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# Decreased prealbumin level is associated with increased risk for mortality in elderly hospitalized patients with COVID-19

Peiyuan Zuo M.D., Ph.D. [a], Song Tong M.D., Ph.D. [b], Qi Yan M.D., Ph.D. [a], Ling Cheng M.D., Ph.D. [a], Yuanyuan Li M.D., Ph.D. [a], Kaixin Song M.Sc. [a], Yuting Chen M.Sc. [a], Yue Dai M.Sc. [a], Hongyu Gao M.D., Ph.D. [a,†], Cuntai Zhang M.D., Ph.D. [a,*]

[a] Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[b] Department of Thoracic Surgery, Union Hospital, Tongji Medical College Huazhong University of Science and Technology, Wuhan, China

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ABSTRACT

*Objectives:* High-risk patients ≥65 y of age with coronavirus disease 2019 (COVID-19) tended to have lower serum prealbumin concentrations. The aim of this study was to investigate the association of prealbumin at baseline on COVID-19–related mortality in elderly patients (≥65 y of age).

*Methods:* We non-selectively and consecutively collected participants from Tongji Hospital in Wuhan from January 17 to February 17, 2020. Univariate and multivariate logistic regression models were employed to evaluate the correlation between prealbumin and in-hospital outcomes (in-hospital mortality, admission to the intensive care unit [ICU], and mechanical ventilation) in elderly patients with COVID-19. Linear trend was performed by entering the median value of each category of prealbumin tertile as a continuous variable and was visually confirmed by using generalized additive models. Interaction and stratified analyses were conducted as well.

*Results:* We included 446 elderly patients with COVID-19 in the final analyses. In-hospital mortality was 14.79%. Of the 446 patients, 15.47% were admitted to the ICU and 21.3% required mechanical ventilation. Compared with patients in the highest tertile, the prealbumin of patients in the lowest tertile had a 19.09-fold higher risk for death [odds ratio (OR), 20.09; 95% confidence interval (CI), 3.62–111.64; $P = 0.0006$], 25.39-fold higher risk for ICU admission (OR, 26.39; 95% CI, 4.04–172.39; $P = 0.0006$), and 1.8-fold higher risk for mechanical ventilation (OR, 2.8; 95% CI, 1.15–6.78; $P = 0.0227$) after adjustment for potential confounders. There was a linear trend correlation between serum prealbumin concentration and risk for in-hospital mortality, ICU admission, and mechanical ventilation in elderly patients with COVID-19 infection.

*Conclusion:* Prealbumin is an independent risk factor of in-hospital mortality for elderly patients with COVID-19. Assessment of prealbumin may help identify high-risk individuals ≥65 y of age with COVID-19.



## Introduction

The coronavirus disease 2019 (COVID-19) epidemic is caused by an infection with a novel coronavirus, officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The infection spread rapidly on all continents and was declared a pandemic by the World Health Organization. As of July 31, 2020, there were 17,459,041 documented cases reported worldwide, and 673,321 patients had died. As there are currently no specific treatments and medications against the new virus, it is crucial to identify risk factors for severe prognosis.

Older patients have poorer prognostic factors and are more likely to experience critical disease [2,3]. Based on recent statistical data of China, among patients who ≥65 y of age, the mortality rate was 34.5%, which was significantly higher than that of younger patients at 4.7% [4]. The proportion of deaths in patients >60 y of age accounts for 81% of the total deaths in nationwide, which indicates that this population is more vulnerable to SARS-CoV-2 [5].

PZ and ST contributed to the study equally. ZP was responsible for the conceptualization, methodology, writing of the original draft, and visualization. TS was responsible for the conceptualization, software, validation, and writing of the original draft. YQ was responsible for the investigation, resources, and data curation.CL, LY, SK, CY, and DY were responsible for the investigation and data curation. GH was responsible for the review and editing of the manuscript and supervision of the study. ZC was responsible for the supervision and project administration of the study.

*Corresponding authors. Tel.: +86 027 63639709; fax: +86 027 63639709
†Joint corresponding authors
*E-mail addresses:* hygao@tjh.tjmu.edu.cn (H. Gao), ctzhang0425@163.com (C. Zhang).

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Until now, there have only been rare reports in the literature focusing on risk factors for poor outcomes in patients ≥65 y of age with COVID-19.

Levels of serum prealbumin, known as transthyretin, may be lowered by malnutrition, as well as by inflammation and aging [6,7]. Compared with albumin, prealbumin has a shorter half-life, a more rapid rate of hepatic synthesis, and a predictable catabolic rate; hence, it may be a more sensitive indicator [8]. However, whether prealbumin could be an independent predictor of mortality in hospitalized elderly patients with COVID- needs to be further elucidated.

The present study aimed to describe the clinical characteristics and to investigate whether prealbumin can serve as a valuable predictor of in-hospital mortality, which might provide evidence for risk stratification in individuals ≥65 y of age and help to improve clinical practice and reduce fatality.

## Methods

### *Study design and participants*

This was a retrospective cohort study. The elderly patients with COVID-19 who were admitted to Tongji Hospital in Wuhan from January 17 to February 17, 2020 were consecutively included. This study was approved by the Medical Ethics Committee of Tongji Hospital, and complied with the Declaration of Helsinki. The data were anonymous and the study was observational, so the informed consent was not gathered. A flowchart illustrating patient selection is provided in Figure 1. Inclusion criteria included patients ≥65 y of age diagnosed with COVID-19 infection. In all, 893 participants were included; however, patients with missing baseline or outcome data, those who died on admission or who were transferred to other designated hospitals during hospitalization were excluded. Thus, 446 patients were included in the final analyses.

### *Data collection*

Data collection was performed using the hospital's electronic medical records system. Information included patients' medical history; demographic data; physical examination; and hematologic, biochemical, radiological, and microbiologic evaluation results. Data collection forms were reviewed independently by CL and LYY. Blood examinations were assessed at the central laboratory of Tongji Hospital following standard operating procedures. Routine blood tests were analyzed using Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan). The Cobas C8000 (Roche, Mannheim, Germany) was used to measure the biochemical parameters. Coagulation tests were detected by STA-R MAX coagulation analyzer (Diagnostica Stago, Saint-Denis, France). Throat swab samples were collected and tested for SARS-CoV-2 with commercial real-time reverse transcription polymerase chain reaction (RT-PCR) kit from DAAN GENE (Guangzhou, China) [9]. The diagnostic criteria and all clinical procedures in this study followed the Diagnosis and Treatment of Pneumonia Caused by New Coronavirus (Trial version 1 to 7) promulgated by the National Health and Health Commission of China.

### *Statistical analysis*

Summary statistics of baseline characteristics of all patients and stratification by prealbumin tertiles were expressed as frequency and proportion for categorical variables, mean ± SD (Gaussian distribution) or median (range; skewed distribution) for continuous variables, and as percentages for categorical variables. The differences between groups were analyzed using the $\chi^2$ (categorical variables), one-way analysis of variance test (normal distribution), or Kruskal–Wallis H test (skewed distribution).

We examined the relationship of the prealbumin as categorized into tertiles with the outcomes of all-cause death, admission to the intensive care unit (ICU), and mechanical ventilation. Univariate and multivariate logistic regression models were used to evaluate these relationships; unadjusted and adjusted odds ratio (ORs) and 95% confidence intervals (CIs) were calculated. Model 1 is a minimally adjusted model with only sociodemographic variables adjusted. Model 2 is a fully adjusted model with covariates including age; sex; smoking status; history of hypertension (HTN), coronary artery disease (CAD), diabetes, chronic kidney disease (CKD), carcinoma, and chronic liver disease; neutrophil and lymphocyte counts; prothrombin time (PTT) and activated partial thromboplastin time (aPTT); D-dimer; alanine transaminase (ALT) and aspartate aminotransferase (AST); total bilirubin; blood urea nitrogen (BUN); creatinine, C-reactive protein (CRP); and neutrophil-to-lymphocyte ratio. We calculated ORs and 95% CIs. The highest tertile was the reference for prealbumin. We performed tests for linear trend by entering the median value of each category of prealbumin tertile as a continuous variable to examine the possibility of nonlinearity.

To ensure the robustness of the results, we performed stratified analyses with the prealbumin as a continuous variable for the overall population and stratified by sex, age, HTN status, and CAD status at baseline. Generalized additive models were used to visually confirm the relationship between prealbumin as a continuous variable and the risk for outcomes (all-cause death, ICU admission, and mechanical ventilation).

Modeling was performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www. empowerstats.com, X&Y Solutions, Inc, Boston, MA). $P < 0.05$ (two-sided) was considered statistically significant.

### *Addressing missing data*

We excluded 447 cases from the present study. We performed a sensitivity analysis to avoid selection bias due to missing data. The results demonstrated that there was no statistical difference between missing and non-missing groups (Supplementary Table 1).

## Results

Of 446 elderly inpatients included in the final analysis, the mean age was 72.95 y (6.39), ranging from 65 to 95 y, and most patients were men (Table 1). The baseline characteristics of these included participants are listed in Table 1. The day of sample drawing after admission was 0.67 ± 0.65 d. No significant statistical difference in sex, smoking status, body weight, body mass index,

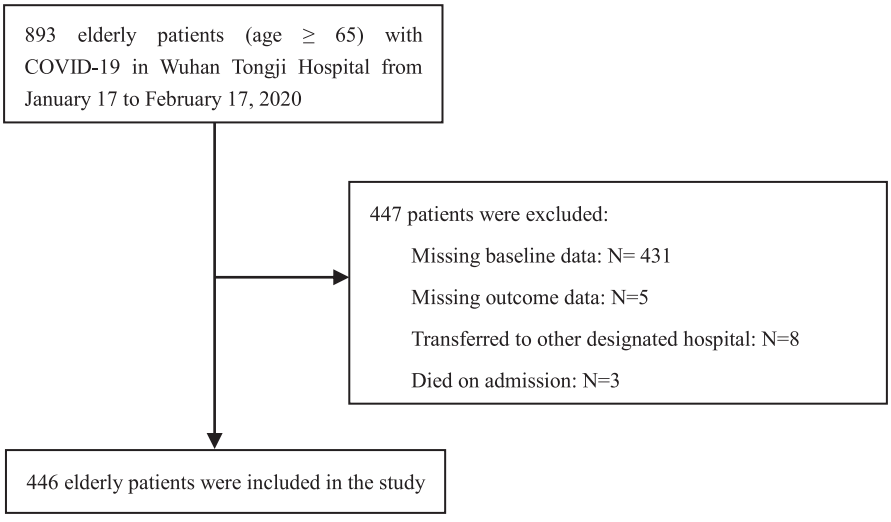


**Fig. 1.** Study population.

**Table 1**
Baseline characteristics in elderly patients with COVID-19 infection and all-cause death during hospital according to the tertiles of prealbumin (N = 446)

| Variable | Tertile 1 (n = 148) | Tertile 2 (n = 148) | Tertile 3 (n = 150) | *P*-value |
|---|---|---|---|---|
| Prealbumin, mg/L | 96.34 ± 19.95 | 184.57 ± 27.17 | 270.45 ± 36.75 | <0.001 |
| Age, y | 74.43 ± 6.67 | 73.61 ± 6.51 | 70.84 ± 5.38 | <0.001 |
| Sex | | | | 0.266 |
| Men | 82 (55.41%) | 80 (54.05%) | 70 (46.67%) | |
| Women | 66 (44.59%) | 68 (45.95%) | 80 (53.33%) | |
| Smoking | 7 (4.73%) | 12 (8.11%) | 10 (6.67%) | 0.497 |
| Body weight, kg | 63 ± 9.51 | 63.12 ± 9.82 | 64.10 ± 7.20 | 0.846 |
| BMI (kg/m$^2$) | 23.16 ± 2.97 | 23.34 ± 3.95 | 24.04 ± 2.72 | 0.416 |
| Hypertension | 80 (54.05%) | 82 (55.41%) | 89 (59.33%) | 0.634 |
| Diabetes | 34 (22.97%) | 28 (18.92%) | 47 (31.33%) | 0.039 |
| CAD | 30 (20.27%) | 27 (18.24%) | 34 (22.67%) | 0.638 |
| CKD | 8 (5.41%) | 2 (1.35%) | 3 (2.00%) | 0.079 |
| CVD | 11 (7.43%) | 5 (3.38%) | 8 (5.33%) | 0.303 |
| Carcinoma | 7 (4.76%) | 6 (4.05%) | 7 (4.67%) | 0.950 |
| Chronic liver disease | 3 (2.03%) | 3 (2.03%) | 1 (0.67%) | 0.551 |
| Fever | 122 (82.99%) | 118 (79.73%) | 111 (74.00%) | 0.157 |
| Cough | 102 (69.39%) | 111 (75.00%) | 109 (72.67%) | 0.557 |
| Myalgia/Fatigue | 60 (40.82%) | 51 (34.46%) | 59 (39.33%) | 0.500 |
| Headache | 9 (6.12%) | 8 (5.41%) | 12 (8.00%) | 0.644 |
| Diarrhea | 29 (19.73%) | 28 (18.92%) | 33 (22.00%) | 0.790 |
| Vomiting | 12 (8.16%) | 4 (2.70%) | 8 (5.33%) | 0.116 |
| Dyspnea | 74 (50.34%) | 47 (31.97%) | 58 (38.67%) | 0.005 |
| White blood cells, 10$^9$/L | 7.65 ± 4.48 | 6.76 ± 3.14 | 6.49 ± 2.26 | 0.009 |
| Neutrophil, 10$^9$/L | 6.30 ± 4.41 | 5.09 ± 3.11 | 4.66 ± 2.12 | <0.001 |
| Lymphocyte, 10$^9$/L | 0.82 ± 0.44 | 1.06 ± 0.51 | 1.21 ± 0.54 | <0.001 |
| Platelet, 10$^9$/L | 188.89 ± 86.85 | 246.23 ± 102.18 | 273.98 ± 103.38 | <0.001 |
| Hemoglobin, G/L | 125.22 ± 17.17 | 123.63 ± 15.96 | 124.17 ± 16.57 | 0.702 |
| PT, sec | 15.48 ± 7.72 | 14.16 ± 1.00 | 14.00 ± 1.76 | 0.011 |
| aPTT, % | 42.44 ± 11.15 | 39.78 ± 5.01 | 38.94 ± 6.09 | <0.001 |
| D-dimer, ng/mL | 2.52 ± 4.21 | 1.80 ± 2.86 | 1.59 ± 2.02 | 0.050 |
| Albumin, g/L | 31.71 ± 4.23 | 33.75 ± 4.52 | 34.90 ± 4.31 | <0.001 |
| ALT, U/L | 42.29 ± 69.89 | 27.86 ± 23.42 | 28.45 ± 17.90 | 0.006 |
| AST, U/L | 53.15 ± 75.33 | 33.76 ± 22.43 | 29.44 ± 18.63 | <0.001 |
| Total bilirubin, mmol/L | 13.71 ± 8.76 | 10.84 ± 5.85 | 9.81 ± 4.85 | <0.001 |
| BUN, mmol/L | 7.90 ± 5.29 | 6.55 ± 5.45 | 6.47 ± 5.35 | 0.037 |
| Creatinine, μmol/L | 97.82 ± 75.08 | 95.83 ± 124.73 | 98.15 ± 121.68 | 0.981 |
| Hs-cTnI, pg/mL | 554.00 ± 2557.01 | 288.56 ± 1421.97 | 20.24 ± 52.45 | 0.046 |
| CRP, mg/L | 88.57 ± 65.21 | 52.22 ± 59.81 | 31.90 ± 49.80 | <0.001 |
| Procalcitonin, ng/mL | 0.74 ± 2.52 | 0.36 ± 1.69 | 0.12 ± 0.34 | 0.014 |
| Serum ferritin, μg/L | 1305.63 ± 2840.63 | 776.31 ± 535.22 | 806.51 ± 1451.37 | 0.132 |
| Ground-glass opacity | 28 (27.72%) | 28 (20.14%) | 40 (26.67%) | 0.307 |
| Bilateral pulmonary infiltration | 87 (87.00%) | 117 (84.17%) | 123 (82.55%) | 0.639 |
| Consolidation | 21 (21.21%) | 28 (20.44%) | 13 (8.72%) | 0.007 |
| All-cause death | 52 (35.14%) | 11 (7.43%) | 3 (2.01%) | <0.001 |
| ICU admission | 55 (37.16%) | 9 (6.08%) | 5 (3.33%) | <0.001 |
| mechanical ventilation | 63 (42.57%) | 20 (13.51%) | 12 (8.05%) | <0.001 |

ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cerebral vascular disease; Hs-cTnI, high-sensitive cardiac troponin I; ICU, intensive care unit; PT, prothrombin time.
Data are mean ± SD, median (interquartile range), or percentage

comorbidity (HTN, CAD, CKD, cerebral vascular disease, carcinoma, chronic liver disease), symptoms (fever, cough, headache, diarrhea, and myalgia/fatigue at admission) were detected across the different groups of prealbumin (tertile). When compared with patients in the highest tertile, those in the lowest tertile were older, more likely to have diabetes, with a higher neutrophil count, lower lymphocyte count, and worse coagulation and liver function. Ninety-five 95 patients (21.3%) required mechanical ventilation, 69 (15.47%) were admitted to the ICU, and 66 (14.79%) died during hospitalization. The incidence of all-cause death, ICU admission, and mechanical ventilation were significantly decreased across prealbumin tertiles (all-cause death: 35.14 versus 7.43 versus 2.01% for tertile 1 versus tertile 2 versus tertile 3; ICU admission: 37.16 versus 6.08 versus 3.33% for tertile 1 versus tertile 2 versus tertile 3; mechanical ventilation: 42.57 versus 13.15 versus 8.05% for tertile 1 versus tertile 2 versus tertile 3, respectively).

To investigate the correlation between prealbumin and in-hospital outcomes, we constructed three models using univariate and multivariate logistic regression models (Table 2). In the unadjusted model, the ORs of all-cause death, ICU admission, and mechanical ventilation was significantly increased as the prealbumin tertiles downgraded. The OR for tertile 1 was significantly higher than for tertile 3 (OR, 26.36; 95% CI, 8.00−86.81; $P$ <0.0001 for all-cause death; OR, 17.15; 95% CI, 6.62−44.43; $P$ <0.0001 for ICU admission; OR, 8.46; 95% CI, 4.31−16.6; $P$ <0.0001 for mechanical ventilation). Additional adjustments for the demographic variables and comorbidities did not reduce the ORs for the association between prealbumin tertiles and in-hospital outcomes. Further adjusting for the baseline levels of blood examinations, including blood routine (neutrophil and lymphocyte counts and neutrophil-to-lymphocyte ratio), coagulation function (PTT, aPTT, and D-dimer), liver function (ALT, AST, total bilirubin), renal function (BUN, creatinine) and infection indicators (CRP) did not affect the relationships in the fully adjusted models (OR, 20.09; 95% CI, 3.62−111.64; $P$ = 0.0006 for all-cause death; OR, 26.39; 95% CI, 4.04−172.39; $P$ = 0.0006 for ICU admission; OR, 2.8; 95% CI, 1.15−6.78; $P$ = 0.0227 for mechanical ventilation). Therefore, the lower tertile of

**Table 2**
Risk association between baseline prealbumin and outcomes

| | Unadjusted OR (95% CIs) | *P*-value | Model 1* OR (95% CI) | *P*-value | Model 2† OR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| All-cause death | | | | | | |
| Tertile 3 | 1 | | 1 | | 1 | |
| Tertile 2 | 3.91 (1.07–14.30) | 0.0395 | 3.63(0.91–14.49) | 0.0682 | 2.48 (0.39–15.56) | 0.3335 |
| Tertile 1 | 26.36 (8.00–86.81) | <0.0001 | 29.35 (7.97–108.14) | <0.0001 | 20.09 (3.62–111.64) | 0.0006 |
| $P_{trend}$ | | <0.0001 | | <0.0001 | | <0.0001 |
| ICU admission | | | | | | |
| Tertile 3 | 1 | | 1 | | 1 | |
| Tertile 2 | 1.88 (0.61–5.74) | 0.2692 | 2.31 (0.60–8.92) | 0.2262 | 1.62 (0.23–11.59) | 0. 6328 |
| Tertile 1 | 17.15 (6.62–44.43) | <0.0001 | 26.66 (7.90–89.98) | <0.0001 | 26.39 (4.04–172.39) | 0.0006 |
| $P_{trend}$ | | <0.0001 | | <0.0001 | | <0.0001 |
| mechanical ventilation | | | | | | |
| Tertile 3 | 1 | | 1 | | 1 | |
| Tertile 2 | 1.78 (0.84–3.80) | 0.1330 | 1.66 (0.76–3.63) | 0.2041 | 0.56 (0.20–1.58) | 0.2710 |
| Tertile 1 | 8.46 (4.31–16.60) | <0.0001 | 8.03 (3.95–16.33) | <0.0001 | 2.80 (1.15–6.78) | 0.0227 |
| $P_{trend}$ | | <0.0001 | | <0.0001 | | 0.0066 |

ICU, intensive care unit.
*Model 1 adjusted for age; sex; smoking status; history of hypertension, coronary heart disease, diabetes, chronic kidney disease, carcinoma, and chronic liver disease.
†Model 2 adjusted for age; sex; smoking status; history of hypertension, coronary artery disease, diabetes, chronic kidney disease, carcinoma, chronic liver disease; neutrophil and lymphocyte counts; prothrombin time and activated partial thromboplastin time; D-dimer; alanine transaminase and aspartate aminotransferase; total bilirubin; blood urea nitrogen; creatinine; C-reactive protein; and neutrophil-to-lymphocyte ratio.

prealbumin exhibited an increased risk for worse in-hospital outcomes (fully adjusted $P_{trend}$ for all-cause death, ICU admission, and mechanical ventilation: $P < 0.0001$, $P < 0.0001$, and $P = 0.0066$, respectively).

Generalized additive models (Fig. 2A–C) were used to visually assess functional relationships between the prealbumin as continuous variate and the risk for in-hospital outcomes. Serum prealbumin was found to have negative linear relationship with the risk for all-cause death, ICU admission, and mechanical ventilation.

To determine the consistency of the relationship between baseline prealbumin as a continuous variable and in-hospital outcomes, we conducted stratified analyses (Table 3). For each unit increase of prealbumin, the adjusted OR for all-cause death was 0.98 in men ($P = 0.0388$) and 0.98 in women ($P = 0.01$). The adjusted OR for all-cause death for individuals <70 y of age was 0.97 ($P = 0.0672$) compared with 0.98 ($P = 0.0019$) for those ≥70 y of age ($P_{interaction} = 0.1252$). For each unit increase of the prealbumin, the OR for all-cause death was 0.98 ($P = 0.0253$) and 0.98 ($P = 0.0059$) for normotensives and hypertensives, 0.98 ($P = 0.0003$) and 0.98 ($P = 0.0966$) for patients without diabetes and those with diabetes, respectively. The difference of interaction was not significant between two groups ($P_{interaction} = 0.2416$, 0.1252, 0.9886, and 0.8430 stratified for sex, age, HTN, and diabetes, respectively). Moreover, the relationship between baseline prealbumin with ICU admission and mechanical ventilation stratified by sex, age, HTN, and diabetes were consistent.

## Discussion

In the present study, we found that lower serum prealbumin significantly associated with an increased risk for worse outcomes and all-cause death during hospitalization. Patients in the lowest tertile of prealbumin were older, and had higher neutrophil count, lower lymphocyte count, and worse coagulation function and liver function than those in the highest tertile. We adjusted relevant covariates including age, sex, smoking status, comorbidities, neutrophil and lymphocyte counts, coagulation function, liver function, renal function, and CRP to minimize the potential effects of confounding. Compared with crude regression analyses, this association still persisted when adjusting for demographic and clinical variables in the multivariable regression analyses. Moreover, stratified by sex, age, HTN, and diabetes, increased level of serum prealbumin was associated with the decreased risk for all-cause death, ICU admission, and mechanical ventilation, which determine the consistency of the relationship between the lowest serum

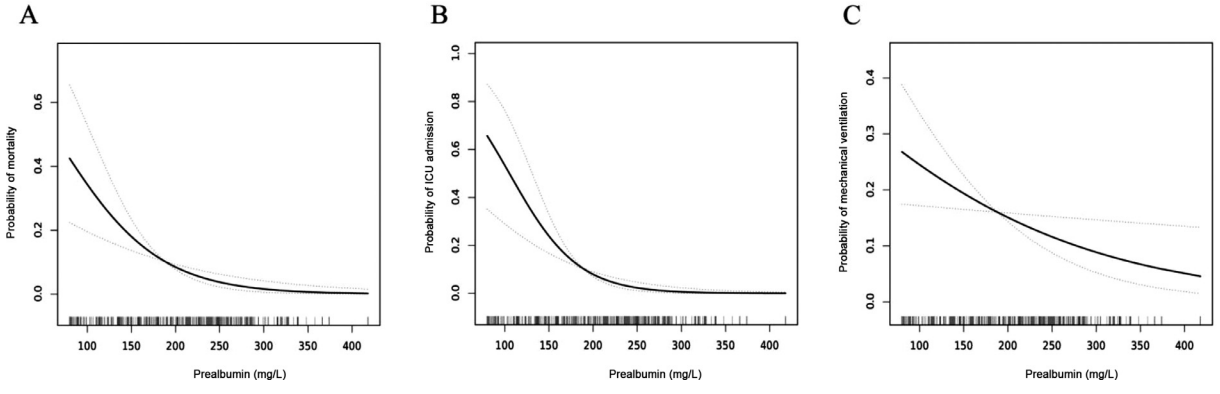


**Fig. 2.** General additive models demonstrate the relationship between prealbumin as continuous variable and the probability of in-hospital outcomes. Serum prealbumin was found to have negative linear relationship with the risk of all-cause death (A), ICU admission (B) and mechanical ventilation (C). Adjusted for age, sex, smoking status, history of hypertension, history of coronary heart disease, history of diabetes, history of chronic kidney disease, history of carcinoma, chronic liver disease, neutrophil, lymphocyte, prothrombin time, activated partial thromboplastin time, d-dimer, alanine transaminase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, C-reactive protein and neutrophil-to-lymphocyte ratio.

**Table 3**
Associations between baseline prealbumin as a continuous variable and outcomes in subgroups of gender, age, history of hypertension and history of diabetes

| | All-cause death OR (95% CI) | *P*-value | ICU admission OR (95% CI) | *P*-value | Mechanical ventilation OR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| Men (n = 232) | 0.98 (0.96–1.00) | 0.0388 | 0.97 (0.96–0.99) | 0.0325 | 0.99 (0.99–1.00) | 0.5281 |
| Women (n = 214) | 0.98 (0.97–1.00) | 0.0100 | 0.93 (0.89–0.98) | 0.0064 | 0.99 (0.98–1.00) | 0.0081 |
| $P_{interaction}$ | | 0.2416 | | 0.3031 | | 0.6466 |
| Age, y | | | | | | |
| ≤70 (n = 207) | 0.97 (0.93–1.00) | 0.0672 | 0.95 (0.88–1.01) | 0.1046 | 0.99 (0.98–1.00) | 0.0250 |
| >70 (n = 239) | 0.98 (0.97–0.99) | 0.0019 | 0.97 (0.96–0.99) | 0.0001 | 0.99 (0.99–1.00) | 0.2090 |
| $P_{interaction}$ | | 0.1252 | | 0.9674 | | 0.0796 |
| Hypertension | | | | | | |
| No (n = 195) | 0.98 (0.96–1.00) | 0.0253 | 0.98 (0.96–1.00) | 0.0273 | 0.99 (0.98–1.00) | 0.1041 |
| Yes (n = 251) | 0.98 (0.97–0.99) | 0.0059 | 0.92 (0.86–0.99) | 0.0151 | 0.99 (0.99–1.00) | 0.1041 |
| $P_{interaction}$ | | 0.9886 | | 0.1159 | | 0.9030 |
| Diabetes | | | | | | |
| No (n= 337) | 0.98 (0.97–0.99) | 0.0003 | 0.98 (0.97–0.99) | <0.0001 | 0.99 (0.99–1.00) | 0.0592 |
| Yes (n= 109) | 0.98 (0.96–1.00) | 0.0966 | 0.94 (0.90–0.99) | 0.0100 | 0.99 (0.98–1.00) | 0.0359 |
| $P_{interaction}$ | | 0.8430 | | 0.0741 | | 0.4585 |

ICU, intensive care unit.
Data adjusted for age; sex; smoking status; history of hypertension, coronary artery disease, diabetes, chronic kidney disease, carcinoma, chronic liver disease; neutrophil and lymphocyte counts; prothrombin time and activated partial thromboplastin time; D-dimer; alanine transaminase and aspartate aminotransferase; total bilirubin; blood urea nitrogen; creatinine; C-reactive protein; and neutrophil-to-lymphocyte ratio.

prealbumin tertile and the increased risk for worse outcomes in elderly patients with COVID-19.

Several previous studies have demonstrated baseline prealbumin change in patients with COVID-19. Decreased levels of prealbumin were observed among patients COVID-19 [10]. Wu et al. investigated 201 patients with COVID-19 and observed that prealbumin was associated with the development of acute respiratory distress syndrome, indicating the potential value of prealbumin levels on COVID-19 clinical ending [11]. To our knowledge, no report exists on the effects of prealbumin in elderly patients with COVID-19.

A high proportion of severe to critical cases and a high fatality rate were observed in the elderly patients with COVID-19, and rapid disease progress was noted in those who died [5]. One possible explanation involves the greater potential of individuals ≥65 y of age to be in a state of inflammation, nutritional deficiency, and other complications. Prealbumin is a globular, non-glycosylated protein, synthesized by the liver, and complexed with a retinol-binding protein, which acts as a transporter of retinol/vitamin A and thyroid hormones [7]. Low plasma prealbumin levels have emerged as an early laboratory indicator of poor nutritional status [12,13]. Additionally, prealbumin also is associated with inflammation. Previous studies have demonstrated that in response to the inflammation, the body responds by synthesizing a large number of cytokines. These include interleukins and tumor necrosis factors that downregulate plasma concentrations of albumin and prealbumin [14,15]. Therefore, assay of serum prealbumin concentration is recommended by some investigators as a screening marker for both malnutrition and inflammation.

Elderly patients with low plasma prealbumin levels are at greater risk for malnutrition and inflammatory conditions, which may lead to poor prognosis. Malnutrition is commonly seen in hospitalized patients in both the developed and developing world, especially among elderly patients. A review of 110 published studies of acute care patients reported that malnutrition incidence ranged from 42% to 91% of hospitalized elderly patients [16]. It was found that compared with non-famine regions of India, individuals experiencing famine had significantly higher influenza mortality rates during the 1918 Influenza pandemic [17]. Aging, frailty, and chronic diseases are associated with impaired immune function and are compounded by immune dysregulation from malnutrition. When immune response is dysregulated, excessive inflammation and even death can occur. The present COVID-19 study found that elderly patients had higher levels of white blood cell counts, CRP, and inflammatory cytokines and are more likely to experience critical disease than younger patients [4,18].

This retrospective cohort study included 446 elderly patients with COVID-19, from January 17 to February 17, 2020. Of the patients, 21.3% required mechanical ventilation, 15.47% were admitted to the ICU, and the total in-hospital mortality was 14.79%. The mortality rate was lower than reported by Wang et al. [5] among elderly COVID-19 patients. This may have been because some patients were still in hospitalized as of February 17, 2020. Nevertheless, this would not bias the relationship between prealbumin and in-hospital outcomes because of the definite observation time we set previously. Wuhan Tongji Hospital is one of the largest third-grade Class A hospitals equipped with advanced life support training and equipment, which may partly account for the moderate mortality.

The results of this study had several clinical implications and strengths. A low prealbumin concentration can be regarded primarily as a signal identifying at-risk elderly patients who would suffer worse outcomes and who require careful assessment and monitoring and for whom nutritional support and inflammation detection may be needed as part of the treatment plan [19]. As observational study was susceptible to various confounders, we adjusted many variables that may affect the relationship between prealbumin and in-hospital outcomes to minimize potential confounding. Additionally, we tested the robustness of the results by repeating the analyses in different subgroups of sex, age, history of HTN, and history of diabetes.

The present study had some limitations. First, by including patients still in hospital as of February 17, 2020, the case fatality ratio in the study was unable to reflect the true mortality of elderly COVID-19 patients. Second, the record of data may be affected by prehospital medication and the time interval between admission and onset. Third, because the participants in the present study were hospitalized elderly Chinese patients diagnosed with COVID-19, results study might not be directly applied to other ethnicities and age groups.

## Conclusions

This retrospective cohort study revealed that prealbumin is an independent risk factor for the in-hospital mortality in elderly

Chinese patients with COVID-19. Nutritional support and inflammation detection should be careful assessed and monitored in elderly patients with low prealbumin concentrations.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2020.110930.

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