

## Letter re: Cause-specific mortality during ECMO: A call for a standardized definition?

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Dear Editor,

We have read with great interest the work by Deinzer and colleagues<sup>1</sup> which addresses the crucial topic of mortality in extracorporeal membrane oxygenation (ECMO) and evaluates independent risk factors and causes of death during venoarterial (VA) and venovenous (VV) support. Their study, based on a large database with a substantial number of patients, provides valuable insights into the complexities surrounding mortality in ECMO patients.

Similarly, our research group conducted a study focusing on mortality among ECMO-treated patients, albeit with a smaller cohort size. Despite the different sample size, we found similarities in patient characteristics. Along with describing cause-specific mortality during ECMO, our attention was focused on quantifying the significance of major bleeding as a cause of death. Indeed, the occurrence of bleeding (especially intracerebral hemorrhage) during ECMO is associated with a high mortality rate<sup>2</sup> but mortality directly related to this event is rarely reported.

In our retrospective analysis spanning 12 years (January 2011 – December 2022) and involving 235 patients treated with VV-ECMO, we observed 73 deaths in the intensive care unit 56 of which (77%) during ECMO support and 17 (23%) after decannulation, with a median time to death of 17 [8–38] days after ECMO removal. The overall mortality rate in our cohort was 31% (73 patients out of 235). Notably, in COVID-19 patients, the mortality rate was 56% (18 patients out of 32) while non-COVID-19 patients had a mortality rate of 27% (55 patients out of 203).

The most common cause of death in our cohort was multiorgan failure (26 patients, 36%). Multiorgan failure was the primary cause of death in non-COVID-19 patients (22 patients, 40%), followed by septic shock (13 patients), and neurologic events (11 patients). In our case, refractory respiratory failure emerged as the fourth cause of death, unlike in Deinzer's group, where it ranked first. COVID-19 patients primarily succumbed to refractory respiratory failure (5 patients, 28%),

followed by multiorgan failure (4 patients), and neurologic events (4 patients).

We would like to emphasize here the difference in the classification of causes of death between our study and that of Deinzer et al. Assessing the cause of death in critically ill patients is challenging due to different contributing factors which may coexist and overlap with one another. For this reason, we defined the cause of death based on the judgment of two expert clinicians who independently reviewed the entire medical record of each patient supported with ECMO and indicated the cause of patient's death. In case of disagreement, a third ICU expert staff physician reviewed the medical records and adjudicated the case. Interrater agreement was high (Kappa 0.8 (95% CI 0.79 – 0.84),  $p < .001$ ) with only a minimal number of discordant cases.

Regarding major bleeding, advancements in technology and clinical management have reduced its incidence. In our study, 44% of patients (32 cases) exhibited major bleeding at the time of death per ELSO 2014 criteria.<sup>3</sup> However, clinical judgment deemed bleeding relevant to the cause of death in only 30% of cases (22 patients). Clinically relevant bleeding fulfilled ELSO-defined major bleeding criteria in 20 out of 32 patients suggesting that ELSO-defined major bleeding may have not significantly impacted mortality in our patient population.

In conclusion, the disparity in classifying causes of death among ECMO patients underscores the challenge of evaluating such outcomes in critically ill individuals with concurrent conditions, even when objective and categorized criteria are employed. Moreover, the

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observed disparity between clinically relevant bleeding and ELSO-defined major bleeding emphasizes the need for refined criteria when assessing bleeding-related mortality in ECMO patients. Having a precise definition of cause-specific mortality during ECMO can be beneficial in the design of future clinical studies to optimize ECMO patient outcomes.

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