

LETTER

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Mortality in non-elderly septic patients was increased with hypothermia and decreased with fever while mortality in elderly patients was not associated with body temperature: beware of some confounders!

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We read with great interest the recent article by Shimazui et al. who concluded that in septic patients, mortality in non-elderly patients was increased with hypothermia and decreased with fever, while mortality in elderly patients was not associated with body temperature (BT) [1]. We would like to make some comments. As was alluded to by the authors themselves, BT measurement can be potentially confounded by various factors, including variation in the site of temperature measurement and whether or not patients receive antipyretics or targeted temperature management [1]. Nearly half of critically ill patients, especially those with septic shock, have or develop acute kidney injury (AKI) and 20–25% need renal replacement therapy (RRT) within the first week of their stay [2]. In the study of Shimazui et al., more than 60% of patients in both groups were in septic shock [1]. So, potentially, a third of patients may have had AKI, with 15% receiving continuous RRT (CRRT). CRRT is

well known for blunting temperature in septic shock patients [3]. Moreover, in the elderly population, the risk of developing AKI is increased by age-related physiological changes, lower renal reserves, and multiple comorbidities that render them more susceptible to acute renal impairment [4]. In addition, elderly patients typically take more medications and undergo more procedures, which may endanger their renal function [4]. Hence, AKI is generally more common among the elderly [4]. A recent study found that frailty was a predictor for the development of AKI, increasing the likelihood by more than three times [5]. Therefore, it is a possibility that there were more patients with artificial hypothermia (below 36 °C) as a result of RRT in the elderly group of Shimazui et al., introducing a confounder to the study [1]. Unfortunately, data regarding AKI and RRT have not been reported in the study of Shimazui et al., so we are unable to confirm our hypothesis.

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Authors' response

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We read with great interest the letter by Honore et al., concerning the potential confounding effect of continuous replacement therapy (CRRT) on body temperature (BT) measurement. The generally higher risk of developing acute kidney injury (AKI) in elderly patients might also influence the results.

To evaluate the impact of CRRT on our primary finding [1], we added analyses focused on AKI on admission and CRRT within the first 24 h from admission in the discovery cohort. According to the data availability, AKI was diagnosed based on the KDIGO criteria with some modification [6]: urine output in the first 24 h < 0.5 mL/kg, or serum creatinine levels on admission ≥ 0.3 mg/dL than baseline creatinine. Baseline creatinine was calculated using the Modification of Diet in Renal Disease (MDRD) study equation modified for the Japanese population [7], assuming an estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73 m² [6].

As Honore et al. have pointed out, the morbidity of AKI on admission was significantly higher in elderly patients compared to non-elderly patients (elderly 82.5%, non-elderly 73.8%, $P = 0.0005$ [chi-square test]). However, non-elderly patients were more frequently initiated on CRRT within first 24 h compared to elderly patients (elderly 17.2%, non-elderly 27.0%, $P < 0.0001$); non-elderly patients had higher chance of temperature alteration by CRRT. In addition, adding "CRRT" as covariates including previously reported analysis in the Cox regression for the hazard of death over 90 days by the BT adjusted with potential imbalances of age (per year), sex, chronic steroid use, and APACHE II score yielded results similar to the primary findings (non-elderly, BT < 36 °C and > 38.3 °C, $P = 0.024$ and $P = 0.14$, adjusted hazard ratio 1.70 and 0.73, 95% CI 1.07–2.71 and 0.48–1.10; elderly, BT < 36 °C and > 38.3 °C, $P = 0.091$ and $P = 0.87$, adjusted hazard ratio 0.62 and 0.96, 95% CI 0.36–1.08 and 0.63–1.47).

According to these results, we conclude that the BT, especially hypothermia, may be associated with mortality in non-elderly septic patients including those treated with CRRT, while the association between BT and mortality remains inconsistent in elderly septic patients even after adjusting the CRRT effects.

Abbreviations

BT: Body temperature; AKI: Acute kidney injury; RRT: Renal replacement therapy; CRRT: Continuous renal replacement therapy

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Authors' contributions

PMH, SR, and DDB designed the paper. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript.

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The authors declare to have no competing interests.

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