Electronic Supplementary Material for:

Intensive Care Medicine

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

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Supplementary Methods

Methods

This was a post-hoc analysis of data from the ADRENAL trial (NCT01448109). ADRENAL was an Australian and New Zealand Intensive Care Society Clinical Trials group endorsed investigator-initiated, blinded, randomised controlled trial comparing a 7 day continuous infusion of 200 mg daily of hydrocortisone or placebo on all-cause mortality at 90 days in 3800 patients with septic shock. The study was conducted in 69 ICUs across Australia, Denmark, New Zealand, Saudi Arabia and the United Kingdom. A detailed description of study methods and results have been previously reported [1, 2].

For the analyses of healthcare resource use and costs, we included 1488 patients enrolled in ADRENAL in the Australian states of New South Wales and Queensland, where data on ongoing healthcare resource use and costs were available by linking the trial and government hosted administrative health databases.

Human research ethics committee approval was obtained for all participating sites. Written informed consent or consent to continue after randomisation was obtained in accordance with local requirements. Ethical approval for data linkage to administrative health records was obtained separately for participating sites in New South Wales and Queensland.

Sex was determined as the legal gender as listed on the participants birth certificate. We recognise the terms sex and gender are inter-related and often confused. We respectfully refer to sex and/or gender as sex in this manuscript.

ICU and hospital outcomes included the frequency and duration of shock, mechanical ventilation and renal replacement therapy, the receipt of blood transfusions and the number of days alive and free of mechanical ventilation, renal replacement therapy, ICU and hospital at 90-days post randomisation.

Recurrence of shock was defined as a new episode of haemodynamic instability requiring treatment with inotropes or vasopressors, after resolution of the initial episode. Recurrence of mechanical ventilation was defined as the proportion of patients requiring re-institution of mechanical ventilation, where mechanical ventilation was defined as being treated with mechanical ventilation at the time of randomisation (including both via presence of an endotracheal tube or non-invasive ventilation with bi-level of continuous positive airway pressure).

Health-related quality-of-life was assessed in survivors using the EuroQoL 5-dimension 5-level Group Association Questionnaire (EQ-5D-5L) [3, 4]. The EQ-5D-5L collates responses to five health-related quality-of-life domains of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression scored across five levels (no problems, slight problems, moderate problems, severe problems, extreme problems or unable to perform the activity). Responses were grouped in categories of no/slight problems and moderate/extreme problems. Health-related quality-of-life utility values were also calculated using the Australian reference algorithm [5], with zero equivalent to death and one indicating full health. Patients who died during the trial were assigned a utility value of zero.

Healthcare resource use and economic outcomes

Healthcare resource use data were collected from the ADRENAL trial database and administrative health records in New South Wales and Queensland through the admitted patient database for a period of 6-months after randomisation. Outcomes included the duration of stay in the ICU and hospital for the initial admission, subsequent admissions to ICU and hospital and the duration of these admissions.

Costs included those incurred for hospital and ICU admissions up to 6-months after inclusion in the ADRENAL trial. Hospital and ICU costs were calculated using Australian Refined Diagnostic Related Group reimbursement costings [6, 7]. Cost information is reported in Euros (€) converted from the Australian dollar (A$) value on October 6th, 2017 (the date of last patient follow-up). As at that date, A$1 = €0.66.

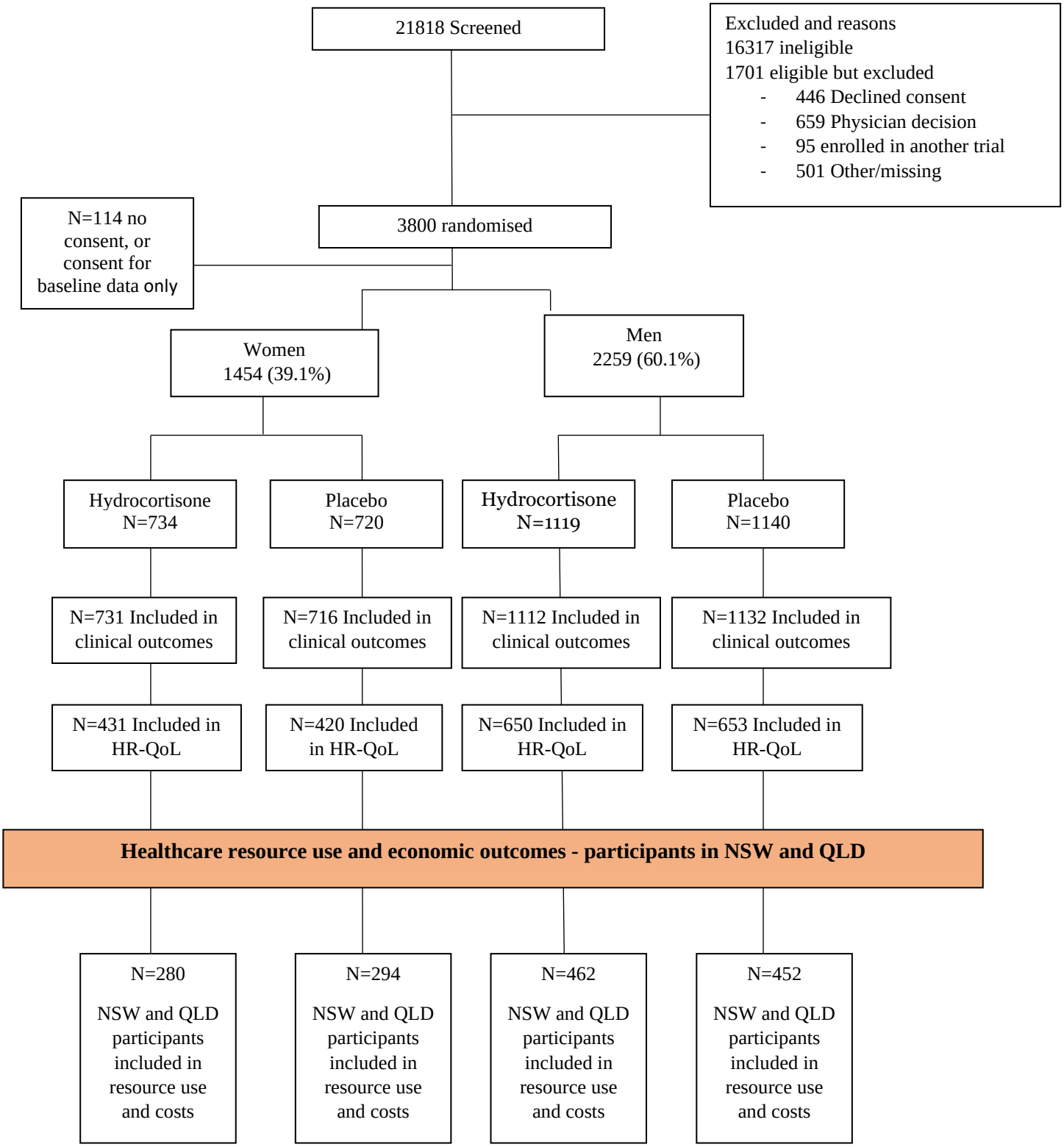
Statistical analysis

The analysis was conducted using methods previously described [8]. Baseline characteristics are reported by sex for all participants enrolled in the ADRENAL trial. A comparison of baseline characteristics and outcomes for patients enrolled in New South Wales and Queensland is provided in the supplement.

For continuous variables, general linear models were used to estimate mean differences, with 95% confidence intervals (95% CIs), between patients in the hydrocortisone or placebo groups for each sex separately, and then as the mean sex difference (women minus men) in treatment differences. For binary data, logistic regression was used to estimate odds ratios (ORs), with 95% CIs, comparing those in the hydrocortisone to those in the placebo group for each sex separately, and then as the ratios of odds ratios (RORs), women compared to men. The time to resolution of shock, mechanical ventilation and discharge from ICU and hospital were analysed using Cox proportional hazards models, with the Fine and Gray method [9] used to account for the competing risk of death. Time to event analyses are reported for each sex separately as the reciprocal of the subdistribution hazard ratio (sHR) (all ORs and HRs less than 1.0 favour hydrocortisone) [10], with 95% CIs, and then as the ratio of sHR (RsHR), women compared to men.

All analyses were adjusted for pre-specified clinically relevant variables (age, Acute Physiology And Chronic Health Evaluation [APACHE] II score [11], and treatment with renal replacement therapy) and for variables that differed between women and men at baseline (weight, admission source, first site of infection, time from ICU admission to randomisation, heart rate, lowest mean arterial pressure, lowest PaO^2/FiO^2 ratio, highest arterial lactate, highest creatinine, lowest haemoglobin, lowest platelets and statin therapy prior to enrolment). Baseline variables were recorded from data collected in the 24 hours prior to randomisation. We tested for the interaction between treatment and sex for all outcomes, reported as p-values. SAS Enterprise Guide 7.1 was used for the analyses.

Supplementary Figure 1: **Consort diagram**



Abbreviations: HR-QoL Health-related quality-of-life, NSW New South Wales, QLD Queensland.

Supplementary Table 1: Baseline characteristics by sex

Characteristic	Women N=1454	Men N=2259	p-value W:M
Age: mean (SD)	61.8 (15.5)	63.0 (14.7)	0.01
Weight, kgs: mean (SD)	80.6 (26.9)	89.0 (25.7)	<0.0001
APACHE II score: mean (SD)	23.6 (7.5)	24.2 (7.8)	0.04
Admission type: n (%)			0.71
Non-operative	989/1451 (68.2)	1550/2255 (68.7)	
Operative	462/1451 (31.8)	705/2255 (31.3)	
Admission source: n (%)			0.02
Emergency Department	437/1451 (30.1)	684/2255 (30.3)	
Hospital Floor	325/1451 (22.4)	546/2255 (24.2)	
Transfer from another ICU	69/1451 (4.8)	94/2255 (4.2)	
Transfer from another hospital	149/1451 (10.3)	211/2255 (9.4)	
Theatre following emergency surgery	427/1451 (29.4)	605/2255 (26.8)	
Theatre following elective surgery	44/1451 (3.0)	115/2255 (5.1)	
Primary infection site: n (%)			<0.0001
Pulmonary	443/1447 (30.6)	857/2251 (38.1)	
Intra-abdominal	362/1447 (25.0)	425/2251 (18.9)	
Blood	249/1447 (17.2)	392/2251 (17.4)	
Skin	97/1447 (6.7)	156/2251 (6.9)	
Urinary	141/1447 (9.7)	138/2251 (6.1)	
Central nervous system	6/1447 (0.4)	20/2251 (0.9)	
Gut	67/1447 (4.6)	90/2251 (4.0)	
Endocarditis	8/1447 (0.6)	18/2251 (0.8)	
Other	74/1447 (5.1)	155/2251 (6.9)	
Physiological variables: mean (SD)			
Heart rate, beats per minute	98 (22)	94 (21)	<0.0001
Central venous pressure, mmHg	12.2 (5.3)	12.0 (5.2)	0.20
Mean arterial pressure, mmHg	72.1 (8.2)	72.5 (8.3)	0.16
Lowest mean arterial pressure, mmHg	56.5 (9.0)	57.6 (8.6)	0.0001
Lowest PaO2/FiO2, mmHg	170.5 (93.4)	162.3 (90.3)	0.008
Lowest Haemoglobin g/L	101.6 (20.3)	106.9 (23.2)	<0.0001
Highest Arterial Lactate, mmHg	3.9 (3.2)	3.7 (3.1)	0.03
Highest Creatinine umol/L	173.4 (148.2)	202.5 (170.8)	<0.0001
Time from ICU admission to randomisation (hours)	22.5 (40.7)	30.7 (85.9)	0.0007
Time of shock onset to randomisation			0.35
< 6 hours	282/1444 (19.5%)	424/2249 (18.9%)	
6 to <12 hours	415/1444 (28.7%)	596/2249 (26.5%)	
12 to <18 hours	331/1444 (22.9%)	537/2249 (23.9%)	
≥18 hours	416/1444 (28.8%)	692/2249 (30.8%)	
RRT in the 24 hours prior to randomisation: n (%)	185/1451 (12.7)	285/2255 (12.6)	0.92
Dialysis for chronic renal failure in last year: n (%)	42/1451 (2.9)	76/2255 (3.4)	0.42
Statin therapy prior to randomisation: n (%)	278/1451 (19.2)	579/2255 (25.7)	<0.0001

Abbreviations: SD=standard deviation; APACHE=Acute Physiological and Chronic Health Evaluation; mmHg=millimetres of mercury; PaO2/FiO2=ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2); umol/L= millimoles per litre; g/L=grams per litre; RRT=renal replacement therapy. The lowest mean arterial pressure, PaO2/FiO2, haemoglobin and highest arterial lactate and creatinine were measured within 24 hours prior to randomisation.

Supplementary Table 2: Impact of hydrocortisone treatment on septic shock outcomes by sex

Characteristic	Women HC - Placebo Mean difference (95% CI)	Men HC - Placebo Mean difference (95% CI)	Women minus. men Difference of mean differences (95% CI)	p-value
All ADRENAL participants				
Differences in days alive and free of at 90-days	**N=1447**	**N=2244**		
Mechanical ventilation	-0.76 (-4.37, 2.85)	2.59 (-0.34, 5.52)	-3.35 (-8.00, 1.29)	0.15
Renal replacement therapy	-0.54 (-4.18, 3.10)	2.29 (-0.66, 5.25)	-2.83 (-7.52, 1.85)	0.23
ICU	-0.47 (-3.98, 3.04)	2.64 (-0.21, 5.48)	-3.11 (-7.62, 1.40)	0.18
Hospital	-0.88 (-4.11, 2.36)	2.08 (-0.54, 4.71)	-2.96 (-7.12, 1.20)	0.16
Difference in quality-of-life utility values (6-months)	0.02 (-0.02, 0.07)	0.01 (-0.03, 0.04)	0.02 (-0.08, 0.04)	0.57
Participants in NSW and QLD	**N=574**	**N=914**		
Differences in outcomes at 6-months				
initial length of ICU stay (days)	0.95 (-0.84, 2.75)	-0.85 (-2.27, 0.57)	1.80 (-0.49, 4.09)	0.12
duration of ICU readmissions (days)	0.95 (-0.85, 2.74)	-0.84 (-2.26, 0.58)	1.79 (-0.50, 4.08)	0.12
initial length of hospital stay (days)	2.67 (-1.33, 6.67)	1.49 (-1.67, 4.66)	1.17 (-3.93, 6.27)	0.65
duration of post discharge hospital readmissions (days)	2.66 (-1.34, 6.66)	1.50 (-1.67, 4.67)	1.16 (-3.94, 6.26)	0.65
Differences in costs at 6-months (€)				
ICU	-315 (-3897, 3266)	965.6 (-1882, 3813)	-1280 (-5851, 3291)	0.58
Hospital	-1424 (-8472, 5113)	5102 (-500, 10706)	-6527 (-15517, 2468)	0.15

Abbreviations: HC = hydrocortisone. ICU = intensive care unit. NSW = New South Wales. QLD = Queensland

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