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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].
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 [67]. 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-19 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 anonymized and the study was observational, so the informed consent was not gathered. All consecutive patients were included. This study was approved by the Medical Ethics Committee of Tongji Hospital in Wuhan from January 17 to February 17, 2020 were included participants are listed in Table 1. The day of sample draw- ing after admission was 0.67 ± 0.65 d. No significant statistical difference in sex, smoking status, body weight, body mass index,

![Study population](image-url)

**Fig. 1. Study population.**
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 decreased. The OR for tertile 1 was significantly higher than for tertile 3 (OR, 2.7; 95% CI, 1.14-6.4; P = 0.006 for all-cause death; OR, 8.46; 95% CI, 4.31-16.6; P < 0.001 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
prealbumin exhibited an increased risk for worse in-hospital outcomes (fully adjusted $P_{\text{rand}}$ 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 $\geq 70$ y of age ($P_{\text{interaction}} = 0.1252$). 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 ($P_{\text{interaction}} = 0.2416, 0.1252, 0.9886$, 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

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**Table 2**

| Risk association between baseline prealbumin and outcomes |
|---------------------------------------------------------|
| All-cause death                                         |
| Tertile 3                                              |
| 1                                                      |
| 3.91 (1.07–14.30)                                      |
| $P_{\text{rand}}$                                       |
| 0.0395                                                 |
| 1                                                      |
| 3.63 (0.91–14.49)                                      |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| 26.36 (8.00–86.81)                                     |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| ICU admission                                           |
| Tertile 3                                              |
| 1                                                      |
| 1.88 (0.61–5.74)                                       |
| $P_{\text{rand}}$                                       |
| 0.2602                                                 |
| 1                                                      |
| 2.31 (0.60–8.92)                                       |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| mechanical ventilation                                  |
| Tertile 3                                              |
| 1                                                      |
| 1.78 (0.84–3.80)                                       |
| $P_{\text{rand}}$                                       |
| 0.1330                                                 |
| 1                                                      |
| 1.66 (0.76–3.63)                                       |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| Tertile 2                                              |
| 1                                                      |
| 8.46 (4.31–16.60)                                      |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| 8.03 (3.95–16.33)                                      |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| Mechanical ventilation                                  |
| Tertile 3                                              |
| 1                                                      |
| 1.78 (0.84–3.80)                                       |
| $P_{\text{rand}}$                                       |
| 0.1330                                                 |
| 1                                                      |
| 1.66 (0.76–3.63)                                       |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| Tertile 2                                              |
| 1                                                      |
| 8.46 (4.31–16.60)                                      |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |
| 8.03 (3.95–16.33)                                      |
| $P_{\text{rand}}$                                       |
| <0.0001                                                |

*Model 1 adjusted for age; sex; smoking status; history of hypertension, coronary heart disease, diabetes, chronic kidney disease, carcinoma, and chronic liver disease.

1Model 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; s-dimer; alanine transaminase and aspartate aminotransferase; total bilirubin; blood urea nitrogen; creatinine; C-reactive protein; and neutrophil-to-lymphocyte ratio.

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**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.
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 patients with COVID-19.

### Table 3

| Sex            | All-cause death OR (95% CI) | P-value | ICU admission OR (95% CI) | P-value | Mechanical ventilation OR (95% CI) | P-value |
|----------------|-----------------------------|---------|--------------------------|---------|----------------------------------|---------|
| 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  |

**Interaction**

| Age, y         | P-value   | ICU admission OR (95% CI) | P-value | Mechanical ventilation OR (95% CI) | P-value |
|----------------|-----------|--------------------------|---------|----------------------------------|---------|
| <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  |
| Diabetes       | P-value   | ICU admission OR (95% CI) | P-value | Mechanical ventilation OR (95% CI) | P-value |
| No (n = 215)   | 0.98 (0.96–0.99) | 0.0253   | 0.98 (0.96–1.00)         | 0.0273  | 0.99 (0.98–1.00)                 | 0.1041  |
| Yes (n = 228)  | 0.98 (0.97–0.99) | 0.0059   | 0.92 (0.86–0.99)         | 0.0151  | 0.99 (0.99–1.00)                 | 0.1041  |
| Diabetes       | P-value   | ICU admission OR (95% CI) | P-value | Mechanical ventilation OR (95% CI) | P-value |
| No (n = 195)   | 0.98 (0.96–1.00) | 0.0966   | 0.94 (0.90–0.99)         | -0.0001 | 0.99 (0.99–1.00)                 | 0.0592  |
| Yes (n = 251)  | 0.98 (0.97–0.99) | 0.0033   | 0.95 (0.92–0.99)         | 0.0100  | 0.99 (0.98–1.00)                 | 0.0359  |

**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; C-reactive protein; prealbumin; and neutrophil-to-lymphocyte ratio.
Chinese patients with COVID-19. Nutritional support and inflammation detection should be carefully 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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