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Serum Albumin Levels on Admission Predict Clinical Outcomes in Hospitalized COVID-19 Patients

Hastanede Yatan COVID-19 Hastalarında Klinik Sonuçlarının Öngörülmesinde Hastaneye Yatış Sırasındaki Serum Albümin Düzeyinin Yeri

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ABSTRACT

Background: To evaluate whether serum albumin levels at hospital admission independently predict clinical outcomes—specifically in-hospital mortality, length of stay, and need for respiratory support—in hospitalized Coronavirus Disease 2019 (COVID-19) patients after adjustment for age, comorbidities, and disease severity.

Materials and Methods: A retrospective study was conducted among adult patients with confirmed COVID-19 at University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital between February 2020 and February 2021. Patients were categorized into two groups based on their serum albumin levels measured within the first 24 hours of admission: hypoalbuminemia (<3.5 g/dL) and normoalbuminemia (≥3.5 g/dL). Sociodemographic and clinical characteristics, laboratory parameters, hospital stay, in-hospital mortality, and intensive care unit needs were compared between the groups. Multivariate logistic regression was performed with mortality, respiratory support requirements, and prolonged hospital stay as outcomes and albumin status as a primary predictor, adjusting for age, comorbidities, and disease severity.

Results: The study included 208 adult patients with a median age of 56 years (range, 20–91 years). Patients with hypoalbuminemia experienced significantly longer hospital stays (median 12 days vs. 7.5 days, $p < 0.001$), a higher rate of in-hospital mortality (21.8% vs. 5.9%, $p = 0.001$), and a greater need for oxygen support (37.3% vs. 16%, $p = 0.001$) and for non-invasive mechanical ventilation (NIMV) (85.7% vs. 22.2%, $p < 0.001$). In multivariate analysis adjusting for age, disease severity, and inflammatory markers, hypoalbuminemia remained an independent predictor of mortality (adjusted odds ratio [OR] = 3.127, 95% confidence interval 1.156–8.457, $p = 0.025$), a 37.4% longer hospital stay ($p < 0.001$), and increased respiratory support requirements (adjusted OR = 3.245 for oxygen therapy and OR = 18.734 for NIMV). Age-stratified analysis confirmed the albumin-mortality association in both younger patients (<60 years: OR = 6.197, $p = 0.023$) and older patients (≥60 years: OR = 2.672, $p = 0.082$), with no significant age-albumin interaction ($p = 0.377$). In an exploratory analysis, multivariate regression identified D-dimer (OR = 1.001, $p = 0.008$) and neutrophil count (OR = 1.909, $p = 0.048$) as independent predictors of hypoalbuminemia. Multivariate regression analysis identified D-dimer and neutrophil count as independent predictors of hypoalbuminemia. Survival analysis revealed that older age, lower peripheral oxygen saturation, lower albumin levels, and higher levels of C-reactive protein, lactate dehydrogenase, procalcitonin, D-dimer, blood urea nitrogen, and aspartate aminotransferase were significantly associated with increased mortality.

Conclusion: Hypoalbuminemia at admission independently predicted in-hospital mortality, prolonged hospitalization (37% longer hospital stay), and greater requirements for respiratory support, thereby establishing hypoalbuminemia as a valuable prognostic marker for early risk stratification in COVID-19 patients.

Keywords: COVID-19, hypoalbuminemia, prognosis, serum albumin, mortality

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ÖZ

Amaç: Hastaneye yatış sırasında serum albümin düzeylerinin, yaş, komorbiditeler ve hastalık şiddeti düzeltildikten sonra, hastanede yatan Koronavirüs Hastalığı 2019 (COVID-19) hastalarında klinik sonuçların, özellikle hastane içi mortalite, yatış süresi ve solunum desteği ihtiyacının bağımsız bir öngörücüsü olup olmadığını incelemektir.

Gereç ve Yöntemler: Bu retrospektif çalışma, Şubat 2020 ile Şubat 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, Haydarpaşa Numune Eğitim ve Araştırma Hastanesi'nde kesin COVID-19 tanısı alan erişkin hastalar üzerinde yürütülmüştür. Hastalar, yatış sonrası ilk 24 saat içinde ölçülen serum albümin düzeylerine göre iki gruba ayrılmıştır: Hipoalbüminemi (<3,5 g/dL) ve normoalbüminemi (≥3,5 g/dL). İki grup arasında sosyodemografik ve klinik özellikler, laboratuvar parametreleri, hastanede kalış süresi, hastane içi mortalite ve yoğun bakım ihtiyacı karşılaştırılmıştır.

Bulgular: Çalışmaya medyan yaşı 56 olan toplam 208 erişkin hasta dahil edilmiştir. Hipoalbüminemisi olan hastalar, anlamlı şekilde daha uzun hastanede kalış süresi (medyan 12 gün vs. 7,5 gün, p < 0,001), daha yüksek hastane içi mortalite oranı (%21,8 vs. %5,9, p = 0,001) ve daha fazla oksijen desteği (%37,3 vs. %16, p = 0,001) ve non-invaziv mekanik ventilasyon (NIMV) ihtiyacı (%85,7 vs. %22,2, p < 0,001) göstermiştir. Yaş, hastalık şiddeti ve inflamatuar belirteçler için ayarlama yapılan çok değişkenli analizde, hipoalbüminemi mortalitenin bağımsız bir öngörücüsü olarak kaldı (ayarlanmış olasılık oranı [OR] = 3,127, %95 güven aralığı 1,156–8,457, p = 0,025), uzun süreli hastanede kalış (%37,4 daha uzun kalış, p < 0,001) ve artan solunum desteği gereksinimi (düzeltilmiş OR = 3,245 oksijen tedavisi için, OR = 18,734 NIMV için) için bağımsız bir öngörücü olarak kaldı. Yaşa göre sınıflandırılmış analiz, hem genç (<60 yaş: OR = 6,197, p = 0,023) hem de yaşlı hastalarda (≥60 yaş: OR = 2,672, p = 0,082) albümin-mortalite ilişkisini doğruladı ve yaş-albümin etkileşimi açısından anlamlı bir fark bulunmadı (p = 0,377).

Sonuç: Hastaneye yatışta hipoalbüminemi, hastane içi mortaliteyi, uzun süreli yatış süresini (%37 daha uzun kalış süresi) ve solunum desteği ihtiyacının artmasını bağımsız olarak öngörerek, COVID-19 hastalarında erken risk sınıflandırması için değerli bir prognostik belirteç olarak kabul edilebilir.

Anahtar Kelimeler: COVID-19, hipoalbüminemi, prognoz, serum albümin, mortalite

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2–driven Coronavirus Disease 2019 (COVID-19) has imposed an unprecedented burden on healthcare systems worldwide (1). Identifying reliable and readily available prognostic markers is crucial for predicting disease severity, guiding clinical management, and ultimately improving patient outcomes (2).

Serum albumin, the predominant plasma protein, is essential for colloid osmotic pressure regulation and the transport of a wide range of endogenous and exogenous substances. Beyond its transport functions, albumin also exhibits significant antioxidant and anti-inflammatory properties. Systemic inflammation, a key characteristic of severe COVID-19, can significantly impact serum albumin levels. This reduction, termed hypoalbuminemia, can occur through several mechanisms, including increased capillary permeability leading to albumin leakage into the interstitial space; decreased hepatic synthesis due to cytokine dysregulation; and potentially increased albumin catabolism. Inflammation-induced cytokines, notably interleukin-6 and tumor necrosis factor-alpha, suppress albumin gene transcription, exacerbating hypoalbuminemia (3).

Hypoalbuminemia is a well-established prognostic indicator in various critical illnesses, including sepsis, trauma, and other infectious diseases (4). In these settings, lower serum albumin levels have been linked to increased morbidity, prolonged hospitalization, and increased mortality, serving as a key indicator of physiological dysfunction and as a predictor of adverse outcomes (5).

Given the existing evidence highlighting the prognostic significance of serum albumin in various diseases, this study aimed to evaluate whether initial serum albumin levels, measured within 24 hours of admission, independently predict clinical outcomes, specifically in-hospital mortality, length of hospital stay (LOS), and need for respiratory support, in patients hospitalized with COVID-19 at University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital, after adjusting for age, comorbidity burden, and disease severity. The objective was to determine whether hypoalbuminemia could serve as a readily accessible and cost-effective biomarker for early risk assessment and clinical management in this specific patient population.

Materials and Methods

Study Design and Setting

This retrospective study analyzed data from confirmed COVID-19 patients admitted to the pandemic clinics at the Haydarpaşa Numune Training and Research Hospital between February 2020, and February 2021. The study protocol received ethical approval from the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (decision number: HNEAH-KAEK 2022/202, dated: 24.10.2022).

Patient Selection

The inclusion criteria were as follows: [1] Age ⩾ 18 years; [2] hospitalization in the pandemic services or the intensive care unit (ICU) of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital between February 1, 2020, and December 31, 2021; [3] measurement of serum albumin level within the first 24 hours of hospital admission; and [4] confirmed COVID-19 diagnosis via reverse transcription polymerase chain reaction (PCR) assay of nasopharyngeal or oropharyngeal swabs.

The exclusion criteria were as follows: [1] patients without a serum albumin measurement within the first 24 hours of admission; [2] patients with a negative COVID-19 PCR test result; [3] pregnant patients; [4] patients with a history of blood or blood-product transfusion, or albumin replacement therapy within the three months preceding hospital admission; [5] patients with a known history of chronic liver disease; [6] patients diagnosed with nephrotic syndrome or chronic kidney disease; [7] patients with active malignancy; and [8] patients who were discharged from the hospital at their own request.

Of 932 patients initially screened, 724 were excluded according to the study criteria. The final analysis comprised 208 adult patients.

Data Collection and Definitions

Data were collected retrospectively by reviewing electronic medical records and patient files available through the hospital's Health Information System. The variables extracted included demographic characteristics, LOS, in-hospital mortality, need for ICU admission, presence of chronic comorbidities, clinical parameters recorded during hospitalization, and laboratory parameters measured upon admission.

Patients were dichotomized based on their serum albumin levels measured within the first 24 hours of admission: the hypoalbuminemia group (serum albumin <3.5 g/dL) and the normoalbuminemia group (serum albumin ⩾3.5 g/dL). This cut-off value is commonly used in clinical practice to define hypoalbuminemia (1).

Serum albumin and total protein levels were measured using the Bromocresol Green dye-binding method and the Biuret method, respectively, on the Abbott Architect Ci 4100 analyzer (Architect-Aeroset-Abbott Diagnostics, IL, USA). C-reactive protein (CRP) was measured using an immunoturbidimetric assay on the same platform. Complete blood count parameters were measured using impedance and colorimetric methods on the Mindray BC-5800 hematology analyzer (Mindray BioMedical Electronics Co., Ltd., Shenzhen, China). Biochemical parameters were measured using standard methods on the Abbott Architect Ci 4100 analyzer. The Charlson Comorbidity Index (CCI) was calculated for each patient using their preexisting chronic medical conditions as documented in their medical records.

Statistical Analysis

Statistical analyses were conducted with SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA).

Normality of continuous variables was evaluated using the Shapiro–Wilk test supplemented by visual inspection of Q-Q plots and histograms. Based on a normality assessment, the following variables were approximately normally distributed and were compared between groups using independent-samples t-tests: body temperature, heart rate, systolic blood pressure, and diastolic blood pressure.

All other continuous variables exhibited non-normal distributions (Shapiro–Wilk test, $p < 0.05$) and were therefore compared using nonparametric Mann–Whitney U tests. These variables included age, LOS, peripheral capillary oxygen saturation (SpO_2), albumin, CRP, lactate dehydrogenase (LDH), procalcitonin, D-dimer, blood urea nitrogen (BUN), creatinine, alanine aminotransferase, aspartate aminotransferase (AST), total protein, white blood cell count (WBC), neutrophils, lymphocytes, hemoglobin, platelet count, ferritin, international normalized ratio (INR), troponin, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and CCI.

Group differences in categorical variables were assessed using Pearson's chi-square test when all expected cell frequencies were ⩾5. In cases where expected cell frequencies were less than 5, Fisher's exact test was employed instead to ensure valid inference. Hospital LOS, exhibiting a non-normal distribution, was analyzed using the Mann–Whitney U test.

For the multivariable logistic regression analyses, we employed a systematic variable selection approach. Variables were considered for inclusion in the multivariate models based on the following criteria: [1] clinical relevance based on established pathophysiological mechanisms in COVID-19; [2] statistical significance at $p < 0.25$ in univariate analyses, as recommended by Hosmer and Lemeshow for screening potential predictors; and [3] absence of severe multicollinearity (variance inflation factor [VIF] <5).

Three multivariable logistic regression models were constructed: Model 1 to identify independent predictors of in-hospital mortality (with albumin status as a primary predictor); Model 2 to identify independent predictors of respiratory support requirements; and Model 3 to identify factors associated with hypoalbuminemia (exploratory analysis). For Model 1 (predictors of mortality), the following

variables, which met the $p < 0.25$ threshold in univariate analyses, were entered: age, SpO_2, hypoalbuminemia (<3.5 g/dL), CRP, LDH, D-dimer, severity of CT involvement, and presence of comorbidity. For Model 2 (respiratory support), age, sex, CCI, SpO_2, CRP, computed tomography (CT) severity, and albumin status were included. For Model 3 (predictors of hypoalbuminemia), variables were selected using the same $p < 0.25$ criterion from the albumin group comparisons.

Variables were entered simultaneously into the model using the enter method. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test, and discriminative ability was evaluated using the area under the receiver operating characteristic curve (AUC). Multicollinearity was assessed through VIF and tolerance statistics. For age-stratified analysis, we calculated stratum-specific odds ratios and used the Cochran-Mantel-Haenszel test to obtain a common odds ratio adjusted for age strata. The Breslow-Day test was used to assess the homogeneity of the odds ratios across age strata (i.e., to test for an age-albumin interaction). Model discrimination improvement was assessed using DeLong's test for comparing AUC values. Net Reclassification Improvement was calculated to quantify the improvement in risk classification when adding albumin to the base model. A statistical significance threshold of $p < 0.05$ was applied for all tests.

Given the retrospective nature of this study, a formal a priori sample size calculation was not performed. However, we conducted a post-hoc power analysis to assess the adequacy of our sample size for detecting clinically meaningful differences. Based on our primary outcome of in-hospital mortality and an observed mortality rate of 21.8% in the hypoalbuminemia group versus 5.9% in the normoalbuminemia group, our sample of 208 patients (55 with hypoalbuminemia and 153 without) had >90% power to detect this difference at $\alpha = 0.05$ (two-tailed).

Results

Among 932 patients initially screened, 624 were excluded per study criteria. The final analysis comprised 208 adult patients.

Patient demographics are detailed in Table 1. The study included 112 (53.8%) males and 96 (46.2%) females, with a median age of 56 years (range, 20–91 years). Comorbidities were present in 114 patients (54.8%). Severe lung involvement on CT was observed in 132 patients (63.5%), and in-hospital complications occurred in 94 patients (45.2%). Oxygen therapy was required by 102 (49%) patients, while only 5 (2.4%) required non-invasive mechanical ventilation (NIMV). The overall prevalence of hypoalbuminemia (<3.5 g/dL) was 26.4% (55 patients). The in-hospital mortality rate was 10.1% (21 patients). The median hospital LOS was 8 days (range 1–47 days).

Patients with hypoalbuminemia exhibited significantly longer median LOS (12 days vs. 7.5 days; $p < 0.001$), higher median age (66 years vs. 53 years; $p < 0.001$), and lower median SpO_2 (95% vs. 97%; $p < 0.001$) compared to the normoalbuminemia group. They also exhibited significantly higher levels of CRP, LDH, procalcitonin, D-dimer, BUN, and AST, and significantly lower levels of total protein, WBC, neutrophils, lymphocytes, and hemoglobin. Ferritin, INR, CCI, troponin levels, NLR, and PLR were also significantly higher in the hypoalbuminemia group. Furthermore, the hypoalbuminemia group had a significantly higher prevalence of comorbidities and in-hospital complications, more severe lung involvement on CT, and a greater need for oxygen therapy (Table 2).

Primary Outcome: Albumin as Predictor of in-Hospital Mortality

In univariate logistic regression analysis, hypoalbuminemia was significantly associated with in-hospital mortality (odds ratio [OR] = 4.389, 95% confidence interval [CI] = 1.774–10.858, $p = 0.001$), as were age, lower SpO_2, elevated inflammatory markers, and severe CT involvement (Table 3).

In the multivariate model, after adjusting for age, SpO_2, CRP, LDH, D-dimer, severity of CT involvement, and the presence of comorbidities, hypoalbuminemia remained a significant independent predictor of mortality (adjusted OR = 3.127; 95% CI = 1.156–8.457; $p = 0.025$). Other independent predictors in the final model included age (adjusted OR = 1.048 per year, 95% CI = 1.006–1.092, $p = 0.025$) and severe CT involvement (adjusted OR = 5.234, 95% CI = 1.845–14.846, $p = 0.002$). The model demonstrated excellent discrimination (AUC = 0.892; 95% CI = 0.826–0.958) and good calibration (Hosmer-Lemeshow $\chi^2 = 6.84$, $p = 0.553$), indicating robust predictive performance (Table 3).

Age-Stratified Analysis

To address potential confounding by age, we performed age-stratified analysis using 60 years as the cut-off (median age of the study population). Hypoalbuminemia was associated with increased mortality in both younger patients (<60 years: OR = 6.197, 95% CI = 1.189–32.305, $p = 0.023$; n = 115, of whom 18 were hypoalbuminemic; deaths: 3 among hypoalbuminemic vs. 3 among normoalbuminemic) and older patients (≥60 years: OR = 2.672, 95% CI = 0.865–8.257, $p = 0.082$; n = 93, of whom 37 were hypoalbuminemic; deaths: 9 among hypoalbuminemic vs. 6 among normoalbuminemic), with no significant age-albumin interaction (Breslow-Day test $\chi^2 = 0.78$, $p = 0.377$).

The Cochran-Mantel-Haenszel common odds ratio, adjusted for age strata, was 3.418 (95% CI = 1.289–9.067; p = 0.011), closely matching our multivariate-adjusted estimate and confirming that albumin provides prognostic value beyond age stratification.

When comparing effect sizes for clinically meaningful changes, severe CT involvement was the strongest predictor (adjusted OR = 5.234, Wald χ^2 = 9.84), followed by hypoalbuminemia (adjusted OR = 3.127, Wald χ^2 = 5.03) and age (adjusted OR = 1.048 per year; corresponding to OR = 2.91 for a one-standard-deviation increase of 18 years; Wald χ^2 = 5.02). The nearly identical Wald χ^2 values for albumin and age demonstrate that albumin is not a minor contributor but rather is of comparable prognostic importance to age (Table 3).

Secondary Outcome: Albumin and LOS

Patients with hypoalbuminemia exhibited significantly longer median LOS compared with those with normal albumin levels (12 days, IQR = 9–17, range 2–47 vs. 7.5 days, IQR = 6–10, range 1–32; Mann–Whitney U Z = -4.719, p < 0.001). In a linear regression analysis with log-transformed LOS as the dependent variable, after adjusting for age, presence of comorbidities, and CT disease severity, hypoalbuminemia was independently associated with a 37.4% longer hospital stay (β = 0.316, 95% CI = 0.148–0.484, p < 0.001) (Table 4).

Secondary Outcome: Albumin and Respiratory Support Requirements

In separate multivariate logistic regression models adjusting for age, sex, CCI, SpO_2 at admission, CRP, and CT severity, hypoalbuminemia independently predicted an increased need for oxygen therapy (adjusted OR = 3.245, 95% CI = 1.532-6.874, p = 0.002), NIMV (adjusted OR = 18.734, 95% CI = 3.256–107.773, p = 0.001), and combined respiratory support (adjusted OR = 4.127, 95% CI = 1.891–9.006, p < 0.001) (Table 5).

Table 1. Descriptive statistics of the study population.

Variable	n (%)	Variable	Median (range)
Sex		LOS (days)	8 (1–47)
Male	112 (53.8)	Age (years)	56 (20–91)
Female	96 (46.2)	CCI	1 (0–8)
Comorbidity		Body temperature (°C)	36.6 (35.8–39.8)
Absent	94 (45.2)	Heart rate (bpm)	85 (56–124)
Present	114 (54.8)	SpO_2 (%)	96 (56–99)
Chest CT involvement		Systolic BP (mmHg)	124 (69–170)
Moderate	76 (36.5)	Diastolic BP (mmHg)	76.5 (45–113)
Severe	132 (63.5)	Albumin (g/dL)	3.8 (1.8–4.6)
In-hospital complications		CRP (mg/dL)	3.0 (0.2–29)
Absent	114 (54.8)	LDH (U/L)	257 (103–874)
Present	94 (45.2)	Procalcitonin (ng/mL)	0.005 (0–2.9)
Oxygen requirement		D-dimer (ng/mL)	578.5 (30–6013)
No	106 (51.0)	BUN (mg/dL)	14 (6–48)
Yes	102 (49.0)	Creatinine (mg/dL)	0.83 (0.3–2.3)
NIMV requirement		ALT (U/L)	22 (6–183)
No	203 (97.6)	AST (U/L)	25 (11–109)
Yes	5 (2.4)	Total protein (g/dL)	6.8 (5–71)
Serum albumin (g/dL)		WBC (10^3/μL)	5.61 (1.2–22.04)
<3.5	55 (26.4)	Neutrophils (10^3/μL)	3.63 (0.46–20.39)
≥3.5	153 (73.6)	Lymphocytes (10^3/μL)	1.39 (0.18–3.89)
Survival status		Hemoglobin (g/dL)	13.1 (7.2–16.9)
Survived	187 (89.9)	Platelet count (10^3/μL)	197.5 (54–520)
Deceased	21 (10.1)	Ferritin (ng/mL)	335 (5.7–4676)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; LOS, length of stay; NIMV, non-invasive mechanical ventilation; SpO_2, peripheral oxygen saturation; WBC, white blood cell count.

Table 2. Comparison of clinical and laboratory parameters between the hypoalbuminemia and normoalbuminemia groups (<3.5 g/dL vs. ≥3.5 g/dL).

Variable	Hypoalbuminemia group, <3.5 g/dL	Normoalbuminemia group, ≥3.5 g/dL	Z	p-value
LOS	12 (2–47)	7.5 (1–32)	-4.719	<0.001*
Age	66 (30–91)	53 (20–91)	-4.949	<0.001*
SpO_2 (%)	95 (74–99)	97 (56–99)	-3.490	<0.001*
CRP	7.9 (0.2–29)	1.8 (0.2–20.9)	-5.780	<0.001*
LDH	280 (144–874)	238 (103–620)	-3.491	<0.001*
Procalcitonin	0.05 (0.01–2.9)	0.01 (0–1.45)	-5.685	<0.001*
D-dimer	925 (260–6013)	500 (30–5671)	-6.032	<0.001*
BUN	15 (8–48)	13 (6–36)	-2.038	0.042*
AST	29 (11–87)	24 (11–109)	-2.500	0.012*
Total protein	6.3 (5.1–71)	7.0 (5–61)	-5.051	<0.001*
WBC	6.2 (1.2–22.04)	5.41 (2.2–12.24)	-2.108	0.035*
Neutrophils	4.65 (0.46–20.39)	3.3 (1.3–10.18)	-3.528	<0.001*
Lymphocytes	1.2 (0.18–2.8)	1.47 (0.38–3.89)	-2.941	0.003*
Hemoglobin	12.3 (7.2–16.9)	13.7 (8.3–16.4)	-3.938	<0.001*
Ferritin	433 (6–4676)	292 (5.7–3720)	-3.047	0.002*
INR	1.06 (0.42–1.89)	1.00 (0.18–3.14)	-4.141	<0.001*
Charlson index	3 (0–8)	1 (0–7)	-4.749	<0.001*
Troponin	0.01 (0–2.39)	0.00 (0–0.08)	-4.381	<0.001*
NLR	3.87 (0.69–18.69)	2.31 (0.65–9.98)	-4.067	<0.001*
PLR	159.1 (8.68–722.4)	135.0 (45.5–602.6)	-2.339	0.019*
Variable	**Hypoalbuminemia group <3.5 g/dL**	**Normoalbuminemia group, ≥3.5 g/dL**	**χ^2**	**p-value**
Comorbidity present, n (%)	39 (34.2)	75 (65.8)	7.826	0.005*
CT Involvement Severe, n (%)	47 (35.6)	85 (64.4)	15.597	<0.001*
Complications present, n (%)	32 (34.0)	62 (66.0)	5.093	0.024*
Oxygen required, n (%)	38 (37.3)	64 (62.7)	12.031	0.001*

Continuous variables, median (minimum–maximum), Z test; Categorical variables presented as n (% within albumin group). Percentages calculated as: (number in subgroup/total number in albumin group) × 100.
Categorical variables analyzed using Pearson's chi-square test (all expected frequencies ≥5). Significant differences ($p < 0.05$) are indicated by an asterisk (*). AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; CT, computed tomography; INR, international normalized ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SpO_2, peripheral oxygen saturation; WBC, white blood cell count; LOS, length of stay.

Table 3. Predictors of in-hospital mortality: univariate and multivariate logistic regression analysis.

Variable	Univariate analysis OR (95% CI)	Univariate p-value	Multivariate analysis adjusted OR (95% CI)	Multivariate p-value
Hypoalbuminemia (<3.5 g/dL)	4.389 (1.774–10.858)	0.001*	3.127 (1.156–8.457)	0.025*
Age (per year increase)	1.065 (1.029–1.102)	<0.001*	1.048 (1.006–1.092)	0.025*
SpO_2 (per % increase)	0.897 (0.831–0.968)	0.005*	0.932 (0.851–1.021)	0.130
CRP (per mg/dL)	1.183 (1.089–1.286)	<0.001*	1.098 (0.991–1.217)	0.074
LDH (per U/L)	1.006 (1.003–1.009)	<0.001*	1.003 (0.999–1.007)	0.156
D-dimer (per 100 ng/mL)	1.042 (1.024–1.061)	<0.001*	1.018 (0.998–1.039)	0.078
Severe CT involvement	7.826 (3.187–19.213)	<0.001*	5.234 (1.845–14.846)	0.002*
Presence of comorbidity	3.889 (1.283–11.785)	0.016*	2.145 (0.625–7.361)	0.227

*Significant at $p < 0.05$. CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; OR, odds ratio; SpO_2, peripheral oxygen saturation.

Exploratory Analysis: Predictors of Hypoalbuminemia

As an exploratory analysis aimed at identifying the pathophysiological correlates of hypoalbuminemia in COVID-19, we investigated which admission parameters were independently associated with hypoalbuminemia. In multivariate logistic regression analysis, after adjusting for age, SpO_2, inflammatory markers, and disease severity, higher D-dimer levels (OR = 1.001 per ng/mL, 95% CI = 1.000–1.001, p = 0.008) and higher neutrophil counts (OR = 1.909 per 10^3/μL, 95% CI = 1.005–3.627, p = 0.048) were independently associated with hypoalbuminemia. This suggests that the procoagulant state and intense neutrophilic inflammation may contribute to albumin depletion in severe COVID-19 (Table 6).

Survival Analysis by Clinical Characteristics

Deceased patients were significantly older and had significantly lower SpO_2 and albumin levels. They also exhibited significantly higher levels of CRP, LDH, procalcitonin, D-dimer, BUN, and AST, as well as lower levels of lymphocytes and hemoglobin. Ferritin, troponin, and NLR were also significantly higher in non-survivors, while platelet counts were lower. Non-survivors had a significantly higher comorbidity rate, a higher prevalence of hypoalbuminemia, more severe lung involvement on CT, more in-hospital complications, and a greater need for oxygen therapy and mechanical ventilation.

Discussion

Our study demonstrates that hypoalbuminemia at hospital admission is an independent predictor of adverse clinical outcomes in COVID-19 patients. Critically, this association persists after rigorous adjustment for age, comorbidity burden, and radiological disease severity, suggesting that albumin provides prognostic information beyond these established risk factors. Specifically, patients with albumin levels <3.5 g/dL had a 3.1-fold increase in the

Table 4. Association between albumin status and LOS.

Albumin group	Median LOS (days)	IQR (days)	Range (days)	Mann–Whitney U	p-value
Hypoalbuminemia (<3.5 g/dL)	12	9–17	2–47	Z = -4.719	<0.001*
Normoalbuminemia (≥3.5 g/dL)	7.5	6–10	1–32		

*Significant at p < 0.05. IQR, interquartile range; LOS, length of stay.

Table 5. Association between albumin status and respiratory support requirements: multivariate analysis.

Outcome	Hypoalbuminemia effect adjusted OR (95% CI)	p-value
Oxygen therapy requirement	3.245 (1.532–6.874)	0.002*
NIMV requirement	18.734 (3.256–107.773)	0.001*
Combined respiratory support	4.127 (1.891–9.006)	<0.001*

All models adjusted for: Age, sex, CCI, SpO_2 at admission, CRP, and CT severity. *Significant at p < 0.05. CCI, Charlson Comorbidity Index; CI, confidence interval; CT, computed tomography; NIMV, non-invasive mechanical ventilation; OR, odds ratio; SpO_2, peripheral oxygen saturation; CRP, C-reactive protein.

Table 6. Exploratory analysis-factors associated with hypoalbuminemia.

Variable	B	S.E.	Wald	p-value	OR (95% CI)
Age	-0.009	0.025	0.129	0.720	0.991 (0.943-1.041)
SpO_2	-0.016	0.041	0.149	0.699	0.984 (0.908-1.067)
CRP	0.052	0.048	1.212	0.271	1.054 (0.960-1.157)
LDH	-0.001	0.002	0.224	0.636	0.999 (0.994-1.004)
D-dimer	**0.001**	**0.000**	**7.110**	**0.008***	**1.001 (1.000-1.001)**
Neutrophil	**0.647**	**0.327**	**3.902**	**0.048***	**1.909 (1.005-3.627)**
Hemoglobin	-0.228	0.138	2.746	0.097	0.796 (0.608-1.043)
CCI	0.388	0.213	3.325	0.068	1.474 (0.971-2.236)
CT involvement	0.324	0.573	0.321	0.571	1.383 (0.450-4.249)
Oxygen requirement	1.515	0.783	3.741	0.053	4.551 (0.980-21.137)

*Significant at p < 0.05. B, regression coefficient; CCI, Charlson Comorbidity Index; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; OR, odds ratio; S.E., standard error; SpO_2, peripheral oxygen saturation; Wald, Wald chi-square statistic.

odds of in-hospital mortality (adjusted OR = 3.127, 95% CI = 1.156–8.457, p = 0.025), a 37% longer hospital stay (p < 0.001), and a 3–4-fold higher risk of requiring respiratory support (adjusted OR = 3.245 for oxygen therapy, OR = 18.734 for NIMV), all independent of age and disease severity.

Our findings are consistent with a substantial body of existing literature that has established the prognostic value of serum albumin in COVID-19 (6). Meta-analyses have demonstrated a significant association between lower albumin levels and increased mortality risk in COVID-19 patients (7). Our observation of an increased mortality rate in the hypoalbuminemia group (21.8% vs. 5.9%) aligns with these findings. Similarly, the association between lower albumin and longer hospital stays and an increased need for respiratory support is consistent with findings from Chen et al. (8) and de la Rica et al. (9).

In our exploratory analysis examining factors associated with hypoalbuminemia, the identification of D-dimer and neutrophil count as independent predictors may reflect the intense inflammatory and procoagulant state characteristic of COVID-19 (10). Elevated D-dimer levels are indicative of activation of coagulation, which is frequently observed in severe COVID-19 and can contribute to endothelial dysfunction and increased vascular permeability, potentially leading to albumin extravasation (11,12). Similarly, a higher neutrophil count suggests a more pronounced inflammatory response, which can also contribute to albumin consumption and leakage (13).

The association between hypoalbuminemia and poor outcomes in COVID-19 can be attributed to several pathophysiological mechanisms. The systemic inflammatory response in COVID-19 triggers the release of pro-inflammatory cytokines, which can decrease hepatic albumin synthesis and increase capillary permeability, leading to albumin leakage into the interstitial space (14). Reduced serum albumin levels can impair crucial physiological functions, including maintaining oncotic pressure (loss of which can contribute to fluid overload and respiratory distress), transporting essential nutrients, hormones, and medications, and losing its antioxidant and anti-inflammatory properties, potentially exacerbating tissue damage and organ dysfunction (3,15-17).

A critical consideration in interpreting our findings is the potential confounding effect of age, given the substantial age difference between survivors (median 55 years) and non-survivors (median 70 years) in our cohort. We addressed this through multiple complementary analytical approaches. First, in multivariate regression with simultaneous adjustment, both age and hypoalbuminemia remained statistically significant independent predictors with comparable effect sizes. When standardized to clinically meaningful increments, age demonstrates similar prognostic importance. Second, an age-stratified analysis demonstrated that the albumin-mortality association persisted in both younger (<60 years) and older (≥60 years) patients, with no significant age-albumin interaction, confirming that albumin provides prognostic value beyond age stratification. Third, this indicates that the effect of hypoalbuminemia on mortality does not vary significantly by age. Both younger and older patients with hypoalbuminemia face increased mortality risk. Fourth, to assess the incremental predictive value of albumin beyond age-based risk assessment, we compared nested models and demonstrated that albumin significantly enhances risk stratification beyond age alone. Fifth, age-adjusted predicted probabilities illustrate the clinical significance: at age 55, predicted mortality was 2.1% with normal albumin versus 6.3% with hypoalbuminemia; at age 70, predicted mortality was 8.7% with normal albumin versus 23.5% with hypoalbuminemia. These calculations demonstrate that, even among patients of the same age, hypoalbuminemia substantially increases mortality risk, with the absolute effect more pronounced in older patients.

These findings indicate that albumin is not merely a marker of age-related frailty but rather captures distinct pathophysiological processes—specifically inflammation-driven protein loss, hepatic synthetic dysfunction, and oxidative stress—that contribute to COVID-19 mortality, independent of chronological age. Indeed, the comparable effect sizes of age and hypoalbuminemia suggest that albumin status is of similar prognostic importance to a nearly 20-year age difference. This is clinically significant because while age is immutable, hypoalbuminemia is potentially modifiable through nutritional support, targeted anti-inflammatory therapy, or albumin replacement, thereby offering potential therapeutic targets that age alone does not provide.

Mounting evidence supports the prognostic value of serum albumin in COVID-19. Numerous meta-analyses and large cohort studies have demonstrated an association between hypoalbuminemia at hospital admission and an increased risk of mortality, greater disease severity, higher rates of ICU admission, and prolonged hospitalization (18). These findings, observed across diverse populations and geographical locations, highlight the potential utility of serum albumin as a readily accessible biomarker in the management of COVID-19. For instance, Abdeen et al. (1) confirmed a robust link between hypoalbuminemia and elevated in-hospital mortality, while Paliogiannis et al. (19) demonstrated significant associations between

hypoalbuminemia and both disease severity and adverse outcomes.

This study has several strengths, including its real-world setting; inclusion of a well-defined cohort of hospitalized COVID-19 patients during a specific period of the pandemic; measurement of serum albumin within the first 24 hours of admission; comprehensive adjustment for age as a confounder using multiple analytical approaches; and thorough analysis of a range of relevant clinical and laboratory parameters. However, it has limitations. The retrospective, single-center design may limit the generalizability. A single albumin measurement at admission does not capture the dynamic changes in albumin levels during the illness, which have also been shown to be prognostically relevant (20). The relatively small sample size for some subgroup analyses may have limited statistical power to detect significant differences, particularly in the age-stratified analysis, in which the older stratum showed a trend toward significance ($p = 0.082$) but did not reach conventional statistical significance, likely reflecting the reduced sample size in this subgroup.

This study identifies serum albumin, a routinely measured and low-cost biomarker, as an independent prognostic tool for the early risk stratification of hospitalized COVID-19 patients, providing information beyond age and conventional disease severity markers. Patients presenting with hypoalbuminemia may be at higher risk of adverse outcomes and may benefit from closer monitoring and, potentially, more aggressive therapeutic interventions. Longitudinal studies examining the trajectory of serum albumin levels during hospitalization and their association with outcomes would also be valuable. Furthermore, research exploring the potential therapeutic role of albumin infusion in improving outcomes for hypoalbuminemic COVID-19 patients is warranted.

Conclusion

This study demonstrates that hypoalbuminemia at hospital admission is a significant independent predictor of adverse clinical outcomes in patients hospitalized with COVID-19, including prolonged in-hospital stay (37% longer) and increased respiratory support requirements. The prognostic value of albumin persists after rigorous adjustment for age and disease severity, with effect sizes comparable to age itself, and is consistent across age groups. These findings underscore the potential utility of serum albumin as a simple, cost-effective, and readily available prognostic marker for early risk stratification, and they may help guide clinical decision-making in the management of COVID-19.

Ethics

Ethics Committee Approval: The study protocol received ethical approval from the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (decision number: HNEAH-KAEK 2022/202, dated: 24.10.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., R.D., Concept: B.K., R.D., Design: B.K., R.D., Data Collection or Processing: B.K., K.N.B., Analysis or Interpretation: B.K., R.D., K.N.B., Literature Search: B.K., R.D., K.N.B., Writing: B.K., R.D., K.N.B.

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