Review Article

Laboratory Findings in COVID-19 Patients and Biomarkers for Early Assessment of Severity and Mortality

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Abstract

The novel coronavirus-19 (severe acute respiratory syndrome coronavirus-2) pandemic has crossed more than 4,006,257 cases with 278,892 deaths worldwide and 67,152 cases and 2206 deaths in India. The disease has a variable clinical course ranging from mild to severe disease. Although most of the patients are asymptomatic, some patients with comorbidities have a high propensity of clinical worsening and mortality and it is this chunk of patients that we need to recuperate. Studies have shown that a number of laboratory parameters, which are easily available and inexpensive, can adequately predict the disease severity at an early stage. In a resource-limited country like India, where costly investigations cannot be routinely carried out in the magnitude as big as that of this pandemic, it is imperative that patients be monitored with these simple and inexpensive parameters that are elucidated in this review. We carried out an electronic search on PubMed and Google Scholar with keywords "laboratory abnormalities in COVID-19," "coagulopathy in COVID-19," "sepsis in COVID-19," "hematologic abnormalities in COVID-19," "kidney injury in COVID-19," "acute respiratory distress syndrome in COVID-19," "cardiac injury in COVID-19," "liver injury in COVID-19," and "severity indicators in COVID-19" till present date (May 11, 2020). All studies that appeared in our search results were scrutinized and 40 studies were selected for the study.

Keywords: COVID-19, laboratory parameters, monitoring, severe acute respiratory syndrome coronavirus-2

Introduction

The novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has taken the world by storm. Global pandemics like this, namely SARS-CoV in 2002–2003, H1N1 influenza in 2009, and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, have been previously recorded in the last 20 years. However, the new virus appears to be more contagious with the outbreak spreading across continents and causing more than 4.006.257 cases with 278,892 worldwide and 67,152 cases and 2206 deaths reported from India. The WHO declared COVID-19 a pandemic on March 11, 2020. SARS-CoV-2 is an enveloped, single-stranded RNA virus with a surface spike glycoprotein giving a crown-like appearance (hence the title Coronavirus). It was first reported in Wuhan, China, where spread from animal sources was speculated. It is conjectured that the coronavirus originated from the bats and spread to other mammalian hosts like civet (SARS-CoV), camel (MERS-CoV), and pangolin (SARS-Cov-2) from where it infected humans. The established current mode of transmission is by respiratory droplets, spread from one infected person to another during coughing, sneezing, and talking. When it comes in contact with the airways, the virus particle attaches to the angiotensin converting enzyme-2 (ACE-2) receptors from where it internalizes and infects the cells. The major pathogenetic mechanism of the virus is through an excessive release of inflammatory mediators leading to a cytokine storm. Furthermore, multiorgan injury occurs from direct cytopathic effect of virus in lung, kidney, and myocardium. The clinical spectrum of disease is variable, ranging from asymptomatic to mild to severe disease, eventually death. Milder form of illness (seen in around 81% of cases) presents as fever, cough,

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or mild pneumonia. Severe disease (seen in 14% of cases) presents with dyspnea and acute respiratory distress syndrome, while critical cases requiring intensive care unit (ICU) admission and mechanical ventilation are seen in 5% of cases and heralded by development of sepsis, coagulopathy, and multiorgan dysfunction.[1-4] In a country like India, with a large vulnerable population and a declining health-care system, the coronavirus-19 outburst is a catastrophe waiting to happen. It will be a herculean, near impossible task to evaluate every patient for confirmation of infection. Besides, the health-care system is largely unfamiliar with this new disease entity and with limited experience and mostly foreign case studies and reviews, it is difficult to map its clinical course and prognostic variables. Therefore, in all suspected patients, a panel of some initial investigations and some minimal follow-up investigations should be structured to stay abreast with the clinical course of patients. Although most of the patients usually recover without any sequelae, the most crucial step is to identify at an early stage the cases which are severe or have a high propensity to develop complications. It is strongly advised that the laboratory parameters which are vital biomarkers of critical illness/mortality, and which are elucidated in this review, be regularly monitored and assessed to ensure salvage at the earliest.

Data Collection

We carried out an electronic search on PubMed and Google Scholar with keywords "laboratory abnormalities in COVID-19," "coagulopathy in COVID-19," "sepsis in COVID-19," "hematologic abnormalities in COVID-19," "kidney injury in COVID-19," "acute respiratory distress syndrome (ARDS) in COVID-19," "cardiac injury in COVID-19," "liver injury in COVID-19," and "severity indicators in COVID-19" till present date (May 11, 2020). All studies that appeared in our search results were scrutinized and 40 studies were selected for the study.

Laboratory Diagnosis

A well-established confirmatory diagnostic test for SARS-CoV-2 is the real-time reverse transcriptase polymerase chain reaction. The assay detects RNA-dependent RNA polymerase gene on viral particle, which is highly specific for CoV-2 and does not show cross-reactivity with other pathogens. The test can be performed any time after symptom onset. Samples for this test are taken from upper respiratory tract (nasopharyngeal/oropharyngeal swab) and from lower respiratory tract (broncho-alveolar lavage, endotracheal aspirate, and expectorated sputum) for patients on mechanical ventilation. Sputum is not the preferred sample because it leads to aerosol generation.[3,4] Early evaluation also encompasses high-resolution computed tomography (CT) imaging of lungs which shows ground-glass opacities (bilateral) which are fairly diagnostic of pneumonia.

Several nucleic acid-based tests are being developed for SARS-CoV-2 detection. One such test is loop-mediated isothermal amplification, which is highly specific.[5]

The illness in COVID-19 patients can range from mild to severe. Some commonly available and inexpensive laboratory tests are shown to predict the risk of severity in diseased individuals at an early stage and should be used as baseline investigation to monitor disease course and assess prognosis. It is also advised that in a developing country where the resources are limited, these minimum to few parameters be used to identify patients that need monitoring at tertiary care facilities.

Hematological Abnormalities

Minimum recommended hematology investigation panel includes complete blood count (CBC), coagulation studies (prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen, and D-dimer), and erythrocyte sedimentation rate (ESR).[6]

CBC is a cost-effective, time-saving, and first-line investigation that gives some valuable insights in the clinical spectrum of COVID-19 patients.

The common hematological abnormalities encountered in COVID-19 patients with a worsening clinical state are low hemoglobin level, leukocytosis, neutrophilia, lymphocytopenia, thrombocytopenia, increased mean platelet volume, and high ESR.[6-12]

Hemoglobin values encountered in patients of COVID-19 with severe disease are found to be low as compared to those with milder illness.[7-11] A meta-analysis of these studies has shown that serial decreasing value of hemoglobin is associated with death, need for mechanical ventilation or ICU admission.[13] It is advised that this parameter be assessed and monitored regularly in patients since it is associated with a worse outcome. However, Indian subjects, especially females, show low baseline hemoglobin levels, so this parameter cannot be adequately used to assess disease severity in India.

Most of the studies have reported a high total leukocyte count (TLC) and neutrophilia and a decreased lymphocyte count in patients of COVID-19 with severe disease,[12,14,15] while some have reported leucopenia in the initial stage.[16] Neutrophilia along with leukocytosis is reportedly associated with increasing disease severity and is possibly a result of secondary bacterial infection. Neutrophilia is seen as a result of cytokine release (interleukin [IL]-6, IL-8, tumor necrosis factor-α [TNF-α], and interferon-γ [IFN-γ]), while lymphocytopenia is due to hampered cellular immunity as a direct effect of viral infection.[17,18]

Several models of prognostication have come up in various studies and deriving ratios of different blood cells is one of them. Most of the patients with severe disease were of older age and their laboratory assessment showed high TLC, neutrophilia, lymphopenia, and a high neutrophil-to-lymphocyte ratio (NLR), elevated derived NLR ratio (d-NLR), high platelet-to-lymphocyte ratio, and an elevated lymphocyte-to-monocyte ratio. NLR is calculated by dividing the values of neutrophils with lymphocytes, and

an increased ratio of >3.3 in patients with age >49.5 years is associated with a worse outcome because 46.1% of such patients would progress to severe disease within 6.3 days, while patients who did not meet this criteria would be discharged within 13.5 days. Hence, increased NLR is advocated to be a vital biomarker of disease progression and an independent risk factor for in-hospital death. Derived-NLR is calculated by dividing neutrophil count with the result of TLC minus neutrophil count.[17,18] Lymphocyte count below 0.8×10^9/L and low CD4 and CD8 cell counts warrant immediate consideration, although CD4-to-CD8 cell ratio is shown to be maintained at normal level.[19]

Several studies have shown low platelet counts in patients with severe disease,[9-12,20] while it is in the normal range or not commented upon in certain studies.[7,8,14,15] Thrombocytopenia in COVID-19 is a result of consumptive coagulopathy. A meta-analysis of some of these studies has established that low platelet count is associated with poor outcome and mortality in COVID-19 patients.[21] Another study has concluded that low platelet count at admission is related with a three times higher risk of mortality and should be regularly monitored.[22] Mean platelet volume is consistently shown to be elevated in various studies, and its high level is shown to be associated with risk of coagulopathy and thromboembolic disorders. ESR is also elevated in COVID-19 patients.[19,23]

Coagulation Studies

Coagulopathy was defined as prolongation in PT and APTT by 3 s and 5 s, respectively. It is consistently seen in COVID-19 patients in the form of microthrombi, viz., cerebral infarcts, lower limb ischemia, and also seen in the setting of antiphospholipid antibodies.[14] The parameters most uniformly deranged in the hemostatic pathway of COVID-19 patients are low platelets and high D-dimer levels.[24] Tang *et al*. reported that 71.4% of the nonsurvivors met the diagnostic criteria for disseminated intravascular coagulation as compared to 0.6% of the survivors. A meta-analysis of several studies has demonstrated that D-dimer >0.5 mg/L is associated with critical illness/mortality in COVID-19 patients. It is worth mentioning that unlike PT and APTT levels, which are not very high in COVID-19 patients, D-dimer is found remarkably high, up to many times its normal value.[25,26] It is advised that clinical methods and diagnostic imaging modalities depending on clinical presentation should be used in conjunction with hematology parameters to ascertain thromboembolic complication in COVID-19 patients.

Abnormalities in Biochemistry Parameters

Hematological investigations are not to be examined alone, rather in conjunction with other abnormalities, most importantly of biochemistry parameters. An array of abnormal biochemistry parameters are shown to be early indicators of severity/mortality.

Immunological/Inflammatory Biomarkers

SARS-CoV-2 infects the alveolar epithelial cells of lungs by attaching to the ACE-2 receptors, causing their downregulation and subsequent increase in angiotensin-2 levels. Elevated angiotensin-2 produces inflammation and leads to an increased accumulation of neutrophils and macrophages as well as of fibrinous exudate in the lung parenchyma. The latter leads to decreased ventilation and oxygenation in lungs. Increased viral replication causes secretion of inflammatory mediators IL-4, IL-6, and IL-10 which lead to an exaggerated cytokine production.[24] At least 14 cytokines have been demonstrated including IL-1 receptor antagonist, CXCL10, and CCL7.[27] This phenomenon is called as cytokine storm syndrome, which is strongly implicated in the pathogenesis of COVID-19. IL-6, which has a key role in it, binds to its receptor (IL-6R) and causes downstream signal transduction, thereby spearheading proliferation and differentiation of B lymphocytes with subsequent antibody production. Moreover, expansion of T-lymphocytes also takes place. A number of acute phase reactants are released thereby (ferritin, C-reactive protein [CRP], and serum amyloid A protein) that are detectable in high levels in critically ill patients of COVID-19. Cytokine storm encompasses the spectrum of multiorgan failure, secondary infection, and death in patients of COVID-19.[28]

Laboratory measurements of inflammatory biomarkers have revealed that increased levels of IL-6, IL-10, CRP, and serum ferritin are observed in patients with severe form of illness and in nonsurvivors.[29]

Procalcitonin and other Markers of Secondary Infection/Sepsis

Sepsis is observed as the most common complication, seen more in nonsurvivors as compared to survivors.[12] The Third International Consensus definition for sepsis and septic shock (2016) defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.[30] Secondary infection was diagnosed when a culture of lower respiratory tract specimen or blood sample revealed a new pathogen. Reportedly, half of nonsurvivors developed a secondary infection. Sizeable number of nonsurvivors showed features of ventilator-associated pneumonia as well.[12] The probable indicators of secondary infection are leukocytosis, neutrophilia, and elevated procalcitonin. Procalcitonin has emerged as a vital indicator of severity/mortality, and patients with high levels (>0.5 ng/ml) have five times higher risk of developing severe disease. The limitation with procalcitonin is that not all patients show elevated levels. Superimposed bacterial infections cause procalcitonin secretion and the high level is maintained by IL-6 and TNF-α, while it is suppressed by IFN-γ. Since IFN-γ is produced in viral infections, in patients with non-severe disease (and with no secondary infection), its level is not high, as compared to patients with bacterial infections and among non-survivors. Hence, serial measurement of procalcitonin is advised for

early assessment of clinical severity and to prevent mortality in COVID-19 patients.[26,29]

Organ Function Tests

A host of factors in SARS-CoV-2 infected patients lead to the development of a spectrum of multiorgan injury encompassing lung, kidney, myocardium, and liver. Direct cytopathic effect of SARS-CoV-2 and cytokine storm (mainly IL-6) are the main instigators but age >65 years and comorbidities such as hypertension, diabetes mellitus, and cardiovascular diseases augment the worse clinical course in COVID-19 patients.

ARDS is the development of hypoxemia needing mechanical ventilation. There is variable evidence of COVID-19 patients developing ARDS and needing ICU admission, but it is claimed that the incidence is rather underestimated. In a recent study, out of 201 patients of confirmed COVID-19, 41.8% developed ARDS and out of those 52.4% patients expired. Comorbidities associated with ARDS are old age, hypertension, and diabetes. Laboratory parameters associated with development of ARDS and progression of ARDS to death include neutrophilia, high lactate dehydrogenase (LDH), and high D-dimer levels. LDH is a vital biomarker of pulmonary injury.[31,32]

The American College of Cardiology released a statement emphasizing the cardiac involvement of COVID-19. A recent study highlighted that 12% of COVID-19 patients showed decline in ejection fraction and troponin I elevation, thus exposing acute cardiac injury. Another study showed 19.7% patients exhibiting cardiac injury among 416 confirmed COVID-19 patients. As compared to patients without cardiac injury, patients with cardiac injury are older and have comorbidities such as diabetes, hypertension, chronic obstructive pulmonary disease, and coronary heart disease.

Biomarkers of myocardial injury found elevated in critically ill patients are cardiac troponins high sensitivity cardiac troponin I (hs-cTnI) and creatine kinase-MB. Cardiac troponin I was found significantly high in patients with critical illness and among nonsurvivors. Other deranged laboratory parameters in these patients include high TLC, low lymphocyte count, and low platelets along with reduced albumin and elevated aspartate aminotransferase (AST), CRP, and procalcitonin. Moreover, myohemoglobin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were also found in increased levels. CT scan and electrocardiography (ECG) can be used as an adjunct in patients with severe disease. ECG has revealed ST-segment depression and T-wave inversion in patients developing cardiac injury.[33,34]

Liver injury in patients infected with SARS-CoV-2 is either due to direct cytopathic effect of virus or due to tissue injury by inflammatory mediators. Drug-induced heptatotoxicity is also reported. Gamma-glutamyl transferase was found elevated in 54% cases in one study. Many studies have reported liver damage in patients of COVID-19.[7,9,10,35] Liver damage as indicated by AST >40U/L and LDH >245U/L is also implicated in patients with severe disease. Other abnormal findings in liver function are reduced albumin and elevated alanine aminotransferase along with high total bilirubin.[26,29] LDH is an intracytoplasmic enzyme that is released in high levels on cell damage. Its level correlates positively with AST, CRP cTnI, as well as with BNP, while negative correlation is seen with lymphocytes and CD4+ and CD8+ T cells. Hence, LDH is an important biomarker of liver injury, besides indicating myocardial, kidney, and lung injury as well.[36]

Many investigators have linked acute kidney injury (AKI) with COVID-19. ACE-2 receptors, which are the route of entry to SARS-CoV-2 virus, are also present on renal tubular epithelial cells and their subsequent infection worsens the local inflammatory response. Various studies support or refute the claim. According to an Italian report, the incidence of AKI was almost 27.8% in more than 2000 patients. Another study done in Wuhan, China, stated that out of 111 confirmed COVID-19 cases without chronic kidney disease, only 12 developed mild increase in serum creatinine and blood urea nitrogen (BUN) and none showed features of AKI. Nevertheless, monitoring of kidney function is important, especially in patients at high risk of developing severe disease. Impairment of kidney function is seen in COVID-19 patients with comorbidities such as old age, diabetes, secondary infections, and cardiac disease. Abnormal kidney function is seen as high BUN and elevated creatinine (≥133 μmol/L). In addition, some new markers of acute tubular damage such as tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 are also described.[37,38]

Muscle injury is revealed with high creatine kinase and high myoglobin.[26,29]

Electrolyte abnormalities such as lower serum concentrations of sodium, potassium, and calcium have been observed in patients with severe disease.[39]

Urine Analysis

Urinalysis is a simple, cost-effective investigation that is shown to reveal kidney impairment better than kidney function tests. It was observed in one study that among 83 patients of COVID-19 that exhibited no previous kidney dysfunction, 54.2% (45 patients) demonstrated hematuria (2.4%+-, 16.9%+, 8.4%++, and 3.6%+++), proteinuria (15.7%+-, 16.9%+, and 2.4%++), and pus cells in urine sediment, ahead of biochemistry parameters such as serum creatinine and BUN. Furthermore, ICU patients showed more severe results of urine analysis as compared to non-ICU patients.[40]

The most commonly altered laboratory parameters and their clinical implications are summarized in Table 1.[41] The parameters in nonsurvivors/critical patients which need careful monitoring are listed below:[26]

- Leukocytosis with neutrophilia (NLR >3.3 at age >49.5 years)
- Lymphocyte count <0.8 × 109/L

Table 1: Most commonly deranged laboratory parameters with their clinical implications

Deranged laboratory parameters	Clinical implications
Leukocytosis	Secondary bacterial infection
Neutrophilia	Secondary bacterial infection
Lymphopenia	Hampered immunological response
Thrombocytopenia	Consumptive coagulopathy
High D-dimer	Consumptive coagulopathy
Prolonged PT	Consumptive coagulopathy
High bilirubin	Liver injury
High AST	Multiorgan injury, especially liver injury
High LDH	Multiorgan injury, especially liver injury and lung injury
Low albumin	Liver dysfunction
High serum creatinine	Kidney injury
High BUN	Kidney injury
High cardiac troponin I	Cardiac injury
High CRP	Viral infection, cytokine storm
High ferritin	Inflammatory cascade, cytokine storm
High IL-6	Cytokine storm
High procalcitonin	Secondary bacterial infection
Proteinuria, hematuria, pyuria on urinalysis	Kidney injury/dysfunction

LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, CRP: C-reactive protein, IL-6: Interleukin-6, BUN: Blood urea nitrogen, PT: Prothrombin time

- D-dimer >0.5 mg/L
- Procalcitonin >0.5 ng/mL
- AST >40U/L
- LDH >245U/L
- Creatinine ≥ 133 μmol/L
- hs-cTnI >28 pg/mL
- CRP >100 mg/dl
- Ferritin >500 ug/L.

Conclusion

The clinical course of SARS-CoV-2 infected patients varies from asymptomatic to mild to severe disease with subsequent mortality. Clinical and laboratory parameters in asymptomatic and mild cases are only mildly deranged and less alarming. However, patients with older age and described comorbidities show severe illness at the time of presentation or show progression to critical illness needing ICU admission. Such patients with worsening clinical condition harbor a host of deranged laboratory parameters which are early indicators of severity/mortality. In such patients, it is imperative that these parameters be regularly monitored and assessed.

However, in a resource-limited country like India, we cannot afford the luxury of expensive investigations such as procalcitonin, ferritin, D-dimer, and interleukins, besides availability of such tests is limited to tertiary care center only. Hence, the reliance on commonly available and inexpensive investigations is foremost. Through this review, we have brought to light the role of inexpensive and easily available investigations such as CBC, biochemistry, and urine analysis in identification and prognostication of COVID-19 patients, so that critical patients can be referred to tertiary care center in a timely manner.

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Conflicts of interest

There are no conflicts of interest.

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