Original Article

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

The Role of the De Ritis Ratio in ICU Mortality Among Critically Ill Patients with COVID-19

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Abstract

Objective: The De Ritis ratio (aspartate aminotransferase/alanine aminotransferase) has emerged as a prognostic biomarker in critical illness. This study aimed to evaluate the independent prognostic value of the De Ritis ratio for ICU mortality in critically ill patients with COVID-19. **Methods:** This retrospective observational cohort study was conducted at a single tertiary center. Medical records of 642 adult patients with RT-PCR–confirmed COVID-19 admitted to the Internal Medicine ICU between January and December 2021 were reviewed. Demographic data, comorbidities, laboratory parameters, severity scores (APACHE II and SOFA), and organ support requirements were recorded at ICU admission. Patients were stratified into survivor and non-survivor subgroups. Independent predictors of ICU mortality were identified through two multivariable logistic regression models. Discriminative performance was assessed by receiver operating characteristic curve analysis. **Results:** ICU mortality was recorded in 341 patients (53.1%). Non-survivors were significantly older and had markedly elevated inflammatory biomarkers, D-dimer, urea, and De Ritis ratio values. Although absolute AST and ALT concentrations did not differ significantly between groups, the De Ritis ratio was independently associated with ICU mortality in both models (Model A: OR 1.27, 95% CI 1.06–1.51, p = 0.009; Model B: OR 1.26, 95% CI 1.05–1.50, p = 0.013). Combining the De Ritis ratio with severity scores improved discriminative performance (AUC up to 0.661). **Conclusion:** The De Ritis ratio at ICU admission was independently associated with mortality in critically ill COVID-19 patients and provided additional prognostic information beyond established severity scores. Given its modest discriminative performance, it should be interpreted as a supplementary rather than a standalone prognostic marker.

Keywords: COVID-19; De Ritis ratio; ICU mortality

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1. Introduction

Multiorgan involvement is a defining pathophysiological feature of severe coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The predilection of SARS-CoV-2 for extrapulmonary tissues is largely attributable to the ubiquitous expression of angiotensin-converting enzyme 2 (ACE2)—its principal cellular receptor—across anatomically diverse sites including the myocardium,

hepatic parenchyma, renal tubules, intestinal epithelium, and vascular endothelium[1,2], conferring a systemic vulnerability that fundamentally distinguishes COVID-19 from classical respiratory viral syndromes.

A dysregulated and self-amplifying cytokine cascade, compounded by endothelial activation and coagulopathy, precipitates organ failure at sites remote from the primary pulmonary focus[3]. Hepatic involvement ranks among the most frequently encountered extrapulmonary complications, with abnormal liver enzyme concentrations documented in 14–53% of hospitalised patients[4]. The pathogenesis of this hepatic derangement is multifactorial, encompassing direct viral cytopathic effects on hepatocytes, cytokine storm-mediated hepatitis, hypoxia-driven ischaemia–reperfusion injury, and pharmacological hepatotoxicity[5].

Conventional hepatic monitoring focuses on absolute alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values, yet the ratio of AST to ALT—the De Ritis ratio—carries prognostic information that neither enzyme alone conveys. First described in 1957 as a tool for viral hepatitis classification[6], the De Ritis ratio has subsequently been validated as a mortality-associated biomarker across a spectrum of critical conditions including sepsis, acute respiratory distress syndrome (ARDS), and cardiovascular disease[7,8]. Accumulating evidence from COVID-19 cohorts indicates that an elevated De Ritis ratio at the time of initial presentation correlates with heightened disease severity, escalating therapeutic demands, and reduced likelihood of survival[9]. Its derivability from universally available routine laboratory data, without imposing any additional diagnostic burden, renders it a highly practicable candidate for early prognostic stratification[10]. Against this background, the present investigation sought to determine whether the De Ritis ratio at ICU admission constitutes an independent prognostic determinant of mortality in critically ill patients with confirmed COVID-19.

2. Materials and Methods

We performed a retrospective cohort analysis at a single tertiary-care center. Medical records of 642 adults aged 18 years or above admitted to the Internal Medicine ICU of Sakarya University Training and Research Hospital between January and December 2021 were reviewed. Entry into the study required both RT-PCR–confirmed SARS-CoV-2 infection and a complete set of clinical and biochemical data available at ICU admission. Exclusion criteria included age below 18 years, unavailable clinical or laboratory records, death preceding formal ICU admission or occurring within the initial 24-hour period of ICU stay, and concurrent terminal malignancy or pregnancy.

Demographic data, chronic comorbid conditions, laboratory and hematological results at ICU admission, ventilatory support requirements, vasopressor and inotropic therapy, and definitive ICU outcome were extracted. Acute illness severity was quantified using the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scoring systems. The De Ritis ratio was defined as the quotient of AST to ALT at ICU admission. Patients were allocated to survivor or non-survivor subgroups based on ICU outcome.

2.1. Statistical Analysis

Baseline characteristics were summarised using standard descriptive measures. Continuous variables satisfying the normality assumption were characterised as mean ± SD; all others as median (IQR). Normally distributed variables were compared using the independent-samples t-test; the Mann–Whitney U test served as the non-parametric counterpart. Categorical variables were compared by chi-square testing. Independent determinants of ICU mortality were identified through two multivariable logistic regression models: Model A combined the APACHE II score with the De Ritis ratio, while Model B

substituted the SOFA score. Calibration was checked with the Hosmer–Lemeshow test; discriminatory capacity was evaluated by ROC curves and AUC values. Two-tailed p values below 0.05 were considered statistically significant. All computations were carried out using IBM SPSS Statistics, version 22.0.

The study protocol was approved by the Clinical Research Ethics Committee of Sakarya University Faculty of Medicine (Approval Date: March 25, 2023; Decision No: 115). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Due to the retrospective design and use of anonymised patient data, the requirement for written informed consent was waived.

3. Results

A total of 642 COVID-19 patients admitted to the Internal Medicine ICU were eligible for analysis. ICU survival was achieved by 301 patients (46.9%); the remaining 341 (53.1%) died. Mean age was 69.50 ± 14.18 years. Non-survivors were modestly older (70.82 ± 14.34 vs. 68.01 ± 13.86 years; p = 0.012). Sex distribution was identical in both groups. Demographic and comorbidity data are given in Table 1.

Table 1. Baseline demographic characteristics and comorbidities at ICU admission

Variable	Survivors (n=301)	Non-survivors (n=341)	Total (N=642)	p
Age (years)	68.01±13.86	70.82±14.34	69.50±14.18	0.012
Female sex, n (%)	136 (45.2)	154 (45.2)	290 (45.2)	0.995
Malignancy, n (%)	18 (6.0)	52 (15.3)	70 (10.9)	<0.001
DM, n (%)	104 (34.6)	107 (31.4)	211 (32.9)	0.393
HT, n (%)	156 (51.8)	187 (54.8)	343 (52.0)	0.445
Coronary artery disease, n (%)	70 (23.3)	98 (28.7)	168 (26.2)	0.115
Heart failure, n (%)	29 (9.6)	42 (12.3)	71 (11.1)	0.280
COPD, n (%)	21 (7.0)	35 (10.3)	56 (8.7)	0.140
Asthma, n (%)	11 (3.7)	15 (4.4)	26 (4.0)	0.633
CKD, n (%)	27 (9.0)	41 (12.0)	68 (10.6)	0.209

Data are presented as mean ± SD or n (%). DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

Malignancy was markedly more prevalent among non-survivors (15.3% vs. 6.0%; p < 0.001; OR: 2.83; 95% CI: 1.62–4.96). Vasopressor therapy was required far more frequently among non-survivors (59.2% vs. 29.9%; OR: 3.41; 95% CI: 2.43–4.78; p < 0.001), as was invasive mechanical ventilation (72.4% vs. 21.9%; OR: 9.35; 95% CI: 6.50–13.45; p < 0.001). Results for all pharmacological and mechanical support interventions are detailed in Table 2.

Table 2. Association between pharmacological and mechanical support interventions and ICU mortality

Clinical Intervention	Survivors (n=301)	Non-survivors (n=341)	Total (N=642)	OR (95% CI)	p
Vasopressor use, n (%)	90 (29.9)	202 (59.2)	292 (45.5)	3.41 (2.43–4.78)	<0.001
Inotropic support, n (%)	41 (13.6)	76 (22.3)	117 (18.2)	1.83 (1.22–2.76)	0.004
Invasive mechanical ventilation, n (%)	66 (21.9)	247 (72.4)	313 (48.8)	9.35 (6.50–13.45)	<0.001
Non-invasive ventilation, n (%)	52 (17.3)	117 (34.3)	169 (26.3)	2.49 (1.71–3.62)	<0.001
High-flow nasal oxygen, n (%)	45 (15.0)	96 (28.2)	141 (22.0)	2.23 (1.48–3.36)	<0.001

Data are presented as n (%). ORs calculated using univariate logistic regression. OR: odds ratio; CI: confidence interval.

Routine blood count indices showed no statistically significant variation between outcome groups. Inflammatory markers diverged sharply: IL-6, CRP, and ferritin were each significantly higher in patients who died ($p = 0.006$, $p = 0.002$, and $p = 0.023$). Absolute AST and ALT values were comparable between outcome groups (AST: $p = 0.177$; ALT: $p = 0.497$). The De Ritis ratio was significantly higher in non-survivors (1.82 ± 0.99 vs. 1.60 ± 0.86; $p = 0.003$). Full laboratory results are in Table 3.

Table 3. Comparison of laboratory parameters at ICU admission between survivors and non-survivors

Parameter	Survivors (n=301)	Non-survivors (n=341)	Total (N=642)	p
Leukocyte ($\times 10^3/\mu L$)	10.70±11.42	11.25±7.34	10.99±9.48	0.469
Lymphocyte ($\times 10^3/\mu L$)	0.84±0.93	1.03±2.05	0.94±1.63	0.121
Neutrophil ($\times 10^3/\mu L$)	9.16±10.00	9.64±6.61	9.41±8.37	0.470
Hemoglobin (g/dL)	12.00±2.11	11.93±2.14	11.97±2.13	0.661
Platelet ($\times 10^3/\mu L$)	235.54±105.00	222.11±103.70	228.41±104.44	0.104
D-dimer (ng/mL)	731 (503–1840)	1050 (559–2215)	890 (540–2030)	0.003
Ferritin (ng/mL)	641 (279–1474)	900 (432–2000)	770 (350–1800)	0.023
IL-6 (pg/mL)	38 (19–96)	58 (24–141)	48 (21–118)	0.006
CRP (mg/L)	93 (54–154)	110 (64–180)	101 (58–170)	0.002
LDH (U/L)	456 (331–590)	485 (376–625)	470 (350–610)	0.058
Urea (mg/dL)	57 (42–88)	67 (45–100)	62 (44–94)	0.006
Creatinine (mg/dL)	1.27±1.36	1.47±1.35	1.37±1.35	0.063
Albumin (g/L)	30.03±4.55	29.08±5.13	29.52±4.89	0.011
Globulin (g/L)	22.77±12.84	24.09±14.13	23.47±13.55	0.219
CK-MB (U/L)	27.10±18.83	31.84±30.67	29.63±25.92	0.022
AST (U/L)	37 (26–55)	39 (26–61)	38 (26–58)	0.177
ALT (U/L)	26 (15–47)	25 (15–44)	25 (15–45)	0.497
De Ritis ratio	1.60±0.86	1.82±0.99	1.72±0.94	0.003

Data are presented as mean ± SD or median (IQR). IL-6: interleukin-6; CRP: C-reactive protein; LDH: lactate dehydrogenase; CK-MB: creatine kinase–myocardial band; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Severity score values were substantially higher among non-survivors: APACHE II 19.07 ± 7.37 vs. 15.60 ± 7.06 ($p < 0.001$), and SOFA 6.80 ± 2.72 vs. 5.35 ± 2.55 ($p < 0.001$) (Table 4).

Table 4. Comparison of prognostic scoring systems between survivors and non-survivors

Parameter	Survivors (n=301)	Non-survivors (n=341)	Total (N=642)	p
APACHE II score	15.60±7.06	19.07±7.37	17.44±7.43	<0.001
SOFA score	5.35±2.55	6.80±2.72	6.12±2.74	<0.001
De Ritis ratio	1.60±0.86	1.82±0.99	1.72±0.94	0.003

Data are presented as mean ± SD. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

Multivariable logistic regression established the De Ritis ratio as an independent predictor of ICU mortality across both models. In Model A, APACHE II (OR: 1.07; 95% CI: 1.05–1.09; $p < 0.001$) and De Ritis ratio (OR: 1.27; 95% CI: 1.06–1.51; $p = 0.009$) each retained significance. Model B yielded analogous findings for SOFA (OR: 1.23; 95% CI: 1.16–1.30; $p < 0.001$) and De Ritis ratio (OR: 1.26; 95% CI: 1.05–1.50; $p = 0.013$) (Table 5).

Table 5. Multivariable logistic regression analysis for ICU mortality

Model	Variable	OR (95% CI)	p
Model A	APACHE II score	1.07 (1.05–1.09)	<0.001
	De Ritis ratio	1.27 (1.06–1.51)	0.009
Model B	SOFA score	1.23 (1.16–1.30)	<0.001
	De Ritis ratio	1.26 (1.05–1.50)	0.013

OR: odds ratio; CI: confidence interval.

Standalone ROC analysis demonstrated modest but significant discrimination for the De Ritis ratio (AUC: 0.562; 95% CI: 0.517–0.606; p = 0.007). When incorporated into composite models, performance improved: AUC 0.652 (95% CI: 0.609–0.694) for the APACHE II–based model and 0.661 (95% CI: 0.619–0.703) for the SOFA-based model (Table 6, Figure 1).

Table 6. ROC curve analysis

Model	AUC	95% CI	p
De Ritis ratio	0.562	0.517–0.606	0.007
APACHE II score + De Ritis ratio	0.652	0.609–0.694	<0.001
SOFA score + De Ritis ratio	0.661	0.619–0.703	<0.001

AUC: area under the curve; CI: confidence interval.

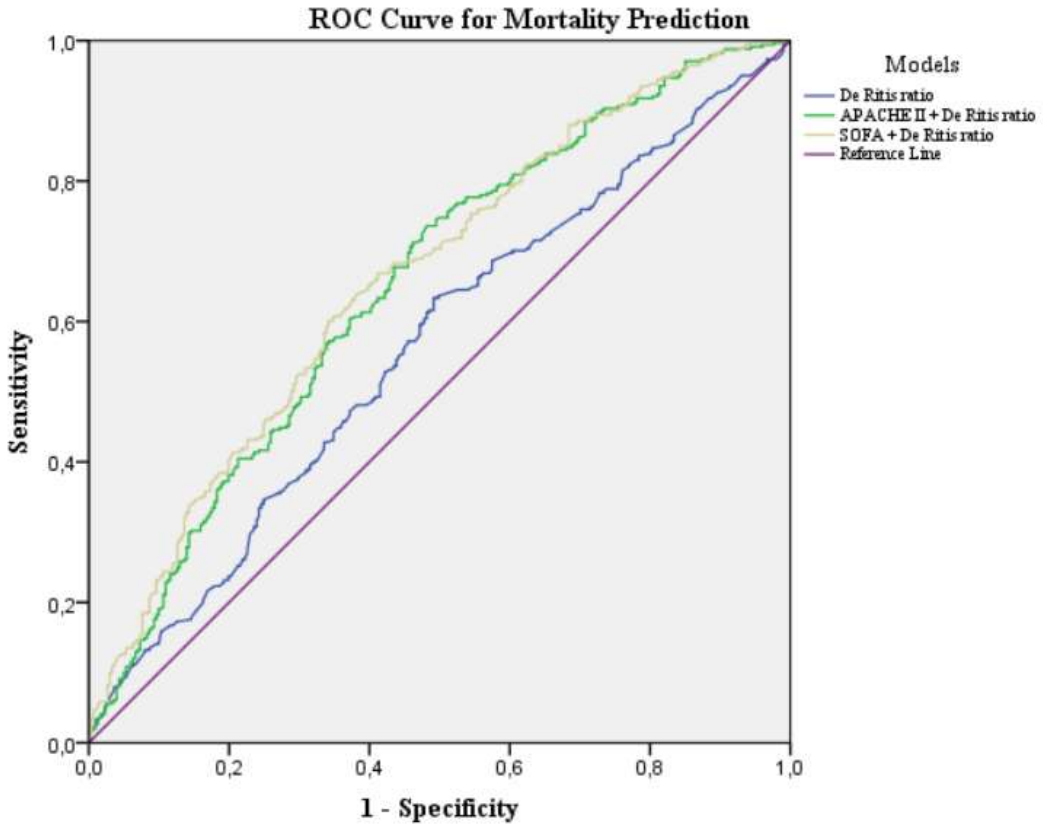

Figure 1. Receiver operating characteristic (ROC) curves for ICU mortality prediction using the De Ritis ratio alone and in combination with APACHE II and SOFA scores.

4. Discussion

Early and reliable identification of COVID-19 patients at elevated risk of ICU mortality remains among the most clinically consequential challenges in critical care medicine. The association between older age and ICU mortality aligns with the widely accepted view that advancing age is a primary mortality driver in COVID-19 critical illness[11]. The absence of a significant sex-based survival differential in our cohort, notwithstanding prior reports documenting higher male mortality[12,13], may be attributable to a ceiling effect inherent to the critical care setting: at the severity of systemic inflammation and

multiorgan dysfunction characterising our patient population, comparatively modest physiological sex differences are likely substantially attenuated[14].

Active malignancy emerged as the comorbidity most strongly and independently associated with ICU mortality, a finding consistent with observations from comparable critically ill populations[15]. Non-survivors required substantially more intensive pharmacological and mechanical organ support. The disproportionate vasopressor requirement reflects the hemodynamic compromise that ensues when cytokine-driven systemic inflammation simultaneously impairs vascular tone, myocardial contractility, and microvascular integrity[16]. The markedly higher prevalence of invasive mechanical ventilation among non-survivors is consistent with the well-documented relationship between refractory hypoxaemic respiratory failure, progressive ARDS, and mortality[17].

The absence of discriminatory power among routine hematological indices is consistent with the hypothesis that the uniformly dysregulated inflammatory milieu at ICU level abolishes marginal prognostic signals[18,19]. Significantly elevated IL-6, CRP, and ferritin in non-survivors are pathophysiologically coherent with hyperinflammation as the principal driver of multiorgan failure[20,21]. Hypoalbuminaemia in non-survivors most plausibly reflects capillary leak, suppressed albumin synthesis, and nutritional compromise[22]. Elevated admission urea in the absence of a corresponding creatinine rise is suggestive of prerenal azotaemia[23]. Significantly elevated D-dimer concentrations are mechanistically consonant with the microvascular thrombosis characterising severe COVID-19[24,25].

The most mechanistically notable observation was the significant divergence in De Ritis ratio between outcome groups ($p = 0.003$) despite the absence of any significant difference in absolute AST or ALT concentrations. Under conditions of widespread oxidative stress, tissue hypoxia, or mitochondrial dysfunction, AST is liberated in disproportionate excess relative to ALT, a consequence of its broader intracellular distribution and shorter biological half-life. The De Ritis ratio thereby encodes a biochemical pattern of systemic tissue injury that neither enzyme measurement independently captures. This mechanistic interpretation is substantiated by analogous observations from both COVID-19 and non-COVID-19 critical care cohorts[7,9,26].

That the De Ritis ratio remained an independent mortality predictor in both multivariable models implies that it captures prognostic information not fully contained within established clinical scoring systems. Its practical value lies in providing incremental information from tests already available at ICU admission[27,28]. Although discriminative performance alone was modest, its integration with established severity scores improved predictive performance. These findings may also have broader implications beyond COVID-19, particularly in critically ill patients with ARDS and multiorgan dysfunction, where systemic inflammation and tissue injury play central roles.

Several limitations warrant explicit acknowledgement. The retrospective single-center design constrains causal inference and may restrict generalisability. Restriction of analysis to admission-time data precludes characterisation of De Ritis ratio trajectories across the ICU course. A clinically applicable cut-off value could not be established, and incomplete documentation of chronic liver disease may have introduced residual confounding. The performance of multiple simultaneous comparisons entails a risk of type I error inflation.

5. Conclusion

In the present cohort of critically ill patients with COVID-19 requiring intensive care, the De Ritis ratio at ICU admission was independently associated with mortality and provided additional prognostic information beyond established severity scoring systems. Given that its derivation requires no investigations beyond those routinely obtained at ICU entry, the De Ritis ratio warrants consideration as a cost-neutral supplementary

stratification parameter in this patient population. Prospective multicenter validation is required to determine optimal cut-off thresholds and to define its position within standardised risk-assessment algorithms for COVID-19 critical illness.

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