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Sex and mortality in septic severe acute kidney injury

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ABSTRACT

Purpose: To investigate the relationship between sex and mortality and whether menopause or the intensity of renal replacement therapy (RRT) modify this relationship in patients with severe septic acute kidney injury (AKI).
Materials and methods: Post-hoc analysis of patients with sepsis included in the Randomized Evaluation of Normal versus Augmented Level renal replacement therapy (RENAL) trial.
Results: Of 724 patients, 458 (63.3%) were male and 266 (36.7%) were female. The mean delivered effluent flow rate was 25.6 ± 7.4 ml/kg/h (80 ± 15% of prescribed dose) in males and 27.4 ± 7.6 ml/kg/h (83 ± 15% of prescribed dose) in females ($p = .01$). A total of 237 (51.7%) males and 118 (44.5%) females died within 90 days of randomization ($p = .06$). The adjusted hazard ratio (HR) for 90-day mortality was significantly decreased in females as compared with males (HR 0.74, 95% CI 0.57 to 0.96, $p = .02$). The relationship between sex and mortality was not significantly altered by menopausal status (adjusted *P* value for interaction 0.99) or by RRT intensity allocation (adjusted P value for interaction 0.27).
Conclusions: In a cohort of patients with sepsis and severe AKI, female sex was associated with improved survival. The relationship between sex and survival was not altered by menopausal status or RRT intensity.

1. Introduction

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection", and is estimated to contribute to >5 million deaths worldwide annually [1,2]. It is the most common cause of acute kidney injury (AKI) in patients admitted to the intensive care unit (ICU), and the combination of both sepsis and AKI is associated with substantially greater mortality than either diagnosis in isolation [3-6].

Previous studies have suggested that female sex may be associated with decreased susceptibility to sepsis, possibly due to protective effects of oestrogen [7-9]. However, the impact of sex on mortality in septic patients remains controversial. In particular, the association between sex and mortality in patients with septic AKI requiring renal replacement therapy is unknown [10-13].

The Randomized Evaluation of Normal versus Augmented Level (RENAL) replacement therapy study included detailed data on characteristics and outcomes of >700 patients with septic AKI requiring continuous renal replacement therapy (CRRT). As such, it provided the opportunity to assess the possible impact of sex on patient-centred outcomes in this specific population [14]. We conducted a post-hoc analysis of the RENAL study to test the primary hypothesis that in septic patients with severe AKI, female sex would be independently associated with decreased mortality, with a secondary hypothesis that such an association would be modified by the presence of the menopause or by RRT intensity.

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2. Material and methods

The RENAL study was a multicentre, prospective, randomized trial comparing two levels of intensity of CRRT in 1508 adult (>18 years) critically ill patients with AKI, conducted in 35 ICUs in Australia and New Zealand. The human research ethics committees of the University of Sydney and all participating institutions approved the study. Written informed consent was obtained from patients or their responsible surrogate.

The features of the trial have been previously described [14]. Patients were treated with continuous veno-venous hemodiafiltration (CVVHDF) using post-dilution and were randomly assigned to either a higher intensity group (effluent flow rate 40 ml/kg/h) or lower intensity group (effluent flow rate 25 ml/kg/h). The primary study outcome was all-cause mortality within 90 days of randomization.

Patients had to meet at least one of six inclusion criteria; oliguria (urine output <400 ml/day) unresponsive to fluid resuscitation, hyperkalaemia (serum potassium >6.5 mmol/l), severe acidemia (pH <7.2), blood urea nitrogen >70 mg/dl (>25 mmol/l), creatinine >3.4 mg/dl (300 μmol/l) or severe organ edema associated with acute kidney disease. The patients' most recent biochemical and haematological results prior to randomization were used as their baseline measurements. For the components of the APACHE III and SOFA scores, the most abnormal results measured during the 24 h prior to randomization were used [15,16]. Further details concerning data collection and the method through which CRRT was performed, is available in the original RENAL study publication [14].

2.1. Study population

For the purpose of this post-hoc analysis, we included patients with a pre-randomization diagnosis of sepsis. Patients were determined to have sepsis if they had both a defined focus of infection, and at least two of the Systemic Inflammatory Response Syndrome (SIRS) criteria. These criteria included core temperature (>38 °C or < 36 °C), white cells (cell count >12 × 10^9/l or < 4 × 10^9/l or > 10% immature neutrophils), tachycardia (heart rate > 90 beats/min) and tachypnoea (respiratory rate > 20 breaths/min or a PaCO2 < 32 mmHg or mechanical ventilation). We recognize that these are not consistent with current diagnostic criteria, though were used as the Sepsis-3 consensus definition had not yet been published when the RENAL trial was designed and completed [1].

2.2. Study outcomes

The primary outcome was 90-day mortality. Secondary outcomes included 28-day mortality, survival to ICU and hospital discharge, length of ICU and hospital stay, RRT dependence at 28 and 90 days, duration of mechanical ventilation, development of non-renal organ failure and the development of RRT complications. These complications included hypophosphatemia, hypokalaemia and arrhythmias.

Prior to completing this post-hoc analysis, we pre-specified two subgroups defined by pre-randomization criteria; menopausal status and CRRT intensity group. Menopause is the permanent cessation of menstrual cycles and ovarian reproductive function, causing a reduction in ovarian oestrogen production [17]. Due to the influence of oestrogen on the immune system, we stratified patients into those above and below the average age of menopause in Australia (51 years) [10,17]. We also analyzed patients based upon the CRRT intensity group to which they were randomized.

2.3. Statistical analysis

Data was analyzed using STATA version 14.2 (Stata, College Station, TX). Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed, or median (interquartile range (IQR)) if non-normally distributed. We compared continuous variables using analysis of variance (ANOVA) or the Wilcoxon rank-sum test, as appropriate. Categorical variables were expressed as numbers (percentages), and were compared using Pearson's chi-squared or Fisher's exact test. Time to death within 90 days was investigated using multivariable Cox regression analysis and presented as both hazard ratios with corresponding 95% confidence intervals, and as Kaplan-Meier curves with comparison using a log-rank test. We included pre-randomization variables with $p < .10$ on univariate comparison in the Cox regression model. To test the robustness of the association between sex and 90-day mortality, we performed multivariable logistic regression analysis, presented as odds ratios with 95% confidence intervals. We also repeated the Cox regression and logistic regression analyses using a stepwise (backward and forward) selection of covariates ($P \geq .2$ for exit and $P < .1$ for entry). Resulting models were assessed for multicollinearity. Goodness-of-fit and model discrimination were determined using Hosmer–Lemeshow goodness-of-fit and area under the curve (AUC) respectively. Proportional hazards assumptions were assessed using Schoenfeld residuals. We performed subgroup analyses for the primary outcome based on the crude and adjusted test of interaction between menopause and sex and between lower CRRT intensity and sex, respectively, in Cox and logistic regression models. A two-sided p-value below 0.05 was considered statistically significant.

3. Results

3.1. Patients

Of the 1508 RENAL patients, we identified 724 (48.0%) with sepsis before randomization. Of these 724 patients, 458 (63.3%) were male and 266 (36.7%) were female. Overall, 224 (48.9%) males and 136 (51.1%) females were randomized to higher intensity CRRT ($p = .56$). Baseline characteristics were similar in males and females. However, males were heavier, more likely to have a cardiovascular admission diagnosis, had greater plasma BUN and creatinine concentrations, and less severe acidemia indices before randomization (Table 1).

3.2. Treatment characteristics

When all patients, randomized to either high or low intensity CRRT, were compared by sex, the mean delivered effluent flow rate was 25.6 ± 7.4 ml/kg/h (80 ± 15% of prescribed dose) in males and 27.4 ± 7.6 ml/kg/h (83 ± 15% of prescribed dose) in females ($p = .01$). Dialysate/replacement fluid flow rate, dose of effluent and net ultrafiltration flow rate were similar in males and females. Overall, 211 (46.1%) males and 126 (47.4%) females received pre-filter heparin for a median (IQR) of 4 (2–6) and 3 (2–5) days, respectively ($p = .04$). Anticoagulation-free CRRT was delivered to 236 (51.5%) males and 123 (46.2%) females for a median of 3 (1–5) days in both groups ($p = .60$). Daily average serum BUN and serum creatinine were greater in males than in females (Table 2).

3.3. Primary outcome

A total of 237 (51.7%) males and 118 (44.5%) females died within 90 days of randomization ($p = .06$) with the majority of deaths occurring in the first 28 days (Table 3, Fig. 1). On multivariable Cox regression analysis, the adjusted hazard ratio for 90-day mortality was significantly decreased in females as compared with males (HR 0.74, 95% CI 0.57 to 0.96) (Table 4). Similar risk estimates were obtained in the logistic regression analysis (OR 0.60, 95% CI 0.42 to 0.87, $p = .006$) and in the Cox and logistic regression analyses using stepwise selection of covariates (Table 5 and Tables S1 – S2 in Supplementary Digital Content 1).

The relationship between sex and mortality was not significantly altered by menopausal status (adjusted P value for interaction 0.99) or by CRRT intensity allocation (adjusted P value for interaction 0.27) on

Table 1
Baseline characteristics of the study patients.*

Characteristic	Males ($n = 458$)	Females ($n = 266$)	p-Value
Age - yr.	65.9 (57.8–74.7)	65.5 (55.9–74.3)	0.55
Randomized to higher intensity CRRT – no. (%)	224 (48.9)	136 (51.1)	0.56
Time in ICU before randomization – hr	21 (6–63)	18 (6–47)	0.43
Mechanical ventilation – no. (%)	359 (78.6)	211 (79.3)	0.81
APACHE III score §	107.3 ± 25.3	106.9 ± 22.7	0.84
SOFA score ¶			
Cardiovascular	4 (3–4)	4 (3–4)	0.83
Respiratory	3 (3–3)	3 (3–3)	0.69
Liver	1 (0–2)	0 (0–2)	0.52
Renal	3 (2–4)	3 (2–3)	0.01
Coagulation	1 (0–2)	0 (0–2)	0.52
Weight – kg	83.3 ± 12.7	76.3 ± 11.7	<0.001
Source of admission – no./total no. (%)			0.59
Emergency department	126/419 (30.1)	78/247 (31.6)	
Hospital ward	147/419 (35.1)	74/247 (30.0)	
Transfer from another ICU	37/419 (8.8)	25/247 (10.1)	
Transfer from another hospital	54/419 (12.9)	31/247 (12.6)	
OR after emergency surgery	38/419 (9.1)0	31/247 (12.6)	
OR after elective surgery	17/419 (4.1	8/247 (3.2)	
Non-operative admission diagnosis – no./total no. (%)			0.49
Cardiovascular	231/390 (59.2)	138/223 (61.9)	
Genitourinary	42/390 (10.8)	31/223 (13.9)	
Respiratory	79/390 (20.3)	39/223 (17.5)	
Gastrointestinal	23/390 (5.9)	9/223 (4.0)	
Other	15/390 (3.8)	6/223 (2.7)	
Operative admission diagnosis – no./total no. (%)			0.0
Cardiovascular	23/68 (33.8)	10/43 (23.3)	
Gastrointestinal	31/68 (45.6)	32/43 (74.4)	
Trauma	5/68 (7.4)	1/43 (2.3)	
Other	9/68 (13.2)	0/43 (0.0)	
Criteria for randomization – no./total no. (%) ◊			
Oliguria (urine, <400 ml/day)	253/458 (55.2)	170/266 (63.9)	0.02
Hyperkalaemia	32/458 (7.0)	11/266 (4.1)	0.12
Severe acidemia	187/458 (40.8)	126/266 (47.4)	0.09
BUN >70 mg/dl (plasma urea >25 mmol/l)	209/458 (45.6)	99/266 (37.2)	0.03
Creatinine >3.4 mg/dl (300umol/l)	227/458 (49.6)	109/266 (41.0)	0.03
Severe organ oedema associated with acute kidney disease	194/458 (42.4)	123/266 (46.2)	0.31
BUN – mmol/l †	22.9 (15.8–32.7)	19.4 (13.0–29.6)	<0.001
Creatinine before randomization – μmol/l ††	297.5 (214–409)	254.5 (191–351)	<0.001
pH	7.26 (7.16–7.35)	7.23 (7.14–7.30)	0.002
Bicarbonate – mmol/l	18.6 ± 6.0	17.1 ± 5.5	0.001
Base excess – mmol/l	−8.1 ± 7.5	−10.1 ± 7.0	lt;0.001
INR	1.5 (1.3–1.9)	1.5 (1.3–1.9)	0.91
aPTT - seconds	40 (34–50)	41 (36–52)	0.09
Albumin – g/l	24.6 ± 6.9	23.6 ± 6.9	0.06
Blood glucose – mmol/l †††	7.2 (5.7–8.9)	6.8 (5.3–9.0)	0.12

* Normally distributed data are presented as means ±SD, and non-normally distributed as median (IQR). APACHE denotes acute physiologic assessment and chronic health evaluation, aPTT activated partial thromboplastin time, BUN blood urea nitrogen, CRRT continuous renal replacement therapy, ICU intensive care unit, INR international normalised ratio, OR operating room, and SOFA sequential organ failure assessment.
§ APACHE III scores range from 0 to 299, with higher scores indicating more severe illness.
¶ SOFA scores range from 0 to 4, with a higher score indicating more severe organ dysfunction.
◊ A given patient may have met more than one of these criteria.
† To convert the values for blood urea nitrogen to milligrams per decilitre, divide by 0.357.
†† To convert the values for creatinine to milligrams per decilitre, divide by 88.4.
††† To convert the values for blood glucose to milligrams per decilitre, multiple by 18.0.

Cox regression analysis or on logistic regression analysis (Tables S3 – S4 and Fig. S1 in Supplemental Digital Content 1).

3.4. Secondary outcomes

Female patients had a lower adjusted hazard ratio for 28-day mortality and were more likely to survive to hospital discharge when compared to males, though survival to ICU discharge was not significantly different (Table S5 – S8 in Supplementary Digital Content 1).

We observed no significant differences between males and females in longer-term renal replacement therapy (RRT) dependence, RRT duration, length of stay, duration of mechanical ventilation or number of non-renal organ failures on univariate or multivariate analyses (Table 3 and Tables S9 – S17 in Supplemental Digital Content 1).

3.5. Complications

Univariate and multivariate analyses of complications associated with RENAL trial CRRT are outlined in Tables S18 – S23 in the Supplemental Digital Content. A greater proportion of females (67.7%) than males (59.0%) experienced hypophosphatemia during the RENAL trial ($p = .02$), though on multivariate analysis the association between female sex and hypophosphatemia was not significant (OR 1.34, 95% CI 0.96 to 1.87, $p = .09$). Hypokalaemia also occurred in a greater proportion of females than males (34.0% vs 24.8%, $p = .01$), and a statistically significant association between female sex and hypokalaemia was demonstrated on multivariate analysis (OR 1.72, 95% CI 1.21 to 2.44, $p = .002$).

No association was identified between sex and other complications.

Table 2
Characteristics of study treatment*.

Characteristic	Males	Females	*p* value
Duration of study treatment – days	4 (2–7)	3 (2–7)	0.43
Flow rate of effluent – ml/kg/h	25.6 ± 7.4	27.4 ± 7.6	0.01
Dose delivered - % of prescribed dose	0.80 ± 0.15	0.83 ± 0.15	0.01
Average dialysate and replacement fluid flow rate – ml/h	2020 ± 676	1984 ± 657	0.54
Dose of effluent – ml/h/day	2111 ± 641	2093 ± 661	0.74
Net ultrafiltration flow rate – ml/h	91 ± 221	109 ± 66	0.27
Type of anticoagulant received – no./total no. (%) ◊			
Pre-filter heparin	211/458 (46.1)	126/266 (47.4)	0.74
Pre-filter heparin duration – days	4 (2–6)	3 (2–5)	0.04
No anticoagulant	236/458 (51.5)	123/266 (46.2)	0.17
No anticoagulant duration – days	3 (1–5)	3 (1–5)	0.60
Heparin and protamine	75/458 (16.4)	48/266 (18.0)	0.56
Heparin and protamine duration – days	3 (2–6)	4 (3–6)	0.28
Systemic heparin	75/458 (16.4)	45/266 (16.9)	0.85
Systemic heparin duration – days	4 (1–5)	3 (2–6)	0.77
Other anticoagulant	19/458 (4.1)	23/266 (8.6)	0.01
Other anticoagulant duration – days	3 (2–8)	3 (1–3)	0.22
Filters used daily – no.	0.90 ± 0.51	0.84 ± 0.48	0.09
Patients treated with IHD in ICU – no. (%)	35/457 (7.7)	16/265 (6.0)	0.41
Daily average BUN – mmol/l/day†	14 (10.7–19.6)	10.8 (7.5–14.7)	<0.001
Daily average serum creatinine – μmol/l/day ††	176 (133–229)	131 (101–170)	<0.001

* Normally distributed data are presented as means ±SD, and non-normally distributed as median (IQR). BUN denotes blood urea nitrogen, ICU intensive care unit and IHD intermittent haemodialysis.
† To convert the values for blood urea nitrogen to milligrams per decilitre, divide by 0.357.
†† To convert the values for creatinine to milligrams per decilitre, divide by 88.4.
◊ Some patients received more than one type of anticoagulant.

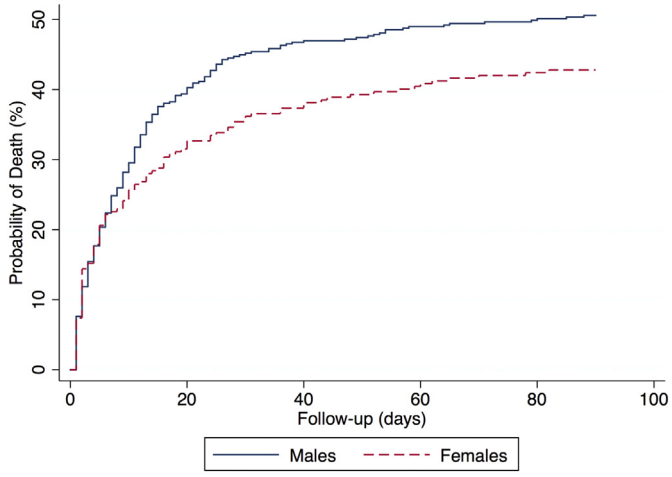

Fig. 1. Kaplan-Meier Estimates of the Probability of Death According to Sex. Log-Rank test, $p = .054$.

4. Discussion

4.1. Key findings

In this post-hoc analysis of the RENAL trial, focusing on critically ill patients with septic acute kidney injury requiring continuous renal replacement therapy, female sex was associated with improved survival to 90-days, hospital discharge and 28-days. However, the association between sex and survival was not altered by post-menopausal age or intensity of CRRT. Female sex was independently associated with slightly greater CRRT dose delivery, lower BUN and creatinine levels and an increased risk of hypokalaemia.

4.2. Relationship with previous studies

Numerous mechanisms may contribute to the improved survival of septic females. Females with severe infections have an increased innate immune response and endothelial activation [18-20], which may be mediated by differences in sex steroid hormones [11,21]. In this regard, oestrogen may be protective in the setting of infection, while testosterone may be harmful due to its immunosuppressive effects [22,23]. The negative effect of testosterone on the immune response of septic males, may account for the seemingly insignificant impact of menopausal status demonstrated in our study. Additionally, the influence of sex hormones on the expression of disease resistance genes may explain a difference in outcomes that is sustained beyond menopause [10]. Alternatively, differences in hormones others than oestrogen and testosterone, such as glucocorticoids and peptide hormones, may affect outcomes and remain unaltered by menopausal status [10].

Endothelial dysfunction may contribute to AKI in patients with sepsis [6,24]. It has recently been shown that septic females have increased

Table 3
Primary and secondary outcomes.*

Characteristic	Males	Females	*p* value
Death – no./total no. (%)			
By day 28	210/458 (45.9)	97/266 (36.5)	0.01
By day 90	237/458 (51.7)	118/265 (44.5)	0.06
Place of death – no./total no. (%)			0.59
ICU	187/237 (78.9)	95/118 (80.5)	
Hospital ward	48/237 (20.3)	23/118 (19.5)	
Outside hospital, after discharge	2/237 (0.8)	0/118 (0.0)	
RRT dependence amongst1 survivors -no./total no. survivors (%)			
At day 28	23/248 (9.3)	17/169 (10.1)	0.79
At day 90	7/221 (3.2)	5/148 (3.4)	0.91
No. of days of RRT, from randomization to day 90	10.9 ± 16.7	10.7 ± 16.3	0.88
No. of days in ICU	11.3 ± 12.4	12.7 ± 14.4	0.16
No. of days in hospital	25.2 ± 25.4	27.3 ± 26.7	0.30
No. of days of mechanical ventilation	7.6 ± 6.9	8.5 ± 8.2	0.11
No. of new non-renal organ failures – no./total no. (%)			0.28
0	217/458 (47.4)	116/266 (43.6)	
1	152/458 (33.2)	105/266 (39.5)	
2	73/458 (15.9)	33/266 (12.4)	
3	15/458 (3.3)	12/266 (4.5)	
4	1/458 (0.2)	0/266 (0.0	

* Normally distributed data are presented as means ±SD, and non-normally distributed as median (IQR). ICU denotes intensive care unit and RRT renal replacement therapy.

Table 4
Cox regression for time to 90-day mortality.*

Characteristic	Unadjusted HR (95% CI)	Unadjusted *p* value	Adjusted HR (95% CI)	Adjusted *p* value
Female sex	0.80 (0.64–1.01)	0.058	0.74 (0.57–0.96)	0.024
Randomized to higher intensity CRRT	0.91 (0.73–1.12)	0.372	0.95 (0.75–1.19)	0.629
Age – years	1.02 (1.01–1.02)	0.000	1.02 (1.01–1.03)	<0.001
Albumin - g/l	0.97 (0.96–0.99)	0.002	0.99 (0.97–1.01)	0.275
APACHE III score	1.01 (1.01–1.02)	0.000	1.01 (1.00–1.02)	0.001
aPTT - seconds	1.01 (1.00–1.01)	0.000	1.00 (1.00–1.01)	0.086
Base excess	1.01 (1.00–1.03)	0.074	1.00 (0.97–1.03)	0.881
Bicarbonate	1.03 (1.01–1.05)	0.004	1.01 (0.97–1.05)	0.665
Creatinine before randomization - per 10 μmol/l increase	0.98 (0.97–0.98)	0.000	0.98 (0.97–0.99)	<0.001
Glucose - mmol/l	0.97 (0.93–1.00)	0.080	0.97 (0.93–1.01)	0.163
Mechanical ventilation	1.60 (1.20–2.13)	0.001	1.07 (0.69–1.66)	0.771
SOFA Coagulopathy	1.19 (1.09–1.29)	0.000	1.08 (0.98–1.19)	0.100
SOFA Liver	1.22 (1.13–1.33)	0.000	1.15 (1.04–1.27)	0.006
SOFA Respiratory	1.30 (1.14–1.49)	0.000	1.11 (0.90–1.36)	0.338
Time in ICU before randomization - Hours	1.001 (1.001–1.002)	0.000	1.001 (1.001–1.002)	<0.001
Weight - kg	0.99 (0.98–1.00)	0.048	0.99 (0.98–1.00)	0.124

Proportional-hazards test, $p = .10$.
* APACHE denotes Acute Physiology and Chronic Health Evaluation, aPTT activated partial thromboplastin time, CRRT continuous renal replacement therapy, HR hazard ratio, ICU intensive care unit and SOFA Sequential Organ Failure Assessment.

endothelial cell activation when compared to males [19]. This variation in endothelial activation, and its potential relationship with AKI, may have led to a greater difference in outcomes between males and females with septic AKI in our study, than previously demonstrated in studies of sepsis alone.

Recent systematic reviews have concluded that the current literature regarding sex differences in sepsis remains inconclusive [12,13]. While results consistent with our own have been previously reported [11,25], a body of research did not report differences in outcomes between males and females [19,21,26-28], or instead observed that females have an increased rate of death [29-32]. These trials have used various survival outcomes and few reported the impact of menopausal status on survival [11,19,25,26,31]. These trials included only a small proportion of patients with AKI, and none specifically analyzed this population as a subgroup.

Several baseline differences were noted between males and females in this study, which we largely attribute to the significant difference in weight between sexes. For example, the higher baseline SOFA renal score in males, as determined by serum creatinine, likely reflects a greater muscle mass in male patients. Additionally, males had higher BUN and serum creatinine at baseline and throughout CRRT study days, which may again be explained not only by the lesser dose of CRRT delivered, but also by muscle mass and increased protein intake as a result of titrating nasogastric feeds to body weight. A greater proportion of females met the RENAL trial enrollment criteria of oliguria (<400 ml urine output/day) which can be attributed to a lower body weight, as the criteria was based upon absolute urine output, as opposed to a milliliters per kilogram measurement. Finally, the higher CRRT dose delivered to females on study days is likely to reflect easier delivery in smaller patients and likely contributed to hypophosphatemia and hypokalemia.

In addition to sex, several other baseline variables were consistently associated with mortality on multivariate analyses. Increased age, APACHE III score and SOFA liver score were all independent predictors of mortality. The significance of APACHE III and SOFA scores relative to males and females is unclear, as the relationship between these scores and expected survival has not been previously assessed separately for each sex. Additionally, an increased length of time in the ICU prior to enrollment in the RENAL trial was also associated with increased mortality.

Finally, raised pre-randomization creatinine and weight were both independently associated with decreased mortality. This relationship has been previously identified and may be attributed to the effect of muscle wasting on such variables [33-37].

4.3. Implications of study findings

Our findings imply that septic females with severe AKI have an inherent survival advantage when compared to septic males with severe AKI. Although the mechanisms through which this occurs are unknown

Table 5
Logistic regression of 90-day mortality.*

Characteristic	Unadjusted OR (95% CI)	Unadjusted p value	Adjusted OR (95% CI)	Adjusted p value
Female sex	0.75 (0.55–1.01)	0.062	0.60 (0.42–0.87)	0.006
Randomized to higher intensity CRRT	0.83 (0.62–1.11)	0.219	0.81 (0.58–1.13)	0.210
Age - years	1.02 (1.01–1.03)	0.000	1.03 (1.02–1.05)	0.000
Albumin - g/l	0.97 (0.94–0.99)	0.002	0.98 (0.96–1.01)	0.164
APACHE III score	1.02 (1.01–1.02)	0.000	1.01 (1.01–1.02)	0.001
Bicarbonate – mmol/l	1.04 (1.01–1.06)	0.005	1.02 (0.99–1.06)	0.135
Creatinine before randomization - per 10 μmol/l increase	0.97 (0.96–0.98)	0.000	0.98 (0.97–1.00)	0.022
Mechanical ventilation	1.90 (1.32–2.75)	0.001	1.24 (0.67–2.30)	0.491
Operative diagnosis	1.41 (0.94–2.12)	0.099	1.03 (0.64–1.66)	0.912
SOFA cardiovascular	1.14 (1.02–1.26)	0.018	0.99 (0.87–1.13)	0.928
SOFA coagulation	1.25 (1.11–1.41)	0.000	1.12 (0.97–1.29)	0.133
SOFA liver	1.33 (1.17–1.50)	0.000	1.29 (1.11–1.51)	0.001
SOFA renal	0.67 (0.58–0.78)	0.000	0.85 (0.69–1.06)	0.155
SOFA respiratory	1.43 (1.21–1.70)	0.000	1.14 (0.86–1.52)	0.365
Weight - kg	0.99 (0.97–1.00)	0.014	0.98 (0.97–0.99)	0.005

Goodness-of-fit with Hosmer-Lemeshow test $p = .24$.
AuROC = 0.74.
* APACHE denotes Acute Physiology and Chronic Health Evaluation, BUN blood urea nitrogen, CRRT continuous renal replacement therapy, OR odds ratio and SOFA Sequential Organ Failure Assessment.

and our results suggest the need to investigate the use of female hormones in this setting.

4.4. Strengths and limitations

Our study has several strengths. As a post-hoc analysis of a multicenter, randomized control trial, prospective data collection and monitoring confer a high level of internal validity and robustness to our findings. The multicenter design produces external validity beyond those of previous single center studies of the topic.

Our study has some limitations. Patients enrolled in the RENAL trial were diagnosed with sepsis based on the presence of ≥2 SIRS criteria, which is not consistent with updated definitions [1]. However, the diagnosis of sepsis was made prior to trial randomization and was standardized throughout the study.

As we are comparing outcomes between sexes, our study is observational with the inability to draw inferences on causality. However, by using both logistic and Cox regressions and two methods of selecting variables for inclusion in multivariate analyses, we have mitigated confounding factors. We conducted multivariate analysis of numerous survival outcomes (survival to ICU and hospital discharge, 28-days and 90-days) which all produced consistent results. We did not have data on menopausal status, however no significant relationship was identified when we assessed for an interaction based on the average age of menopause in Australia. We recognize that the pragmatic use of average menopausal age means that women with early or late menopause have been misclassified. We also acknowledge that the number of women below 51 years of age was small, so our interaction analysis may well reflect a type II error. Nevertheless, we found that female sex was consistently associated with lower mortality after adjusting for age as a continuous variable in the logistic and Cox regression models. Finally, we did not have data relating to the use of hormone replacement therapy which may have been contributing a protective effect, so its use in patients with sepsis or those undergoing CRRT should be investigated in future research.

5. Conclusion

In a large cohort of critically ill patients with sepsis and severe AKI requiring RRT, female sex was associated with improved survival. We found no evidence that the relationship between sex and survival was altered by menopausal status or CRRT intensity.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.10.017.

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