Review Article

Clinical Laboratory Markers in COVID-19

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Abstract

Background: The causative agent of the present COVID-19 pandemic is a novel RNA virus called SARS CoV-2. Clinical laboratory has a central role in the diagnosis, prognosis, and predicting the progression of the disease. Several hematological, biochemical, immunological, and coagulation parameters change during the course of the disease. Based on the information from several studies, it is presumed that virus replication alters the immune system of the body. These alterations cause cellular damage in various organs like the lungs, liver, heart, and bone marrow. Ultimately, it may lead to multi-organ failure and death.

Methods: An internet search in Medline, PubMed, Scopus, and Scholarly articles was performed. Studies reporting on changes in laboratory parameters in COVID-19 were selected, data extracted, and analyzed.

Conclusion: Laboratory markers are helpful in the diagnosis of cases and more importantly, to identify those patients where chances of disease progression to severity are present. This will not only reduce the burden on the health care system but also reduce the mortality rate by channelizing resources to those cases who need critical care and management.

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Key words: COVID-19, Laboratory markers, Severe illness, Non-severe illness, SARS CoV-2.

Introduction:

The first case of COVID-19 was reported in December 2019 from Wuhan city in China. WHO declared it a disease of Public Health Emergency of International Concern in January 2020 and on 12th February 2020, officially named the disease as coronavirus disease 2019 (COVID-19)[1,2]. Ever since the disease has rapidly spread to more than 227 countries across the globe. Since 31 December 2019 and as of 24 August 2020, 23,311,719 confirmed cases of COVID-19, including 806,410 deaths, reported to WHO[3]. In March 2020 the WHO declared COVID-19 as a pandemic, as the disease spread across the globe cutting across geographical boundaries[4]. This pandemic has brought an enormous burden on the healthcare system and almost crippled the world economy. The proportion of the effect is evident more among the lower and middle-class economic countries where the health care system is at its bare minimum.

Background:

Viral pandemics are not new to this civilization. The last two decades have witnessed pandemics such as H1N1 (Influenza A) in 2009 and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) in 2016. Key to the management of any pandemic lies in the early identification, contact tracing, and containment, achievable by accurate diagnosis and strict surveillance. The standard tests used for the diagnosis of COVID-19 infection are molecular tests like the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and the immun-

ological tests. Although RT-PCR is the accurate and the diagnostic test, it is time-consuming and costly. The immunological detection of IgM and IgG antibodies are cheaper, rapid, and supplement in the diagnosis of COVID-19[5].

Countries belonging to the low socioeconomic group are less equipped with laboratories and health care infrastructure to perform extensive molecular testing. Limited resources and the time factor between the collection of sample and confirmation of the diagnosis is crucial in combating the spread of infection. During this period, clinical judgment is vital. Clinical laboratory parameters and radiological imaging have a strong role to help in the provisional diagnosis. The high-risk groups, which include diabetes mellitus, hypertension, and immunocompromised states, are vulnerable to increased mortality and morbidity. Here timely intervention and management based on laboratory findings can differentiate between severe and non-severe cases and channelize the limited health care resources to minimize mortality.

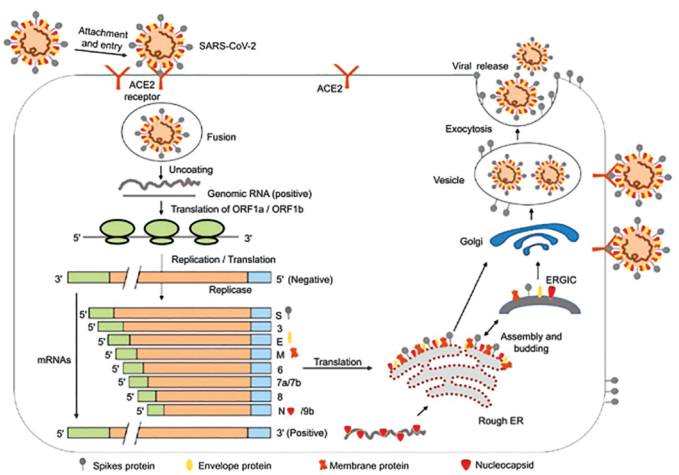

Figure 1: *COVID 19. Replication cycle*

Viral Pathophysiology:

After the virus encounters the human cell, it binds to the host cell through the viral spike protein and the host receptors (mainly ACE 2 receptors). Internalization of the virus takes place by endocytosis, followed by a series of events of like, the release of the viral RNA, Transcription, and Translation of the viral genome, synthesis, and assembly of the viral proteins and finally extrusion of the virus particles through exocytosis, ready to infect another cell[6-8].

The gateway of entry of the COVID-19 virus is usually the respiratory tract from where it spreads to other organs and tissues. At the level of bone marrow, the virus causes apoptosis of hemopoietic cells and a resultant decrease in hemopoiesis. Consequently, there is a decrease in leukopoiesis and thrombopoiesis[9-11].

On entering the blood circulation, the virus particles trigger an activation mechanism in the macrophages and neutrophils, which leads to the synthesis of some inflammatory chemicals, which act as immunomodulation agents called cytokines. These inflammatory chemicals are responsible for the inactivation of the precursor cells in the bone marrow causing leukopenia and thrombocytopenia[10-11].

Another possible pathophysiological mechanism is that the immune system of the body is stimulated causing the synthesis of antibodies and immune complexes that can stick to the platelets and cell surfaces. Consequently, there is tissue damage and a decrease in platelets[9-11]. These pathological events ultimately lead to intravascular coagulation, culminating in widespread tissue damage especially involving the lungs, liver, heart, and kidneys[9,12,13]. The pathological changes caused by the virus are responsible for the altered physiological functioning of the various organs in the body. These changes reflect in the hematological, inflammatory, biochemical, and coagulation laboratory findings, which can contribute to the diagnosis and prognosis of COVID-19 patients.

Aims and Objectives:

The latest articles were collected and analyzed in this study to:

1) Enumerate the important laboratory parameters in Covid-19.
2) Identify those laboratory markers that indicate the progression of the disease from moderate to severe illness.

The study mainly takes into account the routinely tested hematological, biochemical, coagulation, and inflammatory biomarkers that are easily available in a low health care infrastructure scenario.

Method:

An internet search in Medline, PubMed, Scopus, and

Scholarly articles was performed. Studies reporting on changes in laboratory parameters in COVID-19 were selected, data extracted, and analyzed. The data were divided into two groups. (1) Laboratory parameters that contribute to the diagnosis of COVID-19. (2) Laboratory parameters that separate severe illness from non-severe illness.

Statistical Analysis and Discussion

1. Laboratory Markers in COVID 19 Patients:

Several altered laboratory findings observed in COVID-19 patients can serve as an important tool in the diagnosis and prognosis of the disease process. For a better understanding, these laboratory findings are categorized into hematological, inflammatory, biochemical, and coagulation parameters.

a) Hematological Parameters:

Based on the data from the various studies in China, Italy, and Singapore, several hematological markers have been identified (Table 1). These parameters may help in the diagnosis, surveillance, and management of SARS-CoV-2 infection. Although in some studies, the sample size is small and requires further studies for validation; nonetheless, they establish their role in contributing to the diagnosis and categorization of severe and non-severe cases in COVID-19 infection.

Table 1: *Haematological parameters in COVID-19 infection.*

Parameter	Patho-physiology	Main Author and Reference Number
Leukocytosis	Bacterial infection or superinfection	Lippi et al[21], Huang et al 2020[15]
Lymphopenia	Decreased immunological response to the virus	Lippi et al[21]; Huang et al 2020[15]; Chen et al 2020a[14]; Zhang et al 2020b[16]; Li et al 2020a[17]; Li et al 2020b[18]; Liu et al 2020b[19]; Mo et al 2020[20]; Fan et al[23].
Neutrophilia	Bacterial infection or superinfection	Huang et al 2020[15]; Wu et al 2020[22]; Fan et al 2020[23]; Chan et al 2020[24]; Mehta et al 2020[25]; Qin et al 2020[26].
Eosinopenia	Atopy	Zhang et al 2020b[16]
Thrombo-cytopenia	Consumption coagulopathy	Mo et al 2020[20]; Lippi et al[21]; Lippi G et al 2020[12]; Zou et al 2004[27]

Leukocytosis:

The data of total WBC count in COVID-19 infection are varied. Chen et al in their study of 29 patients reported a normal or decreased total WBC count[14]. Li et al in their meta-analysis of 1,994 cases reported a decrease in leukocytes in 29% of cases[18].

Increased leukocyte count signifies a superimposed bacterial infection. The importance of an increased leukocyte count irrespective of whether it is due to, an increase in Neutrophils or Lymphocytes lies in the severity of illness. Huang et al in their report of 41 patients (13 Intensive care unit patients), found an increased WBC count in all the ICU patients[15]. A similar study by Lippi G et al observed leukocytosis in 11.4% of patients with severe disease in comparison to 4.8% in the milder form of the disease[21].

Lymphopenia:

The decreased lymphocyte count arises partly due to the toxic effect of the inflammatory response and partly due to the activity of the virus at the bone marrow level causing damage to the progenitor cells. The majority of the workers have reported a decrease in the lymphocyte count <1.0 × 109/L in their studies. Lymphopenia has emerged as a strong predictor for disease progression to a poor outcome. Huang et al reported Lymphopenia in 63% cases out of which 85% had severe illness[15]. Chen et al showed a decrease in lymphocyte count in 69% patients[14]. Fan et al in their study from Singapore identified Lymphopenia as a criterion for aggressive management in ICU settings.23 Similarly, Zhang et al 75%, Li et al 64.5%, Li YY et al 77.4%, Liu et al 73.3%, and Mo et al reported lymphopenia in their studies[16-20].

Neutrophilia:

The pathophysiology behind the increased neutrophil count is an exaggeration of the inflammatory state and the consequent release of a large number of inflammatory chemicals in the host[12,24-26]. The morphological abnormalities reported in the circulating granulocytes were hypo-segmented nuclei and hyper-granular cytoplasm suggesting a massive inflammatory reaction. Several ot-

her workers have observed an increase in neutrophil count in severely ill patients[15,16,22–26].

Eosinopenia:

In a study of 140 patients from Wuhan city, China, Zhang et al found Eosinopenia in 52.9% of cases[16]. The majority of the patients who had Eosinopenia and Lymphopenia developed severe illness. The study concluded that decreased eosinophil count could predict the severity of illness in suspected cases.

Table 2: *Biochemical parameters in COVID-19 infection.*

Parameter	Response	Pathophysiology	Main Author and Reference number
CRP	Increases	Systemic inflammation	Lippi et al[12]; Chen et al[14]; Zhang et al[16] Li et al[17]; Li YY et al[18]; Liu et al[19]; Mo et al[20]; Lippi G et al[21]; Henry et al[28] Gao et al[30].
Procalcitonin	Increases	Bacterial infection/superinfection	Lippi et al[12]; Huang et al[15]; Zhang et al[16]; Mo et al[20]; Lippi G et al[21] Henry et al[28]
LDH	Increases	Cellular damage	Lippi et al[12]; Chen et al[14]; Huang et al[15]; Li et al[17]; Li YY et al[18]; Liu et al[19]; Mo et al[20]; Lippi G et al[21]; Wu et al[22]; Fan et al[23]; Wang et al[29].
Aminotransferases	Increases	Hepatocellular injury/ Multi-organ damage	Lippi et al[12]; Lippi G et al[21] Fan et al[23].
Bilirubin	Increases	Hepatocellular injury	Lippi et al[12]; Huang et al[15] Lippi G et al[21].
Creatinine	Increases	Renal injury	Chen et al[14] Lippi G et al[21].
Cardiac Troponin	Increases	Cardiac injury	Chen et al[14]; Wang et al[29] Lippi G et al[31].
Ferritin	Increases		Mehta et al[25].
Albumin	Decreases	Impaired liver function	Chen et al[14]; Huang et al[15]; Liu et al[19]; Mo et al[20] Lippi G et al[21].

Thrombocytopenia:

A decreased platelet count has been an accepted marker for many severe illnesses. The majority of studies like Mo et al[20], Lippi et al[21], Lippi G et al[12], and Zou et al[27] reported a decrease in platelet count in severe cases of COVID-19.

b) Biochemical Markers:

The biochemical changes brought about in COVID-19 have led to the identification of several parameters being useful in the identification and predicting the prognosis of the disease.

C - reactive protein (CRP) is an acute-phase protein, synthesized in the liver cells and increases in many inflammatory conditions. In COVID-19, the liver is involved ranging from damage to the hepatocytes to immune-mediated reaction due to the release of a large number of cytokines. An increased CRP level has a strong association with the severity of illness. Several workers have reported an increase in CRP levels in severely ill patients[12,14,16–21,28,30].

Procalcitonin, the precursor of the hormone called Calcitonin, which plays an important role in the regulation of calcium in our body. Many septic conditions associated with secondary bacterial infection demonstrate an increase in the procalcitonin level. Patients requiring intensive care during COVID-19 infection, show marked elevation of Procalcitonin[12,15,16,20,21&28].

The reversible conversion of pyruvate to lactate is catalyzed by the enzyme Lactate dehydrogenase (LDH). It is present in the majority of the living cells of the body. The release of the enzyme is a marker of cell injury. In severely ill COVID-19 patients progressing to widespread tissue damage and organ failure, increased levels of LDH are exhibited[12,14,15,17–23&29].

Aminotransferases are enzymes secreted mainly by the hepatocytes in the liver. Increased levels of Aminotransferases have been observed during hepatocellular injury. It is another biochemical marker of importance, the level of which increases during COVID-19 infection requiring intensive management[12,21&23].

Bilirubin, a product of haem catabolism, excreted through the biliary route, increases during liver dysfunction. Elevated total serum bilirubin levels are present during severe viral infection[12,15&21].

Serum creatinine is a metabolic waste product of muscle protein creatine. It is a marker of renal function. Elevated serum creatinine can separate severe from non-severe COVID-19 illness[14,21].

Cardiac troponins are proteins present in the myocardial cells. They are released in the circulation during injury to the myocardium, especially in myocardial infarction. It is also known that patients with underlying comorbidities such as cardiovascular disease and hypertension have the worst prognosis. Hence, increased cardiac troponins indicate an injury to the myocardium and a poor outcome[14,29&31].

Ferritin is an iron storage protein present in the cytoplasm of the cells. It is an acute-phase protein, the level

Table 3: *Cytokines in COVID-19.*

Parameter	Clinical significance	Response	Main Author & Reference No.
Tumor necrosis factor-alpha (TNF-α)	In severe illness	Increases	Huang et al[15]
Interleukin-1 (IL-1)	Normal in all cases	None	Chen et al[14]
Interleukin-2 (IL-2)	In severe illness	Increases	Huang et al[15]
Interleukin-2 receptor	as severity increases	Increases	Chen et al[14]
Interleukin-6 (IL-6)	as severity increases	Increases	Chen et al[14]; Mo et al[20]; Mehta et al[25]; Wang et al[29] Gao et al[30].
Interleukin-7 (IL-7)	In severe illness	Increases	Huang et al[15]
Interleukin-8 (IL-8)	Normal in all cases	None	Chen et al[14]
Interleukin-10 (IL-10)	In severe illness	Increases	Huang et al[15]

of which increases during an inflammatory condition. Increased ferritin levels positively correlate with increased severity of illness in COVID-19[15].

Albumin is a globular protein predominantly present in the plasma and produced by the hepatocytes. Therefore, any condition that causes dysfunction of the liver or kidney may result in hypoalbuminemia. Low levels of serum albumin have a poor prognosis in COVID-19 patients[14,15&19–21].

c) Cytokines:

Cytokines are chemicals released by the cells of the immune system, which regulate the communication between cells during inflammation. Broadly, the group includes chemokines, lymphokines, interferons, interleukins, and tumor necrosis factor (TNF). They are released by the cells of the immune system in response to infection, inflammation, sepsis, and trauma. Overproduction of cytokines can be catastrophic leading to cytokine storm syndrome and ultimately to massive tissue damage involving multiple organs in the body.

The data from the various studies on the laboratory interpretation of the cytokines in COVID-19 patients may be used as an important tool to separate mild from severe illness. Elevated levels of several of these chemical inflammatory proteins like Tumour necrosis factor-alpha (TNF-alpha)[15] and interleukins like IL-2, IL-6, IL-7, and IL-10[14,15,20,25,29&30] have a strong association with the severity of illness. However, IL-1 and IL-8 remai-ned to be normal in all patients[14].

d) Coagulation parameters:

Physiological activation of the coagulation system in response to several bacterial and viral infections have been previously reported.35–38 In COVID-19, many changes in the hemostatic mechanism in the body take place, including damage to the endothelial lining of the blood vessels, abnormal activation of the coagulation cascade, and intravascular deposition of fibrin. Ultimately, disseminated intravascular coagulation (DIC) ensues with a poor prognosis.

D-dimer is a product of fibrin degsradation present in the blood when enzymes of fibrinolysis break down a thrombus. It increases in all cases of COVID-19 infection in comparison to healthy individuals[33]. In severe infection, the titer of d-dimer increases more than fourfold[16,19,20,22,30,32–34].

Fibrin degradation products (FDP): are small pieces of

Table 4: *Coagulation parameters in COVID-19.*

Parameters	Clinical significance	Main Author & Reference No.
d-dimer	Significant increase in severe cases	Zhang et al[16]; Liu et al[19]; Mo et al[20]; Wu et al[22]; Gao et al[30]; Zhou et al[32]; Han et al[33] Tang et al[34].
Antithrombin (AT)	Decreased in cases	Han et al[33].
Prothrombin time (PT)	Decreased in cases Increased in severe cases	Han et al[33]. Huang et al[15]; Tang et al[34]
Activated partial thromboplastin time (APTT)	Increased in severe cases No significant rise in mild cases	Tang et al[34]. Han et al[33].
Fibrin degradation product (FDP)	Increased in all cases, more in severe cases	Han et al[33]; Tang et al[34].
Fibrinogen	Increased in all cases, more in severe cases	Gao et al[30]; Han et al[33] Tang et al[34].
Thrombin time	Low in severe cases	Gao et al[30]. Han et al[33]

protein released into the circulation when the degradation of a clot takes place by the enzyme plasmin. The level of FDP increases in COVID-1933, but the rise is considerably higher in critically ill patients[34].

Fibrinogen is a protein synthesized by the hepatocytes and circulates in the blood. Whenever there is tissue or vascular injury, it is converted to a thread-like structure called fibrin by the enzyme thrombin. This fibrin forms a mesh in which the platelets are entangled forming a clot. In COVID-19 infection, activation of the clotting mechanism causes an increase in the fibrinogen level. However, the rise in critically ill patients remains insignificant in comparison to those who are less seriously ill[30,33,34].

Prothrombin time (PT) is the time taken for the blood to clot. The application of this test in routine hematology is to investigate the clotting characteristic of blood. Huang et al and Tang et al reported[15,34] an increase in PT among critically ill patients. However, Han et al[33] found low values of PT in his study.

Activated partial thromboplastin time (APTT): is another measure of the clotting characteristic of blood. It signifies the time taken by the blood to form a clot. In COVID-19 cases, elevated levels of APTT are seen in patients with the severe form of illness[34]. However; no significant rise was seen in the milder form of the disease[33].

Antithrombin (AT): It is a protein synthesized by the liver and functions to inactivate the enzymes of the coagulation cascade. Low levels of this protein have been observed in COVID-19 cases[33].

Thrombin time (TT): It is a coagulation-screening test, used to measure the time taken by fibrinogen to form fibrin threads. Variable data are available for TT values. Han et al[33] reported decreased values in severe cases, whereas, Gao et al[30] observed higher values.

2. Clinical Laboratory markers in severe Covid-19 patients.

The COVID-19 pandemic has jeopardized the world economy and health infrastructure. The health care workers are overburdened and scarcity of ICU facilities and ventilators have aggravated the situation further. Under these circumstances, it becomes imperative to identify those patients who are at increased risk of developing the severe form of the disease. Established risk factors like old age and comorbidities like diabetes mellitus, hypertension, and cardiovascular disease are known to progress to severe illness[32]. Several laboratory parameters can serve as prognostic markers as the disease progresses from mild to severe form. These markers can identify those who are at increased risk of developing the severe form of the disease and help in the proper allocation of resources towards better management of at-risk patients.

Table 5: *Parameters in severe COVID-19 patients.*

Parameters	Values	Reference No:
Lymphocytes	Decreased	14–21, 23.
Thrombocytes	Decreased	12, 20, 21, 27
C-reactive protein (CRP)	Increased	14, 16, 20, 21, 28, 30.
Procalcitonin	Increased	15, 16, 20, 21, 28.
Lactate dehydrogenase (LDH)	Increased	12, 14, 15, 17–23, 29.
Aminotransferase (ALT)	Increased	12, 21, 23.
Serum Creatinine	Increased	14, 21.
Serum Albumin	Decreased	14, 15, 19–21.
Cardiac Troponins	Increased	14, 29, 31.
TNF-α	Increased	15
IL-2, IL-6, IL-7 & IL-10	Increased	14, 15, 20, 25, 29, 30.
D-dimer	Increased	16, 19, 20, 22, 32–34.
Fibrin degradation product (FDP)	Increased	33, 34.

Among the various hematological parameters, a low lymphocyte count was the strongest predictor of disease progression to increased mortality[14–21]. Neutrophilia in response to a secondary bacterial infection or sepsis[15,23] and thrombocytopenia due to activation of the coagulation cascade[20,21] are associated with disease progression to fatal outcomes.

A significant association exists between several biochemical parameters and severe COVID-19 disease. CRP, an acute-phase protein and a marker of acute inflammation was increased in 75 – 93% of patients with severe infection. Several workers have reported an elevated

CRP in critically ill patients[14,16,20,21,28,30]. Procalcitonin, a precursor of Calcitonin, has an established association with secondary bacterial infection and sepsis. In cases of critically ill COVID-19 patients requiring intensive care and management, increased values of procalcitonin were reported[15,16,20,21,28] Severe COVID-19 patients exhibited increased values of LDH due to cellular injury progressing to multi-organ failure. In a study from Singapore, Fan et al reported that patients with a low Absolute Lymphocyte Count and high LDH required hospitalization in an intensive care unit[23]. Several other workers reported similar observations[12,14,15,17–22,29]. Aminotransferases are enzymes produced mainly in the hepatocytes. COVID-19 patients who had a poor outcome increased levels of the enzyme were reported[12,21,23].Similarly, serum Albumin, produced in the liver cells was found to be decreased in patients with poor prognosis[14,15,19–21]. Serum creatinine, a marker of renal function increases in patients progressing to renal failure[14,21]. Patients of COVID-19 with pre-existing cardiovascular disease and hypertension are at high risk for poor prognosis. Increased levels of cardio specific troponins are witnessed in severe patients requiring intensive care and management[14,29,31].

The level of some inflammatory markers called cytokine is altered by the SARS-CoV-2 infection. Several workers assessed a number of these cytokines and chemokines, out of which some of them like TNF- α (Tumour necrosis factor-alpha) 15 and interleukins like IL-2, IL-6, IL-7, and IL-10[14,15,20,25,29,30] can predict the progression of the disease towards severity.

Many workers have observed the association of abnormal coagulation parameters with the severity of illness[15,16,19,20,22,32–34]. Patients who progressed a fatal outcome had increased levels of D-dimer and FDP (Fibrin degradation products)[34]. Amongst these parameters, an increased D-dimer of › 1µg/L had the strongest association with high mortality[32].

An analysis of IL-6 and d-dimer between mild and severe cases exhibited a poor outcome. The combined occurrence of these two parameters had a high sensitivity and specificity for early prediction of severe COVID-19[39].

In a report, the data obtained from 21 studies, have identified leukocyte count, lymphocyte count, thrombocyte count, IL-6 and serum ferritin as important markers for severe illness[40].

Conclusion:

Combating the COVID-19 pandemic depends upon early identification and diagnosis of cases, strict isolation, and timely implementation of preventive measures by the government agencies, symptomatic treatment of cases, and institutional management of severely ill patients. Laboratory markers are helpful in the diagnosis of cases and more importantly, to identify those patients where chances of disease progression to severity are present. This will not only reduce the burden on the health care system but also reduce the mortality rate by channelizing resources to those cases who need critical care and management.

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