Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Immune Cell-Based versus Albumin-Based Ratios as Outcome Predictors in Critically Ill COVID-19 Patients

Snjezana Zeba[1], Maja Surbatovic[2], Ivo Udovicic[1], Ivan Stanojevic[3], Danilo Vojvodic[3], Goran Rondovic[1], Katarina Mladenovic[1], Tanja Abazovic[2], Almina Hasanovic[4], Aleksandra N Ilic[5], Dzihan Abazovic[6], Wasim Khan[7], Dragan Djordjevic[1]

[1]Clinic of Anesthesiology and Intensive Therapy, Military Medical Academy, Faculty of Medicine of the Military Medical Academy, University of Defense, Belgrade, Serbia; [2]Clinic of Anesthesiology and Intensive Therapy, Military Medical Academy, Belgrade, Serbia; [3]Institute for Medical Research, Military Medical Academy, Faculty of Medicine of the Military Medical Academy, University of Defense, Belgrade, Serbia; [4]Nephrology Clinic, Military Medical Academy, Belgrade, Serbia; [5]Faculty of Medicine, University of Pristina, Kosovska Mitrovica, Serbia; [6]Atlas Hospital, Belgrade, Serbia, Aba Medica Healthcare Centre, Ulcinj, Montenegro; [7]Division of Trauma & Orthopaedic Surgery, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK

Correspondence: Maja Surbatovic, Clinic of Anesthesiology and Intensive Therapy, Military Medical Academy, 17 Crnotravska Street, Belgrade, 11000, Serbia, Tel +381 11 2665 125, Email maja.surbatovic@gmail.com

Purpose: The aim of the retrospective, single-center study was to assess the prognostic value of immune cell-based and albumin-based ratios regarding lethal outcome in critically ill COVID-19 patients.

Patients and Methods: We analyzed 612 adult critically ill COVID-19 patients admitted to the intensive care unit (ICU) between April 2020 and November 2022. Blood measurement on admission to the ICU encompassed complete blood count (CBC), IL-6, C-reactive protein (CRP), albumin, lactate, lactate dehydrogenase (LDH), serum bicarbonate, arterial base deficit/excess (BD/E), and D-dimer. All the measured and calculated parameters were compared between survivors and nonsurvivors, with the outcome measure being hospital mortality.

Results: Immune cell-based ratios [NLR - Neutrophil-to-Lymphocyte Ratio, MLR - Monocyte-to-Lymphocyte Ratio, PLR - Platelet-to-Lymphocyte Ratio, MPV - Mean Platelet Volume, MPV/PC - Mean Platelet Volume-to-Platelet Count Ratio, Derived (d-)NLR ratio - neutrophil count divided by the result of white blood cell (WBC) count – neutrophil count), N/LP - Neutrophil count x 100/ Lymphocyte count x Platelet count, CLR – C-reactive protein (CRP)-to-Lymphocyte Ratio, CPR - CRP-to-Platelet Ratio, LLR - Lactate dehydrogenase (LDH)-to-Lymphocyte Ratio, Systemic Immune Inflammation Index (SII) - platelet x neutrophil/lymphocyte count, Systemic Inflammation Response Index (SIRI) - neutrophil x monocyte/lymphocyte count] were investigated. White blood cell and neutrophil counts were significantly higher, while lymphocyte and platelet counts were significantly lower in nonsurvivors. MPV, MPV/PC, NLR, d-NLR, MLR, N/LP, CRP, LDH, CPR, CLR, LLR, SII, and SIRI values were significantly higher in nonsurvivors. Monocyte count and PLR values did not differ significantly between groups. Albumin-based ratios included CRP-to-Albumin Ratio (CAR), Lactate-to-Albumin Ratio (LAR) and LDH-to-Albumin Ratio (LDH/ALB). All values were significantly higher in nonsurvivors.

Conclusion: The only independent predictor of lethal outcomes at ICU admission is the albumin-based LDH/ALB ratio. Most of the other parameters were moderate, although highly significant predictors of mortality in critically ill COVID-19 patients.

Keywords: LDH/albumin ratio, critically ill, COVID-19, mortality

Introduction

The hallmark of critically ill patients with infection, regardless of the pathogen, is exacerbated, life-threatening immune dissonance with devastating consequences.[1] Patients with severe forms of COVID-19 do fulfill SEPSIS 3.0 criteria for viral septic shock with specific immunopathogenesis.[2] Recent efforts to provide tailored immunomodulation have

Received: 27 July 2024
Accepted: 8 December 2024
Published: 3 January 2025

focused on analyzing observed heterogeneity into sepsis subtypes, keeping in mind that novel immunomodulatory therapies have not been successful.[3] Even before the COVID-19 pandemic, trends in continuous septic shock mortality rates over time as well as regional disparities suggested that there was still a need for improvement in standard sepsis treatment.[4] Therefore, it is of paramount importance to identify those patients who are at higher risk of mortality, even more so in a state of medical emergency like a COVID-19 pandemic. In this specific clinical setting, low-cost, readily available parameters would be useful. Quite a few of them were investigated as outcome predictors in critically ill patients with bacterial or viral sepsis, often with contradictory results.[5–7]

From the very beginning of the COVID-19 pandemic, efforts have been made to establish the predictive role of specific laboratory parameters as biomarkers regarding severity and outcome. A review of multiple, mostly nonspecific biomarkers (C-reactive protein, ferritin, serum amyloid A, and procalcitonin) and T-lymphocyte markers emphasized that interpretation of the data is limited for the most part due to the small sample size.[8] That same year, in 2020, interesting research regarding plasma albumin levels in critically ill COVID-19 patients was published.[9] The authors demonstrated that decreased levels of albumin could, at an early stage, be used as an independent predictor of lethal outcome. During 2021, as more features of COVID-19 became known, attempts were made to assess their prognostic value regarding lethal outcome. One interesting study included 38 critically ill COVID-19 patients in order to assess ICU admission levels of various endothelial biomarkers as predictors of mortality.[10] The authors showed that elevated levels of soluble E-selectin, angiopoietin 2, and soluble intercellular adhesion molecule 1 in nonsurvivors had a significant prognostic value, with an AUC/ROC of > 0.85. Authors of another study demonstrated that elevated levels of mid-regional pro-adrenomedullin on the ICU admission had predictive capacity of mortality in 95 critically ill COVID-19 patients, with an AUC/ROC of 0.73.[11] In 2022, larger sample size research regarding inflammatory markers as early predictors of disease severity and outcome in critically ill COVID-19 patients emerged. One study performed on 100 patients showed that a triad of C-reactive protein, ferritin, and interleukin-6 at admission may predict the disease severity early in the course.[12] Another study included 380 patients and focused on the role of biomarkers in predicting the outcome in this patient population. Out of several investigated parameters, the authors found that ferritin was the only significant biomarker with higher values in nonsurvivors.[13] Several other parameters were found to be of significant predictive value for the mortality in critically ill COVID-19 patients: IL-6 values and IL-6/lymphocyte ratio (sample size of 117 patients)[14] and lactate dehydrogenase (sample size of 168 patients).[15] Although COVID-19 was declared no longer to be a global health emergency on May 5, 2023, interest in biomarkers as predictors of mortality remained. That same year, an interesting study of 340 critically ill COVID-19 patients was published, focusing on obesity as well as the prognostic values of biomarkers regarding mortality.[16] The authors demonstrated that mortality in obese patients was lower than in the normal weight and overweight groups, yet it did not reach statistical significance. They also found that ferritin and neutrophil/lymphocyte ratio were independent predictors of lethal outcome in obese patients. As an indicator of continued interest in predictive biomarkers of COVID-19 prognosis, just a few months ago, two studies focusing on serum levels of various cytokines were published.[17,18] It is next to impossible to overestimate the importance of routine blood values as predictors of severity and outcome in general; this is particularly true for critically ill patients. Low cost and short turnaround time (TAT) make routine blood parameters very useful in this clinical setting. We have previously investigated several immune cell-based ratios as predictors of lethal outcome in a few subgroups of critically ill patients with secondary bacterial sepsis.[5] Here, we wanted to expand this approach with both immune cell-based and albumin-based ratios in a cohort of critically ill COVID-19 patients. In the literature available to us, we did not find any research with this unique approach and such a wide array of investigated parameters in a large cohort of patients.

The aim of our retrospective, single-center study was to assess the prognostic value of immune cell-based as well as albumin-based ratios regarding lethal outcome in 612 critically ill COVID-19 patients. The outcome measure was hospital mortality. Immune cell-based ratios included Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), Platelet-to-Lymphocyte Ratio (PLR), Mean Platelet Volume (MPV), Mean Platelet Volume-to-Platelet count Ratio (MPV/PC), derived NLR ratio, Neutrophil to Lymphocyte x Platelet ratio (N/LP), C-reactive protein (CRP)-to-Lymphocyte Ratio (CLR) and CRP-to-Platelet Ratio (CPR), and Lactate dehydrogenase (LDH)-to-Lymphocyte Ratio (LLR). We also calculated Systemic Immune Inflammation Index (SII) as well as Systemic

Inflammation Response Index (SIRI). Albumin-based ratios included CRP-to-Albumin Ratio (CAR), Lactate-to-Albumin Ratio (LAR) and LDH-to-Albumin Ratio (LDH/ALB).

Materials and Methods

Study Design

We performed a single-center retrospective analysis of 612 adult critically ill COVID-19 patients who were admitted to the intensive care unit (ICU) of military hospital Karaburma, which is an integral part of the tertiary university hospital (Military Medical Academy, Belgrade, Serbia) during 32 months (April 2020–November 2022). Blood measurement encompassed Complete Blood Count (CBC), IL-6, C-reactive protein (CRP), albumin, lactate, lactate dehydrogenase (LDH), serum bicarbonate, arterial base deficit/excess (BD/E) and D-dimer. Blood samples were collected on admission to the ICU. All of the measured and calculated parameters were compared according to the outcome between survivors and nonsurvivors, with the outcome measure being hospital mortality. Approval in concordance with the Declaration of Helsinki was obtained from the local ethics committee on March 22, 2024 (No. 33/2024).

Qualified and trained phlebotomists drew the patient's venous blood. If several measurements were available on the day of enrollment in the study for some patients, the first one at the time point of diagnostic criteria fulfillment was always used to maximize consistency among the patient population. We placed the blood samples into BD Vacutainer K2 EDTA tubes and analyzed them within 2 hours of the venepuncture. The Siemens Advia 120 hematology system, a flow cytometry-based system, determined a complete blood count. Differentiation of white blood cells is done by the peroxidase and basophil channels. More details of blood sample laboratory analyses were explained and published elsewhere.[5]

Study Population

Adult patients with COVID-19, confirmed by positive SARS-CoV-2 detection tests, who required non-invasive or invasive mechanical ventilation in the ICU were enrolled. There were 723 patients who fulfilled the inclusion criteria. The exclusion criteria included malignant disease of any origin and/or preexisting immunodeficiency (65 patients). Also, patients with liver failure (12 patients) and those on renal replacement therapy (34 patients) were excluded from the study because of the impact on biomarker concentrations. Finally, out of 723 patients, 111 were excluded from the study. The remaining 612 patients were included; regarding the outcome there were 241 survivors and 371 nonsurvivors. Figure 1 represents a study flowchart.

The study population's vaccination status and comorbidities have been determined. There was no statistically significant difference regarding vaccination status (partially or fully vaccinated; booster shot) between survivors and nonsurvivors. Of all comorbidities, cardiac dysfunction, obesity, and cerebrovascular disease were more frequent in nonsurvivors (Table 1).

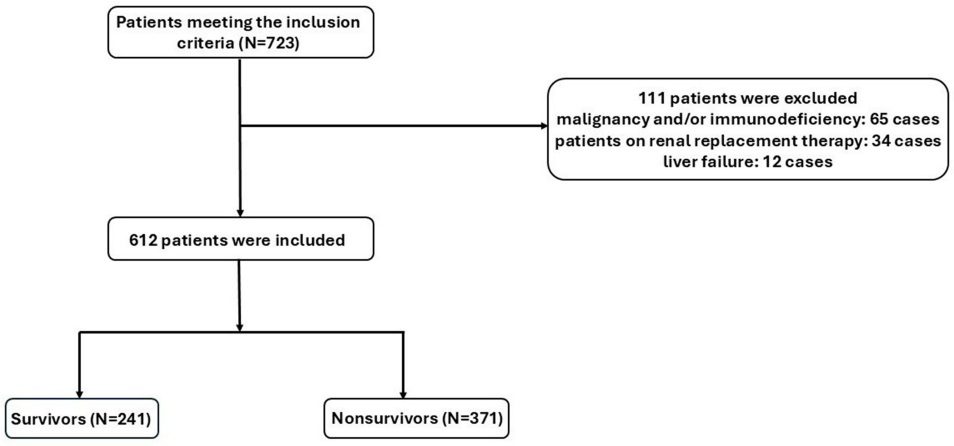

Figure 1 Study flowchart.

https://doi.org/10.2147/JIR.S488972

Table 1 Vaccination Status and Comorbidities of the Study Population According to Outcomes

Characteristics	All Patients	Survivors	Nonsurvivors	p
Total number (%)	**612 (100.0)**	**241 (39.4)**	**371 (60.6)**	
Vaccination status				
Partially vaccinated	128 (20.9)	44 (18.3)	84 (22.6)	0.193
Fully vaccinated	118 (19.3)	38 (15.8)	80 (21.6)	0.078
Booster dose	45 (7.4)	13 (5.4)	32 (8.6)	0.135
Comorbidity				
Hypertension	393 (64.2)	144 (59.8)	249 (67.1)	0.063
Diabetes mellitus	168 (27.5)	58 (24.1)	110 (29.6)	0.130
COPD	69 (11.3)	28 (11.6)	41 (11.1)	0.828
Cardiac dysfunction	185 (30.2)	49 (20.3)	136 (36.7)	<0.001
Obesity	29 (4.7)	4 (1.7)	25 (6.7)	0.004
Cerebrovascular disease	35 (5.7)	8 (3.3)	27 (7.3)	0.039
Dementia	10 (1.6)	3 (1.2)	7 (1.9)	0.540
Mental disorder	12 (2.0)	4 (1.7)	8 (2.2)	0.665
Renal dysfunction	20 (3.3)	9 (3.7)	11 (3.0)	0.601
Hypothyroidism	27 (4.4)	10 (4.1)	17 (4.6)	0.799

Note: Data are presented as a number (percentage) of subjects.
Abbreviation: COPD, Chronic Obstructive Pulmonary Disease.

Lung involvement was determined using a chest CT severity score. The total CT score is measured by the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement), when all five lobes show more than 75% involvement. All patients in our study had scores > 15, which indicated severe involvement on the CT severity grading scale. There was no statistically significant difference between survivors and nonsurvivors in this regard.

Calculation of Various Ratios

Immune cell-based ratios included Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte- to-Lymphocyte Ratio (MLR), Platelet- to-Lymphocyte Ratio (PLR), Mean Platelet Volume (MPV; fl), Mean Platelet Volume-to-Platelet count Ratio (MPV/PC; fL 10^{-5} μL^{-1}), Derived (d-)NLR ratio (neutrophil count divided by the result of white blood cell (WBC) count – neutrophil count); Neutrophil count x 100/Lymphocyte count x Platelet count to calculate N/LP ratio; measured CRP (mg/l) for CRP-to-Lymphocyte Ratio (CLR) and CRP-to-Platelet Ratio (CPR; mg/10^6 cells), as well as measured LDH (U/l) for LDH-to-Lymphocyte Ratio (LLR). We also calculated Systemic Immune Inflammation Index (SII) using following formula: platelet x neutrophil/lymphocyte count as well as Systemic Inflammation Response Index (SIRI) using following formula: neutrophil x monocyte/lymphocyte count.

Measured albumin-based ratios included CRP-to-Albumin Ratio (CAR), Lactate-to-Albumin Ratio (LAR) and LDH-to-Albumin Ratio (LDH/ALB).

Data Collection

Designated members of our research team gathered and synthesized a variety of demographic, clinical, and laboratory data from hospitalized patients' medical records. The patients' confidentiality was protected.

Statistical Analysis

Data are presented using the descriptive statistical methods, for continuous variables, median and interquartile range, Q1-Q3 (first and third quartile) and for categorical variables, absolute and relative frequencies. The normality of the data distribution was confirmed by the Shapiro–Wilk tests.

Differences in examined variables between survivors and nonsurvivors were assessed using Mann–Whitney test and Chi-square test.

The area under the receiver operating characteristic (ROC) curve (AUC) with 95% confidence intervals was calculated for predicted lethal outcomes. The optimal cut-off value was expressed as its sensitivity, specificity and Youden index is shown for all biomarkers.

A large number of independent variables with a statistical significance level of 0.05 in the univariate analysis influenced the careful selection of the independent variables to be used in the multivariate regression analysis model. In order to minimize the effect of multicollinearity, all variables that had a high correlation were excluded from the model, while making sure that the excluded variables were contained in the remaining variables. The multivariate model contained 16 independent variables for outcome prediction (dependent variable).

All statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). The criterion for statistical significance was $p < 0.05$.

Results

Baseline Characteristics of the Study Population

During a 32-month study period, 612 critically ill COVID-19 patients, predominantly male (73%) and older (median age of 70 years), were enrolled. Overall mortality was 60.6%. Comparison of baseline characteristics of the study population according to outcome revealed that female mortality rate of 68.9% was significantly higher ($\chi 2 = 6.535$, $p=0.011$) than male mortality rate of 57.5% (Table 2).

Also, nonsurvivors were significantly older ($U=493.5$, $p=0.037$). Hospital stay was significantly longer in survivors ($U=224.0$, $p<0.001$) while duration of ICU stay did not differ significantly between survivors and nonsurvivors ($U=548$, $p=0.131$).

Table 2 Baseline Characteristics of the Study Population According to Outcomes

Characteristics	**All patients 612 (100.0)**	**Survivors 241 (39.4)**	**Nonsurvivors 371 (60.6)**	**p**
Gender Male, n (%) Female, n (%)	 445 (100.0) 167 (100.0)	 189 (42.5) 52 (31.1)	 256 (57.5) 115 (68.9)	 0.011
Age (years) Median (Min-Max)	 70.0 (25.0–99.0)	 62.0 (25.0–94.0)	 75.0 (27.0–99.0)	 0.037
Hospital stay (days) Median (Min-Max)	 17.0 (1.0–74.0)	 23.0 (2.0–74.0)	 13.0 (1.0–46.0)	 <0.001
ICU stay (days) Median (Min-Max)	 11.0 (1.0–71.0)	 14.0 (2.0–71.0)	 9.0 (1.0–43.0)	 0.131
The day of the illness When blood was drawn Median (Min – Max)	 11.0 (1.0–39.0)	 12.0 (1.0–39.0)	 10.0 (1.0–29.0)	 0.004

https://doi.org/10.2147/JIR.S488972

Laboratory Characteristics of the Study Population on Admission to the ICU

Immune Cell-Based Ratios According to Outcome

White blood cell (WBC) (p<0.001) and neutrophil counts (p<0.001) were significantly higher, while lymphocyte (p<0.001) and platelet counts (p<0.001) were significantly lower in nonsurvivors. Thrombocytopenia was significantly more frequent in nonsurvivors (p=0.003). MPV, MPV/PC, NLR, derived NLR, MLR, N/LP, CRP, LDH, CPR, CLR, LLR, SII, and SIRI values were significantly higher in nonsurvivors (p value for CRP was 0.004; for all other aforementioned parameters, p value was <0.001). So, all differences reached high statistical significance. Monocyte count (p=0.937) and PLR values (p=0.136) did not differ significantly between survivors and nonsurvivors (Table 3).

Albumin-Based Ratios, Interleukin(IL)-6, Bicarbonate, Lactate, Arterial B/DE, and D-Dimer According to Outcome

Lactate, CAR, LAR, LDH/ALB, IL-6, and D-dimer values were significantly higher (p value for IL-6 was 0.001; for all other aforementioned parameters, p value was < 0.001). Albumin (p<0.001), bicarbonate (p=0.003), and BD/E (p=0.001)

Table 3 Immune Cell-Based Ratios According to Outcomes

Characteristics	All patients (n=612)	Survivors (n=241)	Nonsurvivors (n=371)	p
WBC count (10^9/l)	9.90 (7.0–13.3)	9.1 (6.4–12.0)	10.6 (7.4–14.4)	<0.001
Neutrophil (10^9/l)	8.7 (5.9–12.0)	7.8 (5.0–10.5)	9.4 (6.4–13.1)	<0.001
Monocyte (10^9/l)	0.34 (0.23–0.53)	0.36 (0.23–0.36)	0.33 (0.23–0.54)	0.937
Lymphocyte (10^9/l)	0.5 (0.4–0.8)	0.6 (0.5–0.9)	0.5 (0.4–0.7)	<0.001
Platelet (10^9/l)	233.0 (174.5–304.8)	244.0 (189.5–343.0)	225.0 (160.0–288.0)	<0.001
Thrombocytopenia n(%)	105 (17.6)	28 (11.6)	77 (20.8)	0.003
MPV (fL)	8.2 (7.7–9.0)	8.0 (7.5–8.6)	8.3 (7.8–9.2)	<0.001
MPV/PC ratio (fL 10^{-5} μL^{-1})	3.5 (2.5–4.9)	3.2 (2.3–4.3)	3.7 (2.7–5.7)	<0.001
NLR	15.0 (8.1–25.3)	12.0 (6.6–18.0)	18.1 (10.2–29.8)	<0.001
Derived NLR	7.36 (4.56–10.65)	6.0 (3.77–8.68)	8.41 (5.57–11.93)	<0.001
MLR	0.6 (0.4–1.0)	0.5 (0.3–0.7)	0.7 (0.4–1.1)	<0.001
PLR	411.0 (260.0–654.0)	370.5 (252.0–592.4)	422.0 (267.3–686.7)	0.136
N/LP	6.48 (3.38–11.34)	4.66 (2.50–7.89)	7.64 (4.32–15.51)	<0.001
CRP (mg/l)	108.6 (56.2–170.4)	95.1 (49.8–158.7)	116.5 (63.9–178.5)	0.004
LDH (U/l)	451.0 (318.5–619.5)	387.0 (290.0–536.0)	502.5 (352.0–679.5)	<0.001
CPR (mg/10^6 cells)	0.45 (0.21–0.77)	0.37 (0.18–0.63)	0.50 (0.26–0.86)	<0.001
CLR	178.8 (86.2–340.9)	153.6 (61.4–260.6)	210.0 (101.3–377.9)	<0.001
LLR	822.0 (475.0–1383.2)	621.5 (370.2–967.5)	1048.0 (580.8–1777.5)	<0.001
SII	3401.0 (1691.0–6494.5)	2748.0 (1439.0–5291.5)	3963.0 (1943.0–7266.5)	<0.001
SIRI	4.62 (2.38–11.27)	3.40 (1.88–7.35)	5.85 (2.87–12.83)	<0.001

Note: Data are shown as median (interquartile range, IQR) and categorical variables, as number (percentage).

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; MLR, Monocyte- to-Lymphocyte Ratio; PLR, Platelet- to-Lymphocyte Ratio; MPV, Mean Platelet Volume; MPV/PC, Mean Platelet Volume-to-Platelet count Ratio; Derived (d-)NLR ratio - neutrophil count divided by the result of white blood cell (WBC) count – neutrophil count); N/LP, Neutrophil count x 100/Lymphocyte count x Platelet count; CLR – C-reactive protein (CRP)-to-Lymphocyte Ratio; CPR, CRP-to-Platelet Ratio; LLR, Lactate dehydrogenase (LDH)-to-Lymphocyte Ratio; Systemic Immune Inflammation Index (SII), platelet x neutrophil/lymphocyte count; Systemic Inflammation Response Index (SIRI), neutrophil x monocyte/lymphocyte count.

values were significantly lower in nonsurvivors. So, as with most immune cell-based ratios, the differences in all investigated parameters reached high statistical significance (Table 4).

Clinical Accuracy of Immune Cell-Based and Albumin-Based Ratios, IL-6, Bicarbonate, Lactate, Arterial B/DE, and D-Dimer in Predicting Lethal Outcomes

The clinical accuracy of immune cell-based ratios in predicting lethal outcomes was investigated on admission to the ICU. Most of these parameters demonstrated insufficient discriminative power regarding outcomes, despite statistically highly significant differences. Values of Area under the Receiver Operating Characteristic (ROC) Curve (AUC/ROC) for all cells and most ratios were between 0.49 and 0.60. On the other hand, levels of LLR (AUC/ROC 0.68), N/LP (AUC/ROC 0.66) and NLR (AUC/ROC 0.65) higher than cut-off values are moderate predictors of lethal outcomes (Table 5).

The same analysis was performed on albumin-based ratios, IL-6, bicarbonate, lactate, arterial B/DE, and D-dimer on admission to the ICU. Apart from LDH/ALB (AUC/ROC 0.66), LDH (AUC/ROC 0.64), IL-6 (AUC/ROC 0.63), and D-dimer (AUC/ROC 0.63), all other parameters demonstrated insufficient discriminative power regarding outcomes. Levels of LDH/ALB, LDH, IL-6, and D-dimer higher than cut-off values are moderate predictors of lethal outcomes (Table 6 and Figure 2).

Combination of Various Parameters in a Composite Bioscore on Admission to the ICU

To evaluate whether combining LLR, NLR, IL-6, and D-dimer into a single composite bioscore would enhance their predictive performance for fatal outcomes, individual values were assigned a score of 1 or 0 according to how they related (above or below) to previously defined AUC/ROC cut-off levels. The Bioscore I point range is 0–4. It was demonstrated that composite Bioscore I is a statistically highly significant predictor of lethal outcomes with good discriminative power (AUC/ROC 0.70; cut-off value >1 point), better than individual components. When these four parameters were expanded with MLR, LAR, and LDH/ALB and the same type of analysis was performed, composite Bioscore II was created, with a point range of 0–7. However, its predictive performance regarding lethal outcomes did not improve (AUC/ROC 0.672; cut-off value >3 points), although it was statistically highly significant (Table 7 and Figure 3).

Table 4 Albumin-Based Ratios, IL-6, Bicarbonate, Lactate, Arterial B/DE and D-Dimer According to Outcomes

Characteristics	All patients	Survivors	Nonsurvivors	p
Albumin (g/l)	35.0 (32.0–38.0)	36.0 (33.0–39.0)	34.0 (30.8–37.0)	<0.001
Lactate (mmol/l)	1.4 (1.1–1.9)	1.3 (1.0–1.7)	1.5 (1.1–2.1)	<0.001
CAR	3.11 (1.68–5.14)	2.55 (1.43–4.43)	3.52 (1.89–5.44)	<0.001
LAR	0.04 (0.03–0.06)	0.04 (0.03–0.05)	0.05 (0.03–0.07)	<0.001
LDH/ALB	13.30 (9.32–17.70)	11.21 (8.28–15.16)	14.88 (10.68–20.15)	<0.001
IL-6 (pg/mL)	76.2 (35.7–172.6)	65.5 (25.0–123.0)	109.1 (49.5–231.0)	0.001
Bicarbonate (mmol/l)	25.5 (22.3–29.2)	26.6 (23.5–29.7)	25.1 (21.5–28.9)	0.003
BD/E	1.8 (−1.8–5.5)	2.5 (0.2–6.1)	1.4 (−2.7–4.9)	0.001
D-dimer (µg/mL FEU)	1.7 (1.0–4.3)	1.3 (0.8–3.0)	2.1 (1.1–5.4)	<0.001

Note: Data are shown as median (interquartile range, IQR).
Abbreviations: CAR, C-reactive protein (CRP)-to-Albumin Ratio; LAR, Lactate-to-Albumin Ratio; LDH/ALB, Lactate dehydrogenase (LDH)-to-Albumin Ratio; Interleukin (IL)-6, BD/E, base deficit/excess.

https://doi.org/10.2147/JIR.S488972

Table 5 Clinical Accuracy of Immune Cell-Based Ratios in Predicting Lethal Outcomes

Parameter	AUC ROC	95% Confidence Interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden Index	p
		Lower Bound	Upper Bound					
WBC count (10^{9}/l)	0.590	0.549	0.630	>10.5	51.0	64.3	0.15	<0.001
Neutrophil (10^{9}/l)	0.600	0.559	0.640	>9.4	49.7	67.9	0.18	<0.001
Monocyte (10^{9}/l)	0.498	0.457	0.539	<0.34	53.1	52.7	0.06	0.938
Lymphocyte (10^{9}/l)	0.618	0.577	0.657	<0.47	42.3	77.1	0.19	<0.001
Platelet (10^{9}/l)	0.584	0.544	0.624	<202.0	40.0	72.6	0.13	<0.001
MPV (fl)	0.609	0.568	0.649	>7.9	67.2	49.4	0.17	<0.001
MPV/PC (fL 10^{-5} μL^{-1})	0.603	0.562	0.642	>4.7	33.0	83.4	0.16	<0.001
NLR	0.650	0.610	0.688	>18.6	49.1	77.5	0.27	<0.001
Derived NLR	0.644	0.604	0.682	>8.44	49.9	73.7	0.24	<0.001
MLR	0.604	0.563	0.643	>0.75	43.4	76.7	0.20	<0.001
PLR	0.536	0.495	0.577	>654.0	28.9	81.2	0.10	0.133
N/LP	0.667	0.627	0.705	>5.11	69.1	56.7	0.26	<0.001
CRP (mg/l)	0.570	0.529	0.610	>125.9	47.3	65.6	0.13	0.003
LDH (U/l)	0.640	0.600	0.679	>401.0	68.9	54.9	0.24	<0.001
CPR (mg/10^{6} cells)	0.598	0.557	0.637	>0.37	64.8	51.5	0.16	<0.001
CLR	0.600	0.559	0.640	>230.8	47.1	71.7	0.19	<0.001
LLR	0.681	0.641	0.718	>825.0	61.7	67.9	0.30	<0.001
SII	0.588	0.547	0.628	>3364	57.6	60.0	0.18	<0.001
SIRI	0.612	0.572	0.652	>3.88	65.4	55.2	0.21	<0.001

Abbreviations: AUC ROC, Area under the curve Receiver-operating characteristic; NLR, Neutrophil-to-Lymphocyte Ratio; MLR, Monocyte- to-Lymphocyte Ratio; PLR, Platelet- to-Lymphocyte Ratio; MPV, Mean Platelet Volume; MPV/PC, Mean Platelet Volume-to-Platelet count Ratio; Derived (d-)NLR ratio - neutrophil count divided by the result of white blood cell (WBC) count – neutrophil count); N/LP, Neutrophil count x 100/Lymphocyte count x Platelet count; CLR, C-reactive protein (CRP)-to-Lymphocyte Ratio; CPR, CRP-to-Platelet Ratio; LLR, Lactate dehydrogenase (LDH)-to-Lymphocyte Ratio; Systemic Immune Inflammation Index (SII) - platelet x neutrophil/lymphocyte count; Systemic Inflammation Response Index (SIRI) - neutrophil x monocyte/lymphocyte count.

Table 6 Clinical Accuracy of Albumin-Based Ratios, IL-6, Bicarbonate, Lactate, Arterial B/DE and D-Dimer in Predicting Lethal Outcomes

Parameter	AUC ROC	95% Confidence Interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index	p
		Lower Bound	Upper Bound					
Albumin (g/l)	0.619	0.578	0.658	<35.0	62.3	57.7	0.20	<0.001
Lactate (mmol/l)	0.602	0.558	0.645	>1.7	38.7	77.2	0.16	<0.001
CAR	0.593	0.552	0.633	>3.42	52.0	63.2	0.15	<0.001
LAR	0.627	0.583	0.669	>0.05	36.5	82.6	0.19	<0.001

(*Continued*)

Table 6 (Continued).

Parameter	AUC ROC	95% Confidence Interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index	p
		Lower Bound	Upper Bound					
LDH/ALB	0.663	0.623	0.701	>13.24	61.0	65.8	0.27	<0.001
IL-6 (pg/mL)	0.635	0.567	0.699	>111.2	49.1	74.3	0.23	<0.001
Bicarbonate (mmol/l)	0.578	0.533	0.621	<21.3	24.8	88.7	0.14	0.003
BD/E	0.585	0.541	0.628	<-1.9	29.8	86.7	0.17	0.001
D-dimer	0.629	0.589	0.668	>1.37	68.0	54.2	0.22	<0.001

AUC ROC, Area under the curve Receiver-operating characteristic; CAR, C-reactive protein (CRP)-to-Albumin Ratio; LAR, Lactate-to-Albumin Ratio; LDH/ALB, Lactate dehydrogenase (LDH)-to-Albumin Ratio; Interleukin (IL)-6; BD/E, base deficit/excess.

Independent Prognostic Significance of Immune Cell-Based Ratios, Albumin-Based Ratios, IL-6, Bicarbonate, Lactate, Arterial Base Deficit/Excess (B/DE), and D-dimer in Predicting Lethal Outcomes

The study employed logistic regression analyses to investigate potential associations between individual variables and lethal outcomes. To identify the possible predictors of lethal outcomes independent of potential confounders, a forward stepwise multivariate logistic regression analysis was run (Table 8). Multivariate logistic regression model was statistically highly significant ($\chi 2$ = 152.386, p<0.001). Independent predictors of lethal outcomes by multivariate logistic regression analysis were age [β=0.120, p<0.001; OR (95% CI)=1.13 (1.07–1.19)], ICU stay [β=0.295, p= 0.001, OR

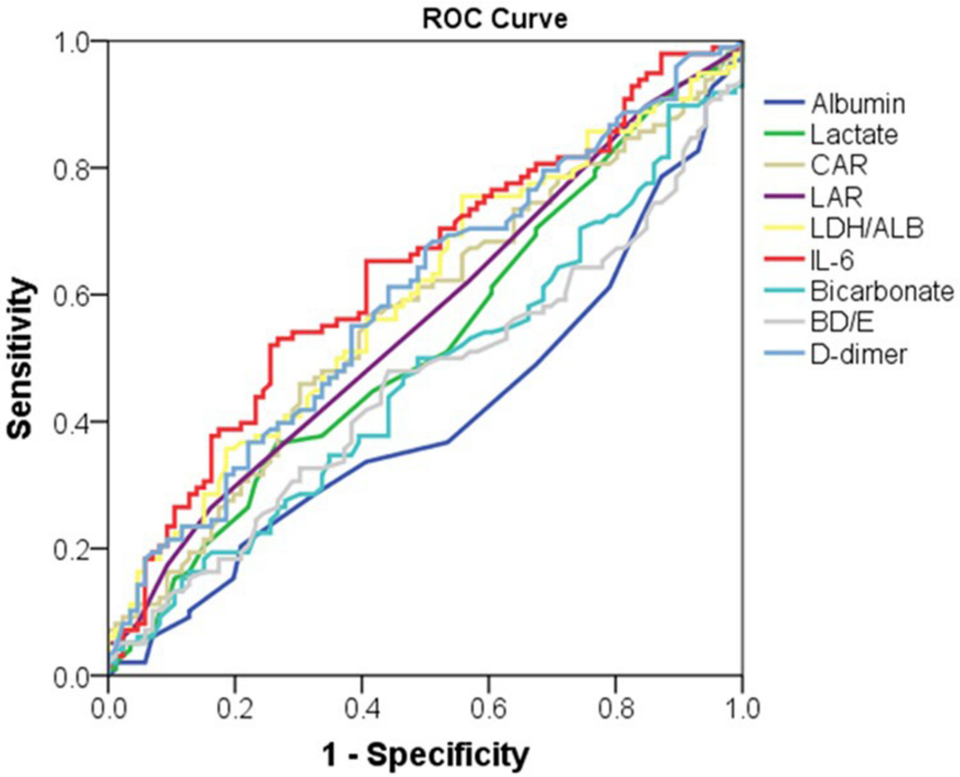

Figure 2 Receiver operating characteristic (ROC) curves of Albumin-Based Ratios, IL-6, bicarbonate, lactate, arterial B/DE and D-dimer in predicting lethal Outcomes.

https://doi.org/10.2147/JIR.S488972

Table 7 Clinical Accuracy of Composite Bioscore I and II in Predicting Lethal Outcomes

Parameter	AUC ROC	95% Confidence Interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index	p
		Lower Bound	Upper Bound					
Composite bioscore I (LLR, NLR, IL-6, D-dimer)	0.704	0.638	0.764	>1	72.7	59.0	0.32	<0.001
Composite bioscore II (LLR, NLR, IL-6, D-dimer, MLR, LAR, LDH/ALB)	0.672	0.600	0.738	>3.0	57.7	73.3	0.31	<0.001

Abbreviation: AUC ROC, Area under the curve Receiver-operating characteristic.

(95% CI)=1.34 (1.16–1.55)], LDH/ALB [β=0.169, p=0.007, OR (95% CI)=1.18 (1.05–1.34] as well as hospital stays [β=−0.455, p<0.001, OR (95% CI)=0.64 (0.54–0.75)]. In general, older patients with longer ICU stay and higher LDH/ALB were more likely to die, while those with longer hospital stays were more likely to survive.

Discussion

From the beginning of the COVID-19 pandemic, clinicians and researchers alike made considerable efforts to investigate possible prognostic biomarkers. Given the fact that the immune response is crucial in the development of severe forms of COVID-19, attention has been focused on the interplay between various cells and mediators of innate and adaptive immunity, as well as cascades of coagulation.[19] COVID-19 is a heterogeneous disease spectrum; therefore, timely risk stratification would be beneficial for selecting adequate therapies and for efficiently utilizing intensive care resources to save as many lives as feasible.[20] As early as 2021, an intriguing review regarding the possible implementation of

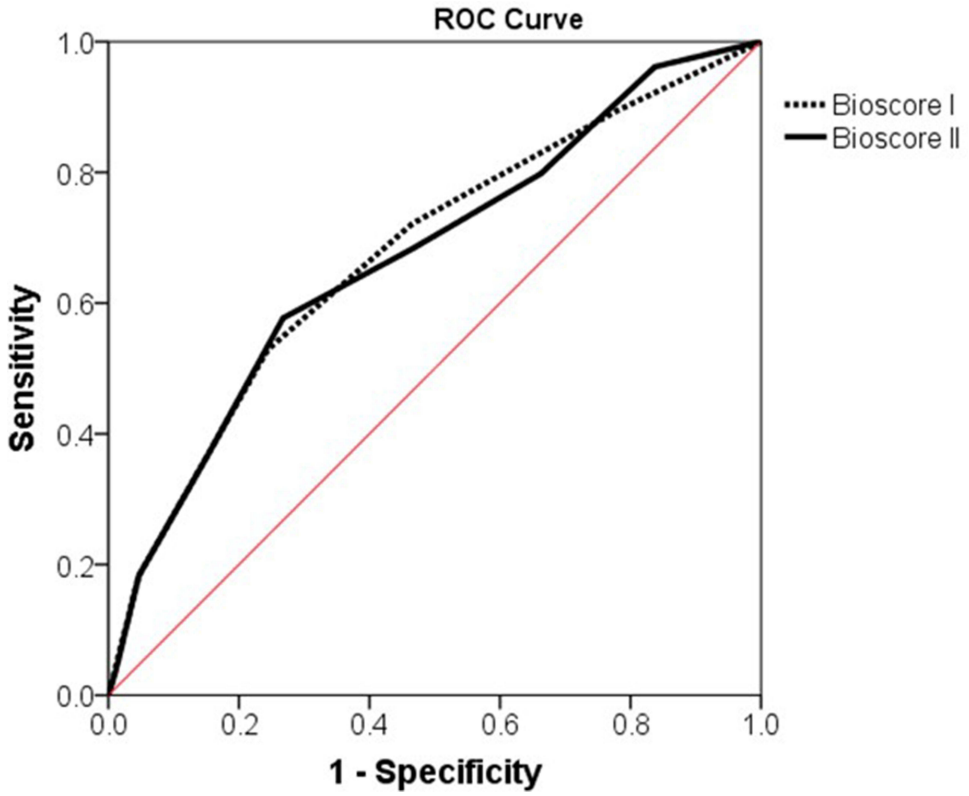

Figure 3 Receiver operating characteristic (ROC) curves of composite Bioscore I and II in predicting lethal outcomes.

Table 8 Multivariate Logistic Regression Analyses of Variables for Predicting Lethal Outcomes

Variables	Multivariate logistic regression		
	β	OR (95% CI)	p
Age	0.120	1.13 (1.07–1.19)	<0.001
Hospital stay	−0.455	0.64 (0.54–0.75)	<0.001
ICU stay	0.295	1.34 (1.16–1.55)	<0.001
Days before ICU	0.050	1.05 (0.92–1.21)	0.471
WBC	0.135	1.14 (0.96–1.36)	0.129
MPV/PC	0.075	1.08 (0.89–1.30)	0.432
CPR	−1.167	0.31 (0.02–4.90)	0.407
CLR	0.003	1.003 (0.996–1.009)	0.416
LLR	0.0	1.00 (0.999–1.001)	0.575
SII	0.0	1.0 (1.0–1.0)	0.508
SIRI	−0.069	0.93 (0.85–1.02)	0.128
CAR	−0.319	0.73 (0.41–1.28)	0.269
LAR, >0.05	0.24	1.28 (0.33–4.90)	0.722
LDH/ALB	0.169	1.18 (1.05–1.34)	0.007
IL-6	0.0	1.00 (0.997–1.004)	0.790
D-dimer	−0.054	0.948 (0.868–1.034)	0.226

Abbreviations: MPV/PC, Mean Platelet Volume-to-Platelet count Ratio; CLR, C-reactive protein (CRP)-to-Lymphocyte Ratio; CPR, CRP-to-Platelet Ratio; LLR, Lactate dehydrogenase (LDH)-to-Lymphocyte Ratio; Systemic Immune Inflammation Index (SII), platelet x neutrophil/lymphocyte count; Systemic Inflammation Response Index (SIRI), neutrophil x monocyte/lymphocyte count; CAR – C-reactive protein (CRP)-to-Albumin Ratio; LAR, Lactate-to-Albumin Ratio; LDH/ALB, Lactate dehydrogenase (LDH)-to-Albumin Ratio; Interleukin (IL)-6; OR – odds ratio; CI, Confidence Interval.

infection-mediated biomarkers for COVID-19 electrical biosensing platforms was published.[21] Apart from immunoinflammatory biomarkers (various immunocompetent cells and mediators) and coagulopathy biomarkers (d-dimer), markers for end-organ injury (lactate dehydrogenase - LDH and lactate) are of interest in this clinical setting.[22,23] Polypeptide inflammatory biomarkers such as CRP, procalcitonin, LDH, and serum albumin (ALB), as one of the most important proteins in human physiology, emerge as the focus of COVID-19 biomarker research.[24] In addition to examining the serum ALB level, recent research has also looked into the prognostic value of clinical indices that take albumin into account as a variable.[25] While many parameters generated from blood tests were rapidly incorporated into standard clinical practice, other suggested circulating biomarkers did not, despite their potential value. This was mostly because these biomarkers were more expensive and had limited availability in general hospital settings during medical emergencies like the COVID-19 pandemic.[26]

Because of the disease's intricate pathophysiology, there is undoubtedly no single biomarker that captures the essence of every remarkable feature of COVID-19. We previously demonstrated that several immune cell-based ratios can be used as prognostic parameters in critically ill patients who developed secondary sepsis.[5] In our present study, our aim was to investigate a variety of immune cell-based and albumin-based ratios as outcome predictors on admission to the ICU, in 612 critically ill COVID-19 patients. As far as immune cell-based ratios, ie, NLR, d-NLR, MPV, MPV/PC, MLR, N/LP,

CRP, LDH, CPR, CLR, LLR, SII, and SIRI values, all were higher in nonsurvivors, with differences reaching high statistical significance. On the other hand, monocyte count, and PLR values did not differ significantly between survivors and nonsurvivors. Contrary to our results, Ullah et al reported that there was no statistically significant difference in NLR and LCR values between COVID-19 survivors and nonsurvivors on day 1.[27] They concluded that high NLR and decreased LCR values predicted higher odds of mortality, but on day 7. Also, these authors included hospitalized COVID-19 patients, unlike our cohort of critically ill ICU patients. Another study regarding older COVID-19 patients evaluated NLR and PLR as predictors of mortality on hospital admission.[28] It was shown that higher values of both ratios are associated with a higher risk of mortality. This is partially in accordance with our results; higher NLR values were associated with lethal outcomes, but PLR values did not differ between survivors and nonsurvivors. In hospitalized COVID-19 patients, Regolo et al demonstrated that NLR is an independent predictor of mortality and ICU admission, unlike PLR.[29] In our study, NLR was a highly significant predictor of lethal outcomes only in univariate logistic regression analysis. It has to be noted that a possible explanation for this lack of independence in multivariate analysis might be that, in our investigation, only ICU COVID-19 patients were included. Two interesting studies included only critically ill COVID-19 patients admitted to the ICU, as we did in our investigation. The first one included 272 patients. Authors investigated NLR, d-NLR, PLR, and MLR as predictors of lethal outcome at time 0 (admission to the ICU), in addition to other variables at different time points.[30] Clinical accuracy of NLR and d-NLR was higher in our study (0.65 and 0.64, respectively, vs 0.62 and 0.60, respectively), while AUCs for PLR, MLR, and SII were between 0.5 and 0.6 in both studies. These authors investigated the dynamic changes of the listed parameters between time 0 and after 48 hours, which is a good approach. However, we opted to include more variables at one time point, ICU admission, in our pragmatic, real-life study. The second study included 348 patients.[31] Several immune cell-based (NLR, PLR, MLR, MPV, MPV/PC, SII) and albumin-based (LDH/ALB, CAR) parameters overlapped with those investigated in our study. In accordance with our results, all these parameters were significantly higher in nonsurvivors, except PLR, which was not statistically different between groups. However, the results of multiple logistic regression analysis showed that independent predictors of lethal outcome in this study were age and NLR, while our study demonstrated that independent predictors of death were age and LDH/ALB.

Given that CPR is an emerging risk factor that can indicate both coagulation state and inflammation, it is surprising that there is so little research on it in sepsis settings.

An interesting cross-sectional study regarding the clinical value of CPR in neonatal sepsis revealed that higher CPR values are an independent predictor of severe neonatal sepsis.[32] These results are in line with our findings of significantly higher levels of CPR in nonsurvivors.

CLR has lately gained popularity as an early sepsis marker[33] as well as an early biomarker to distinguish sepsis from pneumonia;[34] both of these recently published studies focused on neonates. In a multicenter, retrospective French investigation, the predictive value of CLR was examined with respect to COVID-19 severity and mortality at the emergency department (a cohort of around 1000 hospitalized patients with moderate to severe disease).[35] Contrary to our findings, the authors reported that only lymphocyte count was significantly linked with mortality in multivariate analysis. However, only one-quarter of this large French cohort were ICU patients. Regarding the clinical accuracy of CLR to predict mortality, French authors reported 159.5 as a cut-off value (AUC/ROC of 0.60; sensitivity 48%, specificity 70%). We found the same AUC/ROC, with very similar sensitivity and specificity (0.60, 47.1%, and 71.7%, respectively), but with a much higher best threshold of 230.8, presumably because of our different cohort (only ICU patients).

The prognostic ability of LLR was investigated in 145 severe COVID-19 patients.[36] The authors reported that LLR had the highest accuracy (AUC/ROC of 0.86) compared with other scores (NLR, CLR, CK-lymphocyte ratio, PT-lymphocyte ratio, APTT-lymphocyte ratio, and D-dimer-lymphocyte ratio). This is consistent with our results, which demonstrated the highest AUC/ROC of LLR (0.68) compared to other immune cell-based and albumin-based ratios, IL-6, bicarbonate, lactate, arterial B/DE, and D-dimer. Yet, there are differences between these two studies. Our study showed a lower LLR AUC/ROC value but was established on a more than 4-fold larger sample size. In another study,[37] a significant positive correlation was found between LLR and IL-6 levels in 94 hospitalized COVID-19 patients, contrary to our results.

A few years ago, it was reported that high SII is an independent predictor of lethal outcome in patients with metastatic colorectal cancer.[38] Recently, in a large cohort of 2218 hospitalized patients in the Department of Internal Medicine, SIRI quartiles 3 and 4, as well as SII quartiles 3 and 4, were independently associated with mortality.[39] SII, as a novel predictor of intubation requirement and mortality, was retrospectively investigated in 224 hospitalized COVID-19 patients. The authors reported that the severity and outcome of COVID-19 could be reliably predicted at admission by calculating this marker, with an emphasis on routinely assessed and feasible clinical laboratory values.[40] We agree with this approach, which can be particularly useful to improve patient management during a pandemic high-influx crisis. Our study demonstrated that both SI and SIRI values were significantly higher in nonsurvivors. However, their clinical accuracy in predicting lethal outcomes was not impressive (AUC/ROCs of 0.58 and 0.61, respectively), although it was statistically highly significant.

Similar to CLR, CAR has recently emerged as an early prognostic biomarker for neonatal sepsis with or without pneumonia.[7,41] The authors of recently published interesting research created a novel LASSO-COX-based prognostic nomogram regarding the association between CAR and 30-day mortality in ICU sepsis patients.[42] They concluded that the CAR-based model is highly accurate in predicting the risk of hospital mortality in this patient population. In a study of 116 COVID-19 patients, CAR was an independent risk factor for 30-day mortality.[43] However, of 116 enrolled COVID-19 patients, severe form of disease had only 17 and there were only 8 nonsurvivors. So, regarding mortality, there is a highly uneven size of two groups (survivors 108 vs nonsurvivors 8, 13.5-fold larger group). The June 2024 review of biomarkers as outcome predictors in sepsis found that CAR outperformed CRP or albumin alone in terms of sensitivity and specificity.[44] Contrary to these findings, in our cohort of critically ill COVID-19 patients, CRP, ALB, and CAR performed similarly in predicting lethal outcome (AUC/ROCs of 0.57, 0.61, and 0.59, respectively). A retrospective Turkish study enrolled 619 patients with severe COVID-19; the authors analyzed several albumin ratios [blood urea nitrogen (BUN)/ALB ratio (BAR), D-dimer/ALB ratio (DAR), neutrophil/ALB ratio (NAR), as well as CAR] regarding their prognostic ability.[45] Amazingly, all four studied ratios (BAR, NAR, DAR, and CAR) were found to be clinically accurate in predicting lethal outcomes with rather high AUC/ROSs (0.81, 0.82, 0.77, and 0.80, respectively). The authors of another similar large-scale study (611 COVID-19 patients; mortality rate of 73.2%) investigated the ferritin/ALB ratio (FAR) as a predictor of lethal outcomes.[46] They revealed even more impressive results: FAR is not only an independent predictor of mortality, but it also has an astonishing AUC/ROC of 0.95. Keeping in mind how protein catabolism is a major issue in critically ill patients, an interesting study revealed a new albumin-based marker, the urea/ALB ratio (UAR).[47] UAR can reflect inflammation and protein catabolism simultaneously, and the authors demonstrated that this marker is a very good predictor of lethal outcomes (AUC/ROC of 0.77).

LDH is the final marker enzyme in the metabolic pathway of anaerobic glycolysis with the end product of lactate from glucose; therefore, it is the generator of lactate. This enzyme is also a prognostic biomarker for immune surveillance.[48] During inflammatory activation, innate immune cells release a lot of lactates, implying that lactate metabolism plays a significant role in inflammation and appears to be a regulator of immune cell metabolism. Despite the most severe COVID-19 patients meeting the Sepsis-3.0 criteria for septic shock, there is a growing recognition that the absence of hyperlactatemia often results in an underestimation of illness severity and mortality risk. In severe COVID-19 patients, the Sepsis 3.0 criteria of septic shock may exclude approximately one third of patients with a similarly high risk of a poor outcome and mortality rate, which should be equally addressed.[2] This is in line with our findings, demonstrating that, although lactate levels were significantly higher in non-survivors, as shown in other studies,[49] the maximal value was 2.1 mmol/l, which is barely borderline hyperlactatemia in critically ill COVID-19 patients. Nevertheless, lactate level was a statistically highly significant yet modest predictor of lethal outcomes, with an AUC/ROC of 0.60.

LAR, as a prognostic biomarker at ICU admission, has been investigated in sepsis patients; the authors of one study revealed significantly higher 28-day mortality in sepsis patients with elevated LAR.[50] This is in accordance with our results showing that nonsurvivors had significantly elevated LAR at ICU admission. Regarding the clinical accuracy of LAR in predicting lethal outcomes in critically ill COVID-19 patients, we found that the AUC/ROC was 0.62, so LAR is in the group of statistically highly significant yet modest predictors. This is in line with results from the study of a total of 282 critically ill COVID-19 patients.[51] The authors revealed much higher AUC/ROCs values for lactate and LAR (0.79

and 0.82, respectively), while the AUC/ROC of 0.64 for albumin was slightly higher than in our study (the AUC/ROC of 0.61).

Of all investigated immune cell-based and albumin-based ratios, the only independent predictor of lethal outcomes by multivariate logistic regression analysis was LDH/ALB, along with age and hospital stay, in our cohort of 612 critically ill COVID-19 patients. LDH levels may reflect the extent of cellular damage, and ALB is a well-known negative acute-phase protein. This interesting ratio was investigated in a large cohort of 583 ICU sepsis patients as a predictor of outcome in a very interesting Korean study.[52] The authors used the same approach as we did, and they also investigated several albumin-based ratios. Regarding the clinical accuracy of LDH/ALB, LDH, ALB, CAR, and LAR in predicting lethal outcomes, their results were comparable to ours: LDH/ALB AUC/ROC of 0.64 vs 0.66 in our study; LDH AUC/ROC of 0.58 vs 0.64 in our study; ALB AUC/ROC of 0.63 vs 0.61 in our study; CAR AUC/ROC of 0.53 vs 0.59 in our study; LAR AUC/ROC of 0.61 vs 0.62 in our study. In accordance with our results, these authors demonstrated that the LDH/ALB ratio was independently associated with in-hospital mortality, and they concluded that it is useful as a prognostic factor in critically ill patients with sepsis. It has to be noted that we had a different patient population in terms of the causative organism; our patients had viral sepsis. Two studies recently published focused on the LDH/ALB ratio as a prognosticator of outcome in critically ill septic patients. In both of them, authors used data from the Medical Information Mart for intensive Care IV (MIMIC-IV) database for retrospective cohort analysis. First study included 4265 septic patients with a 28-day mortality rate of 51.9%.[53] It was demonstrated that patients with higher LDH/ALB levels had higher mortality. Also, AUC/ROC values for predicting mortality were 0.65 for LDH/ALB, 0.64 for LDH, and 0.55 for ALB. This is consistent with our results. The second study included 6059 septic patients from the MIMIC-IV database.[54] The authors performed retrospective cohort analysis with propensity score matching. Here also, patients with a high LDH/ALB ratio had a significantly higher mortality rate. The clinical accuracy of LDH/ALB in predicting lethal outcomes was comparable with our results; the AUC/ROC of 0.68 was slightly higher than our value of 0.66.

In the aforementioned study investigating LDH/ALD in COVID-19 patients,[31] contrary to our results, LDH/ALB was not an independent predictor of lethal outcomes. Another retrospective cross-sectional study evaluated LDH/ALB as an early outcome predictor in 477 hospitalized COVID-19 patients.[55] The authors revealed a higher AUC/ROC value of 0.76, with sensitivity and specificity of 72% and 70%, respectively. These values in our cohort of only critically ill COVID-19 patients were lower (0.66, 61%, and 65.8%, respectively). The prognostic value of LDH/ALB was investigated in 206 hospitalized COVID-19 patients older than 65 years.[56] Again, here the authors reported higher clinical accuracy of this ratio in predicting lethal outcomes (AUC/ROC of 0.81, sensitivity 75.9%, and specificity 76.3%) in comparison with our results obtained in a cohort of critically ill COVID-19 patients. The LHD/ALB ratio also proved to be useful in predicting COVID-19 severity.[57,58] There is one interesting study investigating LDH/ALB To-Urea Ratio (LAU) as a novel prognostic marker in COVID-19 patients.[59] The authors demonstrated that patients with high LAU have increased mortality rates (AUC/ROC of 0.67).

In an attempt to enhance the predictive value of investigated parameters regarding lethal outcomes, we created two composite bioscores. Bioscore I (LLR, NLR, IL-6, and D-dimer) and Bioscore II (to four existing parameters, MLR, LAR, and LDH/ALB are added). The clinical accuracy of Bioscore I in predicting fatal outcomes was better than that of individual components with an AUC/ROC of 0.7; Bioscor II with an AUC/ROC of 0.67 did not improve performance in comparison with individual parameters. For the most part, individual parameters as well as bioscores are moderate predictors, although statistically highly significant ones. In our patient population, however, both of the composite bioscores we created were better than the well-known SII and SIRI immunoinflammatory scoring systems (AUC/ROC of 0.70 and 0.67 vs 0.58 and 0.61, respectively). Our group used a similar approach in previous research, where composite bioscores were superior to individual parameters in predicting mortality in adult critically ill patients with secondary sepsis.[5,60]

The authors of a fairly recent comprehensive review of sepsis biomarkers concluded that most of them have not been well studied and that the clinical role of these biomarkers needs to be better evaluated.[61] Therefore, finding the perfect biomarker remains an eternal quest.[62] Biomarkers can help clinicians to prognosticate critically ill patients with sepsis of any origin; they should be useful in making informed decisions regarding patient care. Generally, the clinical context

should determine the interpretation of biomarkers, never using them as a stand-alone test. However, biomarkers do remain conceptually attractive.

Cause of death in critically ill COVID-19 patients is a very interesting issue. In 2021, compelling COVID-19-association-dependent categorization of death causes in 100 autopsy cases was published.[63] There were three types of associations: (1) "strong" (n=57), where COVID-19 was the primary cause of death; (2) "contributive" (n=27), where a pre-existing condition unrelated to COVID-19 was the primary cause of death; and (3) "weak" (n=16), where COVID-19 was either barely responsible for death or not at all. For both the "strong" and "contributive" categories, the leading cause of death was lung involvement, which showed up as diffuse alveolar damage (DAD) on the autopsy. Several post-mortem studies demonstrated that microthrombi were a major cause of cardiac injury in COVID-19.[64,65] In our patient population, in the early phase of treatment for critically ill COVID-19 patients, many fatalities were attributed to sudden cardiac death of unknown cause or cardiac arrest due to pulmonary thromboembolism, as these patients have a high risk of immunothrombosis. In contrast, cerebrovascular incidents accounted for a relatively small proportion of deaths among critically ill COVID-19 patients. The majority of deaths, however, resulted from refractory respiratory insufficiency, which typically occurs later in the disease progression. Refractory respiratory insufficiency is often a consequence of pulmonary fibrosis or complications from prolonged mechanical ventilation, such as ventilator-induced lung injury (VILI). Additionally, bacterial superinfections leading to sepsis were also significant contributors to mortality during this stage of the illness. In general, late deaths can be attributed to chronic critical illnesses, manifesting as various clinical endotypes such as persistent inflammation, immunosuppression, and catabolism syndrome (PICS), for instance.[66] Consistent with temporal patterns and clinical outcomes in our study are findings regarding an immunological time course analysis including COVID-19 patients, who had persistent inflammation and immunosuppression over the time and suffered worse clinical outcomes, especially when SARS-CoV-2 infection was followed by secondary bacterial infection.[67]

There are several limitations to the current investigation. Since this was a retrospective, single-center study, it was challenging to avoid any possible residual confounding. We cannot extrapolate our findings to the entire population of critically ill patients who are infected because the study was conducted during the COVID-19 pandemic in a very unique clinical setting. Therefore, these data should be interpreted with caution before applying them to the altered reality of 2023 and beyond (vaccination rates, variants, reinfections). Also, it must be acknowledged that all these investigated markers of inflammation are not specific for COVID-19; they are important parameters for other inflammatory diseases as well. Another drawback of our research is the single measurement of the investigated parameters.

Conclusion

Our study aimed to assess the prognostic value of an array of biomarkers regarding the likelihood of a lethal outcome in critically ill COVID-19 patients. We took advantage of the opportunity to classify them into immune cell-based and albumin-based parameters with a reasonable turnaround time in a critical care setting. The only independent predictor of lethal outcomes at ICU admission is the albumin-based LDH/ALB ratio. Most of the other parameters were moderate, although highly significant predictors of mortality in critically ill COVID-19 patients: levels of LLR, N/LP, NLR, LDH, IL-6, and D-dimer higher than cut-off values are moderate predictors of lethal outcomes.

Data Sharing Statement

Reasonable requests for data will be considered by the corresponding author.

Ethical Statement

Approval in concordance with the Declaration of Helsinki was obtained from the local Ethics Committee of the Military Medical Academy, Belgrade, Serbia on March 22, 2024 (No. 33/2024). Designated members of our research team gathered and synthesized a variety of demographic, clinical, and laboratory data from hospitalized patients' medical records. The patients' confidentiality was protected, and written consent was not required due to the retrospective nature of the study.

Funding

There was no funding.

Disclosure

The authors report no conflicts of interest in this study.

References

1. Rondovic G, Djordjevic D, Udovicic I, et al. From cytokine storm to cytokine breeze: did lessons learned from immunopathogenesis improve immunomodulatory treatment of moderate-to-severe COVID-19? *Biomedicines*. 2022;10(10):2620. doi:10.3390/biomedicines10102620
2. Cidade JP, Coelho LM, Costa V, et al. Septic shock 3.0 criteria application in severe COVID-19 patients: an unattended sepsis population with high mortality risk. *World J Crit Care Med*. 2022;11(4):246–254. doi:10.5492/wjccm.v11.i4.246
3. Shankar-Hari M, Calandra T, Soares MP, et al. Reframing sepsis immunobiology for translation: towards informative subtyping and targeted immunomodulatory therapies. *Lancet Respir Med*. 2024;12(4):323–336. doi:10.1016/S2213-2600(23)00468-X
4. Bauer M, Gerlach H, Vogelmann T, et al. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019-results from a systematic review and meta-analysis. *Crit Care*. 2020;24(1):239. doi:10.1186/s13054-020-02950-2
5. Djordjevic D, Rondovic G, Surbatovic M, et al. Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume-to-platelet count ratio as biomarkers in critically ill and injured patients: which ratio to choose to predict outcome and nature of bacteremia? *Mediators Inflamm*. 2018;2018:3758068. doi:10.1155/2018/3758068
6. Yang AP, Liu JP, Tao WQ, et al. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *Int Immunopharmacol*. 2020;84:106504. doi:10.1016/j.intimp.2020.106504
7. Li T, Li X, Wei Y, et al. Predictive value of C-reactive protein-to-albumin ratio for neonatal sepsis. *J Inflamm Res*. 2021;14:3207–3215. doi:10.2147/JIR.S321074
8. Tjendra Y, Al Mana AF, Espejo AP, et al. Predicting disease severity and outcome in COVID-19 patients: a review of multiple biomarkers. *Arch Pathol Lab Med*. 2020;144(12):1465–1474. doi:10.5858/arpa.2020-0471-SA
9. Li J, Li M, Zheng S, et al. Plasma albumin levels predict risk for nonsurvivors in critically ill patients with COVID-19. *Biomarker Med*. 2020;14(10):827–837. doi:10.2217/bmm-2020-0254
10. Vassiliou AG, Keskinidou C, Jahaj E, et al. ICU admission levels of endothelial biomarkers as predictors of mortality in critically ill COVID-19 patients. *Cells*. 2021;10(1):186. doi:10.3390/cells10010186
11. Oblitas CM, Galeano-Valle F, Ramírez-Navarro J, et al. Mid-regional pro-adrenomedullin, methemoglobin and carboxyhemoglobin as prognosis biomarkers in critically ill patients with COVID-19: an observational prospective study. *Viruses*. 2021;13(12):2445. doi:10.3390/v13122445
12. Gupta D, Jain A, Chauhan M, et al. Inflammatory markers as early predictors of disease severity in COVID-19 patients admitted to intensive care units: a retrospective observational analysis. *Indian J Crit Care Med*. 2022;26(4):482–486. doi:10.5005/jp-journals-10071-24171
13. Havaldar AA, Lobo V, Sushmitha EC, et al. Role of biomarkers and its trend to predict the outcome of COVID-19 patients: a retrospective study. *Indian J Crit Care Med*. 2022;26(9):1031–1035.
14. Pál K, Molnar AA, Huțanu A, et al. Inflammatory biomarkers associated with in-hospital mortality in critical COVID-19 patients. *Int J Mol Sci*. 2022;23(18):10423. doi:10.3390/ijms231810423
15. Sirvent JM, Baro A, Morales M, et al. Predictive biomarkers of mortality in critically ill patients with COVID-19. *Med Intensiva*. 2022;46(2):94–96. doi:10.1016/j.medin.2020.09.010
16. Vélez-Páez JL, Aguayo-Moscoso SX, Castro-Bustamante C, et al. Biomarkers as predictors of mortality in critically ill obese patients with COVID-19 at high altitude. *BMC Pulm Med*. 2023;23(1):112. doi:10.1186/s12890-023-02399-3
17. Dos Santos Medeiros SMFR, Sousa Lino BMN, Perez VP, et al. Predictive biomarkers of mortality in patients with severe COVID-19 hospitalized in intensive care unit. *Front Immunol*. 2024;15:1416715.
18. Uno K, Hasan A, Nakayama EE, et al. Predictive biomarkers of COVID-19 prognosis identified in Bangladesh patients and validated in Japanese cohorts. *Sci Rep*. 2024;14(1):12713. doi:10.1038/s41598-024-63184-8
19. Fouladseresht H, Doroudchi M, Rokhtabnak N, et al. Predictive monitoring and therapeutic immune biomarkers in the management of clinical complications of COVID-19. *Cytokine Growth Factor Rev*. 2021;58:32–48. doi:10.1016/j.cytogfr.2020.10.002
20. Samprathi M, Jayashree M. Biomarkers in COVID-19: an up-to-date review. *Front Pediatr*. 2021;8:607647. doi:10.3389/fped.2020.607647
21. Selvarajan RS, Gopinath SCB, Zin NM, et al. Infection-mediated clinical biomarkers for a COVID-19 electrical biosensing platform. *Sensors*. 2021;21(11):3829. doi:10.3390/s21113829
22. Chen CH, Lin SW, Shen CF, et al. Biomarkers during COVID-19: mechanisms of change and implications for patient outcomes. *Diagnostics*. 2022;12(2):509. doi:10.3390/diagnostics12020509
23. Arturi F, Melegari G, Giansante A, et al. COVID-19 biomarkers for critically ill patients: a compendium for the physician. *Neurol Int*. 2023;15(3):881–895. doi:10.3390/neurolint15030056
24. Sen A, Nigam A, Vachher M. Role of polypeptide inflammatory biomarkers in the diagnosis and monitoring of COVID-19. *Int J Pept Res Ther*. 2022;28(2):59. doi:10.1007/s10989-022-10366-5
25. Gremese E, Bruno D, Varriano V, et al. Serum albumin levels: a biomarker to be repurposed in different disease settings in clinical practice. *J Clin Med*. 2023;12(18):6017. doi:10.3390/jcm12186017
26. Rizzi M, D'Onghia D, Tonello S, et al. COVID-19 biomarkers at the crossroad between patient stratification and targeted therapy: the role of validated and proposed parameters. *Int J Mol Sci*. 2023;24(8):7099. doi:10.3390/ijms24087099
27. Ullah W, Basyal B, Tariq S, et al. Lymphocyte-to-C-reactive protein ratio: a novel predictor of adverse outcomes in COVID-19. *J Clin Med Res*. 2020;12(7):415–422. doi:10.14740/jocmr4227
28. Ortega-Rojas S, Salazar-Talla L, Romero-Cerdán A, et al. The neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio as predictors of mortality in older adults hospitalized with COVID-19 in Peru. *Dis Markers*. 2022;2022:2497202. doi:10.1155/2022/2497202

29. Regolo M, Vaccaro M, Sorce A, et al. Neutrophil-to-Lymphocyte Ratio (NLR) is a promising predictor of mortality and admission to intensive care unit of COVID-19 patients. *J Clin Med*. 2022;11(8):2235. doi:10.3390/jcm11082235
30. Moisa E, Corneci D, Negoita S, et al. Dynamic changes of the neutrophil-to-lymphocyte ratio, systemic inflammation index, and derived neutrophil-to-lymphocyte ratio independently predict invasive mechanical ventilation need and death in critically ill COVID-19 patients. *Biomedicines*. 2021;9(11):1656. doi:10.3390/biomedicines9111656
31. Gozdas HT, Kayis SA, Damarsoy T, et al. Multi-inflammatory index as a novel mortality predictor in critically ill COVID-19 patients. *J Intensive Care Med*. 2022;37(11):1480–1485. doi:10.1177/08850666221100411
32. Li X, Li T, Wang J, et al. Clinical value of C-reactive protein/platelet ratio in neonatal sepsis: a cross-sectional study. *J Inflamm Res*. 2021;14:5123–5129. doi:10.2147/JIR.S334642
33. Li X, Wei Y, Xu Z, et al. Lymphocyte-to-C-reactive protein ratio as an early sepsis biomarker for neonates with suspected sepsis. *Mediators Inflamm*. 2023;2023:9077787. doi:10.1155/2023/9077787
34. Liu X, Mu Y. Lymphocyte to C-reactive protein ratio as an early biomarker to distinguish sepsis from pneumonia in neonates. *J Inflamm Res*. 2023;16:3509–3517. doi:10.2147/JIR.S424897
35. Tonduangu N, Le Borgne P, Lefebvre F, et al. Crems network clinical research in emergency medicine and sepsis Clr. Prognostic value of C-Reactive Protein to Lymphocyte Ratio (CLR) in emergency department patients with SARS-CoV-2 infection. *J Pers Med*. 2021;11(12):1274. doi:10.3390/jpm11121274
36. Li G, Xu F, Yin X, et al. Lactic dehydrogenase-lymphocyte ratio for predicting prognosis of severe COVID-19. *Medicine*. 2021;100(4):e24441. doi:10.1097/MD.0000000000024441
37. Balci U, Demir Onder K, Seremet-Keskin A. Evaluation of the relationship between lactate dehydrogenase/lymphocyte ratio with Interleukin-6 levels in hospitalized patients with COVID-19. *Mediterr J Infect Microb Antimicrob*. 2021;10:62.
38. Xie QK, Chen P, Hu WM, et al. The systemic immune-inflammation index is an independent predictor of survival for metastatic colorectal cancer and its association with the lymphocytic response to the tumor. *J Transl Med*. 2018;16(1):273. doi:10.1186/s12967-018-1638-9
39. Çavuşoğlu Türker B, Ahbab S, Türker F, et al. Systemic immune-inflammation and systemic inflammation response indices are predictive markers of mortality in inpatients internal medicine services. *Int J Gen Med*. 2023;16:3163–3170. doi:10.2147/IJGM.S420332
40. Muhammad S, Fischer I, Naderi S, et al. Systemic inflammatory index is a novel predictor of intubation requirement and mortality after SARS-CoV-2 infection. *Pathogens*. 2021;10(1):58. doi:10.3390/pathogens10010058
41. Kang P, Kang W, Li Y, et al. C-Reactive protein-to-albumin ratio as an early biomarker to identify sepsis in neonates with pneumonia. *Mediators Inflamm*. 2022;2022:4711018. doi:10.1155/2022/4711018
42. Zhou X, Fu S, Wu Y, et al. C-reactive protein-to-albumin ratio as a biomarker in patients with sepsis: a novel LASSO-COX based prognostic nomogram. *Sci Rep*. 2023;13(1):15309. doi:10.1038/s41598-023-42601-4
43. El-Shabrawy M, Alsadik ME, El-Shafei M, et al. Interleukin-6 and C-reactive protein/albumin ratio as predictors of COVID-19 severity and mortality. *Egypt J Bronchol*. 2021;15:5. doi:10.1186/s43168-021-00054-1
44. Zhang N, Liu Y, Yang C, et al. Review of the predictive value of biomarkers in sepsis mortality. *Emerg Med Int*. 2024;2024:2715606. doi:10.1155/2024/2715606
45. Ertekin B, Acar T. The relationship between albumin and its proportion to other markers in predicting mortality in severe COVID-19 patients. *Eur Rev Med Pharmacol Sci*. 2023;27:6429–6436. doi:10.26355/eurrev_202307_33003
46. Taskin O, Yilmaz A, Soylu VG, et al. Ferritin/albumin ratio could be a new indicator of COVID-19 disease mortality. *J Infect Dev Ctries*. 2023;17:37–42. doi:10.3855/jidc.17409
47. Rodrigues HCN, Silva ML, Mantovani MDS, et al. Higher urea-to-albumin ratio is associated with mortality risk in critically ill COVID-19 patients. *Clin Nutr ESPEN*. 2023;56:9–12. doi:10.1016/j.clnesp.2023.04.017
48. Gupta GS. The lactate and the lactate dehydrogenase in inflammatory diseases and major risk factors in COVID-19 patients. *Inflammation*. 2022;45(6):2091–2123. doi:10.1007/s10753-022-01680-7
49. Bajić D, Matijašević J, Andrijević L, et al. Prognostic role of monocyte distribution width, CRP, procalcitonin and lactate as sepsis biomarkers in critically ill COVID-19 patients. *J Clin Med*. 2023;12(3):1197. doi:10.3390/jcm12031197
50. Li F, Ye Z, Zhu J, et al. Early lactate/albumin and procalcitonin/albumin ratios as predictors of 28-day mortality in ICU-admitted sepsis patients: a retrospective cohort study. *Med Sci Monit*. 2023; 29:e940654.
51. Gök A, Kasapoğlu US, Delen LA, et al. Lactate/albumin ratio as a prognostic factor for short-time mortality in critically ill patients with Coronavirus disease-2019. *Turk J Intensive Care*. 2021;19(62). doi:10.4274/tybd.galenos.2021.37167
52. Jeon SY, Ryu S, Oh SK, et al. Lactate dehydrogenase to albumin ratio as a prognostic factor for patients with severe infection requiring intensive care. *Medicine*. 2021;100(41):e27538. doi:10.1097/MD.0000000000027538
53. Liu Z, Liu F, Jie Y, et al. Association between lactate dehydrogenase to albumin ratio and 28-day mortality in patients with sepsis: a retrospective cohort study. *Clin Lab*. 2024;70(1). doi:10.7754/Clin.Lab.2023.230509
54. Guan X, Zhong L, Zhang J, et al. The relationship between lactate dehydrogenase to albumin ratio and all-cause mortality during ICU stays in patients with sepsis: a retrospective cohort study with propensity score matching. *Heliyon*. 2024;10(6):e27560. doi:10.1016/j.heliyon.2024.e27560
55. Alizadeh N, Tabatabaei FS, Azimi A, et al. Lactate dehydrogenase to albumin ratio as a predictive factor of COVID-19 patients' outcome; a cross-sectional study. *Arch Acad Emerg Med*. 2022;10(1):e63.
56. Altuntas G, Yazıcı MM, Celik A, et al. The prognostic significance of lactate dehydrogenase albumin ratio in elderly COVID-19 patients. *Mid Blac Sea J Health Sci*. 2022;8(3):432–439. doi:10.19127/mbsjohs.1129139
57. Avcioglu G, Otal Y, Haydar F. The importance of LDH/Albumin, LDH/Lymphocyte, and LDH/Platelet ratios in the evaluation of COVID-19 B.1.1.7 variant. *Turk J Biochem*. 2022;47(5):656–664. doi:10.1515/tjb-2021-0297
58. Siddeequa A, Volturi J, Fatima AK, et al. Serum lactate dehydrogenase to albumin ratio as a predictor of severity in COVID-19 patients. *Int J Res Med Sci*. 2023;11(1):238–242.
59. Shokr H, Marwah MK, Siddiqi H, et al. Lactate dehydrogenase/albumin to-urea ratio: a novel prognostic maker for fatal clinical complications in patients with COVID-19 infection. *J Clin Med*. 2022;12(1):19. doi:10.3390/jcm12010019
60. Rondovic G, Surbatovic M, Djordjevic D, et al. Composite bioscore is superior to routine biomarkers and established scoring systems in prediction of mortality in adult critically ill patients with secondary sepsis. *Vojnosanit Pregl*. 2021;78(11):1173–1184. doi:10.2298/VSP200312044R

61. Pierrakos C, Velissaris D, Bisdorff M, et al. Biomarkers of sepsis: time for a reappraisal. *Crit Care*. 2020;24(1):287. doi:10.1186/s13054-020-02993-5
62. Póvoa P, Coelho L, Dal-Pizzol F, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. *Intensive Care Med*. 2023;49(2):142–153. doi:10.1007/s00134-022-06956-y
63. Danics K, Pesti A, Törő K, et al. A COVID-19-association-dependent categorization of death causes in 100 autopsy cases. *Geroscience*. 2021;43(5):2265–2287. doi:10.1007/s11357-021-00451-w
64. Sang CJ, Burkett A, Heindl B, et al. Cardiac pathology in COVID-19: a single center autopsy experience. *Cardiovasc Pathol*. 2021;54:107370. doi:10.1016/j.carpath.2021.107370
65. Pellegrini D, Kawakami R, Guagliumi G, et al. Microthrombi as a major cause of cardiac injury in COVID-19: a pathologic study. *Circulation*. 2021;143(10):1031–1042.
66. Chadda KR, Puthucheary Z. Persistent inflammation, immunosuppression, and catabolism syndrome (PICS): a review of definitions, potential therapies, and research priorities. *Br J Anaesth*. 2024;132(3):507–518. doi:10.1016/j.bja.2023.11.052
67. Loftus TJ, Ungaro R, Dirain M, et al. Overlapping but disparate inflammatory and immunosuppressive responses to SARS-CoV-2 and bacterial sepsis: an immunological time course analysis. *Front Immunol*. 2021;12:792448. doi:10.3389/fimmu.2021.792448