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A New Predictor of Mortality in COVID-19 Pneumonia: The BUN/Lymphocyte Ratio

COVID-19 Pnömonisinde Yeni Bir Mortalite Öngördürücüsü: BUN/Lenfosit Oranı

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ABSTRACT

Objective: The high mortality and transmission rates of Coronavirus disease-2019 (COVID-19) lead to severe difficulties being experienced in emergency department management. This study investigated whether the blood urea nitrogen/lymphocyte ratio (BLR) and neutrophil/albumin ratio (NAR) can predict mortality in COVID-19 patients in the emergency department.

Methods: Four hundred sixty-one COVID-19 patients presenting to the emergency department between March 2020 and January 2022 were included in the study. Patients' demographic characteristics and laboratory parameters and outcomes were recorded. The power of the data in predicting mortality was calculated and compared with the Pneumonia Severity Index (PSI) and CURB-65.

Results: Women constituted 277 (60.1%) patients in the study, and men 184 (39.9%). The patients' median age was 69 (interquartile range: 20). In-hospital mortality was determined at 30.5%. ROC analysis was performed to determine the ability of the PSI, CURB-65, the NAR, and BLR to predict mortality in patients with COVID-19. The BLR was found to exhibit a better performance than PSI, CURB-65, and NAR values, and to be capable of use in differentiating mortality with 64.5% sensitivity and 62.8% specificity ($p<0.05$). The BLR also exhibited a high negative predictive value (80.08%) in the diagnosis of sepsis. A negative BLR value emerged as a powerful independent variable in excluding sepsis and predicting low mortality rates.

Conclusion: The BLR was the most accurate predictor of COVID-19 pneumonia-related critical care requirements in this study. It is also a reliable predictor with a powerful negative predictive value for the planned discharges from the emergency department.

Keywords: COVID-19, pneumonia, mortality, predictor

ÖZ

Amaç: Koronavirüs hastalığı-2019'un (COVID-19) yüksek ölüm ve yayılma oranı nedeniyle, acil servis yönetiminde ciddi zorluklar yaşanmaktadır. Biz bu nedenle acil servisteki COVID-19 hastalarında kan üre nitrojeni/lenfosit oranının (BLR) ve nötrofil/albümin oranının (NAR) mortaliteyi tahmin edip etmediğini araştırdık.

Yöntem: Mart 2020-Ocak 2022 tarihleri arasında acil servise başvuran toplam 461 COVID-19 hastası çalışmaya dahil edildi. Hastaların demografik özellikleri ve laboratuvar parametreleri ve sonlanımları kaydedildi. Verilerin mortaliteyi ön görmedeki gücü hesaplanarak Pnömoni Şiddet İndeksi 'Pneumonia Severity Index' (PSI) ve CURB-65 ile karşılaştırıldı.

Bulgular: Çalışmaya alınan hastaların 277'si (%60,1) kadın ve 184'ü (%39,9) erkekti. Hastaların medyan yaşı 69 (çeyrekler arası aralık: 20) olarak hesaplandı. Hastane içi mortalite mevcuttu ve oranı %30,5 idi. PSI, CURB-65, NAR ve BLR'nin COVID-19'lu hastalarda mortaliteyi öngörme yeteneğini değerlendirmek için yapılan ROC analizinde BLR'nin; PSI, CURB-65, NAR değerlerinden daha iyi bir performans gösterdiği ve mortaliteyi ayırt etme gücünün %64,5 duyarlılık; %62,8 seçicilikle kullanılabilir olduğu hesaplandı

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(p<0,05). Bununla beraber, BLR, sepsis tanısında, yüksek bir negatif prediktif değere (%80,08) sahipti. Sepsisin dışlanması ve düşük mortalite oranlarının belirlenmesinde negatif yönlü bir BLR sonucunun oldukça güçlü bir bağımsız değişken olduğu belirlendi.

Sonuç: Çalışmamızda BLR, COVID-19 pnömonisine bağlı kritik bakım ihtiyacının en doğru tahmincisi olarak görünmektedir. Ek olarak, BLR'nin güçlü negatif prediktif değeri acil servislerden planlanan taburculukların da güvenilir bir öngörücüsüdür.

Anahtar Kelimeler: COVID-19, pnömoni, mortalite, prediktör

INTRODUCTION

The Coronavirus disease-2019 (COVID-19) pandemic has taken the world by storm in a short time. Studies showed hospitalization rates of 14% due to the viral pandemic, intensive care admission rates of 2-5%, and mortality rates of 2.3-5%.[1,2]

Emergency departments are the health units to which the great majority of patients first present. High patient numbers and prolonged care times also result in various uncertainties in the functioning of emergency departments. Therefore, there is a need for biomarkers that can accurately predict the severity of COVID-19, allow rapid patient triage and can be easily calculated in the emergency room.

Low levels of albumin are directly associated with mortality independently of the underlying disease.[3] Studies have shown longer hospital stays and higher mortality rates in patients with low albumin levels during a presentation to the emergency department.[4] Blood urea nitrogen (BUN) levels have also been shown to be closely associated with mortality.[5] BUN is one of the nitrogenous metabolism end-products. Studies have shown that an early decrease in lymphocytes, the most common immune cellular elements in the peripheral circulation, is directly associated with the severity of lymphopenia and sepsis.[6,7] The ratios between these and similar markers also exhibit powerful correlation with disease severity or selectivity. The neutrophil/albumin ratio (NAR) is employed as a prognostic marker in patients with pancreatic cancer receiving palliative care and in patients with rectal cancer.[8,9] The NAR has also been described as a marker of mortality in patients with COVID-19.[10]

This study examined the BUN/lymphocyte ratio (BLR) and investigated its effectiveness in predicting disease severity and mortality. To determine its correlation with disease, we also compared it against CURB-65, Pneumonia Severity Index (PSI) and the NAR. The results showed a powerful correlation between the BLR and disease severity and mortality. To the best of our knowledge, this is the first study to evaluate the BLR in this context.

METHODS

Study Design

This retrospective observational study was performed in the emergency department of a tertiary university hospital in Turkey between March-2020 and January-2022. The demographic characteristics and laboratory parameters of patients definitely diagnosed with COVID-19 were subjected to analysis. The power of the data in predicting mortality was calculated and compared with PSI and CURB-65.

Patients and Setting

Patients aged over 18 with positive polymerase chain reaction test results and with COVID-19 pneumonia confirmed by computed tomography were included in the study. Patients with medical histories of end-stage kidney failure or chronic liver diseases, severe pulmonary edema, active lung tumor or malignancy, immunosuppressive patients, and patients leaving the hospital before the conclusion of treatment were excluded from the study.

Data Collection

Data for the patients included in the study were retrieved from the hospital information system, Patients' vital parameters, demographic data, and laboratory test results were recorded on to patient forms for statistical analysis. Exitus and discharge were noted for patients admitted to the COVID-19 and intensive care units. BLR and NAR values and PSI and CURB-65 scores were calculated and compared to determine their value in predicting mortality.

Statistical Analysis

Mean±standard deviation and median (25% and 75% quartiles), percentage and frequency values were calculated for the study variables. Normality assumptions were evaluated using the Shapiro-Wilk test. Student's t-test was applied to evaluate differences between the two groups were parametric test conditions were met, and the Mann-Whitney U test when those conditions were not met.

The categorical variable in mortality was evaluated using logistic regression analysis.

Cut-off points were evaluated using ROC analysis. The area under the curve (AUC) values, sensitivity, and specificity values were calculated.

P values <0.05 and p<0.001, as appropriate, were regarded as statistically significant.

RESULTS

A total of 1281 patients were identified, 461 of whom met the inclusion criteria and were included in the analysis (Figure 1).

Women constituted 277 (60.1%) patients and men 184 (39.9%). The median age of the patients was 69 (interquartile range: 20), and the in-hospital mortality rate was 30.5%.

Increased BUN, albumin, and neutrophil values were associated with mortality ($p<0.001$), whereas no association was observed between lymphocyte values alone and mortality ($p=0.051$). The patients' clinical characteristics are shown in Table 1.

ROC analysis was applied to determine the ability of the PSI, CURB-65, NAR, and BLR to predict mortality in patients with COVID-19 (Figure 2). AUC for PSI was 0.634, and the cut-off value 110. The corresponding values are 0.600 and 1.5 for CURB-65 and 0.632 and 0.21 for NAR. An AUC value of 0.666 was calculated for BLR, while sensitivity and specificity cut-off values were balanced at 23. The AUC value for the BLR exhibited a better performance than the PSI, CURB-65, and NAR values and exhibited 64.5% sensitivity and 62.8% specificity in differentiating mortality ($p<0.05$). The BLR also exhibited a high negative predictive value in the diagnosis of sepsis (80.08%). These results showed that a negative BLR result is a compelling independent variable in excluding sepsis and determining low mortality rates in clinical practice.

The scoring systems' cut-off values and ability to differentiate mortality were compared (Table 2). Mortality rates were 67.4% in case of PSI ≥110 and 63.8% for CURB-65. The mortality rate was 60.1% when the NAR was calculated at ≥0.21 and 64.5% when the BLR was ≥23. The power of BLR to predict disease severity and mortality was similar to those of the other parameters employed ($p<0.001$).

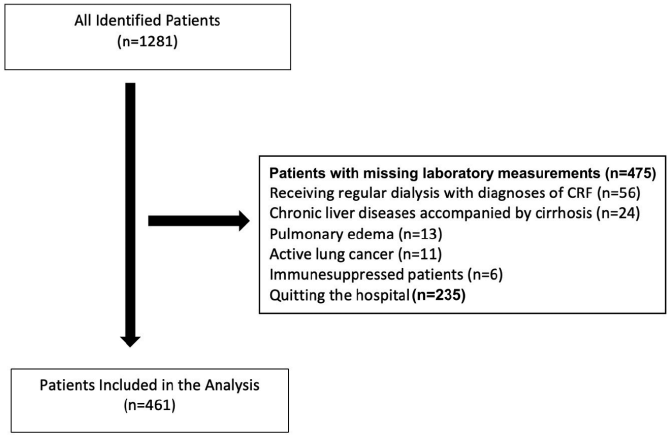


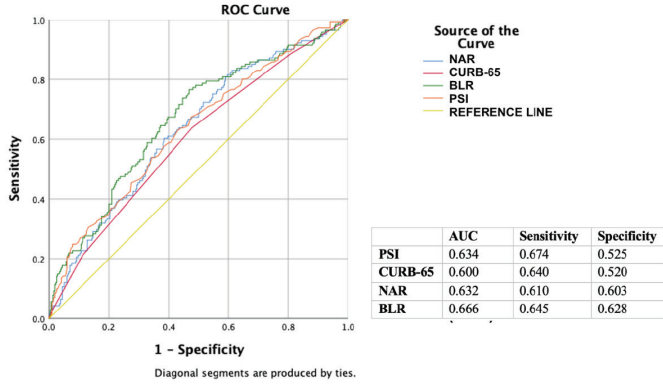
Figure 1. Consult diagram

Odds ratios of 2.283 for PSI, 1.926 for CURB-65, 2.256 for NAR, 3.074 for BLR, 0.975 for BUN, 1.065 for albumin, and 0.941 for neutrophil count were calculated at single variable logistic regression analysis for mortality. Regression analysis revealed that the change in BLR values for each standard deviation is more significant in terms of mortality compared to other markers (Table 3).

DISCUSSION

COVID-19 pneumosepsis has had a devastating effect on the health system. Parameters indicative of sepsis were particularly valuable in patient selection for the effective use of limited hospital resources. Studies therefore investigated several parameters showing inflammation. Although several studies have been published in scientific journals showing that various parameters can identify critically ill patients, the results were insufficient in emergency practice. This study investigated the parameters showing sepsis using a reliable and practical method. Variables indicative of inflammation and inflammatory response parameters were subjected to analysis. The severity of sepsis and high BUN levels and lymphopenia as markers of end-organ damage were examined. We also investigated the power of the ratios between them to predict mortality. The BLR was compared with traditional markers in the literature such as CURB-65, PSI, and the BUN/albumin ratio, yielding important findings.

The fact that traditional scores such as PSI and CURB-65 are insufficient in clinical practice led to a significant increase in the search for alternative algorithms during the pandemic. Anurag and Preetam[1] applied the severe community-acquired pneumonia in one study of COVID-19 and reported a powerful correlation with mortality compared to traditional scoring systems.



	AUC	Sensitivity	Specificity
PSI	0.634	0.674	0.525
CURB-65	0.600	0.640	0.520
NAR	0.632	0.610	0.603
BLR	0.666	0.645	0.628

Figure 2. ROC analysis

PSI: Pneumonia Severity Index, BLR: Blood lymphocyte ratio, NAR: Neutrophil/albumin ratio, AUC: Area under the curve

Table 1. Distributions of patients' vital and laboratory data according to mortality and ıntensive care requirements

	Mortality [median (IQR)]				Intensive care requirement [median (IQR)]			
	No	**Yes**	**Total**	**p***	**No**	**Yes**	**Total**	**p***
Age	69 (21)	69 (19)	69 (20)	0.447	69 (20)	69 (18)	69 (20)	0.682
RR	17.5 (5)	18 (7)	18 (6)	0.107	18 (6)	18 (8)	18 (6)	0.947
SBP	130 (20)	130 (30)	130 (20)	0.306	130 (20)	130 (27)	130 (20)	0.410
DBP	77 (12)	71 (10)	76 (11)	0.475	76 (10)	75 (18)	76 (11)	0.803
Body temperature	36.6 (1)	36.6 (1)	36.6 (1)	0.495	36.6 (1)	36.6 (1)	36.6 (1)	0.397
Heart rate	84 (17)	85 (27)	84 (20)	0.810	84 (18)	87 (27)	84 (20)	0.784
SPO_2	95 (4)	94 (7)	95 (5)	**0.022**	95 (5)	94 (7)	95 (5)	0.166
PaO_2	80.2 (19.10)	78 (23.50)	80 (20.8)	0.200	80.20 (22)	78 (25)	80 (20.8)	0.282
pH	7.40 (0.8)	7.39 (0.13)	7.40 (0.1)	**0.028**	7.40 (0.09)	7.40 (0.1)	7.40 (0.1)	0.183
Lactate	1.7 (1.1)	1.6 (1.2)	1.7 (1.1)	0.517	1.70 (1.10)	1.60 (1.20)	1.7 (1.1)	0.338
BUN	22 (19)	32 (40.5)	24 (20)	**<0.001**	23 (18)	28 (28)	24 (20)	**0.021**
Albumin	34 (8)	32 (10)	34 (8.5)	**<0.001**	34 (9)	34 (10)	34 (8.5)	0.448
Creatinine	1.08 (0.61)	1.32 (1.62)	1.13 (0.75)	**<0.001**	1.12 (0.70)	1.22 (1.27)	1.13 (0.75)	0.17
Neutrophil	5.83 (5.73)	7.56 (6.06)	6.3 (6.14)	**<0.001**	6.29 (6.07)	6.90 (6.20)	6.3 (6.14)	0.243
Lymphocyte	1.31 (0.92)	1.15 (0.90)	1.26 (0.86)	0.051	1.23 (0.88)	1.33 (0.90)	1.26 (0.86)	0.439
CRP	53.50 (110.42)	91.87 (135.58)	65.14 (117.27)	**0.007**	62.26 (115.81)	71.75 (124.63)	65.14 (117.27)	0.960

*Student's t-test, Mann-Whitney U test.

RR: Respiration rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SPO_2: Oxygen saturation, PaO_2: Partial oxygen pressure, BUN: Blood urea nitrogen, CRP: C-reactive protein, IQR: Interquartile range

Table 2. Correlations between scoring systems and mortality

		Mortality		p
		No	**Yes**	
PSI	**<110**	168 (52.5%)	46 (32.6%)	**<0.001**
	≥110	152 (47.5%)	95 (67.4%)	
	Total	320 (100%)	141 (100%)	
CURB-65	**<1.5**	167 (52.2%)	51 (36.2%)	**0.002**
	≥1.5	153 (47.8%)	90 (63.8%)	
	Total	320 (100%)	141 (100%)	
Neutrophil/albumin	**<0.21**	189 (59.1%)	55 (39.0%)	**<0.001**
	≥0.21	131 (40.9%)	86 (61.0%)	
	Total	320 (100%)	141 (100%)	
BUN/lymphocyte	**<23**	201 (62.8%)	50 (35.5%)	**<0.001**
	≥23	119 (37.2%)	91 (64.5%)	
	Total	320 (100%)	141 (100%)	

PSI: Pneumonia Severity Index, BUN: Blood urea nitrogen

Neutrophils and lymphocytes are chemotactic agents of the immune system and important inflammatory markers. Blood levels indicate the strength of the host defense against pathogenic micro-organisms and the effectiveness of the immune system.[2] Neutrophil and lymphocyte elevation, particularly in the early period, are associated with the severity of sepsis.[3,4] However, a negative correlation is observed in exacerbated sepsis and shock.[5] Studies of COVID-19 pneumonia have also noted this negative correlation. Eastin et al.[11] reported lymphopenia in 83.2% of the 1099 patients in their study. However, Vincent et al.[12] reported that lymphopenia in patients hospitalized due to COVID-19 infection is proportional to the severity of the disease. Our clinical

Table 3. Logistic regression analysis for mortality prediction					
	B	p	OR	95% CI for OR	
				Lower	Upper
PSI	0.825	0.000	2.283	1.508	3.456
CURB-65	0.656	0.002	1.926	1.281	2.895
Neutrophil/albumin	0.814	0.000	2.256	1.504	3.383
BUN/lymphocyte	1.123	0.000	3.074	2.034	4.645
BUN	-0.025	0.000	0.975	0.967	0.983
Albumin	0.063	0.000	1.065	1.032	1.100
Neutrophil	-0.061	0.001	0.941	0.908	0.975
PSI: Pneumonia Severity Index, BUN: Blood urea nitrogen, CI: Confidence interval, OR: Odds ratio					

observations in this study showed that the lymphocyte count was negatively correlated with disease severity and mortality (p=0.051).

A decrease in albumin levels is an important risk factor for mortality independently of the underlying disease.[13] In their multi-center study, Violi et al.[13] reported that low albumin levels were associated with mortality in COVID-19 sepsis. Li et al.[14] described a persistent decrease in albumin levels as an important marker in identifying critical patients. Similarly, in this study, mean albumin levels were significantly lower in the exitus group compared with the discharged patients (p<0.001). In another study of COVID-19, Varim et al.[15] investigated the relationship between increased neutrophil and decreased albumin values and mortality and described the NAR as an independent predictor of mortality. Our results are consistent with these finding.

Previous recent studies have associated BUN elevation with poor prognosis in patients diagnosed with pneumonia.[8,9] Shen et al.[3] reported that an increase in BUN levels in COVID-19 sepsis was correlated with end organ damage, septic shock, and severity of the disease. Liu et al.[10] determined a positive correlation between the BUN-creatinine ratio and mortality in COVID-19 and emphasized that increased BUN levels were directly associated with mortality. Similarly, in this research, persistent impairment in BUN levels was associated with the likelihood of mortality and showed the severity of the disease (p<0.001).

This study analyzed the relationship between the BUN-lymphocyte and NARs, with mortality and disease severity. Both variables emerged as important determinants of mortality. We found that the BLR in particular can provide effective prediction of mortality in patients infected with COVID-19. Additionally, considering the powerful negative predictive value of the BLR, we obtained a strong score permitting the identification of non-critical patients in the emergency department. Due to the negative correlation between BUN and lymphocyte values, the BLR emerged as a reliable and easily calculated biomarker. Regression analysis showed that the BLR is of greater value in predicting disease severity than the NAR, PSI, and CURB-65.

Study Limitations

The principle limitation of this study lies in its single-center and retrospective design. Patient data were recorded on the basis of their initial presentations. However, these dynamic parameters will probably fluctuate depending on the severity of the disease and response to treatment. Although the results are reliable, multicenter studies with larger samples are needed to generalize the results.

CONCLUSION

Compared to the NAR, CURB-65, and PSI scores, the BLR appears to be the most accurate predictor of COVID-19 pneumonia-related intensive care requirement and mortality. Additionally, the powerful negative predictive value of BLR is also a reliable predictor of planned discharge from the emergency department. This research is a pioneering study as the first to investigate the BLR in COVID-19 patients and to compare the NAR with CURB-65 and PSI in predicting in-hospital mortality.

Ethics

Ethics Committee Approval: The study was approved by the İzmir Kâtip Çelebi University of Local Ethics Committee (decision no: 0411, date: 22.09.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.G.E., Design: O.S.Ç., Data Collection or Processing: O.S.Ç., M.G.E., U.P., Analysis or Interpretation: U.P., Literature Search: O.S.Ç., M.G.E., Writing: O.S.Ç.

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

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