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The Role of the Lactate/Albumin Ratio in Predicting Mortality in COVID-19 Patients in The Emergency Department

Acil Serviste Covid-19 Hastalarının Mortalite Tahmininde Laktat/Albumin Oranının Önemi

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ÖZET

Amaç: Koronavirüs hastalığı 2019 (COVİD-19) 'un yüksek mortalite oranı ve yetersiz yatak kapasitesi acil servis yönetiminde zorluklar yaşatmaktadır. Bu nedenle, bu çalışma laktat/albümin oranının (LAR) acil servisteki COVID-19 hastalarında mortaliteyi tahmin edip etmediğini araştırdı.
Yöntemler: Çalışmaya Mart-Ağustos 2020 tarihleri arasında acil servise getirilen 504 COVID-19 hastası dahil edildi. Hastaların laktat ve albümin düzeyleri, LAR, yaş, cinsiyet ve hastane içi mortalite durumları kaydedildi. Hastalar hastane içi mortalitesine göre gruplandırıldı ve gruplar arasında istatistiksel bir karşılaştırma yapıldı.
Bulgular: Dahil edilen hastaların 252'si (%50) erkekti ve ortanca yaş 61,5(47-72,75) idi. 79 (%15,7) hastada hastane içi mortalite görüldü. Hayatta kalmayan gruptaki hastaların medyan laktat ve LAR değerleri, hayatta kalan gruba göre anlamlı derecede yüksekti (laktat: 2.05 [1.5–3.4] ve 1.6 [1.2–2], sırasıyla [p<0.001]; LAR: 0,584 [0,406–0,956] ve 0,38 [0,29 0,489], sırasıyla [p<0,001]). Ortalama albumin değeri hayatta kalmayan grupta, hayatta kalan gruba göre anlamlı olarak düşüktü (3,68±0,58 ve 4,19±0,48, sırasıyla; p<0,001). Hastane içi COVID-19 mortalitesini tahmin etmek için elde edilen LAR'ın eğri altındaki alan (EAA) değerleri, laktat için olanlardan daha yüksekti (LAR ve laktatın EAA'sı: sırasıyla 0.730 ve 0.669). LAR'ın EAA değeri laktatın EAA değerinden anlamlı olarak yüksekti (p<0.001).
Sonuç: LAR, COVID-19 hastalarında hastane içi mortalitenin orta derecede doğru bir tahmincisidir ve LAR'ın laktat seviyelerinden daha güvenilir bir tahmin edici olduğu bulunmuştur.

Anahtar Kelimeler: COVID-19, Laktat, Serum Albumin, Hastane içi mortalite

ABSTRACT

Objectives: The high mortality rate of coronavirus disease 2019 (COVID-19) and insufficient bed capacity create significant challenges in emergency department management. Therefore, this study investigated whether the lactate/albumin ratio (LAR) predicts mortality in COVID-19 patients in the emergency department.
Methods: The study included 504 COVID-19 patients who were brought to the emergency department from March to August 2020. Their lactate and albumin levels, LAR, age, gender, and in-hospital mortality status were recorded. The patients were grouped by in-hospital mortality, and a statistical comparison was conducted between the groups.
Results: Of the included patients, 252(50%) were male, and the median age was 61.5(47–72.75) years. There was in-hospital mortality in 79(15.7%) patients. The median lactate and LAR values of the patients in the non-survivor group were significantly higher than those in the survivor group (lactate: 2.05 [1.5–3.4] and 1.6 [1.2–2], respectively [p<0.001]; LAR: 0.584 [0.406–0.956] and 0.38 [0.29–0.489], respectively [p<0.001]). The mean albumin value in the non-survivor group was significantly lower than that in the survivor group (3.68±0.58 and 4.19±0.48, respectively; p<0.001). The LAR area-under-the-curve (AUC) values obtained to predict in-hospital COVID-19 mortality were higher than those for lactate (AUC of LAR and lactate: 0.730 and 0.669, respectively). The AUC value of LAR was significantly higher than the AUC value of lactate (p<0.001).
Conclusion: LAR is a moderately accurate predictor of in-hospital mortality in COVID-19 patients, and LAR was found to be a more reliable predictor than lactate levels.

Key words: COVID-19, lactate, serum albumin, in-hospital mortality

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) appeared in Wuhan, China, in December 2019. It was classified by the World Health Organization (WHO) as a pandemic due to its unpredictable spread throughout the world. Mortality rates of approximately 30% have been recorded in hospitalized cases (1), and due to the excessively high rates of emergency service admission, there has been insufficient bed capacity (2). Therefore, there is a need to identify biomarkers that can be used to predict disease mortality to facilitate emergency department management. It is thought that hypoxia resulting from COVID-19 will cause an increase in lactate levels (3). In the literature, there are studies reporting that lactate levels increase in COVID-19 patients with mortality (4). Albumin is a blood protein and negative acute phase reactant (5) that is used to assess malnutrition (6). Studies have been published that report decreased albumin levels in COVID-19 patients with mortality (7).

Other studies report the use of the lactate to albumin ratio (LAR) to predict the mortality of septic patients who have been admitted to the emergency department (8), the mortality of patients with severe sepsis and septic shock (9), the prognosis of out-of-hospital cardiac arrest (10), and the mortality of critically ill patients (11). However, there are few large-scale studies in the literature predicting COVID-19 mortality using LAR. Therefore, this study investigated the potential of lactate and albumin levels and the LAR as predictors of in-hospital mortality of COVID-19. In addition, the study examined whether the LAR would be a more accurate predictor than the lactate level.

METHODS

Ethics committee approval was obtained from the local committee for this single-center, retrospective, and observational study. This study was carried out in a tertiary university hospital. Patients who were admitted to the emergency department, suspected of having COVID-19, and hospitalized and whose PCR test was positive were included in the study from March to August 2020. Regardless of the number of tests submitted, any PCR result that appeared positive at least once was considered positive, while other results were considered negative. Patients who were discharged against medical advice and referred to other hospitals were excluded from the study.

The following pieces of patient data were recorded from the patients' e-files using the Hospital Information Management Systems program: lactate level; albumin level; his/her complaint (fever, cough, shortness of breath); vital signs; comorbidities; information about their ward/ICU admission; hospital outcome (discharge, exitus in-hospital); and in-hospital mortality status. The LAR was obtained by dividing the lactate level by the albumin level. Patients were grouped as survivor or non-survivor according to the in-hospital mortality. The primary outcomes of the study were the prediction of in-hospital mortality using lactate and albumin levels and the LAR and the determination of whether the LAR was a more accurate predictor than the lactate and albumin levels.

Statistical analyses of the recorded data were made with the SPSS 20.0 package program (SPSS Inc., Chicago, IL). Normality analyses of the data were made using histograms and the Kolmogorov-Smirnov test. Non-normally distributed quantitative data were expressed as median (25%–75% quartiles), while normally distributed quantitative data were expressed as mean±standard deviation, and categorical variables as frequency (percentage). Differences between groups were investigated using the Mann-Whitney U-test for the non-normally distributed quantitative variables and the Student's t-test for the normally distributed quantitative variables. Intragroup comparisons of categorical variables were made using the Chi-square test and Fischer's exact test. Receiver operating characteristic (ROC) analysis was performed to determine the power of the levels of lactate and albumin and the LAR for use in in-hospital mortality decisions. The optimum cut-off levels of biochemical parameters were determined by using Youden's index (sensitivity + 1−specificity). The sensitivity, specificity, positive predictive value, and negative predictive value of parameters were calculated for those optimum cut-off levels. Area under curve (AUC) levels were used to compare the mortality predictive power of the LAR to the mortality predictive power of lactate and albumin levels. A scale was used to interpret the AUCs. An AUC >0.9 indicated high accuracy, an AUC of 0.7–0.9 indicated moderate accuracy, and an AUC of 0.5–0.7 indicated low accuracy (12). When $p<0.05$, the result was considered statistically significant.

RESULTS

Between March and August 2020, 517 patients who were hospitalized from the emergency department with suspected COVID-19 had a positive PCR test. Of the 517 patients, 5 were excluded from the study because they were discharged against medical advice, and 8 were excluded because they were referred to another hospital. The remaining 504 patients were included in the study. Of the 504 patients who were included in the study, 252(50%) were male, the median age was 61.5(47–72.75) years, and the median length of hospital stay was 8(5–13) days. The median lactate value was 1.7(1.3–2.2) mEq/L. The mean albumin value was 4.11±0.53 g/dl. The median LAR value was 0.396(0.299–0.530). At least one comorbidity was detected in the medical history of 327 patients (64.9%), while the most common comorbidity was

Table 1. Features of Participants

Number of Participants		504(100%)
Age		61.5(47–72.75)
Gender	Male	252(50%)
	Female	252(50%)
Vital Signs	Temperature (°C)	36.6(36.2–37)
	Pulse (beats per minute)	93.23±16.4
	Systolic Blood Pressure (mmHg)	132.48±22.37
	Diastolic Blood Pressure (mmHg)	74.94±11.67
	MAP (mmHg)	94.1±13.47
	Saturation (%)	94(91–96)
Complaints	Fever	273(54.2%)
	Cough	287(56.9%)
	Shortness of Breath	232(46%)
Laboratory Results	Lactate (mEq/L)	1.7(1.3–2.2)
	Albumin (g/dl)	4.11±0.53
	LAR	0.396(0.299–0.530)
Medical History	Comorbidity*	327(64.9%)
	Hypertension	175(34.7%)
	Diabetes Mellitus	131(26%)
	Asthma-COPD	85(16.9%)
	Cardiovascular Disease	82(16.3%)
	Malignancy	44(8.7%)
	CRF	22(4.4%)
	Cerebrovascular Disease	10(2%)
Length of Hospital Stay (Days)		8(5–13)
Emergency Service Outcome	Ward Unit	401(79.6%)
	ICU	103(20.4%)
Hospital Outcome	Discharged	425(84.3%)
	Exitus	79(15.7%)
In-Hospital Mortality	Survivor	425(84.3%)
	Non-survivor	79(15.7%)

COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, MAP: mean arterial pressure, ICU: intensive care unit
* Having at least one additional disease in his / her medical history

hypertension, which was found in 175 patients (34.7%). A total of 401 patients (79.6%) were hospitalized in the ward unit, and 103(20.4%) were admitted to the ICU. In-hospital mortality was observed in 79 patients (15.7%) and not observed in 425 patients (84.3%). Table 1 shows the detailed data of the cases.

The median lactate value of the patients in the non-survivor group was statistically significantly higher than that of patients in the survivor group (non-survivor:2.05 [1.5–3.4]mEq/L, survivor:1.6 [1.2–2]mEq/L, p<0.001). The mean albumin value of the patients in the non-survivor group was statistically significantly lower than that of patients in the survivor group (non-survivor:3.68±0.58 g/dl, survivor:4.19±0.48 g/dl, p<0.001). The median LAR value of the patients in the non-survivor group was statistically significantly higher than that of the patients in the survivor group (non-survivor:0.38 [0.29–0.489], survivor:0.584 [0.406–0.956], p<0.001). Table 2 shows the detailed intragroup comparisons by in-hospital mortality.

ROC analysis was conducted to estimate the potential of using lactate and albumin levels and the LAR to predict in-hospital mortality. The AUC value of lactate was 0.669(0.598–0.739) (Figure 1). The AUC value of albumin was 0.767(0.715–0.819) (Figure 1). The AUC value of the LAR was 0.730(0.663–0.797) (Figure 1). While the AUC values of the

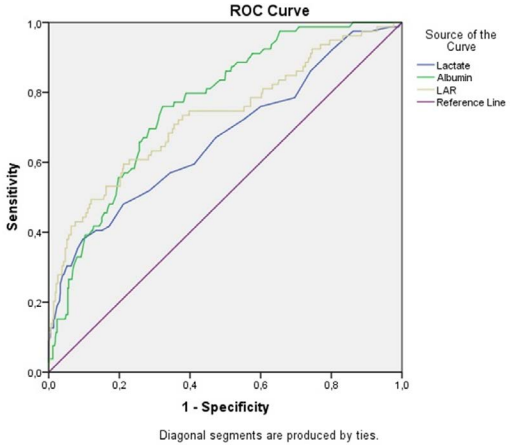

Figure 1. ROC Curve by In-Hospital Mortality

Table 2. Evaluation of Participants by In-Hospital Mortality

		Non-survivor(79)	Survivor(425)	p value
Age		76(66–83)	59(45–70)	<0.001
Temperature (°C)		36.7(36.3–37.02)	36.6(36.1–37)	0.026
Pulse (per minute)		93.26±19.6	93.22±15.76	0.988
SBP (mmHg)		131.88±28.58	132.59±21.06	0.836
DBP (mmHg)		70.97±13.02	75.66±11.27	0.004
MAP (mmHg)		90.95±16.56	94.67±12.77	0.064
Saturation (%)		89(80–93)	94(92–96)	<0.001
Lactate (mEq/L)		2.05(1.5–3.4)	1.6(1.2–2)	<0.001
Albumin (g/dl)		3.68±0.58	4.19±0.48	<0.001
LAR		0.584(0.406–0.956)	0.38(0.29–0.489)	<0.001
Length of hospital stay (Days)		15(10–23.25)	7(5–12)	<0.001
Gender	Male	49(62%)	203(47.8%)	0.020
	Female	30(38%)	222(52.2%)	
Fever		36(45.6%)	237(55.8%)	0.095
Cough		44(55.7%)	243(57.2%)	0.807
Shortness of Breath		55(69.6%)	177(41.6%)	<0.001
Comorbidity*		68(86.1%)	259(60.9%)	<0.001
Hypertension		42(53.2%)	133(31.3%)	<0.001
Diabetes Mellitus		24(30.4%)	107(25.2%)	0.333
Asthma-COPD		13(16.5%)	72(16.9%)	0.916
Cardiovascular Disease		17(21.5%)	65(15.3%)	0.169
Malignancy		11(13.9%)	33(7.8%)	0.075
CRF		9(11.4%)	13(3.1%)	0.001
Cerebrovascular Disease		4(5.1%)	6(1.4%)	0.056

COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, MAP: mean arterial pressure
* Having at least one additional disease in his / her medical history

LAR and albumin were statistically significantly higher than the AUC value of lactate (LAR-lactate, p<0.001; albumin-lactate, p=0.012), no statistically significant difference was found between the AUC values of albumin and the LAR (p=0.258). Detailed results of the ROC analysis are given in Table 3.

DISCUSSION

The aim of this study was to predict in-hospital mortality of COVID-19 using lactate and albumin levels and the LAR. The results showed that albumin and LAR levels are moderately accurate predictors of in-hospital mortality in COVID-19 patients, and that lactate levels predict in-hospital mortality in COVID-19 patients with low accuracy. In addition, while the LAR and albumin levels were found to be more valuable in predicting in-hospital mortality of COVID-19 than lactate levels, no statistically significant difference was found between the mortality predictive potential of the LAR and albumin levels, using AUC values.

In this study, lactate levels were higher in the non-survivor group. Also, lactate levels reached an AUC value of 0.669 according to the ROC analysis that was performed to predict in-hospital mortality, and lactate levels were found to have low accuracy in predicting in-hospital mortality. In the study conducted by Vassiliou et al. (13) with 45 patients with COVID-19 pneumonia admitted to intensive care,

Table 3. ROC Analysis Result by In-Hospital Mortality Status

		Lactate	Albumin	LAR
In-Hospital Mortality	AUC (95% CI)	0.669 (0.598–0.739)	0.767 (0.715–0.819)	0.730 (0.663–0.797)
	p value	0.012*	0.258**	<0.001***
	Cut-off level	>2.65 mEq/L	<4.01 g/dl	>0.511
	Sensitivity	38%	75.9%	59.5%
	Specificity	90.4%	67.8%	78.8%
	PPV	42.3%	30.5%	34.3%
	NPV	88.7%	93.8%	91.3%

CI: confidence interval; AUC: area under the curve
*: p value is obtained from the paired comparisons of the AUCs of lactate and the AUC of albumin
**: p value is obtained from the paired comparisons of the AUCs of Albumin and the AUC of LAR
***: p value is obtained from the paired comparisons of the AUCs of LAR and the AUC of Lactate

lactate levels reached an AUC value of 0.77 and predicted 28 days mortality. There are several possible reasons that may explain the relationship between lactate level and COVID-19 mortality. A high lactate level is an early biomarker of tissue hypoxia (14). Saturation below 90% is a strong predictor of the severity of COVID-19 (15) and this can be a reason for this relationship between lactate level and COVID-19 mortality. In addition, high mortality rates have been reported in COVID-19 patients with acute respiratory distress syndrome (ARDS) and lung involvement (16), and hypoxia is found in COVID-19 patients with ARDS and lung involvement (17); these can be shown as a separate reasons for this relationship. A possible reason for lactate level being a better mortality predictor in the study conducted by Vassiliou et al. (13) than in this study, is that different patient groups were included. Vassiliou et al. (13) conducted their studies in COVID-19 patients admitted to the ICU, and the literature reports that lactate level predicts mortality well in critically ill patients (18).

In this study, albumin levels were statistically significantly lower in the non-survivor group compared to those in the survivor group. Also, albumin levels reached an AUC value of 0.767 according to the ROC analysis that was performed to predict in-hospital mortality, and albumin levels were found to have moderate accuracy in predicting in-hospital mortality. Chen et al. (19) carried out a study with 274 COVID-19 patients (of whom 113 died), and they found that albumin levels were statistically significantly lower in the non-survivor group compared to the survivor group. In a meta-analysis study that included 11 studies, Aziz et al. (20) demonstrated the relationship between hypoalbuminemia and COVID-19 severity. Li et al. (21) carried out a study with 134 hospitalized COVID-19 patients, and they found that albumin levels reached an AUC value of 0.79 according to an ROC analysis that was performed to predict in-hospital mortality. As with lactate level, there are several possible reasons that may explain the relationship between albumin level and COVID-19 mortality. One reason is that albumin is a negative acute phase reactant (5). Furthermore, albumin level is used to evaluate malnutrition (6). Malnutrition is a risk factor for in-hospital mortality (23), the prevalence of malnutrition is higher in COVID-19 geriatric patients (22), and COVID-19 geriatric patients seem to have a higher mortality rate (1). The risk of arterial and venous thromboembolic events increases with hypoalbuminemia (24,25). There is a relationship between COVID-19 patients with respiratory failure in ICU and severe hypercoagulability (26); this can be a reason for the relationship between albumin level and COVID-19 mortality. Finally, the LAR levels in this study were statistically significantly higher in the non-survivor group compared to the survivor group. The LAR levels reached an AUC value of 0.730 according to the ROC analysis performed to predict in-hospital mortality, and LAR levels were found to be moderately accurate in predicting in-hospital mortality. A literature search did not reveal any accessible COVID-19 studies using the LAR. In this study, the AUC values obtained by LAR to predict in-hospital mortality were statistically significantly higher than the values obtained by lactate. In a study conducted to predict in-hospital mortality in 1,381 patients with sepsis, Bou Chebl et al. (8) found that the LAR had better prognostic performance for in-hospital mortality than the initial serum lactate level (AUC of LAR: 0.67; AUC of lactate: 0.61). Wang et al. (27) performed a study to predict organ failure and mortality in 54 patients with severe sepsis and septic shock; they found that odds ratio values obtained by the LAR level were higher than those obtained by the lactate level (odds ratio of LAR: 5.5, odds ratio of lactate: 0.6, in multivariate logistic regression analysis). There may be many reasons why the mortality predictive capability of the lactate level is lower than that of the LAR, and the lactate level was found to have low accuracy in predicting in-hospital mortality. Hypoxia resulting from COVID-19 may not cause hypoxia at the cellular level in the acute period. Also, the fact that the symptom onset time of COVID-19 patients admitted to the hospital is approximately 3–5 days (28,29) may be a reason.

The study limitations were as follows: there was a shortage in case numbers; it was a retrospective and single-center study; discharged COVID-19 patients were not included in the study; and treatment protocols were not evaluated.

CONCLUSION

In this study, lactate and albumin levels and the LAR were statistically significantly higher in the non-survivor group compared to the survivor group. Albumin level and the LAR were found to be moderately accurate predictors of in-hospital mortality in COVID-19 patients. Lactate levels were found to have low accuracy in predicting in-hospital mortality in COVID-19 patients. The AUC value of LAR was statistically significantly higher than the AUC value of lactate level. As a result, the LAR was found to be more valuable than lactate level in predicting in-hospital mortality.

Etik Kurul: Ethics committee approval was received for this study from the Necmettin Erbakan University Meram Medical Faculty Pharmaceutical and Non-Medical Device Studies Ethical Committee (Date: 2022/10/21, decision no: 2022/4016).

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