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Predicting SARS-CoV-2 Omicron outcomes: Investigating the relationship of TLC, ferritin, D-dimer, LDH, C-Reactive protein and HbA1c

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Abstract: This study aimed to explore the relationship between total leukocyte count (TLC), ferritin, D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH) and glycosylated hemoglobin (HbA1c) with the outcomes of SARS-CoV-2 Omicron infections. The retrospective cross-sectional study was conducted on 850 COVID patients, admitted in hospitals in Islamabad and Lahore from January 2021 to December 2022. Baseline data, medical history and laboratory findings including Complete Blood Count (CBC), TLC, D-dimer, serum ferritin, CRP, LDH and HbA1c were collected. The results revealed significant positive correlations between disease outcomes and TLC, CRP, LDH and ferritin (all $p<0.01$), with HbA1c strongly correlating with mortality ($p<0.001$). Correlation analysis revealed significant association among various biomarkers. TLC demonstrated significant positive relationship with serum ferritin ($p=0.006$), CRP ($p=0.000$) and HbA1c ($p=0.002$). Lymphocyte count showed significant positive correlation with TLC ($p<0.001$). Ferritin showed positive correlation with LDH ($p<0.001$), D-dimer ($p=0.008$) and CRP ($p<0.001$). Logistic regression analysis revealed that CRP, LDH and HbA1c were significant predictors of mortality, with CRP and LDH associated with disease severity also. Receiver operating curve (ROC) analysis shows LDH to be the strongest predicter of outcome with area under curve (AUC) 0.76. The biomarkers have significant role in predicting disease outcome in current study.

Keywords: C-reactive protein, ferritin, HbA1c, lactate dehydrogenase, Omicron

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus that causes severe respiratory illness known as coronavirus disease 2019. The initial case of SARS-CoV-2 was reported in Wuhan, China in December 2019, followed by rapid rise and spread of COVID-19 cases globally (Li *et al*., 2020). After its initial outbreak in Asia, the virus spread rapidly across the globe, with the United States, Brazil, Russia, Italy and Europe being the most extensively impacted regions. According to World Health Organization data from May 2022, the global infection count reached 777.5 million (World Health Organization, 2022). The clinical presentation of COVID-19 varies, ranging from non-severe to severe manifestations. Thus, the patients' treatment depends on the severity of the clinical presentation. Eighty percent of SARS-CoV-2 cases developed mild to moderate symptoms, while the 20% progressed to advanced stages of illness within a week, potentially leading to intubation or mortality (Küçükceran *et al*., 2021). Various SARS-CoV-2 variants have been identified, including the Omicron variant, which was first reported in November 2021 and led to the fourth wave of COVID-19 worldwide (Bouzid *et al*., 2022).

Compared to previous strains, the Omicron variant exhibited reduced severity but higher transmissibility, quickly becoming the dominant variant in many regions (Mohsin and Mahmud, 2022). It possesses numerous mutations in the spike protein, which may impact viral behavior and host response. Understanding how these mutations influence disease severity and the associated biomarker profiles is essential for optimizing patient care strategies (Trofin *et al*., 2023).

Monitoring specific blood parameters, such as total leukocyte count (TLC), D-dimer level, serum ferritin, C reactive protein (CRP), Lactate dehydrogenase (LDH) and glycosylated hemoglobin (HbA1c) can provide valuable insights into disease progression, (Ali *et al*., 2020). Elevated TLC often indicates an active immune response to infection. Previous studies have shown that higher leukocyte counts correlate with severe SARS-CoV-2 outcomes (Kaftan *et al*., 2021). As an acute-phase reactant, elevated serum CRP levels reflect systemic inflammation. and is linked to severe disease progression in infected patients (Kaftan *et al*., 2021). Research has identified ferritin as an independent risk factor for COVID-19

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severity (Iqbal *et al*., 2023). D-dimer, a fibrin degradation product is a marker for coagulation disorders. Increased D-dimer levels have been associated with severe form of disease and higher mortality. LDH is an enzyme released during tissue damage. Higher LDH levels have been observed in patients with diseases severity, indicating tissue injury and hypoxia (Kaftan *et al*., 2021). Similarly, patients with elevated HbA1c are at greater risk for severe COVID-19 outcomes, possibly due to underlying metabolic dysfunction (Liu *et al*., 2021). These lab parameters and inflammatory markers, along with symptoms, oxygen saturation, respiratory rate and underlying medical conditions, may be useful for accurately screening SARS-CoV-2 patients at risk of respiratory failure (Moghadaci *et al*., 2024).

Numerous studies have explored the relationship between elevated inflammatory biomarkers, complete blood count (CBC), CRP and LDH with SARS-CoV-2 severity (Kaftan *et al*., 2021, Khedar, R.S *et al*., 2022) However, there is paucity of data particularly focusing on the Omicron variant. The Omicron variant's unique mutations may alter the disease's clinical presentation and progression, necessitating targeted research (Ogawa F *et al*., 2022). Understanding the severity of Omicron infections is crucial for effective patient management and healthcare resource allocation. In this context, our comprehensive study aims to explore the association between key blood biomarkers and the outcomes of SARS-CoV-2 Omicron infections. This study emphasizes on analyzing total leukocyte count, serum ferritin levels, D-dimer, LDH, CRP and HbA1c as potential indicators of Omicron severity. These biomarkers have been associated with various aspects of the immune response and inflammation, making them promising determinants for predicting the clinical outcomes of Omicron infection.

MATERIALS AND METHODS

Study design and settings

It was a multicentric retrospective cross-sectional study, carried out from January 2021 to December 2022, on COVID-19 patients admitted in Railways hospital (affiliated with Islamic International Medical College, Islamabad) and Services hospital Lahore.

Inclusion and exclusion criteria

Patients who were positive for the SARS-CoV-2 virus by real-time polymerase chain reaction (RT-PCR) in their specimen of nasopharyngeal and oropharyngeal swabs. Pregnant females, smokers and patients with incomplete laboratory records or with history of renal disease, active tumours, smoking and with pre-existing lung disease, age less than 25 and above 65 were not included in the study.

Sample size calculation

Daniel's sample size calculation formula was used to determine the sample size using a 95% confidence level, 80% power and an odds ratio of 4.46 (Daniel and Cross, 2018). The sample of 850 patients were collected using random sampling technique.

Sample collection

Researchers used a structured proforma to gather basic participant information, including gender, age, smoking/addiction status, medical history and personal history. Clinical parameters such as symptoms, vital signs and BMI were noted.

Hematological and biochemical analysis

Blood samples of hospitalized patients were collected. Laboratory investigations, including CBC were investigated using Sysmex XP-300 automated analyzer. The standard biochemical analysis of glycosylated hemoglobin (HbA1c) was performed according to the protocol performed in the routine examination in the hospital. D-dimer (D-Dimer Human ELISA Kit, Cat # EHDDIMER), ferritin (Ferritin Human ELISA Kit, Cat # EHFTL), C reactive protein (CRP) (Boster Bio ELISA KIT, Cat # EK7040), LDH were performed according to the instructions provided with the kit (L- LDH reagent kit, Cat # TR20015). Two independent physicians reviewed all reports.

RT-qPCR analysis

All patients were investigated for COVID-19 infection through RT-qPCR. RNA was extracted using the MagMAX™ Viral/Pathogen Nucleic Acid Isolation Kit (Cat # A42352, Applied Biosystems) according to the manufacturer's protocol. The cDNA was then created from the extracted RNA of the COVID virus using the High-Capacity RNA-to-cDNA™ Kit (Cat #: 4387406, Applied Biosystems), following the provided directions. For cDNA amplification, RT-qPCR was performed with the SYBR™ Select Master Mix (Cat #: 4472913, Applied Biosystems) adhering to the kit's recommended procedure.

The severity of illness was defined in accordance with WHO, Covid-19 clinical management: Living guidance (World Health Organization, 2021). Final outcome whether survived and discharged or died were also recorded.

Ethical approval

The study was carried out in accordance with rules of the Declaration of Helsinki (version 2013), once formal ethical approval was obtained for the study from Islamic International Dental Hospital Ref No: IIDC/IRC/2022 /012/004.

STATISTICAL ANALYSIS

The data was analysed using SPSS version 27. The Shapiro-Wilk test was employed to assess the normality of the data, which was then presented as mean ± standard deviation. Pearson's correlation was utilized to determine the relationship among the variables and also correlation of variables with outcomes. Logistic regression analysis was

conducted to predict the outcome based on age groups, serum ferritin, LDH, D-dimer, C-reactive protein, HbA1c and comorbidity.

Additionally, Receiver Operating curve (ROC) analysis was performed to assess the sensitivity and specificity of the inflammatory parameters in predicting the outcomes of SARS-CoV-2. The p-values < 0.05 were considered as significant.

RESULTS

A total of 850 SARS-CoV-2 positive cases screened by RT-PCR were included in the study. The patients ranged in age from 25 to 65 years, with 47.4% being male and 53.6% being female. 153 patients (18%) were between 25-35 years, 296 patients (34.8%) were between 36-45 years and 401 patients (47.1%) were between 46-65 years. The mean BMI of the included cases was 26.5±2.5. Patients received standard clinical management for SARS-CoV-2, with a mean time of 6.32±2.66 days from symptom onset to hospital admission. The clinical presentation was multifaceted, affected by factors like age, gender, symptom severity and comorbidities. These factors were chosen as they are recognized as important in diagnosis and treatment of SARS-CoV-2. The study examined parameters like fever, malaise, loss of taste and smell, with their respective percentages noted in table 1.

Around 39% of participants experienced dyspnea and 56% had cough. Additionally, 57% presented with tachypnoea and 23% had diarrhea. Among the comorbidities, 2.94% being hypertensive, 6.44% had IHD, 4% had COPD and 11.6% being diabetic. The mean SpO_2 was 80.66±9.1. On the basis of severity, 17.41% cases were having mild disease and 82.59% were having moderate to severe disease. Unfortunately, 45 patients included in the study died. Mean values of Haemoglobin (g/dL), TLC(10^3 cells /μL),Lymphocyte count(10^3 cells / μL), HbA1c(mmol/mol) CRP(mg/L), ferritin(ng/L), LDH(U/L) and D- dimer (μg/mL) of the study population is given in table 2.

Table 3 shows the correlation analysis of lab parameters. The results indicate significant correlations among various biomarkers. TLC is significantly positively correlated with Ferritin, CRP and HbA1c (r=0.255, p=0.006; r=0.414, p<0.0001; r=0.253, p=0.002 respectively). Lymphocytes have a significant positive correlation with TLC and LDH (r =0.321, p<0.001; r =0.208, p=0.001) and significant negative correlation with CRP (r=0.321, p=0.016). Conversely, LDH has a significant positive correlation with ferritin, HbA1c and D-dimers (r =0.321, p<0.001; r=0.218, p=0.007; r=0.174, p=0.033 respectively). However, some correlations were found to be insignificant, such as that between TLC, LDH and D-dimers, as well as the correlations between serum ferritin and lymphocytes and between HbA1c with lymphocytes and D-dimers.

Table 4 shows significant positive correlations of TLC, CRP and LDH with disease severity and mortality (p<0.001), indicating higher levels are linked to increased severity and mortality. HbA1c had the strongest correlation with mortality (r=0.547, p<0.001), while its correlation with severity was though significant but weaker (r = 0.202, p = 0.013). Lymphocytes correlated positively with mortality (r=0.169, p=0.039) but not with severity (r=0.001, p=0.992). Ferritin correlated with both mortality (r=0.214, p=0.009) and severity (r=0.250, p=0.002). D-dimer showed no significant correlation with either outcome.

Multivariate logistic regression analysis identified significant risk factors for predicting mortality and disease severity in SARS-CoV-2 Omicron variant infection (table V). The logistic regression model was statistically significant (x^2=56.84, p<0.001). CRP and LDH were found to be significant predictors of both mortality (p=0.013, OR=1.009, 95% CI: 1.002-1.016; p=0.006, OR=1.002, 95% CI: 1.001-1.004) and severity (p = 0.001, OR = 1.016, 95% CI: 1.007-1.026; p=0.013, OR = 1.003, 95% CI: 1.001-1.005). HbA1c was significantly associated with mortality (p<0.001, OR=1.828, 95% CI: 1.369-2.427), but not with disease severity (p=0.20, OR=1.335, 95% CI: 0.852-2.094). D-dimer, ferritin, age groups and comorbidity showed no significant associations with both outcomes (all p>0.05).

The ROC analysis (Fig. 1) shows that the area under the curve for ferritin, LDH, CRP and D-dimer is 0.618, 0.76, 0.538 and 0.639, respectively. This suggests that the overall predictive value of these biochemical parameters in determining the disease severity is highest for LDH as compared to ferritin, CRP and D-dimer, with a p-value of less than 0.001 with cut-off value of 239.4 U/L and sensitivity of 90.1% and specificity 58%.

DISCUSSION

Inflammatory markers are crucial in diagnosing the severity of SARS-CoV-2 and predicting patients' outcomes. These markers also guide practitioners in determining the appropriate management approach. The current cross-sectional study enrolled 850 hospitalized SARS-CoV-2 Omicron variant patients. The findings revealed the predictive role of inflammatory markers; CRP, LDH, D dimers and serum ferritin in determining the outcomes in the form of mortality and severity. ROC curve analysis shows that LDH has a significant role in predicting outcomes with AUC 0.76 and best cut off 239.4 U/L with sensitivity and specificity of 90.1% and specificity of 58%, respectively. Significant correlation among the variables, CRP, TLC, ferritin, LDH and HbA1c was observed in this study. These observations align with the findings of Kaftan *et al*., who reported a significant positive correlation between CRP, serum ferritin and LDH but not with the D

dimers (Kaftan *et al*., 2021). This supports that all these markers are involved in diagnosing and predicting the disease outcome and should be monitored in all hospitalized patients. Kaftan's study included outdoor patients also and additionally the patient had no comorbidity that could justify the reason that D dimer is not significantly correlating with other markers in his study. The current study uncovered a significant correlation of the markers with severity and outcome. Previous studies have also reported that elevated CRP, serum ferritin, D-dimer and LDH were associated with poorer outcomes in the form of disease severity and death, compared to those with decreased levels of markers (Hachim *et al*., 2021, Kadhim A.S *et al.,* 2021). In the current study no significant correlation of lymphocytes and D-dimers was found between the disease severity and outcome, contradictory to the findings of Ölkesen, F and Hachim *et al*. This contradictory finding could be due to fact that mean age of the participants in this study was 62$\pm$7 years so comparatively older patients were inducted in the study which could contribute to varied inflammatory responses and raised D dimer in older covid patients. In Hachim's study the difference from current study could be due to different categorizations of disease severity on the basis of organ dysfunction (Çölkesen, F *et al*., 2021, Hachim *et al*., 2021). It was also noted that CRP, D-dimer, serum ferritin and LDH were significantly elevated in critically ill SARS-CoV-2 patients compared to those with mild to moderate cases (Iqbal *et al.,* 2023). Similarly, Riaz *et al* reported comparable findings (Riaz *et al*., 2023).

The logistic regression analysis in the current study found that elevated levels of CRP and LDH significantly predict the two outcomes of disease. At the same time, HbA1c has a significant role in predicting disease severity and age, serum ferritin, D-dimer levels and comorbidity did not appear to play a role in predicting outcomes. Previous research identified LDH as a predictor of severity, consistent with our results (Li *et al*., 2020). However, their study concluded that there was no significant difference between CRP and LDH in predicting severity and mortality on ROC curve analysis which contradicts our findings. Li *et al* included patients with a variety of comorbidities which could be one reason for the contradictory findings. Moreover, in his study on multivariate regression analysis, CRP, ferritin and D-dimers were not found to be significantly associated with disease outcome but in our study, CRP does have a significant impact on both outcomes. In the current study, age and serum ferritin were insignificant predictors of outcomes. This contrasted with the conclusions of a previous study, which reported that age and serum ferritin were significant predictors of disease severity and outcome while CRP and LDH are insignificantly associated in predicting outcome in logistic regression model (Huang *et al*., 2021). The difference could be most likely attributed to different sample size and mean age of the study population. Previous study reported that HbA1c was not a predictor of outcome in COVID-19 patients. (Patel *et al*., 2021). The difference could be due to the difference in sample size of his and our study. A meta-analysis by Martha JW reported a significant prognostic value of LDH in covid (Martha JW *et al*., 2022). Similarly, findings of Kojima K *et al* reported significant role of LDH in determining disease severity in the form of progression to pneumonia; findings that are consistent with the results of the current study (Kojima K *et al*., 2023). In present study significant association of HbA1c was found with mortality and severity. HbA1c was also found to be a risk factor for increased mortality on logistic regression model. Where various studies support our findings (Liu, Y *et al.,* 2021), a study by Patel *et al* concluded that HbA1c is not associated with mortality and severity in hospitalized diabetic patients (Patel *et al*., 2021). The difference could be due variations in comorbidities in his selected patients and our cohort.

The ROC analysis in the current study demonstrated that these biomarkers are sensitive and specific in predicting outcome, with AUC values of 0.618 for serum ferritin, 0.76 for LDH, 0.538 for CRP and 0.639 for D-dimer. This indicates that the overall predictive value in determining severity is highest for LDH compared to ferritin, CRP and D-dimer, with a p-value of <0.001. It also suggests that these markers should be checked routinely and at intervals in hospitalized patients for monitoring their severity level. Various studies have yielded different results regarding the role of these biomarkers in predicting outcomes. The findings of Huang *et al* also reported LDH as a predictor of mortality with a cut off value of 258 U/L and sensitivity and specificity of 60.0% and 99.1% respectively (Huang *et al*., 2021). A similar study also reported an AUC of 0.85 for LDH, suggesting its predictive role in determining disease severity and clinical outcomes (Mardani *et al*., 2020). Mardani also included control group in the study. In the current study, the AUC for serum ferritin was 0.618, which is slightly lower but closely matches the results reported by Tural Onur *et al*., who reported an AUC of 0.762 for serum ferritin (Tural *et al*., 2021). In contrast, the AUC for CRP in our study was 0.538, differing from the results of Cheng *et al*., who reported an AUC exceeding 0.75 for Neutrophil-to-Lymphocyte Ratio (NLR) and CRP, indicating a more significant role of CRP in predicting disease severity and prognosis (Cheng *et al*., 2020). This discrepancy may be attributable to differences in study populations or sample sizes.

This study has limitations. Its retrospective design prevents establishing causal links between biomarkers and SARS-CoV-2 outcomes, as data were collected at a single time point. The focus on patients aged 25-65 years from teaching hospitals in Islamabad and Lahore limits generalizability. Additionally, the exclusion of factors like proinflammatory cytokines and viral load assessments restricts deeper insights into disease severity. Future research should address these gaps to better understand biomarker utility in SARS-CoV-2 management.

Table 1: Descriptive characteristics of population under study (n=850)

Characteristics	Covid positive (n=850)
Age	
25-35 years	153 (18%)
36-45 years	296 (34.8%)
46-65 years	401 (47.2%)
Gender	
Male	403 (47.4%)
Female	447 (52.6%)
BMI (kg/m^2)	26.5±2.5
Period from the onset of symptoms to time of admission (days)	6.32±2.66
Symptoms	
Fever	92%
Malaise	97%
Loss of taste	38%
Loss of smell	36%
Dyspnoea	39%
Cough	56%
Tachypnoea	57%
Diarrhoea	23%
Oxygen saturation (SpO_2)	80.66±9.1
Comorbidities	
HTN	25 (2.94%)
Ischemic Heart Disease	55 (6.47%)
COPD	34 (04%)
Diabetes	99 (11.6%)
Severity	
Mild	148 (17.41%)
Moderate to severe	702 (82.59%)
Outcome	
Death	45 (5.29%)
Survival and discharged	705 (82.9%)

Continuous data represented as mean and SD, and categorical data represented as number and percentage (%).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; HTN, hypertension

Table 2: Biochemical parameters and laboratory results of the patients

Characteristics	Mean ± SD
Haemoglobin (g/dL)	13.3 ± 2.3
TLC ($\times 10^3$ cells / µL)	14.569 ± 5.689
Lymphocyte count ($\times 10^3$ cells / µL)	3.15 ± 1.50
HbA1c (mmol/mol)	42.1±1.6
C-reactive protein (mg/L)	289.64 ± 73.100
Ferritin level (ng/L)	920.285 ± 403
Lactate dehydrogenase (U/L)	508 ± 315.068
D-dimer (µg/mL)	24.982 ± 9.15

Data presented as Mean ± SD
TLC, Total Leucocyte count; HbA1c, glycosylated haemoglobin

Table 3: Correlation Matrix of the biomarkers (n=850)

		TLC	Lymphocytes	Ferritin	LDH	D-Dimer	CRP	HbA1c
TLC	r	1	.321**	.225**	-.115	.031	.414**	.253**
	p value		.000	.006	.161	.704	.000	.002
Lymphocytes	r	.321**	1	-.097	.208*	.054	-.196*	.118
	p value	.000		.240	.011	.512	.016	.151
Ferritin	r	.225**	-.097	1	.321**	.215**	.298**	.143
	p value	.006	.240		.000	.008	.000	.081
LDH	r	-.115	.208*	.321**	1	.174*	-.064	.218**
	p value	.161	.011	.000		.033	.440	.007
D-Dimer	r	.031	.054	.215**	.174*	1	-.119	.065
	p value	.704	.512	.008	.033		.148	.426
CRP	r	.414**	-.196*	.298**	-.064	-.119	1	.125
	p value	.000	.016	.000	.440	.148		.126
HbA1c	r	.253**	.118	.143	.218**	.065	.125	1
	p value	.002	.151	.081	.007	.426	.126	

**p value significant at the 0.01 level
*p value significant at the 0.05 level

Table 4: Correlation of disease severity and mortality with biomarkers

	Mortality		Severity	
Variable	r	p value	r	p value
TLC ($\times 10^3$ cells / μL)	.300	<.001*	.330	<.001*
Lymphocytes ($\times 10^3$ cells / μL)	.169	.039*	.001	.99
CRP (mg/L)	.243	<.001*	.342	<.001*
D -dimer (μg/mL)	.155	.160	.032	.699
Ferritin (ng/L)	.214	.009*	.250	.002*
LDH (U/L)	.303	<.001*	.287	<.001*
HbA1c (mmol/mol)	.547	<.001*	.202	.013*

TLC, total leucocyte count; HbA1c, glycosylated haemoglobin; SD, standard deviation
CRP, C-reactive protein; LDH, Lactate dehydrogenase
*p value significant at the 0.05 level

Table 5: Logistic regression of risk factors in predicting outcome and severity SARS-CoV-2 Omicron Variant

Variables	Mortality			Severity		
	p -value	OR	95%CI	p -value	OR	95%CI
Age groups	0.135	0.17	0.811-3.64	0.896	0.947	0.420- 2.136
CRP	0.013*	1.009	1.002-1.016	0.001*	1.016	1.007- 1.026
d-Dimer	0.450	1.021	0.967-1.078	0.820	1.003	0.976- 1.031
LDH	0.006*	1.002	1.001-1.004	0.013*	1.003	1.001- 1.005
Ferritin	0.565	1.00	0.998-1.001	0.750	1.000	0.999- 1.002
HbA1c	<0.001	1.828	1.369-2.427	0.208	1.335	0.852- 2.094
Comorbidity	0.208	2.728	0.314-3.377	0.331	1.730	0.582- 4.978

**p value highly significant at the 0.01 level
*p value significant at the 0.05 level
OR; odds ratio, CI; confidence interval

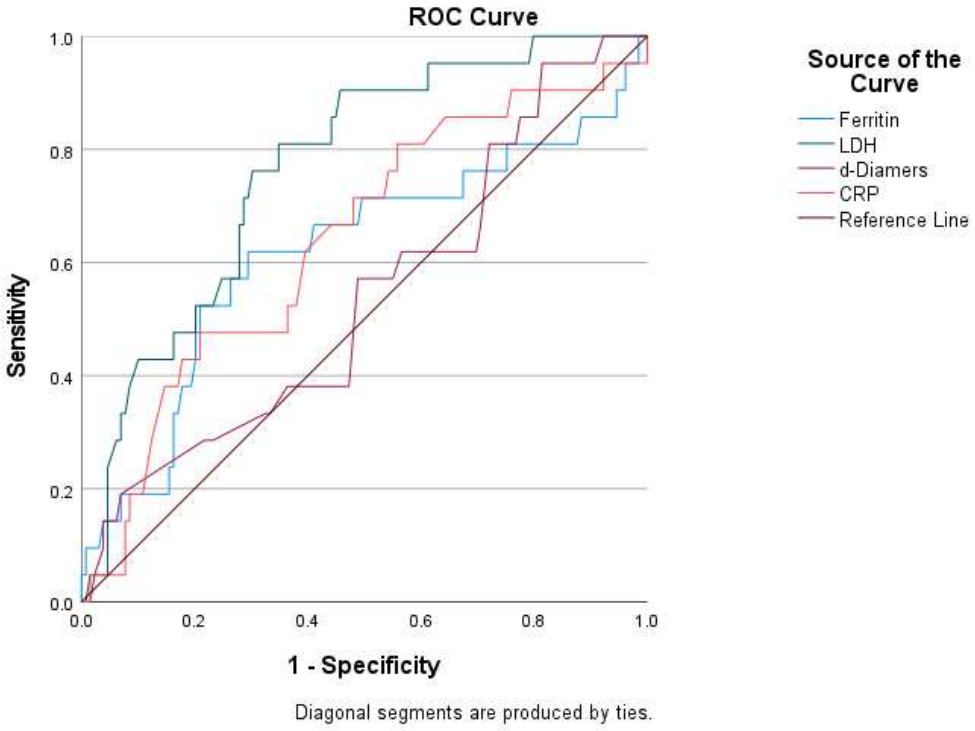

Fig. 1: ROC curve analysis for ferritin, LDH, D-dimer and CRP in predicting severity of SARS-CoV-2

CONCLUSION

This study highlights the significant role of inflammatory and metabolic biomarkers in predicting COVID-19 Omicron outcomes. TLC, CRP, LDH and ferritin showed strong correlations with disease severity, while HbA1c emerged as the strongest predictor of mortality. Logistic regression identified CRP, LDH, ferritin and HbA1c as independent risk factors for poor outcomes, with ROC analysis confirming LDH as the most reliable prognostic marker (AUC 0.76). These findings underscore the clinical utility of routine biomarkers in risk stratification and early intervention for COVID-19 patients.

Conflict of interest

None

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