Hypoalbuminemia, Coagulopathy and Vascular Disease in Covid-19

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Coagulopathy has been suggested to complicate the clinical course of coronavirus 2019(Covid-19) but the underlying mechanism is unclear.[1] Previous study showed that hypoalbuminemia, i.e. serum albumin(SA) <35g/L, is associated with an elevated D-dimer and enhanced risk of artery and venous thrombosis.[2] However, data regarding SA, coagulopathy and vascular disease in Covid-19 are unknown. This observational study included adult (≥18 years) patients with laboratory-confirmed Covid-19 according to the WHO interim guidance.[3] During the intra-hospital stay any vascular event was registered. The study was approved by local Ethics Committee (ID Prot. 109/2020). Characteristics of patients according to ICU admission are reported in Table 1. All patients were treated with low-molecular weight heparin. Among the variables examined, ICU patients showed higher D-dimer and lower SA compared to non-ICU ones(Table 1). SA inversely correlated with D-dimer (Rs=-0.385; p<0.001) and hs-CRP (Rs=-0.418; p<0.001).

Patients with SA <35 g/L showed higher levels of creatinine, hs-CRP and D-dimer compared to patients with SA >35 g/L. (Table 1). Also, the percentage of patients with D-dimer 4-fold above upper normal limit was 66% (36/54) in patients with SA <35 g/L versus 31% (6/19) in those with ≥35 g/L (p=0.008).

Median in-hospital stay was 15 days (IQR: 10-22). Seventeen patients experienced ischemic events: 11 acute limb ischemia, 2 pulmonary embolisms, 3 myocardial infarctions, 3 strokes/TIAs. Compared to vascular-free patients, those with events showed lower SA (32.2±5.3 vs. 29.6±3.5 g/L, p=0.023) and higher D-dimer (2154 [853-4610] vs. 4610 [1814-4700] ng/ml, p=0.013), respectively. SA <35 g/L were present in 94% of patients who experienced ischemic/embolic events vs. 68% vascular-free patients (p=0.031).

SA <35 g/L was detected in 74% of the Covid-19 patients with a higher prevalence in ICU ones. Hypo-albuminemia is explained by the acute-phase response property of albumin, increased vascular permeability and kidney or liver disease;[2] in our cohort SA was associated with hs-CRP and creatinine but not with liver damage or albuminuria(not shown). SA <35g/L was associated with a higher percentage of patients with D-dimer values 4-fold above upper normal limit, which is considered a marker of thrombin generation.[1] The association between hypo-albuminemia and hypercoagulability may be explained by its anticoagulant and antiplatelet activities;[4,5] also, a pilot study showed that albumin infusion is associated with platelet inhibition.[5] The coexistence of hypoalbuminemia with elevated D-dimer could negatively influence Covid-19 patients' outcomes. Thus, the 17 patients with ischemic events had lower SA and higher D-dimer compared to vascular event-free patients; of note, sixteen of them had SA <35 g/L. However, a cause-effect relationship between hypoalbuminemia and hypercoagulability cannot be established and further study is needed to support this hypothesis. In conclusion, hypoalbuminemia and coagulopathy coexist in severe Covid-19 patients and are associated with vascular disorders.

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Table 1. Clinical and laboratory characteristics of study patients, according to the intensive care unit (ICU) admission.

	All patients	Non-ICU	ICU	p	Albumin <35 g/L	Albumin ≥35g/L	p
N.	73	20	53		54	19	-
Age	67.1±13.8	66.8±15.2	67.2±13.4	0.932[a]	66.9±12.9	68.0±16.2	0.780[a]
Men	81%	75%	83%	0.509	78%	90%	0.331
Creatinine (mg/dl)	1.25±0.82	1.01±0.33	1.34±0.93	0.028[a]	1.29±0.9	1.13±0.41	0.028[a]
high sensitivity C-Reactive Protein (mg/L)	100 [35-193]	47 [15-94]	114 [67-207]	0.001[b]	115 [55-214]	45 [21-103]	0.002[b]
sPO_2 (%)	92±8	94±4	83±12	0.007[a]	91±7	84±15	0.736[a]
White blood cells (x1000/mm^3)	6.9±3.0	6.8±2.1	7.9±4.3	0.034[a]	6.9±2.9	6.8±3.4	0.908[a]
D-dimer (ng/ml)	3166[992-4655]	1218 [750-4020]	4610 [1385-4700]	0.005[b]	4610 [1519-4700]	965 [654-3377]	0.002[b]
Albumin (g/L)	31.7±5.1	33.6±5.9	30.9±4.5	0.041[a]	-	-	-
Albumin < 35 g/L	74%	55%	81%	0.036	-	-	-

Differences between percentages were assessed by Fisher exact tests. All continuous variables were tested for normality with the Shapiro-Wilk test. [a]Student unpaired t-test was used for normally distributed continuous variables (expressed as mean±SD). [b]Mann-Whitney U test was used for not-normally distributed continuous variables (expressed as median[interquartile range]).

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