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ORIGINAL ARTICLE
COVID-19 SECTION

Serum albumin, clotting activation and COVID-19 severity: a systematic review and meta-regression analysis of 4579 patients

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ABSTRACT

BACKGROUND: Preliminary data showed that serum albumin (SA), an acute phase protein with anticoagulant property, is inversely associated with thrombotic complications in respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection associated disease (COVID-19). We performed a meta-analysis to corroborate this finding on a large sample population.
METHODS: We performed a systematic review and meta-regression analysis of clinical studies reporting data on SA according to the severity of COVID-19 disease. COVID-19 severity was defined as: 1) admission to the Intensive Care Unit; 2) acute respiratory distress syndrome; or 3) in-hospital death.
RESULTS: We included 16 studies with 4,579 patients with SARS-CoV-2 infection. Mean age was 51.5 years, and 2146 (44.2%) of patients were women. Overall, 1199 (31.3%) of patients had severe COVID-19 (range 5.4% to 72.6%). Mean SA level was 37.15 g/L. The pooled analysis showed a mean difference of SA: -4.06 g/L (95% CI -4.98/-3.15) in severe COVID-19 compared to non-severe ones. This difference ranged from -7.10 g/L to 1.09 g/L. At meta regression analysis, the difference in SA levels between severe and non-severe COVID-19 patients was more evident in studies with high D-Dimer (P<0.001) and procalcitonin (P=0.07), suggesting a more SA reduction in patients with thrombotic/septic disease.
CONCLUSIONS: SA is significantly reduced in severe COVID-19 and associated with elevated D-Dimer. Albumin supplementation may be tested as adjunctive therapeutic strategy to reduce the thrombotic risk.

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KEY WORDS: Albumins; COVID-19; SARS-CoV-2.

Low serum albumin (SA) levels have been associated with an increased risk of cardiovascular events both in primary and secondary prevention clinical settings.[1, 2] Circulating SA levels may be reduced as a consequence of impaired liver synthesis, increased urinary excretion, or in patients with acute/chronic inflammation.[3]

The relationship between SA and cardiovascular disease relies on the role of albumin as modulator of the clotting system[4] and platelet activation.[5, 6] Other studies have also highlighted

the association between hypoalbuminemia and mortality in critically ill and septic patients.[7]

Along with other clinical and biochemical variables,[8] also levels of SA have been recently investigated in studies including patients suffering from the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection associated disease (COVID-19).[9] SA has been shown to be a contributing factor for a prothrombotic phenotype complicating the clinical course of COVID-19 patients,[10] as suggested by the inverse correlation with D-Dimer, and a significant association with thrombosis-related vascular disease, which was more evident in patients with SA<35 g/L; of note, patients with similarly reduced SA were also more likely to experience complications as in-hospital death.[11]

Due to the potential relevance of albumin as anti-inflammatory, antioxidant and anticoagulant protein, analysis of SA predictors would be of interest. As a previous study on a small series reported that severe COVID-19 was associated with low albumin levels,[9] we investigated the robustness of such association in a larger population. Furthermore, we analyzed the factors affecting low SA according to the severity of the disease.

Materials and methods

We performed a systematic review and meta-analysis of literature including all studies that enrolled patients with COVID-19 to investigate the association between SA and COVID-19 severity. COVID-19 severity was defined as the presence of 1 of the following criteria: 1) admission to the Intensive Care Unit (ICU); 2) developing of acute respiratory distress syndrome (ARDS); and 3) in-hospital death. To evaluate the role of SA in COVID-19 severity we compared mean SA concentrations in patients with and without severe COVID-19 manifestations.

In each study we collected data about age, female sex, white blood cells (WBC) count, lymphocytes count, platelet count (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, Creatinkinase, lactate dehydrogenase (LDH), D-Dimer, C-reactive protein (CRP), procalcitonin (PCT) serum levels, analyzing the differences of this analytes levels between patients with and without severe COVID-19 disease.

Eligibility criteria

We included in the research strategy only randomized clinical trials, prospective or retrospective cohort studies that reported Albumin levels and severity degree of the SARS-CoV-2 infection at the baseline, while were excluded from this research case series, case reports, cross sectional studies, review, and studies without baseline levels of SA. Only publications involving humans and written in English language with full text available were included in the metanalysis. For further information see PRISMA flow diagram in Supplementary Digital Material 1: Supplementary Figure 1.

Information sources

The studies were identified by searching electronic databases. This search was applied to PubMed, ISI Web of Science, Scopus and Cochrane database. The last search was run on April 23. Reference lists of all studies included in the present metanalysis were screened for potential additional eligible studies.

Database search

Two investigators (FDS and DM) independently searched in the electronic databases combining the following text terms and MeSH terms: "COVID-19" [All Fields] OR "SARS-CoV-2" [All Fields] OR "2019-nCoV" [All Fields] AND "albumin" [All Fields] OR "serum albumin" [All Fields]. PRISMA flow diagram is reported in Supplementary Digital Material 1: Supplementary Figure 1.

Studies analysed in the selection phase were frequently retrospectives and often involved a low number of patients. Furthermore, a lot of studies included in our meta-analysis had a Chinese cohort that may not show the same characteristics of a Caucasian cohorts.

Study selection and quality assessment

Two authors (FDS and DM) independently reviewed titles and abstracts generated by search.

Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis. For potentially eligible studies or if the relevance of an article could not be excluded with certitude, we procured the full text. Disagreements were resolved by discussion between FDS and DM; if no agreement reached, a third author (DP) decided. The quality of observational studies was assessed by the Newcastle–Ottawa scale. Studies with a score ≥7 were considered of good quality. Quality assessment of each study is reported in Supplementary Digital Material 1: Supplementary Table I.

Statistical analysis

Data were reported as means with standard deviation (SD). When data were reported as median and interquartile range,[12-15] means and SD were approximately estimated by means of the method described by Wan *et al*.[16] Mean differences (MD), and their standard error were calculated.

The proportion of variability in point estimates attributable to between-study heterogeneity was quantified by the I^2 statistic[17] and interpreted qualitatively as low (25-50%), moderate (50-75%), and high (75-100%)[18] Heterogeneity was also examined using τ2 and Cochrane Q statistics. Given heterogeneity across trials, DerSimonian-Laird random effects model was used.

Statistical heterogeneity was explored by modeling study-level characteristics using univariable meta-regression. Following potential modifiers were assessed: age, sex, ALT, AST, D-Dimer, CK, PCT, white blood cells and lymphocytes, platelet count, LDH CRP, and creatinine.

Results of meta-regression were summarized by means of bubble plots, with bubbles proportional to the inverse variance of each study and trends estimated through non-parametric local polynomial regression. Funnel-plots, Egger's regression test[19] were used to assess publication bias. All meta-analytic calculations were made using R 3.6.3 (IBM; Armonk, NY, USA). All significance tests were 2-tailed, with $P<0.05$ considered statistically significant.

Results

We included a total of 16 studies with 4579 patients with SARS-CoV-2 infection (Table I).[12-15, 20-31] Mean age was 51.5 years, ranging from 32.96 to 69.83 among studies; 2146 (44.2%) of patients were women.

Overall, 1199 (31.3%) of patients had severe COVID-19. The proportion of severe patients ranged from 5.4% in the cohort by Huang *et al*., to 72.6% in the study by Violi *et al*. (Table I).[12-15, 20-31]

Mean SA level was 37.15 g/L. In all studies SA levels were lower in patients with a severe disease, with the exception of Zhou *et al*.; however,

TABLE I.—*Studies included in the systematic review and metanalysis.*

Study	Study design	Study population	Age	Women (N.)	Women (%)	Albumin (g/L)	Severe patients (N.)	Severe patients (%)
Huang *et al.*[12]	P	41	49.00	11	26.8	31.40	13	31.7
Zhou *et al.*[13]	R	191	56.00	72	37.7	32.30	54	28.3
Wu *et al.*[14]	R	201	51.00	73	36.3	32.75	84	41.8
Mo *et al.*[15]	R	155	54.00	69	44.5	38.00	85	54.8
Zhang *et al.*[20]	R	115	49.52	66	57.4	38.79	31	27.0
Liu *et al.*[21]	P	78	38.00	39	50.0	40.47	11	14.1
Gong *et al.*[22]	R	189	47.74	88	46.6	38.87	28	14.8
Zhou *et al.*[23]	R	17	41.71	11	64.7	45.23	5	29.4
Violi *et al.*[24]	P	73	67.10	14	19.2	31.70	53	72.6
Bonetti *et al.*[25]	R	144	69.83	49	34.0	35.58	70	48.6
Huang *et al.*[26]	R	2623	62.38	1300	49.6	35.47	615	23.4
Huang *et al.*[27]	R	299	53.40	139	46.5	37.30	16	5.4
Ji *et al.*[28]	R	157	51.00	53	33.8	37.00	69	43.9
Deng *et al.*[29]	R	65	32.96	29	44.6	41.89	12	18.5
Yao *et al.*[30]	R	108	52.00	65	60.2	38.60	25	23.1
Zhou *et al.*[31]	R	123	37.00	68	55.3	41.96	28	22.8

P: Prospective; R: retrospective.

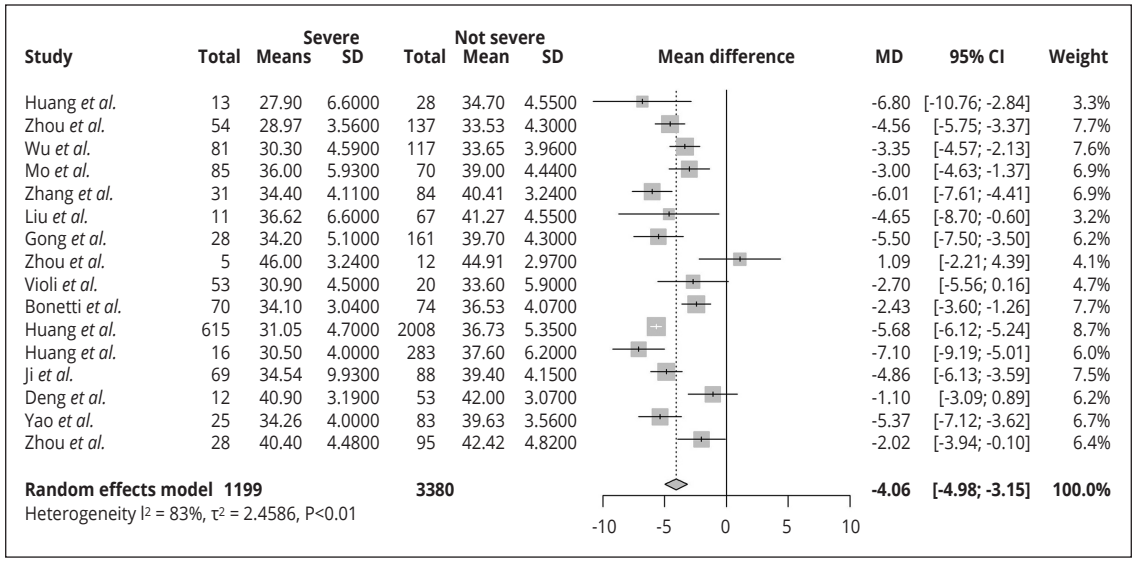

Figure 1.—Forest and funnel plots for the mean difference in albumin serum levels between severe and non-severe COVID-19 patients.[12-15, 20-31]

TABLE II.—*Biochemical characteristics of patients according to the severity of disease.*

Variable	Number of studies	Severe	Non-severe
White blood cells (N./mm^3)	13	6.74±2.27	4.74±0.67
Lymphocytes (N./mm^3)	13	0.79±0.24	1.18±0.14
Platelet count (×10^3/μL)	11	173.31±17.38	184.85±18.18
AST (U/L)	12	37.03±10.9	24.67±7.58
ALT (U/L)	14	26.96±9.18	21.87±4.24
Creatinine (mg/dL)	12	0.95±0.24	0.80±0.12
LDH (mg/dL)	11	384.76±118.02	226.17±49.22
D-Dimer (μg/mL)	12	2.29±2.88	0.76±0.46
CRP (mg/L)	13	74.14±44.61	18.36±17.6
Procalcitonin (ng/mL)	8	0.12±0.085	0.12±0.075
Creatinkinase (U/L)	8	39.95±96.11	33.48±67.78

this study was the one with the smallest sample size (N.=17). The pooled analysis showed a difference of mean difference of SA: -4.06 g/L (95% CI: -4.98/-3.15) in severe COVID-19 compared to non-severe ones. This difference ranged from -7.10 g/L in the study by Huang J to 1.09 in the study by Zhou *et al*. (Figure 1).[12-15, 20-31]

Meta-regression analysis

Table II reports mean values of variables used for meta regression analysis according to the severity of the disease. We found that the difference in SA levels between severe and non-severe patients was independent of age, proportion of women, AST, ALT, and creatinine (Figure 2). Furthermore, the difference in SA was more evident in studies with high D-Dimer (P<0.001 at sensitivity analysis) and PCT (P=0.07) (Figure 2).

Finally, no difference according to WBC count, lymphocyte, CRP, LDH, CK, and platelet count was found (Figure 2).

Discussion

Our analysis shows that serum albumin levels are reduced in patients with severe COVID-19 patients, as compared to non-severe ones and are associated with coagulopathy.

The study supports and extends our previous report showing that SA is reduced in COVID-19: thus, in the entire population SA levels were

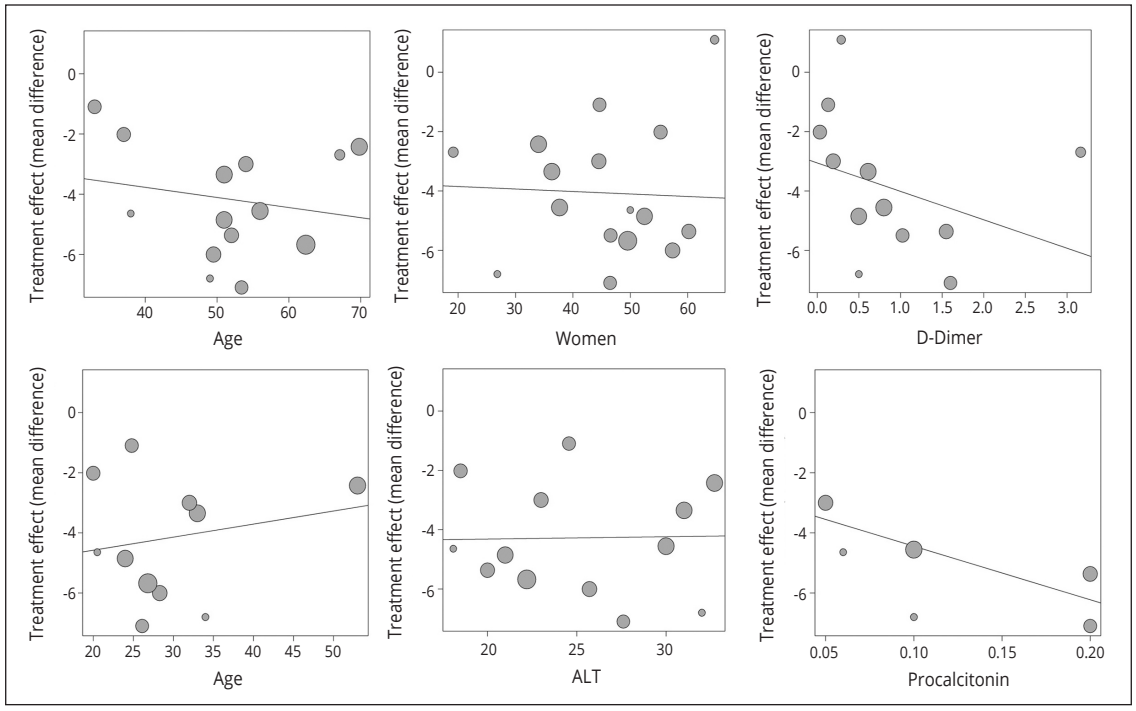

Figure 2.—Bubble plots of factors potentially affecting the difference in serum albumin levels.

37.15 g/L with a marked difference between patients with severe and non-severe disease. Of note, we found 4 g/L difference between patients with severe *versus* non-severe COVID-19, which may be clinically relevant as this decrease of SA is associated with a combined risk ratio of 1.5 for coronary heart disease.[2]

To investigate potential factors affecting SA levels, we performed meta-regression analysis using demographic characteristics and some common laboratory variables used in clinical practice. We did not find any association between SA difference and the proportion of women, mean age and liver serum enzymes. This latter finding is of clinical interest as it suggests that the difference of SA between severe and non-severe patients is not related to a concomitant acute liver damage. Conversely, SA tended to be lower in patients with high PCT patients, suggesting that bacterial over-infection/sepsis of COVID-19 is associated with low albumin levels. This is consistent with the fact that albumin is an acute phase protein and therefore its distribution and structure are rapidly modified in critically ill patients. Thus, an increasing transcapillary escape of albumin (up to 300%) due to an increased capillary permeability has been described during acute inflammatory status.[32] Furthermore, pro-inflammatory interleukins like IL-6 and TNF-α induce a shift toward an increased transcription of mRNA of CRP instead of albumin in different clinical settings.[33, 34] In addition to reduced synthesis, albumin is consumed in conditions of increased oxidative stress such as acute inflammation, as it acts as scavenger of free radical oxidant species.[35] Finally, albumin reduction may be caused by an increased rate of albuminuria secondary to systemic infectious disease;[36] despite creatinine did not influence serum albumin in our analysis, such possibility cannot be excluded.

In a previous study, including COVID-19 patients, we have reported that low SA is associated with elevated D-Dimer, suggesting that this change may negatively influence clinical outcomes by enhancing the thrombotic risk;[24] thus, albumin behaves as an antithrombin-like molecule and lower platelet aggregation in virtue of its antioxidant property. The present study showing that SA difference increased with the level of D-Dimer reinforces the evidence that a more

pronounced reduction of albumin is evident in COVID-19 patients with a pro-thrombotic phenotype.

Limitations of the study

Our analysis has limitations and implications. All studies reported values of SA at admission, so we do not know if changes of SA values occurring during in-hospital staying may be associated with worse prognosis. Furthermore, no study reported data on albuminuria, so we cannot explore if systemic hypo-albuminemia is secondary to increased urinary excretion of albumin.

Conclusions

The significant reduction of SA in severe COVID-19 patients suggests a potential usefulness of its administration to lower inflammation and eventually the thrombotic risk in COVID-19 patients. In conclusion, SA levels are reduced in patients with severe COVID-19. Albumin supplementation could represent an adjunctive strategy to improve the prognosis of COVID-19 patients.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Daniele Pastori, Pasquale Pignatelli, Danilo Menichelli and Francesco Del Sole have given substantial contributions to study conception and design, Danilo Menichelli and Francesco Del Sole to data acquisition and interpretation, Arianna Di Rocco and Annarita Vestri to data analysis, Danilo Menichelli, Daniele Pastori, Francesco Del Sole and Arianna Di Rocco to manuscript writing, Pasquale Pignatelli, Annarita Vestri and Francesco Violi to manuscript revision. All authors read and approved the final version of the manuscript.

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