Albumin Levels as an Independent Risk Factor for Adverse Outcomes in COVID-19 Patients: A Multicenter Restrospective Study.

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Research

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Abstract

Backgroud: Studies of risk factors for prognosis of COVID-19 have increased rapidly, but researches about the association between albumin (ALB) levels and COVID-19 clinical outcomes are limited. This study aimed to investigate the relationship between admission albumin levels and adverse outcomes in patients with COVID-19.

Methods: This study retrospectively-analyzed 199 COVID-19 patients come from five designated hospitals in Fujian Province between January 22 and February 27, 2020. Clinical characteristics and admission laboratory values were collected. 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.

Results: After adjusting for potential confounders (age, sex, BMI, current smoking, hypertension, cardiovascular disease, pulmonary disease, tumor, chronic liver disease, D-dimer, creatinine, CK, leukocytes, neutrophil, LDH, BUN and fibrinogen), a non-linear relationship was detected between ALB and adverse comes, which had an inflection point of 32.6. The odds ratio and the confidence intervals on the left and right sides of the inflection point were 0.204 (0.061 to 0.681) and 0.908 (0.686 to 1.203), respectively.

Conclusion: The relationship between ALB and adverse outcomes is non-linear. ALB was negatively correlated with adverse outcomes when ALB was less than 32.6.

Background

COVID-19 has now become a global pandemic and has been declared a public health emergency of international concern by The World Health Organization (WHO)[1]. According to previous studies, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) can affect multiple organs, leading to adverse outcomes, such as cerebrovascular accidents[2,3], myocardial infarction[4], pulmonary embolism[5], acute liver injury, and death[6]. In order to improve the management of patients, it is critical to search for predictors of adverse outcomes. Albumin is a protein synthesized in the liver, which 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].In critically status, inflammatory mediators reduce albumin synthesis in order 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 literature reports have suggested an association between hypoalbuminemia and poor outcomes in critical patients[11], but the relationship between albumin levels and catastrophic events in COVID-19 remains unclear. The aim of our study is to determine whether there is a link between initial admission albumin concentration and adverse outcomes in COVID-19 patients. Exploring the implications of hypoalbuminemia can help clinicians identify high-risk patients early and take timely preventive measures.

Materials And Methods

Study design and Participants

For this retrospective cohort study, all 199 COVID-19 patients who were admitted to five hospitals in Fujian Province, including Fuzhou, Zhangzhou, Xiamen, Putian, and Quanzhou, from January 22 to February 27, 2020, were consecutively included. The clinical outcomes, discharge from hospital or death, were recorded up to March 3, 2020. These hospitals are responsible for the COVID-19 treatment assigned by the government. All patients were diagnosed with COVID-19 by 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). This study was approved by the ethical committee in Zhongshan Hospital, Xiamen Branch, Fudan University (B2020-003). The requirement for informed consent was waived because the data were urgently collected and analyzed anonymously.

Data Collection

A team of professional physicians retrospectively reviewed clinical electronic medical records, comprising of clinical notes and laboratory values for our cohort of patients. We recorded the following demographic data: age, sex, body mass index (BMI), and smoking status, and comorbidities: hypertension, diabetes, cardiovascular disease, chronic kidney disease, pulmonary disease, tumor and chornic liver disease, as well as symptoms. In terms of laboratory values, initial values on the day of admission were collected. Outcomes recorded included: development of Acute respiratory distresssyndrome (ARDS), Respiratory failure, shock, Multiple organ failure (MOF), Intensive Care Unit (ICU) admissions, in-hospital mortality events, and adverse outcomes (sum of outcomes detailed above).

Statistical analysis

The total procedure of statistical analysis was performed in five steps. First, we analyzed the baseline characteristics of participants in accordance with the following principles (we grouped 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 a univariate linear regression model to assess relationships between ALB and adverse outcomes risk. Third, according to the recommendation of the STROBE statement, the results from unadjusted, minimally adjusted analyses and fully adjusted analyses were reported simultaneously. The covariances, including age, sex, BMI, current smoking, hypertension, cardiovascular disease, pulmonary disease, tumor, chornic liver disease, d-dimer, creatinine, Creatine kinase (CK), leukocytes, neutrophil, Lactic 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. Fourth, 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 the 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. Fifth, subgroup analysis of the association between ALB and adverse outcomes was performed using stratified linear regression models. The modifications and interations of subgroups were examined by likelihood ration tests. All of 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 them were male. Table 1 compared the baseline demographic, clinical, and biochemical characteristics of included patients by tertiles of the ALB. Compared with subjects in the highest tertile of the ALB, those in the lowest tertile were older, and more likely to have pulmonary disease, whereas participants with chronic liver disease was major in middle tertile of the ALB. Moreover, compared with the lowest tertile group, patients had a significantly higher lymphocyte and hemoglobin, and lower PT and D-dimer in the highest tertile group.

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

Characteristic	ALB (g/L)			P-value	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	< 0.001
Sex				0.269	-
Male	31 (46.97%)	40 (60.61%)	34 (50.75%)		
Female	35 (53.03%)	26 (39.39%)	33 (49.25%)		
BMI, kg/m^2	23.68 ± 3.44	23.54 ± 3.14	23.97 ± 3.70	0.776	0.768
Current smoking				0.104	-
No	61 (92.42%)	65 (98.49%)	60 (89.55%)		
Yes	5 (7.58%)	1 (1.52%)	7 (10.45%)		
Comorbidities					
Hypertension				0.180	-
No	53 (80.30%)	54 (81.82%)	61 (91.05%)		
Yes	13 (19.70%)	12 (18.18%)	6 (8.96%)		
Diabetes				0.213	-
No	58 (87.88%)	62 (93.94%)	64 (95.52%)		
Yes	8 (12.12%)	4 (6.06%)	3 (4.48%)		
Cardiovascular disease				0.869	0.822
No	63 (95.46%)	63 (95.46%)	65 (97.02%)		
Yes	3 (4.55%)	3 (4.55%)	2 (2.99%)		

*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* Lactic dehydrogenase, *BUN* Blood urea nitrogen, *CK* Creatine kinase, *CK-MB* Creatine kinase isoenzyme-MB, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *ALB* Albumin, *ARDS* Acute respiratory distresssyndrome, *MOF* Multiple organ failure, *ICU* Intensive Care Unit.

Characteristic	ALB (g/L)			P-value	P-value*
Chronic kidney disease				0.770	0.848
No	64 (96.97%)	65 (98.49%)	66 (98.51%)		
Yes	2 (3.03%)	1 (1.52%)	1 (1.49%)		
Pulmonary disease				0.008	-
No	58 (87.88%)	63 (95.46%)	67 (100.00%)		
Yes	8 (12.12%)	3 (4.55%)	0 (0.00%)		
Tumor				0.608	0.735
No	64 (96.97%)	64 (96.97%)	63 (94.03%)		
Yes	2 (3.03%)	2 (3.03%)	4 (5.97%)		
Chornic liver disease				0.002	-
No	65 (98.49%)	57 (86.36%)	66 (98.51%)		
Yes	1 (1.52%)	9 (13.64%)	1 (1.49%)		
Symptoms					
Cough				0.292	-
No	27 (40.91%)	21 (31.82%)	30 (44.78%)		
Yes	39 (59.09%)	45 (68.18%)	37 (55.22%)		
Fever				0.077	-
No	14 (21.21%)	11 (16.67%)	22 (32.84%)		
Yes	52 (78.79%)	55 (83.33%)	45 (67.16%)		
Chest distress				0.052	-
No	56 (84.85%)	64 (96.97%)	61 (91.05%)		
Yes	10 (15.15%)	2 (3.03%)	6 (8.96%)		

*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* Lactic dehydrogenase, *BUN* Blood urea nitrogen, *CK* Creatine kinase, *CK-MB* Creatine kinase isoenzyme-MB, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *ALB* Albumin, *ARDS* Acute respiratory distresssyndrome, *MOF* Multiple organ failure, *ICU* Intensive Care Unit.

Characteristic	ALB (g/L)			P-value	P-value*
Dyspnea				0.131	0.218
No	64 (96.97%)	66 (100.00%)	67 (100.00%)		
Yes	2 (3.03%)	0 (0.00%)	0 (0.00%)		
Fatigue				0.068	-
No	41 (62.12%)	50 (75.76%)	53 (79.10%)		
Yes	25 (37.88%)	16 (24.24%)	14 (20.90%)		
Expectoration				0.197	-
No	42 (63.64%)	40 (60.61%)	50 (74.63%)		
Yes	24 (36.36%)	26 (39.39%)	17 (25.37%)		
Headache				0.282	-
No	60 (90.91%)	60 (90.91%)	65 (97.02%)		
Yes	6 (9.09%)	6 (9.09%)	2 (2.99%)		
Diarrhea				0.194	-
No	57 (86.36%)	62 (93.94%)	63 (94.03%)		
Yes	9 (13.64%)	4 (6.06%)	4 (5.97%)		
Dizzy				0.916	-
No	61 (92.42%)	62 (93.94%)	63 (94.03%)		
Yes	5 (7.58%)	4 (6.06%)	4 (5.97%)		
Chills				0.819	-
No	60 (90.91%)	59 (89.39%)	62 (92.54%)		
Yes	6 (9.09%)	7 (10.61%)	5 (7.46%)		
Laboratory findings					

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BMI Body mass index, *TBIL* Total bilirubin, *ALT* alanine transaminase, *AST* aspartate transaminase, *LDH* Lactic dehydrogenase, *BUN* Blood urea nitrogen, *CK* Creatine kinase, *CK-MB* Creatine kinase isoenzyme-MB, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *ALB* Albumin, *ARDS* Acute respiratory distresssyndrome, *MOF* Multiple organ failure, *ICU* Intensive Care Unit.

Characteristic	ALB (g/L)			P-value	P-value*
Leukocytes, 10^9/L	5.16 ± 1.96	5.65 ± 2.95	5.49 ± 2.10	0.489	0.607
Neutrophil, 10^9/L	3.16 (2.05–4.39)	3.29 (2.43–4.16)	3.26 (2.22–4.51)	0.723	0.950
Lymphocyte, 10^9/L	1.24 ± 0.58	1.38 ± 0.66	1.58 ± 0.78	0.013	0.051
Platelets, 10^9/L	195.15 ± 66.61	207.70 ± 85.77	207.93 ± 56.73	0.494	0.335
Hemoglobin, g/L	129.77 ± 15.76	137.88 ± 18.14	143.18 ± 17.79	< 0.001	< 0.001
TBIL, μmol/L	12.45 (8.70-17.85)	12.45 (8.07–16.68)	13.00 (7.40–20.60)	0.203	0.625
ALT, U/L	22.50 (16.00–30.00)	27.50 (19.25–37.18)	22.70 (17.50–34.60)	0.090	0.136
AST, U/L	25.40 (21.00–32.00)	25.00 (21.00–33.00)	23.90 (19.00-30.15)	0.257	0.476
LDH, U/L	209.50 (164.00-347.75)	257.70 (174.75-406.75)	217.00 (168.00-436.00)	0.711	0.591
Creatinine, μmol/L	68.91 ± 19.73	66.93 ± 16.29	70.01 ± 17.44	0.605	0.716
BUN, mmol/L	3.95 ± 1.67	3.93 ± 1.53	4.07 ± 1.62	0.876	0.779
CK, U/L	70.00 (45.50-140.50)	70.30 (42.50-103.75)	60.00 (44.00-100.30)	0.444	0.577
CK-MB, U/L	9.70 (3.00–14.00)	7.35 (1.18-15.00)	6.00 (0.81–12.23)	0.274	0.125
PT, sec	12.07 ± 0.99	12.01 ± 1.01	11.61 ± 1.06	0.039	0.040
APTT, sec	31.43 ± 5.30	30.26 ± 4.30	30.87 ± 6.20	0.502	0.517
Fibrinogen, g/L	3.77 ± 0.97	3.56 ± 0.99	3.58 ± 0.92	0.426	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	< 0.001

*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* Lactic dehydrogenase, *BUN* Blood urea nitrogen, *CK* Creatine kinase, *CK-MB* Creatine kinase isoenzyme-MB, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *ALB* Albumin, *ARDS* Acute respiratory distresssyndrome, *MOF* Multiple organ failure, *ICU* Intensive Care Unit.

Characteristic	ALB (g/L)			P-value	P-value*
Adverse outcomes				0.197	-
No	55 (83.33%)	60 (90.91%)	62 (92.54%)		
Yes	11 (16.67%)	6 (9.09%)	5 (7.46%)		
ARDS				0.152	-
No	59 (89.39%)	64 (96.97%)	64 (95.52%)		
Yes	7 (10.61%)	2 (3.03%)	3 (4.48%)		
Respiratory failure				0.335	-
No	60 (90.91%)	62 (93.94%)	65 (97.02%)		
Yes	6 (9.09%)	4 (6.06%)	2 (2.99%)		
Shock				0.360	0.549
No	64 (96.97%)	66 (100.00%)	64 (96.97%)		
Yes	2 (3.03%)	0 (0.00%)	2 (3.03%)		
MOF				0.372	1.000
No	66 (100.00%)	66 (100.00%)	66 (98.51%)		
Yes	0 (0.00%)	0 (0.00%)	1 (1.49%)		
ICU admission				0.585	-
No	60 (90.91%)	63 (95.46%)	62 (92.54%)		
Yes	6 (9.09%)	3 (4.55%)	5 (7.46%)		
In-hospital mortality				0.363	0.663
No	65 (98.48%)	66 (100.00%)	67 (100.00%)		
Yes	1 (1.52%)	0 (0.00%)	0 (0.00%)		

*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* Lactic dehydrogenase, *BUN* Blood urea nitrogen, *CK* Creatine kinase, *CK-MB* Creatine kinase isoenzyme-MB, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *ALB* Albumin, *ARDS* Acute respiratory distresssyndrome, *MOF* Multiple organ failure, *ICU* Intensive Care Unit.

Table 2 showed the univariate logistic regression models between baseline variables and adverse outcomes. The results of univariate analysis showed that Age (OR = 1.063, 95% CI, 1.033–1.094, P = 0.00003), Hypertension (OR = 4.878, 95% CI, 1.867–12.740, P = 0.00122), Cardiovascular disease (OR = 9.611, 95% CI, 2.213–41.737, P = 0.00252), Pulmonary disease (OR = 5.397, 95% CI, 1.440–20.224, P = 0.01238), Tumor (OR = 5.432, 95% CI, 1.203–24.532, P = 0.02782), Fatigue (OR = 3.023, 95% CI, 1.226–7.454, P = 0.01630), Leukocytes (OR = 1.191, 95% CI, 1.013–1.400, P = 0.03481), Neutrophil (OR = 1.134, 95% CI, 1.003–1.282, P = 0.04522), AST (OR = 1.053, 95% CI, 1.017–1.090, P = 0.00343), LDH (OR = 1.002, 95% CI, 1.000–1.005, P = 0.02875), Creatinine (OR = 1.030, 95% CI, 1.006–1.054, P = 0.01512), BUN (OR = 1.449, 95% CI, 1.155–1.818, P = 0.00135), CK (OR = 1.007, 95% CI, 1.002–1.012, P = 0.00876), Fibrinogen (OR = 1.830, 95% CI, 1.153–2.903, P = 0.01031) and D-dimer (OR = 3.240, 95% CI, 1.465–7.169, P = 0.00371) 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.

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

Adverse outcomes	Statistics	Odds ratio (95% CIs), P-value
Age, years	46.3 ± 16.4	1.063 (1.033, 1.094) 0.00003
Sex		
Male	105 (52.8%)	1.000
Female	94 (47.2%)	0.379 (0.142, 1.014) 0.05333
BMI, kg/m2	23.7 ± 3.4	1.054 (0.905, 1.228) 0.49623
Current smoking		
No	186 (93.5%)	1.000
Yes	13 (6.5%)	1.509 (0.312, 7.301) 0.60892
Hypertension		
No	168 (84.4%)	1.000
Yes	31 (15.6%)	4.878 (1.867, 12.740) 0.00122
Diabetes		
No	184 (92.5%)	1.000
Yes	15 (7.5%)	2.171 (0.562, 8.386) 0.26085
Cardiovascular disease		
No	191 (96.0%)	1.000
Yes	8 (4.0%)	9.611 (2.213, 41.737) 0.00252
Chronic kidney disease		
No	195 (98.0%)	1.000
Yes	4 (2.0%)	2.762 (0.275, 27.771) 0.38829
Pulmonary disease		
No	188 (94.5%)	1.000
Yes	11 (5.5%)	5.397 (1.440, 20.224) 0.01238
Tumor		
No	191 (96.0%)	1.000
Yes	8 (4.0%)	5.432 (1.203, 24.532) 0.02782
Chornic liver disease		

Adverse outcomes	Statistics	Odds ratio (95% CIs), P-value
No	188 (94.5%)	1.000
Yes	11 (5.5%)	0.795 (0.097, 6.525) 0.83105
Cough		
No	78 (39.2%)	1.000
Yes	121 (60.8%)	1.145 (0.457, 2.871) 0.77304
Fever		
No	47 (23.6%)	1.000
Yes	152 (76.4%)	0.804 (0.295, 2.188) 0.66917
Chest distress		
No	181 (91.0%)	1.000
Yes	18 (9.0%)	1.006 (0.215, 4.702) 0.99368
Dyspnea		
No	197 (99.0%)	1.000
Yes	2 (1.0%)	8.381 (0.505, 139.005) 0.13790
Fatigue		
No	144 (72.4%)	1.000
Yes	55 (27.6%)	3.023 (1.226, 7.454) 0.01630
Expectoration		
No	132 (66.3%)	1.000
Yes	67 (33.7%)	1.754 (0.716, 4.300) 0.21909
Headache		
No	185 (93.0%)	1.000
Yes	14 (7.0%)	1.375 (0.287, 6.591) 0.69044
Diarrhea		
No	182 (91.5%)	1.000
Yes	17 (8.5%)	1.080 (0.230, 5.072) 0.92231
Dizzy		
No	186 (93.5%)	1.000

Adverse outcomes	Statistics	Odds ratio (95% CIs), P-value
Yes	13 (6.5%)	0.655 (0.081, 5.293) 0.69126
Chills		
No	181 (91.0%)	1.000
Yes	18 (9.0%)	0.448 (0.057, 3.543) 0.44675
Leukocytes, 10^9/L	5.4 ± 2.4	1.191 (1.013, 1.400) 0.03481
Neutrophil, 10^9/L	3.7 ± 2.7	1.134 (1.003, 1.282) 0.04522
Lymphocyte, 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
CK-MB, U/L	8.8 ± 7.7	1.011 (0.956, 1.070) 0.70019
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, g/L	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

Univariate linear regression models were used to evaluate the associations between ALB and adverse outcomes. Meanwhile, we showed the non-adjusted and adjusted models in Table 3. In the crude model, ALB correlated with adverse outcomes (OR = 0.85, 95% CI, 0.78–0.93, P = 0.0004). In the minimally adjusted model (adjusted age, sex, BMI, current smoking), the values also had a significant correlation (OR = 0.88, 95% CI, 0.78–0.99, P = 0.0294). After adjusting other covariates, we still identified the significance in the fully adjusted model (OR = 0.70, 95% CI, 0.56–0.88, P = 0.0020). For the purpose of sensitivity analysis, we also handled ALB as a categorical variable (tertiles) and found the same trend (p for the trend was 0.0303).

Table 3
Relationship between ALB and adverse outcomes in different models

Exposure	Crude model	Minimally adjusted model	Fully adjusted model
ALB, g/L	0.85 (0.78, 0.93) 0.0004	0.88 (0.78, 0.99) 0.0294	0.70 (0.56, 0.88) 0.0020
ALB (g/L, tertiles)			
T1	Ref	Ref	Ref
T2	0.50 (0.17, 1.44) 0.1999	0.47 (0.12, 1.91) 0.2921	0.14 (0.02, 1.07) 0.0579
T3	0.40 (0.13, 1.23) 0.1112	0.66 (0.16, 2.66) 0.5538	0.07 (0.00, 0.86) 0.0377
P for trend	0.0961	0.5074	0.0303
Crude model: we did not adjust other covariants			
Minimally adjusted model: we adjusted Age; Sex; BMI; Current smoking			
Fully adjusted model: we adjusted Age; Sex; BMI; Current smoking; Hypertension; Cardiovascular disease; Pulmonary disease; Tumor; Chornic liver disease; D-dimer; Creatinine; CK; Leukocytes; Neutrophil; LDH; BUN; Fibrinogen			
CI: confidence interval; Ref: reference			

In the present study, we analysed the non-linear relationship between ALB and adverse outcomes because ALB is a continuous variable (Fig. 1). We found that the relationship between ALB and adverse outcomes was non-linear (after adjusting Age, sex, BMI, current smoking, hypertension, cardiovascular disease, pulmonary disease, tumor, chornic liver disease, D-dimer, creatinine, CK, leukocytes, neutrophil, LDH, BUN and Fibrinogen). By using a two-piecewise linear regression model, we calculated that the inflection point was 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 also 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).

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

ALB (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: Age; Sex; BMI; Current smoking; Hypertension; Cardiovascular disease; Pulmonary disease; Tumor; Chornic liver disease; D-dimer; Creatinine; CK; Leukocytes; Neutrophil; LDH; BUN; Fibrinogen		

The results of subgroup analysis revealed that interaction effect of age was significant (P for interaction = 0.0113), while the test for interactions were not significant differences for sex, BMI, hypertension, diabetes, pulmonary disease and chornic liver disease (P values for interactions were larger than 0.05) (Cardiovascular disease, Chronic kidney disease and Tumor were not included in subgroup analysis becasuse the sample size in the subgroup was less than 10). (Fig. 2)

Discussion

In the present study, we used GLM and GAM models to elucidate the relationship between ALB and adverse outcomes among participants. As is shown in the fully adjusted model, ALB was negatively correlated with the risk of adverse outcomes. This relationship seems to diminish with age. When we handled ALB as a categorical variable, the same trend was observed. 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 ALB was negatively associated with adverse outcomes on the left of the inflection point.

Several studies have indicated a decrease in serum albumin concentrations in patients affected by COVID-19[12,13], and some of which addressed the difference of baseline albumin levels between the clinical outcomes in COVID-19 patients[14,15]. Huang et al[16]. reported that ICU admission patients were likely to have lower level of ALB. In a meta-analysis, Aziz et al. confirmed that the risk of COVID-19 adverse outcomes which defined as respiratory distress (with either respiratory rate ≥ 30/min, oxygen saturation ≤ 93% at rest, and/or PaO2/FiO2 ≤ 300 mmHg), ICU admission, and/or death, was associated with hypoalbuminemia[14]. In a retrospective cohort study of 299 patients, Huang et al. showed that hypoalbuminemia was an independent predictor for mortality in COVID-19 patients. Our current study differs from the previous studies in that our patients come from five different hospitals. Furthermore, our study has a number of strengths. First, we not only use the generalized linear model to evaluate the linear relationship between ALB and adverse outcomes but also use the generalized additive model to clarify their nonlinear relationship. GAM has advantages in analyzing non-linear relations, can handle non-parametric smoothing and will fit a regression spline to the data. The use of GAM will help us to better discover the real relationships 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 ALB was less than 32.6 (32.6, per 1 change in the text), and 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 work directly.

The relationship between hypoalbuminemia and more adverse outcomes may have several explanations. First, as an anti-inflammatory and antioxidant protein, albumin display a crucial role in scavenging oxygen free radicals (OFR), which can cause tissue ischemia, reperfusion injury, and even an intense systemic inflammatory response[17,18]. Previous studies indicated that albumin concentrations were inversely correlated with WBC, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein and IL-6, and suggested that hypoalbuminemia might be due to systemic inflammatory state in COVID-19[15,19]. 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 weakened 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[20,21]. 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, CRP, lymphocyte count, D-dimer, troponin I, aspartate transaminase (AST), alanine transaminase (ALT), associated with severe COVID-19[22], serum albumin levels might help in prognostic risk stratification.

There are some limitations in our study. First, the study populations 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 only showed the predictive value of baseline albumin level for outcome of COVID-19, yet the changes in albumin levels during the evolution of COVID-19 disease were not reflected in our data set, and whether or not the dynamic changes of albumin level are more predictive of adverse outcomes remains unknown.

Conclusion

The relationship between ALB and adverse outcomes is non-linear. ALB is negatively correlated with adverse outcomes when ALB (per 1.0 change) is smaller than 32.6.

Abbreviations

ALB: Albumin; WHO: World Health Organization; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; RT-PCR: Real-time reverse transcriptase-polymerase chain reaction; BMI: Body mass index; ARDS: Acute respiratory distresssyndrome; MOF: Multiple organ failure; ICU: Intensive Care Unit; CK: Creatine kinase; LDH: Lactic dehydrogenase; BUN: Blood urea nitrogen; GAM: Generalized additive models; ALT: Alanine transaminase; AST: Aspartate transaminase; TBIL: Total bilirubin; PT: Prothrombin time; APTT: Activated partial thromboplastin time; OR: Odds ratio; CI: Confidence interval; Ref: Reference

Declarations

Acknowledgement

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Authors' contributions

Congyi Xie wrote the initial manuscript and conducted the literature review. Sijiao Wang contributed to data collection. Jian Zhou and Changzhou Shao revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The raw data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

Ethics approval and consent to participate

This study was approved by the ethical committee in Zhongshan Hospital, Xiamen Branch, Fudan University (B2020-003). The requirement for informed consent was waived because the data were urgently collected and analyzed anonymously.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest

References

1. Organization WH. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV).
2. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke*. 2020;15(4):361-364
3. Avula A, Nalleballe K, Narula N et al. COVID-19 presenting as stroke. *Brain Behav Immun*. 2020;87:115-119
4. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17(5):259-260
5. Wichmann D. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. *Ann Intern Med*. 2020;173(12):1030
6. Su TH, Kao JH. The clinical manifestations and management of COVID-19-related liver injury. *J Formos Med Assoc*. 2020;119(6):1016-1018
7. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. *N Engl J Med*. 2020;382(26):2534-2543
8. Moman RN, Gupta N, Varacallo M. Physiology, Albumin. 2021;
9. Fasano M, Curry S, Terreno E et al. The extraordinary ligand binding properties of human serum albumin. *Iubmb Life*. 2005;57(12):787-96

10. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *JPEN J Parenter Enteral Nutr*. 2019;43(2):181-193
11. Yin M, Si L, Qin W et al. Predictive Value of Serum Albumin Level for the Prognosis of Severe Sepsis Without Exogenous Human Albumin Administration: A Prospective Cohort Study. *J Intensive Care Med*. 2018;33(12):687-694
12. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med*. 2020;58(7):1131-1134
13. Paliogiannis P, Zinellu A, Scano V et al. Laboratory test alterations in patients with COVID-19 and non COVID-19 interstitial pneumonia: a preliminary report. *J Infect Dev Ctries*. 2020;14(7):685-690
14. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. *Crit Care*. 2020;24(1):255
15. Huang J, Cheng A, Kumar R et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *J Med Virol*. 2020;92(10):2152-2158
16. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506
17. Taverna M, Marie AL, Mira JP, Guidet B. Specific antioxidant properties of human serum albumin. *Ann Intensive Care*. 2013;3(1):4
18. Shim H, Jang JY, Lee SH, Lee JG. Correlation of the oxygen radical activity and antioxidants and severity in critically ill surgical patients - study protocol. *World J Emerg Surg*. 2013;8(1):18
19. Huang W, Li C, Wang Z et al. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. *Science China Life Sciences*. 2020;63(11):1678-1687
20. Ronit A, Kirkegaard-Klitbo DM, Dohlmann TL et al. Plasma Albumin and Incident Cardiovascular Disease: Results From the CGPS and an Updated Meta-Analysis. *Arterioscler Thromb Vasc Biol*. 2020;40(2):473-482
21. Basili S, Carnevale R, Nocella C et al. Serum Albumin Is Inversely Associated With Portal Vein Thrombosis in Cirrhosis. *Hepatol Commun*. 2019;3(4):504-512
22. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci*. 2020;57(6):389-399

Figures

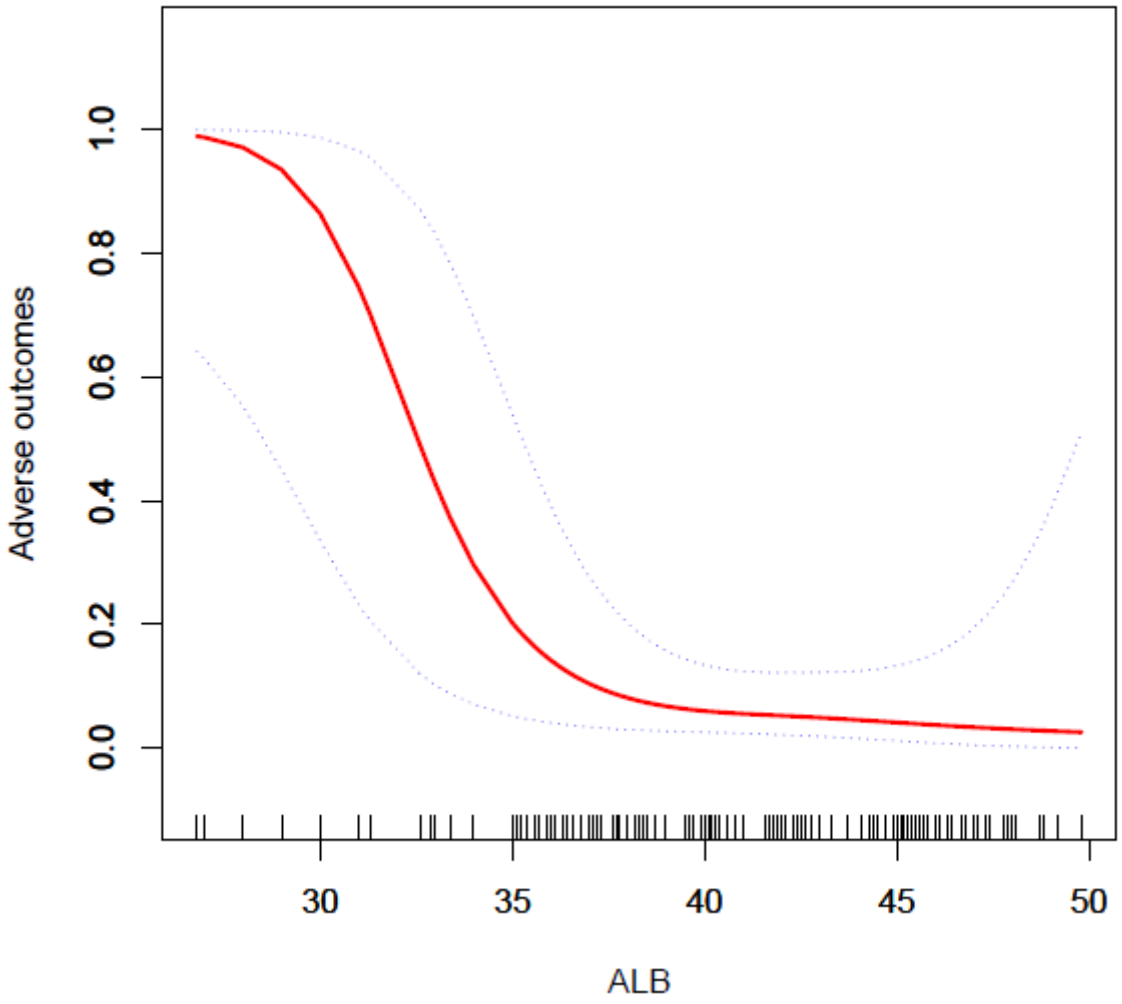

Figure 1

In the present study, we analysed the non-linear relationship between ALB and adverse outcomes because ALB is a continuous variable (Fig. 1). We found that the relationship between ALB and adverse outcomes was non-linear (after adjusting Age, sex, BMI, current smoking, hypertension, cardiovascular disease, pulmonary disease, tumor, chornic liver disease, D-dimer, creatinine, CK, leukocytes, neutrophil, LDH, BUN and Fibrinogen). By using a two-piecewise linear regression model, we calculated that the inflection point was 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 also 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)

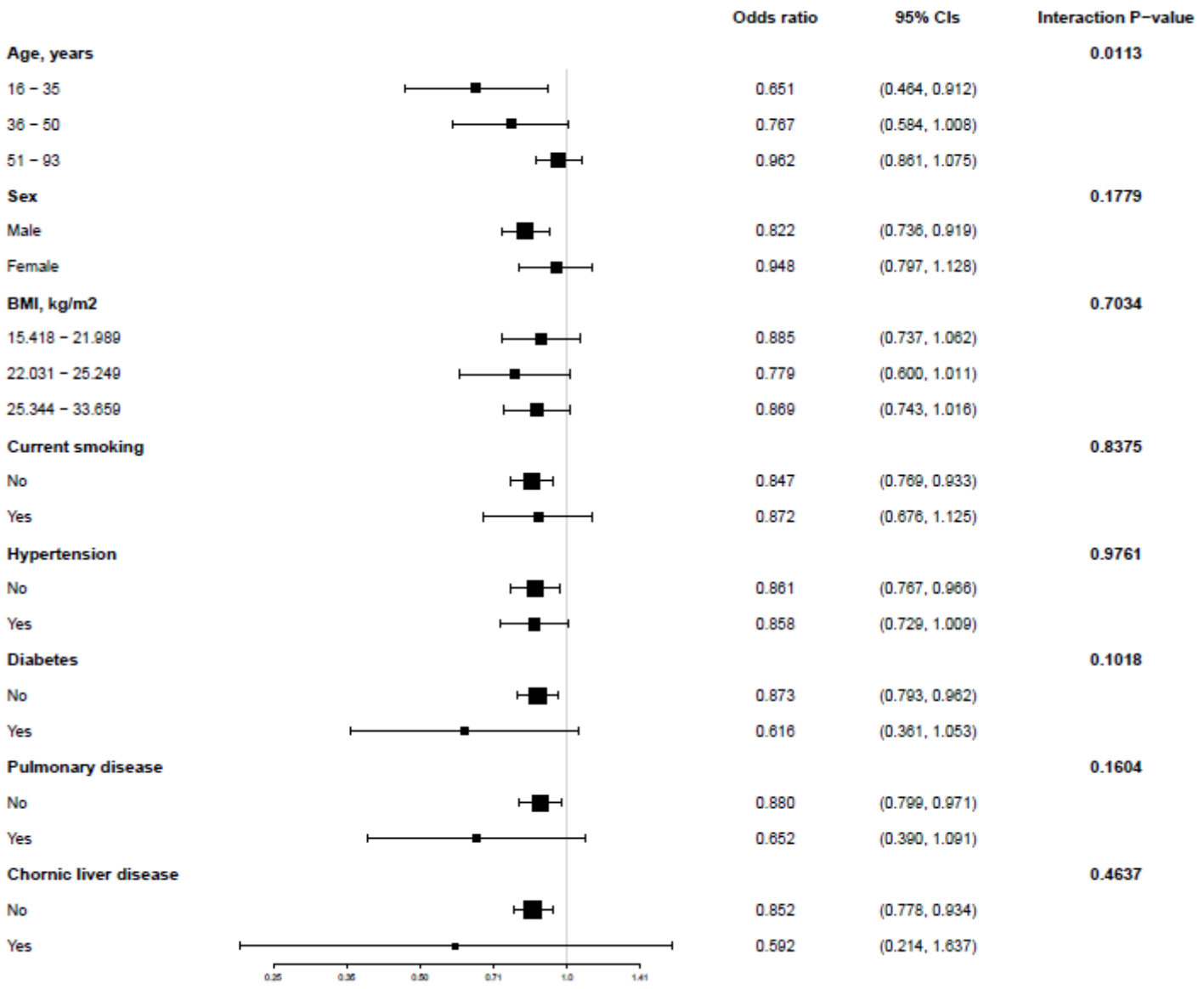

Figure 2

The results of subgroup analysis revealed that interaction effect of age was significant (P for interaction = 0.0113), while the test for interactions were not significant differences for sex, BMI, hypertension, diabetes, pulmonary disease and chornic liver disease (P values for interactions were larger than 0.05) (Cardiovascular disease, Chronic kidney disease and Tumor were not included in subgroup analysis becasuse the sample size in the subgroup was less than 10). (Fig. 2)