

# Review: Non-Specific Laboratory Tests in Patients with COVID-19

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**Abstract.** The COVID-19 outbreak has had a high impact on diagnostic laboratory services recently. The current literature has focused on reviewing tests that are specifically related to the diagnosis of COVIDS-19 infection using either molecular testing or immunoassays detecting viral antigens or antibodies. In this short communication review, we aimed to summarize the most common non-specific laboratory tests that may be requested in patients with suspected COVID-19 infection to help in the assessment of different organs and other vital laboratory tests to avoid complications as a consequence of COVID-19 infection.

**Key words:** COVID-19, SARS-CoV-2, Non-specific Test, ARDS.

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## Introduction

Coronavirus COVID-19, which is known as SARS-CoV-2, is a new form of the Coronavirus family that causes severe acute respiratory syndrome. It has been announced by the World Health Organization that COVID-19 is a pandemic infectious disease [1]. A severe form of pneumonia is seen in some patients and this might lead to acute respiratory distress syndrome (ARDS). COVID-19 is occasionally associated with complications of other organs, such as the kidney or heart, which might lead to death [2]. Clinical laboratory testing provides an essential diagnostic tool in providing diagnosis of COVID-19, as in any other diseases [3]. Usually, the diagnostic tests are used for disease screening, prognosis, monitoring, and evaluating the disease severity [4]. The current literatures have focused on reviewing tests that are directly related to the diagnosis of COVIDS-19 infection using either molecular testing (real-time RT-PCR) or immunoassays investigations to detect the presence or absence of the viral antigens or antibodies [5].

In this current review, we aimed to summarize the most common indirect laboratory tests (**Table 1**) that may be requested in patients with suspected COVID-19 infection to help in the assessment of the function of different organs and to what extent they can be affected or damaged.

## Blood Biochemistry

**Electrolytes.** Early studies reported that disturbance in the levels of different plasma electrolytes including sodium, potassium, chloride, and calcium may be seen upon presentation with COVID-19 infection [6,7]. Patients with advanced COVID-19 infection were reported to demonstrate more severe hypokalemia at baseline compared to those with less advanced infection [8]. Severe hypokalemia may have significant consequences on patients' clinical implications, management, and contribute to the understanding of the mechanism of pathogenic mechanisms causing complications in patients with COVID-19 infection. For example, hypokalemia is known to exacerbate acute respiratory distress syndrome (ARDS) and acute cardiac injury, which are common complications in COVID-19, especially in patients with underlying lung or heart disease. The status of hypokalemia may be explained by the ability of the virus (SARS-CoV-2) to bind to the cell surface angiotensin-converting enzyme 2 (ACE2) receptor. This leads to a reduction in ACE2 expression and, subsequently, increased angiotensin II levels, which can cause increased potassium excretion by the kidneys and cause hypokalemia [8,9]. The presence of other symptoms in the patients with COVID-19, such as gastrointestinal losses and diarrhea, can contribute to the presence of hypokalemia and other electrolyte disturbances [10].

**Albumin.** Albumin is the main protein carrier for different molecules in the blood. Its major role is to stabilize fluid oncotic pressure. The low levels of

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**Table 1.** Characteristics of the main non-specific laboratory tests in COVID-19 infection.

Profile	Test	Result characterization	Reason for testing
Blood Biochemistry	<i>K</i>	↓	Electrolyte imbalance
	<i>Albumin</i>	↓	Liver function and malnutrition
	<i>LDH</i>	↑	Tissue damage (lung injury)
	<i>ALT</i>	↑	Hepatocellular damage
	<i>AST</i>	↑	Hepatocellular damage
	<i>CK</i>	↑	Muscle damage of hypoxia
	<i>Ferritin</i>	↑	Iron accumulation and disposition
	<i>Creatinine</i>	↑	Renal cells damage
Cardiac markers	<i>hs-Trop</i>	↑	Cardiac cells damage due to ARDS
	<i>NT-proBNP</i>	↑	Cardiac cells damage due to ARDS
Inflammatory markers	<i>CRP</i>	↑	Infection and cellular inflammation
	<i>ESR</i>	↑	Infection and cellular inflammation
	<i>PCT</i>	↑	Bacterial infection
Complete Blood Count	<i>Lymphocytes</i>	↓	Viral infection
	<i>Neutrophils</i>	↑	Viral and Bacterial infection
	<i>N/L ratio</i>	↑	Enhanced inflammatory process
Coagulation	<i>D-dimer</i>	↑	Coagulopathy (DIC risk)
	<i>PT</i>	↑	Coagulopathy (DIC risk)
	<i>APTT</i>	↑	Coagulopathy (DIC risk)
	<i>Fibrinogen</i>	↑	Coagulopathy (DIC risk)
Arterial Blood Gas	<i>%O<sub>2</sub></i>	↓	Pneumonia (hypoxia risk)
Cytokines	<i>IL-6</i>	↑	Cellular hyperinflammation (cytokine storm)
	<i>IL-1</i>	↑	Cellular hyperinflammation (cytokine storm)
	<i>TNF-α</i>	↑	Cellular hyperinflammation (cytokine storm)
Urine analysis	<i>WBC</i>	positive	Capillary leak syndrome
	<i>Blood</i>	positive	Capillary leak syndrome
	<i>Albumin</i>	positive	Capillary leak syndrome

**Abbreviations:** ARDS, Acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, Creatine kinase; hs-Trop, high sensitivity troponin; NT-proBNP; N-terminal pro beta natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; IL-1, interleukin-1; IL-6, interleukin-6; TNF, tumor necrotic factor; N/L, neutrophil/lymphocyte ratio; PT, prothrombin time; APTT, activated partial thromboplastin time.

albumin may indicate the presence of infectious diseases [9]. The association between infection and malnutrition is thought to contribute to the decreased level of albumin [11,12]. Hence, hypoalbuminemia is a common laboratory abnormality in patients with COVID-19. A recent study has reported that the reduction in serum albumin is associated with an increased risk of death and is associated with the COVID-19 viral load [9].

**Lactate dehydrogenase.** Lactate dehydrogenase (LDH) is an enzyme involved in glucose metabolism. It is found in most tissues of the body and its main function is to catalyze the conversion of pyruvate to lactate. Usually, it is released from damaged

cells [13]. Therefore, it can be used as a predictive marker for serious lung injury in patients with COVID-19. It has been reported that an increased serum LDH is associated with the viral load of COVID-19 [9]. Chen et al., have reported that LDH is significantly increased in most patients with COVID-19 [14] and at the same time, patients who were admitted to the intensive care unit (ICU) had higher levels of serum LDH compared to patients who did not need to be admitted to ICU [15]. It has been reported that serum LDH is related to the degree of COVID-19 infection severity [16]. The source of the increased serum LDH levels is likely to be due to the cellular damage within the tissues of lung, heart, and/or skeletal muscles.

**Liver enzymes.** Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are markers for hepatocellular damage at an early stage of COVID-19 infection and can be used to predict the development of serious liver symptoms. One study showed that the proportions of COVID-19 patients with elevated levels of AST and ALT ranged from 6.2% to 22.2% and from 21.3% to 28.1%, respectively [6,17]. The proportions were found to be higher in men than women, but no reason for this was identified.

Significant increases in bilirubin and other liver enzymes (alkaline phosphatase and gamma-glutamyltransferase) have rarely been reported in COVID-19 patients [18]. The dysfunction of the liver in COVID-19 infection may be considered as the result of secondary liver damage caused by the use of potential hepatotoxic drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia, and multiple organ failure. It has been reported that critically ill patients with COVID-19 infection are more likely to develop liver dysfunction and bad prognosis [19].

**Creatine kinase.** Individuals with COVID-19 who were admitted to an intensive care unit showed tendencies to have increased serum creatine kinase (CK) levels; this may be due to the effects of virus-induced cytokines or mediators on different tissues as a consequence of hypoxia, shock, or rhabdomyolysis [20]. It has been reported that many patients with the 2009 H1N1 virus also had mild to moderate elevations of serum creatine kinase [21].

**Iron study.** There are many reasons for an increased serum ferritin, such as infection, hemochromatosis, and long-term transfusion [22]. Ferritin is a major iron storage protein and can bind to free ions of iron. It is important for the regulation of cellular oxygen metabolism. A low serum ferritin indicates low iron concentration, while increased levels of serum ferritin may indicate the presence of viral and bacterial infection. Ferritin is part of acute phase reactants and is considered an inflammatory marker. Therefore, it has been associated with the progression of bacterial and viral infection. In patients with COVID-19, increased serum ferritin level has

been reported to be associated with increased severity of the disease and adverse outcomes. The serum levels of ferritin are markedly increased in very severely affected patients compared with less severely affected patients with COVID-19 infection [16].

In case of bacterial and/or viral infection as in COVID-19, the increase of serum ferritin is related to the released iron from the reticuloendothelial system, a reduced ability of ferritin transfer to the liver and spleen, and increased ferritin synthesis and release [23,24]. Previous studies have shown that patients with bacterial infection have higher ferritin level compared to patients with viral infection [25]. Therefore, the increased level of serum ferritin might indicate severe secondary bacterial infection in COVID-19 and would then be a marker of bad prognosis [16].

**Creatinine.** After infection, the virus may enter the circulation, accumulate in kidney, and cause damage to resident renal cells. Kidney damage may be caused by the virus entering renal cells through an ACE2-dependent mechanism [26]. The deposition of viral and its immune complexes may cause a damage to the renal tissue [20]. The prevalence of acute kidney injury in in-patients with COVID-19 is high and is associated with high mortality. The incidence of COVID-19 death with increased baseline levels of serum creatinine has been reported to be significantly higher than in those with normal baseline level of serum creatinine. Measurement of serum baseline level of creatinine may help in early detection of patients with impaired kidney function and this may reduce the mortality of patients with COVID-19 by following an early intervention [20].

### Arterial Blood Gases

**Oxygen saturation.** Pneumonia is the most common serious clinical presentation in patients infected with COVID-19. The virus can progress through the respiratory tract and enter into the patient's lung parenchymal tissue. This causes inflammation and the air sacs, or alveoli can then be filled with fluid and pus. This will subsequently limit the patient's ability to absorb oxygen.

The lung malfunction in patients with COVID-19 may present different levels of blood hypoxia. Diffuse bilateral opacities on chest imaging and accumulation of edema in alveolar spaces of the lung are common features of such patients [27]. Therefore, blood oxygen saturation ( $O_2\%$ ) is often low in patients with COVID-19 infection when they are admitted and the degree of hypoxia is often a marker of prognosis to evaluate the severity of the COVID-19 [7]. It has been reported that most patients who died of COVID-19 had oxygen saturation of 93% or lower and alkalosis was present in 40% of the total number of patients [28].

### Cardiac Markers

**High Sensitive Troponin.** The increased levels of serum high sensitive troponin (hs-Trop) -T or -I indicate myocardial injury. This test is commonly ordered in patients with acute respiratory infections and its levels are associated with disease severity. Elevated serum hs-Trop is also common among patients with COVID-19 infection [29]. The mechanism of myocardial injury in COVID-19 infection is unclear. However, as is the case for other severe respiratory illnesses, direct myocardial damage due to viral infection is almost certainly the most likely cause. It is thought that ACE2 receptor depletion in cardiomyocytes may play an important role in the development of myocarditis and consequential rise in serum hs-Trop levels. The disturbed renin-angiotensin-aldosterone system may play an important role for such pathogenic mechanism [29]. The elevated level of hs-Trop is not sufficient to secure the diagnosis of acute myocardial infarction, which should be based on clinical symptoms, ECG interpretation, and function of other organs.

**NT-proBNP.** The biomarker of myocardial stress N-terminal pro-hormone BNP (NT-proBNP) is widely used for the diagnosis and management of heart failure. It is also frequently elevated in patients with severe respiratory illness typically in the absence of clinical features of heart failure. Much like troponin, elevation of BNP or NT-pro BNP is associated with an unfavorable course among patients with ARDS [30]. Patients with COVID-19 often demonstrate significant elevation of BNP or NT-proBNP [31]. The significance of this finding is uncertain and should not necessarily trigger an evaluation or treatment for heart failure unless

there is clear clinical evidence for the diagnosis. Therefore, abnormal BNP result should not be considered as evidence of heart failure in the absence of supporting clinical evidence.

### Inflammatory markers

**C-reactive protein.** Serum C-reactive protein (CRP) is associated with the level of inflammation [32] and is an acute phase reactant. Serum CRP can activate complement and enhance phagocytosis of microorganisms. Serum CRP levels can be used for early diagnosis of pneumonia [33] and the severity of the pneumonia appears to be proportional to increased levels of CRP [34]. Matsumoto's et al., showed that serum CRP levels and the diameter of the largest lung lesion increased as the disease progressed. CRP levels were positively correlated with lung lesion and disease severity [35]. This suggests that in the early stages of COVID-19, serum CRP levels could reflect lung lesions and severity and be used for disease monitoring [36,37]. The test of CRP is considered to be the most associated inflammatory marker with the severity of COVID-19 infection [37].

**Erythrocyte Sedimentation Rate.** The erythrocyte sedimentation rate (ESR) is a measurement of how quickly red blood cells accumulate at the bottom of a test tube. In the presence of inflammation, the blood's proteins aggregate together. Thus, when measured, the red cells settle faster at the bottom of the test tube. In general, the faster the blood cells settle, the more severe the inflammation.

The ESR is affected by the size, shape, and concentration of red blood cells and plasma characteristics. COVID-19 could trigger the change of the form of erythrocyte or plasma characteristics, including the immune system, by an unknown mechanism to increase the ESR. The sustained high level of ESR may be negatively associated with a COVID-19 patient's outcome [38,39].

**Procalcitonin.** The recent literature suggests that serial serum procalcitonin (PCT) measurements may play a role for predicting the severity of the disease. PCT production into the circulation is amplified during bacterial infections. The level of PCT is actively sustained by enhanced activities of interleukins and tumor necrosis factor.

Therefore, the PCT value would remain within the reference range in most patients with uncomplicated SARS-CoV-2 infection. The level of PCT would be substantially increased when there is bacterial co-infection in those patients with severe form of the disease, thus contributing to complicate the clinical outcomes, as shown in children with viral lower respiratory tract infections [40]. It has been suggested that serum PCT might reflect secondary bacterial infection and an exacerbation of COVID-19 [16].

### Complete Blood Count

**Lymphocytes.** Lymphocyte levels are reduced in viral infection because the virus induces T lymphocyte apoptosis by activating intrinsic and extrinsic mechanisms. Previously it was shown that the development of lymphopenia in severe patients was mainly related to the significantly decreased absolute counts of T cells, especially CD3+, CD4+, and CD8+ T cells, but not to B cells or NK cells [41]. The decrease of T cells in severe cases reached a trough within three days. Lymphocytes, especially CD3+, CD4+, and CD8+ T cells were significantly decreased. The decrease in T cell counts was strongly correlated with the severity of disease, which is in keeping with previous studies on SARS [42,43].

Damage to T lymphocytes might be an important factor leading to exacerbation of disease [44]. A low absolute value of lymphocyte count could be used as a useful index in the diagnosis of new COVID-19 infection. This suggests that the virus might mainly act on T lymphocytes, as does SARS coronavirus. The virus spreads in the respiratory mucosa and infects other cells, inducing a "cytokine storm" and generating a series of immunological reactions [14].

It has been reported that during hospitalization, the absolute lymphocyte count and lymphocyte percentage decreased in the patients with COVID-19, who subsequently died. This may be because the viral infection causes persistent consumption and/or insufficient regeneration of lymphocytes [21].

**Neutrophils.** Neutrophils can kill pathogens by using different mechanisms such as oxidative burst, phagocytosis, and neutrophil extracellular traps (NET) [45,46]. In patients with COVID-19, the increase level of neutrophil predicts a poor outcome [47]. The NETs may contribute to organ

dysfunction and mortality in COVID-19. It has been reported that patients admitted in ICU had higher neutrophil count compared to patients who did not need care in ICU [15].

The increased neutrophil/lymphocyte ratio can be used as an independent risk factor for severe disease and at the same time can reflect an enhanced inflammatory process which may suggest poor prognosis [48,49].

### Coagulation

**D-Dimer.** Organ dysfunction and coagulopathy were reported to be associated with a high mortality rate in patients with COVID-19 infection [50]. A recent report suggests that patients infected by COVID-19 are at risk of developing disseminated intravascular coagulopathy (DIC) [51]. This is caused by the development of sepsis in such patients due to viral infection. Therefore, the incidence of DIC found in most of the patients who subsequently died. The mechanism of DIC development is due to monocytes and endothelial cell activation by cytokines released after injury. Consequently, free thrombin becomes uncontrolled by natural anticoagulants, which ultimately leads to platelets activation and the stimulation of fibrinolysis [52].

Increased fibrinogen, D-dimer, fibrin degradation products, prolonged pro-thrombin (PT) time, and activated partial thromboplastin time (APTT) have been associated with poor prognosis in patients affected by the novel coronavirus [51]. Several studies from Wuhan have shown that elevated D-dimer level in COVID-19 patients is associated with an increased mortality. Recent data show that D-dimer values are frequently enhanced in patients with COVID-19, being variably observed in 36 to 43% of positive cases [2]. In case of severe thrombocytopenia fibrinogen level has been noticed to be decreased dramatically over three days.

D-dimer values are even higher in patients with severe COVID-19 than in those with milder forms and, therefore, D-dimer measurement may be associated with the development of a poorer clinical picture. Tang et al., highlighted that the vast majority of COVID-19 patients who died within hospital stay fulfilled the criteria for diagnosing DIC (71.6 vs. 0.6% in survivors) [51].

A study was conducted on deceased COVID-19 patients showed that prothrombin time was significantly longer in patients who died than in those who recovered, whereas activated partial thromboplastin time was comparable between the two groups. The same study reported that the D-dimer concentrations were markedly elevated in deceased patients than in recovered patients [28].

In general, the dysregulation of the coagulation cascades and the subsequent development of clotting are significantly affected in patients with COVID-19 infections [51].

### Cytokines

Cytokines are small proteins released by many different immune system cells to host immune response. They are considered signaling molecules or mediators to regulate immunity, inflammation, and sometimes hematopoiesis.

Patient with severe COVID-19 may develop a cytokine storm, characterized by increased plasma concentrations of different cytokines, including interleukins, interferon, monocyte chemoattractant protein, macrophage inflammatory proteins, and tumor necrosis factor [41].

These inflammatory mediators regulate neutrophil activity and activate the expression of chemoattractants, which increase the trafficking of neutrophil cells to sites of infection. Moreover, the cytokine storm may lead to acute lung injury, ARDS, and subsequently cause death [41]. In advance infection, the signal interaction between macrophages and neutrophils leads to uncontrolled inflammation [53].

Infection with COVID-19 can be fatal due to an overreaction of the cytokine storm. When SARS-CoV-2 virus enters the lungs and triggers an immune response, it attracts immune cells to the region to attack the virus, resulting in localized inflammation. But in some patients, excessive or uncontrolled levels of cytokines are released, which then activate more immune cells, resulting in hyper-inflammation. This can seriously harm or even cause patient death.

Many of the pro-inflammatory cytokines, including interleukin-1 (IL-1), are important mediators in local and systemic inflammation [54]. In the case of infection, pro-inflammatory cytokines are secreted, which can complicate the clinical picture of the disease. Among these cytokines, interferon-alpha (IFN $\alpha$ ), tumor necrosis factor (TNF), and IL-1 are of considerable importance [55-57]. Inflammation is mediated by pro-inflammatory cytokines, including IL-1, IL-6, TNF, and IL-8. IL-1 is the most studied cytokine with properties that are relevant to several inflammatory diseases, including viral infections. Immune cells are attracted to the place of infection by IL-8, a chemokine that is generated at the inflammatory site. Pro-inflammatory cytokine levels are correlated with COVID-19 replication and disease.

A recent study showed that 38 out of 48 measured cytokines in the plasma of COVID-19 infected patients were significantly elevated compared to healthy individuals. Seventeen cytokines were linked to viral loads. Fifteen cytokines were strongly associated with lung injury and could be used to predict disease severity [58].

### Urine

Testing urine samples can be used to screen for the presence of bacteria, cells, proteins etc. Presence of such abnormal components in urine sample indicates urinary tract infection, renal function abnormality, and other systemic diseases e.g. diabetes.

A recent study showed that positive urine samples for blood, albumin, and leukocytes in patients with COVID-19 can be helpful in detecting COVID-19 associated nephritis and the need for admission to ICU [59]. The presence of nephritis (capillary leak syndrome) in patient with COVID-19 needs to be carefully monitored for the presence of pulmonary oedema due to fluid overload and immune incompetence due to loss of immunoglobulins, albumin and other necessary proteins in the urine [59].

**Conclusion.** In this literature, we have listed the most important non-specific laboratory tests that may be requested to screen, monitor, or assess the severity of different injured organs by COVID-19

infection. They should be used as key indicators for disease monitoring to avoid complications and consequently for guiding treatment.

The information provided here is for guidance only and based on author's recent literature at the time of writing the manuscript. As the information is time relevant, such information may change as new information emerges after publication.

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