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Original Article

Prognostic Value of Hypoalbuminemia on Admission in Patients with COVID-19 at Tishreen University Hospital

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Abstract - *Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has triggered a global health crisis that has affected populations and spread worldwide. It is unclear whether the outcome is modulated by serum albumin levels, in which hypoalbuminemia is associated with adverse outcomes. This study aims to investigate the association between albumin levels on admission and the outcomes of COVID-19 patients. Methods: An Analytic Cohort Study (Prospective) was conducted on patients with a proven diagnosis of COVID-19. They were selected from Pulmonology Department, Tishreen University Hospital in Lattakia-Syria between September 2021 and September 2022. The study population was divided into two groups according to the albumin levels on admission; Group I included patients with hypoalbuminemia (albumin<3.5 g/dl), and Group II included patients with normal albumin. The final outcome was compared between the two groups. Results: The population of 208 patients was predominantly male (60.1%), with a mean age of 62.1±13.5 years. 31.7% of the patients were smokers, and hypertension represented the most frequent comorbidity (41.3%). Mean values of WBC, PCT, D-Dimer, and CRP were significantly higher in patients with hypoalbuminemia (p<0.05). Low level of albumin was associated with an independent risk for mortality (RR: 4.9[2.8-9.9], p:0.0001), need for invasive ventilation (RR: 3.9[1.1-7.3], p:0.0001), need for non-invasive ventilation (RR: 4.3[1.5-11.3], p:0.0001), and admission in intensive care unit (RR: 3.8[2.2-10.5], p:0.0001). The cut-off point for mortality was albumin=3.19 g/dl, with a sensitivity of 71.3% and 63.1% specificity. Conclusion: This study demonstrated unfavorable hypoalbuminemia results on the final outcomes regarding morbidity and mortality in COVID-19 patients.*

Keywords - *COVID-19, Hypoalbuminemia, ICU, Albumin, Mortality.*

1. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by SARS-CoV-2; according to the declaration by World Health Organization (WHO) on March 2020, it represents a global pandemic that disseminated rapidly across the world [1]. It has had a terrible effect on the world, resulting in more than 6 million deaths [2]. Despite the downward current trend of COVID-19 appearance, a significant increase in reported cases and deaths continued to be seen weekly [3].

Clinical manifestations of COVID-19 are various and might differ from asymptomatic infection and mild upper respiratory tract symptoms to respiratory failure, acute respiratory distress syndrome (ARDS), multiple organ dysfunction and death [4]. Numerous factors predispose to severe disease, which include; advanced age presence of comorbidities such as cardiovascular disease, hypertension, and diabetes mellitus [4]. In addition, severe forms of disease showed laboratory changes, including lymphopenia, elevated levels of inflammatory markers and D-dimer [5].

Hypoalbuminemia is considered a very common disorder in hospitalized patients with severe and critical diseases [6]. Many factors lead to hypoalbuminemia, including decreased synthesis of albumin (fasting/nutritive insufficiency), increased loss via the kidney and gastrointestinal tract, increased tissue catabolism and disorders in distribution [7]. In serious illnesses, inflammatory mediators reduce the production of albumin due to the synthesis of other acute phase reactants, and these mediators increase the permeability of vessels and capillary leakage resulting in loss of albumin from the intravascular space into the extravascular space [8].

As a result of severe inflammation, there might be both an increased clearance rate and a decline in the rate of albumin production by the liver [9]. Despite its lack of specificity, serum albumin can have a prognostic significance, and many studies demonstrated that hypoalbuminemia is associated with severe disease and reflects cell injury induced by infection in COVID-19 patients. The pandemic continues to place a major strain on a country's resources, and it is predicted that mortality and morbidity rates will become pronounced with

rising spread among lower-income countries so that finding a simple, fast, sensitive laboratory test is considered crucial to detect patients who are considered at high risk for adverse outcomes. Therefore, the study's objectives were: 1- to detect the prognostic value of low albumin levels in COVID-19 patients and 2- to determine the utility of albumin on admission for predicting mortality.

2. Patients and Methods

This is an Analytic Cohort Study (Prospective) of a group of patients admitted at the Department of Pulmonology at Tishreen University Hospital in Lattakia-Syria during a one-year period (from September 2021 to September 2022).

The inclusion criteria were: patients older than 18 years, males or females, tested positive for SARS-CoV-2 by nucleic acid amplification (NAA). Exclusion criteria were patients with diseases that lead to hypoalbuminemia, such as liver cirrhosis and the final stages of liver failure, chronic kidney failure, nephrotic syndrome, and protein-losing enteropathy.

Complete history, physical examination, and laboratory investigations, including white blood cell (WBC), neutrophils (NEU), C-reactive protein (CRP), lymphocytes count (LYM), platelets (PLT), Procalcitonin (PCT), and lactate dehydrogenase (LDH) were performed. A radiological investigation was performed, and laboratory confirmation of COVID-19 diagnosis was done based on using real-time PCR with a standard protocol.

Patients were stratified according to the albumin level on admission into two groups: group I included COVID-19 patients with albumin levels <3.5 g/dL, and Group II included COVID-19 patients with normal levels of albumin (≥3.5 g/dl). Demographic variables, requirement for respiratory support and final outcome were compared between the two groups.

2.1. Ethical Consideration

All patients were provided complete and clear informed consent after discussing the study. This study was performed in accordance with the Declaration of Helsinki.

2.2. Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations (SD), Frequency and percentages. The chi-square test was used to examine the relationships and comparisons between the two groups. An Independent T-student test was used to compare 2 independent groups.

Multivariate logistic regression analysis was performed to estimate risks associated with decreased albumin levels on prognosis. The receiver operating characteristics (ROC) curve was constructed, and the area under the curve (AUC) was established to assess the ability of albumin to predict mortality. P-value < 0.05 was considered statistically significant.

3. Results

The study included a group of 208 patients with a diagnosis of COVID-19. The baseline characteristics of patients were as shown in Table (1). Age ranged from 22 to 92 years, with a mean age of 62.1±13.5 years. Males represented 60.1%, and females represented 39.9% of the patients, and the male: female ratio was 1.5:1. Of the 208 patients included in the analysis, 66 patients (31.7%) were smokers and comorbidities presented as follows; hypertension (41.3%), diabetes mellitus (27.3%), cardiovascular diseases (17.8%) and chronic pulmonary disease (11.1%).

Table 1. Demographic characteristics of the study population

Variable	Result
Age (years)	62.1±13.5
Sex	
Male	125(60.1%)
Female	83(39.9%)
Smoking	
Present	66(31.7%)
Absent	142(68.3%)
Comorbidities	
Hypertension	86(41.3%)
Diabetes mellitus	57(27.3%)
Cardiovascular diseases	37(17.8%)
Chronic pulmonary disease	23(11.1%)

Table 2. Demographic characteristics of the study population by comparison of the two groups

Variables	Group I Albumin<3.5 (n=84)	Group II Albumin≥3.5 (n=124)	P value*
Age (years)	61.2±13.3	62.5±13.6	0.4
Sex Male Female	 48(57.1%) 36(42.9%)	 77(62.1%) 47(37.9%)	 0.4
Smoking	30(35.7%)	36(29%)	0.3
Comorbidities			
Hypertension	37(44%)	49(39.5%)	0.5
Diabetes mellitus	26(31%)	31(25%)	0.3
Cardiovascular diseases	16(19%)	21(16.9%)	0.6
Chronic pulmonary disease	14(16.7%)	9(7.3%)	0.03

**p-value is significant at < 0.05 level*

Table 3. Vital signs and laboratory investigations of the study population by comparison of the two groups

Variables	Group I Albumin<3.5 (n=84)	Group II Albumin≥3.5 (n=124)	*P value
Vital signs			
SaO2(Oxygen saturation) (%)	74.23±9.6	78.58±11.7	0.03
Heart rate(bpm)	84.57±14.4	86.60±15.5	0.3
Temperature(c°)	37.90±4.2	39.31±4.8	0.2
Systolic pressure(mmHg)	120.8±99	118.4±14	0.7
Diastolic pressure (mmHg)	68.6±15	72.5±11	0.06
Laboratory investigations			
WBC count($\times10^9$/L)	13.66±7.2	10.83±6.4	0.003
Neu(%)	80.15±11.9	77.23±13.4	0.1
Lym count($\times10^9$/L)	1065.78±1130.7	1258.79±1479.6	0.3
PLT count($\times10^9$/L)	219.6±107.7	244.68±109.5	0.07
PCT(ng/ml)	0.66±0.8	0.31±0.5	0.001
D-Dimer(ng/ml)	4013.1±2932.5	1965.1±2038.1	0.0001
LDH(U/L)	826.8±432.5	767.09±307.1	0.2
CRP(mg/l)	106.71±64.5	90.1±61.4	0.04
Hgb(g/dl)	11.27±2.2	12.26±1.5	0.09
Albumin(g/dl)	2.98±0.4	4.38±0.5	0.0001

**p-value is significant at < 0.05 level. Bmp beat per minute; mmHg, millimeters of mercury; WBC, White blood cell count; Neu, neutrophils; Lym, lymphocytes; PLT, platelet count; PCT, Procalcitonin; LDH, Lactate dehydrogenase; CRP, C-reactive protein; Hgb, Hemoglobin*

Table 4. Outcome of the study population by comparison of the two groups

Variables	Group I Albumin<3.5 (n=84)	Group II Albumin≥3.5 (n=124)	*P value
Invasive Mechanical ventilation Present Absent	 54(64.3%) 30(35.7%)	 30(24.2%) 94(75.8%)	 0.0001
Non-invasive Mechanical ventilation Present Absent	 71(84.5%) 13(15.5%)	 56(45.2%) 68(54.8%)	 0.0001
Admission at ICU Present Absent	 54(64.3%) 30(35.7%)	 31(25%) 93(75%)	 0.0001
Final outcome Recovery Death	 24(28.6%) 60(71.4%)	 87(70.2%) 37(29.8%)	 0.0001

**p-value is significant at < 0.05 level . ICU, Intensive Care Unit*

Table 5. Multivariate logistic regression analysis of albumin levels of the study population

Variable	RRa [95%CI]	*P value
Death	4.9[2.8-9.9]	0.0001
Need for invasive mechanical ventilation	3.9[1.1-7.3]	0.0001
Need for non-invasive mechanical ventilation	4.3[1.5-11.3]	0.0001
Admission at ICU	3.8[2.2-10.5]	0.0001

**p-value is significant at < 0.05 level .RRa,adjusted relative risk; CI, Confidence Interval; ICU, Intensive Care Unit.*

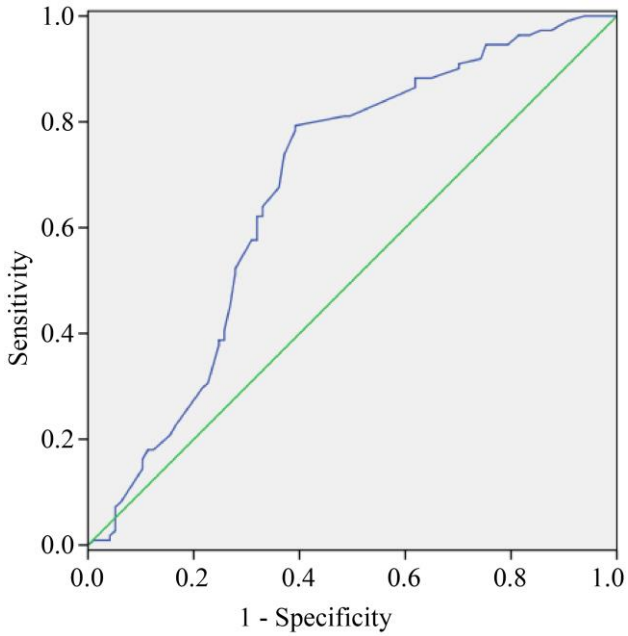

Fig. 1 ROC diagram showing the relationship between albumin values and mortality

As shown in Table (2), no significant difference was found between the two groups in terms of age, gender, smoking and presence of comorbidities (p>0.05) except for chronic pulmonary disease, which was observed in 14 cases (16.7%) in group I versus 9 cases (7.3%), p:0.03.

In group I, the mean age was 61.2±13.3 years versus 62.5±13.6 in group II (p:0.4). Males represented 57.1%, and females represented 42.9% of the patients with the presence of smoking in 30 cases (35.7%) in group I, whereas in group II males represented 62.1% and females represented 37.9% of the patients, with the presence of smoking in 36 cases (29%). In group I, hypertension represented the most frequent comorbidity (44%), followed by diabetes mellitus (31%), cardiovascular diseases(19%), and chronic pulmonary disease(16.7%) versus 39.5%, 25%, 16.9%, and 7.3% respectively in group II without the presence of significant difference, p>0.05.

As shown in Table (3), there were no significant differences between the two groups regarding vital signs on admission except for oxygen saturation (74.23±9.6% in group I versus 78.58±11.7% in group II, p:0.03). Mean values of heart rate, temperature, systolic pressure, and diastolic pressure in group I versus group II were as follows; (84.57±14.4 bmp vs. 86.60±15.5 bmp, p:0.3), (37.90±4.2 c° vs. 39.31±4.8 c°, p:0.2), (120.08±90.9 mmHg vs. 110.84±10.4 mmHg, p:0.7), and (60.86±10.5 mmHg vs. 70.25±10.1 mmHg, p:0.06) respectively. The mean value of albumin in group I was 2.98±0.4 g/dl versus 4.38±0.5 g/dl in group II,p:0.0001.

There were significant differences between the two groups regarding the following laboratory investigations (group I versus group II); WBC (13.66±7.2 vs 10.83±6.4, p:0.003), PCT (0.66±0.8 vs 0.31±0.5,p:0.001), D-Dimer(4013.1±2932.5 vs. 1965.1±2038.1,p:0.0001), and CRP(106.71±64.5 vs. 90.1±61.4,p;0.04).

During hospitalization, non-invasive ventilation was used in 71(84.5%) cases in group I versus 56(45.2%) cases in group II, p: 0.0001, whereas the invasive type of ventilation was applied in 54 cases (64.3%) in group I versus 30(24.2%) in group II, p:0.0001. There was a significant difference between the two groups regarding admission to ICU;64.3% in group I versus 25% in group II, p:0.0001. Recovery occurred in 24(28.6%) cases in group I versus 87 cases (70.2%) in group

II, and 71.4% of the patients died in group I versus 29.8% in group II, p:0.001.

In the multivariate logistic regression analysis, a lower level of albumin was an independent risk factor that was associated significantly with the occurrence of death (RR 4.9, 95%CI 2.8-9.9, p=0.0001), need for invasive mechanical ventilation (RR 3.9,95% CI 1.1-7.3, p=0.0001), need for non-invasive mechanical ventilation (RR 4.3,95% CI 1.5-11.3, p=0.0001), and admission to ICU (RR 3.8,95% CI 2.2-10.5, p=0.0001).

Analysis of the ROC curve illustrated an 0.67 area under the curve (AUC) for albumin levels as a predictor of mortality (95% CI:0.60-0.75). The AUC of this biomarker indicated a high diagnostic value for mortality, with the optimal threshold value being 3.19 g/dl with a sensitivity of 71.3% and specificity of 63.1% (figure 1).

4. Discussion

The COVID-19 pandemic is a worldwide public health problem that has resulted in poor outcomes for patients, and the current study provides evidence of the impact of hypoalbuminemia on the progression of the disease and the final outcomes of patients. The result of the current study revealed that approximately 60% of the patients were males, with the presence of low levels of albumin in 40.4% of cases. There was a significant difference between the two groups regarding oxygen saturation on admission, which was lower in patients with hypoalbuminemia, with the presence of a negative correlation between levels of inflammatory markers and albumin on admission. These findings might be explained by the systematic inflammatory status in COVID-19 and interleukins such as IL-6 and TNF-α, provoking a shift towards increased mRNA transcription specific to CRP rather than albumin [10,11].

The presence of a greater percentage of chronic lung diseases in the group of patients with low albumin levels in our study might provide an explanation for the increase in the severity of their respiratory failure and, thus, the increased need for invasive and non-invasive mechanical ventilation compared to patients with normal albumin levels. Systemic inflammation in COVID-19 leads to an increase in the distribution of albumin into the extravascular space, which reduces the oncotic pressure inside the vessels and therefore increases edema in the tissues, and this may lead to an increased risk of non-cardiogenic pulmonary edema [12,13,14]. Moreover, serum albumin plays an essential role as an antioxidant in the respiratory system [15]. Therefore, decreased levels of albumin reduce the ability to fight oxidative stress, increase the threat of lung damage, and decrease levels of oxygen saturation [16].

The rate of mechanical ventilation, admission to ICU, and mortality was significantly higher in patients with lower albumin levels ($p<0.05$). Lower albumin level was an independent risk factor associated significantly with increased mortality risk, mechanical ventilation need, and ICU admission. The cut-off of albumin 3.19 g/dl was the optimal value for accurate mortality prediction with an AUC of 0.67, and this value corresponded to sensitivity:71.3% and specificity:63.1%.

Poor outcomes that result from hypoalbuminemia in COVID-19 patients might be explained by the following: the endothelial dysfunction, which plays an important role in COVID-19 [17], resulting from several mechanisms, including the response to SARS-CoV-2 in addition to hypoxia, activation and recruitment of immune cells with the production of inflammatory mediators, as this process leads to damage of the epithelial-endothelial barrier and the passage of fluids and proteins, including serum albumin, from intravascular to extravascular spaces, resulting in hypoalbuminemia which may play a role as a marker of the severity of epithelial-endothelial injury in COVID-19 patients [18]. In addition, the role of albumin as an anti-inflammatory and antioxidant protein may provide an explanation for the association between hypoalbuminemia and the increased prevalence of adverse outcomes in COVID-19, in addition to the anticoagulant properties of albumin as it inhibits platelet activation and thrombosis associated with oxidative stress; therefore, the effect of hypoalbuminemia on coagulation activation may be associated with an increased risk of adverse outcomes in COVID-19 [19].

Abdeen et al. (2021) demonstrated in a study conducted in the USA that levels of albumin were significantly lower in COVID-19 non-survivor patients compared to survivors (2.6 g/dL versus 2.9 g/dL, $p<0.001$) and each one-unit increase in albumin is estimated to reduce the odds of mortality by 73% [20]. Viana-Llamas et al. (2021) showed in a study that included 609 COVID-19 in Spain patients that hypoalbuminemia (<3.4 g/dL) was observed more frequently in non-survivors than in survivors (65.6% versus 38% p:0.001). It represented an independent risk factor for admission at ICU (OR:4.6, p:0.001) and the need for mechanical ventilation (OR:5.5, p:0.0001), and it was a predictor of mortality (HR 1.5, p: 0.027) [21].

Chen et al. (2021) demonstrated in a study that included 482 COVID-19 patients in China that severe COVID-19 was detected more frequently in patients with hypoalbuminemia, with higher rates of ARDS occurrence and further abnormal findings on CT-scan and higher levels of CRP, leukocytes, LDH, D-dimer, and lower levels of lymphocytes, and the rate of mortality was higher in patients with low levels of albumin (23.85% versus 0.9%, $p<0.001$) [22]. Arnau-Barres et al. (2021) demonstrated that severe hypoalbuminemia on

admission in COVID-19 patients (≤3 g/dL) increased the risk of in-hospital mortality (OR 2.18, p:0.039) [23].

Zerbato et al. (2022) demonstrated in a study conducted in Italy included 864 COVID-19 patients, that hypoalbuminemia on admission was associated significantly with severe respiratory failure, longer duration of hospitalization, and higher mortality rates; additionally, an optimal cut-off value of albumin for predicting the need for invasive mechanical ventilation was 3.17 g/dL and for 90-day mortality 3.23 g/dL[24].

Thorat et al. (2022) showed that hypoalbuminemia on admission was correlated significantly with mortality in COVID-19 patients (p:0.001). However, it was not found to be an independent risk factor for mortality(OR:1.5), and the ROC curve illustrated an 0.76 AUC for albumin levels as a predictor of survival with an optimal threshold value being ≥3.05 g/dl [25]. A meta-analysis by Soetedjo et al. confirmed the association between hypoalbuminemia and poor prognosis in COVID-19 patients [26].

5. Conclusion

Hypoalbuminemia on admission is a risk factor for poor prognosis in hospitalized COVID-19 patients, as it predicted an increased incidence of mortality, increased need for invasive mechanical ventilation and admission to the intensive care units, as well as the need for non-invasive ventilation, and thus, hypoalbuminemia may contribute to the assessment of disease severity. It may estimate the probability of more serious SARS-CoV-2 infections. We suggest including serum albumin on admission within the laboratory indicators that contribute to assessing the severity of COVID-19 and identifying patients with a high risk of mortality.

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