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CORRESPONDENCE

It takes two to bleed: anticoagulation intensity and the host's vascular susceptibility. Author's reply

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We appreciate the thoughtful letter by Seeliger and colleagues [1] in response to our manuscript published in Intensive Care Medicine [2]. They raise a few important points that are worth discussion.

As we emphasize in our manuscript, we wholeheartedly agree with Seeliger that the lack of information on anticoagulation regimen and laboratory measures of coagulation status is a huge limitation to our analysis. The ELSO registry does not currently collect this data, and admittedly there are challenges to effectively capturing the anticoagulation regimen within the confines of a registry, particularly because the anticoagulant selected and target range for intensity could change across the arc of a patient's extra-corporeal membrane oxygenation (ECMO) run. However, we believe that there are opportunities to meaningfully collect this information that could dramatically enhance the utility of the ELSO registry for examining bleeding and thrombotic events (BTEs), and this data could ultimately help improve clinical practice. We and others have advocated for an update to the ELSO registry data collection forms to include crucial information about anticoagulation agent, laboratory parameter monitored and target range, and at least a couple snapshot lab values to capture the anticoagulation intensity during the run. We hope that our work can serve as an initial blueprint for expanded analyses that will include these parameters in the future.

We agree with Seeliger that the primary etiology of lung injury necessitating veno-venous ECMO (VV-ECMO) support may affect a patient's predisposition to bleeding and thrombotic complications. In an effort to describe that risk, we reported the adjusted odds of having any BTE across the major primary diagnosis groups in Supplemental Fig. 4 and also provided a breakdown of the rates of individual BTEs across these diagnoses in Supplemental Table 7. In response to the questions raised in this letter, we expanded that analysis further to explore the association of these diagnosis groups with "any bleeding" or "any thrombosis". The salient findings were that trauma was the only primary diagnosis with a strong, independent association with both increased bleeding events (adj-OR 1.46, 95% CI 1.24–1.73, $p < 0.0001$) and increased thrombotic events (adj-OR 1.34, 95% CI 1.12–1.59, $p = 0.001$). Viral pneumonia (adj-OR 1.15, 95% CI 0.99–1.34, $p = 0.067$) and aspiration pneumonitis (adj-OR, 95% CI 0.99–1.64, $p = 0.055$) had weak but non-significant associations with higher odds of bleeding events. Asthma had a strong association with lower odds of thrombotic events (adj-OR 0.67, 95% CI 0.49–0.92, $p = 0.01$).

We want to highlight that statistically this analysis requires entering binary variables (e.g. trauma vs "not trauma"; viral pneumonia vs "not viral pneumonia", etc.) into the multivariable model, thus effectively adding seven additional covariates to the model to include all of the major diagnosis groups. While this approach is reasonable when analyzing outcomes with a large number of events, such as "any BTE" where there were nearly 6000 events in the multivariable model, it becomes statistically problematic when considering individual BTEs where the number of events is much smaller (e.g. < 100 intracranial hemorrhage events in the multivariable model). Adding each of the primary

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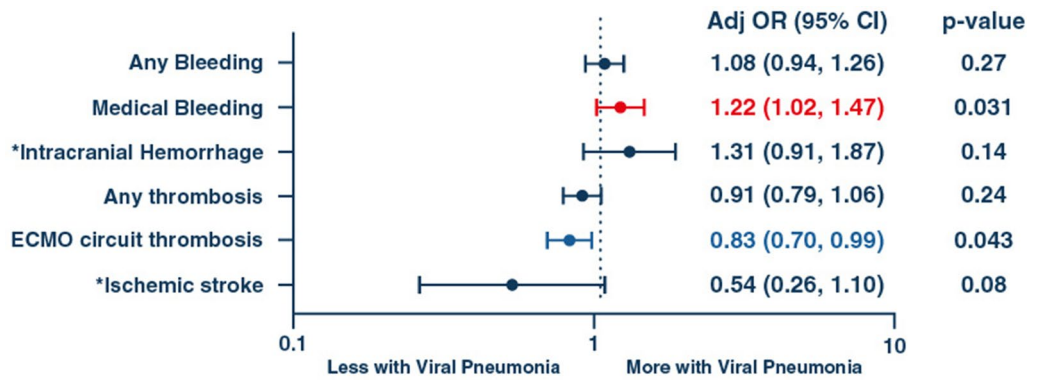

Fig. 1 Association of viral pneumonia with bleeding and thrombotic events during adult VV-ECMO. Forest plot of the adjusted odds ratios from multivariable logistic regression modeling examining the association of a primary diagnosis of viral pneumonia with bleeding and thrombotic events during VV-ECMO. Adjusted for baseline Pre-ECMO characteristics such as: age, sex, race, weight, presence of renal failure, cardiac arrest, pH, use of vasopressors, chronic respiratory conditions, time on ECMO, year of support, type of cannulation, P/F ratio. *Additionally adjusted for delta PO_2 and delta PCO_2 at 24 h post ECMO initiation

diagnoses to those individual BTE models risks "overfitting" the model and generating erroneous conclusions [3]. Similarly, running models for specific BTEs within each diagnosis subgroup leads to multiple testing and increases the probability of chance statistical associations.

In light of the current coronavirus disease 2019 (COVID-19) pandemic, we appreciate the considerable interest to understand if viral pneumonia carries a particular risk of BTEs during VV-ECMO support. We want to emphasize that our ELSO analysis spans patients supported with VV-ECMO through 2017 and thus represents a pre-COVID-19 population. Furthermore, the vascular injury and activation of inflammatory and coagulation cascades probably varies considerably across different respiratory viral pathogens. Nevertheless, we added a binary variable of "viral pneumonia" (versus "not viral pneumonia") to each of the multivariable models for the major BTE groups (Fig. 1), and the results of that analysis are summarized in the figure below. Notably, viral pneumonia tended to have a greater association with bleeding, particularly medical bleeding, and lower odds of thrombosis, particularly circuit thrombosis. We caution that some of the relationships observed could be driven in part by complex associations of the other primary diagnosis groups with BTE risk, as the "not viral pneumonia" group includes diagnoses like trauma and asthma that have strong associations with BTE risk as outlined above. It is tempting to look at these results and conclude that patients with acute respiratory distress syndrome from viral pneumonia are more susceptible to bleeding complications and potentially should be managed with lower intensity anticoagulation. We would urge that similar analyses be conducted in the COVID-19 population and prospective studies be performed in different disease states before making changes to clinical practice.

We do feel that the findings of our primary analysis argue for a greater clinical impact of bleeding events compared to thrombotic events given their stronger association with mortality in VV-ECMO patients. We read with interest the recent study by Seeliger et al. [4] describing the BTEs occurring in adult VV-ECMO patients managed at two high-volume German centers using a higher versus lower intensity heparin protocol for anticoagulation. Patients managed with low-intensity heparin were much more likely to require oxygenator exchange and had a modest but significant increase in thrombotic events. Importantly, patients managed at the low-intensity heparin center had larger venous drainage cannulas (25F vs 23F), typically received femoro-femoral compared to femoro-jugular cannulation, and were managed with more liberal red blood cell and platelet transfusions, all of which could have contributed to a higher risk of thrombotic events irrespective of the heparin intensity. Furthermore, although not statistically different, the rates of severe bleeding complications were numerically higher (20% vs 14%) in the high-intensity anticoagulation

group and severe intracranial bleeding, which was typically fatal, only occurred in the high-intensity group (7 patients versus none). While we appreciate that oxygenator exchange is resource intensive, adds additional expense, and may not be entirely benign, particularly for patients who are highly dependent on the ECMO circuit for gas exchange, it does not carry a strong association with mortality and need not result in any direct clinical insult to the patient. Consistent with that, the patients in the low-intensity heparin group had similar mortality despite a higher rate of oxygenator exchange. On balance, if important medical bleeding events like intracranial hemorrhage, pulmonary hemorrhage, and gastro-intestinal bleeding can be successfully mitigated with lower intensity anticoagulation at the expense of a greater frequency of oxygenator exchange, that may be a price worth paying to help salvage these extremely sick patients.

More importantly, a "one size fits all" approach is probably not the optimal paradigm for anticoagulation intensity during adult VV-ECMO support. As Seeliger alludes in the title of their letter, "it takes two to bleed", patient susceptibility to bleeding and thrombosis likely plays a major role in the development BTEs occurring during ECMO support. In fact, "it takes three to bleed" might be an even more appropriate concept as we consider the intersection of (1) patient susceptibility, (2) management of anticoagulation and transfusions, and (3) ECMO circuit factors like tubing length, heparin bonding, number of connectors, oxygenator type, and circuit flows. We believe that the results of our study help to shine a light on some of the potentially important clinical factors driving patient susceptibility, including age, weight, acute kidney injury, vasopressor requirement, pre-ECMO pH, and potentially the etiology of respiratory failure. We encourage the ECMO community to come together for prospective studies of different anticoagulation intensity stratified by an upfront estimation of BTE risk.

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Declarations

Conflict of interest
The authors do not have any conflicts of interest.

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