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Fluid intake, fluid output or fluid balance, which one matters in ARDS

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To the editor,

In a recent trial including 650 COVID-19 patients with acute respiratory distress syndrome (ARDS) [1], Dr. Ahuja et al. reported a linear association between cumulative fluid balance and successful liberation from invasive ventilation in the restricted cubic spline function models. This study is well designed, and the conclusions are clear. We want to add some comments.

The volume of fluid balance is calculated as fluid intake—fluid output. Although dozens of studies have reported that increased fluid balance volume is associated with poor prognosis in various diseases, it remains unclear which factor really matters with the prognosis: Fluid input? Fluid output or fluid balance? For instance,

in the current study, the fluid intake volume within three days was quite close between the lower and higher tertiles, and the difference in fluid balance was mainly caused by the difference in urine output. However, is urine output or fluid balance the key factor in this relationship?

In clinical practice, fluid intake, output and fluid balance have complex interactions. Based on our previous findings, we suggest that the fluid accumulation index, which is derived from both fluid balance and fluid intake (fluid balance/fluid intake = 1 – fluid output/fluid intake), may play a vital role in the relationship with prognosis. For instance, studies have reported that patients with severe capillary leak may have a worse prognosis [2, 3]. However, as shown in Fig. 1, with different fluid intake and capillary leak severity,

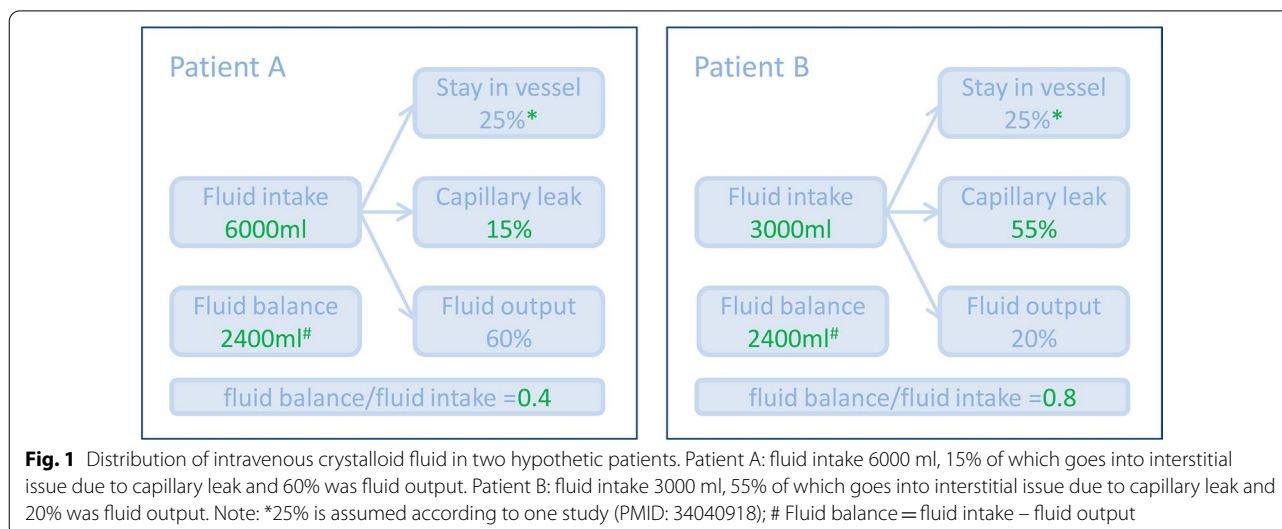
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the fluid balance is the same in patients A and B, while the fluid accumulation index is different (0.4 vs. 0.8). In addition, our previous finding [4] also revealed a complete mediation relationship within fluid balance, fluid balance/fluid intake and mortality in sepsis, which suggested that the association between fluid balance and mortality is completely mediated by fluid balance/fluid intake ratio [5]. Therefore, compared to fluid balance, fluid intake or fluid output alone, the fluid accumulation index (fluid balance/fluid intake) can more accurately reflect the ability to excrete excessive fluid under different fluid loads and predict the prognosis.

Finally, Dr. Ahuja et al.'s study added important information to the current knowledge of COVID-19, and their findings are highly appreciated. We hope our hypothesis will be helpful for further research.

Letter to the editor—Reply

Fluid intake, fluid output or fluid balance: Which one does not matter in ARDS?

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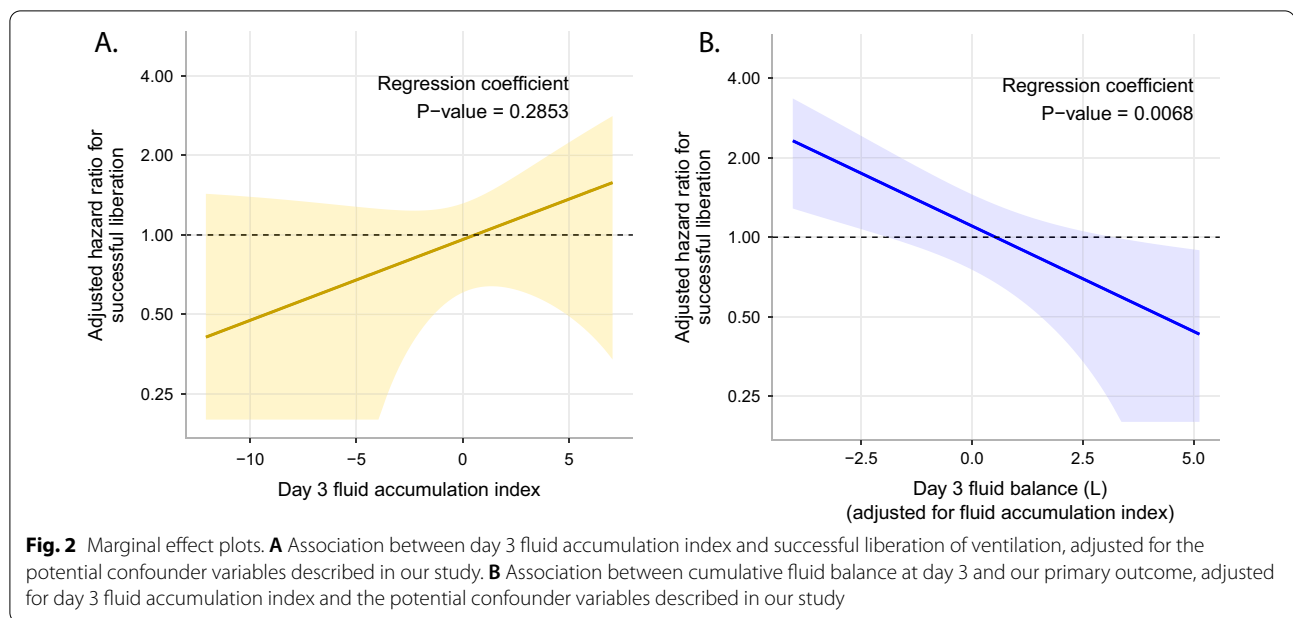
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In your journal, we recently showed that a higher cumulative fluid balance has an association with a longer duration of ventilation in patients with acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19), suggesting that restricted fluid management in these patients may be beneficial [1].

Shen et al. correctly mention that fluid intake, fluid output and fluid balance have complex interactions, and that a 'fluid accumulation index,' an index derived from both the fluid balance and the fluid intake, may play a vital role in this association [4].

To test this hypothesis, we reanalyzed the database of 'Practice of Ventilation in COVID-19 patients' (PRoVENT-COVID), the study we used to test our original hypothesis [6]. Here, we present a sensitivity analysis that modeled the successful liberation of ventilation as a function of the fluid accumulation index in the Cox regression model after adjusting for potential confounders defined in our study. We also adjusted for the 'fluid accumulation index' and refitted our main regression model, i.e., cumulative fluid balance on the hazard of successful liberation from invasive ventilation.

The fluid accumulation index was not associated with successful liberation of ventilation, even after adjusting for potential confounders ($P=0.2853$) (Fig. 2A). The association between cumulative fluid balance at day 3 and successful liberation of ventilation remained consistent by adjusting for the fluid accumulation index ($P=0.0068$) (Fig. 2B).



Based on these findings, we conclude that the fluid accumulation index has no added value in patients with ARDS due to COVID-19.

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YS and GC raised the question, and JY wrote the letter. All authors read and approved the final manuscript.

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