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Personalized strategies for high-risk acute pulmonary embolism: addressing the “catastrophic” subgroup. Author’s reply

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We appreciate the opportunity to engage in discussion with Petit et al. regarding our study on management strategies for high-risk acute pulmonary embolism (PE) [1, 2]. We fully agree that causal inference in observational studies is challenging, both in general and in our study, in particular because of the presence of treatment switches and combined treatment strategies and given the baseline heterogeneity across the four treatment groups. To address the latter issue, we carefully selected 12 potential confounders, including markers of disease severity (e.g., cardiac arrest, cardiopulmonary resuscitation time, cardiogenic shock, initial pH) and employed a variety of advanced statistical techniques, including standardization, propensity score weighting, and targeted maximum likelihood to assess robustness to model misspecification. As shown in Fig. S4 in the supplementary material, it is possible to address the initial covariate imbalance across the four groups using these techniques. While we understand that adjustment for covariate imbalance through stratification may be intuitive, from a methodological perspective stratification has many disadvantages, including issues with non-collapsibility,

effect modification, sensitivity to model misspecification, and loss of statistical power [3]. Rather than the more specific “catastrophic PE” definition, we applied broader inclusion criteria, prioritizing statistical power and generalizability in clinical practice over internal validity. Similarly, while excluding patients who died within 24 h intuitively makes sense, it actually introduces selection bias because post-treatment eligibility criteria jeopardize the alignment of treatment initiation, start of follow-up, and the time when eligibility criteria are met [4]. Additionally, all patients who are admitted to hospital form the population for whom evidence on the effectiveness of treatment choices is needed, regardless of their survival time.

Concerning the definition of treatment groups, we agree that patients initially stabilized with venoarterial extracorporeal membrane oxygenation (VA-ECMO) pose an important challenge in our analysis. Treatment switches and combined strategies, which may occur both in non-randomized and randomized studies in high-risk settings, make the estimation of the independent effects of individual treatments very challenging. We decided to not assign patients to the VA-ECMO treatment group if they were bridged to advanced recanalization because there is no reason to expect VA-ECMO to be an effective treatment option beyond hemodynamic stabilization. Since VA-ECMO is very unlikely to reduce the blood clot itself, we do not think that this choice introduces classification bias. However, we acknowledge that it may introduce immortal time bias. Table S4 in the supplement shows that the comparisons between the treatment groups are largely unchanged when we exclude the VA-ECMO group. Moreover, as shown in Fig. S2, subsequent treatments were initiated at a median of 1 h

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after the initiation of VA-ECMO, indicating a very low risk of immortal time bias in this subgroup. In line with this, excluding four patients who received VA-ECMO and died in the first 5 h did not modify our results in an unpublished sensitivity analysis. Estimating the effect of combined treatment strategies, including initial stabilization with VA-ECMO, would be highly desirable, but it would not only require a much larger sample size than the 991 patients included in our analysis, but also advanced modeling to account for the exact timing in treatment trajectories. Overall, our results suggest that high-risk PE patients, including those initially stabilized with VA-ECMO, benefit from timely recanalization.

Although secondary analyses from ongoing randomized controlled trials (CATCH-PE II NCT06672081; PERSEVERE: NCT06588634; TORPEDO NL: NCT06833827) may offer new insights, prospective data on recanalization strategies for high-risk PE patients requiring VA-ECMO support will likely remain limited. Therefore, high-quality non-randomized analyses remain a crucial source of evidence to guide the management of patients experiencing cardiac arrest, pre-hospital hemodynamic instability, and other factors associated with a poor prognosis.

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Data availability

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requests for the data. De-identified data may be provided after approval from the ethical review board.

Declarations

Conflicts of interest

The authors declare no conflicts of interest related to this manuscript.

Ethical standards

All ethical standards were met in writing and submitting this correspondence.

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References

1. Stadlbauer A, Verbelen T, Binzenhöfer L et al (2025) Management of high-risk acute pulmonary embolism: an emulated target trial analysis. *Intensive Care Med*. <https://doi.org/10.1007/s00134-025-07805-4>
2. Petit M, Levy D, Schmidt M (2025) Personalized strategies for high-risk acute pulmonary embolism: addressing the "catastrophic" subgroup. *Intensive Care Med*. <https://doi.org/10.1007/s00134-025-07885-2>
3. Van der Laan M, Rose S (2011) Targeted learning: causal inference for observational and experimental data. Springer, New York
4. Hernán MA, Sauer BC, Hernández-Díaz S et al (2016) Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol* 79:70–75. <https://doi.org/10.1016/j.jclinepi.2016.04.014>