Several lines of evidence garnered so far attest that coronavirus disease 2019 (COVID-19) is associated with a remarkably high rate of thrombotic events.\(^1\) Di Minno et al recently published the results of a critical literature review and meta-analysis, including 20 studies and totaling 198 COVID-19 patients,\(^2\) which revealed that the weighted mean prevalence of venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) was as high as 31.3% (95% confidence interval [95% CI], 24.3–39.2%), 19.8% (95% CI: 10.5–34.0%), and 18.9% (95% CI: 14.4–24.3%), respectively. The presenting characteristics and outcomes of 455 patients with COVID-19 who developed VTE (83% PE and 17% isolated DVT, respectively) during hospitalization have also been recently described by Fernández-Capitán et al.\(^3\) Interestingly, these patients had a median age of 65 years and most (i.e., over 70%) were male. The most frequent comorbidity was hypertension (42%), followed by diabetes (20%), chronic pulmonary disorders (10%), coronary artery disease (6%), and 4% were active smokers. The vast majority of these patients were immobilized (nearly 80%), while 4% were also diagnosed as having active cancer. Positive personal history for previous episodes of VTE was only present in less than 4% of all these patients. Irrespective of the high likelihood of developing VTE, episodes of VTE was only present in less than 4% of all these patients having active cancer. Positive personal history for previous episodes of VTE was only present in less than 4%

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plasma samples did not signiﬁcantly differ between the two cohorts of COVID-19 patients and healthy controls (data not shown).

The results of this investigation are shown in Table 1 and Fig. 1. As compared with the healthy control group, the values of LT (2.68 vs. 1.87 minute; \( p < 0.001 \)) and TP (4.60 vs. 4.08 minute; \( p = 0.031 \)) were found to be signiﬁcantly enhanced in COVID-19 patients. Similar results were found with using the TM-supplemented assay (LT: 2.71 vs. 1.90 minutes; \( p < 0.001 \); TP: 4.69 vs. 3.81 minutes; \( p = 0.001 \)). Unlike these two parameters, PH and ETP were found to not be signiﬁcantly different between cases and controls with or without TM supplementation (Table 1 and Fig. 1). A high correlation was found between thrombin generation parameters assessed with or without TM in COVID-19 patients, as follows, LT: \( r = 0.97 \) (95% CI: 0.91–0.99; \( p < 0.001 \)); PH: \( r = 0.98 \) (95% CI: 0.94–0.99; \( p < 0.001 \)); TM: \( r = 0.96 \) (95% CI: 0.89–0.99; \( p < 0.0001 \)); ETP: \( r = 0.87 \) (95% CI: 0.65–0.95; \( p < 0.001 \)). A marginally signiﬁcant inverse correlation was found between the days of hospital stay and ETP without TM \( (r = \quad 0.47; \quad 95\% \ CI: \quad -0.78 \quad \text{to} \quad 0.03; \quad p = 0.066) \). The association between length of hospital stay and other thrombin generation parameters did not achieve statistical signiﬁcance. Finally, the ratio calculated between thrombin generation parameters measured with or without TM in all plasma samples did not signiﬁcantly differ between the two cohorts of COVID-19 patients and healthy controls (data not shown).

The findings of normal or even decreased TG according to the assessed parameters in our patients hospitalized for severe COVID-19 illness could be considered almost unpredictable according to the commonplace perception of this condition as a prothrombotic disorder. To this end, however, quite similar ﬁndings have been published by White et al.\(^{12}\) who measured thrombin generation on Stago Genesia in 109 COVID-19 patients (75 with critical illness). In keeping with our ﬁndings, the values of LT and TP (with or without TM) were also found to be higher in critical patients, while no major differences were seen in PH or ETP. In another study, Nougier et al assessed thrombin generation with calibrated automated thrombography in 78 COVID-19 patients (48 needing intensive care).\(^{13}\) Interestingly, prothrombin time was found to be lower in COVID-19 patients with critical illness compared with those with milder disease, while ETP values were overlapping. Conversely, impaired ﬁbrinolysis measured with rotational thromboelastometry was commonplace in patients severe COVID-19 illness. Other studies have been published using indirect biomarkers of thrombin generation, but discussion of these ﬁndings may be inappropriate since they would not directly compare with ours or others, based on an automated thrombin generation assay.

Taken together, these and previous ﬁndings are suggestive of some degrees of coagulation exhaustion in COVID-19, at least at a stage of disease needing oxygen therapy and/or intensive care, which would hence conﬁrm the existence of initial local and/or systemic activation of blood coagulation, followed by signiﬁcant exhaustion, as earlier noted in other studies, even using different markers.\(^{12–15}\) These ﬁndings are also in keeping with solid evidence of prolonged...
prothrombin times and decreased platelet counts in COVID-19 patients, especially those progressing to severe/critical illness, as underpinned in most recent meta-analyses.\textsuperscript{16–18} It is also noteworthy that the almost unvaried evidence in thrombin generation values performed with or without TM would suggest that the protein C system may be a minor player on COVID-19 coagulopathy, while activation of platelets and the factor XII-dependent pathway may alternatively enhance rather than a smooth or even decreased thrombin generation values performed with or without TM. It is also noteworthy that the almost unvaried evidence in thrombin generation values performed with or without TM would suggest that the protein C system may be a minor player on COVID-19 coagulopathy, while activation of platelets and the factor XII-dependent pathway may alternatively appear as major drivers.\textsuperscript{14} Alternate observations of an enhanced rather than a smooth or even decreased thrombin generation may also be reflective of a timeline situation, since different findings would be expected across different phases of COVID-19, from asymptomatic illness to development of episodes of venous and/or arterial thrombosis.\textsuperscript{2} This aspect has been clearly emphasized by Hardy et al.,\textsuperscript{19} who followed up 21 patients with COVID-19 for up to 30 days of ICU stay. The ETP values were found to be considerably increased upon ICU admission, but then progressively declined within, or even below, the normal range ~10 days afterward. This is in total agreement our findings that ETP was inversely associated with the length of hospital stay in our patients. Notably, this investigation was not originally planned as cross-sectional study, as the healthy population was selected for obtaining local reference values for the thrombin generation assay. Although additional studies would hence be needed for addressing the potential contribution of age and other comorbidities on the thrombin generation tests used in this study, the significant age difference between cases and controls would probably not be sufficient to fully explain our findings, since no major impact of aging has been reported on ST Genesia ThromboScreen in the recent study of Calzavarini et al.\textsuperscript{20}

Conflict of Interest
None declared.

References