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Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis

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ABSTRACT

Introduction: We recently reported a high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 admitted to the intensive care units (ICUs) of three Dutch hospitals. In answering questions raised regarding our study, we updated our database and repeated all analyses.

Methods: We re-evaluated the incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction and/or systemic arterial embolism in all COVID-19 patients admitted to the ICUs of 2 Dutch university hospitals and 1 Dutch teaching hospital from ICU admission to death, ICU discharge or April 22nd 2020, whichever came first.

Results: We studied the same 184 ICU patients as reported on previously, of whom a total of 41 died (22%) and 78 were discharged alive (43%). The median follow-up duration increased from 7 to 14 days. All patients received pharmacological thromboprophylaxis. The cumulative incidence of the composite outcome, adjusted for competing risk of death, was 49% (95% confidence interval [CI] 41–57%). The majority of thrombotic events were PE (65/75; 87%). In the competing risk model, chronic anticoagulation therapy at admission was associated with a lower risk of the composite outcome (Hazard Ratio [HR] 0.29, 95%CI 0.091–0.92). Patients diagnosed with thrombotic complications were at higher risk of all-cause death (HR 5.4; 95%CI 2.4–12). Use of therapeutic anticoagulation was not associated with all-cause death (HR 0.79, 95%CI 0.35–1.8).

Conclusion: In this updated analysis, we confirm the very high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 pneumonia.

Recently, we reported a high incidence of venous and arterial thrombotic complications in critically ill patients with COVID-19 admitted to the intensive care units (ICUs) of three Dutch hospitals [1]. We found a cumulative incidence of 31% (95% confidence interval [95%CI] 20–41%), with pulmonary embolism (PE) being the most frequently diagnosed thrombotic complication. In this report, we respond to the Letter to the Co-Editors comments of Greenstein, van Nieuwkoop, Lega and Rosen. They raise relevant questions: 1) if the cumulative incidence of the primary endpoint was lower in patients already treated with therapeutic doses of anticoagulation upon admission to the ICUs for other reasons than a complicated course of COVID-19 pneumonia, 2) if the threshold at which diagnostic tests to diagnose thrombotic complications were initiated, changed over the course of time, 3) whether the observed PEs represent 'classical' venous thromboembolism and 4) whether we choose the optimal primary outcome.

In order to optimally respond to these questions, we decided to update our database with all thrombotic events, i.e. the composite outcome of venous thromboembolism (VTE) and arterial thrombotic complications, until April 22nd 2020 (in the original report this was until April 5th 2020). We captured all confirmed diagnoses of PE, deep-vein thrombosis (DVT), ischemic stroke, myocardial infarction or systemic arterial embolism. Importantly, as in the original analysis,

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Table 1
Description of thrombotic complications.

Type of event	Number of cases	Relevant details
Pulmonary embolism	65	– 46 patients with PE in segmental or more proximal arteries, 19 patients with PE limited to subsegmental arteries
Other venous thromboembolic events	3	– 1 patient with proximal DVT of the leg – 2 patients with catheter related upper extremity thromboses
Arterial thrombotic events	7	– 5 patients with ischemic strokes – 2 patients with systemic arterial embolisms

Note: acute PE was diagnosed with CT-pulmonary angiography; DVT/upper extremity vein thrombosis was diagnosed with ultrasonography; strokes and systemic arterial embolisms were diagnosed with CT angiography.

diagnostic tests were performed in case of clinically suspected thrombotic complications. We calculated the cumulative incidence of the composite outcome as well as the incidence adjusted for competing risk of death. The index date was the moment of ICU admission. Patients were censored upon ICU discharge, when they died, or at April 22nd 2020, whichever came first.

We studied the same 184 ICU patients as previously reported [1]. After the previous censoring date, i.e. April 5th 2020, 18 additional patients died (total 41, 22%) and 56 additional patients were discharged alive (total 78, 43%). The median follow-up observation duration increased from 7 days (interquartile range [IQR] 1–13) to 14 days (IQR 6–19). All patients received pharmacological thromboprophylaxis according to local hospital protocols [1]. During the added observation time, 44 new thrombotic complications were diagnosed: 40 PEs, 2 strokes and 2 peripheral arterial embolisms. The total number of events is shown in Table 1. The crude cumulative incidence of the composite outcome was 57% (95%CI 47–67%; Fig. 1), and after adjustment for competing risk of death 49% (95%CI 41–57%). The incidence rate was 13/patient-year (95%CI 6.1–27). Patients diagnosed with thrombotic complications were at higher risk of all-cause death, for a HR of 5.4 (95%CI 2.4–12). A total of 17 patients (9.2%) were already on long-term therapeutic anticoagulation for various reasons, which was continued at ICU admission. In these 17 patients, 3 PEs were diagnosed. In the competing risk model, the hazard ratio (HR) for the composite outcome associated with long-term therapeutic anticoagulation was 0.29 (95%CI 0.091–0.92). Use of long-term therapeutic anticoagulation was not associated with all-cause death (HR 0.79, 95%CI 0.35–1.8).

What are the implications of our new findings? We acknowledge the fact that cumulative incidences may overestimate the incidence of the event of interest in the setting of a high competing risk of death. We had three main reasons to report the 'crude' cumulative incidence in our first analysis. First, although the mortality rate was considerable (13%), it was only slightly higher than the threshold of 10%, after which adjustment for competing risk becomes relevant, as indicated in the letter by Lega. Second, most of the patients who died had not been referred for imaging tests to diagnose thrombotic complications. It is likely that at least some of the deceased actually had developed PE, in which case adjusting for competing risk of death could have led to an underestimation of the incidence. Lastly, many patients were still in the ICU and followed for only a few days, putting them still at continued and considerable risk of thrombotic events. We believe the validity of our initially observed 31% cumulative incidence is supported and reinforced by the observed adjusted 49% cumulative incidence of this updated analysis with a doubled observation period amounting to 14 days. Several other studies have recently presented comparable estimates, further underlining the validity of our observation [2–7].

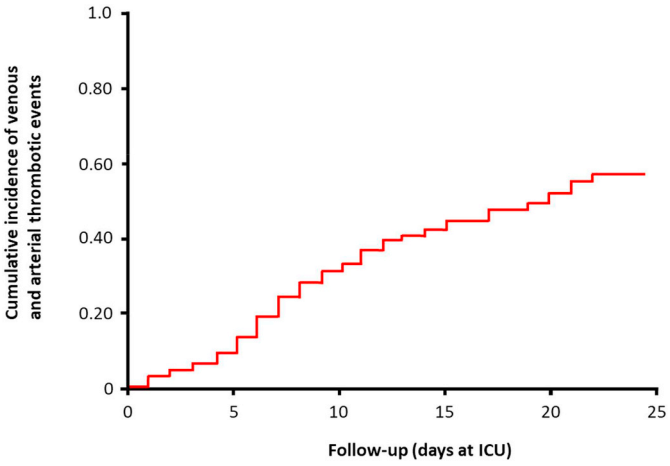

Fig. 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.

Although imaging was only performed upon clinical suspicion, the threshold for considering thrombotic complications has likely lowered since our initial publication, which may partly explain the relatively high number of events that we observed in the added observation time. For instance, "lack of clinical improvement in ventilated patients" was commonly used as a main argument to order CT pulmonary angiography after April 5th. Interestingly, patients with thrombotic complications had a more than 5-fold higher risk of all-cause death. Although PE may contribute to respiratory failure in critically ill patients with COVID-19 pneumonia, it is possible that the most critically ill patients were more likely to be referred for imaging tests, introducing confounding by indication. Some argue that the PEs in patients with COVID-19 are foremost representative of an in-situ immunothrombosis and part of the clinical presentation of severe COVID-19 pneumonia [8–10], although the majority of PE patients in our cohort had at least segmental pulmonary thrombi (Table 1), compatible with conventional thromboembolic origin [11]. Following the immunothrombosis hypothesis, PE would be prevalent and not incident in the patient population under study, especially if the COVID-19 pneumonia is ultimately fatal. Our observation that therapeutic anticoagulation at baseline prevented thrombotic complications but not all-cause death may support the in-situ immunothrombosis hypothesis.

In conclusion, in response to the raised questions, we confirm the very high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 pneumonia. We emphasize our advice to strictly apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU, and realize that our updated results will fuel the ongoing discussion on the optimal prophylactic dose of (low molecular weight) heparin in these patients.

Declaration of competing interest

Frederikus Klok reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion, the Dutch Heart foundation and the Dutch Thrombosis association, all outside the submitted work. Menno Huisman reports grants from ZonMW Dutch Healthcare Fund, and grants and personal fees from Boehringer-Ingelheim, Pfizer-BMS, Bayer Health Care, Aspen, Daiichi-Sankyo, all outside the submitted work. Marieke Kruip reports unrestricted research grants from Bayer, Boehringer-Ingelheim, Daiichi-

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