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The role of cardiometabolic risk factors and endothelial dysfunction in serum albumin levels of patients with COVID-19

Evangelos Oikonomou[1, 2], Nektarios Souvaliotis[1], Stamatios Lampsas[1], Gerasimos Siasos[1, 3], Panagiotis Theofilis[2], Emmanouil Korakas[4], Vaia Lambadiari[4], Ignatios Ikonomidis[4], Theodoros Pesiridis[1], Georgios Zakynthinos[1], Ourania Katsarou[1], Dimitris Tousoulis[2], Manolis Vavouranakis[1]

[1]3rd Department of Cardiology, National and Kapodistrian University of Athens, Medical School, Sotiria Chest Disease Hospital, Athens, Greece
[2]1st Department of Cardiology, National and Kapodistrian University of Athens, Medical School, Hippokration General Hospital, Athens, Greece
[3]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
[4]2nd Cardiology Department, Echocardiography Department and Laboratory of Preventive Cardiology, Athens University Hospital Attikon, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

With more than 500 million cases and 6.2 million deaths worldwide, coronavirus disease 2019 (COVID-19) is the biggest global challenge the world is facing in modern times. Growing evidence focuses on the role of hypoalbuminemia in the COVID-19 course and on the role of vascular inflammation in the progression to capillary leak syndrome (CLS) [1]. Hypoalbuminemia is more common in patients with severe COVID-19, and is indicative of a poor prognosis [2, 3]. CLS is characterized by the combination of severe hypoalbuminemia with diffuse pitting edema, exudative serous cavity effusions, non-cardiogenic pulmonary edema, and hypotension which can progress to resistant hypovolemia and shock in the most severe cases. Insulin resistance and overt diabetes mellitus, obesity, dyslipidemia, hypertension, and coronary artery disease all fall under the umbrella of cardiometabolic disease [4]. The common ground between these disorders is endothelial dysfunction, which may be attributed to hereditary and environmental factors, but it also shares various mechanisms with metabolic derangement, especially insulin resistance [5]. The aim of this study is to investigate the role of cardiometabolic risk factors (CRFact) in the endothelial dysfunction-related hypoalbuminemia of hospitalized COVID-19 patients.

In this study, conducted in the "Sotiria" General Hospital for Chest Diseases, Athens, Greece, 73 patients admitted for COVID-19 were enrolled. COVID-19 was confirmed by real-time reverse transcriptase-polymerase chain reaction assay of nasopharyngeal or bronchial swabs, in at least one biological sample. Study parameters, medical history, and laboratory examinations were collected in the acute phase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (between 24 and 72 h after hospital admission). Endothelial function was evaluated by estimating the flow-mediated dilation (FMD) in the brachial artery. According to the presence of obesity (body mass index > 30 kg/m^2), history of hypertension, dyslipidemia, and diabetes mellitus, COVID-19

Address for correspondence: Dr. Evangelos Oikonomou MD, MSc, PhD, 3rd Department of Cardiology, Athens Chest Hospital "Sotiria", National and Kapodistrian University of Athens, Medical School, Mesogeion 152, Athens 11527, Greece, e-mail: boikono@gmail.com

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patients were categorized as those with CRFact or without CRFact (no-CRFact). From the study population, subjects excluded were with a) established cardiovascular disease, b) end-stage renal failure, c) active malignancy, d) previous or current autoimmune diseases.

All individuals were informed about the study's aims and provided written informed consent.

The study was approved by the hospital's Ethics Committee and conformed to the ethical guidelines of the 2008 Declaration of Helsinki.

All statistical calculations were performed using IBM SPSS software Version 26.0. Categorical variables were presented as frequencies and percentages. The Student t-test or Mann-Whitney test were used to assess the differences between groups of normally and non-normally distributed continuous variables, respectively. Differences between categorical variables were tested by forming contingency tables and performing χ^2 tests. The Pearson and Spearman coefficients were used for parametric and nonparametric correlations, respectively. All reported p-values were based on two-tailed tests, with a p-value < 0.05 being considered statistically significant.

The 73 patients enrolled were (male: 63%), hospitalized for COVID-19 in the present study, with a mean age of 60.6 years. Patients with CRFact (50 patients) were significantly older (63.8 ± ± [standard deviation] 10.9 years vs. 53.8 ± 14.4 years, p = 0.002), with lower FMD (1.2 ± 2.1% vs. 2.7 ± 2.4%, p = 0.006) and higher interleukin-6 (IL-6) (16.1 [5.7, 81.9] pg/mL vs. 3.5 [1.5, 36.8] pg/mL, p = 0.01) compared to those without CRFact. No differences in C-reactive protein (CRP) were noted (6.7 [3.4, 10.7] mg/dL vs. 6.4 [2.5, 12.5] mg/dL, p = 0.71). As far as serum albumin is concerned, significantly lower concentrations were found in patients with CRFact compared to those without CRFact (3.1 ± 0.7 g/dL vs. 3.6 ± ± 0.3 g/dL, p = 0.003) (Fig. 1). Interestingly, serum albumin in patients with CRFact was significantly lower than the lower reference limit (3.5 g/dL) of albumin (p < 0.001), a finding which was not confirmed in patients without CRFact (p = 0.28). Furthermore, regression analysis revealed that, irrespective of age, the presence of CRFact was associated with decreased serum albumin levels (by 0.34 g/dL, 95% confidence interval: –0.65 to –0.03, p = 0.03). Finally, significant correlations of serum albumin with FMD (R = 0.30, p = 0.03) and inverse correlations of albumin with inflammatory biomarkers (IL6: rho = –0.68, p < 0.001 and CRP: rho = –0.47, p < 0.001) were only detected in subjects with CRFact.

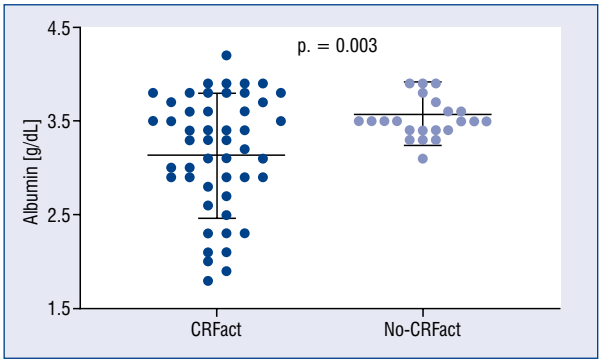

Figure 1. Serum albumin levels in patients with and without cardiovascular risk factors (CRFact).

In this cross-sectional study, patients with CRFact hospitalized for COVID-19 presented with significantly lower serum albumin levels compared to COVID-19 patients without CRFact. Importantly, albumin levels in this group of patients were associated with impaired endothelial function and inflammatory response.

Albumin appears to be a critical mediator of COVID-19 course and outcome. Even though the mechanisms of hypoalbuminemia in COVID-19 have not been elucidated, it is believed that systemic inflammation may precipitate to leakage of albumin to the interstitial space due to increased capillary permeability, the so-called CLS. Hepatocellular injury-induced hypoalbuminemia is unlikely since albumin's half-life (21 days) is much longer than the time from symptom onset in the current study (median 6 days). As decreased serum albumin levels may be related to the hyperinflammatory state and endothelial cell dysfunction in COVID-19 [6–8], a pre-existing inflammatory state paired with impaired endothelial function in the setting of cardiometabolic diseases (obesity, hypertension, diabetes mellitus, dyslipidemia) could be a contributing factor, as we have reported. As serum albumin levels were correlated with indices of dysfunctional endothelium and pro-inflammatory markers only in the group of patients with cardiometabolic risk factors, it may be hypothesized that capillary leakage of albumin is another pathophysiologic mechanism of increased disease severity in these patients. Existing evidence highlights the association of hypoalbuminemia with poor COVID-19 prognosis [9]. At the same time, decreased serum albumin may be observed more frequently in hy-

pertensive or diabetic patients [10], as also seen in the present study.

To conclude, serum albumin levels may be an important clue of capillary leakage in patients with cardiometabolic risk factors, which is associated with inflammation and endothelial dysfunction. Capillary leakage of albumin, through the routine measurement of its serum levels, at least the first few days of hospital admission, should be promptly identified. This is important especially in patients at risk of poor COVID-19 outcome, who may benefit from early advanced treatment modalities and possibly by immunomodulatory or anti-inflammatory therapy. Whether hypoalbuminemia correction may benefit patients merits further research.

Conflict of interest: None declared

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