Beware overestimation of thrombosis in ICU

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Letter to the Editors-in-Chief

Beware overestimation of thrombosis in ICU: Mortality is not the only competing risk!

We read with interest the reports by Klok et al. [1,2] and Thomas et al. [3] published in *Thrombosis Research* about the cumulative incidence of thrombotic complications in patients with COVID admitted to ICU. However, we are concerned that the cumulative incidences estimated may be overestimated, perhaps even substantially so.

Recall that the main assumption of cumulative incidence estimates is that observations that are censored as incomplete observations are assumed to have been censored due to non-informative reasons. This means that the analysis assumes that such incomplete observations will have the same risk of the event as the participants remaining in the analysis.

In 2015, Ay et al. [4] published a paper highlighting the problem of competing risks of mortality in cancer related VTE. Specifically, patients with cancer and VTE have a high risk of mortality. It showed that if competing events are handled as incomplete observations cumulative incidences can be severely overestimated- the degree of overestimation is on par with the amount of competing risk of death. Relative overestimation at 24 months was almost 33% for cancer patients with high mortality (30% at 6 months).

Since then, many VTE researchers appear to be aware of this problem and handle non-VTE death as a competing event. However, not much VTE research strictly analyses in-hospital thrombosis. Here, the problem arises that non-VTE death but also discharge is a competing event - discharged patients are likely have a substantially lower risk than patients that remain in ICU thus in the analysis [5]. More intuitively: it seems incorrect to define discharged patients as incomplete observations with regards to thrombosis occurring during ICU stay.

Why is this not a more general problem in observational research? Probably because in times outside of COVID, we have the luxury of time to complete observations (i.e. 30-day mortality) limiting censoring to participants lost to follow-up.

From both manuscripts, it is not clear that both death and discharges were handled as a competing event. In the analyses by Klok et al., 25% and 67% of the patients had a potential competing risk outcome respectively (although not clear how many of these had a thrombotic outcome prior to this outcome). In the analysis by Thomas et al., 48% of the patients had this as a potential reason for censoring. All these estimates are thus at risk of substantial overestimation due to inappropriate handling of competing events. The estimates reported in the pre-print by Middeldorp et al. [6] cited by the Klok et al. also have this potential shortcoming. In contrast, we have found one report by Poissy et al. [7], using what appears to be estimation considering death and discharge as competing risks: there, the 15-day cumulative incidence of PE was 20.4%.

We wholeheartedly appreciate the hard work and rapid sharing of data by our colleagues working both on wards and ICUs in this challenging time. Notwithstanding, we feel the abovementioned issue needs urgent clarification, as these high cumulative incidence rates, potentially severely distorted upwards by the issues raised above, may erroneously prompt physicians over the world to to prescribe universal empiric therapeutic anticoagulation in these patients.

Declaration of competing interest

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