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ORIGINAL RESEARCH

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The relationship of COVID-19 severity with laboratory findings and neutrophil-to-lymphocyte ratio in patients admitted to a large teaching hospital in Iran: A cross-sectional study

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Abstract

Background and Aims: COVID-19 patients might be admitted to the hospital based on their clinical manifestations or to the intensive care unit (ICU) due to the severity of their symptoms or critical situation. Our main objective was to investigate clinical and demographic factors influencing COVID-19 patients' admission to the ICU and length of stay (LOS) using extracted data from the hospital information systems in Iran.

Methods: The data of hospitalized patients with confirmed COVID-19 were retrieved from the health information system of Imam Khomeini Hospital Complex, Tehran, Iran between March 2020 and February 2022. The primary outcome was the ICU admission, and the secondary outcome was the LOS. The correlation analysis between laboratory findings and demographic data with ICU admission and LOS was done using SPSS 21.0, and $p < 0.05$ was considered significant.

Results: Of all the 4156 patients, 2391 (57.5%) were male and the mean age was 58.69 ± 8.19 years. Of these, 9.5% of patients were admitted to ICU at any time point during their hospital stay. Age and laboratory variables such as neutrophil-to-lymphocyte ratio (NLR), ALT (U/L), albumin (g/dL), plasma glucose (mg/dL), ferritin levels (ng/mL), and phosphorous levels (mg/dL) shown the significant relationship with ICU admission. Also, being a smoker and having hypoxemia had a significant relationship with longer stays in the hospital. In this study, we validated a cut-off value of 4.819 for NLR, calculated at hospitalization, as a useful predictor of disease progression and occurrence of serious clinical outcomes, such as ICU admission.

Conclusion: The study examined various clinical factors associated with ICU admission in COVID-19 patients. The findings suggest that certain factors can increase the risk of ICU admission and influence the length of hospital stay which should be focused in future studies.

KEYWORDS

COVID-19, intensive care unit, neutrophil-to-lymphocyte ratio, prognosis

1 | INTRODUCTION

The 2019 coronavirus disease (COVID-19) infection was caused by a new coronavirus. It first appeared in China and spread worldwide immediately.[1] This infectious disease has various symptoms that range from mild to life-threatening consequences.[2] COVID-19 patients might be admitted to the hospital based on their clinical manifestations or admitted to the intensive care unit due to the severity of their symptoms or critical situation.[3] Though predicting the deterioration of critically ill patients with COVID-19 is still impossible, the evidence has shown that approximately 10%–12% of hospitalized patients require intensive care.[4] Determining the effective clinical and demographic factors associated with respiratory deterioration, the need for critical care, and predicting the length of stay (LOS) in hospital are so important to allocate appropriate resources in better management of the COVID-19 pandemic.[5,6]

Equipping medical care centers with electronic hospital information systems has facilitated patient data collection and provided opportunities to conduct retrospective studies.[7,8] Usually, clinical data related to the condition of patients admitted to the ICU are recorded in hospital systems due to continuous monitoring.[9,10] The clinical data of hospitalized patients are also recorded periodically in the COVID-19 pandemic.[11,12]

Since the emergence of COVID-19, several prognostic factors have been introduced; including laboratory markers.[13-17] As some of these are routinely measured in hospitalized patients, finding a relatively easy-to-use and easy-to-measure biomarker for the prediction of COVID-19 prognosis is of importance. The neutrophil-to-lymphocyte ratio (NLR) has been suggested to be one of the useful biomarkers in immune injury and inflammatory reactions.[18,19] This was observed to have even better sensitivity and specificity than the white blood cell count (WBC) with a longer duration of persistence.[20] Moreover, the use of NLR in the assessment of infectious disease severity and its clinical utility in critically ill patients have been established.[21]

Up to now, several studies have been conducted in different countries to determine the risk factors in the severity of the disease, mortality, and length of hospitalization with aid of health information systems (HISs) or electronic health records.[22-24] Our main objective was to investigate clinical and demographic factors influencing COVID-19 patients' admission to the intensive care unit and LOS using laboratory data extracted from hospital information systems in Iran.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The data of hospitalized patients were retrieved from the health information system (HIS) of Imam Khomeini Hospital Complex, Tehran, Iran between March 2020, and February 2022. All patients hospitalized with COVID-19 diagnosis were included in this study. The patients below 18 years old and pregnant women were excluded. This study was approved by the Tehran University of Medical Sciences Ethics Board (IR.TUMS.VCR.REC.1399.051). Due to the retrospective nature of the study and using electronic health records which did not affect the patients' treatment course, informed consent was waived for this study.

Demographic characteristics, blood test results, comorbid conditions, intensive care unit (ICU) admission, and LOS of hospitalized patients were collected. Complete blood counts (white blood cell, neutrophil, lymphocyte, monocyte, eosinophil, and platelet counts) were extracted from the laboratory subsystem of HIS; after which, the NLR was calculated for each patient. The COVID-19 diagnosis was confirmed based on positive results for COVID-19 nucleic acids on real-time fluorescence reverse-transcription polymerase chain reaction (RT-PCR).

Demographic characteristics included age, sex, smoking history, history of asthma, chronic obstructive pulmonary disease (COPD), stroke, cardiovascular disease, chronic kidney disease, chronic liver disease, diabetes, fatty liver, human immunodeficiency virus, hyperlipidemia, hypertension, hypothyroidism, and cancer history. Laboratory blood measurements included fasting plasma glucose (FPG) and plasma glucose, serum alanine transaminase (ALT), albumin, calcium, magnesium, phosphorous, sodium, ferritin, and erythrocyte sedimentation rate (ESR). Daily morning routine blood test data were used for the analyses and calculation of NLR.

2.2 | Statistical analysis

Data are reported as mean ± standard deviation (SD) or number (percentage). The normality test of the continuous variables was done using the Kolmogorov–Smirnov test. Categorical variables were expressed as proportion and compared using the Chi-square test. The correlation of continuous variables with categorical variables was analyzed using the Mann–Whitney *U* test or the Kruskal–Wallis test as appropriate. Pearson–correlation or Spearman–correlation analysis was performed between each significant independent variable.

The optimal cut-points for NLR and ICU admission were estimated by the Receiver Operating Characteristic (ROC) curve by minimizing the Euclidean distance between the curve and the point (0, 1) in the ROC space. SPSS version 21.0 (SPSS Inc.) and Python language were used for the statistical analysis. All analyses considered a significance level of 0.05. All statistical analyses were performed adhering to relevant recommendations for analysis, reporting, and interpretation of clinical research[25] and "Statistical Analyses and Methods in the Published Literature" (SAMPL) guidelines for reporting statistical analyses.[26]

3 | RESULTS

3.1 | Baseline characteristics

Our initial retrieved data from the HIS system included 8671 records. After preprocessing raw data, deidentifying, and cleaning the data set

from missing data (7%), 4156 records of patients who were hospitalized with a diagnosis of COVID-19 were included in this study. The demographic characteristics of hospitalized patients are represented in Table 1. Among these, 9.5% of patients were admitted to the ICU during their hospital stay and classified as ICU-admitted group. The mean age of our studied population was 58.69 ± 8.18 years old and about 57.5% of the enrolled patients were males. The patients requiring ICU care were noted to be significantly older than the patients who did not require an intensive level of care.

The statistical analysis revealed that there is a significant relationship between ICU admission and demographic variables including age, cardiovascular disease, a history of hypertension, chronic kidney disease, chronic liver disease, transplantation, and history of using corticosteroids ($p < 0.05$).

3.2 | Laboratory and clinical findings relationship with ICU admission

The correlation analysis of laboratory findings for our studied population showed that ICU-admitted patients showed significantly higher NLR ratio, serum ALT, plasma glucose, calcium, FPG, ferritin, magnesium, and phosphorous (Table 2), while serum albumin and lymphocyte count were significantly lower among patients who were admitted to ICU.

The values of NLR in the prediction of disease severity based on ICU admission were analyzed with the ROC curve and found to be statistically significant ($p < 0.001$). The ROC curves and the area under the curve (AUC) in detecting the predictive abilities of NLR for ICU admission among our studied population are shown in Table 3 and Figure 1.

3.3 | Length of stay in hospitalized patients

The mean LOS among hospitalized patients was 7.2 ± 0.12 days which ranged from 1 to 132 days. The analysis showed that there was a significant relationship between admission to the ICU and LOS (14.13 vs. 6.48 days, $p < 0.001$).

The results of the Mann–Whitney test showed that there was a significant relationship between LOS and hypothyroidism ($p = 0.003$), diabetes mellitus ($p = 0.003$), cancer ($p < 0.001$), history of chronic cardiovascular disease ($p = 0.033$), history of chronic kidney disease ($p < 0.001$), history of transplantation ($p = 0.034$), history of malignancy ($p < 0.001$), and having lymphopenia at admission ($p = 0.003$).

Based on the Kruskal–Wallis test, being a smoker ($p = 0.004$) and having hypoxemia ($SpO_2 < 93\%$) had a significant relationship with a longer stay in the hospital ($p < 0.001$). Moreover, patients between 70 and 85 years old were hospitalized for a longer period of time due to COVID-19 infection than other patients. The Pearson–correlation of clinical laboratory tests and LOS is shown in Table 4. There was a weak positive correlation between NLR, plasma glucose, calcium, creatinine, ESR, FPG, magnesium, phosphorous, ferritin, sodium, and LOS. On the other hand, there was a negative correlation between hemoglobin and LOS.

4 | DISCUSSION

This study was designed to investigate the association between laboratory findings and COVID-19 severity and ICU admission. Based on our findings, older patients as well as those with a history of cardiovascular disease, chronic kidney disease, and hypertension had significantly higher rates of ICU admission. In addition, higher NLR, ALT, plasma glucose, calcium, FPG, ferritin, magnesium, and phosphorous were observed in patients admitted to ICU while lower serum albumin. With a cut-off of 4.819, NLR had predictive ability for ICU admission with sensitivity and specificity of 63% and 50%, respectively. These can be beneficial for care providers to assess the predict the ICU admission in patients.

The investigation of factors influencing COVID-19 patient admission to the ICU and LOS using laboratory data extracted from hospital information systems in Iran is a critical step in understanding and managing the disease. By analyzing laboratory data, healthcare professionals can identify the key factors that contribute to patient outcomes, such as disease severity and mortality rates. This information can then be used to create more effective treatment protocols and allocate resources more efficiently. Additionally, understanding the factors that lead to ICU admission and longer hospital stays can help healthcare providers anticipate patient needs and provide more timely interventions. Overall, this investigation has the potential to improve patient outcomes and reduce the burden of COVID-19 on healthcare systems in Iran and beyond.

The NLR is a measure of the balance between neutrophils, which are a type of white blood cell that plays a key role in the body's immune response to infection, and lymphocytes that help to coordinate the immune response. In COVID-19 patients, an elevated NLR has been associated with more severe disease and worse outcomes, including an increased risk of mortality. This is because an elevated NLR reflects an imbalance in the immune response, with an increase in the number of neutrophils relative to lymphocytes, which suggests a more intense inflammatory response known as "cytokine storm" in which the role of neutrophils is significant.[27,28] This is mainly due to the function of neutrophils which are pathogens and debris clearance, cytokine production for restriction of virus replication.[29,30] The main response to viral infection is the release of neutrophil-chemoattractive elements and neutrophil recruitment.[31] It is of higher importance since "cytokine storm" leads to severe COVID-19 conditions.[32] As such, monitoring the NLR may be a useful tool in identifying patients who are at higher risk of severe disease and may require more intensive treatment or monitoring. In this study, we validated a cut-off value of 4.819 for NLR, calculated at hospitalization, as a useful predictor of disease progression and occurrence of serious clinical outcomes, such as ICU admission.

Our results are also consistent with another study in Iran in which their patients had severe disease when their NLR was above 4.21.[33] In determining the optimal NLR cutoff value, two other studies showed that 7.9 (AUC: 0.80; sensitivity: 65.3%; specificity: 90.6%) and 11.8 (AUC: 0.9, sensitivity: 97.5%; specificity: 78.1%) value of NLR could predict mortality.[33] In another study, researchers

TABLE 1 Descriptive statistics of demographic characteristics of patients and correlation with ICU admission.

Variable	Category	Frequency	Study groups		Statistical analysis
			Non-ICU	ICU admitted	
Gender	Male	2391 (57.5%)	2149 (89.88%)	242 (10.12%)	$\chi^2 = 2.909$ $p = 0.088$
	Female	1765 (42.5%)	1614 (91.44%)	151 (8.56%)	
Age groups	18–30	212 (5.3%)	203 (95.75%)	9 (4.25%)	$\chi^2 = 49.771$ $p < 0.001$
	31–45	777 (18.9%)	742 (95.50%)	35 (4.50%)	
	46–60	1151 (27.5%)	1046 (90.88%)	105 (9.12%)	
	61–75	1307 (31.3%)	1137 (86.99%)	170 (13.01%)	
	76–85	542 (13.0%)	488 (90.04%)	54 (9.96%)	
	>85	167 (4.0%)	147 (88.02%)	20 (11.98%)	
Smoking history	Having history consumption	217 (5.2%)	199 (91.77%)	18 (8.29%)	$\chi^2 = 0.361$ $p = 0.548$
	Not having	3939 (94.8%)	3564 (90.48%)	375 (9.52%)	
Hookah history	Having history consumption	50 (1.2%)	46 (92.00%)	4 (8.00%)	$\chi^2 = 0.125$ $p = 0.723$
	Not having	4106 (98.8%)	3717 (90.53%)	389 (9.47%)	
Comorbidity	Asthma	114 (2.7%)	103 (90.4%)	11 (9.6%)	$\chi^2 = 0.027$ $p = 0.868$
	COPD	91 (2.2%)	79 (86.81%)	12 (13.2%)	$\chi^2 = 1.512$ $p = 0.219$
	CVD/stroke	112 (2.7%)	98 (87.50%)	14 (12.5%)	$\chi^2 = 1.254$ $p = 0.264$
	Cardiovascular disease	666 (15.9%)	573 (86%)	93 (14%)	$\chi^2 = 19.107$ $p < 0.001$
	Chronic kidney disease	268 (6.4%)	208 (77.61%)	60 (22.4%)	$\chi^2 = 55.954$ $p < 0.001$
	Chronic liver disease	61 (1.5%)	43 (70.5%)	18 (29.5%)	$\chi^2 = 29.073$ $p < 0.001$
	Diabetes	820 (19.6%)	730 (89%)	90 (11%)	$\chi^2 = 2.899$ $p = 0.089$
	Fatty liver	32 (0.8%)	32 (100%)	0 (0%)	$\chi^2 = 3.262$ $p = 0.071$
	HIV	8 (0.2%)	7 (87.5%)	1 (12.5%)	$\chi^2 = 0.088$ $p = 0.768$
	Hyperlipidemia	275 (6.6%)	244 (88.7%)	31 (11.3%)	$\chi^2 = 1.182$ $p = 0.277$
	Hypertension	1014 (24.3%)	894 (88.2%)	120 (11.8%)	$\chi^2 = 8.859$ $p < 0.01$
	Hypothyroidism	181 (4.3%)	162 (89.5%)	19 (10.5%)	$\chi^2 = 0.454$ $p = 0.500$
	History of malignancy	307 (7.3%)	270 (87.9%)	37 (12.1%)	$\chi^2 = 2.67$ $p = 0.102$

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HIV, human immunodeficiency virus; ICU, intensive care unit.

revealed that NLR values above 4.94 on admission have associations with longer mean ICU stay and decorations ($p < 0.02$).[34] This shows that NLR depends on several factors including race, country of residence, comorbidities, and geographical conditions. Other studies have investigated this issue and it has been shown that white races show a higher ratio of NLR than other races.[35]

In addition to NLR, magnesium was also found to be different among those admitted to the ICU and those who did not. A study

TABLE 2 Analytic analysis of laboratory and clinical findings relationship with ICU admission.

Variables	Non-ICU admitted (mean ± SD)	ICU admitted (mean ± SD)	*r*	*p* Value
NLR	6.85 ± 0.11	8.40 ± 0.40	0.071	<0.001
ALT (U/L)	38.14 ± 79.73	49.17 ± 93.02	0.075	<0.001
Albumin (g/dL)	4.61 ± 0.81	3.66 ± 1.30	0.110	<0.001
Plasma glucose (mg/dL)	115.33 ± 1.67	161.54 ± 5.52	0.138	<0.001
Calcium (mg/dL)	5.956 ± 0.06	7.403 ± 0.11	0.41	<0.05
FPG (mg/dL)	55.05 ± 1.56	82.72 ± 5.97	0.076	<0.05
Magnesium (mg/dL)	1.561 ± 0.017	1.745 ± 0.043	0.050	<0.001
Lymphocyte (per μL)	5,779.501 ± 88.59	1,472.18 ± 226.95	−0.44	<0.05
Ferritin (ng/mL)	285.31 ± 10.25	519.91 ± 45.46	0.059	<0.001
Phosphorous (mg/dL)	2.52 ± 0.03	2.86 ± 0.09	0.041	<0.001

Abbreviations: ALT, alanine aminotransferase; FPG, fasting plasma glucose; ICU, intensive care unit; NLR, neutrophil-to-lymphocyte ratio.

TABLE 3 Sensitivity, specificity, area under ROC curve (AUC), and an optimal cut-off value of NLR as screening index in ICU admission in COVID-19 infection.

Variable	AUC	Cut-off	Sensitivity	Specificity
NLR	0.570	4.819	62.94	49.60

Abbreviations: ICU, intensive care unit; NLR, neutrophil-to-lymphocyte ratio.

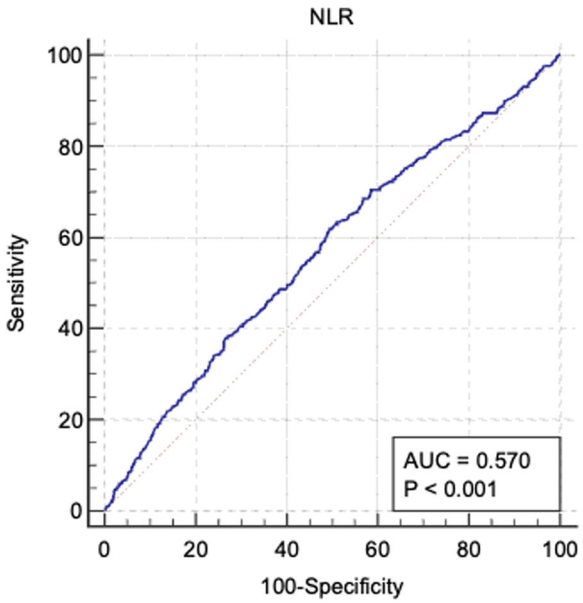

FIGURE 1 The Receiver Operating Characteristic curves and the area under ROC curve in detecting the predictive abilities of neutrophil-to-lymphocyte ratio for intensive care unit admission.

conducted in Saudi Arabia showed that patients admitted to ICU had higher levels of blood magnesium, similar to our findings.[36] Regarding ALT, it was shown in a meta-analysis that patients with COVID-19 had significantly higher levels of ALT in comparison with controls.[37] Our study showed that ALT was associated with ICU admission.

The LOS in the hospital for COVID-19 patients has been found to be associated with various factors. A systematic review and meta-analysis study found that the mean ICU and hospital LOS values were 7.4 and 13.9 days, respectively.[38] Da Costa Sousa et al. concluded that patients who died had a significantly longer LOS compared to those who were discharged. The mean LOS for COVID-19-positive individuals was 10.1 days, and among them, 33.5% died.[39] In our study, the mean duration of LOS among hospitalized patients was 7.20 ± 0.12 while the mean ICU LOS was 14.13 days. Based on these findings, it can be concluded that a longer LOS in the hospital for COVID-19 patients is associated with ICU admission, and some comorbidities such as hypothyroidism, diabetes mellitus, chronic cardiovascular disease, a history of hypertension, chronic kidney disease, transplantation, and cancer. Timely testing and efficient patient follow-up can help reduce the length of hospital stay for COVID-19 patients.

Despite assessing the role of NLR and other features of patients admitted to ICU with COVID-19 diagnosis, some considerations and limitations should be mentioned for the interpretation of the results described here. First, the fact that all participants were from one center and hence, these findings should be verified in other studies with different settings to generalize our results. Second, there might be limitations regarding the time of sample collection and the interpretation of the test results. The blood samples were collected right after hospitalization, and the interpretation of the results has been done accordingly. Another limitation is missing data which was less than 10% in our study, however, its removal might lead to changes in the results observed and hence, affect our findings. Finally, due to circadian variation in platelet levels,[40] platelet-to-lymphocyte ratio (PLR) was not calculated for the patients. However, it should be noted that we took the samples at almost the same time from all the patients, trying to minimize this effect for other laboratory measures.

TABLE 4 Correlations analysis between length of stay and clinical parameters.

Variables	*r* (Pearson correlation)	*p* Value
Plasma glucose (mg/dL)	0.142	<0.001
Calcium (mg/dL)	0.156	<0.001
Creatinine (mg/dL)	0.031	<0.001
ESR (mm/h)	0.036	0.026
FPG (mg/dL)	0.111	<0.001
Hemoglobin (g/dL)	−0.027	<0.001
Ferritin (ng/mL)	0.108	<0.001
Magnesium (mg/dL)	0.085	<0.001
Phosphorous (mg/dL)	0.099	<0.001
Sodium (mEq/L)	0.031	0.036
NLR ratio	0.059	<0.001

Abbreviations: ESR, erythrocyte sedimentation rate; FPG, fasting plasma glucose; NLR, neutrophil-to-lymphocyte ratio.

5 | CONCLUSION

Our study which was conducted at a large referral center in Tehran, showed that patients with COVID-19 admitted to ICU had distinct demographic characteristics and disease history in addition to several different laboratory findings (higher NLR, ALT, plasma glucos calcium, FPG, ferritin, magnesium, and phosphorous) which can predict the worse severity of the disease. It can be useful for clinicians in risk stratification and researchers in designing appropriate studies.

AUTHOR CONTRIBUTIONS

Zahra Khazaeipour: Supervision, conceptualization, writing—review and editing, writing—original draft. **Marsa Gholamzadeh**: Conceptualization, writing—original draft, formal analysis, visualization. **Amir Hossein Behnoush**: Writing—original draft, data curation. **Khalil Pestei**: Conceptualization, writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data is available upon reasonable request from the corresponding author.

ETHICS STATEMENT

This study was approved by the Tehran University of Medical Sciences Ethics Board (IR.TUMS.VCR.REC.1399.051). Due to the retrospective nature of the study and using electronic health records which did not affect the patients' treatment course, informed consent was waived for this study.

TRANSPARENCY STATEMENT

The lead author Zahra Khazaeipour, Khalil Pestei affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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