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LETTER TO THE EDITOR

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Dynamic change of serum albumin level can predict the prognosis of COVID-19 patients with hypoalbuminemia

Hypoalbuminemia usually predicts higher mortality, longer hospital stay, and more frequent readmission.[1] About 40%–60% of coronavirus disease (COVID-19) patients develop hypoalbuminemia at admission.[2,3] This may be due to an increase of capillary permeability caused by a systemic inflammatory response,[4] which leads to the leakage of serum albumin (ALB) into interstitial space,[5] poor nutritional status, and impaired liver function.[1] COVID-19 patients with hypoalbuminemia are more severe and/or critical,[2] and have a higher probability of intensive care unit admission and higher risk of death.[6,7] However, few studies have evaluated the dynamic change of serum ALB level in COVID-19 patients with hypoalbuminemia on the patients' death.

We retrospectively analyzed the electronic medical records of 3041 patients who were diagnosed with COVID-19 at the Huoshenshan Hospital in Wuhan from February 2020 to April 2020. The inclusion criteria were as follows: (1) COVID-19 patients had a serum ALB level of <35 g/L at admission and/or during hospitalization; and (2) serum ALB level was retested. The exclusion criteria were as follows: (1) COVID-19 patients had pre-existing hepatobiliary diseases, such as chronic liver disease, liver cirrhosis, liver cancer, and bile duct obstruction; and (2) COVID-19 patients did not measure serum ALB level at admission and during hospitalization. This study was approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command [No. Y (2021) 017] and was performed in accordance with the Declaration of Helsinki.

The severity of COVID-19 patients was classified into mild, moderate, severe, and critical according to the New Coronavirus Pneumonia Prevention and Control Program published by the National Health Commission of China.[8] The reference range of serum ALB level is 40–55 g/L at this hospital. Hypoalbuminemia is defined as a serum ALB level of <35 g/L.[9] Baseline serum ALB level refers to serum ALB level obtained when hypoalbuminemia was found for the first time at admission or during hospitalization. In the human ALB infusion group, ΔALB is defined as serum ALB level obtained on the first retest after human ALB infusion minus baseline serum ALB level; in the nonhuman ALB infusion group, ΔALB is defined as serum ALB level obtained on the second test after hospitalization minus baseline serum ALB level.

Continuous variables were described using mean ± standard deviations and compared by the Mann–Whitney *U* test or the Student *t*-test. Categorical variables were described using percentages and compared by the χ^2 test. Univariate and multivariate logistic regression analyses were conducted to explore the predictors of death in COVID-19 patients. The receiver operating curve (ROC) analysis was used to explore the predictive performance of ΔALB for death. Data analysis was performed using SPSS version 20.0 (IBM Corp) and MedCalc version 11.4.2.0 (MedCalc Software). A two-tailed $p < 0.05$ was considered to be statistically significant.

A total of 535 COVID-19 patients with hypoalbuminemia were included in the present study. There were 297 (55.50%) males, and the median age was 67 years. Among them, 163 (30.50%) patients received human ALB infusion, and 40 (7.50%) died.

Patients who died had a significantly lower ΔALB (0.90 vs. 2.60, $p < 0.001$) than those who survived (Table 1). Univariate analysis also demonstrated that a lower ΔALB could significantly predict a higher risk of death in COVID-19 patients (odds ratio [OR] = 0.812, 95% confidence interval [CI] = 0.720–0.916, $p = 0.001$). After adjusting age, sex, severe/critical COVID-19, and human ALB infusion, ΔALB was an independent predictor of death (OR = 0.786, 95% CI = 0.692–0.892, $p < 0.001$). ROC analysis showed that ΔALB could significantly predict death in COVID-19 patients (AUC = 0.689, cut-off value = 1.1, $p = 0.001$). Patients with ΔALB ≤ 1.1 g/L had a significantly higher mortality than those with ΔALB > 1.1 g/L (14.50% vs. 4.50%, $p < 0.001$).

In the subgroup analysis of patients who received human ALB infusion, patients who died had a significantly lower ΔALB (1.05 vs. 3.70, $p < 0.001$) than those who survived. The univariate analysis also demonstrated that a lower ΔALB could significantly predict a higher risk of death in COVID-19 patients (OR = 0.807, 95% CI = 0.710–0.917, $p = 0.001$). After adjusting age, sex, and severe/critical COVID-19, ΔALB was an independent predictor of death (OR = 0.808, 95% CI = 0.709–0.920, $p = 0.001$). ROC analysis showed that ΔALB could significantly predict death in COVID-19 patients (AUC = 0.733, cut-off value = 3.3, $p < 0.001$). Patients with ΔALB ≤ 3.3 g/L had a significantly higher mortality than those with ΔALB > 3.3 g/L (34.50% vs. 7.90%, $p < 0.001$).

In the subgroup analysis of patients who did not receive human ALB infusion, patients who died had a significantly lower ΔALB (−1.05 vs. 2.30, $p = 0.006$) than those who survived. Univariate analysis also demonstrated that a lower ΔALB could significantly predict a higher risk of death in COVID-19 patients (OR = 0.626, 95% CI = 0.447–0.877, $p = 0.006$). However, after adjusting age, sex, and severe/critical COVID-19, ΔALB was not an independent predictor of death (OR = 0.618, 95% CI = 0.375–1.017, $p = 0.058$). ROC analysis showed that ΔALB could significantly predict death in COVID-19 patients (AUC = 0.901, cut-off value = 0.9, $p < 0.001$). Patients with ΔALB ≤ 0.9 g/L had a significantly higher mortality than those with ΔALB > 0.9 g/L (3.90% vs. 0.00%, $p = 0.007$).

TABLE 1 Differences in patient characteristics between survivor group and non-survivor group

Variables	Overall		Survivors		Non-survivors		*p* Value
	No. pts	Median (range) or frequency (percentage) Mean ± SD	No. pts	Median (range) or frequency (percentage) Mean ± SD	No. pts	Median (range) or Frequency (percentage) Mean ± SD	
ΔALB (g/L)	535	2.40 (−7.90–15.90) 2.66 ± 2.93	495	2.60 (−7.90–14.60) 2.78 ± 2.76	40	0.90 (−7.50–15.90) 1.17 ± 4.29	***<0.001***
Age (years)	535	67.00 (24.00–100.00) 66.74 ± 12.10	495	67.00 (24.00–100.00) 66.41 ± 12.01	40	70.00 (25.00–93.00) 70.82 ± 12.65	***0.027***
Sex (male) (%)	535	297 (55.50%)	495	271 (54.70%)	40	26 (65.00%)	0.209
Severe/critical COVID-19 (%)	535	264 (49.30%)	495	228 (46.10%)	40	36 (90.00%)	***<0.001***
Laboratory tests							
TBIL (μmol/L)	535	9.80 (2.10–112.20) 11.08 ± 6.96	495	9.70 (2.10–112.20) 10.95 ± 7.00	40	11.55 (3.40–31.50) 12.75 ± 6.30	***0.030***
ALT (μmol/L)	535	27.90 (1.70–602.40) 44.25 ± 50.51	495	28.50 (1.70–285.80) 43.31 ± 42.66	40	25.25 (4.20–602.40) 55.85 ± 108.31	0.404
CRP (mg/L)	290	19.43 (0.04–257.77) 41.25 ± 48.04	272	17.34 (0.04–257.77) 38.72 ± 46.71	18	69.69 (8.36–191.09) 79.49 ± 52.95	***<0.001***
Procalcitonin (ng/ml)	156	0.08 (0.02–14.38) 0.43 ± 1.74	146	0.08 (0.02–14.38) 0.35 ± 1.56	10	0.50 (0.13–11.16) 1.59 ± 3.38	0.059
Interleukin-6 (pg/ml)	78	14.53 (0.00–365.50) 38.56 ± 69.75	75	13.83 (0.00–365.50) 37.42 ± 70.66	3	65.28 (31.89–104.10) 67.09 ± 36.13	0.692
Hb (g/L)	340	114.50 (42.00–318.00) 114.03 ± 22.76	315	114.00 (67.00–318.00) 114.07 ± 22.53	25	117.00 (42.00–150.00) 113.48 ± 26.02	***<0.001***
WBC (10^9/L)	342	6.10 (2.20–49.30) 7.08 ± 4.37	317	6.00 (2.20–26.50) 6.66 ± 3.06	25	8.80 (3.40–49.30) 12.47 ± 10.72	***<0.001***
Neutrophil count (10^9/L)	342	4.35 (1.32–57.20) 5.56 ± 4.99	317	4.28 (1.32–57.20) 5.12 ± 4.01	25	8.09 (3.04–46.78) 11.17 ± 10.33	***<0.001***
PLT (10^9/L)	341	232.00 (16.00–589.00) 232.98 ± 109.99	316	234.00 (44.00–589.00) 237.61 ± 92.91	25	163.00 (16.00–426.00) 174.48 ± 112.63	***0.004***
INR	237	1.11 (0.91–3.59) 1.14 ± 0.21	221	1.10 (0.91–3.59) 1.13 ± 0.20	16	1.19 (0.91–2.10) 1.27 ± 0.30	***0.007***
D-dimer (mg/L)	237	1.08 (0.10–40.00) 2.48 ± 4.05	220	1.02 (0.10–40.00) 2.44 ± 4.15	17	2.47 (0.49–7.92) 3.04 ± 2.37	***0.015***
PT (s)	237	13.36 (10.23–43.09) 13.74 ± 2.64	221	13.31 (10.23–43.09) 13.64 ± 2.53	16	14.23 (10.95–25.15) 15.06 ± 3.72	***0.039***
APTT (s)	237	28.10 (14.79–200.00) 29.74 ± 13.36	221	28.04 (14.79–115.78) 28.67 ± 7.14	16	30.19 (23.86–200.00) 44.52 ± 42.54	***0.008***

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; CRP, C-reactive protein; Hb, Hemoglobin; INR, international normalized ratio; PLT, platelet count; PT, prothrombin time; Pts, patients; TBIL, total bilirubin; WBC, white blood cell.

In conclusion, a reduction of serum ALB level seems to be a predictor for the death of COVID-19 patients with hypoalbuminemia, regardless of human ALB infusion. This can be explained by the possibility that reduced serum ALB levels can reflect a deterioration in liver dysfunction and malnutrition, which will further lead to worse outcomes.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Xingshun Qi. *Methodology*: Ruirui Feng, Bing Wang, Zhuang Ma, Hui Lu, and Xingshun Qi. *Validation*: Ruirui Feng, Bing Wang, Zhuang Ma, Hui Lu, and Xingshun Qi. *Formal analysis*: Ruirui Feng, Bing Wang, Zhuang Ma, Hui Lu, and Xingshun Qi. *Investigation*: Ruirui Feng, Bing Wang, Zhuang Ma, Hui Lu, and Xingshun Qi. *Data curation*: Ruirui Feng, Bing Wang, Zhuang Ma, Hui Lu, and Xingshun Qi. *Writing–original draft*: Ruirui Feng and Xingshun Qi. *Writing–review and editing*: Ruirui Feng, Bing Wang, Zhuang Ma, Xiaozhong Guo, Hongyu Li, Yufu Tang, Hao Meng, Hao Yu, Chengfei Peng, Guiyang Chu, Xinwei Wang, Yue Teng, Quanyu Zhang, Tianyi Zhu, Zhenhua Tong, Haitao Zhao, Hui Lu, and Xingshun Qi. *Supervision*: Hui Lu and Xingshun Qi. All authors have made an intellectual contribution to the manuscript and approved the submission.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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KEYWORDS

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Abbreviations: ALB, albumin; COVID-19, coronavirus disease.

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