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RESEARCH ARTICLE

Comparative analysis of various laboratory biomarkers based on the severity of COVID-19 in a tertiary care hospital in South India

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Abstract

COVID-19 (Corona Virus Disease 2019) was a life-changing pandemic with impact on social, environmental, health, and economic issues. Various inflammatory and hematological biomarkers studied individually or in combination in the literature have shown significant results with regard to COVID-19 pathology, severity, and prognosis. Yet the question of interest is how covid-19 inflammatory cascade impacts the interlink between the biomarkers during different stages. This study aims to retrospectively analyse ferritin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, blood urea nitrogen (BUN), creatinine, D-dimer, Lactate Dehydrogenase (LDH), C Reactive Protein (CRP) and Interleukin-6 (IL-6) levels between two groups based on COVID-19 severity. A retrospective cross-sectional study was conducted with laboratory data of COVID-19 patients admitted at Sri Ramachandra Medical College Hospital, India. The sample size was 104 (Group1: severe disease, n=52; Group-2: mild disease, n=52). After normality testing, data were compared between the two groups followed by correlation analysis between the variables. A $p<0.05$ was considered statistically significant. On comparison, Group 2 (severe COVID-19 disease) showed significant difference in the levels of all the biomarkers ($p<0.005$) except Creatinine ($p<0.128$) when compared with Group 1 (mild COVID-19 disease). Significant correlation was obtained between all biomarkers ($p<0.005$) except creatinine. The correlation analysis primarily explains the inflammatory cascade involved in disease. Ferritin appears to have a standalone effect on disease severity, progression, organ dysfunction. This understanding can be used to provide better and more timely care.

1. INTRODUCTION

COVID-19 was a transformative pandemic that has provoked evidence-based medicine in diagnosis and treatment, conceptualized as a disease impacting the endothelium and its associated complications. The dynamic trend of changing protocols that were employed during the pandemic waves needs to be reviewed for scientific evidence. As per World Health Organisation till July 2023, nearly 76,82,37,788 cases have been diagnosed worldwide, with 4,49,94,955 cases in India, making it the third most affected nation. Laboratory markers and radiological evidence served as parallel diagnostic aids for managing COVID-19. The imperative role of labs has been continuously in the limelight during the pandemic. Though COVID-19 real-time reverse transcription–

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polymerase chain reaction (RT-PCR) was the lead player, other such as hematological, immunological, or inflammatory biomarkers had an impact on isolation, treatment and prognosis. The advent of new biomarkers and the suitability of available markers were slowly imbibed into the protocols and it helped the clinicians to overcome the workload and effectively treat patients based on severity. Biomarkers of inflammation like ferritin, CRP and enzyme markers like alanine aminotransferase (ALT), aspartate aminotransferase (AST) and Lactate Dehydrogenase (LDH) has been studied individually. LDH has been associated with a higher risk of Acute respiratory distress syndrome (ARDS), ICU (Intensive Care Unit) support, and death (1). CRP levels are correlated with the level of inflammation for early diagnosis of pneumonia (2).

COVID-19 is characterized by hyper-ferritinemia, which could act as an active pathogenic mediator and also be a consequence of inflammation. Ferritin levels are shown to be associated with high rate of mortality and disease severity (1). Ferritin synthesis can be induced and vice versa increases several pro-inflammatory cytokines, such as IL-6. In COVID-19, elevated IL-6 seems to be associated with rapid progression of the disease by producing cytokine storm (3). Patients with severe COVID-19 often exhibit higher rates of liver dysfunction. Data suggest that ALT and AST elevations are found in 38%-63% and 29%- 39% of patients respectively among patients with COVID-19 in the United States (4,5). Hypoxia and inflammation induced microvascular thrombosis is a dreadly complication of COVID-19. D-Dimer has shown significant efficacy in assessing coagulopathy and is used as a therapeutic target.

While individual markers have yielded significant results regarding their role of these biomarkers in disease pathogenesis and severity, there is a lack of comprehensive research on their combined effects. Since SARS-CoV-2 has rapid and aggressive progression, the use of no single marker has justified the purpose. There is a need for analysing the effects of the biomarker (Ferritin, CRP, LDH, IL-6 and D-Dimer) on each other and also with end organ functions (Liver and Kidneys). This analysis enhances our understanding of these markers in the inflammatory cascade, enabling their appropriate use in the early stages of the disease to mitigate complications.

The study is designed to conduct a retrospective analysis and comparison of the levels of Ferritin, Albumin, LDH, ALT, AST, Total Bilirubin, Direct bilirubin, Blood urea nitrogen (BUN), Creatinine, D-dimer, C-Reactive protein (CRP) and interleukin-6 (IL-6) between two distinct groups of covid-19 patients admitted with mild or no symptoms and moderate to severe symptoms. The primary research questions addressed by this investigation are whether there is difference in the levels of these biomarkers based on the severity of COVID-19 symptoms, and whether an increase of one biomarker correlates with changes in the level of other biomarkers studied. This analysis aims to contribute to our understanding of the biomarker profiles associated with COVID-19 severity and their interrelations, potentially informing diagnostic and prognostic approach in clinical practice.

2. MATERIALS AND METHODS

2.1. Study Design and Data Collection

Males and nonpregnant Females of 20-70 years of age, diagnosed with positive COVID-19 RT- PCR/ viral nucleic acid test and treated at Sri Ramachandra Medical College Hospital, Chennai, Tamil Nadu were eligible for inclusion in the study. The sample size was determined to be 104 with a 95% confidence interval and a desired margin of error of 5%. The study population was divided into two groups based on the disease severity according to established guidelines (6).

Group1 – mild cases (n=52): COVID-19 positive individuals with Mild or no symptoms of COVID-19 like fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell but do not have shortness of breath, dyspnoea, or abnormal chest imaging admitted in COVID isolation wards.

Group 2-severe cases (n=52): COVID-19 positive individuals with Moderate to severe symptoms such as shortness of breath, dyspnoea, Respiratory rate >20 breaths per minute, abnormal chest imaging with lung infiltrates and oxygen saturation <94% requiring oxygen support admitted in COVID intensive care units.

Data of 200 COVID 19 patients were selected initially based on their admission to the COVID designated areas. Laboratory records were accessed retrospectively to collect the baseline characteristics, laboratory and imaging details of these patients. Based on the availability of the required data, 104 participants were selected, including 52 with mild disease in Group 1 and 52 with severe disease in Group 2 for further analysis.

2.2. Methodology for the Biomarkers

All biomarkers were assayed using automated platforms, immunoassay markers on Cobas 8000 e602 (Roche, Basel, Switzerland), and routine chemistry markers on the AU series instruments (Beckman Coulter, CA, USA). The specific methodology for each biomarker is detailed in Table 1. The study protocol was approved by the

Institutional Ethical Committee, Sri Ramachandra Institute of Higher Education and Research (Ref.No-IEC-N1/21/AUG/79/106), ensuring compliance with ethical guidelines. Patient confidentiality was rigorously maintained throughout the study process.

Table 1. Data on biomarkers included in the study and their method of analysis with reference intervals

Biomarker	Analyser	Method of Analysis	Sample used for analysis	Reference interval with units
Ferritin	Roche Cobas	Electro chemiluminescence immunoassay	Plasma	24 - 336 ng/mL
LDH	Beckman Coulter AU series	IFCC -Lactate to Pyruvate	Serum	208 - 378 U/L
CRP	Beckman Coulter AU series	Immunoturbidimetry	Serum	less than 1 mg/L
D-Dimer	Sysmex	Immunoturbidimetry	Plasma	Less than 1 mg/L
Interleukin-6	Roche Cobas	Electro chemiluminescence immunoassay	Plasma	Less than 6.4 pg/mL
Albumin	Beckman Coulter AU series	Bromocresol green	Serum	3.5-5.2 g/dL
ALT	Beckman Coulter AU series	UV without P5P	Serum	Less than 50 U/L
AST	Beckman Coulter AU series	UV without P5P	Serum	Less than 50 U/L
Total Bilirubin	Beckman Coulter AU series	DPD	Serum	0.3-1.2 mg/dL
Direct Bilirubin	Beckman Coulter AU series	DPD	Serum	Less than 0.2 mg/dL
Blood Urea Nitrogen	Beckman Coulter AU series	Urease	Serum	7.9-20.1 mg/dL
Creatinine	Beckman Coulter AU series	Modified Jaffe's	Serum	0.7-1.3 mg/dL

Note: LDH-Lactate Dehydrogenase, CRP- C-Reactive protein, ALT- Alanine aminotransferase, AST- Aspartate aminotransferase, IFCC- International federation of Clinical Chemistry, UV without P5P- measurement of rate at Ultraviolet wavelength 340nm; P5P- pyridoxal-5-phosphate, DPD- Dichloro Phenyl Diazonium salt.

2.3. Statistical Analysis

The statistical analyses were conducted using SPSS, Version 20.0 (SPSS Inc., Chicago. IL, USA). Normality of the data was assessed using Kolmogorov-Smirnov test. Data are represented by Median and Interquartile ranges. Mann whitney U test was performed to evaluate the comparison between groups and p-value of < 0.05 was considered statistically significant. Since the obtained data was not normally distributed spearman correlation was performed to investigate the relationship between the variables.

3. RESULTS AND DISCUSSION

COVID-19, a systemic disorder, can lead to multiple organ dysfunctions in severe cases resulting in complications such as Acute Respiratory Distress Syndrome (ARDS), shock, and disseminated intravascular coagulation (7). The elevation of inflammatory biomarkers is attributable to factors like hypoxia, hypoperfusion, and thrombosis. The prognostic utility of raised D-dimer, CRP and IL-6 levels in disease severity and mortality has been concurred in various other studies (8–10).

The mean age for Group 1 (mild cases) was 53 years, and for Group 2 (severe cases), it was 56 years. The comparison analysis of the biomarkers between the two groups is presented in two separate tables (Table 2 and Table 3- Inflammatory and Routine markers respectively). The values of all biomarkers, except Albumin (Table 2 and Table 3), were elevated in severe patients (Group 2) compared to the mild patients (Group 1). Interestingly, albumin levels were lower in severe patients (Group 1). Similarly, the comparison between the two groups showed a statistically significant difference ($p<0.05$) for all the biomarkers except creatinine ($p=0.128$).

3.1. Analysis of inflammatory biomarkers between mild and severe COVID-19 patients

In Table 2, inflammatory markers including Ferritin, LDH, hsCRP, D-Dimer, and Interleukin-6 were compared between two groups. All these markers showed significant elevation in severe cases compared to mild cases ($p<0.05$). This indicates a strong association between disease severity and heightened levels of these inflammatory biomarkers in COVID-19 patients.

Table 2. The comparison of Inflammatory markers of COVID-19 between Group 1 (mild disease) and Group 2 (severe disease) groups and their statistical significance

Inflammatory markers (Units)	Group 1 Mild disease Median (IQR)	Group 2 Severe disease Median (IQR)	p Value*
Ferritin (ng/mL)	168.2 (74.2 – 398.9)	1035 (475.8 – 1537.4)	0.000*
LDH (U/L)	252 (191.8 – 318)	619 (448.5 – 776.5)	0.000*
CRP (mg/L)	2.4 (0.9 – 8.1)	16.9 (8.5 – 27.7)	0.000*
D-Dimer (mg/L)	0.4 (0.2 - 1.1)	2.9 (1.3 - 7.7)	0.000*
Interleukin-6 (pg/mL)	9.7 (3.6 – 33.3)	77.6 (31.4 – 147.9)	0.000*

Note: *p Value of less than 0.05 was considered statistically significant. LDH- Lactate Dehydrogenase, CRP- C-Reactive protein

SARS-CoV-2 likely relies on iron for replication and its functions. Ferritin, a positive acute phase reactant and iron-binding molecule, increases in response to bacterial or viral infection. In our study, higher ferritin levels of 1035 (475.8-1537.4) were observed in individuals with severe infection compared to 168.2 (74.2-398.9) in individuals with mild infection. This finding aligns with a study by Perricone C et al., which noted an acute hyperferritinemic response in septic patients (10). Labile iron within cell promotes tissue damage and fibrosis through the generation of reactive oxygen species. Additionally, Ferritin regulates an iron-independent feedback loop pathway that activates transcription factors such as nuclear factor-κB (NF-κB), and interferon regulatory factor 3, leading to increased production of interleukins (1,2,4,7,10,12,13,17), Granulocyte colony-stimulating factors, interferon γ (IFN-γ), and Tumor Necrosis Factor (1). Pro-inflammatory cytokines, particularly IL-6, play a significant role in these processes along with upregulation of hepcidin.

IL-6 is a multifunctional cell signaling cytokine that regulates immune cells and has potent proinflammatory effects, with an important role in inflammation, tumor, and hematological diseases (11). Ferritin interlinked elevation of Interleukin 6 by the humoral immune pathway acts as a critical mediator for respiratory failure, shock, and multiorgan dysfunction. Dysregulation of host immune responses by IL-6, which is a primary trigger results in the development of cytokine release syndrome (CRS) in severe Covid-19, characterizing IL-6 as an important target for therapeutics (12).

Studies by Coomes et al., have demonstrated that peripheral blood IL-6 levels can independently predict the progression of COVID-19 (12,13), which is consistent with our study findings showing higher IL-6 levels in patients with severe disease 77.6 (31.4- 147.9) compared to mild disease 9.7 (3.6-33.3). Hence, the role of IL-6 warrants significant attention in understanding and managing the pathophysiology and severity of COVID-19. Targeting IL-6 signaling pathways may offer potential therapeutic strategies for mitigating severe disease outcomes.

CRP is a non-specific acute-phase protein induced by macrophage and T cell-secreted IL-6 in the liver and a sensitive biomarker of inflammation, infection, and tissue damage. The levels of CRP are usually low but increase rapidly and significantly as an acute inflammatory response to bacterial/viral infections (14). IL-6 is also known to induce gene expression, thus causing elevated levels of CRP. Liu F et al., explored the relationship between CRP and COVID-19, revealing that patients with CRP > 41.8 mg/L were more likely to develop severe disease (15). Similarly, multivariate analyses by Villard O et al., showed significantly higher CRP levels in patients with a severe clinical course 152 (34-389) compared to those with a mild or moderate course 83 (3-298) (16), which aligns with our study findings. These findings suggests that CRP levels in the early stage of COVID-19 may reflect lung lesions and disease severity, emphasizing its potential utility as a prognostic marker.

LDH is an enzyme belonging to the oxidoreductase group, consisting of five isoenzymes that catalyze the conversion of lactate to pyruvate using the coenzyme NADH. Severe infections can induce cytokine-mediated

tissue damage, leading to the release of LDH. There exists a positive correlation between LDH levels and pro-inflammatory cytokines like IL-6, and tumor necrosis factor, which have been associated with worse outcomes in viral infections. Isoenzyme 3 of LDH (HHMM) is predominantly present in lung tissue, suggesting that patients with severe COVID-19 infections may release LDH into circulation due to severe interstitial pneumonia, often progressing to acute respiratory distress syndrome (17).

A study conducted by Li C et al., stated an LDH cut-off of 359.50 U/L predicts COVID-19 mortality with 93.8 % sensitivity and 88.2% specificity. The same study also suggested LDH as an independent risk factor for the COVID-19 severity and patients with severe disease had higher LDH levels (18). The findings of our study aligns with the established data on the role of Ferritin, LDH and other Liver biomarkers in the severity of the disease insisting on the use of age-old markers as a reliable tool for severity (7). These biomarkers can serve as valuable indicators for clinical prognosis and management in patients with COVID-19.

Coagulopathy is a common complication of critically ill COVID-19 patients and autopsy studies supports systemic microvascular thrombosis (19). Our findings correlated with studies by Li Y et al., that have revealed a poor prognosis of COVID-19 with dynamical changes in D-dimer levels greater than 1 µg/ml (20). Hypoxia in covid-19 severe patients stimulates thrombosis by increasing the viscosity of blood and transcription factor-dependent signaling pathway (21). A retrospective study by Fei Zhou et.al also revealed that D-dimer levels were elevated in 81% of the nonsurvivors of COVID-19. In sepsis-induced coagulation dysfunction, the increase of D-dimer may be an indirect inflammatory marker, as inflammatory cytokines could cause the imbalance of coagulation and alveolar fibrinolysis. A study by Tang n et al., indicated abnormal levels of D-dimer (i.e. over 3 µg/ml) were associated with a 28-day mortality rate supporting our study finding (22,23).

These studies collectively highlight the critical role of D-dimer as a prognostic marker in COVID-19, reflecting disease severity and serving as an indicator of coagulation dysfunction and poor outcomes in affected individuals. Monitoring D-dimer levels may provide valuable insights for clinical management and therapeutic interventions.

3.2. Analysis of liver and renal biomarkers between mild and severe COVID-19 patients

In Table 3, various other markers including Albumin, ALT, AST, Total Bilirubin, Direct Bilirubin, Blood Urea Nitrogen, and Creatinine were compared between the two groups. The levels of these biomarkers were increased in patients with severe disease except albumin which was low in severe patients. Importantly, the difference in the levels of the biomarkers were statistically significant ($p<0.05$) except for creatinine ($p=0.128$).

Table 3. The comparison of routine biochemistry markers of COVID-19 between two groups and their statistical significance

Biomarker (Units)	Group 1 Mild disease Median (IQR)	Group 2 Severe disease Median (IQR)	p Value*
Albumin (g/dL)	3.9 (3.4-4.1)	3 (2.3-3.3)	0.000*
ALT (U/L)	29.5 (19-47.3)	42 (28-96)	0.001*
AST (U/L)	29 (22.3-47.3)	45 (31-74.3)	0.000*
Total Bilirubin (mg/dL)	0.5 (0.4-0.7)	0.8 (0.5-1.2)	0.001*
Direct Bilirubin (mg/dL)	0.12 (0.09-0.16)	0.19 (0.12-0.47)	0.000*
Blood Urea Nitrogen (mg/dL)	11 (9-14.8)	26 (17-36.5)	0.000*
Creatinine (mg/dL)	0.8 (0.7-1)	0.8 (0.7-1.4)	0.128

Note: *p Value of less than 0.05 was considered statistically significant. ALT- Alanine aminotransferase, AST- Aspartate aminotransferase

Multiorgan dysfunction as a part of systemic complications in COVID-19 can cause elevation of any diagnostic panel out of which liver panel (AST, ALT, Bilirubin and Albumin) and renal panel (Blood Urea nitrogen and Creatinine) were studied between the groups. All the liver markers were found to be elevated in patient with severe disease, except for Albumin, which was decreased in the severe group. Hepatic hypoxia and presence of

ACE2 receptors in cholangiocytes and hepatocytes are proposed as pathway contributing to the liver's inflammatory response to COVID-19 (24).

In our study population, there was no significant difference in creatinine levels between the groups, and only a moderate correlation was observed between creatinine and ferritin, D-Dimer. However, BUN levels were significantly elevated in severe groups ($p<0.05$) and showed a significant positive correlation with inflammatory markers. Studies have highlighted an increased prevalence of Acute Kidney Injury, proteinuria and hematuria in severe cases (25), since our study collected the data of the patients on day of admission itself the increased levels of BUN alone could explain the possibility of AKI in severe patients. Elevated BUN levels may serve as an early indicator of renal dysfunction and should prompt close monitoring and intervention to prevent kidney injury in severe COVID-19 cases. These findings underscore the importance of monitoring liver and renal function markers in COVID-19 patients, to assess multiorgan involvement and guide appropriate clinical management strategies.

3.3. Significant correlation between each inflammatory biomarkers and with renal and liver biomarkers

Further to evaluate the relationship between the effect of the inflammatory biomarkers over other biomarkers, a Spearman correlation was performed. The results are provided as correlation coefficients (r-value) along with its statistical significance in Table 4. The inflammatory markers like ferritin, LDH, CRP, IL-6 and D-Dimer had a statistically significant ($p<0.05$), positive correlation (r-value) with all biomarkers except albumin. Albumin, being a negative acute phase reactant significantly correlated negatively with the inflammatory markers ($p<0.05$). Additionally, creatinine demonstrated correlations only with ferritin and D-dimer. This correlation analysis reveals that elevation in any of inflammatory biomarkers (ferritin, LDH, CRP, IL-6 and D-Dimer) has a significant impact on all other parameters included in our study. It underscores the interconnectedness of inflammatory biomarkers within the COVID-19 inflammatory cascade and their effects on the end organs. These findings emphasize the complex and systemic nature of COVID-19 pathophysiology, where inflammatory processes can influence multiple organ systems, contributing to disease severity and outcomes.

Table 4. The results of Spearman correlation showing correlation coefficients (r-value) between inflammatory biomarkers (Ferritin, LDH, CRP, D-Dimer, IL-6) and all biomarkers included in the study. Statistically significant r-values are represented with **/*

Biomarker	Ferritin (ng/mL)	LDH (U/L)	CRP (mg/L)	D-Dimer (mg/L)	IL-6 (pg/mL)
Ferritin (ng/mL)	-	0.751**	0.716**	0.478**	0.531**
LDH (U/L)	0.751**	-	0.661**	0.666**	0.615**
CRP (mg/L)	0.716**	0.661**	-	0.497**	0.587**
D-Dimer (mg/L)	0.478**	0.666**	0.497**	-	0.535**
Interleukin-6 (pg/mL)	0.531**	0.615**	0.587**	0.535**	-
Albumin (g/dL)	-0.683**	-0.764**	-0.726**	-0.674**	-0.625**
ALT (U/L)	0.621**	0.553**	0.423**	0.293**	0.435**
AST (U/L)	0.598**	0.522**	0.456**	0.314**	0.389**
Total Bilirubin (mg/dL)	0.494**	0.501**	0.380**	0.293**	0.393**
Direct Bilirubin (mg/dL)	0.565**	0.553**	0.492**	0.309**	0.394**
Blood Urea Nitrogen (mg/dL)	0.615**	0.615**	0.563**	0.608**	0.514**
Creatinine (mg/dL)	0.207*	0.144	0.089	0.249*	0.114

Note: **The correlation (r value) is statistically significant $p<0.01$. *The correlation (r value) is statistically significant $p<0.05$. CRP- C-Reactive protein, LDH – Lactate Dehydrogenase, AST- Aspartate aminotransferase, ALT-Alanine aminotransferase.

The findings from our study are consistent with established data from various studies across the globe. The novelty of the study and importance of understanding the interlinkages within the inflammatory cascade are highlighted by our correlation analysis. Ferritin, showing correlation with all the parameters, emerges as a initial nidus for the inflammatory cascade. Hence ferritin could be a promising standalone marker for assessing disease severity, prognosis and organ dysfunction in early stages of COVID-19. Similarly, the strong correlation of D-Dimer would reflect the intensive role of the cascade in producing coagulopathy and can aid the need for anticoagulatory medications.

IL-6 levels can serve as an indicator of Cytokine storm, highlighting the necessity for intensive monitoring and potential targeted interventions. Additionally, CRP and LDH, while useful as inflammatory biomarkers

especially in resource-limited settings, may be surpassed by the availability and utility of ferritin and IL-6 in this disease context.

These findings align with the studies that have emphasized the critical role of inflammatory biomarkers in assessing infection severity, both within individuals and across different patient cohorts (26–28). Understanding these interrelationships can inform clinical decision-making, guide therapeutic strategies, and enhance risk stratification in the management of COVID-19 patients. The insights gained from our study contribute to advancing the understanding of COVID-19 pathophysiology and optimizing patient care strategies based on biomarkers assessments.

3.4. Limitations and future scope

The sample size is relatively small, given the retrospective design and the widespread nature of the pandemic. Future studies with larger cohorts are essential to validate our findings. Additionally, our study utilized data collected during a specific COVID-19 outbreak, which may not fully represent the disaease's natural history. It would be valuable to validate our results using data from periods of lower disease prevalence. Moreover, this study was conducted at a single centre, limiting the generalizability of our findings to broader populations. Demographic influences beyond rural and urban settings are not fully evaluated in this study, warranting further investigation in future research.

Incorporating multivariate analysis and validated severity assessment tools could enhance the robustness of our study findings. Future research should consider these methodological improvements to provide more comprehensive insights into the relationship between biomarkers and COVID-19 outcomes.

The future scope of this study includes assessing molecular biomarkers and conducting follow-up studies to examine the long-term impact of these biomarkers on COVID-19 outcomes. Establishing specific cut-off values for predicting disease complications based on biomarkers profiles could enhance clinical decision-making. Furthermore, given the ongoing emergence of new SARS-CoV-2 variants, future studies should investigate the implication of our research findings related to disease severity for different COVID-19 variants to help in tailored diagnostic and therapeutic approaches.

4. CONCLUSIONS

Our study findings highlight significant elevations in Ferritin, LDH, CRP, IL-6, D-dimer, AST, ALT, total and direct bilirubin, and BUN levels among patients with severe COVID-19 compared to those with mild disease ($p < 0.05$). Conversely, Albumin levels were significantly decreased in the severe disease group ($p < 0.05$), while creatinine levels did not show a significant difference ($p = 0.128$).

The correlation analysis underscores the role of the inflammatory cascade in driving disease severity, revealing interconnections among the studied biomarkers. Ferritin emerges as a primary initiator of inflammatory cascade, rendering it as a standalone marker for assessing COVID-19 severity, followed by IL-6 to monitor cytokine storm and D-Dimer for coagulopathy. CRP and LDH, suitable for use in low-resource settings, can be used concurrently with Ferritin, IL-6, and D-Dimer for comprehensive patient monitoring.

Furthermore, organ-specific biomarkers can aid in the follow-up of multiorgan dysfunction in COVID-19 patients, providing insights into disease progression and therapeutic responses.

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