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Prognostic values of urea/lymphocyte and LDH/lymphocyte ratios for predicting mortality in COVID-19 patients

Dilay Satilmis[1]*, Egemen Yildiz[1], Erdem Cevik[1]

1. Department of Emergency Medicine, University of Health Sciences Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey.

***Corresponding author:** Dilay Satilmis; **Email:** drdilay09@gmail.com

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Abstract: **Objective:** Serum biomarkers are important for accurately predicting clinical outcomes in coronavirus disease 2019 (COVID-19) patients. Although previous studies showed that lymphopenia in COVID-19 patients is related to disease severity, it is unclear how other serum biomarkers improve the prognostic accuracy of lymphopenia. Changes in urea, and lactate dehydrogenase (LDH) were noted to have considerable predictive value in determining the severity of disease in COVID-19 patients. Therefore, the purpose of this study is to determine whether increases in urea, and LDH are linked to worse outcomes in COVID-19 patients and whether the urea/lymphocyte and LDH/lymphocyte ratios improve the prognostic accuracy of lymphopenia.

Methods: The data of confirmed COVID-19 patients in our emergency department (ED) between March 2020, and January 2021, were analyzed retrospectively. The area under the curve (AUC) and logistic regression analysis were used to evaluate the discriminative power of the urea/lymphocyte and LDH/lymphocyte ratios in estimating 30-day mortality.

Results: The study included 795 confirmed COVID-19 patients admitted to the ED. Twenty-three patients (2.9%) died, and 772 (97.1%) survived in 30 days. The median age of the patients was 51. The number of males (n: 447, 56.2%) was higher than females (n: 348, 43.8%). The ratios of urea/lymphocyte and LDH/lymphocyte were significantly higher in non-survivors (median: 71.21 and 754.1, respectively) compared to survivors (median: 19.51 and 297.42, respectively) (P<0.001). The AUC for 30-day mortality for the urea/lymphocyte and LDH/lymphocyte ratios was 0.864 and 0.840, respectively. Multivariate logistic regression adjustment found the urea/lymphocyte ratio to be an independent and significant predictor of mortality (P=0.007). The optimum cut-off point for the urea/lymphocyte ratio was 28.07, which had a 91.3% sensitivity and a 68.6% specificity.

Conclusion: The urea/lymphocyte and LDH/lymphocyte ratios are useful markers that can be evaluated independently to identify high-risk patients and predict the prognosis of COVID-19.

Keywords: Biomarkers; COVID-19; LDH/Lymphocyte Ratio; Mortality; Urea/Lymphocyte Ratio

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is a global public health problem, and the clinical course of patients ranges from asymptomatic disease to critical illness and death (1). The use of serum biomarkers, in addition to common clinical features, is also important in reliably predicting clinical outcomes such as the need for mechanical ventilation, intensive care unit (ICU) admission, and mortality in COVID-19 patients (2). Especially in the pandemic period, we also need specific biomarkers to facilitate patient triage and increase survival by being able to predict the outcome of the disease at an early stage. In previous studies, some parameters have been shown to have predictive characteristics for COVID-19 in peripheral blood. It has been determined that there is a decrease in the number of lymphocytes and increases in D-dimer, interleukin 6 (IL-6), C-reactive protein (CRP), procalcitonin, troponin, lactate dehydrogenase (LDH), urea, and ferritin levels in clinically severe patients, and studies are ongoing in this area (3).

Although, studies have suggested that the degree of decrease in lymphocyte count in COVID-19 patients is related to disease severity, it is unclear how lymphopenia and serum inflammatory biomarkers are related to poor clinical outcomes (4). A study examining renal viral nucleocapsid protein in post-mortem COVID-19 patients showed that SARS-CoV-2 antigens accumulate in renal tubules in high amounts, SARS-CoV-2 directly infects and induces acute kidney injury in the renal system, and acute tubular injury and leukocyte infiltration observed (5). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE 2) as its entry receptor into cells due to its high affinity, and it was claimed that this receptor is approximately 100 times more potent in renal tissue than in the lungs, and that the high expression of this receptor can play a role by increasing cellular sensitivity. The most reported comorbidities in COVID-19, are acute kidney injury and cardiac dam-

age, which suggests that SARS-CoV-2 may have a high affinity for these organs (6,7).

LDH is a cytoplasmic enzyme synthesized in various tissues. LDH converts pyruvate, the final product of glycolysis, into lactate in case of oxygen deficiency (8). An increase in LDH was observed in tissue damage, hypoxia, necrosis, hemolysis, or malignancy. Studies showed that LDH is a prognostic factor in predicting survival in diseases such as community-acquired pneumonia, acute heart failure, and acute pancreatitis that can develop into multi-organ failure (9-11). Studies on the effectiveness of LDH in predicting mortality showed that LDH is a positive prognostic biomarker with high accuracy in predicting hospital mortality and that more aggressive treatment was needed in these patients (12). Blood LDH, lymphocyte, and urea level measurements are easy, cost-effective, widely used, and reliable laboratory parameters. Studies on the effectiveness of these parameters in predicting the prognostic process in COVID-19 are also available. Our aim in this study is to investigate whether changes in urea and LDH are associated with poor outcomes in COVID-19 patients and whether the urea/lymphocyte and LDH/lymphocyte ratios improve the prognostic accuracy of lymphopenia.

2. Methods

2.1. Study design and population

Study data were taken retrospectively from the medical files of patients with a pre-diagnosis of COVID-19 who visited the emergency medicine department of Sultan 2. Abdulhamid Han Training and Research Hospital, Turkey between March 1, 2020 and January 15, 2021. The study, excluded patients who tested negative for the COVID-19 throat swab test, were on dialysis, or had chronic kidney disease. A total of 795 patients with PCR-confirmed COVID-19 by both nasal and throat swab results, who were diagnosed and treated in the ED, were included in the study.

2.2. Data collection

To access the data, the hospital automation system and patient files retrieved from the hospital archive were used. The demographic characteristics of the patients, comorbid diseases, and laboratory parameters were recorded. A total of 15 patients were excluded from the study due to a lack of laboratory data. None of them had 30-day mortality. The mortality status of the patients was reached by phone calls via numbers registered in the hospital system. Results of urea, lymphocytes, and LDH from laboratory parameters were recorded separately, urea/lymphocyte and LDH/lymphocyte ratios were calculated, and area under the curve (AUC) was used to evaluate the discrimination power in predicting 30-day mortality in COVID-19 patients.

2.3. Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics 26.0 (IBM Corp, Armonk, NY) and MedCalc Statistical Software version 20.1 (MedCalc Software Ltd, Ostend, Belgium). In this study, all continuous data were expressed as a median and interquartile range (IQR). Normality was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U-test was used to compare continuous variables between two groups, while the chi-squared and Fisher's exact test were used to compare categorical variables. The performance of the laboratory parameters was evaluated using the area under the ROC curve (AUROC), and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated. Youden's ROC index was used to determine cut-off points. Univariate and multivariate binary logistic regression analyses were used to determine the predictive factors for 30-day mortality. All analyses were evaluated using the 95% confidence interval (CI), and significance was determined at the P value<0.05 level.

2.4. Ethical consideration

Approval was obtained from the ethics committee of the University of Health Sciences and Hamidiye Scientific Research ethics committee (no: 23.06.2022-14/22–48, date: 23/06/2022). It was conducted in compliance with the principles of the Declaration of Helsinki. The hospital ethics committee waived written informed consent because the study was retrospective and evaluated only the clinical data of the patients and did not involve any potential risk.

3. Results

The study included 795 patients admitted to the ED and diagnosed with COVID-19. Twenty-three patients (2.9%) died, and 772 (97.1%) survived in 30 days in the study population. The median age of the patients was 51 (IQR: 30, range: 2-98 years). The number of males (n: 447, 56.2%) was higher than females (n: 348, 43.8%). In 408 patients (51.3%), at least one comorbid illness was present, and the frequency of comor-bid diseases in deceased patients was significantly higher than in those who survived (P=0.002). Cancer and coronary artery disease (CAD) were more common in non-survivors (P<0.001).

The median oxygen saturation of survivors and deceased patients was 97 (IQR: 2, range: 60-100) and 94 (IQR: 18, range: 60-100), respectively (P=0.002). There were no statistically significant differences in other vital signs between survivors and non-survivors. The frequency of COVID-19 pneumonia suggesting imaging on chest computed tomography scan was significantly higher in deceased patients compared to survivors (65.2% and 44.6%, P<0.05). The clinical, and radiographic characteristics of the patients were shown in table 1. The main laboratory findings were shown in table 2. The ratio of urea/lymphocyte was significantly higher in non-survivors

Table 1 Demographic, clinical, and radiographic characteristics of the patients

Variables	Total population, N: 795	Survivors, N: 772	Non-survivors, N: 23	P-value
Age, median (IQR) [min-max], years	51 (30) [18-98]	50 (30) [18-98]	77 (12) [53-89]	**<0.001**†
Sex, no, (%)				
Male	447 (56.2%)	429 (55.6%)	18 (78.3%)	**0.031***
Female	348 (43.8%)	343 (44.4%)	5 (21.7%)	
Coexisting diseases, no, (%)	408 (51.3%)	389 (50.4%)	19 (82.6%)	**0.002***
Hypertension	232 (29.2%)	223 (28.9%)	9 (39.1%)	0.287*
Cerebrovascular disease	17 (2.1%)	16 (2.1%)	1 (4.3%)	0.396*
Coronary artery disease	96 (12.1%)	88 (11.4%)	8 (34.8%)	**0.004***
Diabetes mellitus	128 (16.1%)	123 (15.9%)	5 (21.7%)	0.593*
Cancer	31 (3.9%)	25 (3.2%)	6 (26.1%)	**<0.001***
COPD	45 (5.7%)	43 (5.6%)	2 (8.7%)	0.378*
Asthma	58 (7.3%)	57 (7.4%)	1 (4.3%)	0.581*
Admission vital signs, median (IQR) [min-max]				
Temperature, °C	36.8 (1) [35.0-40.7]	36.8 (1) [35.0-40.7]	36.9 (1.6) [36.0-39.3]	0.720 †
Heart rate, beats/min	89.5 (19) [51-145]	89.25 (19) [51-138]	95 (28) [55-145]	0.194 †
SBP, mmHg	131 (23) [72-219]	131 (23) [72-219]	136 (32) [90-187]	**0.222** †
DBP, mmHg	79 (17) [37-155]	79 (16) [37-155]	79.5 (29.3) [50-110]	0.362 †
Chest CT scan or radiography, no, (%)				
Normal	436 (54.8%)	428 (55.4%)	8 (34.8%)	**<0.05***
COVID-19 pneumonia	359 (45.2%)	344 (44.6%)	15 (65.2%)	
ED final status, no, (%)				
Discharge from ED	198 (24.9%)	196 (25.3%)	2 (8.7%)	
Hospitalization	546 (68.7%)	530 (68.7%)	16 (69.6%)	0.179*
ICU admission	51 (6.4%)	46 (6.0%)	5 (21.7%)	**0.005***

†: Mann–Whitney U-test was used to compare differences;
*: Chi-squared test was used for analysis; COPD: Chronic obstructive pulmonary disease;
CT scan: Computed tomography scan; DBP: Diastolic blood pressure; ED: Emergency department; ICU: Intensive care unit;
IQR: Interquartile range; SBP: Systolic blood pressure

Table 2 The main laboratory findings of survivor and non-survivor patients

Laboratory findings, median (IQR) [min-max]	Survivors, N: 772	Non-survivors, N: 23	P-value
WBC, $10^3/mm^3$	6.13 (3.2) [0.66-42.91]	8.61 (9.59) [4.05-42.76]	0.001†
Lymphocyte count, $10^3/mm^3$	1.43 (0.94) [0.21-7.48]	0.88 (0.58) [0.33-1.78]	<0.001†
ALT, U/L	25 (20) [4-647]	34 (43) [5-102]	0.187†
AST, U/L	23 (15) [7-577]	41 (47) [10-305]	0.001†
Lactate dehydrogenase, U/L	394 (213) [82-4273]	622 (263) [312-1482]	<0.001†
CRP, mg/L	9.6 (35.8) [0.1-340]	101.96 (138.2) [2-228.4]	<0.001†
D-dimer, µg/L	268 (540.5) [100-9940]	862 (4858) [100-8080]	0.007†
Urea, mg/dL	28 (16) [1.2-259]	64 (57) [26-273]	<0.001†
Creatinine, mg/dL	1.02 (0.35) [0.2-7.56]	1.38 (0.71) [0.79-5.38]	<0.001†
Urea/lymphocyte ratio	19.51 (19.81) [0.52-387.25]	71.21 (89.13) [18.3-827.27]	<0.001†
LDH/lymphocyte ratio	297.42 (295.62) [40-6782.54]	754.1 (686.45) [249.67-2148.48]	<0.001†

†: Mann–Whitney U-test was used to compare differences; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase;
CRP: C-reactive protein; IQR: Interquartile range; WBC: White blood cell count

(median: 71.21, IQR: 89.13, range: 18.3-827.27) compared to survivors (median: 19.51, IQR: 19.81, range: 0.52-387.25) (P<0.001). The ratio of LDH/lymphocyte was also significantly higher in deceased patients (median: 754.1, IQR: 686.45, range: 249.67-2148.48) compared to survivors (median: 297.42, IQR: 295.62, range: 40-6782.54) (P<0.01). The number of lymphocytes was statistically significantly lower in deceased patients (median: 0.88, IQR: 0.58, min-max: 0.33-1.78) compared to survivors (median: 1.43, IQR: 0.94, range: 0.21-7.48) (P<0.01). White blood cell count, aspartate aminotransferase, LDH, CRP, D-dimer, urea, and creatinine values were statistically significantly higher in deceased patients compared to survivors.

The AUC for 30-day mortality for urea/lymphocyte and LDH/lymphocyte ratios was 0.864 (95% CI: 0.84,0.89) and 0.840 (95% CI: 0.81,0.86), respectively (Figures 1 and 2). The best cut-off point for LDH/lymphocyte ratio was 606.82 and demonstrated a sensitivity of 73.9% (95% CI: 51.6,89.8,

Table 3 Univariate and multivariable regression analysis for predictors of mortality

	Univariate model		Multivariate model [a]	
Variables	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
WBC, $10^3/mm^3$	1.104 (1.051-1.161)	**<0.001**	1.015 (0.94-1.09)	0.704
CRP, mg/L	1.013 (1.008-1.018)	**<0.001**	1.006 (1.00-1.01)	0.057
Urea/lymphocyte ratio	1.021 (1.013-1.028)	**<0.001**	1.01 (1.003-1.018)	**0.007**
LDH/lymphocyte ratio	1.001 (1.001-1.002)	**0,001**	1.001 (1.00-1.001)	0.200
Creatinine, mg/dl	2.201 (1.424-3.402)	**<0.001**	1.747 (0.989-3.087)	0.055
D-dimer, µg/L	1.000 (1.00-1.001)	**<0.001**	1.006 (1.00-1.012)	0.057

CI: Confidence interval; CRP: C-reactive protein; IQR: Interquartile range; LDH: Lactate dehydrogenase; WBC: White blood cell count; [a]: Multivariate model was adjusted for age, gender, oxygen saturation, history of coronary artery disease, and history of cancer

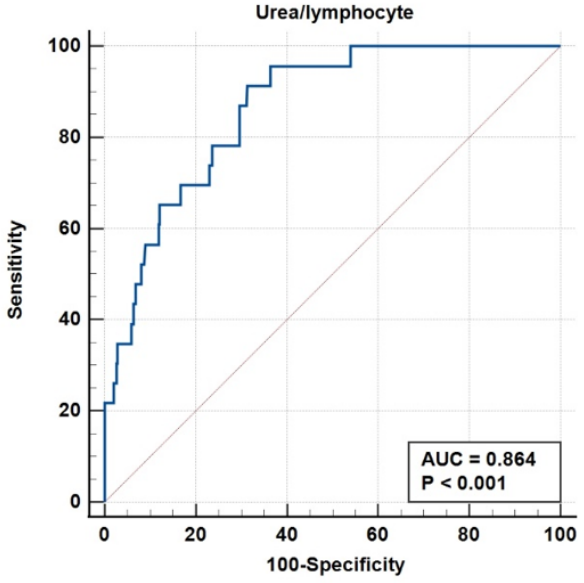

Figure 1 ROC analysis of urea/lymphocyte ratio in predicting 30-day mortality

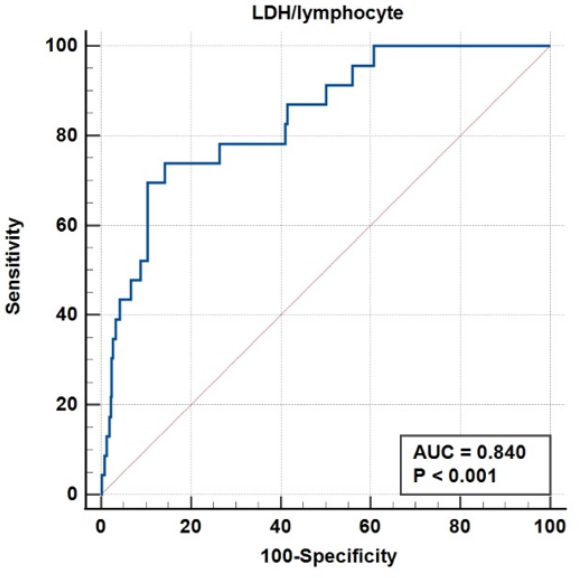

Figure 2 ROC analysis of LDH/lymphocyte ratio in predicting 30-day mortality

LR+: 5.18) and a specificity of 85.7% (95% CI: 3.83,7.01, LR-: 0.3). PPV was 14.3 (95% CI: 11,18.4) and NPV was 99 (95% CI: 98.1,99.5). The optimum cut-off point for the urea/lymphocyte ratio was 28.07, which had a 91.3% sensitivity (95% CI: 72,98.9, LR+: 2.91) and a 68.6% specificity (95% CI: 65.1,72, LR-: 0.13). PPV was 8.5 (95% CI: 7.3,9.8) and NPV was 99.6 (95% CI: 98.5,99.9). The results of univariate and multivariate logistic regression analyses of predictive factors for mortality were shown in table 3.

4. Discussion

In our study, we evaluated the prognostic performance of changes in urea and LDH, which were mentioned to have significant predictive value in assessing the severity of disease in patients with positive COVID-19 throat swab test results. We also evaluated whether or not the prognostic capacity was strengthened by adding lymphocyte count. In this study group, the AUCs for predicting 30-day mortality for the urea/lymphocyte and LDH/lymphocyte ratios were 0.864 and 0.840, respectively, and were highly accurate compared to urea, LDH, and lymphocyte count alone (0.841, 0.792, and 0.751, respectively).

Previous studies showed that COVID-19 was more frequently seen in male patients compared to female patients, and the mortality rate was higher in male patients (13,14). In our study, 56.2% of the patients were male, and 43.8% were female, and there was a significant difference between these groups in terms of survivors and non-survivors. Similarly, the mortality rate was significantly higher in male (78.3%) patients compared to female patients (21.7%, P=0.031).

In a study of hypoxemia and mortality in 140 COVID-19 cases, Xie et al. discovered that patients with hypoxia and dyspnea had a higher mortality rate and that easily assessed hypoxia had a significant effect on mortality in COVID-19 related pneumonia, regardless of age or gender (15,16). Similarly, when we evaluated the relationship between oxygen saturation and mortality in our study, we found that the mortality rates of patients with low oxygen saturation (<94%) were significantly higher than patients with normal oxygen saturation (P=0.002).

In studies examining the dynamic changes in laboratory findings in COVID-19 patients, it was discovered that lymphocyte levels decreased and urea and LDH levels increased significantly in patients who died, implying that changes in laboratory parameters may be effective in predicting the risk of mortality in patients in the early period (17). In our study, similar to other studies, the lymphocyte count was decreased, and LDH and urea levels were increased significantly in patients who died. We investigated whether the prognostic capacity of lymphocytopenia was enhanced by changes in urea and LDH levels, and multivariate logistic regression adjustment found the urea/lymphocyte ratio to be an independent and significant predictor of mortality (P=0.007). The median value of the urea/lymphocyte ratio was 71.21 in the deceased patients and 19.51 in the survivors, which was significantly higher (P<0.001). Again, when we look at the LDH/lymphocyte ratios in our study, the median value of the LDH/lymphocyte ratio was 754.1 in the patients who died and 297.42 in the survivors, which was significantly higher (P<0.001). These findings showed us that, similar to other studies, close follow-up of changes in laboratory parameters during the COVID-19 pandemic may be effective in the early evaluation of clinical changes and in estimating the risk of mortality.

There is no study in the literature on the prognostic values of the urea/lymphocyte and LDH/lymphocyte ratios in COVID-19. Therefore, our study should be considered a study examining whether these ratios can be prognostic biomarkers for COVID-19 in patients who presented to the ED during the pandemic. Multicenter studies should be conducted to determine and confirm whether these rates have prognostic significance.

5. Limitations

The major limitation of this study was its retrospective nature. Also, the study was single-centered, and the data were obtained from electronic recording environments. However, all consecutive patients meeting the criteria in an ED with a high volume of pandemic patients were included in the study, thus limiting patient selection bias.

6. Conclusion

The urea/lymphocyte and LDH/lymphocyte ratios are useful markers that can be evaluated independently to identify high-risk patients for predicting the severity and prognosis of COVID-19 disease.

7. Declarations

7.1. Acknowledgement

None.

7.2. Authors' contribution

Conceptualization: DS, EC, EY; Design: DS, EY; Supervision: DS, EC; Resources: DS, EY, EC; Materials: EY; Data collection and/or processing: EY; Analysis and/or interpretation: DS, EC; Literature search: DS, EY; Writing manuscript: DS, EY; Critical review: DS, EC.

7.3. Conflict of interest

All authors have no potential conflicts of interest.

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