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Review Article

# Review on biochemical alterations in COVID-19 patients

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) pandemic is leading to a Public Health Emergency of International Concern (PHEIC) across the globe. COVID-19 has been found to be associated with the dysfunction of several vital organs in addition to respiratory failure. Though biochemical findings among COVID-19 patients have been partially characterized in some case studies, published systematic reviews with consolidated biochemical findings of COVID-19 are not yet available. The role of biochemical monitoring in the screening of COVID-19 cases has not been definitely established. Hence, the significance of laboratory parameters in assessing the severity and prognosis of COVID-19 cases is discussed with a focus on various hematological, biochemical, and metabolic alterations in patients suffering from COVID-19 infection. We conclude that biochemical monitoring of COVID-19 patients helps in identifying critically ill patients even earlier, aiming to reduce mortality and improve the recovery rate.



## 1. Introduction

Novel Coronavirus (2019-nCoV), also known as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a newly emerging zoonotic agent causing the Coronavirus Disease 2019 (COVID-19).[1] Common complications observed more frequently in deceased patients included acute respiratory distress, sepsis, acute cardiac injury, heart failure, alkalosis, acute kidney injury, and hypoxic encephalopathy.[2] Although studies and case reports have already been published in major international scientific and medical journals from China and other countries, a systematic review to consolidate what has been learned from each case study is to-date missing. The mortality rate is reported to be higher among patients developing into severe or critical levels. It is important to identify critically ill patients at an early stage, to reduce mortality and improve the recovery rate. Monitoring of biochemical parameters in COVID-19 patients is critical for assessing disease severity and progression as well as monitoring therapeutic intervention. Hence, we summarized hematological, biochemical and metabolic alterations in COVID-19 patients.

## 2. Hematological and Biochemical Alterations in COVID-19 Patients

Hematological profile of severe COVID 19 patients showed increased WBC count and neutrophil count, decreased lymphocyte, platelet, eosinophil count, and hemoglobin levels.[3] Patients with severe disease had only a mild increase in WBC count while patients who died had a more clinically significant increase in WBC count. As such in patients with severe disease, a significant increase in WBCs may signify clinical worsening and increased risk of a poor outcome. Monitoring of WBC count, lymphocyte count, platelet count, and serum ferritin can be used as markers for potential progression to critical illness particularly in hospitalized COVID-19 patients.[4]

Leukocytosis was present in 56 (50%) patients who died and 6 (4%) who recovered and lymphopenia was present in 103 (91%) and 76 (47%) respectively in a study with 113 COVID patients who died and 161 COVID patients who recovered.[5] Lymphopenia is reported to be

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a predictor of poor prognosis in COVID-19 patients. Lymphocyte percentage of different stages of COVID-19 patients indicate that the lymphocyte count is reduced with increased severity of the disease. The mechanisms leading to lymphocyte deficiency were speculated to be the direct effect of the virus on lymphocytes resulting in lymphocyte death, the effect of the virus on lymphatic organs, disordered inflammatory cytokines perhaps lead to lymphocyte apoptosis and inhibition of lymphocytes by metabolic molecules produced by metabolic disorders (severe COVID-19 patients had elevated blood lactic acid levels) such as hyper lactic acidemia.[6] A study of 138 novel coronavirus (2019-nCoV)–infected pneumonia patients revealed lymphopenia, prolonged prothrombin time, and elevated lactate dehydrogenase in 70.3%, 58% and 39.9% of the cases respectively.[7]

Biochemical changes like leukocytosis, neutrophilia, lymphopenia, cytokine storm, decreased albumin, increase in alanine transaminase (ALT), total bilirubin, lactate dehydrogenase (LDH), and procalcitonin levels were significant predictors of ICU admission among 140 COVID-19 patients (13 with severe disease).[8] Elevated levels of procalcitonin was observed in critical patients and hence reported to be the marker the to assess the prognosis of COVID patients. Comparison of biochemical parameters of survivor and non-survivor patients (852 patients) revealed that increased levels of WBC, neutrophils, urea, creatinine, creatine kinase, hypersensitive cardiac troponin, lactate dehydrogenase, D-dimer and IL-6 increased the risk of death in COVID-19 patients.[9]

Thrombocytopenia is observed in critically ill COVID-19 patients and suggests serious organ malfunction or physiologic decompensation as opposed to primary hematologic etiology as well as the development of intravascular coagulopathy, often evolving towards disseminated intravascular coagulation. A meta-analysis of 1725 COVID-19 cases with 375 severe cases revealed that significantly lower platelet count in patients was associated with over fivefold enhanced risk of severity and mortality and thus, it can serve as a clinical indicator of worsening illness during hospitalization.[10]

Coagulopathy is associated with progression to critical states and hence, one of the important prognostic factors in patients with COVID-19. The most typical finding in patients with COVID-19 coagulopathy is an increased D-dimer concentration, a relatively modest decrease in platelet count, and a prolongation of the prothrombin time.[11] Similar findingsof increased D-Dimer levels was observed in other patients (0.91 $\mu$g/L in severe vs 0.27 $\mu$g/L in mild patients).[12]

Similar findings were observed among 140 COVID-19 patients (58 severe patients). A Two-fold increase in the serum concentration of D-dimer, C-reactive protein (CRP), and procalcitonin was observed in patients with severe disease compared to those with a milder form.[13]

Biochemical findings in COVID-19 patients include decreased albumin and higher levels of AST, ALT, total bilirubin, BUN, creatinine, creatinine kinase, lactate dehydrogenase, myoglobin, creatinine kinase MB, cardiac troponin I. Significant elevation in liver enzymes (ALT and AST), renal biomarkers (blood urea nitrogen and creatinine) and CRP levels were reported in patients with the severe form of the disease.[4]

A study on 597 COVID-19 patients to examine the serum levels of cholesterol (mild: 394; severe: 171; critical: 32) revealed that LDL-cholesterol and total cholesterol levels were significantly lower in COVID-19 patients as compared with normal subjects. There was a significant and gradual decrease in levels of LDL – C, and TC across all three groups. HDL-cholesterol levels decreased significantly in critical cases as compared to levels in mild and severe cases. LDL - C and TC levels inversely correlated with CRP protein and positively correlated with the number of lymphocytes in patients.[14] similar results of decreased total cholesterol, HDL-cholesterol and LDL-cholesterol levels i.e 3.70$\pm$0.09mmol/L, 1.18$\pm$0.03 mmol/L and 1.82$\pm$0.08 mmol/L respectively and increased monocyte/HDL cholesterol ratio (0.37$\pm$0.02) in were reported in COVID-19 patients.[15]

The CRP concentration was significantly higher in the severe (39.37 $\pm$ 27.68 mg/L) than the mild COVID patients (18.76 $\pm$ 22.20 mg/L).[12]Higher ALT, CRP, neutrophils, LDH, urea and lower WBC count was reported to have very good accuracy in predicting cases with positive RT-PCR for COVID-19.[16] Blood analysis of COVID 19 patients showed decreased albumin, high C-reactive protein, and high LDH, lymphopenia, and high erythrocyte sedimentation rate (ESR).[17] During the first 6-9 days of hospitalization, significantly higher levels of serum LDH, CK was observed in patients in the severe group than those in moderate group. Whereas CRP levels fluctuated around day 3 and dropped down on day 6 to 9 in both moderate and severe group of patients. COVID-19 m RNA clearance ratio was significantly correlated with the decline of serum CK and LDH levels.[18]

Higher blood glucose value (7.4 mmol/L) was reported in COVID patients which might be due to underlying diseases that caused a high glucose level.[19]Similar results of a significantly higher level of glucose in severe patients (9.91 mmol/L) compared to the mild cases (7.07 mmol/L) were reported.[12]

Unfavorable progression can be anticipated with cytokine elevation in COVID-19 where respiratory distress is common. Plasma IL-1 beta and IL-6 levels were consistent and efficient predictors of unfavorable outcome in acute respiratory disease syndrome.[20] The level of IL-6 was significantly higher in the severe COVID patients (59.20 pg/mL) than in the mild patients (24.18 pg/mL).[12]

The routine blood analysis of 207 patients who were RT-PCR tested, after being admitted to the emergency room with COVID-19 symptoms revealed statistically significant differences in the plasma levels of WBC, CRP, AST, ALT, and LDH between those who were positive at the genetic test and those who were negative. Using RT-PCR as the gold standard, almost 70% of the patients could be classified as COVID-19 positive or negative based on their hematological parameters.[21]

Five studies with a total sample size of 1415 COVID-19 patients showed hypokalemia, hyponatremia, and hypocalcemia in patients with severe disease.[22] Hypokalemia is known to exacerbate acute respiratory distress syndrome and acute cardiac injury, which are common complications in COVID-19, especially in patients with underlying lung or heart disease. Hypokalemia may potentially contribute to unraveling pathogenic mechanisms underlying COVID-19 and hence may have clinically significant implications for patient management. Increased plasma angiotensin II concentration has been described in patients with COVID-19, possibly acting as a mediator of acute lung injury, as earlier confirmed in SARS-CoV animal models.[23,24] Hypokalemia also provides a pathophysiologic clue, as SARS-CoV-2 binds to its host receptor, angiotensin-converting enzyme 2 (ACE2), a likely reduction in ACE2 expression, leads to increased angiotensin II. This can cause increased potassium excretion by the kidneys, ultimately leads to hypokalemia in COVID-19 cases.[5,23] Gastrointestinal losses with diarrhea and nausea present in as many as 34.0% and 3.9% of COVID-19 patients respectively, may also contribute to hypokalemia and other electrolyte imbalances.[25]

## 3. Metabolic Alterations in COVID-19 Patients

Disturbed metabolic patterns have been found to be correlated with the progress of COVID from mild to critical cases. In COVID-19 affected patients, plasma metabolomics analysis revealed the altered energy metabolism and hepatic dysfunction as indicated by reduced malic acid of the TCA cycle, glycerol-3-phosphate and carbamoyl phosphate of the urea cycle respectively.[26] Malic acid besides its role in energy metabolism, it is also found to be involved in acceleration of urea synthesis and protect endothelial cells from damage. Glycerol 3-phosphate, a component of energy producing reactions, also serves as an important regulator of systemic acquired immunity.[27,28]

Carbamoyl phosphate was found to be profoundly down-regulated in fatal patients compared with mild patients. Carbamoyl phosphate is synthesized from free amino donors by carbamoyl phosphate synthetase I (CPS I) in mitochondria of liver cells and participates in the urea cycle to remove excess ammonia and produce urea.[29] Its reduction in fatal cases of COVID-19 suggests the possibility of liver damage. Xylulose-5-Phosphate, a metabolite of the pentose phosphate pathway, is also found to be altered in COVID-19 patients reflecting impairment of glucose and lipid metabolism in liver.[30]

Dihydrouracil, an intermediate breakdown product of uracil and guanosine monophosphate (GMP) is significantly reduced between healthy subjects and COVID-19 patients, as well as between the mild and fatal groups. Significant changes in both GMP and carbamoyl phosphate show between fatal and mild patients indicates the association of disease progression with immune dysfunction and nucleotide metabolism.[26]

The diabetes patients affected with COVID-19 were reported to have enhanced dysregulation of glucose metabolism associated with a higher risk of severe pneumonia, the release of nonfunctional serum enzymes, uncontrolled inflammation responses, and hypercoagulable state. The higher susceptibility of diabetes patients to an inflammatory storm during COVID-19 is substantiated by elevated levels of IL-6, CRP, ferritin, and coagulation index (D-dimer) in serum compared to those patients without diabetes.[31]

**Table 1:** Potential variations in laboratory findings andtheir significance in COVID-19.

| Laboratory parameter | Potential clinical and biological significance |
|---|---|
| Lymphopenia | Decreased immunological response to the virus |
| Leukocytosis, Netrophilia, and increased procalcitonin | Bacterial (super)infection |
| Increased value of CRP | Severe viral infection / viremia / viral sepsis |
| Increased serum LDH activity | Pulmonary injury and/or widespread organ damage |
| Increased activity of serum ALT and AST | Hepatic injury, widespread organ damage |
| Increased value of serum urea and creatinine | Kidney injury |
| Increased value of cardiac troponins | Cardiac injury |
| Decreased serum albumin and increased serum bilirubin | Impairment of liver function |
| Thrombocytopenia | Consumption (disseminated) coagulopathy |
| Prolongation of prothrombin time, increased D-dimer | Activation of blood coagulation and/or disseminated coagulopathy |

Lippi and Plebani, 2020.[31]

## 4. Conclusion

The common laboratory abnormalities in COVID-19 deceased patients included coagulation disorder (elevation of prothrombin time and D-dimer), impaired liver and kidney function (mild or moderate elevation of ALT, AST, total bilirubin, alkaline phosphatase, $\gamma$-glutamyl

transpeptidase, BUN, creatinine, hypoalbuminemia, haematuria, and albuminuria), electrolyte disturbance (hypokalemia and hyponatremia), elevated inflammatory markers (CRP, ferritin, and ESR) and cytokine storm.

Based on the analysis of the currently available data, we suggest that deranged biochemical parameters of blood may be useful as significant predictors of adverse clinical outcomes in COVID-19 disease. Several common biochemical parameters of blood like LDH, CRP, ALT, IL-6, Potassium, lymphocytes, platelets, and NEU are significantly altered during COVID-19 unfavorable progression, thus provide important prognostic information. Identifying critically ill patients even earlier than clinical manifestations helps to reduce mortality and improve the recovery rate. Thus, biochemical monitoring of COVID-19 patients through in vitro diagnostic testing is critical for assessing disease severity and progression as well as monitoring therapeutic intervention.

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