severity.[35] Furthermore, CRP levels are said to be correlated with the size of lesions (consolidation or ground glass appearance) detected by computed tomography in COVID-19 patients with lung involvement, while another study has reported increased CRP levels to be associated with the development of ARDS, venous thromboembolism, acute renal failure and increased mortality rate in COVID-19 patients.[36,37] Additionally, it has been documented that CRP levels rise when secondary bacterial infections are present.[38] Finally, levels above 40 mg/dL have been identified as a warning sign, with an increased rate of mortality above this level.[39]

PROCALCITONIN

Procalcitonin is normally released by the parafollicular C cells in the thyroid gland and is found in small amounts (≤0.1 ng/mL) in the body. Procalcitonin is released also from extrathyroidal tissues upon stimulation by IL-6, TNF-α and endotoxins in the presence of a bacterial infection and can reach high concentrations. Procalcitonin is reported to be normal in the majority of COVID-19 patients upon initial presentation and in those with a mild disease course, while elevated levels have been observed in those requiring ICU admission and in patients with organ dysfunction and sepsis. The possibility of bacterial co-infection must be taken into consideration in patients with high procalcitonin levels. Studies have reported the prognostic significance of procalcitonin levels greater than 0.5 ng/mL, and so the monitorization of procalcitonin levels is essential given the association of levels with disease prognosis.[1,40-42]

FERRITIN

Serum ferritin is an acute-phase reactant, and hyperferritinemia is associated with high mortality, independent of the underlying pathology.[43] Studies of COVID-19 patients have reported a link between ferritin levels and disease prognosis.[41] Hyperferritinemia has been reported to be frequently observed in patients with cytokine storm, ARDS to and organ damage, and so the monitorization of ferritin levels throughout the course of the disease is recommended.[1,41,42]

ESR

The ESR is an acute-phase reactant value that is commonly used in clinical practice. Although levels increase with age, a level above 30 mm/hr is pathological in all age groups. Studies have reported that ESR elevates in relation with disease course, and is associated with mortality in COVID-19 patients. A study comparing the ESRs of ICU patients and non-ICU patients identified 56.5 mm/hr as a critical ESR value, with levels in excess of this threshold being associated with ICU admission.[44] Studies have identified ESR as an important prognostic marker, and patients with high ESR have also been reported to have higher white blood cell, neutrophil, lymphocyte, CRP, procalcitonin, D-dimer and ferritin values.[42,44]

IL-6/TNF-α

IL-6 and TNF-α are frequently used in the routine follow-up of COVID-19 patients, with studies reporting elevated levels in association with organ dysfunction, poor prognosis and increased mortality in severe COVID-19 patients.[11,32,35,42,45]

ORGAN DAMAGE INDICATOR

COVID-19 is a systemic disease, and biochemical monitorization is essential for the detection of heart, kidney, liver and pancreas damage in the early period, and thus for the reduction of mortalities.[46]

MARKERS OF CARDIAC DAMAGE

It has been found that the causative agent of COVID-19 could have cardiac complications upon the detection of severe myocarditis, systolic dysfunction and other cardiac pathologies in COVID-19 patients re-

quiring hospitalization and ICU admission.[46] It is believed that SARS-CoV-2 could cause viral myocarditis, or lead to cytokine-mediated myocardial injury, and that the virus could lead to cardiovascular complications by causing microangiopathies and exacerbating cardiovascular diseases.[33] Cardiac troponin is often the first-line test for the evaluation of cardiac function. A range of studies have been conducted to investigate cardiac troponin levels in COVID-19 patients, identifying elevated troponin levels and a correlation with mortality.[46,47] Creatine kinase-myocardial band (CK-MB) and myoglobin are markers of myocardial damage and reperfusion. Studies have reported that elevated CK-MB and myoglobin levels are indicators of poor prognosis.[30] Pentraxin-3 (PTX3) is a member of the pentraxin family that is structurally similar to CRP. Studies have reported elevated PTX3 levels in severe COVID-19 patients and an association with mortality. Although not studied in routine practice, there have been studies identifying changes in sST2 (a member of the IL-1 family), growth differentiation factor-15, copeptin, mid-regional adrenomedullin, endothelin-1, and osteopontin/(A)symmetric dimethylarginine/myeloperoxidase levels in patients with cardiac involvement.[48]

MARKERS OF HEPATIC DAMAGE

The liver has many functions in the body, and different markers are utilized for the evaluation of these functions. Aspartate transaminase (AST) and alanine transaminase (ALT) can be studied to evaluate the metabolic functions of the liver; albumin and PT are used to evaluate synthesis function; and bilirubin, alkaline phosphatase and gamma-glutamyl transferase are used to evaluate biliary excretion (cholestasis). PT, albumin and bilirubin are of prognostic value.[49] Studies have reported evidence of hepatic damage in COVID-19 patients, and it has been stated that immune-mediated reaction occurs following infection in these patients related to severe inflammatory response, while direct cytotoxicity occurs related to the viral replication in ACE-2-expressing biliary epithelial cells. It has also been reported that hepatitis can develop secondary to hypoxia and the drugs used in the treatment.[33]

Normal AST and ALT values range between 10 and 50 U/L. Although extremely high AST and ALT levels have been observed in severe cases of the disease that resulted in mortality, levels can often be 2-3 times above normal in COVID-19 patients.[50] Elevated AST and ALT levels together with decreased albumin levels indicate organ damage, and are often associated with ICU patients. The monitorization of hepatic markers is essential for the identification of drug-induced hepatitis and organ damage.[46]

MARKER OF RENAL INJURY

Urea, creatinine, blood urea nitrogen, neutrophil gelatinase-associated lipocalin, cystatin C, kidney injury molecule-1 and electrolytes can be tested for the evaluation of kidney function, while albumin and glucose can be tested in the urine. Reports have stated that acute renal failure can occur in COVID-19 patients. As with liver damage, injuries related to inflammation and the direct cytopathic effect of SARS-CoV-2 can result in acute kidney injuries. Furthermore, cross-reactions among organs and hypoperfusion can also lead to acute kidney injury.[33] Kidney injury is not expected in patients with mild disease, but is more common in patients requiring ICU admission. The monitorization of increases in serum creatinine, decreases in serum albumin and increases in urine albumin are essential, as these findings are associated with prognosis and mortality.[46] Studies have also reported increased levels of 11-dehydrothromboxane B2, 8-hydroxy-2′-deoxyguanosine and liver-type fatty acid binding protein in the urine of hospitalized patients.[51]

MARKERS OF PANCREATIC DAMAGE

Studies have reported that pancreatic damage can occur in COVID-19 patients through a direct cytopathic effect or immune-mediated injury, and that amylase and lipase may be elevated in this patient group.[50]

MARKERS OF PULMONARY INJURY

The lungs are the main organs affected by SARS-CoV-2 infections, and respiratory symptoms are observed in the majority of patients. Elevated

ACE-2, IL-1R, IL-2, IL-6, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α and TNF-α levels have been recorded in severe stage patients with the prevalent respiratory symptoms.[52] During the first stages of the disease, the measurement of neuron-specific enolase can be used to differentiate patients who would experience dyspnea.[51]

MARKERS OF CELLULAR DAMAGE

Lactate dehydrogenase (LDH) can be used as a marker of cellular damage, and elevated levels have been found in COVID-19 patients with a severe disease course. It has also been reported that elevated levels of α-hydroxybutyrate dehydrogenase-another cellular marker suggesting kidney, heart and red blood cell damage-could be related to disease severity in COVID-19 patients.[33]

BIOMARKERS DETECTED AT VARIOUS PHASES OF CLINICAL PROGRESSION

The infection caused by SARS-CoV-2 is characterized by three distinct phases: early symptoms, acute phase, and recovery. To a poor prognosis.[54]

The majority of patients typically undergo initial phase of the disease without any noticeable symptoms, while a few people may exhibit cold-like symptoms such as cough, muscle pain, headache, diarrhea, sore throat, or abnormalities in their sense of smell or taste. During this stage, there was a mild decrease in lymphocyte count, however other abnormalities in the blood were few.[55]

Certain patients undergo a highly mild acute phase subsequent to the initial phase and achieve recovery. Nevertheless, patients who do not show signs of improvement transition into the acute phase roughly 3-7 days following the initial manifestation of symptoms. During this phase, severe complications may arise, marked by the occurrence of respiratory failure, ARDS, and thromboembolic events. At these stage, there are elevated levels of ILs (IL-1β, IL-2, IL-8, IL-17, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, inducible protein 10, MCP-1, and TNF-α). Elevated concentrations of CRP, procalcitonin, and ferritin; lymphopenia, eosinopenia, neutrophilia, elevated neutrophil/lymphocyte ratio, elevated platelet/lymphocyte ratio; elevated D-dimer levels and increased concentrations of cardiac troponin, brain natriuretic peptide (BNP), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), LDH, serum creatinine, and serum lactate may be seen. Observation of elevated levels of cardiac troponin, BNP, NT-proBNP, LDH, serum creatinine, and serum lactate may occur, depending on the organs affected.

Typically, mild cases fully recover within a span of 2 to 3 weeks. Nevertheless, serious cases may have enduring, prolonged effects. Long-lasting deviations in blood biomarkers are linked to a poor prognosis.[54]

CONCLUSION

Many laboratory tests have been suggested to provide insight into the diagnosis, course and prognosis of the disease and to guide clinicians in updating treatment algorithms at every stage of the disease, thanks to the devoted work of the clinicians and researchers since the very beginning of the COVID-19 pandemic. The data acquired from these studies can support the triaging of patients, leading some to be treated as outpatients, while those with more severe forms of the disease may be hospitalized or admitted to the ICU if exhibiting poor prognostic features. While monitoring a patient diagnosed with COVID-19, it must be kept in mind that SARS-CoV-2 affects mainly the lungs, but can also affect other organs such as the brain, endothelium, heart, kidneys and liver, and that age, body weight and comorbid conditions can also affect the clinical course. Studies to date have reported lymphopenia, neutrophilia, thrombocytopenia, elevated inflammatory markers, impaired coagulation parameters and impaired organ function tests to be related to poor prognosis and mortality. In this review it should be emphasized that laboratory tests must be considered together with clinical findings and radiological imaging studies for the development of a holistic approach to patient care.

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No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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