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Significance of Hypoalbuminemia in the Development of Thromboembolic Complications in Severe Cases of SARS-CoV-2 Coronavirus Infection

Aida Tarzimanova[a], Anna Bragina[a], Anna Pokrovskaya[a, c], Alexander Ivannikov[a], Ekaterina Sokolova[a], Igor Cherkesov[b], Tatyana Safronova[a], Tatyana Vargina[a], Liubov Ponomareva[a], Alyona Isaeva[a], Karine Oganesyan[a], Valery Podzolkov[a]

Abstract

Background: The course of coronavirus disease 2019 (COVID-19) is associated with the progression of a wide range of complications, among which thrombosis and thromboembolism are of particular importance. The significance of hypoalbuminemia in the development of thromboembolic complications (TECs) in patients with a severe course of COVID-19 is currently under active discussion. The objective of our study was to evaluate the significance of hypoalbuminemia in the development of TECs in patients with severe SARS-CoV-2 coronavirus infection.

Methods: In a single-center observational retrospective study, case histories of 1,634 patients with a verified diagnosis of SARS-CoV-2 coronavirus infection were analyzed. Patients were divided into two groups according to the presence of TECs: 127 patients with venous TECs constituted the main group and 1,507 patients, in whom the course of COVID-19 was not complicated by the development of TECs, constituted the comparison group.

Results: The patients with TECs were older, and the prevalence of arterial hypertension, coronary heart disease, chronic heart failure, chronic kidney disease, and diabetes mellitus was higher than that in the comparison group. A single-factor regression analysis showed that a decrease in albumin levels of less than 35 g/L is associated with an eightfold increase in the risk of developing TECs in patients with severe SARS-CoV-2 coronavirus infection (area under the curve (AUC): 0.815, odds ratio (OR): 8.5389, 95% confidence interval (CI): 4.5637 - 15.977, P < 0.001). The sensitivity of the method was 76.34%, and the specificity was 72.58%.

Conclusion: The study revealed that hypoalbuminemia is a predictor of development of TECs in severe cases of SARS-CoV-2 coronavirus infection.

Keywords: COVID-19; Hypoalbuminemia; Thromboembolic complications

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[a]Department of Faculty Therapy No. 2, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation
[b]Department of plastic surgery, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation
[c]Corresponding Author: Anna Pokrovskay, Department of Faculty Therapy No. 2, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation.
Email: pokrovskaya_a_e@staff.sechenov.ru

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, remains a topical issue for the global community. COVID-19 advancement is fraught with a broad spectrum of complications, notably thrombosis and thromboembolism [1].

Known indicators associated with a high risk of thromboembolic complications (TECs) in COVID-19 include elevated levels of D-dimer, C-reactive protein (CRP), and pro-inflammatory cytokines. The significance of hypoalbuminemia in the development of TECs in patients with high inflammatory response is also being currently discussed [2].

The physiological effects of serum albumin include the maintenance of colloid osmotic pressure and anti-inflammatory, antioxidant, anticoagulant and antiaggregant activity [3].

Some fundamental studies have shown the significance of albumin in variations of vascular wall permeability. Aldecoa et al showed albumin and lipoproteins to play an important role in delivering sphingosine-1-phosphate to endothelial cells' surface to alter vascular wall permeability [4].

Clinical researches done showed low albumin to be a marker of venous thromboembolism developing in patients with ischemic heart disease, atrial fibrillation, and/or chronic heart failure (CHF) [5, 6]. Hypoalbuminemia may be an independent predictor of the development of infectious endocarditis [7, 8]. However, to date, there have been no clinical studies investigating the significance of hypoalbuminemia in the development of TECs in severe COVID-19 patients.

Materials and Methods

Study design and data collection

In a single-institution retrospective observational study, we reviewed the case histories of 1,634 patients, aged 68.5 on average (53.7 - 75.1), with a verified diagnosis of SARS-CoV-2 coronavirus infection, admitted to the University Clinical Hospital No. 4 of the Sechenov University that was then operating as a COVID-19 hospital.

We divided our patients into two cohorts depending on whether they had TECs. The group with TECs (group I) included 127 patients with venous TECs (pulmonary artery thromboembolism (PATE) or lower extremity deep vein thrombosis, developed during hospitalization). One thousand five hundred and seven (1,507) patients with COVID-19 not complicated by any thromboembolic events constituted our comparison group (TEC-free, group II).

Their COVID-19 diagnosis was verified as SARS-CoV-2 RNA was found by PCR method in their nasopharyngeal swabs, or using chest computed tomography (CT) scans. The diagnosis of PATE was verified using contrast-enhanced chest CT scans.

All the patients' blood plasma albumin was measured on their first day of hospitalization before infusion therapy was prescribed.

Ethics statement

The study was conducted with the approval of the Institutional Review Board of the Sechenov University (No. 07-22, April 7, 2022). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Statistical analysis

We used the jamovi project (2023, version 2.3, retrieved from https://www.jamovi.org). The quantitative data are presented as the median and interquartile range (Me (Q1 - Q3)). Binomial and categorical variables are presented in terms of both absolute number and percentage. Comparative analysis used the Mann-Whitney U test to compare the quantitative variables. The predictors were established using univariate logistic regression with odds ratio (OR) calculation and a 95% confidence interval (CI). The classification model's cut-off point threshold value was established using receiver-operating characteristic (ROC) analysis with area under the curve (AUC) calculation. Variations with $P < 0.05$ were considered statistically significant.

Results

Basic characteristics of the study group

Our TEC patients were generally older than patients in the TEC-free group. The incidence of arterial hypertension, ischemic heart disease, CHF, chronic kidney disease, and diabetes mellitus was higher in group I than in group II.

CHF with reduced left ventricular ejection fraction was observed in 18 (19.35%) TECs group patients and 35 (9.09%) TEC-free group patients ($P = 0.0047$). TEC patients' glomerular filtration rate was lower than in the TEC-free group (50.9 (37.6 - 71.9) vs. 69.8 (56.3 - 82.0) mL/min/1.73 m^2) ($P < 0.001$). The study excluded patients with glomerular filtration rate below 15 mL/min/1.73 m^2. Decompensated diabetes mellitus was found in 14 (11%) and 52 (3.5%) patients, respectively. Body mass index was 30.9 (25.0 - 35.4) kg/m^2 in the TECs group and 29.2 (25.4 - 33.3) in the TEC-free group ($P = 0.388$).

The percentage of lung tissue involvement was veritably higher in the TECs group than in the TEC-free group (55% (37.5 - 67.5) on average vs. 37.5% (25.0 - 47.5)) ($P < 0.001$). TEC patients' oxygen saturation (SpO_2) on room air was veritably lower than in the TEC-free group (92.0% (88.0 - 95.0) vs. 95.0% (93.0 - 97.0)) ($P < 0.001$) (Table 1).

The treatment of comorbid diseases, which patients received before hospitalization, corresponded to modern recommendations. During hospitalization, intravenous glucocorticoids were prescribed to 62 (48.8%) TEC patients and 502 (33.3%) TEC-free patients, tocilizumab or netakimab to 36 (28.3%) and 409 (27.1%) of the patients, respectively, and all the patients received non-fractionated heparins.

All the 127 (100%) TECs group patients were diagnosed with PATE, and 100 cases (78.74%) were fatal. All the lethal outcomes were caused by massive PATE confirmed by autopsy.

Changes of laboratory findings in the groups under scrutiny

Group I patients had lower hemoglobin levels (126 (109 - 139) g/L) than group II patients (135 (125 - 146) g/L) ($P < 0.001$), and their average thrombocyte and leukocyte counts were within the normal range.

The TEC patients' chemistry panel showed significantly higher levels of urea (8.40 (6.20 - 12.9) mmol/L) and creatinine (109 (87.5 - 133) µmol/L) than the TEC-free group (5.50 (4.30 - 7.10) mmol/L and 92.5 (80.9 - 106) µmol/L, respectively). Group I patients presented with higher glucose levels (6.08 (4.73 - 8.18) mmol/L) than group II (5.10 (4.60 - 5.90) mmol/L) ($P < 0.001$).

The plasma concentration of D-dimer was 3.37 (1.87 - 5.83) mg/mL in group I, veritably higher than that in group II patients (0.831 (0.4 - 1.87) mg/mL). TEC patients presented with significantly higher levels of CRP and interleukin-6 (IL-6) than patients in the TEC-free group (Table 2).

Significance of hypoalbuminemia in TEC development

Hypoalbuminemia was observed in 45 (35.43%) group I patients and 62 (4.11%) group II patients ($P < 0.001$). The TEC patients' plasma albumin level was veritably higher (30.9 (26.2 - 35.3) mg/L) than in the TEC-free group (39.0 (35.1 - 41.7)

Table 1. Patients' Clinical Profile

Attribute	TECs group	TEC-free group	P-value
Number of patients, n (%)	127 (100%)	1,507 (100%)	-
Average age, Me (Q1 - Q3)	75 (62.5 - 82.0)	58 (47.0 - 68.0)	< 0.001
Male patients, n (%)	71 (55.9%)	776 (51.49%)	0.339
Arterial hypertension, n (%)	113 (88.97%)	884 (58.65%)	< 0.001
Ischemic heart disease, n (%)	116 (91.33%)	447 (29.66%)	< 0.001
Chronic heart failure, n (%)	53 (41.73%)	148 (9.82%)	< 0.001
Chronic kidney disease, n (%)	105 (82.67%)	981 (65.09%)	< 0.001
Type 2 diabetes mellitus, n (%)	54 (42.51%)	238 (15.79%)	< 0.001
Obesity, n (%)	23 (18.11%)	175 (11.61%)	0.031
Average pulmonary involvement, Me (Q1 - Q3)	55% (37.5 - 67.5)	37.5% (25.0 - 47.5)	< 0.001
Oxygen saturation on room air (SpO_2), Me (Q1 - Q3)	92.0% (88.0 - 95.0)	95.0% (93.0 - 97.0)	< 0.001

Me: median; TEC: thromboembolic complication.

mg/L) (Fig. 1).

Correlation analysis showed negative correlations between albumin level and inflammation markers. Reduced blood plasma albumin concentrations were correlated with heightened levels of IL-6 ($r = -0.359$, $P < 0.001$), CRP ($r = -0.438$, $P < 0.001$), and D-dimer ($r = -0.413$, $P < 0.001$) (Fig. 2).

In our study, we evaluated the prognostic significance of hypoalbuminemia in the development of TECs in patients with severe COVID-19. By performing single-factor regression analysis, it was shown that a decrease in plasma albumin concentration has a statistically significant effect on the development of TECs in patients with severe course of SARS-CoV-2 infection. It was found that each subsequent 1 g/L decrease in plasma albumin concentration increased the odds of developing TECs by a factor of 1.16 (OR: 0.858, 95% CI: 0.817 - 0.902, $P < 0.001$). This pattern was described by the logistic regression equation as follows:

$$p = 1/(1 + e^{-z}) \times 100\%$$
$$z = 3.914 - 0.153 \times X_{albumin}$$

where p is a probability of TECs developing (%), z is a linear combination of input variables and their coefficients, and $X_{albumin}$ is the albumin concentration in blood plasma (g/L).

In this study, we assessed the prognostic significance of hypoalbuminemia in TECs development in severe COVID-19 patients. Univariate regression analysis showed a reduced plasma concentration of albumin to have a statistically significant effect on the development of TECs by grave SARS-CoV-2 patients. ROC analysis established the breakpoint values of blood plasma albumin. Albumin below 35 g/L increases the chance of TEC development eightfold (AUC: 0.815, OR: 8.5389, 95% CI: 4.5637 - 15.977, $P < 0.001$). The method's sensitivity was 76.34%, and specificity was 72.58% (Fig. 3).

Discussion

It is now proven that cardiovascular diseases are significant contributors to the development of TECs in COVID-19 [9]. TECs are the most frequent in patients with arterial hypertension and atrial fibrillation [10, 11], and the significance of inflammation for TEC development in COVID-19 is also being discussed.

Our study shows an adverse prognostic significance of hypoalbuminemia for the development of TECs in severe cases of SARS-CoV-2 coronavirus infection. Albumin is known to possess anti-inflammatory, antioxidant and antithrombotic properties [12].

A number of major studies demonstrated the significance of hypoalbuminemia as a prognostic marker of TECs across the general population. A meta-analysis by Seidu et al that included 54 studies on a total of 1,492,237 patients found reduced albumin levels to be accompanied by a heightened risk of TEC development (OR: 0.71, 95% CI: 0.61 - 0.83) [13]. An APEX study showed patients with hypoalbuminemia to face a double risk of TECs (OR: 2.119, 95% CI: 1.592 - 2.820) [14].

A number of papers show the significance of hypoalbuminemia as a predictive marker of an unfavorable course of

Table 2. Plasma Concentrations of Inflammation Markers in the Groups Under Scrutiny

Indicator	TECs group	TEC-free group	P-value
C-reactive protein, mg/L	129 (60.1 - 211)	41.0 (12.2 - 97.6)	< 0.001
Ferritin, µg/L	363 (207 - 516)	314 (186 - 516)	0.481
IL-6, pg/mL	176 (52.9 - 471)	39.4 (11.0 - 107)	< 0.001
Fibrinogen, g/L	6.95 (4.98 - 9.13)	5.70 (4.98 - 9.13)	0.003

IL-6: interleukin-6; TEC: thromboembolic complication.

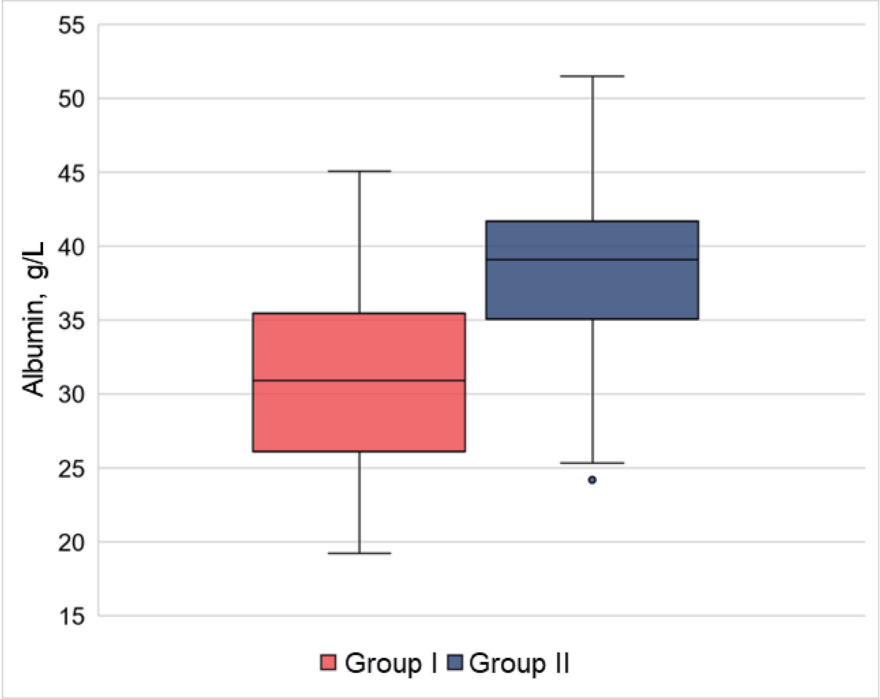

Figure 1. Significance of blood plasma albumin in the groups under scrutiny. The TEC patients' plasma albumin level was veritably higher than in the comparison group. Group I: with TECs, Group II: TEC-free. TECs: thromboembolic complications.

SARS-CoV-2 coronavirus infection [15]. Li et al show the degree of lung involvement in COVID-19 to be related to a lower level of albumin. The authors conclude that hypoalbuminemia may be used as an independent predictor of lethal outcomes for grave COVID-19 patients [16].

Paliogiannis et al explored the link between serum albumin level and COVID-19 outcome. Their meta-analysis included 67 studies involving a total of more than 19,000 patients. The authors showed serum albumin concentrations to have been significantly lower in fatal cases. Low serum albumin was significantly associated to the gravity of COVID-19 [17].

The most important mechanisms of the development of hypoalbuminemia in severe cases of SARS-CoV-2 include a marked inflammatory syndrome resulting in a considerable in-

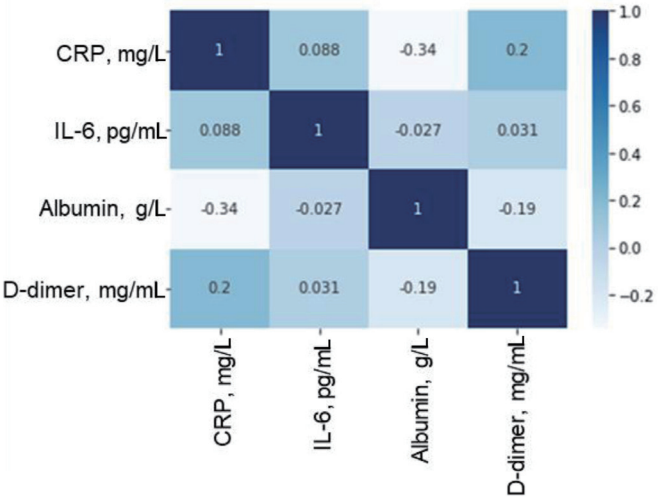

Figure 2. Correlation matrix of relationships between plasma concentrations of albumin, inflammatory markers and D-dimer. CRP: C-reactive protein; IL-6: interleukin-6.

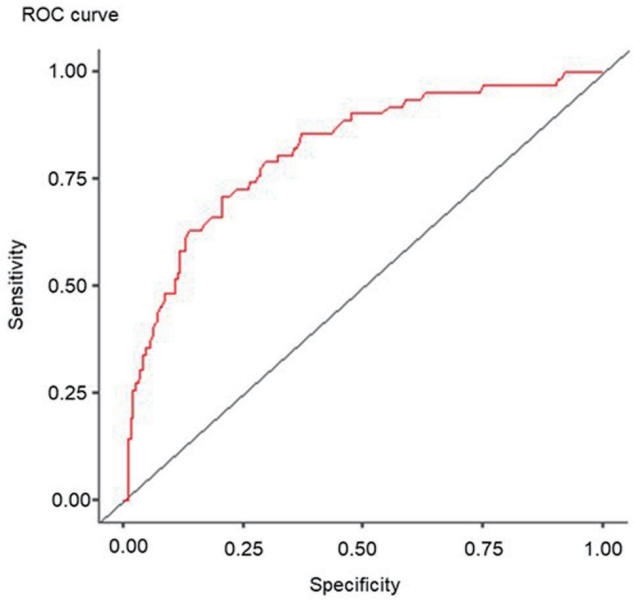

Figure 3. ROC curve of the significance of albumin concentration in severe cases of SARS-CoV-2 coronavirus infection. ROC: receiver-operating characteristic; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

crease in capillary permeability and serum albumin loss into interstitial space [18]. Wu et al suggest that reduced blood plasma albumin in grave COVID-19 patients may be associated with high pulmonary capillary permeability [19].

In our study, we showed TEC patients' pulmonary parenchyma involvement and level of inflammation markers to have been veritably higher than in the TEC-free group. The correlations found demonstrate that a considerable increase in inflammation markers (IL-6 and CRP) is accompanied by a reduced level of blood plasma albumin and development of hypoalbuminemia.

Violi et al arrived at similar findings as they showed plasma albumin level to be inversely related to the levels of D-dimer ($r = -0.385$, $P < 0.001$) and CRP ($r = -0.418$, $P < 0.001$) [20].

Albumin is known to have heparin-like activity [21]. A considerable decrease in blood plasma albumin serves to activate oxidative stress processes and increase thrombocyte aggregation, which are the primary components in the pathogenesis of thrombotic complications [22]. Reduced albumin levels can be observed in a broad range of urgent clinical situations involving a high risk of TECs [23].

Thus, in addition to such well-known predictors of cardiovascular complications as advanced age, comorbidities and high inflammation activity, albumin level can be factored into a comprehensive assessment of TEC risk in hospitalized patients with SARS-CoV-2 coronavirus infection.

Conclusions

Hypoalbuminemia aggravates the risk of TEC development in severe cases of SARS-CoV-2 coronavirus infection.

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

The consent was not obtained from patients as data were analyzed anonymously.

Author Contributions

Conceptualization: AT, AB, VP and AI; methodology: AT, AB, VP and AI; software: AI; validation: AT, AB and AI; formal analysis: AI; investigation: AI and ES; resources: KO; data curation: ES, LP, AT, ND, TV, AP, TS, IC and AI; writing - original draft preparation: AI and AT; writing - review and editing: AT, VP and AB; supervision: VP; project administration: VP. All authors have read and agreed to the published version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

AUC: area under the curve; CI: confidence interval; CRP: C-reactive protein; CT: computed tomography; IL-6: interleukin-6; OR: odds ratio; SpO_2: oxygen saturation; TECs: thromboembolic complications

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