Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Comparison of Fibrin Monomers and D-dimers to predict thrombotic events in critically ill patients with COVID-19 pneumonia: A retrospective study

Coronavirus disease 2019 (COVID-19) is associated with a high risk of thrombotic events, particularly in critically ill patients. Anticoagulants at higher than standard thromboprophylaxis doses have been advocated by our group [1]. Although higher doses may help reduce thrombotic complications, the risk of hemorrhage could limit the benefit of such a strategy unless individualized to high thrombotic risk patients. D-dimers have been extensively studied in COVID-19, and elevated levels are associated with increased mortality, but whether it predicts thrombotic events is unclear. Another fibrin-related biomarker is Fibrin Monomers (FM), which seems promising to detect hypercoagulable state earlier than other coagulation biomarkers [2]. To investigate if FM can predict thrombotic events in critically ill COVID-19 patients, we conducted a subanalysis of the COVICLOT study [3] and evaluated all patients with at least one FM measurement. The protocol was approved by the University Hospital of Strasbourg Ethics Committee (reference CE-2020-76).

All consecutive patients with RT-PCR-confirmed COVID-19 who were hospitalized in an intensive care unit (ICU) for severe hypoxemia were included. Baseline characteristics were collected at admission (Day 0), and patients were managed according to the standard of care. Guidance from the French Interest Group in Perioperative Hemostasis (GIHP) and the French Study Group on Hemostasis and Thrombosis (GFHT) suggesting higher dose of heparin prophylaxis was implemented on April 3rd 2020: briefly, all patients received heparin; intermediate dose prophylactic anticoagulation (twice standard thromboprophylaxis) was administered if high flow oxygen therapy or mechanical ventilation were needed; therapeutic dose prophylactic anticoagulation was administered if iterative catheter thrombosis or dialysis filter clotting occurred, in case of hyperinflammation/hypercoagulability (with suggested fibrinogen and D-dimers levels thresholds of 8 g/L and 3000 μg/L respectively), and in patients on extracorporeal membrane oxygenation (ECMO) support [1]. All macrothromboses events were collected, including venous thromboembolism, arterial thromboses, catheter-related thromboses, dialysis filter and ECMO-related clotting. Suspected microthromboses based on organ failures were not collected. No systematic screening for the diagnosis of thrombotic events was performed. Pulmonary emboli were confirmed by computed tomography pulmonary angiography. Arterial thromboses were diagnosed with CT imaging or coronary angiography. The follow-up period was 14 days, on the basis that thrombotic events occur primarily within the first ten days after admission [4]. In addition, Hardy et al. observed an increase in thrombin generation associated with a decrease in overall fibrinolytic capacity during the first week of hospitalisation, resulting in a strong procoagulant state [5]. Laboratory results were collected at six time points when available: day 0, day 2, day 5, day 8, day 11, day 14. D-dimers (STA–LIATEST D-Di Plus, Stago, Asnières sur Seine, France) and FM (STA-Liatest FM) were measured with a STA-R Max analyzer. We compared FM and D-dimers plasma levels measured on the same sample between patients with at least one thrombotic event and those without thrombotic events. We did not analyze FM and D-dimer plasma levels after the thrombotic event. The association between FM levels and thrombotic events was examined with a logistic regression model. A logarithmic transformation of data was used to approach a normal distribution. The optimal FM and D-dimers level cutoff points were evaluated by receiver operator characteristic (ROC) curve analysis.

Between March 21st and April 10th 2020, 164 patients were included in four tertiary university French hospitals. Median age was 63 (IQR: 53–69), 40 (24%) patients were non pregnant females, median BMI was 29 kg/m^2 (IQR: 25–33), 6 patients had active cancer. Time between symptoms onset and ICU admission was 7 days (median; IQR 4–11). Median SOFA score at admission was 4 (IQR: 3–9), and 19 patients (12%) were treated with ECMO. There were six cases of overt disseminated intravascular coagulation (as defined by ISTH criteria with a D-dimers cutoff of 3000 μg/L) and 17 deaths (10%). Anticoagulation regimens over time are shown in Fig. S1. During ICU stay, most patients switched from a standard-dose prophylactic anticoagulation to an intermediate or therapeutic-dose prophylactic anticoagulation. Standard-dose prophylactic anticoagulation was administered to 101 (63%) patients at day 0 and 11 (18%) at day 14. We observed thrombotic events in 46 (28%) patients, including 22 (13%) pulmonary embolism, 10 (6%) deep venous thromboses, 9 (5%) catheter-related thromboses, 5 (3%) dialysis filter or ECMO-related clotting, and 4 (2%) arterial thromboses (2 ischemic strokes, 1 myocardial infarction and 1 acute mesenteric ischemia). Thrombotic events were diagnosed on day 5 (median; IQR 1.5–8).

We analyzed 341 FM/D-dimers paired results. Distribution of FM and D-dimers levels over time is shown in Fig. 1. A moderate correlation ($r = 0.58$) was observed between FM and D-dimers. Most FM plasma levels (58%) were under the limit of detection (5000 μg/L). Patients on ECMO support showed similar FM levels compared to patients without ECMO, whereas there was a trend to higher D-dimers levels (Supplementary Table 1). The odds of developing thrombotic events (all types of events or venous/arterial events) based on Fibrin Monomers and D-dimers plasma level are shown in Supplementary Table 2. Log-transformed FM level on day 2 was significantly associated with thrombotic events. Log-transformed D-dimers level was associated with thrombotic events at every day of measurement, with a higher odds ratio on day 2. When considering only venous thromboembolism and arterial thromboses, log-transformed FM level on day 0 was significantly associated with thrombotic events. Differences between two consecutive FM or peak value measurements were not associated with thrombotic events. ROC analysis showed that the FM level at day 2 was comparable to the D-

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dimer assay to predict thrombotic events (Fig. 2). The optimal cutoff value was determined at 5700 μg/L for FM to predict thrombotic events, with a sensitivity of 67% (95% CI 39–86) and a specificity of 77% (95% CI 61–88). Optimal cutoff for D-dimers was 3300 μg/L with a sensitivity of 75% (95% CI 47–91) and a specificity of 71% (95% CI 55–84). Diagnostic performance was comparable when considering only pulmonary embolism, or when excluding catheter, dialysis filter and ECMO-related thromboses.

FM levels reflect thrombin activity and seem promising to predict thrombotic events, despite minimal evidence to implement them into clinical practice [2]. In non-COVID surgical patients, high soluble FM on postoperative day 1 is associated with a hypercoagulable state [6], and was found to be more sensitive than D-dimers and other fibrin-related markers to predict thrombotic events [7]. In COVID-19 patients, high D-dimers levels are associated with the extent of lung injury and could reflect extravascular fibrin deposits [8]. On the contrary, soluble FM is theoretically limited to the intravascular space. We found that FM plasma level distributions over time differ from D-dimers, with most FM levels being under the limit of detection, although we did not find an increased diagnostic performance of FM over D-dimers to predict thrombotic events. These findings are in line with other studies. Sridharan et al. found that FM levels were elevated in only 18.5% of COVID-19 patients with elevated D-dimers [9]. Hardy et al. reported in critically ill COVID-19 patients that the majority of FM levels were within the manufacturer's range, in sharp contrast with D-dimers [10]. As stated by the authors, this could be advantageous to capture an abrupt rise in FM levels. Whether FM alone or in combination with D-dimers could be more useful than D-dimers alone to individualize anticoagulation management remains to be determined.

This study has several limitations: it is a retrospective study, with a relatively small sample size. Patients rarely had FM measurements at all time points, and 68 (41%) had only one measurement over the study period. Data were collected every three days, whereas FM have a short half-life (2.3 h) with transient peaks [8,10]. We may therefore lack the statistical power to demonstrate a clear usefulness of FM over D-dimers. Although FM levels are increased in patients with disseminated intravascular coagulation, cancer, and pregnancy [2], few patients in our study had these conditions.

In conclusion, FM plasma levels were often under the limit of detection in critically ill COVID-19 patients and showed no clear superiority over D-dimers to predict thrombotic events. Prospective studies with closer monitoring of this hemostatic biomarker are needed to determine its usefulness to stratify thrombotic risk and individualize anticoagulation management.

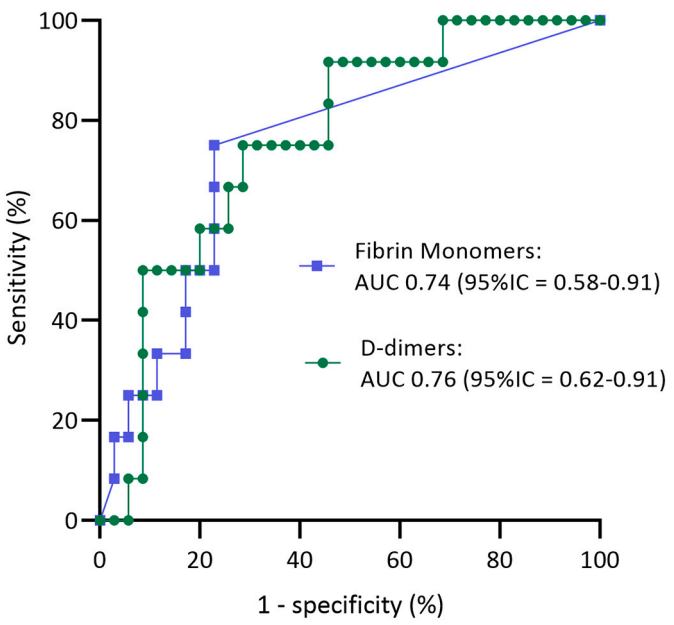

Fig. 2. ROC analysis of Fibrin Monomers (displayed in blue) and D-dimers (displayed in green) plasma levels on day 2 to predict thrombotic events. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.06.009.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Anne Godier: honoraria and travel fees from Bayer-Healthcare, Boehringer-Ingelheim, Bristol-Myers-Squibb/Pfizer and Sanofi.
Jerrold H Levy: steering committees for Instrumentation Labs, Merck, and Octapharma

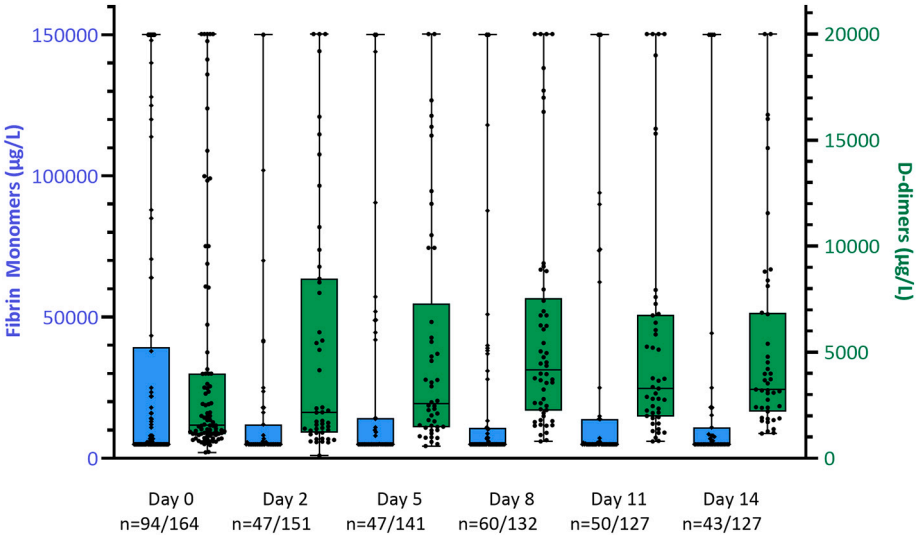

Fig. 1. Distribution of Fibrin Monomers (displayed in blue) and D-dimers (displayed in green) plasma levels. Number of paired results available among patients still free of thrombotic events is shown under each time point. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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