


LETTER



Sex differences in response to adjunctive corticosteroid treatment for patients with septic shock

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Dear Editor,

The Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) trial investigators reported no treatment-related sex difference in mortality [1], but hydrocortisone treatment was more cost effective in women, compared to men [2]. Previous studies have reported differences in glucocorticoid responsiveness to endotoxin and stress between sexes [3]. To determine sex differences in response to hydrocortisone treatment in patients with septic shock, we conducted a sex-disaggregated analysis of the ADRENAL trial.

Outcomes included the recurrence of shock, the frequency and duration of mechanical ventilation, renal replacement therapy, intensive care unit (ICU) and hospital admissions and the receipt of blood transfusions at 90 days post-randomisation. Health-related quality-of-life was assessed at 6 months post-randomisation. Healthcare resource use and cost data were collected from administrative health records in a subset of patients ($N=1488$) at 6 months post-randomisation.

We assessed outcomes in women and men separately using general linear models, logistic regression and Cox regression, respectively reported as mean differences, odds ratios (OR) and hazard ratios (HR). To compare treatment effects in women and men, we assessed differences in mean differences (DMD), ratio of odds ratios

(ROR) or ratio of hazard ratios (RHR) and report p values for heterogeneity. We adjusted for clinically relevant variables (age, APACHE II score [4], treatment with renal replacement therapy) and variables that differed between women and men at baseline (Supplementary Methods).

Of 3713 participants, 1454 (39%) were women (Supplementary Figure and Table 1). Hydrocortisone treatment increased the risk of shock recurrence in women but not in men (OR 1.38 versus 0.93; ROR 1.48; 95% CI 1.03, 2.14; $p=0.03$). In men, but not in women, hydrocortisone treatment significantly decreased the time to ICU discharge (HR 0.85; 95% CI 0.76, 0.93 versus 0.95; 95% CI 0.85, 1.09) and liberation from mechanical ventilation (HR 0.84; 95% CI 0.76, 0.93 versus 0.97; 95% CI 0.86, 1.10), although the RHR were not significant ($p=0.13$, $p=0.06$, respectively). There were no sex differences, women compared to men, in the effect of hydrocortisone treatment on the recurrence of mechanical ventilation (ROR 1.19; 95% CI 0.72, 1.99; $p=0.49$), receipt of blood transfusions (ROR 1.0; 95% CI 0.73, 1.39; $p=0.98$) or treatment with renal replacement therapy (ROR 0.98; 95% CI 0.66, 1.47; $p=0.93$). There were no sex differences in health-related quality-of-life, readmissions to hospital (ROR 0.84; 95% CI 0.53, 1.33; $p=0.44$) or costs of hospital visits (DMD -€6527; 95% CI -€15,517, €2,468; $p=0.15$) (Fig. 1 and Supplementary Table 2).

In 22 trials assessing low-dose corticosteroids in patients with septic shock, corticosteroids significantly reduced the duration of mechanical ventilation and ICU stay [5]. In our analysis, this was true in men but not in women. Sex-related differences in the clinical presentation, course and outcomes of disease are well recognised in certain medical specialties [6]. The potential for sex

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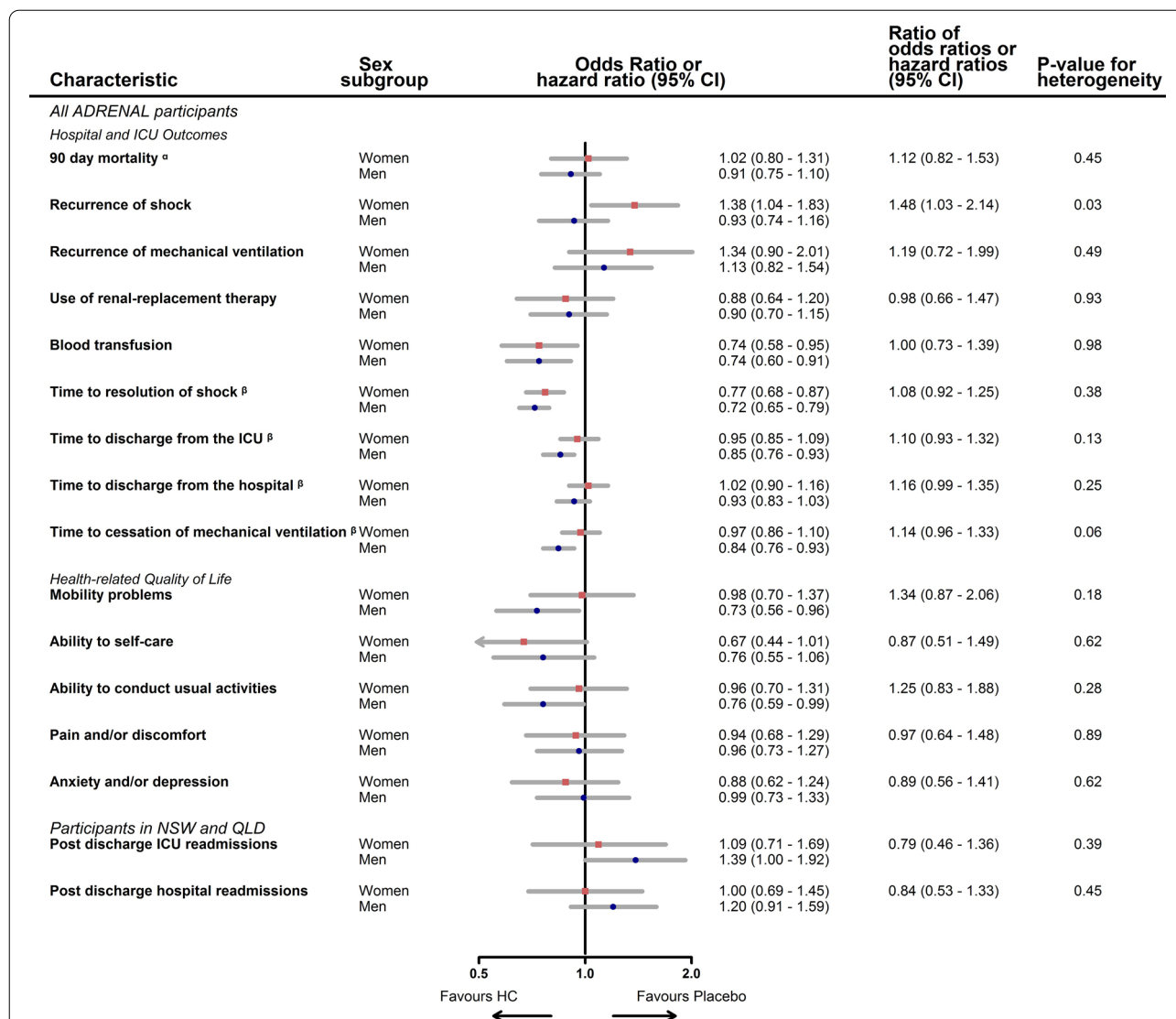


Fig. 1 Impact of hydrocortisone treatment on septic shock outcomes by sex

ICU intensive care unit; NSW New South Wales; QLD Queensland; HC hydrocortisone

^a This is a sub-distribution Hazard ratio (sHR) and ratio of sub-distribution Hazard ratio

^β In these time to event analyses the reciprocal sHR is displayed, reflecting the impact of hydrocortisone treatment on the outcome expressed in the forest plot. i.e. ratios > 1 favour placebo and < 1 favour hydrocortisone

differences in critically ill patients with sepsis is starkly illustrated by data from the SARS-CoV-2 pandemic. In the RECOVERY trial that examined the effect of dexamethasone on patients with coronavirus disease 2019 (COVID-19), 36% of the recruited patients were women but only 27% of mechanically ventilated patients were women [7]. This raises important considerations for interpretation of results, where women and men may be more or less likely to acquire severe forms of disease

and where treatment effects are dependent on disease severity, true effects in women and men may be masked if sex-disaggregated analyses are not performed in the appropriate subgroups.

The increased recurrence of shock in women treated with hydrocortisone may be due to sex differences in vascular responsiveness. Previous research has found women of reproductive age exhibit increased vascular responsiveness in the normal condition, and have a

lower decrease in vascular responsiveness after traumatic shock, compared to men of a similar age [8]. Further research is needed to determine whether our finding is replicated, and explore possible mechanisms.

In the ADRENAL trial, hydrocortisone produced differential effects on some secondary outcomes in women and men. Routine consideration of the impact of trial results separately for women and men, including conducting sex-disaggregated analyses, is appropriate and important in large critical care trials.

Supplementary Information

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Compliance with Ethical Statement

Conflict of interest

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