

Letter to the Editor

Elena Aloisio*, Ludovica Serafini, Mariia Chibireva, Alberto Dolci and Mauro Panteghini

Hypoalbuminemia and elevated D-dimer in COVID-19 patients: a call for result harmonization

<https://doi.org/10.1515/cclm-2020-1038>

Received July 6, 2020; accepted July 8, 2020; published online July 21, 2020

Keywords: coagulation; Covid-19; D-dimer; harmonization; hypoalbuminemia.

To the Editor,

Recently, Violi et al. described a link between hypoalbuminemia and hypercoagulability, revealed by increased plasma D-dimer levels, in a group of 73 COVID-19 patients [1]. The authors found that patients with serum albumin <35 g/L showed significantly higher concentrations of D-dimer compared to patients with albumin ≥35 g/L and, more importantly, had a higher probability of intensive care treatment. Furthermore, the percentage of patients with D-dimer results 4-fold above the upper reference limit (URL) was significantly higher in patients with low albumin concentrations.

We recently performed a study on 427 COVID-19 patients deriving cut-off values for six biochemistry tests showing high sensitivity and negative predictive value for excluding the need of admission in intensive care unit (ICU) during hospital stay [2]. Particularly, the best cut-offs for serum albumin and plasma D-dimer, the latter expressed as fibrinogen-equivalent units (FEU), associated with the ability in detecting patients not at risk of ICU admission, were ≥29 g/L and <1704 µg/L FEU, respectively. It is interesting to note that for D-dimer this cut-off is only

slightly lower than the 4-fold change above the URL (in our laboratory: 500 µg/L FEU for patients ≤50 years old and 'age years × 10' µg/L FEU for patients >50 years old) reported as a sign of increased thrombin generation by Violi et al. and other authors [1, 3].

In the population of our original study, 349 patients out of 427 had at least one determination of both D-dimer and serum albumin, and were therefore included in the following evaluation. Characteristics of these patients are reported in Table 1. Quite similarly to Violi et al. [1], we found that serum albumin concentrations inversely correlated with D-dimer ($r=-0.351$, $p<0.001$), and that D-dimer values 4-fold above URL were significantly associated both with serum albumin <29 g/L and an increased probability of ICU admission. In terms of absolute biomarker levels in the respective populations, it is however somewhat difficult to compare our results with those of Violi et al. as the authors do not make any remark about the methodology used to determine albumin nor about the units used to express D-dimer results. It is known that immunoturbidimetric assays for the determination of serum albumin, such as the one in use in our institution, are specific for the protein measurement contrary to nonspecific colorimetric methods which are in use in the majority of clinical institutions worldwide [4]. This issue probably explains why albumin concentrations in our population appear to be lower than those reported by Violi et al. and also why the great majority of our COVID-19 patients (89%) had albumin levels <35 g/L, regardless of ICU admission (Table 1). In our clinical setting, the application of the <35 g/L cut-off, which in our laboratory simply represents the lower limit derived from a reference population, is unable to discriminate efficaciously between complicated COVID-19 patients requiring ICU admission and other patients. On the other hand, the expression of D-dimer results as µg/L FEU, which relate the mass of D-dimer to the mass of fibrinogen, or as D-dimer µg/L units (DDU), which relate to the mass of D-dimer alone, leads in average to a 1.75-fold difference in the numerical result obtained by measuring the same sample, with results expressed as FEU being higher than those expressed as DDU. The use of FEU has

***Corresponding author: Elena Aloisio**, MD, Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Via GB Grassi 74, 20157, Milan, Italy, Phone: +39 02 50319848, Fax: +39 02 39042896, E-mail: elena.aloisio@unimi.it

Ludovica Serafini and Mariia Chibireva: Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Milan, Italy

Alberto Dolci: Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Milan, Italy; Department of Biomedical and Clinical Sciences 'Luigi Sacco', University of Milan, Milan, Italy

Mauro Panteghini: Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Milan, Italy; Department of Biomedical and Clinical Sciences 'Luigi Sacco', University of Milan, Milan, Italy; and Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

Table 1: Characteristics of studied COVID-19 patients according to intensive care unit (ICU) admission and serum albumin concentrations.

	All patients	Non-ICU	ICU	p	Albumin <29 g/L	Albumin ≥29 g/L	p
n	349	302 (87%)	47 (13%)		232 (66%)	117 (34%)	
Age, years	62 (50–72)	61 (50–73)	64 (57–70)	0.791	68 (58–74)	50 (44–60)	<0.001
Male	241 (69%)	200 (66%)	41 (87%)	0.007	170 (73%)	71 (61%)	0.030
D-Dimer, µg/L FEU	1554 (796–5650)	1299 (727–4355)	11,870 (3614–28,919)	<0.001	3109 (1172–9271)	762 (474–1526)	<0.001
D-Dimer >4 × upper reference limit	135 (37%)	95 (31%)	40 (85%)	<0.001	116 (50%)	19 (16%)	<0.001
Albumin, g/L	26 (22–30)	27 (24–31)	18 (16–20)	<0.001	-	-	-
Albumin <35 g/L	310 (89%)	263 (87%)	47 (100%)	0.018	-	-	-
Albumin <29 g/L	232 (66%)	188 (62%)	44 (94%)	<0.001	-	-	-

Data are reported as absolute number with percentage for categorical variables and median with interquartile range for quantitative variables. Differences between variables were assessed by applying the chi-squared test (categorical) and the Mann-Whitney rank-sum test (quantitative). Normality was preemptively excluded for all continuous variables by performing the Shapiro-Wilk test.

been recommended to avoid erroneous classification of normal and abnormal D-dimer results and reporting values using alternative units may be misleading [5]. Although Violi et al. did not explicitly mention in which unit their D-dimer results are expressed, one can speculate the use of DDU and this may represent a confounding factor for result interpretation and application in other settings.

In conclusion, our data support the hypothesis that hypoalbuminemia may be related to hypercoagulability, a condition that has been widely associated with severe clinical conditions in COVID-19, and that the cause-effect relationship between these two biomarkers should be investigated more thoroughly [1]. We want, however, to remark here how the issues of analytical and post-analytical harmonization are fundamental for providing optimal health care. Only the use of assays and units of measurement providing harmonized results will allow the application of common decision limits and the comparability of results obtained in clinical studies performed in different institutions, without any ambiguity in their interpretation. Quite recently, Favaloro and Thachil have similarly stressed the need to harmonize D-dimer assays to a single unit of measurement in order to decrease confusion and avoid misinformation [5].

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' Institutional Review.

References

- Violi F, Ceccarelli G, Cangemi R, Alessandri F, d'Ettoire G, Oliva A, et al. Hypoalbuminemia, coagulopathy and vascular disease in Covid-19. *Circ Res* 2020. <https://doi.org/10.1161/CIRCRESAHA.120.317173> [Epub ahead of print].
- Aloisio E, Chibireva M, Serafini L, Pasqualetti S, Falvella FS, Dolci A, et al. A comprehensive appraisal of laboratory biochemistry tests as major predictors of COVID-19 severity. *Arch Pathol Lab Med* 2020, in press.
- Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemostasis* 2020. <https://doi.org/10.1111/jth.14810> [Epub ahead of print].
- Infusino I, Panteghini M. Serum albumin: accuracy and clinical use. *Clin Chim Acta* 2013; 419: 15–8.
- Favaloro EJ, Thachil J. Reporting of D-dimer data in COVID-19: some confusion and potential for misinformation. *Clin Chem Lab Med* 2020; 58: 1191–9.