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RESEARCH ARTICLE

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Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity

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Abstract

The coronavirus disease 2019 (COVID-19) has evolved into a pandemic rapidly. Most of the literature show that the elevated liver enzymes in COVID-19 are of little clinical significance. Lower albumin level is seen in severe COVID-19 and is not parallel to the changes in alanine aminotransferase and aspartate aminotransferase levels. We aimed to explore the impact of hypoalbuminemia in COVID-19. This retrospective cohort study included adult patients with confirmed COVID-19. The relationship between hypoalbuminemia and death was studied using binary logistic analysis. A total of 299 adult patients were included, 160 (53.5%) were males and the average age was 53.4 ± 16.7 years. The median time from the onset of illness to admission was 3 days (interquartile ranges, 2-5). Approximately one-third of the patients had comorbidities. Hypoalbuminemia (<35 g/L) was found in 106 (35.5%) patients. The difference in albumin was considerable between survivors and non-survivors (37.6 ± 6.2 vs 30.5 ± 4.0, $P < .001$). Serum albumin level was inversely correlated to white blood cell ($r = -.149$, $P = .01$) and neutrophil to lymphocyte ratio ($r = -.298$, $P < .001$). Multivariate analysis showed the presence of comorbidities (OR, 6.816; 95% CI, 1.361-34.133), lymphopenia (OR, 13.130; 95% CI, 1.632-105.658) and hypoalbuminemia (OR, 6.394; 95% CI, 1.315-31.092) were independent predictive factors for mortality. In conclusion, hypoalbuminemia is associated with the outcome of COVID-19. The potential therapeutic value of albumin infusion in COVID-19 should be further explored at the earliest.

KEYWORDS
COVID-19, hypoalbuminemia, mortality, prediction, risk factor

1 | INTRODUCTION

The World Health Organization has officially announced coronavirus disease 2019 (COVID-19) as pandemic,[1] and its death toll far exceeded Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome.[2,3] However, there is currently no effective treatment for this novel disease.[4]

Several unique characteristics have been found in severe COVID-19, such as lymphopenia, old age, high C-reactive protein (CRP) level and underlying co-morbid diseases.[5-11] Significantly de-

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CVD, cerebrovascular disease; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IQRs, interquartile ranges; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; RT-PCR, real-time polymerase chain reaction; WBC, white blood cell count.

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creased albumin level is common in severe COVID-19,[7,12] but the change in albumin does not parallel the severity of hepatocellular injury in COVID-19.[12] This suggests that there may be mechanisms other than a hepatocellular injury that explains the profound hypoalbuminemia seen in COVID-19. One of the possible mechanisms is the intense systemic inflammation being reported in severe COVID-19.[13] Hypoalbuminemia is common in many inflammatory diseases because increased capillary permeability can result in the escape of albumin to the interstitial space.[14]

The role of albumin in the progression of COVID-19 remains unknown. We hypothesized that serum albumin levels at admission might reflect the severity of systemic inflammation and thus can serve as a predictive factor for COVID-19 outcomes. To address this question, we performed a retrospective study to compare the outcome in patients with or without hypoalbuminemia and to explore the impact of albumin in the prognosis of COVID-19.

2 | METHODS

2.1 | Study population

This is a retrospective cohort study including adult patients with COVID-19 disease hospitalized in the Third People's Hospital of Yichang, Hubei from 25th January to 24th March 2020. The inclusion criteria for enrollment into the study were; (1) age ≥ 18 years; (2) positive real-time polymerase chain reaction (RT-PCR) assay from naso-pharyngeal swab specimens; (3) meet diagnostic criteria set out by World Health Organization for COVID-19[15]; (4) with complete clinical data. The study was approved by the National Health Commission and the institutional board of the Third People's Hospital of Yichang, and complied with the Declaration of Helsinki.

2.2 | Data collection and defining variables

2.2.1 | Patient characteristics

Data were extracted from the review of case notes and electronic medical records. Onset time was defined as the time since the development of first relevant symptoms of COVID-19 to presentation in the hospital. Those who smoked more than 10 cigarettes/day in the past 30 days were considered as current smokers.[16] Heavy drinking was defined as long-term habitual alcohol consumption, usually longer than 5 years, of more than 40 g/d in males and 20 g/d in females, or a history of binging on alcoholic beverages within the past 2 weeks with a converted alcohol intake > 80 g/d.[17] The comorbidity of interest that was recorded was hypertension, diabetes mellitus (DM), coronary heart disease (CHD), cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and cancer.

2.2.2 | Laboratory data

All blood samples were obtained at admission and analyzed by standard methods in the laboratory. The routine hematological and biochemical tests included white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, CRP, procalcitonin, erythrocyte sedimentation rate (ESR), d-dimer, fibrinogen, and liver and kidney function tests. Neutrophil-to-lymphocyte ratio (NLR) value was measured by dividing the neutrophil count by the lymphocyte count.

2.2.3 | Definition of hypoalbuminemia and lymphopenia

The normal range value of the serum albumin was 35-55 g/L. Based on the previous research, we defined hypoalbuminemia as albumin less than 35 g/L.[18]

The normal range of lymphocyte count was $(1\text{-}4) \times 10^9$/L, thus lymphopenia was defined as lymphocyte count of $<1 \times 10^9$/L.

2.3 | Statistical analysis

Continuous variables were expressed as means ± SD or medians with interquartile ranges (IQRs), according to whether the distribution was normal or skewed. Categorical variables were expressed as percentages. The Student *t* test (for variables normally distributed) and Mann-Whitney *U* test (for variables non-normally distributed) were performed. The difference between categorical variables was examined with the χ^2 test or Fisher's exact test as appropriate. A *P*-value < .05 was considered statistically significant. Pearson correlation analysis was used to analyze the relationship between albumin and inflammatory indicators. Data management and analysis were performed using R software (R version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Baseline characteristics of patients

A total of 299 adult patients were included in the study, 16 of them died of COVID-19 and 283 survived. There were 160 (53.5%) males, and the average age of the cohort was 53.4 ± 16.7 years old. The median time from the onset of illness to admission was 3 days (IQR, 2-5). Approximately one-third of the patients had comorbidities, of which hypertension, DM, CHD, CVD, COPD, and cancer were present in 74 (24.7%), 35 (11.7%), 18 (6.0%), 13 (4.3%), 8 (2.7%) and 9 (3.0%) cases, respectively. A total of 113 patients (37.8%) had been to Wuhan before the illness. The most common symptoms on admission were fever (79.6%) and cough (74.2%), followed by increased phlegm/sputum production (45.2%) and dyspnea (14.0%). Lymphopenia was found in 127 (42.5%) and hypoalbuminemia in 106 (35.5%) patients. Forty-six patients required intensive care unit (ICU) admission and treatment (Table 1).

TABLE 1 Baseline characteristic of the patients on admission

Variables	Total	Survivors	Non-survivors	*P*
N	299	283	16	
Male (%)	160 (53.5)	149 (52.7)	11 (68.8)	.318
Age, y	53.4 ± 16.7	52.5 ± 16.6	69.2 ± 9.7	<.001
Onset time, median (IQR)	3 (2, 5)	3 (2, 5)	5 (2.5, 7.75)	.228
ICU (%)	46 (15.4)	31 (11)	15 (93.8)	<.001
Lymphopenia	127 (42.5)	112 (39.6)	15 (93.8)	<.001
Hypoalbuminemia	106 (35.5)	92 (32.5)	14 (87.5)	<.001
Current smoker (%)	48 (16.1)	42 (14.8)	6 (37.5)	.028
Heavy drinking (%)	21 (7.0)	20 (7.1)	1 (6.2)	1
Comorbidity	99 (33.1)	85 (30)	14 (87.5)	<.001
Presence of at least one comorbidity	99 (33.1)	85 (30.0)	14 (87.5)	<.001
Hypertension (%)	74 (24.7)	63 (22.3)	11 (68.8)	<.001
DM (%)	35 (11.7)	31 (11.0)	4 (25.0)	.103
CHD (%)	18 (6)	14 (4.9)	4 (25.0)	.011
CVD (%)	13 (4.3)	11 (3.9)	2 (12.5)	.148
COPD (%)	8 (2.7)	5 (1.8)	3 (18.8)	.006
Cancer (%)	9 (3.0)	5 (1.8)	4 (25.0)	<.001
Trip to Wuhan (%)	113 (37.8)	106 (37.5)	7 (43.8)	.81
Fever (%)	238 (79.6)	224 (79.2)	14 (87.5)	.54
Cough (%)	222 (74.2)	208 (73.5)	14 (87.5)	.376
Sputum (%)	135 (45.2)	125 (44.2)	10 (62.5)	.24
Dyspnea (%)	42 (14)	32 (11.3)	10 (62.5)	<.001
Diarrhea (%)	7 (2.3)	6 (2.1)	1 (6.2)	.322
WBC, $\times 10^9$/L	4.9 ± 2.4	4.8 ± 2.1	7.0 ± 5.2	.111
Neutrophil, $\times 10^9$/L	3.3 ± 2.1	3.2 ± 2	5.6 ± 3.4	.012
Lymphocyte, $\times 10^9$/L	1.2 ± 0.5	1.2 ± 0.5	0.6 ± 0.3	<.001
NLR	3.8 ± 5.8	3.3 ± 4.3	13.3 ± 14.3	.013
Monocyte, $\times 10^9$/L	0.3 ± 0.3	0.3 ± 0.2	0.5 ± 0.9	.501
CRP, mg/L	26.3 ± 34.6	24.7 ± 33.2	53.5 ± 47.7	.03
Procalcitonin, μg/L	0.2 ± 0.6	0.2 ± 0.6	0.3 ± 0.3	.245
ESR, mm/h	35.7 ± 25.9	35.1 ± 25.9	45.3 ± 25.7	.143
FIB, g/L	3.2 ± 1.0	3.2 ± 1	3.2 ± 1.3	.98
D-dimer, mg/L	1.6 ± 5.4	1.3 ± 3.9	6 ± 16.1	.266
Total bilirubin, μmol/L	11.0 ± 6.6	11.0 ± 6.7	11.0 ± 4.6	.993
Albumin, g/L	37.3 ± 6.3	37.6 ± 6.2	30.5 ± 4.0	<.001
LDH, U/L	246.3 ± 178.4	229.1 ± 12-2.5	531.1 ± 487.3	.026
ALT, U/L	27.6 ± 21.6	27.5 ± 21.2	29.4 ± 28.5	.8
AST, U/L	26.1 ± 18.2	25.5 ± 18.2	35.4 ± 16.8	.037
Creatinine, μmol/L	74.6 ± 46.8	74.9 ± 48	70.2 ± 14.8	.326

Note: Continuous variables were expressed as means ± SD or medians with interquartile ranges (IQRs).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cerebrovascular disease; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell count.

TABLE 2 Differences in patient characteristics between hypoalbuminemia and normal albumin group

Variables	Hypoalbuminemia	Normal albumin	*P*
N	106	193	
Male (%)	60 (56.6)	100 (51.8)	.501
Age, y	62.9 ± 13.1	48.2 ± 16.1	<.001
Onset time, median (IQR)	4 (2, 7)	3 (2, 5)	.002
ICU (%)	34 (32.1)	12 (6.2)	<.001
Death (%)	14 (13.2)	2 (1)	<.001
Lymphopenia	60 (56.6)	67 (34.7)	<.001
Current smoker (%)	25 (23.6)	23 (11.9)	.014
Heavy drinking (%)	10 (9.4)	11 (5.7)	.331
Comorbidity			
Presence of at least one comorbidity	55 (51.9)	44 (22.8)	<.001
Hypertension (%)	41 (38.7)	33 (17.1)	<.001
DM (%)	24 (22.6)	11 (5.7)	<.001
CHD (%)	13 (12.3)	5 (2.6)	.002
CVD (%)	10 (9.4)	3 (1.6)	.002
COPD (%)	6 (5.7)	2 (1)	.025
Cancer (%)	8 (7.5)	1 (0.5)	.001
Trip to Wuhan (%)	36 (34)	77 (39.9)	.375
Fever (%)	88 (83)	150 (77.7)	.348
Cough (%)	82 (77.4)	140 (72.5)	.439
Sputum (%)	60 (56.6)	75 (38.9)	.005
Dyspnea (%)	27 (25.5)	15 (7.8)	<.001
Diarrhea (%)	3 (2.8)	4 (2.1)	.702
WBC, $\times 10^9$/L	5.6 ± 3.3	4.5 ± 1.7	.003
Neutrophil, $\times 10^9$/L	4.1 ± 3	2.9 ± 1.4	<.001
Lymphocyte, $\times 10^9$/L	1 ± 0.5	1.3 ± 0.5	<.001
NLR	6.2 ± 9	2.5 ± 1.5	<.001
Monocyte, $\times 10^9$/L	0.4 ± 0.4	0.3 ± 0.2	.753
CRP, mg/L	43.9 ± 45.3	16.5 ± 21.7	<.001
Procalcitonin, μg/L	0.3 ± 1	0.1 ± 0.2	.019
ESR, mm/h	51.3 ± 27.9	26.9 ± 20	<.001
FIB, g/L	3.6 ± 1.1	3 ± 0.9	<.001
D-dimer, mg/L	3.1 ± 8.9	0.7 ± 1.2	.01
Total bilirubin, μmol/L	11.3 ± 7.6	10.8 ± 6	.556
Albumin, g/L	31.1 ± 3.8	40.6 ± 4.7	<.001
LDH, U/L	315.5 ± 269.6	209.1 ± 78.4	<.001
ALT, U/L	27.9 ± 20.7	27.5 ± 22.1	.877
AST, U/L	30.1 ± 24.5	23.9 ± 13.3	.018
Creatinine, μmol/L	81.3 ± 62.6	71 ± 35.2	.126

Note: Continuous variables were expressed as means ± SD or medians with interquartile ranges (IQRs).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cerebrovascular disease; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell count.

3.2 | Comparison of baseline characteristics between survivors and non-survivors

Table 1 illustrates the baseline values of variables in the whole population and the statistical comparison between survivors and non-survivors. Compared with survivors, non-survivors were older, had a higher prevalence of comorbidities and were more likely to have dyspnea and required moreICU management. The laboratory examination revealed higher levels of neutrophil, CRP, and LDH, while a lower level of lymphocyte in non-survivors ($P < .05$). Specifically, the liver function tests showed comparable aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, which were both statistically and clinically insignificant. However, the difference in albumin between the survival group and the non-survivor group was considerable (37.6 ± 6.2 vs 30.5 ± 4.0 $P < .001$). Gender, alcohol consumption, the time difference from the onset of symptom to admission (onset time), epidemiology history, and other symptoms were not significantly different between the two groups ($P > .05$, no significance).

3.3 | Comparison characteristics of the patient with hypoalbuminemia and normal albumin groups

Table 2 illustrates the differences in the studied parameters between the hypoalbuminemia and the normal albumin group. Patients with hypoalbuminemia tended to be older, had longer onset time, and frequently required ICU management. In addition, patients with hypoalbuminemia had a higher mortality rate of 13.2% vs 1% in normal albumin group ($P < .001$). The frequencies of lymphopenia, smoking status, comorbidities, increased phlegm/sputum production, and dyspnea were higher in the hypoalbuminemia group. As for the laboratory indicators, higher levels of inflammatory biomarkers (including WBC, neutrophil, NLR, CRP, ESR and procalcitonin), d-dimer, fibrinogen, LDH, and AST were found ($P < .05$) in hypoalbuminemia group. The other variables including gender, alcohol consumption, onset time, epidemiological history, fever and/or cough at presentation, serum creatinine, and other liver function tests were not statistically different between the two groups ($P > .05$, no significance).

3.4 | Correlation analysis of serum albumin with inflammatory indicators

Pearson correlation analysis was used to explore the relationship between albumin and inflammatory indicators. Albumin level was inversely correlated with WBC ($r = -.149$, $P = .01$), NLR ($r = -.298$, $P < .001$), CRP ($r = -.345$, $P < .001$), and PCT ($r = -.162$, $P = 007$). Pearson linear correlation analysis scatter plot is shown in Figure 1.

3.5 | Univariate and multivariate analysis for death outcome

To explore the risk factors of death, univariate and multivariate logistics regression was conducted. Univariate analysis revealed age, comorbidity, lymphopenia, and hypoalbuminemia as risk factors for death. However, in multivariate analysis, only the presence of at least one comorbidity (OR, 6.816; 95% CI, 1.361-34.133), lymphopenia (OR, 13.130; 95% CI, 1.632-105.658), and hypoalbuminemia (OR, 6.394; 95% CI, 1.315-31.092) were found to be independent predictors of death (Table 3).

4 | DISCUSSION

The most important finding of our study is that there is an inverse relationship between the level of albumin and the risk of death in

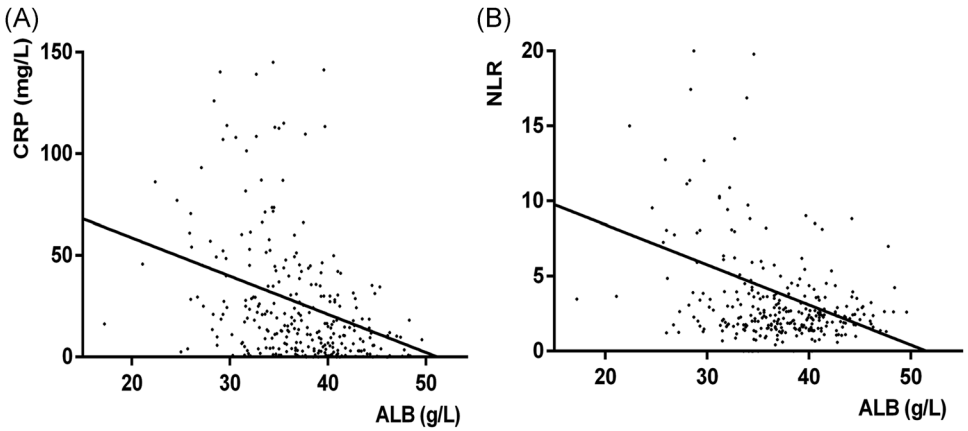

FIGURE 1 Pearson linear correlation analysis scatter plot is shown. A indicated that the level of albumin and CRP were positively correlated; B indicated that the levels of albumin and NLR were positively correlated

TABLE 3 Univariate and multivariate analysis of factors for risk of death (non-survivors)

	Univariate analysis			Multivariate analysis		
Variables	Adjusted OR	95%CI	*P*	Adjusted OR	95%CI	*P*
Male	1.979	0.67-5.841	0.217	1.245	0.358-4.334	0.731
Age	1.080	1.036-1.126	<0.001	1.026	0.972-1.083	0.353
Presence of at least one comorbidity	16.306	3.627-73.315	<0.001	6.816	1.361-34.133	0.020
Lymphopenia	22.902	2.983-175.815	0.003	13.130	1.632-105.658	0.016
Hypoalbuminemia	14.533	3.235-65.282	<0.001	6.394	1.315-31.092	0.021

COVID-19 patients. This retrospective study revealed that serum albumin level <35 g/L at presentation independently increased the risk of death in COVID-19 by at least 6-fold.

Hypoalbuminemia in severe COVID-19 has been repeatedly addressed in the literature,[6,12,19-22] but the predictive value of albumin has never been explored. In this study, we found that lower albumin levels on admission can predict the outcome of COVID-19 independent of other known indicators such as lymphocyte count or comorbidities.[3] This result is consistent with a previous study reporting hypoalbuminemia or decline of albumin, which is associated with the severity of ARDS[23] or acute kidney injury.[24] A meta-analysis showed that about 80.4% of patients with abnormal liver function in COVID-19 had hypoalbuminemia, which was associated with prognosis and outcome.[25]

The mechanisms for hypoalbuminemia in COVID-19 have not been thoroughly studied or explained. Albumin is synthesized in the liver with a serum half-life of approximately 21 days.[26] Although ALT and AST slightly increased in COVID-19 patients, they were not of predictive value for the outcome. However, hypoalbuminemia was seen predominantly in severe COVID-19 cases compared with mild cases in a previous study[12] and the present study. This phenomenon cannot be explained by liver dysfunction secondary to hepatocellular dysfunction alone. Additionally, the median time from the onset of illness to admission was only 3 days, far shorter than the half-life of serum albumin, suggesting that hypoalbuminemia was less likely to be a result of decreased albumin synthesis in severe COVID-19.

In this study, a significant correlation was found between albumin level and inflammatory indicators (CRP, WBC, and NLR). Systemic inflammation is common in severe COVID-19.[13] Inflammation has been shown to cause the escape of serum albumin into interstitial space due to increased capillary permeability, and eventually lead to increased volume distribution of albumin.[14] Thus, our study strongly implies that hypoalbuminemia might due to the systemic inflammation in COVID-19.

Therapeutic efficacy of albumin in sepsis and cirrhosis demonstrates that it can act through a modulatory effect on inflammation and oxidative stress in addition to the plasma volume expansion.[14,27,28] Albumin treatment has been shown to improve oxygenation in ARDS by a meta-analysis.[29] As there is no specific treatment for the systemic inflammation in COVID-19 until now, an albumin treatment with low side-effect could be a potential approach. However, the efficacy and safety of albumin in COVID-19 requires to be verified in prospective studies as the majority of severe COVID-19 is elderly with cardiovascular comorbidities.

Our study should be interpreted in light of some limitations. We have reported a single-center experience and data in this retrospective study; however, the baseline factors in our study is consistent with the presently available literature and the single-center experience may not be a limitation. 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 mortality remains unknown. Also, at our center albumin therapy for the management of COVID-19 has not been used, prospective trials/studies with albumin treatment may answer the question.

In conclusion, hypoalbuminemia defined as a serum albumin level of less than 35 g/L, is associated with the outcome of COVID-19. The potential therapeutic value of albumin in COVID-19 needs urgent further evaluation.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JH and SL designed the study and drafted the manuscript. YF, GC, and AC acquisited and did the statistical analysis. RK and AC made a critical revision. YZ and SL did the study supervision.

ETHICS STATEMENT

Ethical approval for the study was obtained from the ethics committee of The Third People's Hospital of Yichang. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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