CORRESPONDENCE

Estimation bias resulting from sparse data: response to comments by Zhang and Ren

F. Pappalardo* and G. Landoni

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We thank Drs. Zhang and Ren [1] for their interest in our study [2]. After initial promising findings [3] we performed the first randomized controlled trial (RCT) on protein C zymogen in adult septic patients. We found no difference in the primary composite endpoint (prolonged ICU stay and/or 30-day mortality) and an alarming signal towards an increased ICU mortality (79 vs 39 %, $p = 0.02$) and hospital mortality (84 vs 44 %, $p = 0.01$) in the study group that was confirmed by Kaplan–Meier ($p = 0.035$) and a multivariate analysis, where protein C zymogen was the only independent predictor of ICU mortality ($p = 0.011$).

We agree with Zhang and Ren that the study was underpowered to reach definitive conclusions about survival in the study population, but the absence of a beneficial effect on the primary outcome was clear and the baseline clinical characteristics were not different between groups. We confirm that the findings of our study clearly suggest not to use this expensive drug in septic patients. We acknowledge that this result might be flawed by some statistical limitation due to ‘estimation

bias from sparse data’; however, the clinical impact of our findings is so striking and meaningful that study termination was definitely necessary. Further RCTs must be performed before considering the use of protein C zymogen in pediatric or adult septic patients.

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*Correspondence: pappalardo.federico@hsr.it
San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy

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