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Association between Serum Albumin and Mortality in Delta COVID-19 Patients in ICU and General Ward

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ABSTRACT

Background: Coronavirus disease (COVID-19) primarily affects the respiratory system, with a mortality rate of 1.4 to 4%. Albumin, an acute-phase reactant protein with antioxidant properties, plays a key role in health assessment. Low serum albumin levels often indicate malnutrition, disease, or infection. This study examines the relationship between serum albumin levels and mortality in COVID-19 patients. **Methods:** This study is a retrospective cross-sectional analysis of 793 COVID-19 patients categorized into two groups based on serum albumin levels: hypoalbuminemia and normal albumin. Mortality rate, background diseases (e.g., hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cancer, cardiovascular disease), c-reactive protein, hospitalization duration, platelets, lymphocytes, and neutrophils were evaluated. The correlation between serum albumin levels and mortality was analyzed both independently and after adjusting for confounding factors to assess its impact on patient outcomes. **Results:** The results showed that the average duration of hospitalization, as well as neutrophil, lymphocyte, and platelet count was higher in hypoalbuminemia group. Although the average time of hospitalization and neutrophils in two groups did not differ (P>0.05), lymphocytes and platelets were significantly different in two groups (P<0.05). A significant interaction was observed between serum albumin and mortality in patients. These associations remained significant after adjusting for age, sex, underlying diseases, and the number of COVID-19 vaccine doses received (P=0.0001). **Conclusions:** Serum albumin levels is associated with the mortality rate in patients infected with delta coronavirus. It is recommended that future prospective studies evaluate the relationship between serum albumin levels and mortality rates.

Introduction

The prevalence of Coronavirus disease (COVID-19) until the end of April 2023 reached 690 million cases, with over 6 million deaths reported globally (World Health Organization, 2020). COVID-19, caused by the SARS-CoV-2 virus, can result in mild to severe respiratory symptoms, including intensive care unit (ICU) admission (Huang *et al.*, 2020). ICU patients with COVID-19 often experience systemic inflammatory response syndrome and organ dysfunction, rendering them susceptible to adverse outcomes.

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In this context, understanding the role of serum albumin level is very important, since serum albumin is a multifunctional protein that plays a crucial role in maintaining oncotic pressure, transporting essential molecules, and modulating inflammatory and oxidative stress responses. As a negative acute-phase reactant, albumin synthesis decreases during systemic inflammation due to cytokine-mediated hepatic suppression, increased vascular permeability, and redistribution into the interstitial space (Sheinenzon *et al.*, 2021). This decline is particularly evident in critically ill patients, where hypoalbuminemia is associated with increased severity of illness, prolonged hospitalization, and higher mortality (Jin *et al.*, 2022). Nutritional status plays a fundamental role in immune function and recovery from infectious diseases, including COVID-19. Malnutrition, particularly protein-energy malnutrition, can impair immune responses and increase susceptibility to severe infections (Abate *et al.*, 2021). Since albumin is commonly used as an indicator of nutritional status, its decline in critically ill patients may not only reflect an inflammatory burden but also underlying malnutrition, which can further exacerbate disease severity and impact patient outcomes (Eckart *et al.*, 2020). Several studies have identified biomarkers associated with multiple organ failure and severe systemic diseases in COVID-19 patients (Kermali *et al.*, 2020, Ponti *et al.*, 2020).

However, serum albumin levels can be affected by multiple factors including medication use (e.g., corticosteroids, diuretics) (Chang *et al.*, 2025), and immune function markers (e.g., cytokines) (Feng *et al.*, 2023), which may affect disease progression and patient outcomes. These variables are often underexplored in existing studies, emphasizing the need for a more comprehensive assessment of albumin as a prognostic marker in COVID-19 patients.

Given this dual role, investigating the relationship between hypoalbuminemia and ICU mortality in COVID-19 patients can provide valuable insight into disease progression, risk stratification, and clinical management strategies. This research may help identify patients at greater risk of adverse outcomes and guide therapeutic interventions to improve patient survival.

Materials and Methods

Study design and participants

This study was a retrospective cross-sectional study in Shahid Sadouqi Hospital, Yazd. All patients in the 18-80 age range whose COVID-19 infection was confirmed via polymerase chain reaction (PCR) test or lung computed tomography (CT) scan during the summer and fall of 2021 and whose serum albumin levels measured at admission or one day after admission were included in the study.

Demographic information recorded during hospitalization and underlying diseases that cause a decrease in serum albumin (i.e., underlying liver diseases including hepatitis and liver cirrhosis, kidney diseases including nephrotic syndrome, renal failure and proteinuria, any liver malignancy and any malignancy with liver involvement, cachexia) was recorded by the researcher by studying the patients' files or asking the recovered patients. People with the mentioned diseases were excluded from the study.

In general, 844 patients met the initial criteria for entering the study; among them, 189 were deceased, and according to the information extracted from the patient records, 40 of them had at least one of the diseases of hepatitis, liver cirrhosis, and liver cancer, which were excluded from the study. Ultimately, the study included 149 deceased patients. Six hundred fifty-five of the patients were discharged, the patients' files were also reviewed, and during phone calls with the patients, a demographic questionnaire was completed for these patients. Their underlying disease was asked and recorded before hospitalization. Furthermore, eleven patients were excluded from the study due to hepatitis, liver cirrhosis, liver cancer, kidney failure, and dialysis. Moreover, a total of 793 patients were included in the study and were evaluated.

The duration of the patient's hospitalization (admission date and discharge date), age, and

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laboratory information (platelet, leukocyte, lymphocyte, CRP, Albumin) was extracted from the Hospital Information System (HIS) with permission from the hospital security to determine whether or not to be admitted to the ICU. Based on the albumin diagnostic kit in Shahid Sadouqi Hospital, an albumin level less than 3.5 g/dL was defined as hypoalbuminemia. Patients were categorized into hypoalbuminemia and regular albumin groups based on their serum albumin levels. Patients' mortality rate in hypoalbuminemia and common albumin groups was evaluated during hospitalization.

During phone calls with patients, underlying diseases such as blood pressure, diabetes, chronic respiratory failure, cancer, and cardiovascular disease were also evaluated for all patients, and a comparison was made between hypoalbuminemia and standard albumin groups.

The vaccination records of patients, including the type of vaccine injected and number of injected doses administered, were recorded, and the relationship between type and number of vaccine doses received and mortality rate and disease severity, along with the effect of albumin, was investigated using a multivariable regression model.

Ethical considerations

As per ethical principles, the subjects were asked to provide informed consent at the start of the study. The present study has a code of ethics approved by IR.IAU.SRB.REC.1401.264 of Islamic Azad University, Science and Research Branch of Tehran.

Data analysis

The Kolmogorov-Smirnov test was utilized to assess the normality of continuous variables. For normally distributed data, results were expressed as mean (standard deviation) and compared using an independent *t-test*. Non-normally distributed data were compared using the Mann-Whitney U test. Categorical variables were presented as frequencies (percentages) and analyzed using chi-square test. To control for confounding variables, appropriate regression models were used based on type of variable. A multivariable logistic regression model was employed to evaluate the independent association between hypoalbuminemia and mortality while adjusting for covariates. Statistical analyses were conducted using SPSS version 27 software, with a significance level set at P-value<0.05.

Results

As presented in **Table 1**, mortality rate in hypoalbuminemia group was 33.7% more than normal albumin group, and this difference was statistically significant (P<0.05). The COPD rate in normal albumin group was 1.5% higher than the other group, and this difference was not statistically significant (P>0.05). The history of heart attack in hypoalbuminemia group was 3.8% more than normal hypoalbuminemia group, which was not statistically significant (P>0.05). The history of heart failure was 2% more in the hypoalbuminemia group, and this difference was not statistically significant (P>0.05). The frequency of hypertriglyceridemia in normal albumin group was 3.1% higher than the other group, and this difference was not statistically significant (P>0.05). The frequency of high cholesterol in hypoalbuminemia group was 16.6% higher than the other group, but this difference was not statistically significant (P>0.05). In hypoalbumin group, diabetes and hypertension were 14.7 and 14% higher than in normal hypoalbuminemia group, respectively, and this difference was statistically significant (P<0.05). The frequency of cancer in hypoalbuminemia group was 3.1% higher than in the other group, but this difference was not statistically significant (P>0.05). The frequency of positive CRP in hypoalbuminemia group was 0.7% higher than in the other group, but this difference was not statistically significant (P>0.05).

The severity of disease was also checked based on the hospitalization of patients in the ICU in the group. According to **Table 2**, the severity of disease in hypoalbuminemia group was significantly 27.4% higher than the other group (P<0.05). **Table 2** shows the average length of

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hospital stay, neutrophil count, lymphocyte count, and platelet count in hypoalbuminemia and normal albumin groups, using an independent t-test for abnormal data. The average of all variables was higher in hypoalbuminemia group. There was a significant difference in mean number of lymphocytes and number of platelets in two groups (P<0.05). The mean length of hospitalization and number of neutrophils in two groups did not differ significantly (P>0.05).

Table 1. Clinical and biochemical characteristics of patients with COVID-19 in two hypoalbuminemia and standard albumin groups.

Variable	Normal albumin group (n=718)	Hypoalbuminemia group (n=75)	P-value[a]
Life situation			
Death	112 (15.6)[b]	37 (49.3)	0.0001
Alive	606 (84.4)	38 (50.7)	
COPD			
Yes	30 (4.2)	2 (2.7)	0.933
No	688 (95.8)	73 (97.3)	
Heart attack			
Yes	30 (4.2)	6 (8.0)	0.130
No	688 (38.0)	69 (92.0)	
Heart failure			
Yes	5 (0.7)	2 (2.7)	0.083
No	713 (99.3)	73 (97.3)	
Hypertriglyceridemia			
Yes	80 (11.1)	6 (8.0)	0.405
No	638 (95.8)	69 (92.0)	
Hypercholesterol			
Yes	86 (12.0)	6 (28.6)	0.306
No	632 (88.0)	69 (25.0)	
High blood pressure			
Yes	158 (22.0)	27(36.0)	0.006
No	560 (78.0)	48 (64.0)	
Diabetes			
Yes	182 (25.3)	30 (40.0)	0.006
No	536 (74.7)	45 (64.0)	
Cancer			
Yes	16 (2.2)	4 (5.3)	0.103
No	702 (97.8)	71 (94.7)	
C-reactive protein			
Negative	71 (10.0)	7 (9.3)	0.851
Positive	638 (90.0)	68 (90.7)	
Illness severity			
Severe	137 (21.9)	37 (49.3)	0.0001
Mild	38 (50.7)	581(78.1)	

[a]: *The Chi-Square test;* [b]: *n(%).*

Table 2. Comparison of mean scores of quantitative variables in two groups of hypoalbuminemia and normal albumin in patients with COVID-19.

Variable	Normal albumin group[2]	Hypoalbuminemia group[2]	P-value[a]
Duration of hospitalization **(Day)**	5.35 ± 4.48[b]	6.14 ± 5.94	0.166
Neutrophils **(%)**	69.83 ± 24.18	17.74 ± 27.26	0.522
Lymphocytes **(%)**	18.40 ± 9.90	14.16 ± 9.73	0.001
Platelets ($\times 10^3/\mu l$)	195.66 ± 82.54	217.33 ± 145.84	0.048

[a]: Independent t-test and Mann–Whitney test; [b]: Mean ± SD.

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As shown in **Table 3**, using the correlation test, the correlation and relationship of each of variables of serum albumin, age, gender, underlying diseases, and number of vaccine doses were investigated separately with mortality rate. There was a negative and significant correlation (P<0.05) between serum albumin and hypertriglyceridemia with mortality rate of patients. On the other hand, the relationship between gender, COPD, hypercholesterolemia, heart failure, and number of vaccine doses with mortality rate of patients was negative and insignificant (P>0.05). The relationship between age, heart attack, high blood pressure, and diabetes with death rate of patients was positive and significant (P<0.05). Linear regression tests before and after age adjustment, sex, heart attack diseases, heart failure, hypertriglyceridemia, hypercholesterolemia, high blood pressure, and diabetes, COPD and the number of vaccine doses were performed in different models.

Table 4 presents the results of linear regression analysis assessing the association between serum albumin levels and mortality before and after adjusting for confounding variables. Model 1 shows the unadjusted relationship between albumin and mortality, where a 1 g/dl decrease in albumin is associated with a significant increase in mortality (β=-0.231, P<0.0001). Model 2 adjusts for age and gender, demonstrating that the association between albumin and mortality remains significant (β=-0.200, P<0.0001). Model 3 further adjusts for age, gender, underlying diseases (such as COPD, hypertriglyceridemia, and diabetes), and the number of vaccine doses, maintaining a significant inverse association between albumin and mortality. The inclusion of these additional covariates slightly attenuates the effect size, indicating that these variables partially mediate the relationship between albumin and mortality.

Discussion

The results indicated a significant inverse relationship between serum albumin levels and mortality rates. In other words, lower serum albumin levels are associated with a higher risk of mortality. This relationship remained significant and inverse even after adjusting for confounding factors such as age, gender, and underlying diseases across three different statistical models. The findings align with previous studies, such as one demonstrating that low albumin levels are a strong predictor of mortality in hospitalized patients (Zhuang *et al.*, 2024). The persistence of this inverse relationship after adjusting for confounders suggested that low albumin levels may independently predict mortality beyond the effects of age, gender, and underlying diseases. These findings highlighted the importance of monitoring serum albumin levels as part of clinical assessments, particularly in high-risk patients.

Table 3. Correlation coefficient between studied variables with Life situation.

Variable	Correlation	P-value[a]
Serum albumin	-0.367	0.0001
Age	0.286	0.0001
Gender	-0.063	0.0620
Cancer	-	0.0001
COPD	-0.024	0.2810
Heart attack	0.165	0.0001
Heart failure	-0.063	0.0630
Hypertriglyceridemia	-0.166	0.0001
Hypercholesterolemia	-0.069	0.0460
High blood pressure	0.204	0.0001
Diabetes	0.173	0.0001
Number of vaccine doses	-0.048	0.122

[a]: *Data were analyzed using Spearman test.*

Our analysis also revealed a significant association between serum albumin levels and the severity of illness, as well as underlying conditions such as hypertension and diabetes. These results are consistent with other research. A study showed that low serum albumin levels in patients with diabetes and hypertension are linked to greater disease severity and poorer prognosis. Given albumin's critical role in maintaining osmotic pressure and modulating inflammation, it may serve as a valuable marker for predicting disease severity (Ahbap *et al.*, 2016). However, no significant relationship was observed between serum albumin levels and other underlying

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diseases, a finding supported by prior research. Another study indicated that in conditions like asthma or chronic kidney failure, serum albumin levels remain relatively stable, potentially due to differences in pathophysiological mechanisms and their impact on serum proteins.

Table 4. linear regression analysis for assessing the association between serum albumin levels and mortality before and after adjusting for confounding variables.

Variable	Non-Standard beta	Standard error	Standard beta	P-value
Constant	1.206	0.101		0.0001
Albumin	-0.231	0.024	-0.376	0.0001
Model 1				
Constant	0.786	0.124		0.0001
Albumin	-0.200	0.024	-0.317	0.0001
Age	0.006	0.001	0.211	0.0001
Model 2				
Constant	0.875	0.140		0.0001
Albumin	-0.202	0.024	-0.321	0.0001
Age	0.006	0.001	0.204	0.0001
Gender	-0.045	0.033	-0.052	0.163
Model 3				
Constant	0.701	0.147	N/A	0.0001
Albumin	-0.180	0.023	-0.285	0.0001
Age	0.007	0.001	0.262	0.0001
Gender	-0.024	0.031	-0.028	0.445
COPD	-0.019	0.095	-0.007	0.840
Heart attack	0.118	0.077	0.058	0.128
Heart failure	-0.436	0.145	-0.108	0.003
Hypercholesterolemia	0.129	0.086	0.088	0.133
Hypertriglyceridemia	-0.422	0.087	-0.278	0.0001
High blood pressure	0.089	0.042	0.086	0.034
Diabetes	0.070	0.042	0.071	0.095
Number of vaccine doses	-0.090	0.022	-0.158	0.0001

***Model 1**: adjusted for age variable; **Model 2**: adjusted for age and gender; **Model** 3: adjusted for variables of age, sex, underlying diseases, and number of vaccine doses.*

In the present study, increasing age and presence of underlying conditions such as myocardial infarction, hypertension, diabetes, and hypertriglyceridemia were significantly associated with higher mortality risk. These findings align with research indicating that cardiovascular diseases and diabetes are independent risk factors for mortality, with aging further exacerbating the risk (Ancion *et al.*, 2017).

There was an inverse relationship between survival status and hypertriglyceridemia. This finding may be attributed to complex metabolic effects that warrant further investigation. Some studies have also observed this inverse relationship, suggesting that elevated triglyceride levels may be a less harmful indicator in certain cases particularly in older individuals compared to other risk factors. This may be due to metabolic adaptations with aging (Xia *et al.*, 2019). Furthermore, a significant association was found between serum albumin levels and hospital length of stay. While hypoalbuminemia patients tended to have longer hospitalizations, this increase was not statistically significant. Various factors, such as underlying conditions and treatment strategies, may have affected this outcome. Some studies have linked low albumin levels with prolonged hospital stays and severe respiratory failure (Zerbato *et al.*, 2022).

The current study results demonstrated a

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significant relationship between platelet and lymphocyte counts and serum albumin levels, possibly due to albumin role in immune function. However, no significant relationship was found between albumin and neutrophils, as their levels were elevated in hypoalbuminemia individuals. In contrast, another study that stratified COVID-19 patients by albumin levels found no significant association between albumin and platelet counts (Varim *et al.*, 2020).

Future studies should adopt a prospective design to better evaluate the relationship between serum albumin levels and mortality, incorporating key factors such as nutritional status, BMI, medication use, and dynamic changes in albumin levels over time.

While this study adjusted for major comorbidities, it did not account for these variables, and hypoalbuminemia was defined using a fixed threshold (<3.5 g/dl) without assessing its fluctuations during hospitalization. Moreover, although vaccination status was recorded, the specific vaccine type and its potential impact on mortality were not examined. Future research should integrate these aspects to provide a more comprehensive understanding of the prognostic role of albumin in COVID-19 patients

Conclusion

Based on the findings of this study, patients with lower serum albumin levels have a higher disease severity and an increased risk of mortality. Assessing serum albumin levels at the time of hospitalization may serve as a valuable predictor for identifying high-risk patients and guiding clinical management.

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Authors' contributions

All authors contributed equally to all aspects of the study and approved the final version of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

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