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Original Article

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Low Serum Albumin Predicts Severe Outcomes in COVID-19 Infection: A Single-Center Retrospective Case-Control Study

Roshan Acharya[a, f], Dilli Poudel[b], Riley Bowers[c], Aakash Patel[a], Evan Schultz[a], Michael Bourgeois[a], Rishi Paswan[a], Scott Stockholm[a], Macelyn Batten[a], Smita Kafle[d], Kriti Lonial[e], Irlene Locklear[e]

Abstract

Background: Coronavirus disease 2019 (COVID-19) can cause serious complications such as multiorgan failure and death which are difficult to predict. We conducted this retrospective case-control observational study with the hypothesis that low serum albumin at presentation can predict serious outcomes in COVID-19 infection.

Methods: We included severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed, hospitalized patients from March to July 2020 in a tertiary care hospital in the USA. Patients were followed for 21 days for the development of the primary endpoint defined as the composite outcome which included acute encephalopathy, acute kidney injury, the requirement of new renal replacement therapy, acute hypercoagulability, acute circulatory failure, new-onset heart failure, acute cardiac injury, acute arrhythmia, acute respiratory distress syndrome (ARDS), high flow oxygen support, intensive care unit (ICU) stay, mechanical ventilation or death; and the secondary endpoint of death only. Univariate and multivariate logistic regression analyses were performed to study the effect of albumin level and outcomes.

Results: The mean age was 56.76 years vs. 55.67 years (P = 0.68) in the normal albumin vs. the low albumin group. We noticed an inverse relationship between serum albumin at presentation and serious outcomes. The low albumin group had a higher composite outcome (93.88% vs. 6.12%, P < 0.05) and higher mortality (13.87% vs. 2.38%, P < 0.05) in comparison to the normal albumin group. The multivariate logistic regression analysis revealed higher odds of having composite outcomes with lower albumin group (odds ratio (OR) 10.88, 95% confidence interval (CI) 4.74 - 24.97, P < 0.05). In the subgroup analysis, the multivariate logistic regression analysis revealed higher odds of having composite outcomes with the very low albumin group (OR 7.94, 95% CI 1.70 - 37.14, P < 0.05).

Conclusions: Low serum albumin on presentation in COVID-19 infection is associated with serious outcomes not limited to mortality. The therapeutic option of albumin infusion should be investigated.

Keywords: COVID-19; SARS-CoV-2; Hypoalbuminemia; Serious outcomes; Mortality; Albumin; ARDS; Hypercoagulopathy

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel viral disease first discovered in December 2019 in Wuhan, China. Within 1 month, it was confirmed in 19 countries [1] and the World Health Organization declared it a pandemic shortly thereafter [2]. As of now, it has been established as a highly contagious viral disease, primarily affecting the respiratory system but with complications including kidney injury, liver injury, cardiac injury, stroke, encephalopathy, post-viral debility, coagulopathy, long hospital stay, and significant risk of mortality [3-12]. The majority of the patients survive the infection without complications, but a notable proportion of patients develop serious complications. Since the beginning, high levels of acute inflammatory markers were observed in the patients who had poor outcomes but the factors that lead to serious complications remain inadequately understood [3-5].

Albumin serves as a major anti-inflammatory agent in our body [13, 14], and one of the lesser discussed properties in the literature are its anti-oxidative and anti-thrombotic property [15, 16]. Albumin is a major defense that protects the host cells

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[a]Department of Internal Medicine, Cape Fear Valley Medical Center, Fayetteville, NC 28304, USA
[b]Department of Rheumatology, Indiana Regional Medical Center, Indiana, PA 15701, USA
[c]Department of Pharmacy, Cape Fear Valley Medical Center, Fayetteville, NC 28304, USA
[d]RN-BSN Program, Fayetteville State University, Fayetteville, NC 28301, USA
[e]Department of Pulmonology and Critical Care, Cape Fear Valley Medical Center, Fayetteville, NC 28304, USA
[f]Corresponding Author: Roshan Acharya, Department of Internal Medicine, Cape Fear Valley Hospital, Campbell University Jerry M. Wallace School of Osteopathic Medicine, 1638 Owen Drive, Fayetteville, NC 28304, USA. Email: roshan.ach@gmail.com

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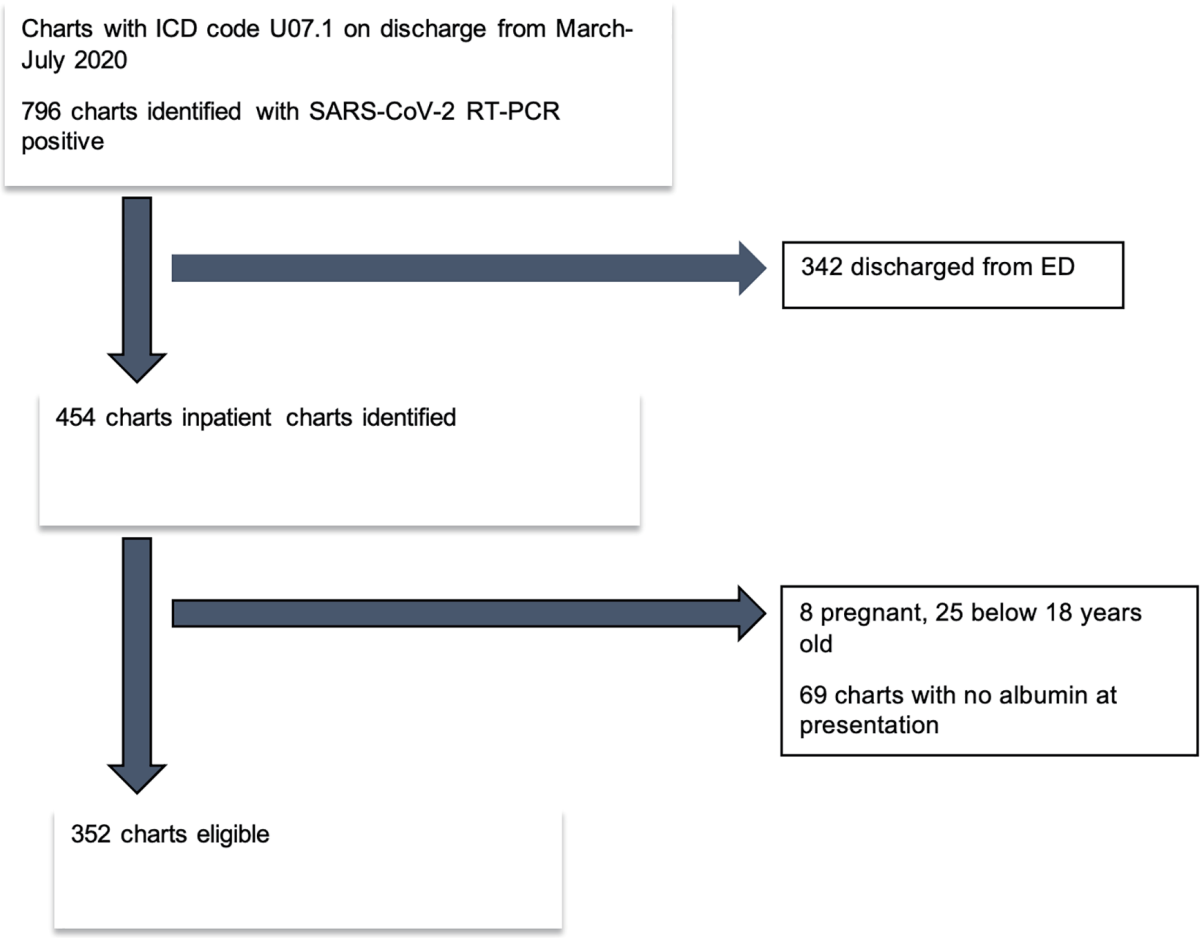

Figure 1. Flow diagram of eligible patient selection. RT-PCR: reverse transcriptase polymerase chain reaction; SARS-CoV-2: severe respiratory syndrome coronavirus 2.

from the oxidative burst that occurs against the infection or inflammation [17-19]. Albumin has a long half-life (3 weeks) and 90% of it is in plasma [20]. The level of plasma is dropped rapidly during acute inflammation due to transcapillary leakage, consumption, and other mechanisms [13, 19, 21, 22].

As of now, we lack proven and effective therapeutic options to treat serious complications of COVID-19 infection. We also lack the ability to predict the serious outcomes of COVID-19 infection. In many studies, low levels of albumin, in addition to high inflammatory markers had been observed with those patients that had poor outcomes. Some studies have suggested that low serum albumin can predict mortality in COVID-19 infection [23-27].

We conducted this study to explore this relationship further with the hypothesis that low serum albumin at presentation can predict serious outcomes in COVID-19 infection.

Materials and Methods

The study was approved by Cape Fear Valley Medical Center's Institutional Review Board (IRB ID number 319-20). This study was conducted in compliance with the ethical standards of the IRB on human subjects.

Study design and population

The study was a single-center retrospective case-control study. We reviewed the charts of patients with the discharge diagnosis of "COVID-19, virus identified" (ICD code U07.1) from March 1 to July 31, 2020 in a tertiary care center in North Carolina, United States of America (USA). We identified 796 charts that had confirmed SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) results of nasopharyngeal swab. After exclusions, a total of 352 charts of unique patients were included in the study (Fig. 1). Inclusion criteria included: 1) patients with SARS-CoV-2 detected using the RT-PCR method, 2) age 18 and above, and 3) admission date between March 1, 2020 and July 31, 2020. Patients with 1) emergency department (ED) visits only, 2) less than 18 years of age, 3) pregnancy, and 4) no serum albumin available at presentation in the ED were excluded (Fig. 1).

Included patients were classified into two groups based on serum albumin at presentation: normal serum albumin

(NSA) group with a value of ≥ 3.5 g/dL, and low serum albumin (LSA) group < 3.5 g/dL. The low albumin group was further sub-grouped as mild low albumin (MLA) group with a value of 2.5 - 3.4 g/dL and very low albumin (VLA) group with a value of < 2.5 g/dL for subgroup analysis. The patients were followed up for 21 days or until death if it happened sooner.

Outcomes

The primary outcome was defined as a composite outcome of death or any serious complications. The variables of serious complications were death, acute encephalopathy, acute kidney injury, the requirement of new renal replacement therapy, acute hypercoagulability, acute circulatory failure, new-onset heart failure, acute cardiac injury, acute arrhythmia, acute respiratory distress syndrome (ARDS), high flow oxygen support, intensive care unit (ICU) stay, and mechanical ventilation. The study definitions and definitions of serious complications are outlined in Table 1. The secondary outcome was death due to any cause during the 21 days follow-up period. The abbreviations, normal ranges, and units of variables are outlined in Table 2.

Statistical analysis

A formal sample size calculation was not carried out as all patients meeting criteria in the pre-specified timeframe were included. The differences in categorical variables were analyzed using a Chi-square test, or Fisher's exact test as appropriate. A Student's *t*-test was utilized to evaluate differences in continuous variables that were normally distributed, and a Wilcoxon rank sum test was utilized if the data were not normally distributed. Continuous variables were expressed as mean ± SD and categorical variables were expressed as the frequency with percentages. The association of albumin level category and outcome was estimated in univariate and multivariate logistic regression analyses in terms of odds ratio (OR). Multivariate analyses were adjusted for age, sex, race, diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), end-stage renal disease on hemodialysis (ESRD on HD), chronic obstructive pulmonary disease (COPD), other lung diseases, congestive heart failure (CHF), coronary artery disease (CAD), human immunodeficiency virus (HIV) infection, malignancy, smoking, alcohol dependency, obesity, and cirrhosis. A P-value of < 0.05 was considered significant. Data analysis was performed using STATA 13.1 (Stata Corp., College Station, TX).

Results

Demographic features

Baseline demographic and lab characteristics by albumin level categories are depicted in Table 3. The overall population was predominantly males (n = 184, 52.27%), and African-American (n = 176, 50%). Eighty-one percentage (n = 288) had at least one co-morbidity. Cough (62.78% vs. 73.81%, P = 0.16), fever (58.90% vs. 64.29%, P = 0.5), and shortness of breath (64.08% vs. 59.52%, P = 0.56) were the most common presenting symptoms in the LSA and NSA groups, respectively. The frequency of CKD was higher among the NSA group (35.71% vs. 17.10%, P < 0.05). Among the subgroups of low albumin, the presenting symptoms and co-morbidities were similar between the two groups (Table 3).

Primary outcome

The LSA group had a significantly higher proportion of composite outcome compared to the NSA group (93.88% vs. 6.12%, P < 0.05). This difference was true in between the subgroups of only low albumin as well, where 96.72% of the VLA group had composite outcome as compared to 81.12% in the MLA group (P < 0.05) (Table 4).

Logistic regression analysis revealed higher odds of having composite outcome with the lower albumin group during univariate (OR 7.83, 95% confidence interval (CI) 3.94 - 15.58, P < 0.05) and multivariate (OR 10.88, 95% CI 4.74 - 24.97, P < 0.05) analyses. Subgroup analysis also revealed a similar relationship (Table 5).

In comparison to the NSA group, the LSA group had higher length of stay (9.33 days vs. 4.48 days, P < 0.05), higher incidence of acute kidney injury (AKI) (42.90% vs. 14.29%, P < 0.05), acute encephalopathy (22.90% vs. 7.14%, P < 0.05), mechanical ventilation use (13.23% vs. 2.38%, P < 0.05), development of ARDS (19.35% vs. 2.39%, P < 0.05) and post-viral physical debility (24.19% vs. 3%, P < 0.05). Similar differences were observed between the VLA and MLA groups with a higher incidence among the VLA group (Table 4). Multivariate analysis revealed that malignancy had the strongest influence on the primary outcome (OR 11.34, 95% CI 2.05 - 62.64, P < 0.05) (Table 6).

Secondary outcome

The LSA group was found to have higher mortality within 21 days as compared to the NSA group (13.87% vs. 2.38%, P < 0.05). Subgroup analysis of the low albumin group revealed 31.15% mortality in the VLA group vs. 9.64% in the MLA group (P < 0.05) (Table 4). We were unable to perform the regression analysis on mortality outcomes due to the very low number of mortalities in the normal albumin group.

Discussion

In this single-center study, we found that low serum albumin at the presentation in hospitalized patients with COVID-19 infection predicted higher mortality. Lower serum albumin at presentation was found to be an independent predictor of serious outcomes even after controlling for the multitude of factors such as age, sex, and presence of co-morbid conditions.

Low albumin level has been reported in hospitalized pa-

Table 1. Study Definition

Study variables	Definitions
Coronavirus disease 2019 (COVID-19) patients	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) detected on reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swab
Hypoalbuminemia (low albumin)	Serum albumin less than 3.5 g/dL
Mild low albumin	Serum albumin 2.5 - 3.4 g/dL
Very low albumin	Serum albumin less than 2.5 g/dL
Composite outcome (at least one of the following complications	Death, acute encephalopathy, acute kidney injury, the requirement of new renal replacement therapy, acute hypercoagulability, acute circulatory failure, new-onset heart failure, acute cardiac injury, acute arrhythmia, ARDS, high flow oxygen support, intensive care unit (ICU) stay, mechanical ventilation.
Death	Death due to any cause within 21 days
Chronic kidney disease (CKD)	Glomerular filtration rate < 60 mL/min (CKD 3-5)
Smoking	Active smoker with > 100 cigarettes smoking in lifetime
Alcohol dependency	Men ≥ 15 drinks/week; female ≥ 8 drinks/week
Malignancy	Cancer patient getting active treatment or finished treatment within 6 months
Onset of symptoms	First day of onset of symptoms to presentation to hospital in days
Use of one of the following medicines	Tocilizumab, remdesivir, dexamethasone and/or convalescent plasma
Secondary infection (one of the following)	Procalcitonin level > 0.5; lactic acid > 2.0; positive blood; urine; body fluid; respiratory secretion culture
Quick sequential organ failure assessment (qSOFA)	Altered mental status, respiratory rate ≥ 22/min, systolic blood pressure ≤ 100 mm Hg
Acute kidney injury	Increase in serum creatinine by 0.3 mg/dL or more within 48 h or increase in serum creatinine to 1.5 times baseline or more within the last 7 days
New renal replacement therapy (RRT)	The requirement of new RRT within 21 days in patients who were not dialysis-dependent
Acute encephalopathy	Worsening of alertness and awareness compared to baseline, and/or change in mental status
Acute liver injury	Development of severe acute liver injury (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times normal) with encephalopathy and impaired synthetic function (INR of ≥ 1.5) in a patient without cirrhosis or preexisting liver disease
Acute hypercoagulability	D-dimer level > 0.5 ng/mL
Stroke	New focal neurological deficit and/or radiological evidence in computed tomography (CT) or magnetic resonance imaging (MRI)
Acute circulatory failure	Systolic blood pressure (SBP) less than 90 mm Hg and/or requiring pressure support
Acute cardiac injury	Increase in serum troponin value of > 0.015 in two occasions 6 h apart, and or ST-segment elevation or depression in electrocardiogram (EKG)
Arrhythmia	New-onset rhythm disorder proven on 12-lead EKG on two separate occasions
New-onset heart failure	New-onset systolic or diastolic heart failure on echocardiogram
Acute respiratory distress syndrome (ARDS)	The $PaO_2/FiO_2 \leq 300$ mm Hg, on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cm H_2O.
High flow oxygen support	Requiring high flow oxygen of 15 L or more to maintain an oxygen saturation of 92% or more
New-onset oxygen dependency	Any amount of supplemental oxygen required to maintain an oxygen saturation of 92% and above on discharge
Physical debility	Discharge to a skilled nursing facility or rehabilitation center
Obesity	Body mass index (BMI) of 30.0 or higher

tients with COVID-19 that had poor outcomes from the beginning of the pandemic [3-5, 28]. A similar trend was observed in other studies that were conducted outside of China as well [26, 27, 29]. A few studies that compared low albumin level with mortality concluded that low albumin can predict mortality in COVID-19 patients [23-25]. In addition to low albumin, high levels of inflammatory markers were also noted in those studies. The findings of our study are consistent with these prior

Table 2. Abbreviations, Normal Ranges and Units

Abbreviations	Full forms	Normal ranges and units (where applicable)
AKI	Acute kidney injury	
Albumin		3.5 - 5.0 g/dL
ALT	Alanine aminotransferase	12 - 78 U/L
AMS	Altered mental status	
AST	Aspartate aminotransferase	15 - 37 U/L
CAD	Coronary artery disease	
CHF	Congestive heart failure	
CKD	Chronic kidney disease	
COPD	Chronic obstructive pulmonary disease	
COVID-19	Coronavirus disease 2019	
CRP	C-reactive protein	< 3 mg/L
D-dimer		0.9 - 0.5 mg/dL
DM	Diabetes mellitus	
ESR	Erythrocyte sedimentation rate	0 - 15 mm/h
ESRD on HD	End-stage renal disease on hemodialysis	
Ferritin		26 - 388 ng/mL
HIV	Human immunodeficiency virus	
HTN	Hypertension	
IL-6	Interleukin-6	0 - 13 pg/mL
INR	International normalized ratio	
Lactic acid		0.4 - 2 mmol/L
LDH	Lactate dehydrogenase	87 - 241 U/L
LO	Length of	
Lymphocyte		0.9 - 2.9 × 10^3/μL
Neutrophil		1.7 - 7 × 10^3/μL
NL ratio	Neutrophil to lymphocyte ratio	
Platelets		150 - 450 × 10^3/μL
Procalcitonin		0.07 - 0.5 ng/mL
qSOFA	Quick sequential organ failure assessment	
RT-PCR	Reverse transcriptase-polymerase chain reaction	
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2	
SOB	Shortness of breath	

findings.

Low albumin has been found to predict higher mortality, a longer length of stay in hospitalized patients, and the general elderly population [30-34]; normalization of albumin prior to discharge was found to lower the mortality [33]. Albumin therapy has been shown to improve the oxygenation in ARDS [35, 36], and improve mortality in spontaneous bacterial peritonitis patients [37]. In the letter to the editor by Wiedermann et al and its response, the authors reported pooled analysis of three large-scale randomized controlled trials on sepsis and found that albumin therapy had a significant reduction in mortality which was attributed partly to albumin's anti-oxidative and anti-immunosuppressive property [38]. The mechanistic theory for this includes albumin's ability to bind reactive oxygen and reactive nitrogen species (ROS and RNS) preventing cellular damage and tissue injury during overwhelming inflammatory response [17-19]. These findings have given rise to the concept of the potential therapeutic use of albumin for COVID-19 infection [27, 39].

One of the limitations of our study is being a single-center study. More than 50% of the charts needed to be excluded decreasing the sample size. However, our study sample size was comparable to many similar studies done recently. The population was of mixed races unlike many studies done in China or

Table 3. Baseline Characteristics of Normal and Low Serum Albumin Groups

	NSA vs. LSA group (primary group)			MLA vs. VLA group (subgroup)		
	NSA (n = 42)	LSA (n = 310)	P-value	MLA (albumin 2.5 - 3.4, n = 249)	VLA (albumin < 2.5, n = 61)	P-value
Age, m (SD)	56.76 (16.18)	55.67 (18.23)	0.68	55.91 (18.90)	54.68 (15.26)	0.59
Female, n (%)	18 (42.86)	150 (48.39)	0.50	109 (43.78)	41 (67.21)	0.001*
Race			0.48			0.01*
White, n (%)	10 (23.81)	73 (23.55)		49 (19.76)	23 (37.70)	
African American, n (%)	24 (57.14)	152 (49.03)		126 (50.81)	26 (42.62)	
Others, n (%)	8 (196.05)	85 (27.42)		73 (29.44)	12 (19.67)	
Comorbid conditions						
Diabetes mellitus, n (%)	20 (47.62)	111 (35.81)	0.13	95 (38.15)	16 (26.23)	0.08
Hypertension, n (%)	34 (80.95)	191 (61.61)	0.014*	155 (62.25)	36 (59.02)	0.64
CKD, n (%)	15 (35.71)	53 (17.10)	0.004*	41 (16.47)	12 (19.67)	0.55
ESRD on HD, n (%)	5 (11.90)	21 (6.77)	0.23	18 (7.23)	3 (4.92)	0.52
COPD, n (%)	4 (9.52)	31 (10)	0.92	25 (10.04)	6 (9.84)	0.96
Other lung diseases, n (%)	5 (11.90)	47 (15.21)	0.57	36 (14.52)	11 (18.03)	0.49
CHF, n (%)	7 (16.67)	37 (11.94)	0.38	29 (11.65)	8 (13.11)	0.75
CAD, n (%)	11 (26.19)	55(17.74)	0.18	45 (18.07)	10 (16.39)	0.75
HIV, n (%)	1 (2.38)	6 (1.94)	0.84	1 (0.40)	5 (8.20)	< 0.001*
Malignancy, n (%)	6 (14.29)	24 (7.74)	0.15	19 (7.63)	5 (8.20)	0.88
Smoking, n (%)	11 (26.19)	55 (18.52)	0.24	39 (16.53)	16 (26.23)	0.082
Alcohol dependency, n (%)	4 (9.52)	22 (7.10)	0.53	19 (7.63)	3 (4.92)	0.46
Obesity, n (%)	18 (42.86)	161 (51.94)	0.26	129 (51.81)	32 (52.46)	0.92
Cirrhosis, n (%)	1 (2.38)	5 (1.62)	0.72	4 (1.61)	1 (1.64)	0.98
Symptoms						
Onset of symptoms (days), m (SD)	4.11 (3.6)	5.62 (4.97)	0.018*	5.52 (5.03)	5.98 (4.76)	0.51
Fever, n (%)	27 (64.29)	182 (58.90)	0.50	146 (58.63)	36 (59.02)	0.95
Cough, n (%)	31 (73.81)	194 (62.78)	0.16	150 (60.24)	44 (72.13)	0.085
SOB, n (%)	25 (59.52)	198 (64.08)	0.56	152 (61.04)	47 (77.05)	0.019*
Diarrhea, n (%)	6 (14.29)	33 (10.68)	0.48	21 (8.43)	13 (21.31)	0.004*
AMS, n (%)	6 (14.29)	35 (11.33)	0.57	31 (12.45)	4 (6.56)	0.192
Chest pain, n (%)	12 (28.57)	39 (12.66)	0.006*	30 (12.10)	9 (14.75)	0.57
Others, n (%)	12 (28.57)	74 (47.13)	0.026*	74 (47.13)	15 (24.59)	0.002*
Laboratory results						
Albumin (g/dL), m (SD)	3.77 (0.28)	2.84 (0.41)	< 0.001*	3.01 (0.24)	2.15 (0.24)	< 0.001*
ESR (mm/h), m (SD)	24 (15.52)	57.90 (34.24)	< 0.001*	53.43 (34.40)	72.21 (29.30)	0.010*
CRP (mg/L), m (SD)	35.02 (43.28)	84.32 (60.49)	< 0.001*	81.33 (60.62)	101.21 (64.27)	0.043*
Neutrophil (× 10^3/μL), m (SD)	3.65 (2.24)	5.99 (4.05)	< 0.001*	5.45 (3.18)	8.35 (6.87)	0.005*
Lymphocyte (× 10^3/μL), m (SD)	1.38 (0.91)	1.14 (0.70)	0.21	1.21 (0.74)	0.89 (0.45)	< 0.001*
NL ratio, m (SD)	3.94 (3.68)	6.88 (6.74)	0.001*	6.28 (6.75)	8.87 (6.23)	0.011*
Platelets (× 10^3/μL), m (SD)	220.90 (73.77)	233.51 (90.11)	0.83	217.86 (82.40)	245.48 (114.16)	0.07
Ferritin (ng/mL), m (SD)	571.83 (961.77)	925.69 (2,012.85)	0.14	744.46 (1,150.94)	1,650.90 (3,696.46)	0.073
IL-6 (pg/mL), m (SD)	92.87 (161.77)	244.18 (533.03)	0.032*	200 (433.68)	352.87 (601.61)	0.20
LDH (U/L), m (SD)	287.85 (148.17)	398.79 (377.32)	0.007*	367.92 (166.65)	515.76 (752.83)	0.16

*Significant P-values. NSA: normal serum albumin; LSA: low serum albumin; MLA: medium low albumin; VLA: very low albumin; m: mean; SD: standard deviation; n: number; CKD: chronic kidney disease; ESRD: end-stage renal disease; HD: hemodialysis; COPD: chronic obstructive pulmonary disease; CHF: congestive heart disease; CAD: coronary artery disease; HIV: human immunodeficiency virus; SOB: shortness of breath; AMS: altered mental status; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NL: neutrophil to lymphocyte; IL-6: interleukin-6; LDH: lactate dehydrogenase.

Table 4. In-Hospital Complications and Duration of Stays in Normal and Low Serum Albumin Groups

	NSA vs. LSA group (primary group)			MLA vs. VLA group (subgroup)		
	NSA (n = 42)	LSA (n = 310)	P-value	MLA (albumin 2.5 - 3.4, n = 249)	VLA (albumin < 2.5, n = 61)	P-value
Composite outcome, n (%)	17 (6.12)	261 (93.88)	< 0.001*	202 (81.12)	59 (96.72)	0.003*
Death, n (%)	1 (2.38)	43 (13.87)	0.035*	24 (9.64)	19 (31.15)	< 0.001*
Tocilizumab, n (%)	4 (9.52)	73 (23.62)	0.038*	51 (20.48)	22 (36.07)	0.010*
Remdesivir, n (%)	1 (2.38)	71 (22.98)	0.002*	54 (21.69)	17 (27.87)	0.30
Dexamethasone, n (%)	10 (23.81)	106 (34.30)	0.17	87 (34.94)	19 (31.67)	0.63
Convalescent plasma, n (%)	2 (4.76)	35 (11.33)	0.194	22 (8.84)	13 (21.31)	0.006*
qSOFA 2-3, n (%)	3 (7.14)	68 (21.94)	0.025*	50 (20.08)	18 (29.51)	0.11
Acute circulatory failure, n (%)	1 (2.38)	64 (20.65)	0.004*	43 (17.27)	21 (34.43)	0.003*
Secondary infection						
Procalcitonin > 0.5 ng/mL, n (%)	3 (9.09)	96 (35.29)	0.002*	62 (28.57)	35 (63.64)	< 0.001*
Lactic acid > 2 mmol/L, n (%)	4 (15.38)	53 (20.08)	0.56	38 (17.92)	16 (30.77)	0.04*
Blood culture, n (%)	0 (0)	19 (7.12)	0.138	12 (5.53)	8 (16)	0.011*
Urine culture, n (%)	0 (0)	16 (9.25)	0.146	13 (8.97)	4 (14.29)	0.38
Body fluid culture, n (%)	1 (4.55)	6 (6.41)	0.97	5 (4.39)	1 (4.55)	0.97
Respiratory secretion culture, n (%)	7 (26.92)	47 (24.35)	0.77	38 (23.75)	9 (27.27)	0.66
AKI, n (%)	6 (14.28)	133 (43.36)	0.004*	95 (38.30)	38 (62.29)	0.002*
Requiring new HD, n (%)	1 (2.38)	17 (5.52)	0.38	5 (2.02)	12 (19.67)	< 0.001*
INR > 1.5	0 (0)	22 (8.83)	0.34	13 (6.63)	9 (16.98)	0.071
AST or ALT > 5 times normal	2 (4.76)	32 (10.49)	0.24	19 (7.79)	13 13 (21.31)	0.002*
Acute hypercoagulability			< 0.001*			< 0.001*
D-dimer > 1 mg/dL, n (%)	7 (21.21)	132 (50.96)		92 (44.66)	40 (75.47)	
D-dimer 0.5 - 1 mg/dL, n (%)	3 (9.09)	62 (23.90)		55 (26.70)	7 (13.21)	
Acute encephalopathy, n (%)	3 (7.14)	71 (22.90)	0.019*	48 (19.28)	23 (37.70)	0.002*
Cerebrovascular accident, n (%)	0 (0)	0 (0)	n/a	0 (0)	0 (0)	n/a
Acute cardiac injury, n (%)	3 (7.32)	89 (29.87)	0.002*	67 (28.03)	22 (37.29)	0.164
New-onset heart failure, n (%)	1 (2.44)	13 (4.22)	0.58	9 (3.63)	4 (6.67)	0.29
New-onset arrhythmia, n (%)	4. (9.76)	34 (10.97)	0.81	21 (8.43)	13 (21.31)	0.004*
ARDS, n (%)	1 (2.27)	60 (20.98)	0.008*	34 (15.04)	26 (43.33)	< 0.001*
Mechanical ventilation, n (%)	1 (2.38)	41 (13.27)	0.041*	23 (9.27)	18 (29.51)	< 0.001*
Requiring > 3 L O_2, n (%)	8 (19.05)	166 (53.55)	< 0.001*	117 (46.99)	49 (80.33)	< 0.001*
Requiring > 15 L high flow O_2, n (%)	4 (9.52)	88 (28.39)	0.009*	57 (22.89)	31 (50.82)	< 0.001*
New-onset oxygen dependency, n (%)	1 (2.38)	41 (13.80)	0.035*	27 (11.20)	14 (25)	0.007*
LO stay (days), m (SD)	4.16 (5.55)	9.32 (9.70)	< 0.001*	8.14 (8.53)	14.18 (12.40)	< 0.001*
LO ICU stay (days), m (SD)	0.24 (1.56)	1.96 (5.59)	< 0.001*	1.4 (4.9)	4.24 (7.44)	0.005*
LO mechanical vent (days), m (SD)	0.24 (1.56)	1.60 (4.96)	< 0.001*	1.13 (4.16)	3.59 (7.13)	0.01*
Physical debility (days), n (%)	3 (7.32)	75 (24.51)	0.013*	56 (22.67)	19 (32.20)	0.12
Discharged, n (%)	41 (97.62)	270 (87.10)	0.046*	221 (88.76)	49 (80.33)	0.078*
Readmission, n (%)	5 (11.90)	47 (15.16)	0.57	38 (15.26)	9 (14.75)	0.92

*Significant P-values. NSA: normal serum albumin; LSA: low serum albumin; MLA: medium low albumin; VLA: very low albumin; m: mean; SD: standard deviation; n: number; qSOFA: quick sequential organ failure assessment; AKI: acute kidney injury; CVA: cerebrovascular accident; HD: hemodialysis; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ARDS: acute respiratory distress syndrome; LO: length of; ICU: intensive care unit.

Table 5. Results From Logistic Regression Analyses - Odds of Composite Outcome Based on Albumin Level Category

	Univariate analysis			Multivariate analysis[a]		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Main group (LSA vs. NSA)	7.83	3.94 - 15.58	< 0.001*	10.88	4.74 - 24.97	< 0.001*
Subgroup (VLA vs. MLA)	6.86	1.62 - 29.10	0.009*	7.94	1.70 - 37.14	0.009*

*Significant P-values. [a]Controlled for age; sex; race; diabetes mellitus; hypertension; chronic kidney disease; end-stage renal disease on hemodialysis; chronic obstructive pulmonary disease; other lung diseases; congestive heart failure; coronary artery disease; human immunodeficiency virus infection; malignancy; smoking; alcohol dependency; obesity; and cirrhosis. NSA: normal serum albumin; LSA: low serum albumin; MLA: medium low albumin; VLA: very low albumin; CI: confidence interval.

Europe. We could not do the multivariate analysis of mortality because there was only one death in the normal albumin group.

COVID-19 has been diagnosed in more than 200 countries [40]. In the USA alone more than 30 million people were infected, and 556 thousand had died [41]. So far, there is no effective treatment for COVID-19 infection [40, 42-47], and the success of developed vaccines being unanswered due to emerging new strains of SARS-CoV-2. Due to recurrent waves of infection caused by emerging strains of SARS-CoV-2 the South Asian region, South American, Europe and other parts of the world had been through series of lockdowns. In addition, the vaccines are still out of reach of many low-medium income countries. We believe that this study will help health providers recognize that lower albumin carries a higher risk of severe complications and mortality in COVID-19 infection. It will be interesting to see the studies that utilize albumin as a treatment for serious COVID-19 illness.

Conclusion

Low serum albumin on presentation in COVID-19 infection

Table 6. Results From MV Analysis in Normal and Low Albumin Groups

Outcome	Normal vs. low albumin group (primary group)			Medium low vs. very low albumin group (subgroup)		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Albumin level (lower ref to higher)	10.88	4.74 - 24.97	< 0.001*	7.94	1.70 - 37.14	0.009*
Age	1.00	0.98 - 1.02	0.56	0.99	0.91 - 1.02	0.81
Sex	0.77	0.41 - 1.47	0.44	1.5	0.71 - 3.18	0.27
Race						
White	0.37	0.16 - 0.82	0.015*	1.77	0.59 - 5.32	0.30
Others	0.73	0.33 - 1.63	0.45	1.16	0.49 - 2.71	0.72
Smoking	1.93	0.81 - 4.5	0.13	0.52	0.20 - 1.33	0.17
DM	0.61	0.32 - 1.19	0.15	1.12	0.52 - 2.40	0.76
HTN	1.04	0.46 - 2.36	0.91	0.38	0.14 - 1.04	0.06
CKD	0.54	0.22 - 1.32	0.18	2.04	0.66 - 6.32	0.21
ESRD on HD	1.11	0.30 - 4.11	0.86	0.38	0.08 - 1.69	0.20
COPD	0.41	0.13 - 1.21	0.1	1.30	0.34 - 4.92	0.69
CHF	1.40	0.45 - 4.32	0.55	4.78	1.06 - 21.38	0.041*
CAD	0.67	0.26 - 1.72	0.40	0.75	0.26 - 2.16	0.60
HIV	1.46	0.14 - 14.93	0.74	1		
Malignancy	11.34	2.05 - 62.64	0.005*	0.78	0.20 - 2.99	0.72
Alcohol dependency	1.58	0.40 - 6.19	0.50	3.35	0.62 - 17.86	0.15
Obesity	0.66	0.35 - 2.14	0.22	0.66	0.31 - 1.39	0.28
Other lung disease	0.87	0.35 - 2.14	0.77	0.31	0.12 - 0.78	0.014*
Cirrhosis	0.06	0.08 - 0.57	0.014*	1.45	0.09 - 22.22	0.78

MV controlled for age; sex; race; diabetes mellitus (DM); hypertension (HTN); chronic kidney disease (CKD); end-stage renal disease (ESRD) on hemodialysis (HD); chronic obstructive pulmonary disease (COPD); other lung diseases; congestive heart failure (CHF); coronary artery disease (CAD); human immunodeficiency virus (HIV) infection; malignancy; smoking; alcohol dependency; obesity; and cirrhosis. *Significant P-values. MV: multivariate; CI: confidence interval.

is associated with a higher incidence of serious outcomes like kidney injury, cardiac injury, hypercoagulability, post-viral physical debility, and encephalopathy; and higher mortality. Further investigation of the utility of albumin replacement as a treatment of COVID-19 infection should be done as soon as possible.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

The informed consent was waived by IRB as the study was a retrospective study.

Author Contributions

RA designed the study, portions of statistical analysis, manuscript writing; DP and RB did the statistical analysis and contributed to manuscript writing; RA, AP, ES, MB, RP, SS, MB and SK did the portions of statistical analysis, and contributed to manuscript writing; KL and IL contributed to manuscript writing and supervision of the study. All authors read and approved the final manuscript.

Data Availability

The database used and/or analyzed during the current study is available from the corresponding author on reasonable request.

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