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The lethal dance of COVID-19 with sepsis: predicting mortality using C-reactive protein, red cell distribution width, albumin and their ratios

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ABSTRACT

Aims: This study aimed to assess the impact of sepsis or secondary infection on mortality among COVID-19 patients admitted to the intensive care unit (ICU), and to evaluate the prognostic utility of C-reactive protein (CRP), red cell distribution width (RDW), albumin levels, and their derived ratios—CRP/albumin (CAR), RDW/albumin (RAR), and CRP×RDW/albumin (CRAR).

Methods: A retrospective cohort of 471 patients aged 18–75 years, treated between January and May 2021 at Ankara Bilkent City Hospital, was analyzed. Patients were classified into three groups: isolated COVID-19, COVID-19 with sepsis, and COVID-19 with secondary non-sepsis infection. Demographic and clinical characteristics, as well as ICU mortality rates, were compared between survivors and non-survivors. The predictive value of CAR, RAR, and CRAR ratios was statistically evaluated.

Results: Sepsis was associated with significantly higher mortality, age, APACHE II scores, lactate, and procalcitonin levels. Deceased patients had lower albumin levels and higher RDW and RAR values. ROC analysis revealed that RDW and RAR were significant predictors of mortality in the isolated COVID-19 group, while albumin and RAR were significant in the secondary infection group. Although univariate analysis highlighted associations between RAR and CRAR with mortality, multivariate analysis identified age, lactate, and sepsis status as independent predictors; notably, sepsis increased mortality by approximately 2.8-fold.

Conclusion: Sepsis dramatically increases mortality risk in COVID-19 ICU patients. RDW, albumin, and their corresponding ratios offer practical value for risk stratification, but must be interpreted within the context of established risk factors such as age and lactate. These biomarkers can aid prognostication, yet should be validated across larger and multicentric cohorts for wider clinical application.

Keywords: Ratio of C-reactive protein to albumin (CAR), ratio of red cell distribution width to albumin (RAR), COVID-19, sepsis, mortality, secondary infection

INTRODUCTION

Since its initial emergence in Wuhan, China in December 2019, COVID-19 has manifested with symptoms ranging from mild fatigue and myalgia to severe pneumonia and respiratory distress, with ICU mortality rates reaching as high as 40%.[1-3] Many patients admitted to intensive care present with symptoms directly related to COVID-19, but the co-occurrence of secondary infections or sepsis is common and frequently accompanied by multi-organ failure, further worsening prognosis.[4-6]

Inflammatory mechanisms are fundamental in organ dysfunction and mortality in COVID-19, notably through cytokine-driven lymphopenia and hyperinflammation.[7,8] COVID-19 patients typically show elevations in inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate, and lactate dehydrogenase.[9] CRP, an acute phase protein primarily synthesized by the liver, rises rapidly in plasma following tissue injury or infection, often within 48 hours, and high CRP levels are consistently associated with poor prognosis and increased mortality in critically ill patients.[10,11]

Similarly, albumin is produced by hepatocytes; its synthesis is suppressed by proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, making hypoalbuminemia a marker of severe inflammatory

response.[12] The CRP/albumin ratio (CAR) has been introduced in several studies as a valuable prognostic marker for disease severity in COVID-19.[13,14]

Red cell distribution width (RDW), calculated as the standard deviation of red blood cell volume divided by the mean corpuscular volume, is a cost-effective index of erythrocyte size variability and is widely used in hematological diagnostics.[15] Elevated RDW serves as a predictor of ICU mortality and is strongly correlated with disease severity and poor outcomes in COVID-19.[16-18] Furthermore, RDW elevation at hospital admission independently predicts mortality and advanced support needs, while high RDW/albumin ratios (RAR) also reflect systemic inflammation and nutritional impairment, indicating higher risk for ICU admission and mortality.[19]

Studies have established the prognostic value of CRP, CAR, RDW, and RAR in COVID-19.[11,19] The unique aspect of this study is stratifying ICU-admitted COVID-19 patients into isolated COVID-19 (COV), COVID-19 with sepsis (COV-S), and COVID-19 with non-sepsis secondary infection (COV-SE) subgroups. The hypothesis is that CRP, RDW, albumin, CAR, RAR, and CRP×RDW/albumin (CRAR) ratios yield improved prediction of mortality in patients with secondary infection or sepsis.

The aim of this study is to evaluate the predictive value of CRP, RDW, albumin, CAR, RAR, and CRAR for mortality in COVID-19 patients with or without secondary infection or sepsis.

METHODS

This study has been approved by the Ethics Committee of Clinical Researches No. 1 at Ankara Bilkent City Hospital (Date: 23.03.2022, Decision No: E1-22-2487). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patient data were obtained from hospital electronic medical records and files, retrospectively. Between January 1 and May 31, 2021, COVID-19 ICU patients aged 18-75 years were included; cases with missing data were excluded, yielding 471 evaluated patients. Patients were classified into three groups: COV, COV-S, and COV-SE. COV-SE were defined as microbiologically or clinically confirmed infections that did not meet Sepsis-3 criteria (i.e., no SOFA score increase ≥2 attributable to infection). This group included conditions such as hospital-acquired or ventilator-associated pneumonia, urinary tract infections, catheter-related bloodstream infections, and soft-tissue infections. The timing of infection onset, clinical findings, laboratory results, and culture data were reviewed to classify patients accurately. Sepsis diagnosis was based on 2021 SSC guidelines, procalcitonin levels, and blood culture positivity.[20] Sepsis diagnosis was made in accordance with the 2021 Surviving Sepsis Campaign (SSC) guidelines and fully aligned with the sepsis-3 definition. An acute increase of ≥2 points in the SOFA score was required for diagnosing sepsis. SOFA scores were available for all patients and were systematically evaluated at ICU admission. Elevated procalcitonin levels and blood culture positivity were used as supportive findings to differentiate sepsis from non-sepsis secondary infections, but SOFA ≥2 remained the essential diagnostic criterion.

Demographic data (age, sex), comorbidities (hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease (CKD), asthma, chronic obstructive pulmonary disease, heart failure, prior stroke, malignancy), pregnancy status, presence of sepsis or secondary infection at ICU admission, ICU and hospital length of stay, laboratory values at admission (CRP, RDW, albumin, procalcitonin, WBC, urea, creatinine, lymphocyte, lactate), APACHE II score, and clinical outcomes (survival, death) were recorded. APACHE II scores were recorded at ICU admission for all patients. The variability in APACHE II values reflects the heterogeneity in clinical severity at presentation. Some patients were admitted while receiving non-invasive respiratory support such as CPAP or high-flow nasal oxygen, whereas others had already been intubated before ICU transfer. Because patients entered the ICU at different stages of respiratory failure and organ dysfunction, baseline APACHE II scores naturally showed wide variation.

Statistical Analysis

The data analyses were performed using SPSS version 27.0 with a 95% confidence level. The distribution of numerical variables was assessed using Shapiro–Wilk and Kolmogorov–Smirnov tests. Normally distributed variables were analyzed with independent samples t-test or one-way ANOVA, while non-normally distributed variables were evaluated with Mann–Whitney U or Kruskal–Wallis tests. Categorical data were compared using Chi-square tests.

Correlations between numerical variables were examined using Pearson or Spearman methods based on normality. Logistic regression analysis was applied first in a univariate model to identify variables potentially associated with mortality. Variables with $p<0.10$ in univariate analysis were included in the multivariate logistic regression model.

Due to high multicollinearity between RDW, RAR, and CRAR, RDW was excluded from the multivariate model to avoid model instability and overfitting. Receiver operating characteristic (ROC) curves were used to assess the discriminatory power of CRP, albumin, RDW, CAR, RAR, and CRAR. ROC AUC values were interpreted as follows: 0.5–0.6 (poor), 0.6–0.7 (fair), 0.7–0.8 (acceptable), 0.8–0.9 (excellent), and >0.9 (outstanding). Cut-off values were selected using Youden's index. Interpretation of ROC findings was performed clinically as well as statisticall.

RESULTS

Of the 471 patients, 71.3% were in the COV group, 17.2% in COV-S, and 11.5% in COV-SE. The male proportion was 58.4%. Hypertension (48.4%), diabetes mellitus (33.3%), and coronary artery disease (19.3%) were the most common comorbidities. Overall mortality was 47.1% (**Table 1**).Comparing group characteristics, comorbidity count (p=0.014), CKD (p=0.000), prior stroke (p=0.001), malignancy (p=0.038), and mortality (p=0.000) differed significantly; COV-SE had higher comorbidity (%31.5) and stroke rates(%13.0), while the COV-S group showed higher

CKD (%27.2), malignancy (%17.3), and mortality rates (74.1) (**Table 1**).

Among deceased patients, comorbidity count (p=0.004), CKD (p=0.001), and heart failure (p=0.023) were significantly higher (**Table 1**).

The mean age was 65.29±16.15 years, with significant differences between groups (p=0.002); COV-S had the highest mean age, significantly more than COV (p=0.008). Mean APACHE II score was 18.1±13.77, lowest in COV (16.41±13.6) and higher in COV-S (22.95±12.92) and COV-SE (21.33±13.99) (**Table 2**).

Table 1. Comparison of patients' demographic and clinical characteristics in terms of diagnosis and mortality

		COV[a]	COV-S[b]	COV-SE[c]	Total	p	p[a-b]	p[a-c]	p[b-c]	Alive	Deceased	p
		(n=336)	(n=81)	(n=54)	(n=471)					(n=249)	(n=222)	
Gender	Male	198 (58.9)	53 (65.4)	24 (44.4)	275 (58.4)	0.051				141 (56.6)	134 (60.4)	0.412
	Female	138 (41.1)	28 (34.6)	30 (55.6)	196 (41.6)					108 (43.4)	88 (39.6)	
Number of comorbidities	None	69 (20.5)	6 (7.4)	8 (14.8)	83 (17.6)					57 (22.9)	26 (11.7)	
	1	62 (18.5)	22 (27.2)	8 (14.8)	92 (19.5)					46 (18.5)	46 (20.7)	
	2	88 (26.2)	17 (21)	10 (18.5)	115 (24.4)	0.014*	0.012*	0.08	0.349	65 (26.1)	50 (22.5)	0.004*
	3	63 (18.8)	15 (18.5)	11 (20.4)	89 (18.9)					44 (17.7)	45 (20.3)	
	≥4	54 (16.1)	21 (25.9)	17 (31.5)	92 (19.5)					37 (14.9)	55 (24.8)	
Comorbidity	HT	158 (47)	43 (53.1)	27 (50)	228 (48.4)	0,6				119 (47.8)	109 (49.1)	0.777
	DM	112 (33.3)	25 (30.9)	20 (37)	157 (33.3)	0.759				81 (32.5)	76 (34.2)	0.695
	CAD	62 (18.5)	16 (19.8)	13 (24.1)	91 (19.3)	0.633				42 (16.9)	49 (22.1)	0.153
	CKD	31 (9.2)	22 (27.2)	10 (18.5)	63 (13.4)	0.000**	0.000**	0.068	0.342	21 (8.4)	42 (18.9)	0.001*
	Asthma	24 (7.1)	4 (4.9)	3 (5.6)	31 (6.6)	0.872				15 (6)	16 (7.2)	0.741
	COPD	30 (8.9)	5 (6.2)	4 (7.4)	39 (8.3)	0.802				17 (6.8)	22 (9.9)	0.296
	History of stroke	11 (3.3)	10 (12.3)	7 (13)	28 (5.9)	0.001*	0.003*	0.006*	0.999	11 (4.4)	17 (7.7)	0.197
	Malignancy	26 (7.7)	14 (17.3)	7 (13)	47 (10)	0.038*	0.016*	0.194	0.663	20 (8)	27 (12.2)	0.181
	HF	20 (6)	9 (11.1)	7 (13)	36 (7.6)	0.069				12 (4.8)	24 (10.8)	0.023*
Pregnancy	No	331 (98.5)	80 (98.8)	54 (100)	465 (98.7)	0.999				244 (98)	221 (99.5)	0.22
	Yes	5 (1.5)	1 (1.2)	0 (0)	6 (1.3)					5 (2)	1 (0.5)	
Exitus	No	201 (59.8)	21 (25.9)	27 (50)	249 (52.9)	0.000**	0.000**	0.226	0.007*			
	Yes	135 (40.2)	60 (74.1)	27 (50)	222 (47.1)							

COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HF: Heart failure
**p<0.001 *p<0.05 statistically significant relationship, p>0.05 not significant; Pearson Chi-square test

Table 2. Comparison of patients' clinical, demographic, and laboratory measurements in terms of diagnosis and mortality

	COV[a]	COV-S[b]	COV-SE[c]	Total	p	a-b p	a-c p	b-c p	Alive	Deceased	p
	(n=336)	(n=81)	(n=54)	(n=471)					(n=249)	(n=222)	
Age	63.65±16.29	69.6±15.42	68.96±14.78	65.29±16.15	0.002*	0.008*	0.072	0.999	61.07±15.69	70.01±15.36	0.000**
APACHE II	16.41±13.6	22.95±12.92	21.33±13.99	18.1±13.77	0.000**	0.000**	0.040*	0.999	11.86±8,45	25.11±15.16	0.000**
ICU stay	13.98±16.3	11.26±10.66	16.83±17.66	13.84±15.68	0.23				15.06±17.96	12.47±12.56	0.936
Hospital stay	21.24±21.01	17.36±15.82	28.06±32.96	21.36±22.08	0.114				26.39±26.06	15.71±14.63	0.000**
CRP	109.73±77.98	168.76±106.26	113±71.77	120.26±85.6	0.000**	0.000**	0.999	0.000**	116.04±87.68	124.99±83.15	0.136
Albumin	35.6±5.14	32.11±5.85	35.11±7.54	34.94±5.72	0.000**	0.000**	0.999	0.007*	35.73±5.35	34.06±6	0.002*
RDW	14.76±2.15	15.91±2.29	15.4±2	15.03±2.2	0.000**	0.000**	0.006*	0.174	14.6±1.98	15.52±2.33	0.000**
CAR	3.14±2.24	5.47±3.57	3.42±2.4	3.57±2.67 (3)	0.000**	0.000**	0.999	0.000**	3.36±2.67	3.82±2.67	0.06
RAR	0.43±0.1	0.51±0.12	0.46±0.13	0.44±0.12	0.000**	0.000**	0.084	0.026*	0.42±0.1	0.47±0.12	0.000**
CRAR	46.56±35.02	86.16±55.35	53.19±38.57	54.13±42.21	0.000**	0.000**	0.762	0.000**	49.26±40.48	59.59±43.60	0.008*
PRC	0.26±0.29	10.74±13.19	3.39±8.22	2.42±7.26	0.000**	0.000**	0.000**	0.000**	1.54±5.41	3.42±8.79	0.000**
WBC	10.1±4.84	12.55±7.17	9.98±4.83	10.5±5.38	0.012*	0.003*	0.819	0.044*	9.93±4.87	11.15±5.84	0.042*
Urea	61.49±44.74	110.42±64.97	76.74±46.87	71.65±52.24	0.000**	0.000**	0.002*	0.000**	57.74±41.48	87.27±58.39	0.000**
Lymphocyte	0.74±0.48	0.73±0.62	0.71±0.4	0.74±0.5	0.303				0.71±0.43	0.76±0.56	0.951
Lactate	2.08±1.54	3.12±3.25	2.19±1.49	2.27±1.97	0.032*	0.009*	0.487	0.203	1.76±0.76	2.85±2.64	0.000**

COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, CRP: C-reactive protein, RDW: Red cell distribution width, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, WBC: White blood cell, **p<0.001 *p<0.05 indicates significant difference, p>0.05 indicates no significant difference

In COV-S, CRP, RDW, CAR, RAR, and CRAR values were highest; albumin was lowest. These biomarker values were significantly higher in COV-S than in both other groups (p<0.05), but not between COV and COV-SE. RDW was substantially higher in COV-S compared to COV (p=0.000), and in COV-SE compared to COV (p=0.006), (**Table 2**).

Procalcitonin, WBC, and lactate levels were highest in COV-S and lowest in COV; procalcitonin had significant differences across all groups (p=0.000), but WBC only differed between COV and COV-S. Lactate was significantly elevated in COV-S versus COV (p=0.009). Urea was lowest in COV (61.5±44.7) and highest in COV-S (110.4±65.0), (**Table 2**).

Deceased patients had significantly higher age (70.0±15.36), APACHE II (25.11±15.16), (p=0.000), and biomarker values (CRP, RDW, CAR, RAR, CRAR, PRC, WBC, urea, lymphocyte, lactate), whereas albumin was lower (**Table 2**).

ROC analysis demonstrated that, in the COV-SE group, albumin and RAR were significant predictors for survival (p<0.05); in the COV group, RDW and RAR were significant (p<0.05). Other biomarkers showed no significant predictive value (p>0.05) (**Table 3**). The cut-off values in COV-SE were 33.5 for albumin (**Figure 1**) and 0.4886 for RAR (**Figure 2**), with correct prediction rates for deceased patients of 0.593 and 0.519, and for survivors, 0.741 and 0.666. In the COV group, RDW and RAR cut-off values were 14.35 (**Figure 3**) and 0.4236 (**Figure 4**), with corresponding correct prediction rates for deceased patients of 0.637 and 0.504 and for survivors, 0.621 and 0.787 (**Table 4**).

Table 3. ROC analysis results

Measurement	Group (n)	ROC area	sh	p	%95 CI	
					Lower	Upper
CRP	COV (n=336)	0.537	0.032	0.251	0.474	0.599
	COV-S (n=81)	0.403	0.080	0.187	0.246	0.560
	COV-SE (n=54)	0.464	0.079	0.647	0.308	0.619
Albumin	COV (n=336)	0.549	0.032	0.131	0.485	0.612
	COV-S (n=81)	0.557	0.071	0.438	0.417	0.697
	COV-SE (n=54)	0.676	0.073	0.027*	0.532	0.820
RDW	COV (n=336)	0.630	0.031	0.000*	0.569	0.692
	COV-S (n=81)	0.547	0.068	0.525	0.414	0.680
	COV-SE (n=54)	0.582	0.079	0.303	0.427	0.736
CAR	COV (n=336)	0.542	0.032	0.187	0.480	0.605
	COV-S (n=81)	0.408	0.081	0.209	0.248	0.567
	COV-SE (n=54)	0.538	0.080	0.634	0.382	0.694
RAR	COV (n=336)	0.599	0.032	0.002*	0.537	0.661
	COV-S (n=81)	0.556	0.068	0.444	0.423	0.690
	COV-SE (n=54)	0.665	0.075	0.037*	0.518	0.812
CRAR	COV (n=336)	0.560	0.032	0.061	0.498	0.623
	COV-S (n=81)	0.418	0.081	0.265	0.258	0.578
	COV-SE (n=54)	0.549	0.080	0.539	0.392	0.705

ROC: Receiver operating characteristic, CI: Confidence interval, CRP: C-reactive protein, RDW: Red cell distribution width, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, *p<0.05

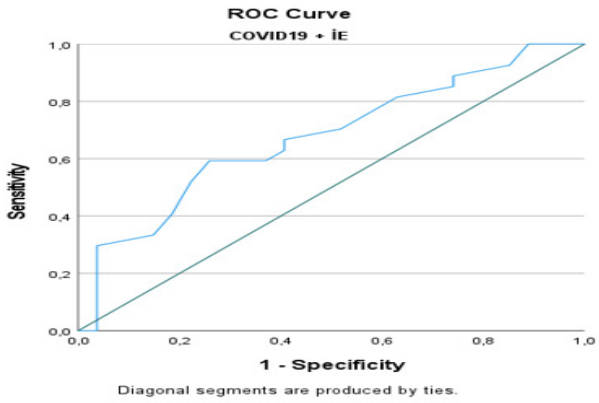

Figure 1. Albumin: COV-SE ROC curve
COV-SE: COVID-19 with non-sepsis secondary infection, ROC: Receiver operating characteristic

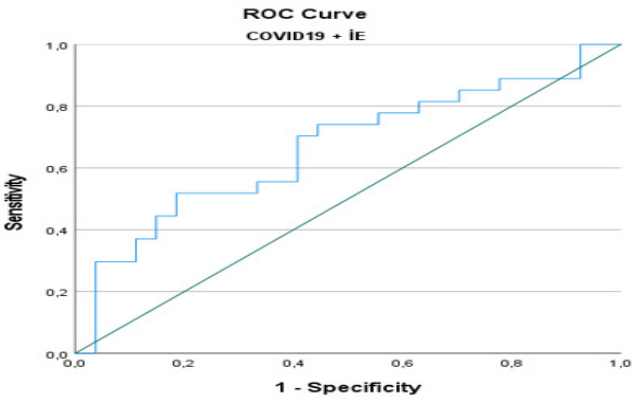

Figure 2. RAR: COV-SE ROC curve
RAR: Red cell distribution width/albumin, COV-SE: COVID-19 with non-sepsis secondary infection, ROC: Receiver operating characteristic

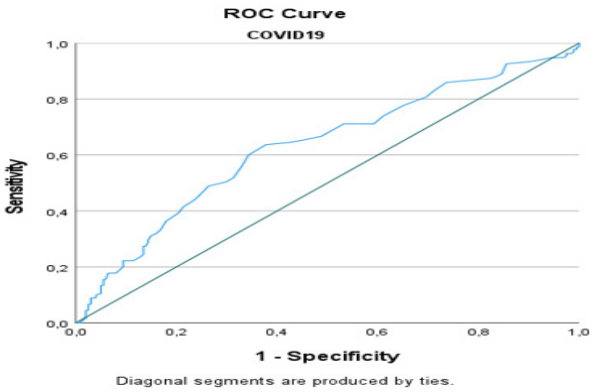

Figure 3. RDW: COV ROC curve
RDW: Red cell distribution width, COV: Isolated COVID-19, ROC: Receiver operating characteristic

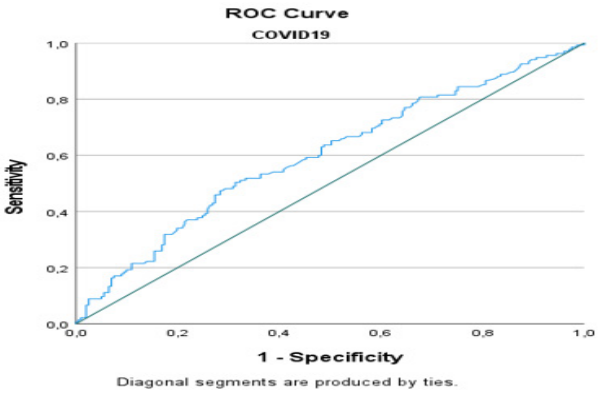

Figure 4. RAR: COV ROC curve
RAR: Red cell distribution width/albumin, COV: Isolated COVID-19, ROC: Receiver operating characteristic

Table 4. Predictive probabilities of measurements regarding mortality status in groups

	Cut-off value	Sensitivity	Specificity	NPD-	PPD+	Accuracy
Albumin: COV-SE	33.5	0.593	0.741	0.304	0.335	0.333
RDW: COV	14.35	0.637	0.621	0.718	0.531	0.628
RAR: COV	0.4236	0.504	0.787	0.673	0.519	0.613
RAR: COV-SE	0.4886	0.519	0.666	0.629	0.737	0.667

RDW: Red cell distribution width, RAR: RDW/albumin, COV: Isolated COVID-19, COV-SE: COVID-19 with non-sepsis secondary infection

Univariate logistic regression identified the following as significant predictors of survival: group allocation (COV, p=0.000), age (p=0.000), comorbidity count (p=0.004), CKD (p=0.001), heart failure (p=0.017), WBC (p=0.015), lactate (p=0.000), albumin (p=0.002), RAR (p=0.000), and CRAR (p=0.009). COV-S status increased mortality 4.254-fold, comorbidity count ≥4 by 3.259-fold, CKD by 2.533-fold, and heart failure by 2.394-fold. Increased WBC, PRC, lactate, age, RAR, and CRAR, as well as decreased albumin, were associated with higher mortality (**Table 5**).

Multivariate logistic regression (X^2=126.627; p=0.000; R^2=0.315) found group allocation (COV, p=0.032), age (p=0.000), and lactate (p=0.000) as significant predictors. Sepsis increased mortality 2.770-fold; higher lactate and age also raised mortality risk (**Table 6**).

DISCUSSION

The severity of COVID-19 is determined by viral load, inflammation, and the patient's immune response. Advanced age and underlying comorbidities (such as diabetes and hypertension) contribute to increased disease severity by promoting excessive inflammatory responses and impaired viral clearance.[21] In our study, the mean age of deceased patients (70.01±15.36) was significantly higher than that of survivors. A comorbidity count of four or more increased mortality 3.259-fold, the presence of chronic renal failure increased mortality 2.533-fold, and heart failure increased mortality 2.394-fold.

In our study, several demographic and clinical factors—particularly age, comorbidity burden, CKD, heart failure,

Table 5. Univariate logistic regression analysis results

Variable	Reference group	B	sh	p	OR	95% CI for OR	
						Lower	Upper
	Group			0.000**			
COV group	COV-S	1.448	0.277	0.000**	4.254	2.472	7.320
	COV-SE	0.398	0.294	0.176	1.489	0.837	2.649
Gender	Male	0.154	0.188	0.412	1.166	0.808	1.685
Age		0.037	0.006	0.000**	1.038	1.025	1.051
	Number of comorbidities			0.004*			
	1	0.785	0.315	0.013*	2.192	1.181	4.068
Number of comorbidities	2	0.523	0.302	0.084	1.686	0.932	3.050
	3	0.807	0.318	0.011*	2.242	1.203	4.179
	≥ 4	1.181	0.318	0.000**	3.259	1.747	6.079
HT	Yes	0.052	0.185	0.777	1.054	0.734	1.513
DM	Yes	0.077	0.196	0.695	1.080	0.736	1.584
CAD	Yes	0.334	0.234	0.154	1.396	0.882	2.209
CKD	Yes	0.930	0.285	0.001*	2.533	1.448	4.431
Asthma	Yes	0.192	0.372	0.606	1.212	0.585	2.511
COPD	Yes	0.406	0.337	0.228	1.501	0.775	2.906
Stroke	Yes	0.585	0.399	0.142	1.794	0.822	3.918
Malignancy	Yes	0.461	0.311	0.138	1.585	0.862	2.915
HF	Yes	0.873	0.366	0.017*	2.394	1.167	4.909
WBC		0.043	0.018	0.015*	1.044	1,009	1.081
PRC		0.041	0.016	0.009*	1.042	1.010	1.075
Lactate		0.625	0.113	0.000**	1.868	1.496	2.332
CRP		0.001	0.001	0.258	1.001	0.999	1.003
Albumin		-0.053	0.017	0.002*	0.948	0.917	0.981
CAR		0.066	0.035	0.061	1.068	0.997	1.143
RAR		4.226	0.897	0.000**	68.427	11.784	397.343
CRAR		0.006	0.002	0.009*	1.006	1.001	1.010

**p<0.001 *p<0.05 indicates significant effect, p>0.05 indicates no significant effect; Logistic regression. OR: Odds ratio, CI: Confidence interval, COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, HT: Hypertension, DM: Diabetes mellitus, CAD; Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HF: Heart failure, CRP: C-reactive protein, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, WBC: White blood cell, PRC: Procalcitonin

Table 6. Multivariate logistic regression analysis results

Variable	Reference group	B	sh	p	OR	95% CI for OR	
						Lower	Upper
	Group			0.032*			
COV group	COV-S	1.019	0.393	0.010*	2.770	1.282	5.985
	COV-SE	0.066	0.340	0.845	1.069	0.548	2.082
Age	Age	0.036	0.008	0.000**	1.036	1.020	1.052
	Number of comorbidities			0.485			
	1	0.606	0.365	0.096	1.834	0.897	3.747
Number of comorbidities	2	0.101	0.349	0.773	1.106	0.558	2.192
	3	0.230	0.380	0.545	1.259	0.598	2.652
	≥ 4	0.232	0.407	0.568	1.261	0.568	2.800
CKD	Yes	0.592	0.351	0.091	1.808	0.909	3.593
HF	Yes	0.214	0.444	0.629	1.239	0.519	2.961
PRC		-0.024	0.021	0.252	0.977	0.938	1.017
WBC		0.013	0.022	0.556	1.013	0.971	1.057
Lactate		0.753	0.137	0.000**	2.124	1.625	2.776
Albumin		0.016	0.039	0.683	1.016	0.941	1.097
CAR		-0.209	0.291	0.473	0.812	0.459	1.435
RAR		2.071	2.437	0.395	7.933	0.067	942.194
CRAR		0.014	0.019	0.469	1.014	0.977	1.053

*p<0.001 *p<0.05 indicates significant effect, p>0.05 indicates no significant effect; Logistic regression, OR: Odds ratio, CI: Confidence interval, COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, CKD: Chronic kidney disease, HF: Heart rate, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, WBC: White blood cell, PRC: Procalcitonin

elevated WBC and lactate levels, and low albumin—were associated with increased mortality. These findings align with the established understanding that advanced age and multimorbidity contribute to impaired immune response and poorer outcomes in COVID-19. The strong effect of lactate on mortality is consistent with evidence linking hyperlactatemia to global tissue hypoxia and septic cardiometabolic stress.

Although CRP, CAR, RDW, RAR, and CRAR were significantly different between survivors and non-survivors, only age, lactate, and sepsis remained independently predictive in multivariate analysis. This pattern indicates that while inflammatory biomarkers provide supportive prognostic information, they may not outperform major clinical determinants. Similar to previous reports by Kim et al.[30] and Shan et al.,[31] albumin-based ratios (particularly RAR) demonstrated meaningful predictive value, but their contribution diminished after adjustment for established risk factors. This suggests that these ratios are most informative when combined with classical clinical indicators rather than used in isolation.

Furthermore, the ROC analysis revealed that the performance of these biomarkers differed according to clinical subgroups. RDW and RAR showed fair discrimination in patients with COV, whereas albumin and RAR performed better in patients with secondary infections. These findings reflect the dynamic nature of inflammatory responses and emphasize that biomarker utility may vary by phenotype. Overall, our results highlight the importance of integrating clinical variables with simple laboratory indices to improve risk stratification among ICU patients with COVID-19.

Various prognostic scoring systems, such as the widely used APACHE II scale, are employed in ICUs to estimate mortality risk.[22] Consistent with prior findings, our cohort showed significantly higher APACHE II scores in non-survivors (25.11±15.16) compared to survivors (11.86±8.45).

Since demographic factors alone cannot reliably predict COVID-19 prognosis,[23] early prognostic biomarkers are needed to guide clinical decisions. Serum albumin plays roles in the transport of ions, drugs, and metabolites, the maintenance of osmotic balance, and exhibits antioxidant properties.[24] Hypoalbuminemia in critically ill patients is multifactorial and can be attributed to increased capillary permeability, decreased protein synthesis, reduction in total serum albumin mass, expansion of distribution volume, and elevated expression of vascular endothelial growth factor.[25] A similar phenomenon has been observed in COVID-19 disease; a meta-analysis of 11 studies showed that the mean serum albumin at admission was 3.50g/dl in severe cases and 4.05g/dl in non-severe cases.[26]

The RAR, LDH, cerebrovascular disease, congestive heart failure, and coronary artery disease have all been identified as independent risk factors for mortality in COVID-19.[27] Uncontrolled inflammation associated with elevated inflammatory markers, especially CRP, also plays a significant role.[13]

Kalabin et al.[13] investigated the prognostic value of the CAR in mechanically ventilated and non-ventilated COVID-19 patients. Although CAR were significantly higher in ventilated and deceased patients compared to their counterparts, multivariate logistic regression analysis demonstrated that the ratio was not an independent predictor of mortality (OR 1.21, 95% CI 0.96–1.51, p=0.06). Similarly, Li et al.[14] examined admission albumin and CRP levels in 465 COVID-19 patients. They found that the CAR was

significantly elevated in patients with severe disease or death (3.29 [2.02–5.26]) compared to those discharged (0.72 [0.10-1.70]; p<0.001). The optimal cutoff for predicting disease progression was determined to be 1.843 (sensitivity 91.1%, specificity 78.0%).

Among hospitalized pregnant women with COVID-19, those requiring intensive care had significantly lower albumin (2.25±0.31 vs. 2.95±0.47, p=0.000) and higher CAR (5.13±2.01 vs. 1.00±1.00, p=0.000). For CAR, a cutoff of 1.8 delivered 100% sensitivity and 86.5% specificity for predicting ICU need.[28]

Uzum et al.[29] found, in 272 COVID-19 patients, lower albumin and higher CRP and CAR in severe cases. The CAR cutoff of 21.52 had a moderate ability to predict ICU admission (80.4% sensitivity, 55.7% specificity).

In our cohort, survivors had significantly higher albumin levels (35.73±5.35) than non-survivors (34.06±6). Survivor and non-survivor CRP and CAR were, respectively, 116.04±87.68 vs. 124.99±83.15 and 3.36±2.67 vs. 3.82±2.67. Despite higher ratios in the deceased, our multivariate analysis found CAR was not a statistically significant independent predictor (OR 8.12, 95% CI 0.46-1.43, p=0.47).

Kim et al.[30] identified CAR as an independent predictor of mortality in patients with severe sepsis or septic shock. Shan et al.[31] reported that RAR offered good accuracy for 28-day mortality in adult septic patients (AUC=0.695). In our study, age, comorbidity count, CKD, heart failure, WBC, lactate, and albumin were significant predictors of survival; presence of sepsis increased mortality 4.254-fold. These findings align with prior literature and emphasize the importance of integrated clinical and laboratory risk assessment advocated by Kim[30] and Shan.[31]

RDW reflects the variability in red blood cell size and is known to increase with systemic inflammation.[32] Ramachandran et al.[15] found that 49.7% of 294 COVID-19 patients had high RDW (>14.6%) at admission; these patients had higher in-hospital mortality, though the difference was not statistically significant. Jandaghian et al.[33] observed that survivors' mean RDW was lower than non-survivors (13.9±1.88 vs. 15.3±2.7; p<0.0001), and that patients with RDW>14.5% had a 3.1-fold higher risk of death (OR 3.1; 95% CI 2.6-3.8).

Ertekin et al.[19] found that mechanical ventilation and vasopressor need correlated with significantly higher RDW and RAR levels. Elevated RDW (>55.2%) and low albumin (<2.87) were strongly associated with mortality (98.5% sensitivity, 96.2% specificity for RDW; 83.2% sensitivity, 88.6% specificity for albumin/RAR).

In our study, albumin and RAR were significant predictors for survival in the COVID-SE group, and RDW and RAR in the COV group (p<0.05). COVID-SE albumin and RAR cutoffs were 33.5 and 0.4886, respectively; COV RDW and RAR cutoffs were 14.35 and 0.4236.

We also evaluated the effect of CRAR on survival. While survivors had significantly lower CRAR values, ROC analysis showed CRAR did not have significant predictive value (p>0.05).

Limitations

Our study's single-center, retrospective design limits the generalizability of findings to other patient populations and hinders definitive conclusions regarding causal relationships. The study was conducted at one center, and variability in patient profiles, treatment approaches, and laboratory methods among centers may constrain the broad applicability of results. The patient sample was recruited between January-May 2021, so SARS-CoV-2 variant and pandemic phase influences cannot be excluded, and results might not apply to other variant periods. Unequal sample sizes in patient subgroups—particularly the lower number of secondary infection cases compared to COVID sepsis and COVID groups—may reduce statistical power and limit subgroup analysis interpretations. This study evaluated only outcomes during ICU and hospital stays, not long-term prognosis or functional results. Another important limitation is that treatment protocols were not systematically recorded. Detailed information regarding the use of corticosteroids, antiviral agents, immunomodulatory therapies, vasopressors, and mechanical ventilation strategies was not available, and these therapies may directly affect inflammatory markers and clinical outcomes. Additionally, patients' nutritional status and the use of albumin replacement therapy were not documented. Because albumin levels and albumin-based ratios (CAR, RAR, CRAR) can be influenced by nutritional intake and exogenous albumin administration, the absence of these data may limit the interpretation of albumin-related prognostic markers.

CONCLUSION

Sepsis dramatically increases mortality in COVID-19 ICU patients, especially among older individuals with higher APACHE II scores. RDW and RAR are strong mortality predictors in isolated cases, while albumin and RAR matter more for those with secondary infections. Age, lactate, and sepsis are the main independent risk factors; CAR and CRAR alone are not reliable. Early detection of sepsis and aggressive intervention are vital to reduce mortality in this high-risk group.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Ethics Committee of Clinical Researches No. 1 at Ankara Bilkent City Hospital (Date: 23.03.2022, Decision No: E1-22-2487).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

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