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Coronavirus Pandemic

Albumin level as an independent predictive factor for adverse outcomes in COVID-19 patients: a retrospective cohort study

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Abstract

Introduction: Research on the association between albumin (ALB) level and clinical outcomes of coronavirus disease 2019 (COVID-19) are limited. This study aimed to investigate the relationship between albumin level at the time of admission and adverse outcomes in patients with COVID-19.

Methodology: This was a retrospective cohort study with 199 COVID-19 patients from five designated hospitals in Fujian Province who were enrolled between 22 January and 27 February, 2020. Clinical characteristics and laboratory values at the time of admission were collected. Adverse outcomes were defined as meeting at least one of the following criteria: development of acute respiratory distress syndrome (ARDS), respiratory failure, shock, multiple organ failure (MOF), intensive care unit (ICU) admission and in-hospital mortality event. The univariate and multivariate linear regression models and generalized additive models (GAM) were used to analyze the relationship between ALB and adverse outcomes.

Results: A non-linear relationship with an inflection point of 32.6g/L was detected between ALB and adverse outcomes after adjusting for potential confounders. The odds ratio and the confidence intervals on the left and right sides of the inflection point were 0.204 (0.061-0.681) and 0.908 (0.686-1.203), respectively. This suggested that ALB was negatively correlated with adverse outcomes when ALB was less than 32.6 g/L, and for every 1 unit increase in ALB, the risk of adverse outcomes was reduced by 79.6%.

Conclusions: The relationship between ALB and adverse outcomes of COVID-19 is non-linear. ALB level is an independent predictive factor for adverse outcomes in COVID-19 patients.

Key words: COVID-19; albumin; predictive factor; outcome.

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Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic and has been declared a public health emergency of international concern by the World Health Organization (WHO) [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) can affect multiple organs, leading to adverse outcomes, such as cerebrovascular events [2,3], myocardial infarction [4], pulmonary embolism [5], acute liver injury, and death [6,7]. In order to improve the management of patients, it is critical to identify predictors of adverse outcomes.

Albumin is a protein synthesized in the liver, and performs a variety of physiological roles in the body, such as providing oncotic pressure, binding and transporting materials, and maintaining acid base balance [8,9]. When the body is in critical condition, inflammatory mediators reduce albumin synthesis to preferentially synthesize other proteins required for acute phase response. Additionally, these mediators increase vascular permeability and cause albumin to escape into interstitial space and lead to hypoalbuminemia [10]. Previous studies have suggested an association between hypoalbuminemia and poor outcomes in critical patients [11], but the relationship between the albumin level and catastrophic events in COVID-19 remains unclear.

We explored the relationship between initial admission albumin concentration and adverse outcomes in COVID-19 patients, with the hypothesis that albumin level can be an independent predictive factor for adverse outcomes in COVID-19 patients. This can help clinicians identify high-risk patients early and take timely preventive measures.

Methodology

Study design and participants

A total of 199 COVID-19 patients (age range: 16-93 years) who were admitted to five hospitals in the Fujian Province, including Fuzhou, Zhangzhou,

Xiamen, Putian and Quanzhou, from 22 January to 27 February, 2020, were consecutively enrolled for this retrospective study. The clinical outcomes, discharge from hospital or death, were recorded up to March 3, 2020. The hospitals are designated for COVID-19 treatment by the government. All the patients were diagnosed with COVID-19 through real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay, according to the Guideline for Diagnosis and Treatment for Novel Coronavirus Pneumonia released by the National Health Commission of China (5th edition) [12]. This study was approved by the ethical committee in Zhongshan Hospital (Xiamen), Fudan University (B2020-003). The requirement for informed consent was waived because the data were urgently collected and analyzed anonymously.

Table 1. Baseline characteristics of participants according to the tertiles of ALB (n = 199). Values are mean ± SD/median (Q1-Q3) or n (%).

Characteristics	ALB (g/L)			*p* value
	T1 (26.8-37.8)	T2 (38.0-42.3)	T3 (42.4-49.8)	
No. of participants	66	66	67	
Age, years	53.61 ± 16.55	45.89 ± 15.02	39.49 ± 14.67	< 0.001
Female	35 (53.03%)	26 (39.39%)	33 (49.25%)	0.269
BMI, kg/m^2	23.68 ± 3.44	23.54 ± 3.14	23.97 ± 3.70	0.768
Current smoking	5 (7.58%)	1 (1.52%)	7 (10.45%)	0.104
Comorbidities				
Hypertension	13 (19.70%)	12 (18.18%)	6 (8.96%)	0.180
Diabetes	8 (12.12%)	4 (6.06%)	3 (4.48%)	0.213
Cardiovascular disease	3 (4.55%)	3 (4.55%)	2 (2.99%)	0.822
Chronic kidney disease	2 (3.03%)	1 (1.52%)	1 (1.49%)	0.848
Pulmonary disease	8 (12.12%)	3 (4.55%)	0 (0.00%)	0.008
Tumor	2 (3.03%)	2 (3.03%)	4 (5.97%)	0.735
Chronic liver disease	1 (1.52%)	9 (13.64%)	1 (1.49%)	0.002
Symptoms				
Cough	39 (59.09%)	45 (68.18%)	37 (55.22%)	0.292
Fever	52 (78.79%)	55 (83.33%)	45 (67.16%)	0.077
Chest distress	10 (15.15%)	2 (3.03%)	6 (8.96%)	0.052
Dyspnea	2 (3.03%)	0 (0.00%)	0 (0.00%)	0.218
Fatigue	25 (37.88%)	16 (24.24%)	14 (20.90%)	0.068
Headache	6 (9.09%)	6 (9.09%)	2 (2.99%)	0.282
Diarrhea	9 (13.64%)	4 (6.06%)	4 (5.97%)	0.194
Laboratory findings				
Leukocytes, 10^9/L	5.16 ± 1.96	5.65 ± 2.95	5.49 ± 2.10	0.607
Neutrophils, 10^9/L	3.16 (2.05-4.39)	3.29 (2.43-4.16)	3.26 (2.22-4.51)	0.950
Lymphocytes, 10^9/L	1.24 ± 0.58	1.38 ± 0.66	1.58 ± 0.78	0.051
Platelets, 10^9/L	195.15 ± 66.61	207.70 ± 85.77	207.93 ± 56.73	0.335
Hemoglobin, g/L	129.77 ± 15.76	137.88 ± 18.14	143.18 ± 17.79	< 0.001
TBIL, μmol/L	12.45 (8.70-17.85)	12.45 (8.07-16.68)	13.00 (7.40-20.60)	0.625
ALT, U/L	22.50 (16.00-30.00)	27.50 (19.25-37.18)	22.70 (17.50-34.60)	0.136
AST, U/L	25.40 (21.00-32.00)	25.00 (21.00-33.00)	23.90 (19.00-30.15)	0.476
LDH, U/L	209.50 (164.00-347.75)	257.70 (174.75-406.75)	217.00 (168.00-436.00)	0.591
Creatinine, μmol/L	68.91 ± 19.73	66.93 ± 16.29	70.01 ± 17.44	0.716
BUN, mmol/L	3.95 ± 1.67	3.93 ± 1.53	4.07 ± 1.62	0.779
CK, U/L	70.00 (45.50-140.50)	70.30 (42.50-103.75)	60.00 (44.00-100.30)	0.577
PT, sec	12.07 ± 0.99	12.01 ± 1.01	11.61 ± 1.06	0.040
APTT, sec	31.43 ± 5.30	30.26 ± 4.30	30.87 ± 6.20	0.517
Fibrinogen, mg/dL	3.77 ± 0.97	3.56 ± 0.99	3.58 ± 0.92	0.289
D-dimer, mg/L	0.28 (0.18-0.49)	0.19 (0.02-0.32)	0.23 (0.02-0.34)	< 0.001
Adverse outcomes	11 (16.67%)	6 (9.09%)	5 (7.46%)	0.197
ARDS	11 (16.67%)	6 (9.09%)	5 (7.46%)	0.152
Respiratory failure	6 (9.09%)	4 (6.06%)	2 (2.99%)	0.335
Shock	2 (3.03%)	0 (0.00%)	2 (3.03%)	0.549
MOF	0 (0.00%)	0 (0.00%)	1 (1.49%)	1.000
ICU admission	6 (9.09%)	3 (4.55%)	5 (7.46%)	0.585
In-hospital mortality	1 (1.52%)	0 (0.00%)	0 (0.00%)	0.663

*Continuous variable was obtained by Kruskal-Wallis rank sum test. If the count variable had a theoretical number < 10, the probability was calculated accurately using Fisher's exact test. BMI: Body mass index; TBIL: Total bilirubin; ALT: Alanine transaminase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; CK: Creatine kinase; PT: Prothrombin time; APTT: Activated partial thromboplastin time; ALB Albumin; ARDS: Acute respiratory distress syndrome; MOF Multiple organ failure; ICU: Intensive Care Unit.

Data collection

A team of professional physicians retrospectively reviewed the electronic medical records, comprising of clinical notes and laboratory values for our cohort of patients. We recorded the demographic data including age, gender, body mass index (BMI), and smoking habit, the comorbidities including hypertension, diabetes, cardiovascular disease, chronic kidney disease, pulmonary disease, tumor, and chronic liver disease, and the symptoms. In the case of laboratory values, initial values on the day of admission were collected. The outcomes were recorded, including development of acute respiratory distress syndrome (ARDS), respiratory failure, shock, multiple organ failure (MOF), intensive care unit (ICU) admissions, in-hospital mortality events, and total adverse outcomes (sum of the adverse outcomes detailed above).

Statistical analysis

Adverse outcomes were defined as meeting at least one of the following criteria: development of ARDS, respiratory failure, shock, MOF, ICU admissions and in-hospital mortality events. Statistical analysis was performed in five steps. First, we analyzed the baseline characteristics of participants in accordance with the following principles and we grouped albumin (ALB) in tertiles: (1) continuous variables were expressed as the means ± standard deviations (normal distribution) or medians (interquartile) (skewed distribution), and categorical variables were expressed as frequency (percentage); and (2) the one-way ANOVA (normal distribution), Kruskal-Wallis H (skewed distribution) test and Chi square test (categorical variables) were used to analyze any significant differences between the means and proportions of the groups. Second, we used univariate and multivariate Cox regression analyses to assess relationships between ALB and adverse outcomes risk. The covariances, including age, gender, body mass index (BMI), current smoking, hypertension, cardiovascular disease, pulmonary disease, tumor, chronic liver disease, D-dimer, creatinine, creatine kinase (CK), leukocytes, neutrophil, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and fibrinogen, when added to this model changed the matched odds ratio by at least 10% and were adjusted. Third, generalized additive models (GAM) were used to identify non-linear relationships because ALB was a continuous variable. If a non-linear correlation was observed, a two piecewise linear regression model was used to calculate the threshold effect of ALB on adverse outcomes in terms of the smoothing plot. When the ratio between adverse outcomes and ALB appeared obvious in a smoothed curve, the recursive method automatically calculates the inflection point, where the maximum model likelihood will be used. The statistical analysis of this part was carried out using "mgcv" [13] package of R software. Fourth, subgroup analysis of the association between ALB and adverse outcomes was performed using stratified linear regression models. The modifications and interactions of subgroups were examined by likelihood ratio tests. All the analyses were performed with the statistical software package R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). p values less than 0.05 (two-sided) were considered statistically significant.

Results

The average age of the cohort was 46.3 ± 16.4 years, and approximately 52.8% of the patients were male. We compared the baseline demographic, clinical, and biochemical characteristics of the patients by tertiles of ALB (Table 1). Patients in the lowest tertile were older, and more likely to have pulmonary disease compared to the subjects in the highest tertile of ALB. Participants with chronic liver disease were mainly in the middle tertile of ALB. Patients in the highest tertile group had significantly higher lymphocyte and hemoglobin, and lower prothrombin time (PT) and D-dimer compared to the lowest tertile group.

The univariate logistic regression models between baseline variables and adverse outcomes are presented in Table 2. The results of univariate analysis showed that age, hypertension, cardiovascular disease, pulmonary disease, tumor, fatigue, leukocytes, neutrophil, aspartate transferase (AST), LDH, creatinine, BUN, CK, fibrinogen and D-dimer were positively correlated with the risk of adverse outcomes. The ALB (OR = 0.850, 95% CI, 0.776 - 0.931, p = 0.00045) was negatively correlated with the risk of adverse outcomes.

Univariate linear regression models were used to evaluate the associations between ALB and adverse outcomes. We have presented the results of multivariate Cox regression analyses in Table 3. After adjusting potential confounders, we found that ALB was negatively correlated with adverse outcomes (OR = 0.70, 95% CI, 0.56 - 0.88, p = 0.002). We also analyzed ALB as a categorical variable (tertiles) for the purpose of sensitivity analysis, and found the same trend (p = 0.0303).

Table 2. The results of univariate analysis (n = 199). Values are mean ± SD or n (%).

Variables	Statistics	Odds ratio (95% CIs)	*p* value
Age	46.3 ± 16.4	1.063 (1.033, 1.094)	0.00003
Female	94 (47.2%)	0.379 (0.142, 1.014)	0.05333
BMI	23.7 ± 3.4	1.054 (0.905, 1.228)	0.49623
Current smoking	13 (6.5%)	1.509 (0.312, 7.301)	0.60892
Hypertension	31 (15.6%)	4.878 (1.867, 12.740)	0.00122
Diabetes	15 (7.5%)	2.171 (0.562, 8.386)	0.26085
Cardiovascular disease	8 (4.0%)	9.611 (2.213, 41.737)	0.00252
Chronic kidney disease	4 (2.0%)	2.762 (0.275, 27.771)	0.38829
Pulmonary disease	11 (5.5%)	5.397 (1.440, 20.224)	0.01238
Tumor	8 (4.0%)	5.432 (1.203, 24.532)	0.02782
Chronic liver disease	11 (5.5%)	0.795 (0.097, 6.525)	0.83105
Cough	121 (60.8%)	1.145 (0.457, 2.871)	0.77304
Fever	152 (76.4%)	0.804 (0.295, 2.188)	0.66917
Chest distress	18 (9.0%)	1.006 (0.215, 4.702)	0.99368
Dyspnea	2 (1.0%)	8.381 (0.505, 139.005)	0.13790
Fatigue	55 (27.6%)	3.023 (1.226, 7.454)	0.01630
Headache	14 (7.0%)	1.375 (0.287, 6.591)	0.69044
Diarrhea	17 (8.5%)	1.080 (0.230, 5.072)	0.92231
Leukocytes, 10^9/L	5.4 ± 2.4	1.191 (1.013, 1.400)	0.03481
Neutrophils, 10^9/L	3.7 ± 2.7	1.134 (1.003, 1.282)	0.04522
Lymphocytes, 10^9/L	1.4 ± 0.7	0.441 (0.194, 1.001)	0.05035
Platelets, 10^9/L	203.6 ± 70.6	0.995 (0.988, 1.003)	0.21206
Hemoglobin, g/L	137.0 ± 18.0	0.980 (0.958, 1.003)	0.09441
TBIL, μmol/L	14.3 ± 8.2	1.017 (0.966, 1.070)	0.52417
ALT, U/L	28.9 ± 17.3	1.005 (0.981, 1.029)	0.70716
AST, U/L	27.1 ± 10.8	1.053 (1.017, 1.090)	0.00343
LDH, U/L	295.7 ± 170.9	1.002 (1.000, 1.005)	0.02875
Creatinine, μmol/L	68.6 ± 17.8	1.030 (1.006, 1.054)	0.01512
BUN, mmol/L	4.0 ± 1.6	1.449 (1.155, 1.818)	0.00135
CK, U/L	89.2 ± 69.1	1.007 (1.002, 1.012)	0.00876
PT, sec	11.9 ± 1.0	0.819 (0.510, 1.316)	0.40989
APTT, sec	30.9 ± 5.3	0.928 (0.840, 1.026)	0.14283
Fibrinogen, mg/dL	3.6 ± 1.0	1.830 (1.153, 2.903)	0.01031
D-dimer, mg/L	0.3 ± 0.4	3.240 (1.465, 7.169)	0.00371
ALB, g/L	40.2 ± 5.1	0.850 (0.776, 0.931)	0.00045

BMI: Body mass index; TBIL: Total bilirubin; ALT: Alanine transaminase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; CK: Creatine kinase; PT: Prothrombin time; APTT: Activated partial thromboplastin time; ALB: Albumin; CI: confidence interval.

Table 3. Relationship between albumin and adverse outcomes.

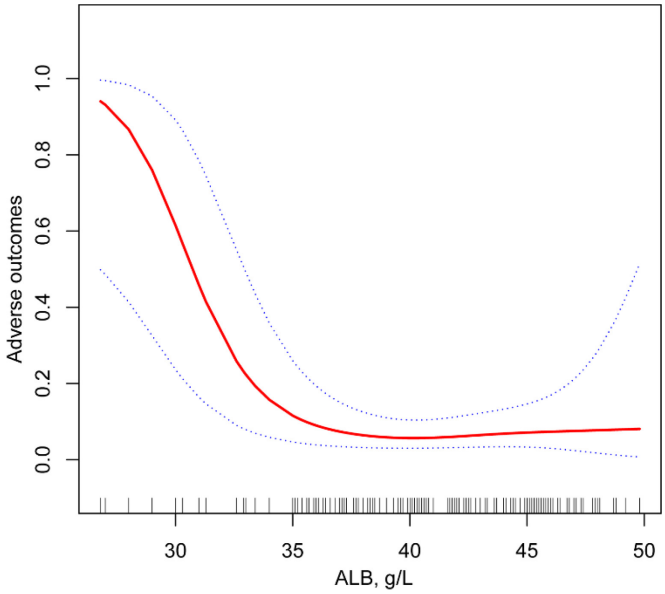
Exposure	Odds ratio (95% CIs)	*p* value
Albumin, g/L	0.70 (0.56, 0.88)	0.0020
Albumin (tertiles), g/L		
T1	Ref	Ref
T2	0.14 (0.02, 1.07)	0.0579
T3	0.07 (0.00, 0.86)	0.0377
p for trend		0.0303

Adjusted for age, gender, body mass index, current smoking, hypertension, cardiovascular disease, pulmonary disease, tumor, chronic liver disease, D-dimer, creatinine, creatine kinase, leukocytes, neutrophil, lactate dehydrogenase, blood urea nitrogen and fibrinogen.

In the present study, we analyzed the non-linear relationship between ALB and adverse outcomes because ALB is a continuous variable (Figure 1). We found that the relationship between ALB and adverse outcomes was non-linear (after adjusting for age, gender, BMI, smoking status, hypertension, cardiovascular disease, pulmonary disease, tumor, chronic liver disease, D-dimer, creatinine, CK, leukocytes, neutrophil, LDH, BUN and fibrinogen). By using a two-piecewise linear regression model, we calculated the inflection point as 32.6. On the right of the inflection point, the odds ratio, 95% CI and *p* value were 0.908, 0.686 to 1.203 and 0.5032, respectively. However, we observed a negative relationship between ALB and adverse outcomes on the left side of the inflection point (OR = 0.204, 95% CI, 0.061 - 0.681, *p* = 0.0097) (Table 4). This suggests that when ALB was less than 32.6 g/L, for every 1 unit increase in ALB, the risk of adverse outcomes was reduced by 79.6%.

The results of subgroup analysis indicated that interaction effect of age was significant ($p = 0.0113$), while the test for interactions had no significant differences for gender, BMI, hypertension, diabetes, pulmonary disease and chronic liver disease (*p* values for interactions were > 0.05; cardiovascular disease, chronic kidney disease and tumor were not included in subgroup analysis because the sample size in the subgroup was less than 10) (Figure 2).

Figure 1. Illustrated curved line relation between ALB and adverse outcomes.



The area between two dotted lines represents 95% CI. Each point indicates the magnitude of the ALB and is connected to form a continuous line. The magnitude of the ALB was not correlated with adverse outcomes when it was > 32.6 g/L. Conversely, the magnitude of the ALB showed a significant correlation with adverse outcomes when it was ≤ 32.6 g/L. The risk of adverse outcomes decreased as the ALB increased. ALB: Albumin.

Table 4. The results of the two-piecewise linear regression model.

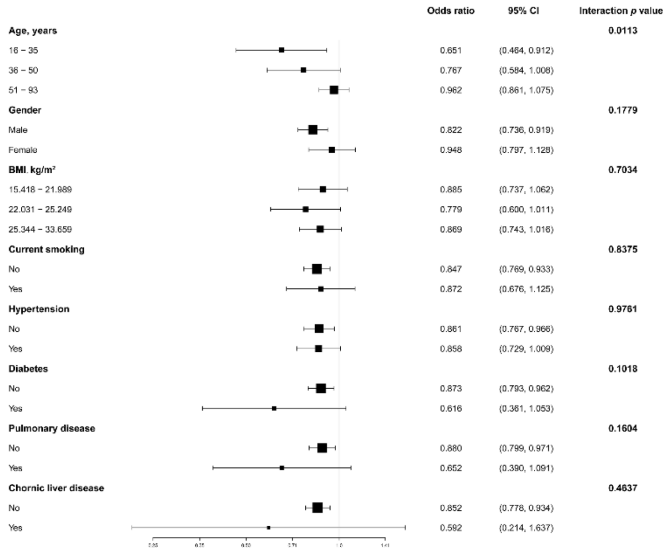
Albumin (g/L)	Odds ratio (95% CIs)	*p* value
≤ 32.6	0.204 (0.061, 0.681)	0.0097
> 32.6	0.908 (0.686, 1.203)	0.5032

Adjusted for age, gender, body mass index, current smoking, hypertension, cardiovascular disease, pulmonary disease, tumor, chronic liver disease, D-dimer, creatinine, creatine kinase, leukocytes, neutrophil, lactate dehydrogenase, blood urea nitrogen and fibrinogen.

Discussion

We used generalized linear model (GLM) and GAM models to elucidate the relationship between ALB and adverse outcomes among participants. As is shown in multivariate Cox regression analyses, ALB was negatively correlated with the risk of adverse outcomes. This relationship seems to diminish with age. The same trend was observed when we analyzed ALB as a categorical variable. However, the results obtained from GAM and two-piecewise linear regression model showed that the relationship between ALB and adverse outcomes was non-linear, and the correlations between ALB and adverse outcomes were different on the left and right sides of the inflection point (ALB = 32.6). ALB, as assessed at baseline, was not statistically significant on the right side of the inflection point, but it was negatively associated with adverse outcomes on the left of the inflection point. It means that ALB is negatively correlated with adverse outcomes when

Figure 2. Subgroup analysis of the association between ALB and adverse outcomes.



BMI: Body Mass Index; CI: Confidence Interval.

ALB is less than 32.6 g/L, and for every 1 unit increase in ALB, the risk of adverse outcomes was reduced by 79.6%.

Several studies have indicated a decrease in serum albumin concentrations in patients affected by COVID-19 [14,15]. Hypoalbuminemia has a negative impact on clinical outcomes in COVID-19 patients [16-19]. Hypoalbuminemia has been identified as an independent predictor of mortality in COVID-19 patients [17]. However, our study differs from the previous studies in that our patients were from five different hospitals. Furthermore, our study has a few strengths. First, we not only used GLM to evaluate the linear relationship between ALB and adverse outcomes, but also used GAM to clarify their non-linear relationship. GAM has advantages in analyzing non-linear relations; it can handle non-parametric smoothing and will fit a regression spline to the data. The use of GAM helped us better discover the real relationship between exposures and outcomes. Second, this study is an observational study, including unavoidable potential confounders; therefore, we used strict statistical adjustment to minimize residual confounding. Third, we had the positive finding that when ALB was less than 32.6 g/L (32.6, per 1 change in the text), for every 1 unit increase in ALB, the risk of adverse outcomes was reduced by 79.6%. The clinical value of this finding is that the association of ALB and adverse outcomes can only be observed when ALB levels do not reach a certain threshold (ALB = 32.6g/L), which can guide clinical practice directly.

The relationship between hypoalbuminemia and more adverse outcomes may have several explanations. First, as an anti-inflammatory and antioxidant protein, albumin plays a crucial role in scavenging free oxygen radicals, which can cause tissue ischemia-reperfusion injury and even an intense systemic inflammatory response [20,21]. Previous studies indicated that albumin concentrations were inversely correlated with white blood cell, neutrophil-to-lymphocyte ratio, C-reactive protein and interleukin-6, which suggested that hypoalbuminemia might be due to the systemic inflammatory state in COVID-19 [17,22]. It is well known that inflammation may be responsible for the extravasation of serum albumin into the interstitial space due to an expanded capillary vascular permeability, with an increased volume distribution of albumin [10]. In this context, the role of albumin in scavenging oxygen free radicals is not potent enough to protect against the cytokine storm and the ensuing organ failure. Besides, albumin not only has anticoagulant properties, but also inhibits oxidative stress-related coagulation and platelet activation [23,24]. Therefore, the negative impact of hypoalbuminemia on coagulation activation may be associated with a higher risk of COVID-19 adverse outcomes. Hence, in addition to prior known biomarkers, such as procalcitonin, C-reactive protein, lymphocyte count, D-dimer, troponin I, aspartate transaminase and alanine transaminase, associated with severe COVID-19 [25], serum albumin level might help in prognostic risk stratification.

There are some limitations in our study. First, the study population may not be large enough and some bias may have occurred. Second, the subgroup analysis was not adjusted for potential confounding variables because of the limited number of positive events. Third, we showed only the predictive value of baseline albumin level for outcome of COVID-19, yet the changes in albumin level during the evolution of COVID-19 were not reflected in our data set, and whether the dynamic changes of albumin level are more predictive of adverse outcomes remains unknown. Fourth, this dataset only included the clinical data at the beginning of the pandemic, and the analysis period was short, which limits generalizations and further observations, especially since new strains emerged later on.

Conclusions

We demonstrated that the relationship between ALB and adverse outcomes of COVID-19 is non-linear. ALB is negatively correlated with adverse outcomes when ALB is less than 32.6 g/L. These findings further expand the potential role of ALB as a prognostic predictor in COVID-19, suggesting that for COVID-19 patients who had admission ALB lower than 32.6g/L, the risk of adverse outcomes was much higher, and they need more intensive and active treatment.

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Authors' Contributions

Congyi Xie conducted the data analyses and wrote the initial manuscript. Sijiao Wang and Jian Zhou contributed to data collection. Lin Tong and Changzhou Shao designed the study, revised the data analyses and the manuscript. All authors read and approved the final manuscript.

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