Critical Care

COMMENT

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Prone position during venovenous extracorporeal membrane oxygenation: survival analysis needed for a time-dependent intervention

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To the Editor,

We read with great interest the paper of Giani and colleagues titled "Prone positioning during venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a pooled individual patient data analysis" published in the critical care journal [1]. We are surprised that their meta-analysis failed to show a survival benefit for prone positioning during venovenous extracorporeal membrane oxygenation (VV ECMO). We would like to postulate that this was due to the limitation of the statistical methods.

Prone positioning patients with moderate to severe acute respiratory distress syndrome (ARDS) for an extended time during their illness has been shown to reduce their 28 and 90-day mortality [2]. This is thought to be due to a combination of improved ventilation/perfusion matching, better distribution of transpulmonary pressures, reduced pulmonary vascular resistance, and right ventricular afterload [3]. In addition, respiratory system compliance is improved directly through enhanced lung compliance and indirectly through reducing chest and abdominal wall pressure [4]. More importantly, prone positioning may reduce ventilator-induced lung injury (VILI) [3]. Despite these benefits, prone ventilation remains underutilized; only 33% of patients in the APRONET trial, a large multicenter study of patients, with severe ARDS were placed in prone position [5].

The same physiologic benefits for prone positioning have been shown during VV ECMO support for severe ARDS. Despite this, observational outcome studies are conflicting, showing both improved and worsened survival. In an observational analysis of 25 ECMO patients with COVID-19 severe ARDS, prone positioning showed improved oxygenation but a higher mortality rate which was attributed to the severity of illness [6]. Meta-analysis is a standard technique to reduce differences between treatment groups by increasing sample size. However, Giani and colleagues did not find an improvement in outcome with prone positioning during VV ECMO. We believe this could be due to failing to consider the temporal properties of prone ventilation, despite an adequate sample size of 889 patients. Our survival analysis of 232 VV ECMO patients in the Coronavirus Disease 2019 Critical Care Consortium international registry showed prone positioning during ECMO was associated with a reduced probability of death (hazard ratio, 0.31; 95% CI 0.14–0.68) [7]. Our results are consistent with the meta-analysis of 1836

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patients from thirteen studies, which showed prone positioning of VV ECMO patients with severe ARDS led to reduced mortality at 28, 60-, and 90-days [8].

This inconsistency could be a failure to address the fact that prone positioning has temporal dimensions, having both a duration and a time course in the patient's illness journey. We used a multistate survival model to address this issue, which is a more realistic model of patient progression through their journey [9]. Patients in prone positioning can move to the supine state and vice versa, and this transition contributes to the complexity of the model and eventually affects the outcome [10]. Hazard ratios from the survival model provide an estimate for transitions between states. A survival approach can account for the average time spent in the prone position, the number still at risk over time, and the probability of transitions [11]. It can also account for the effect of multiple confounders on the transition and outcomes while accounting for the key confounder of time prone positioning began. Analyzing time-dependent treatments using cross-sectional groups that ignore time (e.g., "any prone during stay" and "no prone during stay") can cause significant biases in the effects of the treatment [12]. These cross-sectional comparisons are confounded by time in ICU, which predicts both the probability of receiving prone treatments, and key outcomes such as death and length of stay.

In conclusion, we believe that prone positioning is beneficial for VV ECMO patients with Covid-19 ARDS and continue to recommend its use. Consideration of the temporal aspects of prone ventilation such as day of initiation, time of day of proning, the duration of prone positioning, and number of proning episodes is essential in both retrospective analyses and future randomized controlled clinical trials.

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AZ, AB, SH, GP conceived the study. AZ, AB, SH, GP drafted the manuscript. All authors helped to revise the draft of the manuscript. All authors read and approved the final manuscript.

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