ORIGINAL RESEARCH

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Effect of Biomarkers on Predicting Mortality in COVID-19 Pneumonias: A Retrospective Clinical Study

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) remains a significant challenge in emergency services worldwide. This study investigated the relationship between hematocrit (Htc), hemoglobin (Hb), amylase, lactate, and interleukin 6 (IL-6) levels and hospitalization and mortality in patients diagnosed with COVID-19.

Materials and Methods: Htc, Hb, amylase, lipase, lactate, and Interleukin 6 (IL-6) levels of patients with a positive COVID-19 polymerase chain reaction (PCR) test (Bio-speedy® Severe acute respiratory syndrome-Coronavirus-2 Triple Gene Reverse transcription quantitative PCR, Türkiye) who presented to the emergency department were analyzed. Hospitalizations and short-term (28 days) mortality were retrospectively examined. The data were analyzed using SPSS for Windows 20.0. Normality analysis of continuous data was conducted using the Shapiro-Wilk test. Multiple logistic regression analysis was performed to analyze predictors of mortality and discharge.

Results: Data from 6,627 emergency department patients were examined. The gender ($p<0.001$), age ($p<0.001$), Hb ($p<0.001$), lactate ($p<0.001$), and lipase ($p<0.001$) levels of the hospitalized patients. Increasing age was associated with mortality ($p<0.001$). In the analysis of biomarkers, a decrease in Hb and Htc ($p<0.001$; $p=0.038$) and an increase in lactate, lipase, amylase, and IL-6 ($p<0.001$; $p<0.001$; $p=0.022$; $p<0.001$) were determined to be associated with mortality. The area under the receiver operating characteristic curve for the mortality model was calculated as 0.724, with specificity and sensitivity determined as 91.8% and 97.5%, respectively.

Conclusion: Age, amylase, lipase, serum lactate, and interleukin-6 levels, when calculated together, are important predictors of both mortality and hospitalization in COVID-19 pneumonia.

Keywords: Biomarkers, COVID-19, emergency department, pneumonia

Introduction

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) virus [1]. Despite a decline in the potency of the SARS-CoV-2 virus, it continues to be a global health crisis [2,3]. As of January 2024, the WHO reported over 774 million confirmed cases and more than seven million deaths worldwide, with a concurrent increase in hospitalizations [4].

The clinical presentation of patients seeking care in emergency departments with a COVID-19 diagnosis varies widely, ranging from mild upper respiratory tract infections to severe pneumonia, acute respiratory distress syndrome, and multiple organ failure, leading to fatalities [3,5].

Certain biomarkers, including hematocrit (Htc), hemoglobin (Hb), amylase, lipase, lactate, and interleukin 6 (IL-6), are used in clinics and intensive care units (ICUs) for diagnosis, effective treatment, and prognosis assessment of patients with COVID-19. Proper interpretation of these parameters is essential for accurate clinical decision-making and successful treatment [6,7]. A meta-analysis revealed associations between low Hb,

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lymphocyte, platelet, and albumin levels and COVID-19 mortality [8]. Another study explored the prognostic properties of IL-6, C-reactive protein, and procalcitonin in COVID-19 pneumonia and highlighted IL-6 as a prognostic factor [9]. IL-6, produced in response to infections and tissue damage, acts as a pleiotropic cytokine that participates in inflammatory responses [10]. The overproduction of IL-6 can lead to a cytokine storm, causing severe systemic inflammation, vascular hyperpermeability, multiple organ failure, and death [11].

Emergency departments remain the primary point of contact for individuals with symptoms of COVID-19 pneumonia. Evaluating the prognosis of these patients is vital for managing the emergency department workload and planning examinations and treatments appropriately.

This study aimed to investigate the correlation between Htc, Hb, amylase, lipase, lactate, and IL-6 levels and the severity of COVID-19 in patients. Notably, there is a gap in the existing literature because previous studies did not collectively examine these biomarkers. Establishing the efficacy of these parameters and advocating for their widespread use in emergency departments can significantly enhance patient assessment and treatment. Additionally, our findings aim to contribute valuable insights into the scientific literature on COVID-19, serving as a foundation for future research.

Materials and Methods

Data Source

Patients diagnosed with COVID-19 pneumonia who presented to the emergency department of one of the largest hospitals in Türkiye between May 01, 2021 and October 30, 2021, were retrospectively examined. The data were retrieved by the researchers from the hospital information system and physician orders.

Patients older than 18 years and those whose data could be accessed were included in the study. Among patients with pneumonia according to the ICD code, those whose polymerase chain reaction (PCR) test result was positive for COVID-19 were included in the study.

Patients whose data could not be accessed, patients <18 years of age, pregnant women, and those who applied to the emergency department due to trauma were not included in the study.

The article was prepared using the STROBE checklist.

Data Collection

Htc, Hb, amylase, lipase, lactate, and IL-6 values of patients with positive COVID-19 PCR (Bio-speedy® SARS CoV-2 Triple Gene RT-qPCR, Türkiye) in nasopharyngeal swab samples who presented to the emergency department with COVID-19 symptoms were scanned. Whether the patients were discharged from the emergency department, were hospitalized (service and ICU), or had short-term (28-day) mortality was recorded.

Statistical Analysis

The analyses of the study were performed using SPSS for Windows 20.0. Normality analysis of continuous data was performed using the Shapiro-Wilk test. Median comparisons of data that did not show normal distribution were made using the Mann-Whitney U test. Ratio comparisons of categorical variables were made using the Pearson's chi-square test. Multiple logistic regression analysis was performed to identify predictors of mortality and discharge. The regression model was created by excluding factors related to multicollinearity analysis. In addition, receiver operating characteristics (ROC) analysis was performed for diagnostic accuracy, and the area under the curve is presented. The $p<0.05$ level was used for statistical significance.

Ethics Statement

This study was approved by the Ankara City Hospital No. 2 Clinical Research Ethics Committee (decision number: E2-21-987, date: 10.11.2021) and was conducted in accordance with the Declaration of Helsinki. Because this was an observational study using an anonymized dataset, the requirement to obtain informed consent from the participants was waived.

Results

Demographic Data of Patients

A total of 6.975 patients were identified by examining the hospital's electronic information system and physician orders. Among them, 334 (4.8%) were excluded from the study because they were younger than 18 years. Of the remaining 6.641 (95.2%) patients, 14 were excluded because of a lack of data. Consequently, analyses were conducted on the remaining 6.627 patients.

Table 1 presents the descriptive information and the results of the biomarkers of the patients. The median age of the patients is 58 (range between 18-105 years). Patients were most frequently male, 50.1% (n=3322). It was determined that 638 (9.6%) of the 6.627 patients died and 4.058 (61.2%) were alive. The mean±standard deviation, median, and minimum-maximum values of the biomarkers are presented in Table 1.

Clinic Outcomes

Table 2 presents data on the age, sex, and biomarker levels of patients with mortality. Increased age was associated with mortality ($p<0.001$). When analyzing the biomarkers, decreases in Hb and Htc ($p<0.001$; $p=0.038$); Increase in lactate, lipase, amylase, IL-6 ($p<0.001$; $p<0.001$; $p=0.022$; $p<0.001$) were determined to be associated with mortality.

Table 3 shows the gender ($p<0.001$), age ($p<0.001$), Hb ($p<0.001$), Htc ($p<0.001$), lactate ($p<0.001$), and lipase ($p<0.001$) levels of the hospitalized patients. and was

Table 1. Demographic, outcome, and biomarker analyses

Variables			n (%)	Mean±SD	Median (25-75%)	Min.-Max.
Total			6627 (100.00)			
Gender	Male		3322 (50.10)			
	Female		3305 (49.90)			
Age (year)				57.80±18.60	58 (44-72)	18-105
Mortality	Survival		5989 (90.40)			
	Mortal		638 (9.60)			
Discharge	Discharge		4058 (61.20)			
	Hospitalization		2569 (38.80)			
Blood analysis		Hb		12.70±2.10	12.80 (11.40-14.10)	3.50-19.40
		Htc		38.50±6.10	38.80 (34.70-42.50)	2.20-60.90
		Lactate		2.20±1.40	1.84 (1.40-2.53)	0.07-17.88
		Lipase		57.20±98.10	40.00 (28.10-58.25)	9.0-2332.0
		Amylase		78.90±85.20	61.00 (44-87)	5-2032
		IL-6		93.30±377.00	20.60 (8.35-56.4)	2.70-7153.20

Hb: Hemoglobin, Htc: Hematocrit, IL-6: Interleukin-6, Min.-Max.: Minimum, Maximum

Table 2. Groups in terms of mortality

Variables		Mortality				p
		Survival		Non-survivor		
		n (%)	Median (25-75%)	n (%)	Median (25-75%)	
Gender	Male	2979 (89.7)		343 (10.3)		0.054*
	Female	3010 (91.1)		295 (8.9)		
Age (year)			57.0 (43.0-71.0)		73.0 (61.0-83.0)	<0.001**
Hb			12.8 (11.40-14.20)		12.4 (10.60-13.90)	<0.001**
Htc			38.9 (34.90-42.50)		38.3 (33.20-42.90)	0.038**
Lactate			1.77 (1.37-2.40)		2.22 (1.60-3.10)	<0.001**
Lipase			40.7 (29.0-58.35)		35.55 (23.65-58.05)	<0.001**
Amylase			61.0 (44.0-86.0)		64.0 (42.0-108.0)	0.022**
IL-6			17.3 (7.40-44.70)		54.6 (23.40-167.60)	<0.001**

Hb: Hemoglobin, Htc: Hematocrit, IL-6: Interleukin-6,
*Pearson's chi-square test, **Mann Whitney-U test

Table 3. Comparison of patients' hospitalization/discharge status and age, gender and laboratory data

Variables		Hospitalization/discharge				p
		Discharge		Hospitalization		
		n (%)	Median (25-75%)	n (%)	Median (25-75%)	
Gender	Male	1933 (58.20)		1389 (41.80)		<0.001*
	Female	2125 (64.30)		1180 (35.70)		
Age (year)			55.0 (40.0-68.0)		65.0 (51.0-77.0)	<0.001**
Hb			12.90 (11.60-14.20)		12.5 (10.90-14.0)	<0.001**
Htc			39.10 (35.30-42.60)		38.3 (33.90-42.40)	<0.001**
Lactate			1.740 (1.36-2.36)		1.94 (1.44-2.70)	<0.001**
Lipase			41.00 (30.15-58.75)		38.0 (26.0-58.0)	<0.001**
Amylase			62.0 (45.0-86.0)		60.0 (42.0-90.0)	0.680**
IL-6			15.0 (6.8-34.2)		29.40 (10.9-81.55)	<0.001**

Hb: Hemoglobin, Htc: Hematocrit, IL-6: Interleukin-6,
*PPearson's chi-square test, **Mann Whitney-U test

discharged without being hospitalized (p=0.001), there was a significant relationship with IL-6 (p<0.001) levels. No significant relationship was detected with amylase (p=0.680).

Logistic regression analysis for mortality is presented in Table 4. Gender and Hb levels were not found to be significant predictors of mortality. A relationship was found between increased age, lactate, amylase, and IL-6 levels, and mortality (p<0.001; p<0.001; p=0.008; p<0.001).

As a result of logistic regression analysis, age, lactate, amylase, and IL-6 levels were found to be independent predictors of mortality. Although the area under the ROC curve of the model regarding mortality was calculated as 0.724, its specificity was determined as 91.8% and its sensitivity was determined as 97.5%. The ROC curve of the model is presented in Figure 1.

Table 5 presents the logistic regression analysis for hospitalization/discharge status. It was determined that age, lactate, amylase, IL-6 increase, and discharge were significantly related. There were no significant relationships between the patients' hospitalization/discharge status, gender, and Hb value.

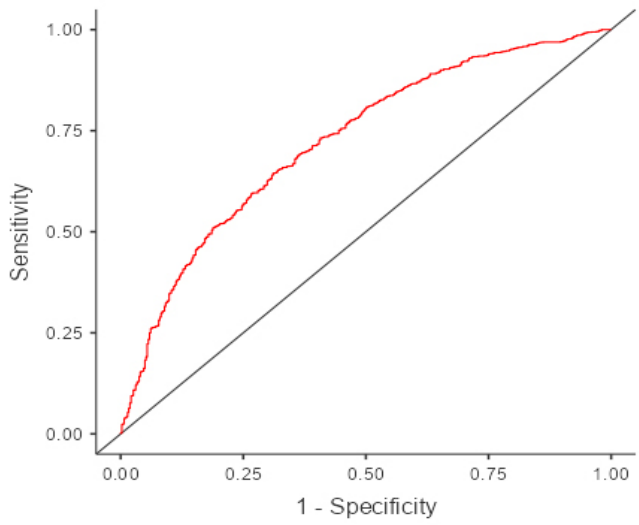

Figure 1. ROC curve for mortality: Although the area under the ROC curve of the model regarding mortality was calculated as 0.724, its specificity was determined as 91.8% and its sensitivity was determined as 97.5%

ROC: Receiver operating characteristics

Table 4. Logistic regression analysis: model coefficients and mortality

				95% Confidence interval	
Predictor	**Estimate**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-4.76376	<0.001	0.008	0.003	0.024
Gender	0.099	0.418	1.104	0.868	1.404
Age	0.036	<0.001	1.037	1.029	1.045
Hb	0.021	0.443	1.021	0.967	1.077
Lactate	0.215	<0.001	1.240	1.128	1.364
Amylase	0.002	0.008	1.002	1.000	1.003
IL-6	0.001	<0.001	1.001	1.001	1.002

Hb: Hemoglobin, IL-6: Interleukin-6,
Estimates represent the log odds of "Mortality = Mortal" vs, "Mortality = Survival"

Table 5. Logistic regression analysis-model coefficients-discharge

				95% Confidence Interval	
Predictor	**Estimate**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-0.458	0.314	0.632	0.259	1.540
Gender	-0.187	0.077	0.829	0.674	1.020
Age	0.014	<0.001	1.014	1.008	1.020
Hb	-0.040	0.098	0.961	0.916	1.010
Lactate	0.352	<0.001	1.423	1.262	1.610
Amylase	0.002	0.036	1.002	1.000	1.002
IL-6	0.001	0.001	1.001	1.001	1.001

Hb: Hemoglobin, IL-6: Interleukin-6,
Estimates represent the log odds of "Discharge = Admitted" vs. "Discharge = Discharge"

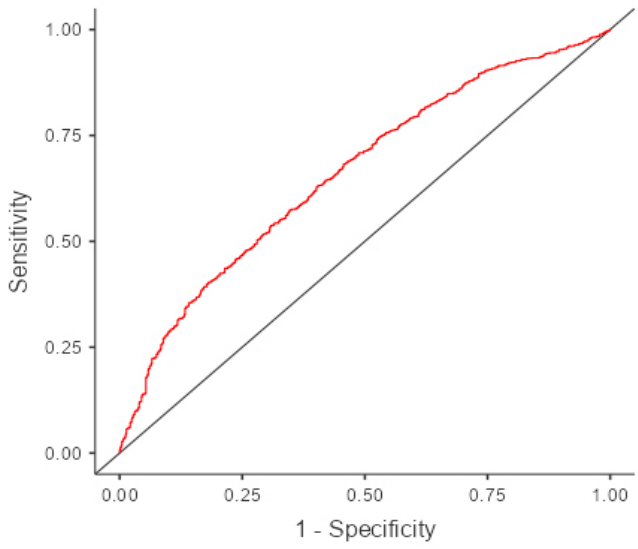

Figure 2. ROC curve for discharge: The area under the ROC curve of the discharge model was calculated as 0.650, its specificity was determined as 14.2% and its sensitivity was 93.5%

ROC: Receiver operating characteristics

In the logistic regression analysis, age, lactate, amylase, and IL-6 level were found to be independent predictors of discharge. Although the area under the discharge model's ROC curve was calculated as 0.650, its specificity was 14.2%, and its sensitivity was 93.5%. The model's ROC curve is presented in Figure 2.

Discussion

The inflammatory response to the COVID-19 virus is implicated in developing COVID-19-related complications. An unbalanced proinflammatory immune response indicates that the disease can have life-threatening consequences. Accordingly, studies have reported that high levels of circulating cytokines and acute phase reactants are associated with poor outcomes in COVID-19 patients [12].

The most important aspect of our study is the high sample size. Data from 6.627 patients were examined. Since the hospital where the study data is provided is one of the largest central hospitals in Türkiye, has a high patient capacity, and is a reference hospital in surrounding cities, it includes patients of all characteristics (age, gender, chronic diseases, etc.). Although there was no relationship between patient sex and a decrease in Hb level and hospitalization/discharge or mortality, increasing age and an increase in lactate, amylase, lipase, and IL-6 levels were associated with mortality and hospitalization. When these biomarkers were examined together, the specificity for hospitalization was determined as 14.2% the sensitivity as 93.5%, and the specificity for mortality was determined as 91.8% and the sensitivity was 97.5%. These results are highly significant for patient outcomes.

Some studies have found the same findings as our study and did not detect a relationship between gender and mortality [13]. In our study, no relationship was found between sex and mortality or hospitalization in patients with COVID-19 pneumonia.

Some studies have shown the opposite, finding that males have a higher risk of getting COVID-19 [14,15]. In our study, patient age was associated with mortality and hospitalization. The median age of patients who died was 73, which was a statistically significant result. In a study examining the prognostic features of age, sex, and comorbid diseases in patients with COVID-19 pneumonia, patients aged ≥65 years were more mortal than patients aged <65 years, and men were more likely to die than women [16].

The decreases in Hb and Htc levels were significant for mortality and hospitalization/discharge in our study. Likewise, Asghar et al. [17] conducted their study in 2020. In a retrospective study in which 364 cases were examined, Hb decrease was found to be associated with mortality. In their study published in 2023, Alizad et al. [18] examined disease severity using hematological parameters and found that low Hb levels were associated with both mortality and disease severity.

In a study examining amylase and lipase values of 176 COVID-19-positive patients and 103 COVID-19-negative patients, the relationship between amylase and lipase increase and the severity of COVID-19 pneumonia was determined, but its relationship with mortality was not examined [14]. In our study, increased amylase and lipase levels were found to be associated with mortality. However, although lipase elevation made a significant difference in admission/discharge, amylase elevation did not make a significant difference.

There are not many studies in the literature examining the relationship between COVID-19 pneumonia and serum lactate levels. In one of these studies, the lactate content and mortality of COVID-19 pneumonia patients hospitalized in the ICU were examined. The relationship between the increase in lactate value and mortality was determined [13]. Our study found that the increase in serum lactate levels were significantly associated with mortality and hospitalization/discharge status.

Gür Vural et al. [9] found that IL-6 was 53.8% effective in predicting mortality in patients with COVID-19 pneumonia, and its specificity was 84.1%. In another study, IL-6, PRC, and neutrophil-to-lymphocyte ratios were found to be prognostic for mortality in patients with COVID-19 (sensitivity specificity; 94.9%-93.2%; 76.3%-79.5%; 71.7%-80.3%, respectively) [12]. In a systematic review of 16 articles, a correlation was detected between elevated IL-6 levels and prolonged COVID-19 [19]. Our study found that when age, lactate, amylase, and IL-6 were

considered together, we achieved a specificity of 91.8% and sensitivity of 97.5%. Combining age, lactate, amylase, and IL-6 levels appeared to be more predictive of both mortality and hospitalization/discharge.

Study Limitations

Although our study provides valuable information, it is important to acknowledge its limitations. The major limitation of this study is its retrospective, single-center design. Limited to a single center may limit the generalizability of our findings to larger populations. Additionally, notable limitations include the lack of a graded severity classification for COVID-19 pneumonia and the exclusion of other potential biomarkers.

Conclusion

In conclusion, calculating age, serum lactate, amylase, lipase, and IL-6 levels together constitute an important criterion for both mortality and hospitalization in terms of COVID-19 pneumonia. It is informative for studies in which more comprehensive biochemical parameters are examined.

Ethics

Ethics Committee Approval: This study was approved by the Ankara City Hospital No. 2 Clinical Research Ethics Committee (decision number: E2-21-987, date: 10.11.2021).

Informed Consent: The requirement to obtain informed consent from the participants was waived.

Footnotes

Authorship Contributions

Concept: T.D., H.O., Design: T.D., H.O., Data Collection or Processing: T.D., H.S.Ö., Analysis or Interpretation: H.S.Ö., H.O., Literature Search: H.S.Ö., H.O., Writing: T.D., H.S.Ö., H.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this studyreceived no financial support.

References

1. WHO Health Topics, Coronavirus disease (COVID-19). Available from: https://www.who.int/health-topics/ coronavirus#tab=tab_1. Accessed: January 30, 2024.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-33.
3. Kim YS, Lee SH, Lim HJ, Hong WP. Impact of COVID-19 on out-of-hospital cardiac arrest in Korea. J Korean Med Sci. 2023;38:92.
4. WHO COVID-19 epidemiological update. Available from: https://www.who.int/publications/m/item/covid-19-epidemiological-update---19-january-2024. Accessed: January 30, 2024.
5. Chavez S, Long B, Koyfman A, Liang SY. Coronavirus Disease (COVID-19): a primer for emergency physicians. Am J Emerg Med. 2021;44:220-9.
6. Li J, Rong L, Cui R, Feng J, Jin Y, Chen X, et al. Dynamic changes in serum IL-6, IL-8, and IL-10 predict the outcome of ICU patients with severe COVID-19. Ann Palliat Med. 2021;10:3706-14.
7. Rendon A, Rendon-Ramirez EJ, Rosas-Taraco AG. Relevant cytokines in the management of community-acquired pneumonia. Curr Infect Dis Rep. 2016;18:10.
8. Kowsar R, Rahimi AM, Sroka M, Mansouri A, Sadeghi K, Bonakdar E, et al. Risk of mortality in COVID-19 patients: a meta- and network analysis. Sci Rep. 2023;13:2138.
9. Gür Vural D, Usta B, Daştan MSE, Tanriverdi Çaycı Y, Bilgin K, et al. Evaluation of the effects of interleukin-6, C-reactive protein, and procalcitonin on the prognosis of the disease in patients with COVID-19. Turk J Immunol. 2022;10:149-54.
10. Ibáñez-Prada ED, Fish M, Fuentes YV, Bustos IG, Serrano-Mayorga CC, Lozada J, et al. Comparison of systemic inflammatory profiles in COVID-19 and community-acquired pneumonia patients: a prospective cohort study. Respir Res. 2023;24:60.
11. Vecchié A, Bonaventura A, Toldo S, Dagna L, Dinarello CA, Abbate A. IL-18, and infections: is there a role for targeted therapies? J Cell Physiol. 2021;236:1638-57.
12. Sayah W, Berkane I, Guermache I, Sabri M, Lakhal FZ, Yasmine Rahali S, et al. Interleukin-6, procalcitonin, and neutrophil-to-lymphocyte ratio: potential immune-inflammatory parameters to identify severe and fatal forms of COVID-19. Cytokine. 2021;141:155428.
13. Yadigaroğlu M, Çömez VV, Gültekin YE, Ceylan Y, Yanık HT, Yadigaroğlu N, et al. Can lactate levels and lactate kinetics predict mortality in patients with COVID-19 with using qCSI scoring system? Am J Emerg Med. 2023;66:45-52.
14. Prasad H, Ghetla SR, Butala U, Kesarkar A, Parab S. COVID-19 and serum amylase and lipase levels. Indian J Surg. 2023;85:337-40.
15. Pijls BG, Jolani S, Atherley A, Derckx RT, Dijkstra JIR, Franssen GHL, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission, and death: a meta-analysis of 59 studies. BMJ Open. 2021;11:044640.
16. Mi J, Zhong W, Huang C, Zhang W, Tan L, Ding L. Gender, age and comorbidities as the main prognostic factors in patients with COVID-19 pneumonia. Am J Transl Res. 2020;12:6537-48.
17. Asghar MS, Haider Kazmi SJ, Khan NA, Akram M, Hassan M, Rasheed U, et al. Poor prognostic biochemical markers predicting fatalities caused by COVID-19: A retrospective observational study from a developing country. Cureus. 2020;12:9575.
18. Alizad G, Ayatollahi AA, Shariati Samani A, Samadizadeh S, Aghcheli B, Rajabi A, et al. Hematological and biochemical laboratory parameters in COVID-19 patients: a retrospective modeling study of severity and mortality predictors. Biomed Res Int. 2023;2023:7753631.
19. Yin JX, Agbana YL, Sun ZS, Fei SW, Zhao HQ, Zhou XN, et al. Increased interleukin-6 is associated with long COVID-19: a systematic review and meta-analysis. Infect Dis Poverty. 2023;12:43.