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Assessment Of Inflammatory Variables As Diagnostic And Prognostic Biomarkers For Covid-19 Patients

Muhammad Mansoor Hafeez[1]*, Muhammad Tahir Khan[1], Muhammad Asim Rana[2], Muhammad Javed[3]

1.Institute of Molecular Biology and Biotechnology (IMBB), The University of Lahore, Lahore, Pakistan
2.Amna Inayat Medical College, Sheikhupura/Bahria Town International Hospital, Lahore, Pakistan
3.Services Institute of Medical Sciences, Lahore, Pakistan

Corresponding Author: Muhammad Mansoor Hafeez

Abstract

Background

Coronavirus Disease 2019 (COVID-19) presents with a wide clinical spectrum, ranging from asymptomatic infection to critical illness and death. Early identification of patients at risk of severe disease is essential for timely clinical intervention. Inflammatory biomarkers have emerged as potential tools for diagnosing disease severity and predicting outcomes, but evidence from local populations remains limited.

Objective

To assess the diagnostic and prognostic significance of inflammatory variables in COVID-19 patients and determine their ability to predict disease severity and 28-day mortality.

Methods

A prospective observational study was conducted at Bahria Town International Hospital, Lahore, including 200 RT-PCR–confirmed COVID-19 patients from December 2019 to December 2021. Patients were categorized into non-severe and severe groups based on WHO criteria. Blood samples collected at admission were analyzed for inflammatory biomarkers including total leukocyte count (TLC), lymphocyte percentage, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, serum ferritin, IL-6, TNF-α, MMP-3, and MMP-9. Diagnostic accuracy was assessed using ROC curve analysis. Survivors and non-survivors were compared to determine prognostic significance.

Results

Severe COVID-19 cases demonstrated significantly higher levels of TLC, LDH, CRP, D-dimer, ferritin, IL-6, TNF-α, MMP-3, and MMP-9, while lymphocyte counts were markedly lower (all $p<0.001$). D-dimer showed the highest diagnostic accuracy (AUC=0.997), followed by MMP-9 (AUC=0.981) and MMP-3 (AUC=0.966). Among oxidative stress markers, SOD showed excellent diagnostic performance (AUC=0.974). Mortality was significantly higher in the severe group (14% vs. 6%, $p=0.049$). Non-survivors exhibited higher TLC, CRP, D-dimer, MMP-3, and MDA levels, and lower lymphocyte counts ($p<0.05$). Prognostic ROC analysis identified CRP (AUC=0.701), D-dimer (AUC=0.688), lymphocyte percentage (AUC=0.694), MMP-3 (AUC=0.650), and MDA (AUC=0.673) as significant predictors of 28-day mortality.

Conclusion

Inflammatory variables,including TLC, lymphocyte percentage, CRP, D-dimer, IL-6, TNF-α, MMP-3, and MMP-9, serve as reliable diagnostic indicators of COVID-19 severity. D-dimer and MMP-9 demonstrate exceptional diagnostic accuracy. Key inflammatory markers, particularly CRP, D-dimer, lymphocyte percentage, and MMP-3, also possess prognostic value for predicting short-term mortality. Early measurement of these biomarkers can enhance risk stratification and guide timely clinical decision-making for COVID-19 patients.

Keywords COVID-19; Inflammatory biomarkers; Disease severity; Prognosis; D-dimer; C-reactive protein; MMP-9; Lymphopenia; ROC analysis

Introduction:

The COVID-19 pandemic has posed unprecedented challenges to global health systems, necessitating the identification of effective diagnostic and prognostic biomarkers. Inflammation plays a central role in the pathogenesis of COVID-19, where a dysregulated immune response contributes to severe clinical manifestations. Several inflammatory biomarkers, including total leukocyte count (TLC), lymphocyte percentage, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, serum ferritin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), matrix metalloproteinase-3 (MMP-3), and matrix metalloproteinase-9 (MMP-9), have been evaluated for their diagnostic and prognostic relevance in predicting disease severity and clinical outcomes.

Elevated TLC has been consistently associated with severe infections, reflecting heightened immune activation or the onset of cytokine storm in COVID-19 patients (1,2). Conversely, lymphopenia, a reduction in lymphocyte percentage, remains one of the most reliable indicators of poor outcomes and higher mortality risk, as demonstrated across multiple studies (2–4). Elevated LDH, a marker of tissue injury and hypoxia, has also been recognized as a strong predictor of severe disease progression (5,6).

Similarly, CRP, an acute-phase reactant, has shown strong correlation with inflammatory burden, with markedly higher values observed in critically ill patients (7,8).

D-dimer, a fibrin degradation product, has emerged as a particularly important biomarker due to its strong association with thrombotic complications and mortality in severe COVID-19 cases. Elevated D-dimer levels reflect hypercoagulability, a characteristic feature of severe and critical illness (9,3). Moreover, serum ferritin, a marker of both iron metabolism and systemic inflammation, has demonstrated consistent associations with hyperinflammatory states and severe respiratory involvement (10,11). Pro-inflammatory cytokines, particularly IL-6 and TNF-α, play a pivotal role in the cytokine storm syndrome, and their elevated levels have been linked to clinical deterioration and higher mortality risk (6,12,13).

Recent studies have explored the role of MMP-3 and MMP-9, enzymes involved in extracellular matrix remodeling and inflammatory regulation. Their elevated expression in severe cases suggests an important role in tissue injury and pulmonary involvement associated with COVID-19 (14,15). Together, this comprehensive inflammatory profile underscores the dynamic and multifactorial nature of COVID-19 pathophysiology, highlighting the importance of multi-marker approaches for stratifying disease severity and guiding timely interventions.

In Pakistan, where the healthcare system faces resource limitations and a high prevalence of comorbidities such as diabetes and hypertension, the use of inflammatory biomarkers for early risk stratification is particularly valuable. Local research has demonstrated that abnormal biochemical and inflammatory markers significantly correlate with worse outcomes among Pakistani COVID-19 patients (16). Establishing a robust framework for biomarker-based evaluation may thus improve patient triage, optimize resource allocation, and reduce mortality in a population heavily impacted by the pandemic.

Methodology:

This prospective observational cohort study was conducted at Bahria Town International Hospital, Lahore, Pakistan, with the objective of assessing inflammatory variables as diagnostic and prognostic biomarkers in COVID-19 patients. The study spanned from December 2019 to December 2021 and included 200 consecutively enrolled adult patients who had a confirmed SARS-CoV-2 infection based on real-time polymerase chain reaction (RT-PCR). Only patients aged 18 years or older, admitted within 24 hours of symptom onset or clinical deterioration, and with complete laboratory profiles were included. Patients who were pregnant, immunocompromised, suffering from end-stage renal or hepatic failure, undergoing chemotherapy, or with incomplete clinical records were excluded. Individuals with a recent history of COVID-19 within the past three months were also not considered.

Upon admission, each patient was assigned a unique study identification code, and detailed demographic, clinical, and outcome-related information was recorded. COVID-19 severity was categorized using WHO criteria. Patients with mild to moderate disease were classified as non-severe, whereas those with respiratory distress, oxygen saturation less than 93 percent, PaO_2/FiO_2 ratios below 300 mmHg, or requiring ICU-level support were labeled as severe. This stratification enabled a clear assessment of the diagnostic performance of the selected biomarkers.

Venous blood samples were collected during the first 24 hours of admission using standard aseptic procedures. A wide panel of inflammatory biomarkers was analyzed, including total leukocyte count, lymphocyte percentage, lactate dehydrogenase, C-reactive protein, D-dimer, serum ferritin, interleukin-6, tumor necrosis factor-α, matrix metalloproteinase-3, and matrix metalloproteinase-9. All assays were performed in an ISO-certified laboratory using automated analyzers and ELISA-based immunoassays as per manufacturer protocols. These biomarkers were selected based on their known roles in systemic inflammation, immune dysregulation, and tissue injury associated with COVID-19.

The primary diagnostic outcome of interest was the ability of these inflammatory variables to discriminate between non-severe and severe COVID-19 cases at hospital admission. The prognostic objective was to determine their capacity to predict 28-day all-cause mortality. Sample size was calculated using standard formulas for comparative studies, incorporating a population variance of 12.1, a clinically significant difference of 1 unit, and a power of 90 percent at a 5 percent significance level, resulting in a minimum required sample of 196; therefore, 200 patients were enrolled.

Ethical approval was obtained from the Institute of Molecular Biology and Biotechnology, University of Lahore, as well as the Institutional Review Board and Ethics Committee of Bahria Town International Hospital. Informed consent was obtained from all patients or their legally authorized representatives, and strict confidentiality was maintained throughout the study.

All statistical analyses were conducted using SPSS version 25. Continuous variables were expressed as mean and standard deviation or median and interquartile range, depending on normality distribution, while categorical variables were summarized as frequencies and percentages. The independent t-test was used for normally distributed continuous variables, whereas the Mann-Whitney U test was applied for non-normal data. The chi-square test or Fisher's exact test was used to compare categorical variables. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the diagnostic accuracy of each biomarker, including sensitivity, specificity, area under the curve, and optimal cut-off values. Prognostic accuracy for 28-day mortality was evaluated using similar ROC-based methods. A p-value less than 0.05 was considered statistically significant for all analyses.

Results:

The demographic analysis revealed that the mean age of the study population was 58.03 ± 11.18 years, with no significant age difference between the Non-Severe and Severe groups ($p=0.533$). Gender distribution was also comparable, with males constituting 54 percent of the total sample (. Body mass index, however, differed significantly between groups, as patients with Severe COVID-19 had a higher mean BMI compared with those in the Non-Severe group ($p=0.001$). The prevalence of major comorbidities such as hypertension, diabetes, ischemic heart disease, renal dysfunction, and cancer did not differ significantly between groups. Notably, 28-day mortality was more than twice as high in the Severe group (14 percent) compared with the Non-Severe group (6 percent), reaching statistical significance ($p=0.049$). (Table 1)

Table 1. Demographic Characteristics of the Study Population

Variable	Total (n=200)	Non-Severe (n=100)	Severe (n=100)	p-value
Age (years), Mean ± SD	58.03 ± 11.18	57.57 ± 10.95	58.56 ± 11.46	0.533
BMI, Mean ± SD	25.14 ± 3.36	23.49 ± 2.70	26.79 ± 3.16	0.001
Male sex, n (%)	108 (54%)	53 (53%)	55 (55%)	0.444
Hypertension, n (%)	70 (35%)	37 (37%)	33 (33%)	0.328
Diabetes, n (%)	48 (24%)	25 (25%)	23 (23%)	0.434
Ischemic heart disease, n (%)	38 (19%)	18 (18%)	20 (20%)	0.429
Renal dysfunction, n (%)	18 (9%)	9 (9%)	9 (9%)	0.597
Cancer, n (%)	8 (4%)	2 (2%)	6 (6%)	0.140
28-day mortality, n (%)	20 (10%)	6 (6%)	14 (14%)	**0.049**

A comparison of inflammatory biomarkers demonstrated clear differences between severity groups (table 2). Haemoglobin levels were similar across groups, but all other inflammatory markers showed significant elevations among Severe COVID-19 patients. These included total leukocyte count, LDH, CRP, D-dimer, ferritin, IL-6, TNF-α, MMP-3, and MMP-9, each with p-values <0.001. In contrast, lymphocyte percentage was significantly reduced in the Severe group (p<0.001), consistent with the lymphopenia frequently associated with severe SARS-CoV-2 infection. The marked rise in D-dimer, ferritin, and MMP markers in the Severe cohort highlights a pronounced hyperinflammatory and pro-thrombotic response in these patients.

Table 2. Comparison of Inflammatory Biomarkers Between Groups

Biomarker	Non-Severe Median (IQR)	Severe Median (IQR)	p-value
Haemoglobin (g/dL)	118 (115–122)	121 (117–125)	0.680
TLC (10^9/L)	11.47 (10.60–12.24)	15.04 (13.19–15.79)	**<0.001**
Lymphocytes (%)	14.36 (11.44–15.63)	7.20 (6.03–8.07)	**<0.001**
LDH (U/L)	293.28 (283.59–315.73)	370.18 (333.75–410.24)	**<0.001**
CRP (mg/dL)	24.86 (18.62–27.10)	36.80 (33.06–40.58)	**<0.001**
D-dimer (ng/mL)	397.19 (324.86–447.00)	3094.98 (2764.22–3350.76)	**<0.001**
Ferritin (ng/mL)	1631.70 (1499.45–1955.44)	2553.74 (2283.28–2828.18)	**<0.001**
IL-6 (pg/mL)	35.04 (31.77–39.81)	47.29 (43.47–50.94)	**<0.001**
TNF-α (pg/mL)	23.59 (21.05–25.01)	30.29 (27.93–32.02)	**<0.001**
MMP-3 (ng/mL)	21.20 (18.79–22.44)	46.30 (43.18–50.19)	**<0.001**
MMP-9 (ng/mL)	178.12 (162.85–190.57)	483.41 (476.28–494.79)	**<0.001**

The diagnostic accuracy of inflammatory biomarkers for predicting disease severity was evaluated using ROC curve analysis (Table 3). D-dimer demonstrated the highest diagnostic performance with an AUC of 0.997, followed by MMP-9 (AUC 0.981) and MMP-3 (AUC 0.966). Lymphocyte percentage also showed strong discrimination capability with an AUC of 0.820. CRP, TNF-α, IL-6, TLC, LDH, and ferritin exhibited moderate diagnostic utility. These findings suggest that D-dimer, MMP-3, and MMP-9 are highly sensitive markers for identifying patients at risk of progressing to severe disease at the time of admission. (Figure 1)

Table 3. ROC Curve Analysis for Diagnostic Accuracy (Severity Prediction)

Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p-value
TLC	11.05	81	52	0.734 (0.664–0.804)	<0.001
Lymphocytes (%)	12.26	98	44	0.820 (0.762–0.878)	<0.001
LDH (U/L)	330.5	61	32	0.687 (0.611–0.763)	<0.001
CRP (mg/dL)	25.30	78	47	0.766 (0.701–0.831)	<0.001
D-dimer (ng/mL)	861.20	**99**	9	**0.997 (0.991–1.000)**	<0.001
Ferritin (ng/mL)	1630.80	79	50	0.725 (0.655–0.796)	<0.001
IL-6 (pg/mL)	35.43	81	48	0.738 (0.671–0.805)	<0.001
TNF-α (pg/mL)	24.29	80	42	0.769 (0.705–0.832)	<0.001
MMP-3 (ng/mL)	32.20	**99**	9	0.966 (0.938–0.995)	<0.001
MMP-9 (ng/mL)	436.13	**99**	5	0.981 (0.957–1.000)	<0.001

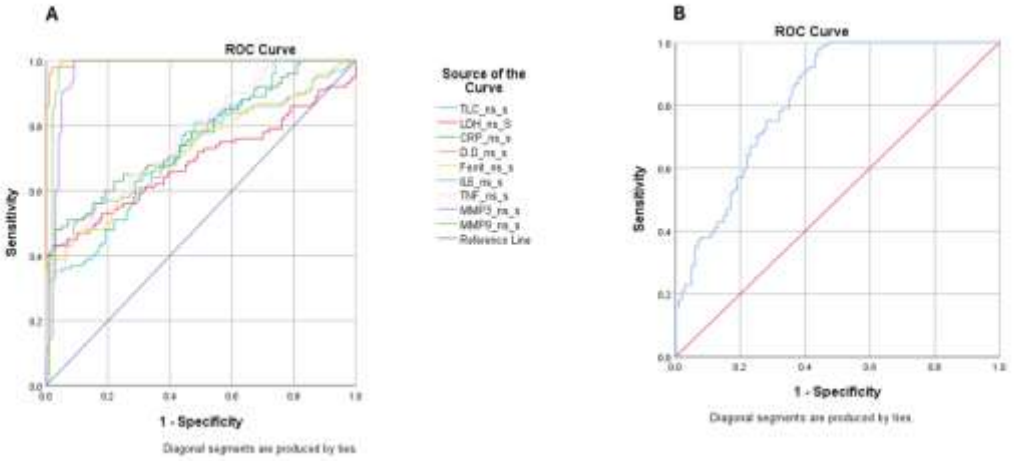

Figure 1 . ROC curve analysis of inflammatory markers

A comparison between survivors and non-survivors revealed that non-survivors were significantly older than survivors (p=0.018), and had higher rates of hypertension, diabetes, and cancer (p=0.044, p<0.001, and p<0.001, respectively), indicating that advanced age and comorbid burden substantially increase mortality risk (Table 4).

Table 4. Demographic Differences Between Survivors and Non-Survivors

Variable	Survivors (n=180)	Non-survivors (n=20)	p-value
Age (years), Mean ± SD	57.68 ± 10.75	61.54 ± 14.47	**0.018**
BMI	25.05 ± 3.37	25.99 ± 3.26	0.473
Hypertension (%)	32.8	55.0	**0.044**
Diabetes (%)	20.0	60.0	**<0.001**
Cancer (%)	1.7	25.0	**<0.001**

Several inflammatory markers differed significantly between survivors and non-survivors (Table 5). Non-survivors exhibited higher TLC, CRP, D-dimer, and MMP-3 levels, along with lower lymphocyte percentages, supporting the association of systemic inflammation, immune dysregulation. Ferritin, IL-6, TNF-α, and MMP-9 did not reach statistical significance in mortality comparison, though median values remained higher in non-survivors.

Table 5. Comparison of Inflammatory Biomarkers Between Survivors and Non-Survivors

Biomarker	Survivors (n=180) Median (IQR)	Non-survivors (n=20) Median (IQR)	p-value
Haemoglobin (g/dL)	117 (115–121)	127.50 (114–136)	0.070
Total leukocyte count (10^9/L)	12.36 (11.74–13.12)	14.65 (12.81–16.42)	**0.025**
Lymphocytes (%)	9.93 (8.90–10.85)	6.46 (4.95–8.32)	**0.004**
Lactate dehydrogenase (U/L)	316.69 (298.50–334.48)	388.84 (317.70–410.63)	0.144
C-reactive protein (mg/dL)	28.09 (26.05–32.19)	37.54 (30.34–55.59)	**0.003**
D-dimer (ng/mL)	861.20 (522.72–1788.23)	2449.90 (1595.71–3454.96)	**0.006**
Ferritin (ng/mL)	2168.68 (1857.99–2286.72)	2240.18 (1402.07–2858.77)	0.816
IL-6 (pg/mL)	40.61 (37.60–43.47)	46.49 (37.23–52.03)	0.130
TNF-α (pg/mL)	25.82 (24.86–27.83)	27.75 (22.10–32.02)	0.273
MMP-3 (ng/mL)	32.55 (26.20–35.43)	42.85 (34.61–48.97)	**0.028**
MMP-9 (ng/mL)	436.25 (223.82–445.53)	462.79 (239.28–501.42)	0.144

Prognostic ROC curve analysis identified CRP, lymphocyte percentage, D-dimer, MMP-3, MDA, and TLC as significant predictors of 28-day mortality (Table 6). CRP demonstrated the strongest prognostic value (AUC 0.701), followed by lymphocyte percentage (AUC 0.694) and D-dimer (AUC 0.688). MMP-3 showed moderate predictive utility. (Figure 2)

Table 6. Prognostic ROC Curve Analysis

Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p-value
TLC	12.1	80	54	0.653 (0.543–0.764)	0.025
Lymphocytes (%)	7.3	65	31	0.694 (0.585–0.804)	0.004
CRP (mg/dL)	30.03	80	46	0.701 (0.580–0.823)	0.003
D-dimer (ng/mL)	1271.2	85	47	0.688 (0.602–0.775)	0.006
MMP-3 (ng/mL)	25.84	85	59	0.650 (0.548–0.752)	0.028

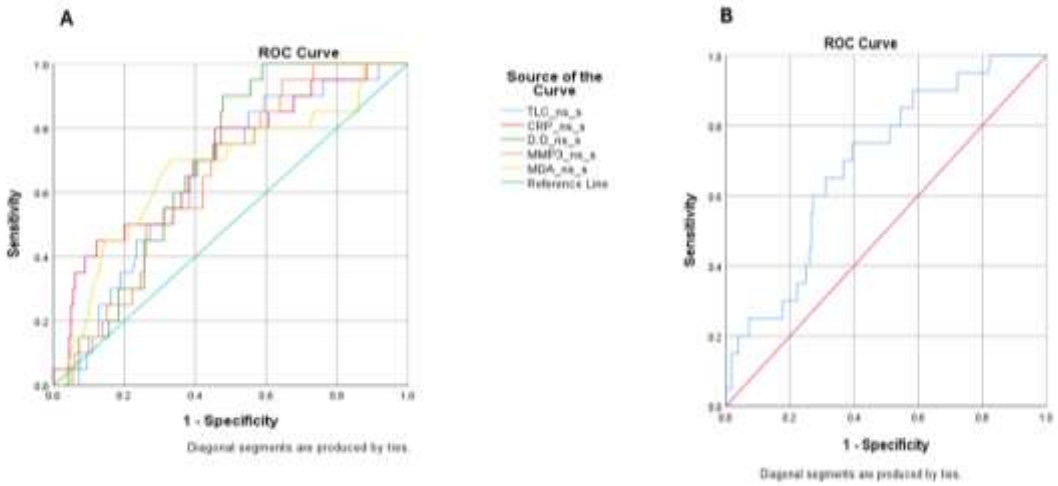

Figure 1 ROC curve analysis of inflammation as prognostic biomarkers

Discussion:

The demographic characteristics in our study showed that age and gender did not significantly differ between the Non-Severe and Severe groups, which aligns with prior reports demonstrating that demographic variables do not always serve as reliable indicators for disease severity in COVID-19 patients. Sarıcı et al. similarly reported that age and sex often fail to show significant associations with clinical outcomes, emphasizing the need to interpret demographic data in the broader context of underlying physiological responses rather than as isolated predictors (17). Although age did not statistically differ across severity groups in our cohort, the mean age of 58.03 years remains consistent with previous studies that identified older age as an important prognostic factor, even when it does not necessarily differentiate severity categories directly (18,19).

A notable finding in our analysis was the significantly higher BMI among Severe cases, supporting evidence that elevated BMI increases the risk of adverse COVID-19 outcomes. Fanagely et al. also demonstrated a clear association between high BMI and disease severity, suggesting that metabolic stress and adipose-related inflammation may contribute to worsening clinical trajectories (18). Meanwhile, comorbidities such as hypertension and diabetes did not differ significantly between groups. This observation is similar to findings from Singh, who reported that some comorbidities may not directly intensify disease severity but can shape the patient's baseline vulnerability and overall health reserve before infection (20).

Our data showed a significantly higher 28-day mortality rate in Severe patients, consistent with the trends described by Liu et al., who observed that severe clinical presentations and elevated inflammatory responses correlate strongly with poorer survival outcomes (21). Comparable mortality patterns have been reported in international studies where heightened inflammatory activity, hypoxia, and multiorgan involvement drive the risk of death (22,23). These parallels reinforce the predictive relevance of severity markers in determining patient prognosis.

Inflammatory biomarkers demonstrated striking differences across severity groups in our study. Severe cases exhibited significantly higher levels of IL-6, CRP, D-dimer, ferritin, TNF-alpha, and matrix metalloproteinases, supporting the well-documented role of systemic inflammation in exacerbating COVID-19 pathology. Damiati et al. similarly highlighted that elevations in these markers are strongly associated with severe disease progression, reflecting extensive cytokine activation and tissue injury (24). D-dimer, in particular, showed a highly significant rise among Severe patients. This finding is supported by Poudel et al., who demonstrated that D-dimer is a powerful biomarker for identifying hypercoagulability and predicting adverse clinical outcomes in hospitalized COVID-19 patients (25). The overarching role of inflammatory responses in determining disease progression aligns with Liu et al., who described the cytokine storm as a primary driver of organ dysfunction in COVID-19 (21).

Our ROC analysis further strengthened these observations by demonstrating exceptional diagnostic accuracy for D-dimer and MMP-9, with AUC values of 0.997 and 0.981 respectively. Kardus et al. also reported strong discriminatory performance of D-dimer in assessing COVID-19 severity, supporting its role as a rapid and reliable biomarker in clinical practice (26). Additionally, our findings correspond with the conclusions of Yamamoto et al., who emphasized that combining multiple inflammatory biomarkers improves diagnostic sensitivity and enhances clinical decision making (27).

Survivor and non-survivor comparisons revealed that non-survivors were significantly older and had higher rates of hypertension, diabetes, and cancer. These results align with observations from Al-Aghbari et al., who identified advanced age and comorbidity burden as crucial determinants of mortality in COVID-19 patients (28). Our findings regarding significantly elevated TLC, CRP, D-dimer, and MMP-3 in non-survivors further corroborate evidence from Gopalakrishnan et al., who noted that heightened systemic inflammation and coagulation abnormalities strongly predict mortality and reflect underlying disease severity (29).

Overall, the concordance between our findings and existing literature highlights the central role of inflammatory biomarkers in forecasting both disease severity and mortality. The integration of these biomarkers into routine clinical assessment may aid in early risk stratification, timely therapeutic intervention, and optimized resource allocation. This growing body of evidence underscores the need for continued research on biomarker-based prognostic models to improve clinical outcomes in COVID-19.

Conclusion

This study shows that inflammatory biomarkers play a key role in identifying both the severity and short-term prognosis of COVID-19. Markers such as D-dimer, MMP-9, MMP-3, CRP, TLC, and lymphocyte percentage demonstrated strong diagnostic and prognostic value. D-dimer and MMP-9 showed excellent accuracy for predicting severe disease, while CRP, lymphocyte percentage, D-dimer, and MMP-3 were useful predictors of 28-day mortality. Early assessment of these biomarkers can support timely clinical decisions, improve risk stratification, and help optimize patient management, especially in resource-limited healthcare settings.

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