

# The Association Between the Albumin and Viral Negative Conversion Rate in Patients Infected with Novel Coronavirus Disease 2019 (COVID-19)

Li-wei Lang<sup>1\*</sup>, Zhen-zhen Zhu<sup>1\*</sup>, Zhe Xu<sup>2\*</sup>, Shan-wei Zhu<sup>1</sup>, Peng Meng<sup>3</sup>, Hong-yan Wang<sup>1</sup>, Zhan-dong Song<sup>1</sup>, Ying Wang<sup>4</sup>, Jing-feng Bi<sup>5</sup>

<sup>1</sup>Clinical Trial Research Center, Department of Pharmacy, Medical Supplies Center of PLA General Hospital, Beijing, 100039, People's Republic of China; <sup>2</sup>Department of Infectious Diseases, The Fifth Medical Center of Chinese PLA General Hospital, National Clinical Research Center for Infectious Diseases, Beijing, 100039, People's Republic of China; <sup>3</sup>Department of Outpatient, Zi-Bo Central Hospital of Shan Dong, Shan Dong, 255036, People's Republic of China; <sup>4</sup>Respiratory Department No. 960 Hospital, The People's Liberation Army, Jinan, 250014, People's Republic of China; <sup>5</sup>Clinical Trial Research Center, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, 100039, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Jing-feng Bi, Clinical Trial Research Center, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, 100039, People's Republic of China, Email 123bjf@163.com; Ying Wang, Respiratory Department No. 960 Hospital, The People's Liberation Army, Jinan, 250014, People's Republic of China, Email babyjinan@163.com

**Purpose:** The novel coronavirus disease 2019 (COVID-19) epidemic is the severe global pandemic with large numbers of infected cases and deaths in recent decades. The previous studies were all about the influence of albumin (ALB) for the severity and mortality of in-patients infected with COVID-19. But few studies exist about the influence factors to achieve viral negative conversion. Therefore, this study conducted an exploratory study to investigate the effect of albumin on negative conversion rate.

**Methods:** Among the 190 hospitalized patients with moderate COVID-19 who had a course of disease longer than 30 days, 102 achieved viral negative conversion in 30–45 days and 88 not after 45 days. Taking other variables as concomitant variable, Cox proportional hazard regression model was applied to explore the influence of albumin to negative conversion rate under various factors.

**Results:** By comparing patients who could and could not achieve the finally viral negative conversion, a possible nonlinear relationship between the continuous variables and clinical outcomes was examined by a restricted cubic spline regression model. An association was found between albumin levels and hazard ratio of viral negative conversion rate ( $P = 0.027$ ). The increase of albumin was accompanied with decreases of hazard ratio of viral negative conversion rate (the value of albumin  $<38$  g/L). But when the value of albumin was higher than 38 g/L, the hazard ratio of viral negative conversion rate approached 1, it means that albumin is not a risk factor for the viral negative conversion rate of COVID-19 disease.

**Conclusion:** For patients with COVID-19, albumin is a common and observed laboratory parameter. It is associated with final viral negative conversion rate although its underlying mechanism and relationship with the viral negative conversion rate still need to be clarified.

**Keywords:** COVID-19, albumin, negative conversion rate

## Introduction

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread around the world rapidly.<sup>1</sup> As of Oct 30th, 2020, there were more than 44.6 million confirmed cases and 1,175,000 deaths (2.6%) in more than 219 countries.<sup>2</sup> According to the clinical classification method, the patients

were divided into four types: mild type, moderate type, severe type and critically ill type according to the severity of the disease.<sup>3,4</sup>

Most of the current studies indicated that albumin had effect on the severity of pulmonary disease in patients with COVID-19.<sup>5–16</sup> Here, a paper was reported the prevalence of low levels of albumin in a cohort of 207 patients with COVID-19 and its relationship with disease severity and clinical outcome. A negative association was found between albumin levels and severity of COVID-19 disease and death in this study.<sup>14</sup> Meantime, a systematic review and meta-analysis study showed that four studies assessed the low levels of albumin and severity of COVID-19 and increased risk was demonstrated in other paper.<sup>5</sup> In addition, there are many other studies on the albumin levels and the severity of COVID-19 diseases.<sup>2,6,10,12,14–17</sup> In these articles, an increase in the severity of COVID-19 pneumonia was positively associated with lower levels of albumin. Therefore, based on previous literature, we believe that albumin is associated with the severity of COVID-19 disease.

In the process of fighting COVID-19 disease of Huo Shen Shan hospital of Wuhan, Hubei, China, 2020, the clinical observation of COVID-19 diseases showed that a part of patients with the low levels of albumin had the increasing tendency of negative conversion time. Therefore, we aimed to develop a retrospective study of patients in Huo Shen Shan hospital in Wuhan who had not turned negative for a long time (more than 30 days), to clarify the association between albumin levels and negative conversion rate.

## Materials and Methods

### Patients

In this retrospective study, we included confirmed mild cases of COVID-19 from February 4, 2020, to April 14, 2020 in Huo Shen Shan hospital in Wuhan, Hubei, China.

### Diagnostic Standard

COVID-19 was diagnosed according to the WHO interim guidance and confirmed by at least two positive real-time reverse transcriptase polymerase-chain-reaction (RT-PCR) tests for viral nucleic acids.<sup>7,8,18</sup> Throat swab samples were collected for determination SARS-Cov-2 RNA from patients. The real time RT-PCR assay was conducted using a SARSCov-2 nucleic acid detection kit according to the factory's instruction (Guangzhou DaAn Gene Limited Company). The RT-PCR assay was conducted under the following conditions: incubation at 50°C for 15 minutes and 95°C for 15 minutes, 45 cycles of the denaturation at 94°C for 15 seconds, and extending and collecting fluorescence signal at 55°C for 45 seconds. A cycle threshold value equal and less than 40 was defined as a positive test result, and a cycle threshold value more than 40 was defined as a negative test. Two target genes—open reading frame 1ab (ORF1ab) and nucleocapsid protein (N)—were simultaneously amplified and assayed during the real time RT-PCR assay.<sup>8</sup>

### Criteria for Negative Conversion

All patients were observed negative for nucleic acid tests. The standard of criterion is nucleic acid tests negative twice consecutively on respiratory tract samples such as sputum and nasopharyngeal swabs at least 24 h apart.

### Inclusion Criteria

(1) all adult patients enrolled in this study were diagnosed according to the criteria of diagnosis and treatment protocol for novel coronavirus pneumonia; (2) all the subjects were mild cases since these patients showing fever and respiratory symptoms with radiological findings of pneumonia; (3) positive time of nucleic acid test  $\geq 30$  days; (4) all patients proceed nucleic acid test every 1–3 days after 30 days to determine whether the nucleic acid test turning negative.

### Excluded Criteria

(1) patients with malignant tumors and malignant hematological diseases; (2) patients with acquired immunodeficiency syndrome (AIDS); (3) the blood routine examination or blood biochemical examination was not carried on the range of

$\pm 4$  days for onsets of COVID-19 disease; (4) liver failure (total bilirubin 10 mg/dL and/or severe coagulation disorders); (5) renal function failure (urine  $0.5 \text{ m}^3\text{kg}^{-1}\text{h}^{-1}$ , creatinine (Cr) or blood urea nitrogen (BUN)  $1.5\times$  upper limits of normal (ULN) although there is adequate circulating blood and cardiac output).

## Clinical Data

The following data were retrieved from clinical charts at presentation: (1) demographic data (sex, age, smoking and alcohol history); (2) concomitant diseases (such as with or without diabetes, hypertension, cardiovascular disease, cerebrovascular disease, respiratory disease, chronic liver disease and so on); (3) therapeutic medication situation (specification, dosage, usage and time); (4) time of nucleic acid test turning negative; (5) the routine blood examinations and blood biochemical tests, which was turning negative at the range of 30–45 days ( $\pm 4$  days), and not turning negative after 45 days ( $\pm 4$  days); (6) treatments strategies of COVID-19 infection (thymus peptide, interferon, convalescent plasma, hormones, immunoglobulin and so on).

## Ethics Approval

The study was approved by the Ethics Committee of No. 960 Hospital (RE2020-70), the People's Liberation Army, Jinan, China, and informed consent was signed.

## Statistical Analyses

The quantitative data was expressed as Mean $\pm$ SD when accorded with normality, when the variance was homogeneous or not, *t* test or correction *t* test was used for group comparison, respectively. The quantitative data was expressed as Median (IQR) when did not accord with normality and was compared using Wilcoxon's rank-sum. The categorical data was expressed as percentage and was compared using chi-square test. First, Cox proportional hazard regression model was used for single factor analysis with negative conversion rate as dependent variable and its influence single factor as independent variables. Then variables with the *p* value less than 0.2 was taken as concomitant variable, albumin as independent variable. Cox proportional hazard regression model was applied to explore various factors to negative conversion rate. A possible nonlinear relationship between the continuous variables and clinical outcomes was examined by a restricted cubic spline regression model.<sup>19</sup> Statistical analysis was performed using SAS9.4. All the tests were two-sided test ( $\alpha=0.05$ ).

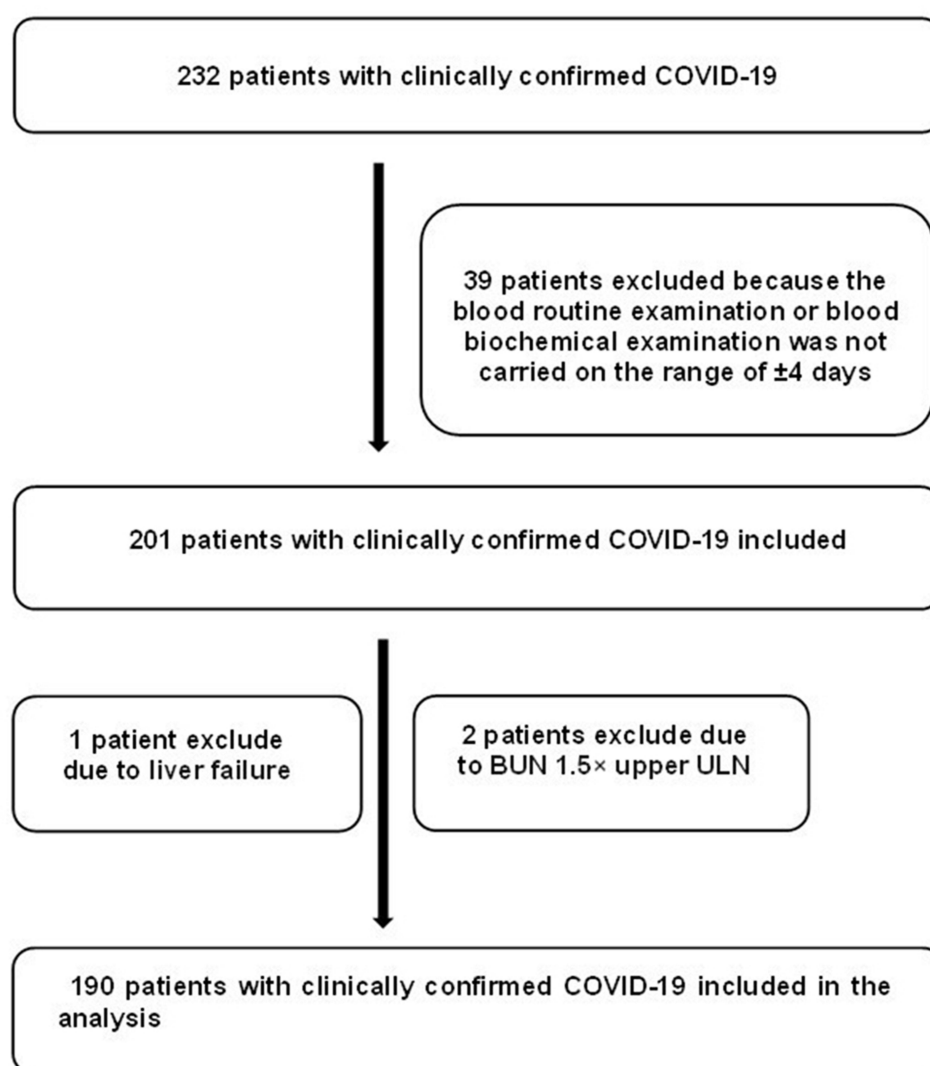
## Results

In total, the study population included 232 patients with clinically confirmed COVID-19 (more than 30 days). All patients were selected by excluded criteria. Finally, 190 patients were recruited and 42 patients were excluded. The flow chart is shown in [Figure 1](#). 190 patients had an overall course beyond 30 days from February 4 to April 14, 2020. Among these, 102 were to achieve viral negative conversion in 30–45 days and 88 were not after 45 days.

[Table 1](#) lists the baseline characteristics of the two groups. The frequencies or proportions of patients in the two groups were given for all the categorical variables in the table. Among those variables, significant difference between the two groups was found in the following categories: albumin (ALB)( $P=0.010$ ), total protein (TP) ( $P=0.006$ ), globulin (GLO) ( $P=0.020$ ), Immunoglobulin ( $P=0.0154$ ) (All the *P* value  $<0.05$ ). There were no statistically obvious differences for others.

[Table 2](#) lists results of its single factor to negative conversion rate. Cox proportional hazard regression model method was used for single factor analysis. The result showed that the values of albumin those who came out of hospital was associated with viral negative conversion rate (the *P* value was 0.009 ( $<0.05$ )).

Meantime, taking variables that the *P* value was less than 0.2 as concomitant variable (variables come from [Table 2](#)), albumin as independent variable. Cox proportional hazard regression model was applied to explore albumin to negative conversion rate under the various factors. The result also showed that the values of albumin was associated with viral negative conversion rate (the *P* value was 0.027). [Figure 2](#) showed that a negative association was found between albumin levels and hazard ratio of viral negative conversion rate. When the value of albumin was less than 38 g/L, the increase of albumin levels was accompanied with decreases of hazard ratio of viral negative conversion rate. But when the value of albumin was about more than 38 g/L, the hazard ratio of viral negative conversion rate approached 1, it shows that albumin is not a risk factor for the viral negative conversion rate of COVID-19 disease.



**Figure 1** Study flow chart.

**Abbreviations:** BUN, blood urea nitrogen; ULN, upper limit of normal.

## Discussion

The previous studies are all about influence of albumin on the severity and mortality of in patients infected with COVID-19. The previous literatures also demonstrated that the decrease of immunity of the organism could be induced by the hypoalbuminemia.<sup>22</sup> Therefore, we paid more attention to the albumin levels and nutritional status of critically ill type patients on clinical. But few studies exist about the influence factors to achieve viral negative conversion rate. Also, the underlying mechanisms have not been clarified, yet. Here, we made explorative research on the relationship between albumin levels and viral negative conversion rate in a cohort of 190 patients with COVID-19 and its mechanism of action.

In our study, we observed a negative association between albumin levels and hazard ratio of viral negative conversion rate (the value of albumin was less than 38 g/L). Meantime, the result of various factors analysis showed that there are the significant statistical differences in the effect of albumin levels for viral negative conversion rate ( $P < 0.05$ ). It further illustrates that albumin is a risk factor for the viral negative conversion rate of COVID-19 disease when the value of albumin was less than 38 g/L. But when the value of albumin was about more than 38 g/L, the hazard ratio of viral negative conversion rate approached 1, which means that albumin is no longer a risk factor for the viral negative conversion rate.

**Table I** Clinical Characteristics of Patients with 190 COVID-19 Between the Non-Negative Conversion and Negative Conversion of Group (n = 190)

Characteristic	Non-Negative Conversion (N=88)	Negative Conversion (N=102)	P value
<b>Age, Year</b>	58.22±12.78	61.4±13.71	0.101
<b>Gender (n, %)</b>			
Male	39 (44.32%)	58(56.86%)	0.085
Female	49(55.68%)	44(43.14%)	
<b>Clinical Symptoms (%)</b>			
Fever	68(77.27%)	75(73.52%)	0.551
<b>Routine Blood Examinations</b>			
WBC (3.69–9.16), 10 <sup>9</sup> /L	5.4(4.7,6.7)	5.8(4.8,6.8)	0.568
RBC (3.68–5.13), 10 <sup>12</sup> /L	3.95±0.45	3.86±0.6	0.237
HGB (113–151), g/L	123(114,132)	120.5(108,132)	0.356
PLT (101–320), 10 <sup>9</sup> /L	196(169,241.5)	211(182,253)	0.120
NEU (2–7), 10 <sup>9</sup> /L	3.16(2.66,4.18)	3.4(2.71,4.18)	0.715
LYM (0.8–4.0), 10 <sup>9</sup> /L	1.55(1.14,1.93)	1.53(1.09,1.89)	0.995
MON (0.12–1.0), 10 <sup>9</sup> /L	0.39(0.33,0.48)	0.44(0.34,0.53)	0.153
<b>Blood Biochemical Tests</b>			
ALT (5–35), U/L	22.1(12.5,36.05)	22.75(15,38.4)	0.425
AST (8–40), U/L	19.15(15.05,26.1)	18.8(15.7,25.4)	0.960
TP (60–83), g/L	66.79±6.28	64.38±5.57	0.006
ALB (40–55), g/L	38.95(37.8,41.1)	38.00(35.3,40.4)	0.010
GLO (20–40), g/L	28(25.1,30.9)	26.1(24,28.8)	0.020
A/G (1.2–2.4)	1.41(1.25,1.56)	1.43(1.28,1.59)	0.806
TBIL (3.4–20.5), umol/L	10.15(7.6,12.25)	8.8(7.1,11.6)	0.180
DBIL (0–6.8), umol/L	3.2(2.4,4.2)	2.9(2.3,3.8)	0.396
BUN (2.5–6.4), mmol/L	4.58(3.92,5.62)	4.67(3.66,5.83)	0.799
CRE (53–97), umol/L	65.6(55.65,73.05)	65.35(56.5,80.4)	0.394
ALP (40–150), U/L	69.1(59.2,85.35)	71.15(59.7,82.3)	0.867
GGT (7–32), U/L	32.25(20.25,54)	28.25(20.2,43.4)	0.355
<b>Chronic Disease (%)</b>			
Chronic Hepatitis B	2(2.27%)	6(5.88%)	0.290
Hypertension	28(31.82%)	33(32.35%)	0.937
Diabetes	8(9.09%)	18(17.65%)	0.087
Cerebral Infarction	3(3.41%)	7(6.86)	0.344
Coronary Heart Disease	6(6.82%)	11(10.78%)	0.340
Cerebral Disease	3(3.41%)	6(5.88%)	0.508
<b>Treatment Strategies (%)</b>			
Thymus Peptide	28(31.82)	22(21.57%)	0.110
Interferon	20(22.73%)	21(20.59%)	0.721
Convalescent Plasma (CP)	6(6.82%)	7(6.86%)	0.990
Hormones	8(9.09%)	9(8.82%)	0.949
Immunoglobulin	31(35.23%)	20(19.61%)	0.015

**Abbreviations:** WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; NEU, neutrophil; LYM, lymphocyte; MON, monocyte; ALT, alanine transaminase; AST, transglutaminase; TP, total protein; ALB, albumin; GLO, globulin; A/G, blood clean/globulin; TBIL, total bilirubin; DBIL, direct bilirubin; BUN, blood urea nitrogen; CRE, creatinine; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase.

As previously demonstrated, the viral negative conversion rate strongly is correlated with low levels of serum albumin at admission. Several mechanisms may be involved in the albumin levels on the viral negative conversion rate with COVID-19 disease. (a) Albumin plays a key role in the homeostasis of vascular endothelium, offering

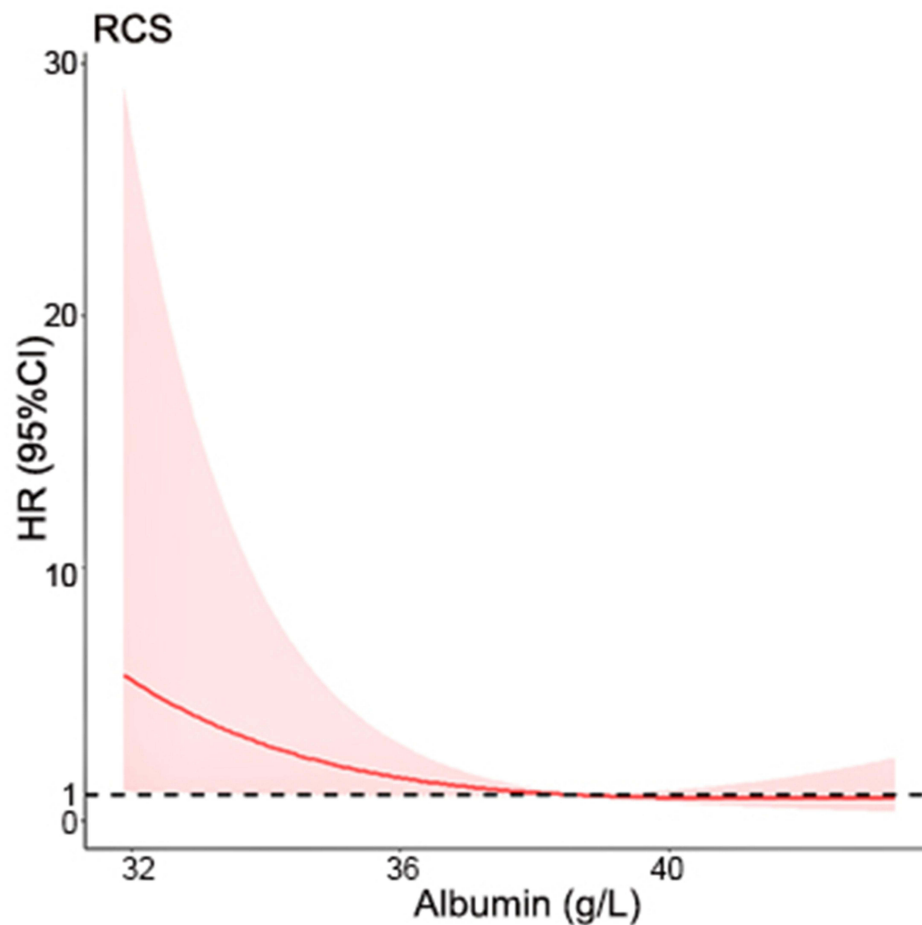
**Table 2** The Single Factor Analysis Results of Cox Proportional Hazard Regression Model

Characteristic	P value	Linear Correlation	Hazard Ratio (HR) (95% CI)
<b>Quantitative Data</b>			
Age	0.230	0.783	NA
WBC	0.653	0.361	NA
RBC	0.046	0.032	NA
HGB	0.246	0.229	NA
PLT	0.316	0.879	NA
NEU	0.375	0.184	NA
LYM	0.046	0.094	NA
MON	0.193	0.098	NA
ALT	0.548	0.296	NA
AST	0.971	0.935	NA
TP	0.021	0.246	NA
ALB	0.009	0.936	NA
GLO	0.085	0.054	NA
A/G	0.603	0.738	NA
TBIL	0.346	0.233	NA
DBIL	0.580	0.527	NA
BUN	0.901	0.837	NA
CRE	0.292	0.398	NA
ALP	0.813	0.919	NA
GGT	0.539	0.428	NA
<b>Categorical Data</b>			
Gender	0.112	NA	1.37 (0.93–2.03)
Fever	0.703	NA	0.92 (0.59–1.43)
Chronic Hepatitis B	0.167	NA	1.79 (0.78–4.09)
Hypertension	0.808	NA	0.95 (0.63–1.44)
Diabetes	0.089	NA	0.56 (0.94–2.59)
Cerebral Infarction	0.387	NA	1.40 (0.65–3.02)
Coronary Heart Disease	0.609	NA	0.18 (0.63–2.20)
Cerebral Disease	0.526	NA	1.31 (0.57–2.98)
Convalescent Plasma (CP)	0.686	NA	0.85 (0.40–1.84)
Thymus Peptide	0.093	NA	0.67 (0.42–1.07)
Interferon	0.557	NA	0.87 (0.54–1.40)
Hormones	0.810	NA	0.92 (0.46–1.82)
Immunoglobulin	0.024	NA	0.57 (0.35–0.93)

**Abbreviations:** NA, not available; CI, confidence interval.

protection from inflammation and remaining the primary determinant of colloid osmotic pressure (COP). It appears that albumin administration may affect vascular permeability, cell signaling, neutrophil adhesion, redox homeostasis. It also has anticoagulant and antithrombotic properties. Consequently, albumin play an important role in the recovery of diseases.<sup>20</sup> (b) Albumin also has immunomodulatory and anti-inflammatory effects through binding of bacterial products, modulation of antigen-presenting cell function, modulation of cytokine production.<sup>15,21</sup>

Based on the results of our research when the value of albumin was less than 38 g/L, the level of albumin is a risk factor for the viral negative conversion rate, and the normal range of albumin is 40–55 g/L in the healthy body. The low level of albumin can affect its protection role from inflammation situation, antigen-presenting cell function and cytokine production, and hence, impact the effect of virus clearance and the viral negative conversion rate. Therefore, we should also pay attention to the albumin levels of mild type patients. The value of albumin should be maintained a high levels, such as more than 38 g/L, which is beneficial to SARS-CoV-2 RNA turned negative. It is speculated that a high albumin



**Figure 2** Hazard ratio function for albumin to negative conversion rate.

**Abbreviations:** RCS, restricted cubic splines; HR, hazard ratio; CI, confidence interval.

level is also needed for critically ill type and mild type patients, which has great clinical significance of viral negative conversion rate and prognosis.

There are several limitations in our study. First, this is also a small cohort study. Second, some unmeasured factors which not included in the analysis may potentially bias the result. Third, the nucleic acid detection intervals are different among individuals. Hence, detection of virus negative conversion might be delayed than estimated. Further large randomized prospective studies are still needed to confirm the reliability of the results.

## Conclusion

Albumin which is a common and observed laboratory parameter is strictly associated with finally viral negative conversion rate in patients with COVID-19. In our study, when the value of albumin was less than 38 g/L, we observed a negative association between albumin level and hazard ratio of viral negative conversion rate. It was believed that albumin is a risk factor for the viral negative conversion rate of COVID-19 disease. Nevertheless, when the albumin levels recovered to normal (more than 38 g/L), albumin is no longer a risk factor for the viral negative conversion rate.

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## Disclosure

The authors report no conflicts of interest in this work.

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