

Plasma Antithrombin Values Are Significantly Decreased in Coronavirus Disease 2019 (COVID-19) Patients with Severe Illness

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Antithrombin, a 432-aminoacid serpin produced by the liver, is now recognized as one of the most powerful endogenous anticoagulants, which functions by competitively inhibiting the activity of thrombin and activated factor X (FXa).^{1,2} Both inherited and acquired antithrombin deficiencies are associated with a magnified thrombotic risk, especially venous thromboembolism.³ Importantly, reduced antithrombin levels are also observed in patients with intravascular consumption coagulopathies, including those caused by bacteria, viruses, and other microorganisms.² Since both venous and arterial thrombotic complications are commonly observed in patients with coronavirus disease 2019 (COVID-19) and appear to have a significant impact on patient prognosis,⁴ we performed a literature search to identify all clinical studies that measured antithrombin in COVID-19 patients and correlated the values of this endogenous inhibitor with disease severity.

A digital search was conducted of PubMed, Scopus, and Web of Science, with the keywords “coronavirus disease 2019” OR “COVID-19” AND “antithrombin” in all fields, up to present time (i.e., July 25, 2020), without language restriction. Two independent reviewers analyzed the title, abstract, and full text of all documents. Studies reporting plasma antithrombin values in patients with or without severe COVID-19 illness and with a sample size of > 10 patients were finally selected. The reference lists of all articles were also analyzed, with the scope of detecting additional potentially eligible studies. A pooled analysis was finally performed, calculating the weighted mean difference (WMD) along with its 95% confidence interval (95% CI), of

antithrombin values in COVID-19 patients with or without severe illness. When mean value and standard deviation were not directly reported, they were calculated from the sample size, median, and interquartile range, according to the method proposed by Hozo et al.⁵ A random-effect model was applied for adjusting for potential heterogeneity arising across the different studies. Heterogeneity was evaluated with χ^2 test and I^2 statistic. The statistical analysis was performed using MetaXL software Version 5.3 (EpiGear International Pty Ltd.). The study was performed in accordance with the declaration of Helsinki and within the terms of local legislation.

Our initial electronic search generated a total number of 60 documents, of which 54 were excluded because they were review articles ($n = 24$), did not report antithrombin data ($n = 12$), were editorial material ($n = 9$) or case reports ($n = 5$), did not stratify antithrombin values according to disease severity ($n = 3$), or had an insufficient sample size ($n = 1$). No inter-reviewer disagreement emerged. The final analysis thereby included six studies,^{6–11} five cross-sectional and one prospective, totaling 471 COVID-19 patients, of whom 197 (41.8%) had severe disease (► **Table 1**). Three studies were performed in China, two in Italy, and one in France. Severe COVID-19 illness was defined as the need for intensive care unit (ICU) admission in four studies, and terminal stage of disease or severe hemostatic derangement in the remaining two investigations.

The results of both individual investigations and the pooled analysis are shown in ► **Fig. 1**. In five studies, antithrombin values were found to be lower in COVID-19 patients with severe illness (in all except for one, the difference was statistically significant), with differences ranging

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Table 1 Summary of clinical studies that investigated the antithrombin values in coronavirus disease 2019 (COVID-19) patients with or without severe illness

Authors	Setting	Study design	Sample size	Age, years	Females (%)	Endpoint
Han et al ⁷	China	Cross-sectional	59	N/A	49	ICU admission
Nougier et al ⁹	France	Cross-sectional	78	60 ± 14	35	ICU admission
Ranucci et al ¹⁰	Italy	Prospective	16	61 ± 3	6	Severe hemostatic derangement
Zhang et al ¹¹	China	Cross-sectional	19	62 ± 13	45	Terminal stage
Boscolo A et al ⁶	Italy	Cross-sectional	64	65 ± 4	16	ICU admission
Liao et al ⁸	China	Cross-sectional	235	63 ± 6	46	ICU admission

Abbreviations: ICU, intensive care unit; N/A, not available.

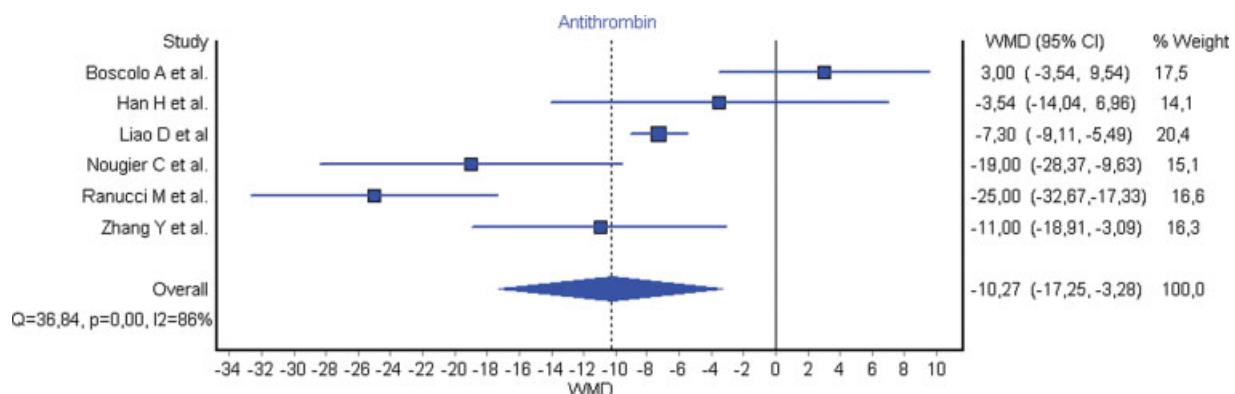
from -4 and -25 IU/dL. In a single study, mean antithrombin value was found to be slightly higher in severe COVID-19 patients, though such difference did not reach statistical significance. In a pooled analysis, the WMD of antithrombin values in COVID-19 patients with severe illness compared with those with milder disease was -10 IU/dL (95% CI: -3 to -17 IU/dL; I^2 : 86%).

This pooled analysis of recent scientific literature attests that antithrombin values are significantly lower in COVID-19 patients developing more severe illness. In keeping with these findings, Panigada et al¹² studied 11 COVID-19 patients admitted to the ICU for severe disease and found that more than half (6/11; 55%) had antithrombin values below the lower limit of the reference range.

These findings may have some important clinical implications. First, the observed antithrombin decrease, which mirrors what frequently occurs in patients with some forms of consumption coagulopathy and/or disseminated intravascular coagulation, seemingly suggests that this potent natural inhibitor may be gradually consumed during COVID-19 progression as a result of localized (i.e., pulmonary) or diffuse thrombosis, as clearly shown in both clinical studies and autopsies.^{13,14} The progressive antithrombin decay not only monitors an ongoing thrombotic process but may also represent an additional contributing factor to enhance the

risk of additional future thrombotic events. A second important consideration concerns the use of anticoagulant treatment in COVID-19 patients. Although heparin is now universally regarded as one of the anticoagulants of choice in these patients,¹³ especially in those on mechanical ventilation and prolonged immobilization, a sustained decrease of antithrombin concentration may jeopardize the effectiveness of heparin therapy, in which the presence of antithrombin is essential for assuring the effective anticoagulant activity of the drug.¹⁵ The obtained data suggest that antithrombin measurement should hence be included in the routine panel of laboratory investigations for the monitoring of patients with COVID-19.¹⁶ Moreover, it supports the consideration of therapeutic supplementation with antithrombin concentrates in hospitalized patients with COVID-19, as already proven clinically effective in other clinical settings characterized by acquired antithrombin deficiency.¹⁷

Due to the limited number of studies and patients that could be included in our meta-analysis, additional larger studies are urgently needed to verify whether diagnosing and managing antithrombin deficiency in COVID-19 may provide a significant contribution to ameliorate the prognosis of this severe pandemic disease and also improve management with heparin therapy.

**Fig. 1** WMD and 95% CI of antithrombin values in coronavirus disease 2019 (COVID-19) patients with severe illness compared with those with milder disease. CI, confidence interval; WMD, weighted mean difference.

Conflict of Interest

None declared.

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