Lactate dehydrogenase/albumin ratio as a prognostic factor in severe acute respiratory distress syndrome cases associated with COVID-19

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Abstract

Background: Patients with severe acute respiratory distress syndrome (ARDS) have high mortality rates; therefore, new biomarkers are necessary to predict the prognosis in the early stages. Serum lactate dehydrogenase (LDH) level is a specific marker of lung damage, but it is not sensitive because it is affected by several factors. This study aimed to determine whether the LDH/albumin ratio could be used as a prognostic biomarker in patients with severe ARDS due to COVID 19.

Methods: Tertiary intensive care unit (ICU) patients with severe ARDS and confirmed COVID-19 diagnosis between August 1, 2020, and October 31, 2021, were included. The demographic and clinical characteristics of the patients were recorded from the hospital databases, together with laboratory results on the day of admission to the ICU and the length of stay in the ICU and hospital. LDH/albumin, lactate/albumin, C-reactive protein (CRP)/albumin, and BUN/albumin ratios were calculated. Logistic regression analysis was performed to determine independent risk factors affecting mortality.

Results: Nine hundred and five patients hospitalized in a tertiary ICU were evaluated. Three hundred fifty-one patients with severe ARDS were included in this study. The mortality rate of the included patients was 61.8% (of 217/351). LDH/albumin, lactate/albumin, and BUN/albumin ratios were higher in the nonsurvivor group ($P < .001$). The area under the curve (AUC) from the receiver operating characteristic analysis that predicted in-hospital mortality was 0.627 (95% confidence intervals (CI): 0.574–0.678, $P < .001$) for the LDH/albumin ratio, 0.605 (95% CI: 0.551–0.656, $P < .001$) for lactate/albumin, and 0.638 (95% CI: 0.585–0.688, $P < .001$) for BUN/albumin. However, LDH/albumin ratio was independently associated with mortality in multivariate logistic regression analysis.

Conclusion: LDH/albumin ratio can be used as an independent prognostic factor for mortality in patients with severe ARDS caused by COVID-19.

Abbreviations: AKI = acute kidney injury, APACHE II = acute physiology and chronic health evaluation II, ARDS = acute respiratory distress syndrome, AUC = area under the curve, CI = confidence intervals, CRP = C-reactive protein, ICU = intensive care unit, LDH = lactate dehydrogenase, OR = odds ratios.

Keywords: ARDS, COVID-19, lactate dehydrogenase/albumin, mortality

1. Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2, a novel coronavirus, has been identified as the cause of a global respiratory disease outbreak called COVID-19. COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), acute kidney and heart damage, sepsis, septic shock, and multi-organ failure in severe cases. COVID-19 may cause moderate to severe acute respiratory distress syndrome and requires invasive mechanical ventilation for several weeks.[1,2] As patients with severe ARDS have a higher mortality rate, there is a need for new biomarkers for predicting prognosis in the early stages. Endothelial cell damage plays a crucial role in the pathogenesis of ARDS. The serum lactate dehydrogenase (LDH) level is a specific marker of endothelial damage in the lung; however, it is not sensitive because it is affected by several factors.[3]

LDH plays an essential role in the body's tissues in glucose metabolism, catalyzing pyruvate to lactate. Cells release it after damage to their cytoplasmic membranes.[4]

Prior research has highlighted the importance of LDH for its ability to detect lung diseases. LDH is a metabolic and prognostic biomarker of immune surveillance, and high levels predict poor outcomes in immunocompromised patients.[5]

It increases lactate production, leading to an increase in immunosuppressive cells such as macrophages and dendritic cells. It also inhibits cytolytic cells, including natural killer cells and cytotoxic T-lymphocytes.[4] LDH is usually promoted by the activation and proliferation of T cells.[6,7]

A retrospective analysis of a cytotoxic T-lymphocytes antigen-4 antibody that can increase T cell activity and proliferation demonstrated that increased LDH levels indicate a poor outcome[8] According to the autopsy results of patients who died due to COVID-19, T cells play a vital role in this disease.[9] Serum albumin has been used as a prognostic factor for infections because it potentially decreases with infection exacerbation; it is low in patients with sepsis and has been reported to be a crucial factor affecting mortality and prognosis.[10–12]

Hypoalbuminemia is also associated with chronic comorbid diseases or lifestyle factors such as smoking, alcoholism, and obesity. Therefore, there have been studies regarding albumin as a single prognostic indicator in infections and as a combination indicator of albumin-based ratios.

Various indices, such as BUN/albumin, lactate/albumin, and C-reactive protein (CRP)/albumin ratios, have been used to predict the severity and prognosis of patients with pneumonia and sepsis.[13–18]

Several studies have used the LDH/albumin ratio as a prognostic factor in pneumonia patients.[19] Patients hospitalized with COVID-19 need regular monitoring of vital signs and, where possible, early recognition of the deteriorating patient and biomarkers that predict prognosis. The present study was designed to confirm whether LDH/albumin ratio can be used as an independent prognostic factor in patients with severe ARDS due to COVID-19.

2. Material and Methods

Patients hospitalized in the tertiary intensive care unit (ICU) due to COVID-19 between August 1, 2020, and October 31, 2021, were evaluated. Patients were excluded if they had a negative result for polymerase chain reaction, had no albumin level at the time of hospitalization, or had mild or moderate ARDS.

Data were extracted from the electronic medical records of the hospitals. Before collecting the data, the principal researcher established a standardized protocol for data extraction.

This study was approved by the local ethics committee (no.359/2022). The Berlin criteria were used to diagnose ARDS 1. The variables that may be associated with in-hospital mortality were evaluated in this retrospective cohort study. This study included 351 patients with confirmed COVID-19 pneumonia and severe ARDS using the Berlin criteria.

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Demographic and clinical characteristics of the patients were recorded. The hospital databases were used for hematological and biochemical laboratory results on the day of admission to the ICU, and the length of stay in the hospital ICU was determined in the same manner.

The LDH/albumin, lactate/albumin, CRP/albumin, and BUN/albumin ratios on the first admission day to the ICU were calculated. Kidney Disease: Improving Global Outcomes criteria were used for acute kidney injury (AKI) diagnosis.[21] The acute physiology and chronic health evaluation II (APACHE II) and Sequential Organ Failure Assessment scores were calculated at the end of hospitalization. The primary outcome was in-hospital mortality rate.

3. Statistics

Statistical analyses were performed using the IBM SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, NY). Continuous variables with a normal distribution are presented as mean ± SD deviation and those with a skewed distribution as median (min-max) values. Categorical variables are expressed as numbers (n) and percentages (%). Patients were categorized into two groups: survivors and nonsurvivors. Student *t* test or Mann–Whitney *U* test was used to analyze statistical significance according to the data distribution. Between-group comparisons of categorical variables were performed using the chi-squared test or Fisher exact test.

Forward stepwise binary logistic regression with variables having a *P* value of less than 0.1 in univariate analysis was performed to determine independent factors predicting mortality. Results are presented as odds ratios (OR) and confidence intervals (CI). The linearity was tested by interacting with the logarithmic transformation of each parameter. A receiver operating characteristic (ROC) curve was constructed to determine the best cutoff values of the CRP/albumin, lactate/albumin, LDH/albumin, and BUN/albumin ratios for predicting all-cause mortality.

4. Results

Nine hundred and five patients were evaluated in a tertiary ICU. Polymerase chain reaction test results were negative in 119 patients, and 49 patients did not have albumin levels at the time of hospitalization. There were no diagnoses of severe ARDS at the time of admission in the 386 patients. Thus, 351 patients with confirmed COVID-19 pneumonia and severe ARDS were included in the study. The mortality rate of the included patients was 61.8% (of 217/351). The mean age of the included patients was 64.13 ± 12.6 years, and 204 (58.11%) were male.

Patients who died were older than those who survived (*P* < .001). There was no sex difference between the living and dead patients (*P* = .173). The patient demographics and clinical characteristics are shown in Table 1. Patients who died had higher sequential organ failure assessment and APACHE II scores than those who died (*P* < .001). Laboratory information on living and dead patients is summarized in Table 2.

BUN (*P* < .001), LDH (*P* = .002), CRP (although not significant, *P* = .456), and lactate (*P* = .001) levels were higher in patients who died than in those who survived. Albumin levels were lower in patients who died (*P* = .001). The LDH/albumin ratio (*P* < .001) and BUN/albumin ratio (*P* < .001) were higher in deceased patients, while the lactate/albumin ratio (*P* < .001) was lower.

The CRP/albumin ratio (*P* = .259) was similar between the groups (Table 2).

Figure 1 shows the area under the curve (AUC) for albumin-based ratios used to estimate mortality in patients with severe ARDS.

The AUC for the LDH/albumin ratio was 0.627 (*P* < .001; 95% CI: 0.574–0.678). Other albumin-based ratios of AUCs were 0.638 for BUN/albumin ratio (*P* < .001, 95% CI: 0.585–0.688), 0.605 for the lactate/albumin ratio (*P* < .001, 95% CI: 0.551–0.656), and 0.536 for CRP/albumin ratio (*P* = .256, 95% CI: 0.482–0.589). LDH/albumin sensitivity and specificity were 43% and 78.36%, respectively. A total of 843 was a cutoff value that could predict mortality. The highest sensitivity was observed for lactate/albumin (62.04%), whereas the highest specificity was observed for BUN/albumin ratio (85.07%) (Fig. 1).

In univariate analysis, only LDH/albumin affected hospital mortality among stand-alone and albumin-based ratios. When examined together with other factors affecting mortality by multivariate analysis, the LDH/albumin ratio was found to be an independent risk factor affecting hospital mortality. (*P* < .001, OR = 1.081, 95% CI = 1.035–1.129). Other independent

Table 1

Demographic and clinical characteristics of severe acute respiratory distress syndrome cases associated with severe COVID-19 patients.

	Overall (n = 351)	Survivors (n = 134)	Nonsurvivors (n = 217)	P value
Mean age (yr ± SD)	64.13 ± 12.6	60.56 ± 13.58	66.33 ± 11.45	**<.001***
Gender n (%)				
Female	147 (41.88)	50 (37.31)	97 (44.7)	.173
Male	204 (58.11)	84 (62.69)	120 (55.3)	
Comorbidities n (%)				
CKD	28 (7.97)	4 (2.99)	14 (6.45)	.153
Diabetes mellitus	100	45 (33.58)	55 (25.35)	.097
COPD	28 (7.97)	12 (8.96)	16 (7.37)	.595
Hypertension	161 (45.86)	58 (43.28)	103 (47.47)	.445
CAD	72 (20.51)	26 (19.4)	46 (21.2)	.686
Vital Signs				
SBP mm Hg	119.27 ± 24.62	122.41 ± 21.89	118.57 ± 26.19	.277
DBP mm Hg	70.66 ± 17.81	72.64 ± 17.04	69.44 ± 18.2	**.041**
Heart rate/min	112.1 ± 20.52	109.72 ± 21.39	113.58 ± 19.86	**.020**
Respiration rate/min	33.38 ± 6.66	31.91 ± 6.32	34.29 ± 6.72	**.001***
Body temperature	36.67 ± 0.92	36.85 ± 1	36.78 ± 0.97	**.049**
PO_2/FiO_2	58.55 ± 21.14	61.06 ± 21.66	57 ± 20.72	.058
Glasgow coma scale	13.71 ± 3.01	14.24 ± 2.1513	13.38 ± 3.4	**.021**
SOFA	3.81 ± 1.59	3.31 ± 1.08	4.12 ± 1.77	**<.001**
APACHE II	16.88 ± 5.64	14.59 ± 4.91	18.29 ± 5.62	**<.001**
Mechanical ventilation	277 (78.91)	66 (49.25)	211 (97.24)	**<.001**
AKI, n (%)				
Stage 1	45 (12.82)	13(9.7)	32 (14.75)	**<.001**
Stage 2	36 (10.25)	5 (3.73)	31 (14.29)	
Stage 3	79 (22.50)	4 (2.99)	77 (35.48)	
RRT	78 (22.22)	5 (3.73)	73 (33.64)	**<.001**
Use of vasoactive agent	180 (51.28)	12 (8.96)	168 (77.42)	**<.001**
Median days in ICU (min-max)	13 (2-62)	11.5 (3–55)	14 (2–62)	**.003**
Median days in hospital (min-max)	17 (2-70)	21.5 (4–70)	15 (2–62)	**<.001**

Bold values indicate *P* < .05, statistically significant.

AKI = acute kidney injury, APACHE II = acute physiology and chronic health evaluation II, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DBP = diastolic blood pressure, ICU = intensive care unit, RRT = renal replacement therapy, SBP = systolic blood pressure, SD = standard deviation, SOFA = sequential organ failure assessment.

Table 2

Baseline laboratory parameters of patients included.

	Overall (n = 351)	Survivors (n = 134)	Nonsurvivors (n = 217)	P value
Blood urea nitrogen mg/dL	32.28 ± 22.39	26.82 ± 19.03	35.65 ± 23.65	<.001
Creatinine mg/dL	0.9 (0.15–13)	0.85 (0.2–7.87)	0.9 (0.15–13)	.009
Aspartate aminotransferase IU/L	36 (8–1233)	34.5 (9–1233)	39 (8–1052)	.023
Alanine aminotransferase IU/L	28 (2–741)	25 (2–741)	29.5 (4–454	.293
Lactate dehydrogenase U/L	506.5 (57–3401)	496.72 ± 188.09	601.36 ± 348.33	.002
Albumin g/L	32.82 ± 4.7	33.04 ± 4.71	32.68 ± 4.7	.476
Ferritin µg/L	883.5 (26–16,605)	814 (40–7828)	956.5 (26–16,605)	.113
CRP mg/L	107.5 (6.2–480)	105 (8.2–472)	111 (6.2–480)	.456
Procalcitonin µg/L	0.25 (0.01–74)	0.18 (0.01–74)	0.29 (0.01–63)	.019
White blood cell/mm³	12,106.06 ± 6185.84	11,808.94 ± 5040.84	12,289.54 ± 6802.07	.780
Neutrophil/mm³	10,559.08 ± 5385.96	10,380.22 ± 4743.98	10,669.52 ± 5754.57	.823
Lymphocyte/mm³	700 (80–25,000)	740 (260–8680)	670 (80–25,000)	.113
Hemoglobin g/dL	13.02 ± 2.09	13.15 ± 1.99	12.94 ± 2.16	.366
Hematocrit %	38.84 ± 6.13	38.89 ± 5.84	38.81 ± 6.31	.907
Platelets/mm³	236,026.78 ± 96,137.4	257,105.97 ± 95,038.6	223,010.14 ± 94,703.18	.001
CK U/L	96.5 (6–4653)	78 (6–3317)	115 (15–4653)	.018
CK-MB U/L	37 (10–344)	34.5 (10–260)	40.5 (12–344)	.051
hs Troponin T ng/L	18 (2–2264)	13.33 (3–1351)	22 (2–2264)	<.001
INR	1.22 ± 0.71	1.08 ± 0.2	1.3 ± 0.88	<.001
Fibrinogen mg/L	6411.81 ± 1803.15	6466.73 ± 2018.45	6376.79 ± 1655.53	.654
D dimer µg/L	1250 (12.13–9000)	1168.5 (12.13–9000)	1340 (110–9000)	.370
Lactate mmol/L	2.1 (0.5–11.4)	1.85(0.5–10)	2.3 (0.5–11.4)	.001
LDH/albumin	15,77 ± 10.48	13.34 ± 8.64	17.28 ± 11.23	<.001
Lactate/albumin	0.656 (0.01–0.52)	0.57 (0.01-0.30)	0.07 (0.02–0.52)	<.001
CRP/albumin	3.14 (0.00–15.48)	2.92 (0.00–15.23)	3.29 (0.00–15.48)	.259
BUN/albumin	0.79 (0.11–5.63)	0.69 (0.11–4.36)	0.89 (0.15–5.63)	<.001

APACHE II = acute physiology and chronic health evaluation II, CK = creatine kinase, CK-MB = creatine kinase myoglobin, CRP = C-reactive protein, LDH = lactate dehydrogenase.
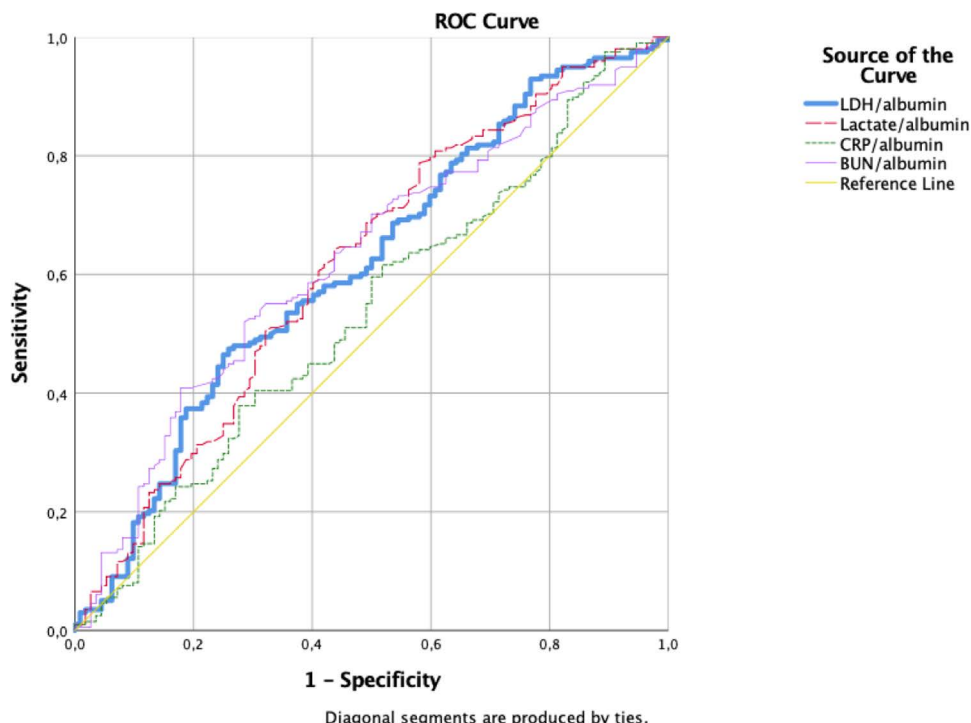
Figure 1. The AUC of the LDH/ALB ratio compared to other albumin-based indexes. AUC = area under the curve, LDH = lactate dehydrogenase.

risk factors were advanced age (*P* = .007, OR = 1.046, 95% CI = 1.012–1.081), stage 3 acute renal failure (OR:12.405, 95% CI = 3.177–48.438), high APACHE II (OR = 1.107, 95% CI = 1.032–1.188) and a high number of days in the ICU (OR = 1.458, 95% CI = 1.317–1.614) (Table 3).

5. Discussion

The current study showed that the LDH/albumin ratio was an independent risk factor for in-hospital mortality in patients with severe ARDS due to COVID-19. In addition, advanced age, presence of AKI, and ICU stay were independent risk factors affecting hospital mortality. To the best of our knowledge, this is the first study to examine the prognostic effect of LDH/albumin ratio in patients with severe ARDS due to COVID-19.

In the literature, it has been demonstrated that the LDH/albumin ratio independently affects mortality in severe infections requiring intensive care[19] and stroke-related pneumonia[22] in lower respiratory tract infections.[23] High LDH levels are an interesting biomarker associated with poor outcomes in patients with previous viral infections.[24,25]

Increased serum LDH levels have been commonly demonstrated in COVID-19 patients and are higher in severely ill patients. Moreover, initial high LDH levels were correlated with the risk of developing ARDS (HR:1.61, 95% CI: 1.44–1.79) and mortality (HR:1.30, 95% CI: 1.11–1.52).[26]

All patients in our study had high LDH levels, which were even higher in patients who died (*P* = .002). However, in the logistic regression analysis, LDH alone did not affect the mortality in these patients.

Albumin plays several physiological roles in the body, including the maintenance of osmotic pressure, regulation of vascular permeability, and acid-base balance, and is an anti-inflammatory and antioxidant molecule.[27,28] It has been reported that an albumin level of < 3.5 g/dL affects the 30-day mortality rate in the general patient population hospitalized.[29,30] In a meta-analysis of 90 studies, hypoalbuminemia was associated with prolonged ICU and hospital stays, morbidity, and mortality.[31] In addition, albumin level is lower in

patients with severe COVID-19 and has been shown to affect mortality.[32,33]

Hoeboer et al showed that LDH is associated with 28-day mortality in ARDS and is valuable in predicting and monitoring the severity and course of acute respiratory distress syndrome.[34]

In this study, albumin levels were similar between groups and did not affect mortality.

This result may have been obtained in our study because there was no comparison between severe and mild-to-moderate ARDS or it may be related to the insufficient sample size of the study.

Lee et al reported lower albumin levels and higher LDH and LDH/albumin ratios in patients who did not experience lower respiratory tract infections. In the same study, the LDH/albumin ratio was found to be an independent factor affecting mortality.[23]

Table 3

Multiple logistic models for the risk factors of mortality.

	B	SE	*P*	OR	95% CI for exp(*B*) Lower	Upper
Constant	−4.545	1.258	**<.001**			
Age	0.045	0.017	**.007**	1.046	1.012	1.081
DM	−0.971	0.422	**.021**	0.379	0.166	0.866
AKI			**<.001**			
Stage 1	1.774	0.601	**.003**	5.892	1.815	19.133
Stage 2	2.034	0.798	**.011**	7.643	1.599	36.533
Stage 3	2.518	0.695	**<.001**	12.405	3.177	48.437
APACHE II	0.102	0.036	**.005**	1.107	1.032	1.188
LDH/albumin	0.078	0.022	**<.001**	1.081	1.035	1.129
Days in ICU	0.377	0.052	**<.001**	1.458	1.317	1.614
Days in hospital	−0.355	0.050	**<.001**	0.701	0.636	0.774

Bold values indicate *P* < .05, statistically significant.

AKI = acute kidney injury, APACHE II = acute physiology and chronic health evaluation II, DM = diabetes mellitus, ICU = intensive care unit, LDH = lactate dehydrogenase.

Mortality is associated with a poor prognosis as lactate levels increase in sepsis patients.[35]

In a multicenter study from Italy, although there was no statistically significant relationship with mortality, lactate levels were higher in patients who died in the ICU due to COVID-19 than in those who survived.[36]

The lactate/albumin ratio is a good prognostic marker for predicting in-hospital mortality in sepsis patients. Considering patients with septic shock, it has been reported that the lactate/albumin ratio is better than lactate alone in predicting mortality.[37]

When the lactate/albumin ratio was examined in sepsis, the present study revealed significantly higher levels in patients who died, but there was no effect on mortality in the multivariate analyses.

Few studies have explored BUN/albumin ratio as a prognostic predictor. These studies reported that BUN/albumin ratio increased as mortality increased in critically ill patients.

When the lactate/albumin ratio based on sepsis was examined, the present study revealed significantly higher levels in patients who died, but this did not affect mortality in multivariate analyses.[38–40]

Based on these studies, we examined BUN/albumin ratio in patients with severe ARDS caused by COVID-19. The BUN/albumin ratio was lower in the nonsurvivors than in the survivors ($P < .001$). The specificity of the BUN/albumin ratio was higher than that of other albumin-based ratios. However, it was not an independent risk factor for mortality.

The CRP/albumin ratio has been used as a biomarker for critically ill patients. It was shown to have statistical significance in patients with sepsis compared to patients without sepsis, but it did not affect mortality in sepsis.[41] In our study, neither CRP nor the CRP/albumin ratio affected mortality in patients with severe ARDS.

In this study, advanced age and DM were independent risk factors for mortality in COVID-19 patients, similar to previous studies.[32,42] The incidence of AKI in patients hospitalized for COVID-19 ranged from 46% to 36%. While the incidence of AKI was 76% in patients hospitalized in the ICU, 56% had stage 3.[43–45] In our study, the incidence of AKI was 45.58%, and 22.5% of all the patients had stage 3 AKI. In addition, the presence of AKI is an independent risk factor for mortality.

The APACHE II score is frequently used to measure the severity of disease in the intensive care unit, such that higher scores in our study were also an independent risk factor for mortality.

In conclusion, predictors of mortality are vital in severe ARDS due to COVID-19, which has very high mortality and morbidity. In our study, advanced age, presence of AKI, high APACHE II score, and ICU stay were independent risk factors for mortality. No single parameter affected mortality when laboratory values were examined; however, the LDH/albumin ratio was an independent risk factor for mortality.

6. Limitations

Only patients with severe ARDS were included in our study. Better results were obtained if patients with mild to moderate ARDS and those without ARDS were included in the study. In addition, we did not exclude other causes of hypoalbuminemia, and we recorded only the baseline albumin values on the day of hospitalization for all patients.

Author contributions

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