Research Article

# Effects of COVID-19 Infection on Biochemical Parameters and Biomarkers Associated with Disease Prognosis and Severity

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## ABSTRACT

**Objectives:** COVID-19 is a disease associated with biochemical disruptions. This study aimed to evaluate changes in biochemical parameters in COVID-19 patients and to identify clinically applicable biomarkers for disease prognosis and severity assessment.

**Methods:** This study enrolled 155 hospitalized COVID-19 patients classified as mild (n=35), moderate (n=40), severe (n=35), or critical (n=45), along with 40 healthy controls. Serum levels of blood glucose (BG), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T Bil), direct bilirubin (D Bil), lactate dehydrogenase (LDH), high sensitivity C reactive protein (hs CRP), and electrolytes ($Na^+$, $K^+$) were measured. Logistic regression was performed to assess disease severity. Receiver operating characteristic (ROC) curve analyses were conducted to identify independent predictors and optimal cut off values for prognosis (patients vs. controls) and severity (mild vs. moderate, severe, and critical groups).

**Results:** All hepatic, renal, and glycemic parameters, as well as LDH and hs CRP, were elevated across all patient groups compared to controls ($P < 0.001$). Adjusted logistic regression identified hs CRP (odds ratio (OR) = 25.76), D Bil (OR = 4.56), Cr (OR = 3.17), and LDH (OR = 1.26) as the strongest independent predictors of increased infection severity. ROC analysis determined LDH as the best biomarker for disease prognosis (AUC = 97.72%, cut off > 317 U/L) and D Bil for disease severity (AUC = 72.81%, cut off > 0.23 mg/dL).

**Conclusion:** LDH and D Bil represent the most clinically useful biomarkers for COVID 19 prognosis and severity detection, respectively. These results advocate for their routine integration into standard biochemical surveillance to facilitate early risk assessment; however, broader prospective investigations with larger cohorts are essential to confirm their generalizability.

**Keywords:** COVID-19, Biochemical parameters, Disease prognosis, Disease severity, Lactate dehydrogenase, Direct bilirubin

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## Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as one of the most significant global public health emergencies of the modern era. As of 2023, cumulative data indicates over 700 million confirmed cases and nearly 7 million fatalities globally, exhibiting diverse clinical manifestations from asymptomatic infection to fatal multi-organ failure (1, 2). The virus primarily targets the respiratory system by binding its spike protein to angiotensin-converting enzyme 2 (ACE2) receptors which are abundantly expressed in alveolar epithelial cells (3). The widespread presence of ACE2 in vascular endothelium, renal tubules, hepatocytes, pancreatic β-cells, and enterocytes elucidates the diverse extra-pulmonary manifestations that typify severe disease (4, 5). Post-acute sequelae of COVID-19 (PASC), commonly referred to as "Long COVID," has garnered increasing clinical attention, affecting an estimated 10–30% of survivors and manifesting as persistent debilitating symptoms including cognitive impairment, exercise intolerance, and metabolic dysregulation lasting months beyond the acute phase of infection (6). This diverse clinical spectrum highlights the urgent necessity for dependable biomarkers that can forecast disease progression and inform therapeutic strategies (7).

At the molecular level, the pathogenesis of COVID-19 is driven by an intricate crosstalk between direct viral cytopathic effects and host immune dysregulation (8). The viral nucleocapsid protein has been demonstrated to induce mitochondrial oxidative stress and endoplasmic reticulum stress, whereas the envelope protein activates the NOD-like receptor protein 3 (NLRP3) inflammasome, establishing a pro-inflammatory environment (9). Elevated interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and other mediators contribute to endothelial injury, micro-thrombosis, and multi-organ dysfunction, resulting in the "cytokine storm" (10). Notably, diabetic patients with pre-existing metabolic comorbidities, demonstrate significantly worse clinical outcomes, with reported mortality rates 2-3 times higher than those observed in non-diabetic patients (11). This susceptibility arises from multiple factors: elevated ACE2 receptor density in insulin-secreting β-cells, hyperglycemia-induced dysfunction of neutrophils and macrophages, and accelerated vascular inflammation (12). Hepatic involvement, evidenced by elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and bilirubin (Bili) in 14–53% of hospitalized patients, reflects both direct viral infection of hepatocytes and hypoxic injury secondary to respiratory failure (13). Renal dysfunction, characterized by rising blood urea nitrogen (BUN) and creatinine (Cr) levels, occurs in 20–40% of patients with severe disease and is primarily attributable to complement cascade activation, microvascular thrombosis, and direct viral tropism for tubular epithelial cells (14).

Recent evidence highlights the prognostic significance of dynamic changes in biochemical parameters as the disease progresses (15). Hyperglycemia, even in individuals who were previously normoglycemic, is associated with adverse outcomes due to the glucose-induced upregulation of pro-inflammatory cytokines (16). Liver function test abnormalities indicate a heightened risk of mechanical ventilation, whereas acute kidney injury is independently correlated with mortality (17). Electrolyte imbalances, especially hypokalemia affecting up to 60% of patients, may indicate viral disruption of renal outer medullary potassium channels and gastrointestinal losses (18). High-sensitivity C-reactive protein (hs-CRP) and lactate dehydrogenase (LDH) are two examples of inflammatory markers that can be used to measure systemic inflammation and tissue damage, respectively (19).

In the present study, we aim to evaluate severitydependent alterations in some of biochemical parameters, including blood glucose (BG), renal markers (BUN and Cr), hepatic markers (AST, ALT, total bilirubin (TBil), and direct bilirubin (DBil)), electrolytes (sodium ($Na^+$), and potassium ($K^+$)), and inflammatory indices (hsCRP and LDH), across clinically defined COVID19 severity groups. Additionally, we aim to stablish clinically applicable cutoff values for each parameter to aid in prognostic evaluation and severity stratification.

## Material and Methods

### Subjects

This case-control study included 40 healthy individuals and 155 COVID-19 patients that were matched based on gender and admitted to Bushehr University of Medical Sciences' Persian Gulf Martyrs Hospital in Bushehr, Iran. Additionally, the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran, has authorized this study, which complies with the Declaration of Helsinki on research involving human beings (IR.KMU.REC.1399.239). The following were the requirements for inclusion: patients who were at least 25 years old, hospitalized in the hospital with COVID-19 symptoms, had a positive real-time PCR test result, and had completed an informed consent form. Severe liver disease, renal insufficiency (GFR < 60 ml/min), being pregnant, and receiving renal replacement treatment of any kind were among the exclusion criteria. According to research by Bastin et al., the chosen patients were split into four groups depending on their clinical manifestation, such as symptoms, radiographic evidence of the respiratory tract, oxygen saturation, breaths/min, lung infiltrates, etc. (20). COVID-19 patient group

includes (1) patients with mild COVID-19 infection (n = 40), (2) patients with moderate infection (n = 40), (3) patients with severe infection (n = 35), and (4) patients with critical infection (n = 45) (21).

### Samples and data collection

Demographic information, such as age and gender, was recorded through interviews with the participants. 5 mL of venous blood samples were drawn from each patient and poured into a gel separator for evaluating biochemical parameters. For the measurement of biochemical analytes, the blood samples were centrifuged (2000 x g for 10 minutes), and serum was separated and stored at -20°C until analysis.

### Measurement of biochemical analytes

Serum levels of hs-CRP, BG, BUN, Cr, D-Bil, T-Bil, AST, ALT, and LDH were assessed using standard kits (Pars Azmoon, Tehran, Iran) with an autoanalyzer (Selectra XL instrument; Randox Laboratories Ltd, Antrim, UK) in a standardized laboratory setting. The serum levels of $Na^+$, and $K^+$ were measured by an electrolyte analyzer (22).

### Statistical analysis

SPSS (version 27) was used for the analysis, and GraphPad Prism (version 10) was used for visualization. Statistical significance was assessed at a significance level of $P < 0.05$. Numbers (%) were used to indicate qualitative factors, while mean ± standard errors of the mean (SEM) were used to represent quantitative parameters. One-way analysis of variance (ANOVA)/ Kruskal–Wallis with post hoc Tukey/Mann–Whitney U tests and chi-square tests were used to illustrate the variances between the groups according to the test of normality. To strengthen the linear model's normality presumption, the frequencies of hs-CRP, T-Bil, and D-Bil were changed to natural logarithm (LN) due to their abnormal distributions. After adjusting for age and sex, a multivariate logistic regression model was used to determine the odds ratios (ORs) for biochemical parameters associated with disease severity (mild, moderate, severe, and critical). The usefulness of the parameters for disease prognosis (patients vs. control) and disease severity (mild vs. severe and critical groups) was assessed using the Receiver Operating Characteristic (ROC) with an Area Under Curve (AUC) at 95% Confidence Interval (CI). Cut-off values for each parameter were determined using the Youden index, which takes into consideration the parameters' greatest sensitivity and specificity (23).

## Results

### Demographic characteristics of the participants

The study population (N=195) was categorized into five groups; mild (N=35, 16 (18.18%) female), moderate (N=40, 19 (21.59%) female), severe (N=35, 18 (20.45%) female), critical (N=45, 13 (14.77%) female), and healthy controls (N=40, 21 (23.86%) female). No statistically significant difference was observed between the patient and normal groups for gender ($P = 0.07$). Also, in moderate ($P = 0.02$) and severe ($P < 0.001$) groups, the mean age was higher than control group (Table 1).

### Kidney function tests and electrolytes ($Na^+$, $K^+$)

The results of kidney function tests and electrolytes shows that Cr and BUN levels were elevated in the mild, moderate, severe, and critical COVID-19 patient groups compared to the healthy controls ($P < 0.001$). No significant difference in $Na^+$ levels was found across the groups; however, $K^+$ levels were elevated in the critical group compared to the healthy controls ($P = 0.003$) (Figure 1).

### Liver function tests

Liver function tests demonstrated that the levels of AST and ALT were higher in patients with mild, moderate, severe, and critical COVID-19 infection than they were in healthy controls ($P < 0.001$). D-Bil and T-Bil were significantly higher in all patient groups compared to healthy controls ($P < 0.001$) (Figure 2).

### Blood glucose, hs-CRP and LDH

Figure 3 displays the data related to the levels of hs-CRP, BG, and LDH in both the case and the control groups. The levels of hs-CRP, BG, and LDH were found to be significantly higher in the group with mild, moderate, severe, and critical COVID-19 infection compared to the control group ($P < 0.001$).

### Logistic regression

Logistic regression was conducted to evaluate the

**Table 1.** Demographic information in the study groups.

| Groups / Variables | | Normal | Mild | Moderate | Severe | Critical | P-value |
|---|---|---|---|---|---|---|---|
| **Age (Years)** | | 47.34+2.21 | 45.56+2.56 | 54.21+2.54a* | 60.34+2.55 b*** | 54.13+2.45 | < 0.001 |
| **Frequency, n (%)** | Female | 21(23.86) | 16 (18.18) | 19 (21.59) | 18 (20.45) | 13 (14.77) | 0.075 |
| | Male | 19 (17.59) | 19(17.5) | 21 (19.44) | 17(15.74) | 32(29.62) | |
| | Total | 40 (20.51) | 35 (17.94) | 40 (20.51) | 35 (17.94) | 45 (23.07) | |

Data are presented as mean ± SEM/number (%) and significance level is as: * $P$ <0.05, *** $P$ <0.001.
a: Comparison between moderate and normal groups; b: Comparison between severe and normal groups

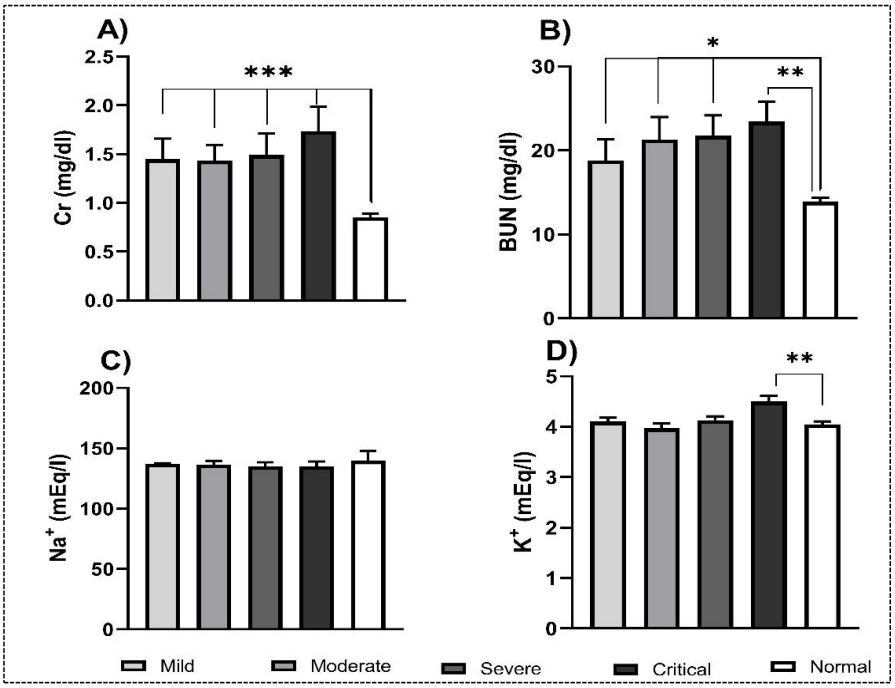



**Figure 1.** Comparison of kidney function tests and electrolytes in COVID-19 infection and control groups. A) Cr, B) BUN, C) $Na^+$, D) $K^+$ in the mild, moderate, severe, and critical groups. Parameters are presented as mean ± SEM and significance level is as: $^{*}$ $P < 0.05$, $^{**}$ $P < 0.01$, $^{***}$ $P < 0.001$.

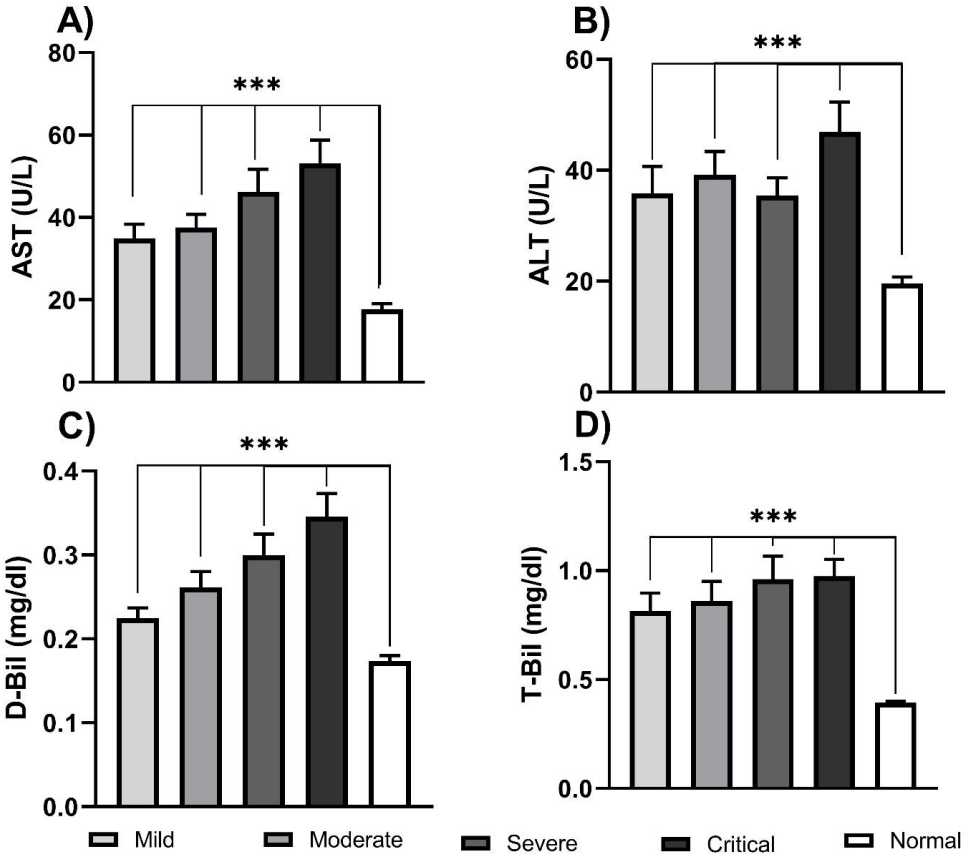



**Figure 2.** Comparison of liver function tests in in COVID-19 infection and control groups. A) AST, B) ALT, C) D-Bil, D) T-Bil in the mild, moderate, severe, and critical groups. Parameters are presented as mean ± SEM and significance level is as: $^{***}$ $P < 0.001$.

association between the biochemical parameters and COVID-19 severity in crude and adjusted with age and gender. As shown in Table 2, adjusted hs-CRP (OR = 25.76, $P < 0.001$), adjusted BG (OR = 1.17, $P < 0.001$), adjusted BUN (OR = 1.1, $P = 0.007$), adjusted Cr (OR = 3.17, $P < 0.001$), adjusted T-Bil (OR = 3.63, $P < 0.001$), adjusted D-Bil (OR = 4.56, $P < 0.001$), adjusted AST (OR = 1.14, $P < 0.001$), adjusted ALT (OR = 1.09, $P < 0.001$), and adjusted LDH (OR = 1.26, $P < 0.001$) increase the risk of COVID-19 severity. Furthermore, no difference was detected in $Na^+$ and $K^+$ levels.

### ROC curve

The results of ROC curve are shown in Table 3, which illustrates the AUC and ROC analysis of biochemical markers for detecting the disease prognosis (COVID-19 infection vs. control) and disease severity (severe-critical vs. mild), as well as the best cut off method used. The biochemical parameters with the highest AUC to identify disease prognosis were LDH, BG, T-Bil, and AST; and the highest AUC to identify disease severity were D-Bil, LDH, $Na^+$, and AST. The best parameters for detecting disease prognosis are as follows: 1) LDH had an AUC of 97.72 (cutoff > 317 U/L, $P < 0.001$), 2) BG with an AUC of 91.42 (cutoff > 99.5 mg/dl, $P < 0.001$), 3) T-Bil with an AUC of 89.55 (cutoff > 0.475 mg/dl, $P < 0.001$), and 4) AST with an AUC of 86.36 (cutoff > 25.5 U/L, $P < 0.001$). Also, the best parameters to detect disease prognosis are as follows: 1) D-Bil (AUC = 72.81, cutoff > 0.23 mg/dl, $P = 0.002$), 2) LDH (AUC = 71.41, cutoff > 444 U/L, $P = 0.004$), 3) $Na^+$ (AUC = 67.53, cutoff < 136 mEq/L, $P = 0.003$), and 4) AST (AUC = 63.74, cutoff > 35.5 U/L, $P = 0.02$).

## Discussion

This case-control study provides robust evidence

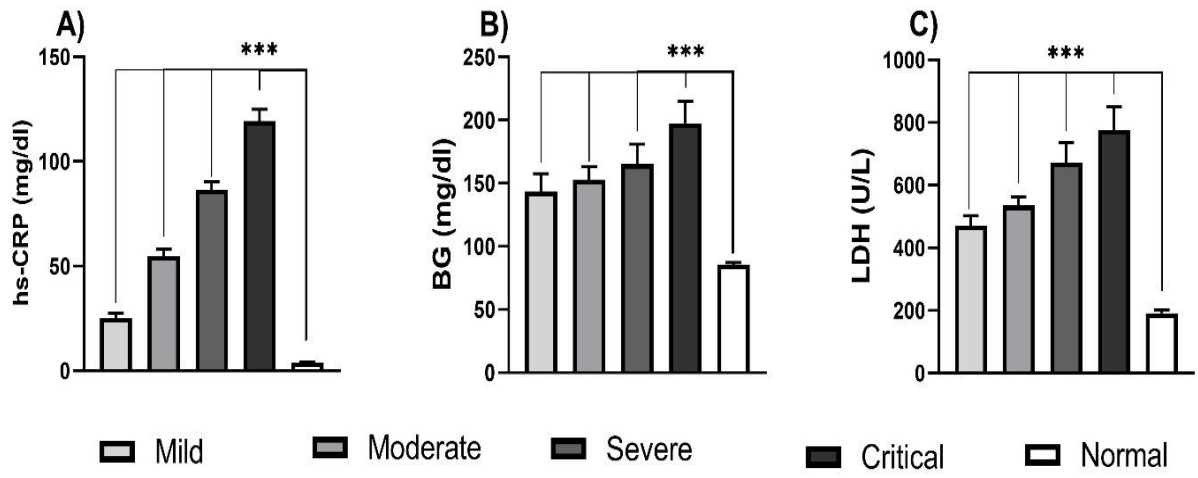



**Figure 3**. Comparison of hs-CRP, BG, and LDH in COVID-19 infection and control groups. A) hs-CRP, B) BG, C) LDH in the mild, moderate, severe, and critical groups. Parameters are presented as mean ± SEM and significance level is as: *** $P < 0.001$.

**Table 2.** Association between COVID-19 severity and biochemical parameters

| Parameters | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|
| | B | OR | CI-95 % | *P*-value | B | OR | CI-95 % | *P*-value |
| **LN-hs-CRP** | 3.25 | 25.35 | 5.26-116 | < 0.001 | 3.27 | 25.76 | 5.76- 127 | < 0.001 |
| **BG** | 0.11 | 1.13 | 1.06-1.16 | < 0.001 | 0.12 | 1.17 | 1.07-1.18 | < 0.001 |
| **BUN** | 0.11 | 1.12 | 1.04-1.21 | 0.001 | 0.1 | 1.1 | 1.02-1.19 | 0.007 |
| **Cr** | 1.2 | 3.23 | 1.94-8.5 | < 0.001 | 1.19 | 3.17 | 1.22-9.4 | < 0.001 |
| **LN-D-Bil** | 1.87 | 4.46 | 1.2-15.9 | < 0.001 | 1.89 | 4.56 | 1.3-20.94 | < 0.001 |
| **LN-T-Bil** | 1.29 | 3.88 | 1.54-8.61 | < 0.001 | 1.15 | 3.63 | 1.97-3.06 | < 0.001 |
| **AST** | 0.14 | 1.15 | 1.09-1.21 | < 0.001 | 0.14 | 1.14 | 1.09-1.2 | < 0.001 |
| **ALT** | 0.08 | 1.09 | 1.04-1.13 | < 0.001 | 0.09 | 1.09 | 1.05-1.14 | < 0.001 |
| **LDH** | 0.2 | 1.22 | 1.01-1.03 | < 0.001 | 0.2 | 1.26 | 1.02-1.03 | < 0.001 |
| **$Na^+$** | -0.27 | 0.75 | 0.68-1.84 | 0.074 | -0.26 | 0.76 | 0.74-1.35 | 0.089 |
| **$K^+$** | 0.5 | 1.65 | 0.83-3.26 | 0.14 | 0.43 | 1.54 | 0.75-3.13 | 0.23 |

Data are presented as crude and adjusted for age and gender.

Abbreviation: LN: Natural logarithm, hs-CRP: high-sensitivity C-reactive protein, BG: Blood glucose, BUN: blood urea nitrogen, Cr: Creatinine, D-Bil: Direct Bilirubin, T-Bil: Total Bilirubin, AST: Aspartate aminotransferase, ALT: Alanine Aminotransferase, LDH: Lactate dehydrogenase, CI-95%: 95% Confidence Interval, OR: odds ratio.

that COVID-19 infection causes significant alterations in multiple biochemical parameters that are highly correlated with disease severity and possess substantial diagnostic and prognostic value. Patients in all groups (mild, moderate, severe, and critical) exhibited markedly higher levels of inflammatory markers (hsCRP and LDH), liver function tests (AST, ALT, TBil, and DBil), kidney function tests (BUN and Cr), and BG compared to healthy controls. Logistic regression analysis confirmed these parameters as independent risk factors for COVID-19 severity after adjusting for age and gender. These findings underscore the systemic nature of SARS-CoV-2 infection and its profound effects on metabolic and organ function (24). Furthermore, LDH (AUC = 97.72%, cutoff > 99.5 U/L) emerged as the best biomarker for disease prognosis, while DBil (AUC = 72.81%, cutoff > 0.23 mg/dL) demonstrated the highest utility for severity discrimination.

A significant finding is the critical role of hyperglycemia in the pathogenesis and prognosis of COVID-19. High BG was not only a marker of underlying metabolic dysfunction but also an independent predictor of infection risk (adjusted OR = 1.17) and disease prognosis. Our ROC analysis determined that a BG level exceeding 99.5 mg/dL serves as a highly sensitive (78.23%) and specific (100%) threshold for detecting poor COVID-19 prognosis (AUC = 91.42%). This finding aligns with the evidence that SARS-CoV-2 directly disrupts pancreatic βcell function and induces insulin resistance through inflammatory cytokines such as IL6, thereby exacerbating hyperglycemia regardless of preexisting diabetes (25). Hyperglycemia also impairs immune function by inhibiting neutrophil chemotaxis and phagocytosis, leading to a vicious cycle of viral replication and tissue damage (26). COVID-19 triggers a cytokine storm and elevates stress hormones (e.g.,

**Table 3.** ROC curve analysis and optimal cut-off values for biochemical parameters in disease prognosis and disease severity**.**

| Parameters | Model | AUC | Sensitivity | Specificity | Cut Off | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|
| **BG (mg/dl)** | Disease prognosis | 91.42 | 78.23 | 100 | > 99.50 | 0.97-0.95 | < 0.001 |
| | Disease severity | 61.77 | 46.75 | 81.82 | > 139.5 | 0.5-0.72 | 0.051 |
| **BUN (mg/dl)** | Disease prognosis | 67.56 | 42.86 | 100 | > 18.80 | 0.59-0.75 | 0.008 |
| | Disease severity | 56.14 | 43.86 | 75.76 | > 19.85 | 0.45-0.65 | 0.3 |
| **Cr (mg/dl)** | Disease prognosis | 82.19 | 82.99 | 66.67 | > 0.925 | 0.75-0.89 | < 0.001 |
| | Disease severity | 51.2 | 18.18 | 93.94 | > 1.750 | 0.39-0.61 | 0.84 |
| **D-Bil (mg/dl)** | Disease prognosis | 80.43 | 58.5 | 100 | > 0.235 | 0.74-084 | < 0.001 |
| | Disease severity | 72.81 | 72.73 | 70.23 | > 0.23 | 0.63-0.82 | 0.002 |
| **T-Bil (mg/dl)** | Disease prognosis | 89.55 | 82.88 | 97.37 | > 0.475 | 0.84-0.94 | < 0.001 |
| | Disease severity | 58.89 | 22.08 | 93.94 | > 1.330 | 0.47-0.7 | 0.14 |
| **AST (U/L)** | Disease prognosis | 86.36 | 71.92 | 87.18 | >25.5 | 0.80-0.91 | < 0.001 |
| | Disease severity | 63.74 | 56.58 | 72.73 | > 35.50 | 52.6-74.9 | 0.02 |
| **ALT (U/L)** | Disease prognosis | 77.49 | 48.63 | 94.87 | >33.5 | 0.70-0.84 | < 0.001 |
| | Disease severity | 55.08 | 32.9 | 84.85 | > 42.50 | 0.43-0.66 | 0.4 |
| **LDH (U/L)** | Disease prognosis | 97.72 | 89.8 | 100 | > 317.0 | 0.95-0.99 | < 0.001 |
| | Disease severity | 71.41 | 77.63 | 54.55 | > 444.0 | 0.61-0.81 | 0.004 |
| **$Na^+$ (mEq/L)** | Disease prognosis | 80.65 | 78.91 | 69.23 | < 139 | 0.73-0.87 | < 0.001 |
| | Disease severity | 67.53 | 61.04 | 72.73 | < 136.0 | 0.56-0.78 | 0.003 |
| **$K^+$ (mEq/L)** | Disease prognosis | 55.76 | 18.49 | 94.87 | > 4.89 | 0.46-0.56 | 0.269 |
| | Disease severity | 59.21 | 26 | 90.9 | > 4.650 | 0.48-0.7 | 0.12 |

Models: Disease prognosis (patients vs. control), Disease severity (mild vs. severe and critical groups).

glucocorticoids and catecholamines), which can induce insulin resistance and hyperglycemia. In fact, nearly 50% of hospitalized COVID-19 patients present with elevated blood glucose levels (27). The strong association between BG levels and disease severity underscores the importance of rigorous glucose monitoring and early glycemic intervention in hospitalized COVID-19 patients (16).

All patient groups had significantly higher BUN and Cr levels, indicating kidney impairment. Logistic regression also identified Cr and BUN as independent predictors of disease severity. SARS-CoV-2 induces acute tubular necrosis by directly infecting renal tubular cells and podocytes via ACE2 receptors (28). Cytokine storm also reduces renal perfusion by damaging the endothelium and causing microthrombi (29). Notably, while BUN and Cr effectively distinguished patients from controls, their utility in differentiating severity groups was limited, suggesting they are robust diagnostic but less sensitive prognostic indicators for infection severity (14). COVID-19 patients also had considerably higher levels of liver damage markers (AST, ALT, TBil, and DBil). Elevated transaminases reflect hepatocyte damage from direct viral cytopathic effects or immunemediated injury (30). Hyperbilirubinemia suggests cholestatic involvement, which may be caused by drug toxicity or virusinduced damage to the bile duct epithelium (31). Among COVID19 patients, liver function tests frequently show mildtomoderate elevations. However, elevated T-Bil and D-Bil are typically observed only in those with severe disease (32). Notably, among all liver indicators and other biochemical parameters, D-Bil (DBil > 0.23 mg/dL, AUC = 72.81%) was the best biomarker for detecting infection severity, suggesting a potential role in monitoring disease progression (33).

Inflammatory parameters (hsCRP and LDH) were elevated in all patient groups. The hsCRP yielded the highest hazard agent for severity (OR = 25.76), underscoring its role in cytokine storm amplification (34). LDH > 317 U/L exhibited the best diagnostic accuracy for disease prognosis (AUC = 97.72%), indicating extensive tissue damage due to hypoxia and inflammation. Additionally, LDH > 444 U/L (AUC = 71.41%) after D-Bil predicted severe disease, consistent with its role as a marker of pulmonary parenchymal destruction and multiorgan involvement (35).

Different patterns of electrolyte imbalances were observed. Group differences in $Na^+$ levels were not statistically significant. Although the lack of groupwise significance warrants caution, elevated $Na^+$ in severe cases may indicate syndrome of inappropriate antidiuretic hormone secretion (36). In contrast, $K^+$ was significantly higher only in critical patients, most likely due to tissue necrosis, transcellular shifts caused by acidosis, or dysregulation of the reninangiotensinaldosterone system (37). However, $K^+$ did not independently predict severity in regression models (OR = 1.54, P = 0.23), limiting its clinical utility.

The present study has several strengths and limitations. We categorized COVID19 patients based on clinical symptoms, examined biochemical differences between groups, and evaluated how well these parameters could predict infection prognosis and severity. However, this study has several limitations. We only enrolled hospitalized patients and did not follow them up to determine whether biochemical levels correlated with survival or disease progression. Additionally, we did not measure inflammatory cytokines such as IL6 and TNFα, even though they play a central role in COVID19 and are likely connected to the biochemical disturbances we observed. Nevertheless, our findings demonstrate that COVID19 severity manifests as a cluster of biochemical abnormalities. Hyperglycemia, kidney dysfunction, and liver injury together form a diagnostic triad indicative of progressive disease. Finally, LDH and DBil emerged as the best parameters for predicting prognosis and severity COVID19, respectively.

## Conclusion

This study demonstrates that COVID-19 infection produces significant severity-dependent disruptions in hepatic, renal, glycemic, and inflammatory biochemical parameters, all of which serve as independent predictors of disease severity. LDH emerged as the best biomarker for disease prognosis (AUC = 97.72%, cut-off > 317 U/L), while D-Bil demonstrated the highest utility for disease severity discrimination (AUC = 72.81%, cut-off > 0.23 mg/dL). These findings collectively advocate for the routine incorporation of multi-parameter biochemical monitoring, with particular emphasis on LDH and D-Bil, into standardized COVID-19 clinical management protocols to enable earlier identification of high-risk patients.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

## Ethical approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (IR.KMU.REC.1399.239).

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