

LETTER

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# Association between metformin use prior to admission and lower mortality in septic adult patients with diabetes mellitus: beware of potential confounders

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We read with great interest the recent paper by Liang et al. who conclude that their meta-analysis indicated an association between metformin (MET) use prior to admission and lower mortality in septic adult patients with diabetes mellitus [1]. We would like to make some comments. 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 admission [2]. Because of its low molecular weight and minimal protein binding, metformin is equally (highly) eliminated by ultrafiltration (convection) and dialysis (diffusion). Furthermore, its large volume of distribution within a two-compartment pharmacokinetic model implies that metformin may be more effectively cleared by prolonged RRT. This was corroborated by Keller et al., who showed a dramatic reduction of metabolic acidosis and metformin plasma concentrations within the first 24 h after initiating CRRT in patients with MET-induced lactic acidosis, followed by normalization on the second day in all subjects [3]. Although we do not know the exact rate of CRRT in both arms [1], it may well be that one group had more CRRT than the other, particularly the metformin group. For instance, in the study of Doenys-Barak et al., which had a huge impact on the conclusions of this meta-analysis, the use of RRT was higher in the MET-treated population (38.6 vs. 21.2%,  $p = 0.13$ ) [1, 4]. Accordingly, we suspect that the observed difference in

mortality rate may be due to the more frequent use of RRT in the MET-treated population. A protective effect of RRT has already been suggested by Peters et al., who found that despite higher illness severity, the mortality rate in patients with MET-associated lactic acidosis treated with intermittent hemodialysis (IHD) was no different to that of non-dialyzed subjects [5].

#### Abbreviations

MET: Metformin; AKI: Acute kidney injury; RRT: Renal replacement therapy; IHD: Intermittent hemodialysis; CRRT: Continuous renal replacement therapy

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The authors declare to have no competing interests.

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