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Original Article

Distinct laboratory parameters as strict prognostic values in the setting of COVID-19 severity

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Abstract
Introduction: To the best of our knowledge, a new emerging viral infection induced by SARS-CoV-2 was named COVID-19 with high morbidity and mortality on a global scale. To date, COVID-19 is implied as a respiratory disease with varied manifestations from asymptomatic to long-standing complications. In this regard, discerning a potential prognostic value of critical outcomes in the early stages would be more appreciable to stratify the risk of disease severity and 28-day mortality. In this clinical study, we aimed to evaluate distinct laboratory biomarkers, including neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), and lactate dehydrogenase (LDH), as reliable indicators to predict disease severity in COVID-19 patients admitted in a medical referral center.
Methods: Following the COVID-19 diagnosis, all consecutive patients (n = 685) with confirmed SARS-CoV-2 infection were included since September 2020 for one year. Data were collected using electronic medical records.
Results: Based on obtained results, NLR and serum level of LDH showed a positive correlation with length of hospital stay. Moreover, the mortality rate and MV required in patients with either positive CRP or the high levels of LDH were remarkably greater than that of the non-severe group ($P = 0.01$). Finally, we could not find significant differences between female and male patients regarding the evaluated parameters.
Conclusion: Our findings highlighted those high values of NLR, CRP, and LDH can be considered valuable clinical prognostic aids for risk stratification, identification of disease severity, and triage of patients at the time of admission.

Introduction

Recently, a novel pandemic disease, named COVID-19, which is induced by SARS-CoV-2, has led to a global health concern.[1] The majority of infected people presented a wide array of clinical manifestations ranging from asymptomatic or mild (characterized by flu-like symptoms) to severe forms of the disease mainly marked by lower respiratory tract involvement (pneumonia, hypoxemia with SpO2 < 92%), and critical states characterized by acute respiratory distress syndrome (ARDS), or viral sepsis, which could be eventually considered to be a life-threatening condition.[2] The disease's mortality rate was estimated between 5%-15%, with a dramatic rise in patients suffering from a severe form, reported mostly among the subjects with underlying conditions and elderlies.[3,4] Prior to para-clinical examinations, polymerase chain reaction (PCR) assay is a reliable and gold standard test for detecting SARS-CoV-2 infection.[5] In addition, diagnostic imaging approaches, especially spiral chest computed tomography (CT), are performed to identify the pulmonary involvement.[6] Regarding the related pathogenesis, overwhelming inflammatory responses, increased VEGF secretion, and subsequently, cytokine storm possess a substantial role in COVID-19 progression.[7] Moreover, it has been well-documented that prevailing inner inflammatory and immunological responses induced by SARS-CoV-2 infection mainly promote the critical form, life-threatening multiple-organ failure (MOF), and even death.[8,9]

According to the previous literature, it has been well-established that laboratory values, including hematological profile, biochemistry, and inflammatory parameters

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change in patients with confirmed COVID-19.[10,11] For instance, decreased levels of white cell count (WCC), neutrophilia, lymphopenia, thrombocytopenia, increased levels of serum lactate dehydrogenase (LDH), ferritin, d-dimer, and C-reactive protein (CRP) have been reported.[12] In addition, the neutrophil to lymphocyte ratio (NLR), interleukin-6 (IL-6), and IL-1β (as well-known inflammatory cytokines involved in COVID-19 pathogenesis), rising approximately up to 1000-fold at the sites of infection, are known as simple initial and valid tools widely used to detect systemic inflammation in a variety of pathological diseases.[13] Thereby, early diagnosis of the disease prognosis through laboratory parameters measurement can play a crucial role in better management of the disease and preventing mortality.[14] To this end, identifying the potential predictors primarily would be more appreciable, in which mounting evidence provided a list of laboratory parameters, considered reliable values to anticipate disease severity.[13,14]

Given that the standard blood laboratory tests can be potential diagnostic and prognostic indicators for recognizing the terrible outcomes in COVID-19 patients,[5] in the current retrospective study, we sought to decipher some inflammatory biomarkers, consisting NLR, CPR, and LDH as the valuable early-stage prognostic values to determine the COVID-19 severity in admitted subjects who tend to switch into ill patients at intensive care unit (ICU). We also evaluated the impacts of dynamic changes of NLR (more or less than 2), CRP, and LDH on in-hospital prognosis (discharge or 28-day mortality), requiring mechanical ventilation (MV), and length of hospital stay.

Methods

Data collection and study population

In the current retrospective and observational study, conducted since September 2020 for one year, demographic variables (including age, gender, length of hospital stay, and requiring for MV), the levels of CRP, neutrophils, lymphocytes, LDH, as well as the inpatient disposition (death or discharge) were collected using the electronic medical records. The obtained data were recorded in a relevant prepared checklist. In addition, a proper NLR cut-off value was defined based on Zeng et al.[15]

Using the following formula, with calculating the mortality rate = 0.302, as one of the major factors in the effectiveness of the prognostic tools, confidence level (Cl) of 95%, and the accuracy rate of 4%, the sample size was estimated as 685 patients:

$$N = \frac{z^2_{1-\frac{\alpha}{2}}\delta^2}{d^2}$$

Inclusion/exclusion criteria

All patients (18 years and over) suspected of having SARS-CoV-2 infection with laboratory measurements of CBC, LDH, and CPR within 24 hours of admission were included. Patients who had a history of corticosteroid therapy, as well as the history of blood disorders, inflammatory diseases (such as bacterial infection), and underlying diseases, including diabetes, kidney failure, and chronic obstructive airways disease or who did not have complete and accurate laboratory tests, were excluded from the study.

Statistical analysis

The data were analyzed using SPSS software version 20, and the quantitative data were reported as mean ± standard deviation (SD). Regarding the qualitative variables, the chi-square (Fisher's exact) test was used. For in-between group comparison of independent variables, Mann-Whitney test was used. Due to the abnormality of two quantitative variables, Spearman's rank correlation coefficient was applied to evaluate the relationship between serum LDH levels and the length of hospital stay. For each parameter the median was also calculated, and compared with the reference values in our laboratory. The significance level of the *P*-value was considered less than 0.05.

Results

Evaluation of demographic characteristics

According to the statistical analysis performed on demographical characteristics, the mean age was 47.96 ± 4.91 years (min = 16, max = 93 years). Out of 685 patients, 339 were male (49.5%) and 346 were female (50.5%). Among the patients, 41 were smokers (6%). The mean duration of hospital stay in hospitalized patients was 6.87 ± 4.55 days (min = 0.8, max = 37 days). Also, 62 (9.1%) patients required mechanical ventilation, and 59 (8.6%) patients were expired. In Table 1, the measured laboratory parameters in confirmed patients were listed.

The effect of NLR modification on in-hospital outcomes and length of hospital stay

As shown in Table 2, the relationship between NLR on in-hospital prognosis (death or discharge) was evaluated in patients with COVID-19, considering the gender differences. In male patients, in both categories with high and low NLR, the mortality rate was higher in discharge outcome, and there were no significant differences between high and low NLR ($P > 0.05$).

Besides, the female patients with low NLR were expired, while in the group with high NLR, 89.3% of patients died, which also did not show a remarkable difference between the two groups. Notably, the mean duration of hospital stay in male and female patients with high NLR was statistically higher than in those with low NLR ($P = 0.01$, Table 2). Nevertheless, NLR can be considered a reliable prognostic tool, in part, for the length of hospital stay but not in-hospital implications.

Table 1. Baseline characteristics for included positive patients

Variables	Number	Percent
Gender	Gender	Gender
Male	339	49.5
Female	346	50.5
Smoker	41	6
	Mean ± SD	**Min-Max**
Age	47.96 ± 4.91	16-93
WBC	13428.33±7592.55	550-225000
Hb	13.73 ± 4.3	1.3-114
Plt	193237.52 ± 1756.44	7400-3030000
N	76.25 ± 11.04	39-95
Lymph	19.6 ± 10.7	3-108
ESR	38.44 ± 27.95	1-452
LDH	560.21 ± 267.11	43-3000
AST	45.30 ± 30.31	2-274
ALT	50.24 ± 39.3	11-362
Bilirubin	0.26 ± 0.13	0.1-1.1
Total Bilirubin	0.7 ± 0.3	0.3-2.4
Cr	6.87 ± 4.05	0.8-37

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; LDH, lactate dehydrogenase; Lymph, lymphocyte; N, Neutrophil; Plt, Platelet; WBC, white blood cell.

The effect of dynamic CRP on in-hospital outcomes and requiring MV prognosis

Based on the results from Fisher exact test analysis, among male and female patients, 9.4% and 11.3% of cases with positive CRP were expired, respectively. It is worth noting that the relationship between positive CRP and mortality rate in both genders was statistically significant ($P = 0.01$, Table 3). In the case of MV requiring, a large number of both male and female patients with positive CRP needed MV (P value = 0.01, Table 3).

A correlation between serum level of LDH with in-hospital outcomes and requiring MV

Further, we aimed to ascertain whether the dynamic LDH serum level is different between discharged and dead patients. According to the obtained results, the mean serum level of LDH in both male and female patients who died was considerably higher than in discharged patients (P value < 0.001, Table 4). Also, the mean and median serum level of LDH in both male and female patients who needed MV was significantly higher than those without MV (P value < 0.001, Table 4). In turn, it has been revealed that the serum level of LDH was positively correlated with the prognosis of the duration of hospital stay in both male and female patients with spearman r = 0.29 and 0.27, respectively, which also showed a statistically significant difference ($P < 0.001$).

Discussion

Given the importance of predicting COVID-19 severity in hospitalized patients, early diagnosis based on laboratory parameter assessment is of particular interest. In this sense, we designed a study to explore distinct inflammatory biomarkers along with NLR value and subsequently evaluated the possible potential on in-hospital prognosis, length of hospital stay, and MV requiring. Our findings showed that NLR is not a proper predictive value regarding the in-hospital outcomes due to not finding significant differences between the low and high NLR levels, which was not parallel with previous findings.[16-19] Of note, our results demonstrated that in dead patients and in patients who required the MV, a remarkably higher serum level of LDH and positive CRP were observed. Moreover, in the present study, it was revealed that the higher levels of LDH and NLR positively correlate with the length of hospital stay. Belice et al explored the NLR value in positive patients considering gender differences.[20] Interestingly, they found that NLR in male patients was significantly higher than that of female patients, leading to a higher mortality rate in males, particularly in advanced ages.[20] In contrast, we could not find any differences between the two genders in this regard.

In line with our purpose, Moorthy et al recently

Table 2. Relationship between NLR on in-hospital prognosis and length of hospital stay based on gender differences

	Variables	High NLR (>2)	Low NLR (<2)	*P* value
Gender				
Male	Death	262 (91.6%)	54 (96.4%)	0.09[a]
	Discharge	24 (8.4%)	2 (3.6%)	
Female	Death	276 (89.3%)	26 (100%)	0.27[a]
	Discharge	33 (10.7%)	0 (0%)	
Gender				
Male	Length of hospital stay	7.03 ± 4.15	5.4 ± 1.1	0.02[b]
	Median (Q1-Q3)	6 (5-7)	5 (5-6)	
Female	Length of hospital stay	7.05 ± 4.25	5.91 ± 3.04	0.02[b]
	Median (Q1-Q3)	6 (5-7)	5 (5-6)	

[a] Fisher Exact test, [b] Mann-Whitney test.

Table 3. Relationship between CRP on in-hospital prognosis and MV requiring based on gender differences

	Variables	Positive CRP	Negative CRP	*P* value[a]
Gender				
Male	Death	25 (9.4%)	1 (1.3%)	0.01
	Discharge	242 (90.6%)	78 (98.7%)	
Female	Death	33 (11.3%)	0 (0%)	0.01
	Discharge	260 (88.7%)	46 (100%)	
Gender				
Male	With MV	34 (11.6%)	0	0.01
	Without MV	259 (88.4%)	46 (100%)	
Female	With MV	27 (10.1%)	1 (1.3%)	0.01
	Without MV	240 (89.9%)	78 (98.7%)	

[a] Fisher Exact test.

Table 4. The correlation between serum level of LDH with in-hospital outcomes and MV requiring in COVID-19 patients

	Variables	Death	Discharge	*P* value[a]
Gender				
Male	Mean LDH serum level	959.42 ± 444.95	534.84 ± 221.63	< 0.001
	Median (Q1-Q3)	922 (621-1305.5)	500.5 (392.5-623.75)	
Female	Mean LDH serum level	907.35 ± 577.0	515.10 ± 176.332	< 0.001
	Median (Q1-Q3)	770.5 (568-893.5)	484.5 (396.5-610.25)	
	Variables	**With MV**	**Without MV**	***P* value**[a]
Gender				
Male	Mean LDH serum level	956.24 ± 438.551	533.80 ± 221.257	< 0.001
	Median (Q1-Q3)	919 (636-1290.25)	500 (392.5-621.5)	
Female	Mean LDH serum level	907.35 ± 577.00	515.10 ± 176.332	< 0.001
	Median (Q1-Q3)	785 (585.5-898.25)	484 (396.5-610)	

[a] Mann-Whitney test.

investigated the prognostic potential of inflammatory and liver biomarkers in COVID-19 patients.[21] Without considering the effect on in-hospital outcomes, requiring MV, and length of hospital stay, they reported that beyond the conventional dynamic changes of hematologic parameters, NLR, LDH, and CRP were remarkably elevated in positive patients. Moreover, the correlation between NLR, absolute lymphocyte count, CRP, LDH, and ferritin was evaluated on disease severity in hospitalized patients with COVID-19 in an Indonesian referral hospital.[22] Interestingly, beside a strong correlation between NLR and CRP (r = 0.738; $P < 0.001$), they found that NLR and absolute lymphocyte count, but not ferritin, play a role in discriminating between non-severe and severe COVID-19 cases.[22] Similarly, in a study conducted in India, it was indicated that the higher levels of ferritin and NLR could be clinical support tools, particularly in resource-limited settings and remote healthcare facilities, for both triage and early referral to identify vulnerable patients.[14,22]

Also, Liu et al, declared that NLR value is a critical predictor for assessment of COVID-19 severity, which in the severe patients was dramatically higher than that of the non-severe patients (10.4 vs 2.6; $P < 0.001$).[23] They further clarified that the NLR value was positively correlated with the CRP ($R = 0.5921$, $P < 0.001$), LDH ($R = .4509$, $P < 0.001$), procalcitonin ($R = 0.5504$, $P < 0.001$), fibrinogen ($R = 0.4710$, $P < 0.001$), D-dimers ($R = 0.4425$, $P < 0.001$), and interleukin-6 value ($R = 0.3594$, $P < 0.05$) [23]. In another study, using multivariate logistic regression, it was shown that anemia (3.6, 1.8–7.0, 95% CI), high NLR > 8 (9.0, 3.6–22.6, 95% CI), high platelet-to-lymphocyte ratio > 192 (3.0, 1.3–7.1, 95% CI), and high d-dimer levels > 0.9 mg/L (2.5, 1.3–4.7, 95% CI) were appeared to be simply available predictors at the time of admission to determine disease severity for requiring ICU admission.[24] In a retrospective cohort study, the prognostic potential of the combined utility of NLR and CRP to identify 7 day- disease severity was also evaluated in 86 inpatients with pneumonia in China.[19] The results discovered that the constructed nomogram model and combined index calculated for both values are clinically potential and reliable predictors of COVID-19 prognosis, which can triage patients at the time of admission.[19]

Recently, in Italy, using multivariate logistic regression analysis, it was established that NLR can be a potential predictive factor regarding disease progression into a critical outcome and in-hospital mortality ($P = 0.03$).[10]

Eid et al also designed a study to evaluate NLR sensitivity and specificity on COVID-19 severity based on age stratification. The results of study revealed that in the patients aged > 50 years and NLR ≥ 3.10, the sensitivity and specificity were 95.24% and 92.86%, respectively, for anticipating the need for admission at ICU. While in patients with age less than 50 years, and NLR ≥ 4.21, the sensitivity and specificity were estimated 70.3% and 93.7%, respectively.[25]

Conclusion

Our results highlighted a strong association between distinct laboratory values with COVID-19 severity and subsequent clinical outcomes. Further, it was proved that NLR, CRP, and LDH may be critical and easy-to-use predictors, particularly for diagnosis in the early stages of the disease. Consequently, close monitoring of prognostic and diagnostic laboratory biomarkers can be imperative in managing hospitalized patients to avoid preventable mortality.

Authors' Contribution
Conceptualization: Yousef Roosta.
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Software: Amanj Nabavi.
Supervision: Yousef Roosta.
Validation: Farhad Behzadi.

Study Highlights

What is current knowledge?

- The laboratory parameters have prognostic and diagnostic potential in various Infectious and non-Infectious diseases.

What is new here?

- The high levels of NLR, CRP, and LDH can be considered with prognostic values in the setting of COVID-19 severity.

Visualization: Rahim Nejadrahim.
Writing–original draft: Yousef Roosta.
Writing–review & editing: Yousef Roosta, Farhad Behzadi.

Competing Interests
All authors declared that they have no conflict of interests.

Consent for Publication
Not applicable.

Data Availability Statement
All data generated or analyzed during this study are included in this published article.

Ethical Approval
The ethical approval for this study was issued from the Urmia University of Medical Sciences with Ethics Committee Number: IR.UMSU.REC.1400.073. Given that the current study was designed as a retrospective study, the informed consent form was not applicable. It should be also noted that the information of all patients' files was confidential and identified by a specified code number.

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