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Gender differences in mortality and quality of life after septic shock: A post-hoc analysis of the ARISE study[☆]

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ABSTRACT

Purpose: To assess the impact of gender and pre-menopausal state on short- and long-term outcomes in patients with septic shock.

Material and methods: Cohort study of the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial, an international randomized controlled trial comparing early goal-directed therapy (EGDT) to usual care in patients with early septic shock, conducted between October 2008 and April 2014. The primary exposure in this analysis was legal gender and the secondary exposure was pre-menopausal state defined by chronological age (≤ 50 years).

Results: 641 (40.3%) of all 1591 ARISE trial participants in the intention-to-treat population were females and overall, 337 (21.2%) (146 females) patients were 50 years of age or younger. After risk-adjustment, we could not identify any survival benefit for female patients at day 90 in the younger (≤ 50 years) (adjusted Odds Ratio (aOR): 0.91 (0.46–1.89), $p = .85$) nor in the older (> 50 years) age-group (aOR: 1.10 (0.81–1.49), $p = .56$). Similarly, there was no gender-difference in ICU, hospital, 1-year mortality nor quality of life measures.

Conclusions: This post-hoc analysis of a large multi-center trial in early septic shock has shown no short- or long-term survival effect for women overall as well as in the pre-menopausal age-group.

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1. Introduction

There is an increasing awareness that gender may play a role in the outcome of critical illness. This may be due to physiology [1–3], immunology [4,5] or even structural differences in the care offered to women [6–8]. Furthermore, preclinical and clinical data suggest that estrogens may play a beneficial role in the recovery from critical illness [5,9–15] and that pre-menopausal women may have better chances to survive intensive care unit (ICU) admission [16–18].

Sepsis is common and accounts for high morbidity and mortality worldwide. There are some reports that there is a disparity in outcomes

related to gender for these patients [19–22]. However, limitations in the methods of previous studies preclude drawing firm conclusions.

Therefore, we conducted a post-hoc study of the ARISE trial to determine the impact of gender as well as pre-menopausal state on short- and long-term clinical outcomes in a large cohort of patients with early septic shock. We hypothesized that, due to the possible protective effect of estrogens, pre-menopausal women with septic shock would have better clinical outcomes compared to men and post-menopausal women.

2. Materials and methods

2.1. Study design and setting

We performed a cohort study using data collected in the ARISE trial, a large multicenter randomized study comparing early goal-directed therapy (EGDT) to usual care in patients presenting to the emergency department (ED) with septic shock. The trial was conducted between October 2008 and April 2014 in 51 hospitals in Australia, New Zealand, Finland, Hong Kong, and the Republic of Ireland and showed no difference in 90-day all-cause mortality between patients in the

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EGDT and usual care groups [23]. We included data from all 1591 trial participants included in the ARISE intention-to-treat population.

The health-related quality of life (HR-QoL) data as well as survival state at 12 months post-randomization were derived from the 'Quality of life and long-term survival in patients with early septic shock' database [24]. HR-QoL was assessed using the Short Form 36 (SF-36) version 2 [25] and the EuroQoL-5D-3 L assessment tool [26]. The three levels of the five EuroQoL dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression were converted to a single summary index number: the utility score (using the UK time trade-off value set [27]). The patients or their next-of-kin were also asked to indicate their present health state on the visual analogue scale (VAS) which ranges from "0" (worst imaginable health state) to "100" (best imaginable health state). The SF-36 uses 36 items to measure eight QoL domains and has two population-normalized summary scores described as Physical Component Summary (PCS) and Mental Component Summary (MCS) scores with a population mean score of 50 and each 10 point increment (decrement) equal to a SD from the mean [28].

2.2. Population

Patients were eligible for inclusion in ARISE if they were 18 years or older, had confirmed or suspected infection with two or more systemic inflammatory response criteria and refractory hypotension (systolic blood pressure of <90 mmHg or a mean arterial pressure of <65 mmHg after an intravenous fluid challenge), or hyperlactatemia (blood lactate level of ≥ 4.0 mmol/L), or both. The patient's sex was ascertained to be male or female according to their legal gender definition.

2.3. Exposure

The primary exposure in this analysis was legal gender and the secondary exposure was pre-menopausal state. The latter was defined by chronological age and women being 50 years of age or younger were defined to be pre-menopausal. The age cut-off was chosen according to the reported average age of menopause by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and in the current literature [29,30].

2.4. Outcomes

The co-primary outcomes were the difference in all-cause illness severity-adjusted mortality at 90 days post-randomization between male and female patients a) overall and b) according to pre- vs post-menopausal state. Secondary outcomes were differences between male and female patients in hospital and ICU mortality, time on mechanical ventilation, time on vasopressor/inotrope therapy, use and duration of renal replacement therapy, time to death/duration of survival as well as survival state and HR-QoL assessment at 12-months after randomization.

2.5. Statistical analysis

Clinical data are presented as mean $\pm$ standard deviation (SD), median with interquartile range (IQR) or percentages as appropriate. Chi-squared analyses with Fisher's exact test (where appropriate) and Student's *t*-test (Mann Whitney *U* test for non-normal distributions) were used to compare data between gender and age-groups with statistical significance declared for probability values of 0.05 or less.

We used logistic regression for binomial outcomes and Cox-proportional hazards regression for time to event data fitting main effects for gender and age group (≤ 50 years vs > 50 years) and an interaction between the two to determine if a gender effect differed significantly between age categories. Additional multivariable models were employed adjusting for baseline variables that were imbalanced

between genders in the univariate analysis (cut-off *p*-value: 0.01) to ensure that the observed results were not due to confounding variables. The final list included patient illness severity (APACHE III score), pre-existing comorbidities (Charlson comorbidity index), cardiac arrhythmia and intravenous resuscitation fluid (per kilogram) administered before ICU admission. No adjustment was made for multiplicity of tests. All analysis was performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

Of all 1591 participants included in the ARISE trial analysis, 40.3% (641) were females, with a mean age of 62 ± 17.3 years. Overall, 337 (21.2%) patients were younger than 51 years and of those, 146 (43.3%) female patients comprised the pre-menopausal group. Compared to males, females presented with lower illness severity (APACHE III) and SOFA and also had lower mean Charlson comorbidity scores (Table 1). On the other hand, consistent with gender, female patients presented with lower serum hemoglobin and creatinine. However, they had lower blood pressure and pH levels and received more weight-adjusted resuscitation fluids before randomization.

In both gender groups, the leading sources of sepsis were respiratory (32.7% vs 36% (female vs male), $p = .17$) and urinary tract infections (21.6% vs. 17.9% (female vs male), $p = .07$). Furthermore, there were no gender differences concerning distribution of causative organisms, time from emergency department presentation to appropriate antimicrobial therapy, proportion of patients transferred to ICU or the number of patients who needed surgical intervention for infection source control across the two genders (Table 1 and Supplement Digital Content Table S1).

3.2. Process of care

In the first 72 h after randomization, female patients continued to receive higher relative volumes of intravenous fluids (81.2 vs 73.2 ml/kg (female vs male), $p = .006$; absolute intravenous fluid volume: 4846 ml vs 5030 ml, $p = .29$) (Table 2). Overall, neither the total number of patients requiring blood product transfusions (13.9% vs 10.9% (female vs male), $p = .08$), vasopressor infusions (70.8% vs 71.4% (female vs male), $p = .67$) nor the duration of vasopressor therapy differed across gender and, in both groups, noradrenaline was the most commonly used vasopressor agent. Similarly, we observed no difference in the receipt nor duration of mechanical ventilation, renal replacement therapy, hospital or ICU length of stay between the gender (Table 2) or age-groups (Supplement Digital Content Table S2).

3.3. Mortality

At day 90 after randomization 116 (18.2%) female and 181 (19.1%, $p = .65$) male patients were deceased (Table 2). After adjusting for illness severity, chronic comorbidities and other baseline imbalances, there was no detectable gender-difference in 90-day mortality in the younger (≤ 50 years) age-group (aOR for female patients: 0.91 (0.46–1.89), $p = .85$) nor in the older (> 50 years) age-group (aOR for female patients: 1.10 (0.81–1.49), $p = .56$) (Table 3, Fig. 1). Furthermore, we could not identify any gender-difference in causes of death nor number of patients with treatment limitations (Supplement Digital Content Table S3).

Similarly, there was no overall difference in ICU, hospital or 1-year mortality between the two genders (Table 3, Supplement Digital Content Fig. S1 and S2).

In the multivariable logistic regression model including APACHE III score and Charlson comorbidity index, gender again was not an

Table 1
Baseline characteristics of female and male study participants.

Characteristics	Female (n = 641)	Male (n = 950)	P value
Age (years)	62 (17.3)	63.5 (15.8)	0.07
Weight (kg)	73.5 (25.0)	83.5 (23.6)	<0.0001
APACHE III score ¹	48.1 (20.4)	50.2 (20.0)	0.05
SOFA score ²	3.7 (2.7)	4.2 (2.8)	<0.0001
Charlson comorbidity score median [IQR], mean*	1 [0–2], 1.1	1 [0–2], 1.4	<0.0001
Chronic conditions (any) – n (%)	351 (54.8)	613 (64.5)	<0.0001
Cardiovascular	46 (7.2)	128 (13.5)	<0.0001
Respiratory	53 (8.3)	90 (9.5)	0.41
Endocrine	123 (19.2)	200 (21.1)	0.37
Central nervous system	44 (6.9)	90 (9.5)	0.07
Liver disease	26 (4.1)	57 (6)	0.09
Renal	21 (3.3)	43 (4.5)	0.21
Haematological/oncological	87 (13.6)	161 (16.9)	0.07
Diabetes mellitus (insulin-dependent)	27 (4.2)	58 (6.1)	0.10
Source of sepsis – n (%)			0.29**
Lungs	209 (32.7)	342 (36)	
Genitourinary tract	138 (21.6)	170 (17.9)	
Blood stream	68 (10.6)	93 (9.8)	
Gastrointestinal/biliary	50 (7.8)	74 (7.8)	
Soft tissue (medical & surgical)	55 (8.6)	111 (11.7)	
Central nervous system	11 (1.7)	8 (0.8)	
Other (medical & surgical)	54 (8.4)	70 (7.4)	
Cryptic	55 (8.6)	82 (8.6)	
Procedures			
Intravenous resuscitation fluid ³ before randomization (ml)	2572 (1342)	2541 (1252)	0.64
Intravenous resuscitation fluid ³ before randomization (ml/kg)	34.7 (20.8)	29.5 (16.3)	<0.0001
Time from ED presentation to first antibiotic (minutes)	69 [38–119]	68 [39–109]	0.30
Time from randomization to CVC insertion (hours)	1.03 [0.3–2.2]	0.95 [0.3–2.0]	0.43
Direct ICU admission from ED – n (%)	522 (81.4)	782 (82.3)	0.65
Physiologic and laboratory variables at baseline			
Invasive mechanical ventilation – n (%)	53 (8.3)	82 (8.6)	0.80
Vasopressor infusion – n (%)	138 (21.5)	208 (21.9)	0.86
Cardiac arrhythmia present – n (%)	133 (14)	55 (8.6)	0.001
Mean arterial pressure (mmHg)	65 [58.7–75.0]	68 [60–78.3]	<0.0001
Heart rate (beats per minute)	104 (21.1)	106 (23.0)	0.06
White cell count (x10 ⁹ /l)	13.8 (10.7)	13.5 (8.9)	0.49
Hemoglobin (g/l)	122 (23.2)	130 (25.7)	<0.0001
Platelet count (x10 ⁹ /l)	204 [145–277]	190 [128–252]	0.001
pH (n = 727)	7.33 (0.137)	7.36 (0.112)	0.001
Bicarbonate (mmol/l) (n = 703)	19.9 (6.8)	19.6 (4.7)	0.42
Serum lactate (mmol/l)	4.36 (3.44)	4.26 (2.79)	0.59
Serum creatinine (μmol/l)	113 [81–187]	139 [104–211]	<0.0001

Means reported with (SD), medians with [IQR], numbers (n) with percent (%), *mean included for increased interpretability **8 × 2 chi-square p-value. ¹without urine output, ²without neurological score (max. score: 20 points), ³Total intravenous fluids (includes fluids administered before arrival at the hospital); Abbreviations: ICU = intensive care unit, APACHE = Acute Physiology And Chronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, IQR = interquartile range, ED = Emergency Department, CVC = central venous catheter.

independent predictor of mortality at any time-point (Supplement Digital Content Table S4).

3.4. Quality of life

Health-related quality of life measures were available in 85.3% (390/457) of the female and in 85.0% (550/647) of the male survivors at 12 months post-randomization.

There were no significant gender-differences in HR-QoL measures after 12 months (EuroQoL-5D-3 L utility score at 12 months in female patients 0.62 ± 0.35 vs male patients 0.66 ± 0.32; *p* = .07 (Table 4,

Table 2
Process of care and outcomes.

Characteristics	Female (n = 641)	Male (n = 950)	P value
Overall ICU admission – % (no.)	562 (87.7)	825 (86.8)	0.63
Process of care in the first 72 h after randomization			
Total volume of iv fluids (ml)	4846 (3403)	5030 (3405)	0.29
Total volume of iv fluids (ml/kg)	81.2 (61.6)	73.1 (52.4)	0.006
Total volume of iv crystalloids (ml/kg)	72.4 (56.6)	64.9 (46.6)	0.004
Received transfusion of blood products – n (%)	85 (13.9)	100 (10.9)	0.08
Volume of packed red blood cells transfused, ml	260 [0–512]	264 [0–535]	0.68
Use of organ support in ICU – n (%)			
Invasive mechanical ventilation	209 (32.6)	280 (29.5)	0.18
Vasopressor support	454 (70.8)	678 (71.4)	0.82
Renal replacement therapy	90 (14.0)	124 (13.1)	0.57
Median (IQR) duration of organ support ¹ – hours			
Invasive mechanical ventilation	62.5 [20–166]	63.8 [25–162]	0.50
Vasopressor support	32 [14–63]	30.2 [13–64.9]	0.96
Renal replacement therapy	65.8 [19–161]	73.2 [34–203]	0.26
Length of stay (days)			
ICU ²	2.8 [1.4–5.2]	2.7 [1.4–5.0]	0.72
Hospital ²	8.3 [5.1–16.1]	8.8 [5–17.2]	0.53
Mortality rates, n (%)			
ICU	71 (12.7)	93 (11.3)	0.43
Hospital	100 (15.6)	143 (15.1)	0.73
90-day	116 (18.2)	181 (19.1)	0.65
1 year (n = 1515, 612 female/903 male)	155 (25.3)	25 (28.3)	0.19

Means reported with (SD), medians with [IQR], numbers with percent (%), ¹Duration of intervention after randomization and only in patients who received the respective organ support. ²Median duration of first ICU and hospital stay only. Abbreviations: ICU = intensive care unit, IQR = interquartile range, iv = intravenous.

Supplement Digital Content Table S5). There was also no significant change in HR-QoL measures between baseline and 12 months post-randomization between male and female participants. However, in both groups and at both timepoints, the EQ VAS and the utility scores as well as the SF-36 PCS and MCS scores were significantly lower compared to age-matched population norms [31–33].

4. Discussion

4.1. Key findings

In this post-hoc analysis of the ARISE trial, we assessed the impact of gender and pre-menopausal state on short- and long-term clinical outcomes in patients with septic shock. We found that female patients with septic shock had different baseline characteristics from male patients. Moreover, contrary to our hypothesis, we found no survival benefit for pre-menopausal women when compared to age-matched male patients or post-menopausal women. Finally, we found no difference in long-term mortality nor quality of life measures between male and female patients.

4.2. Relations to previous studies

Contrary to our findings, several observational [34] and retrospective studies have reported higher mortality for women with sepsis than for men. The largest observational study, including 18,757 (8702 women) patients with severe sepsis and septic shock [35], showed higher unadjusted and adjusted ICU mortality in women. However, the authors of this study also reported significant differences in the

Table 3Adjusted^a odds ratios (95% CI) for female compared to male patients.

	Age group ≤ 50 years (n = 380)		Age group > 50 years (n = 1211)		P value for interaction ^b
	Adjusted OR	P Value	Adjusted OR	P Value	
Mortality					
ICU	1.18 (0.47–2.86)	0.74	1.33 (0.90–1.96)	0.15	0.72
Hospital ^c	0.95 (0.40–2.27)	0.92	1.23 (0.89–1.72)	0.20	0.61
90-day	0.91 (0.41–2.00)	0.82	1.10 (0.81–1.49)	0.56	0.58
12-month ^d	0.93 (0.46–1.89)	0.85	0.98 (0.74–1.29)	0.89	0.77
Hospital discharge destination					
Home	1.52 (0.75–3.03)	0.25	0.74 (0.54–1.00)	0.05	0.09

Odds ratio refers to the comparison between female and male patients with male patients being used as the reference group.

^a Model adjusted for: APACHE III, Charlson comorbidity index, cardiac arrhythmia at ED presentation, total amount of fluid per kg body weight received prior to randomization^b Interaction between age-group and gender^c Censored at day 60^d Data available in age group ≤50 years: 155 female & 194 male patients; age group >50 years: 457 female & 709 male patients

delivery of care with women being more likely to have limitation of therapy orders and less likely to receive invasive ventilation or hemodialysis regardless of respiratory dysfunction or acute renal failure. In our study, we could not identify any differences in care delivery or organ support between female and male patients with septic shock. However, patients with impending death and treatment limitations, that would have precluded the delivery of the trial algorithm have not been included in the ARISE trial. Nevertheless, the view that women may have a survival advantage over men in critical illness is common among clinicians [36] and might contribute to covert gender biases in the delivery of care in non-standardized settings.

An extensive retrospective review [18] of the APACHE IV database of 261,255 consecutive ICU patients in the United States showed a statistically significant interaction between gender and age. Among critically ill patients, women <50 years of age had lower ICU mortality compared to men, while there was no gender-difference in the age-group older than 50 years. When comparing different sub-groups however, the authors did not find any difference in mortality in patients presenting with acute coronary syndrome, sepsis or trauma. Accordingly, in our population with early sepsis, we found no significant interaction between gender and age.

However, there are reports of gender-differences in sepsis-mortality, at least in one age group [2,18,37], with two studies reporting a higher likelihood of death in older women [18,38]. However, these authors

also reported a significant mortality benefit in younger women. Contrary to such reports, Adrie et al. [37] reported lower hospital mortality for sepsis in women older than 50 years, but not in the younger group. Their different approach to control for confounders and co-variables may have contributed to these conflicting results. In our study, we could not identify any gender-difference or survival benefit for women overall or in the pre-menopausal sub-group.

In our study, female patients had significantly lower SOFA and APACHE scores, a finding that has also been reported in other sepsis studies [7,39]. Our female patients also presented with significantly lower creatinine and bilirubin and higher platelet count contributing to lower total illness severity and organ failure scores. It is, however, possible and indeed likely, that these laboratory differences are merely due to gender differences [40] (less muscle mass, less red cell mass generating less bilirubin, less platelet mass) leading to an underestimation of the actual illness severity in women in the risk-adjusted analysis. Illness severity scores do not adjust for such physiological differences between men and women.

Apart from short-term outcomes, this analysis of the ARISE study has also shown no gender-difference in mortality or quality of life in patients 12 months after septic shock. However, in both groups, quality-of-life scores were lower compared to the reference population [41] at any time-point. A negative impact of sepsis on long-term quality of life has been found in several other studies [41,42]. Although we could

Fig. 1. Kaplan-Meier Curve (+ censored at 12 months after randomization) for age-group >50 years stratified by gender.

Table 4
Quality of life measures.

Characteristic, mean (SD)	Female	Male	P value
EuroQoL-5D-3 L Visual Analog Scale			
Baseline ¹	64.0 (24.4)	61.0 (24.4)	0.19
12 months ²	69.0 (20.9)	67.1 (20.7)	0.16
P value for paired t-test ^a	0.01	<0.0001	
EuroQoL-5D-3 L quality of life assessment tool utility score			
Baseline ³	0.64 (0.35)	0.68 (0.33)	0.17
12 months ⁴	0.62 (0.35)	0.66 (0.32)	0.07
P value for paired t-test ^b	0.24	0.91	
SF-36 physical component summary score			
Baseline ⁵	39.5 (13.2)	39.7 (12.8)	0.82
12 months ⁶	39.2 (13.2)	39.6 (11.9)	0.74
P value for paired t-test ^c	0.14	0.11	
SF-36 mental component summary score			
Baseline ⁵	46.6 (14.9)	45.9 (14.5)	0.58
12 months ⁶	46.9 (13.0)	46.2 (13.8)	0.60
P value for paired t-test ^c	0.46	0.14	

EuroQoL-5D-3 L = Euro Quality of Life assessment tool, VAS Visual Analogue Scale (range 0–100), SF-36 = Short Form 36

¹ EQ5D-3 L VAS scores available in 285 female and 484 male patients at baseline

² EQ5D-3 L VAS scores available in 380 female and 542 male patients at 12 months follow up

^a EQ5D-3 L VAS scores available both at baseline and 12 months in 224 female and 342 male patients, respectively

³ EQ5D-3 L utility scores available in 297 female and 491 male patients at baseline

⁴ EQ5D-3 L utility scores available in 390 female and 550 male patients at 12 months follow up

^b EQ5D-3 L utility scores available both at baseline and 12 months in 214 female and 339 male patients, respectively

⁵ SF-36 PCS and MCS scores available in 228 female and 385 male patients at baseline

⁶ SF-36 PCS and MCS scores available in 183 female and 253 male patients at 12 months follow up

^c SF-36 PCS and MCS available both at baseline and 12 months in 99 female and 154 male patients, respectively

not identify any study reporting gender-differences regarding health-related quality of life measures, in patients after septic shock; a recent observational study looking at the impact of disability in ICU survivors [43] could not identify gender as an independent predictor for moderate to severe disability six months after ICU discharge, which is in line with our findings.

4.3. Implications of study findings

We found no short- or long-term survival benefit for premenopausal women with severe sepsis or septic shock. This implies that the proposed beneficial effects of estrogens in critical illness [7,11–17] might not translate to a survival benefit in such patients. In our analysis, men and women had similar risk-adjusted ICU, hospital and one-year mortality implying that, although there is a male dominance among patients with sepsis and septic shock, gender might not affect short- or long-term mortality. However, we also found significant gender-differences in specific components of widely used illness severity scores (creatinine, hemoglobin, bilirubin, platelets) which are known to physiologically differ between male and female patients, implying that gender adjustments for such components may be necessary for future gender comparisons and the evolution of gender-specific scores. Finally, we found no gender-related difference in health-related quality of life measures implying that septic shock impacts health-related quality of life similarly in men and women.

4.4. Strengths and limitations

The main strength of this study is that it is based on a large prospectively collected dataset from a well-designed and executed multicenter randomized-controlled trial with independent data monitoring and pre-specified inclusion criteria. Secondly, the setting of a randomized controlled trial has allowed us to study possible divergent outcomes between male and female patients under standardized conditions with minimal differences in the delivery of care. Third, the current study allowed us to study >600 female patients with severe sepsis and to describe the influence of gender on long-term mortality and quality of life in these patients.

Our study has several limitations. It is post-hoc and observational in nature and addresses questions the original trial was not designed to answer. However, we included all patients from the intention-to-treat analysis of the main trial powered to detect a mortality difference at 90 days after randomization. Our study was limited to patients presenting to the ED with early septic shock who were eligible for recruitment into the ARISE trial, and no conclusions can be drawn for patients who were excluded or who develop sepsis in either the general ward or in the ICU. However, although the overall mortality is likely to be higher in the general population with severe sepsis, it is unlikely that the influence of gender on mortality would be different. We defined premenopausal state arbitrarily by age and we do not have any information about sex-hormone levels, use of hormone replacement therapy (HRT), or information about surgically or chemically induced premature menopause of the patients included in this analysis. However, the age-cutoff we used to define pre- and postmenopausal subgroups has been derived from large international observational data [30], has little variation, and has been used in several other studies as a valid approach [44,45].

5. Conclusions

This post-hoc analysis of a large multi-center trial in early septic shock could not detect any short- or long-term survival benefit for premenopausal women. Although there was a male dominance among patients with severe sepsis and septic shock, risk-adjusted short and long-term mortality was not affected by gender but by illness severity. Furthermore, there was no gender-difference in long-term quality of life measures after an episode of septic shock. These findings support the view that in sepsis randomized controlled trials, the percentage of patients who are female or premenopausal does not affect findings related to short or long-term mortality or quality of life.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcrc.2019.11.002>.

Conflict of interest and source of funding

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Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne. Ms. Higgins was supported by an NHMRC post-graduate scholarship (No. 579709). The remaining authors have disclosed that they do not have any conflicts of interest.

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Appendix

A.1. The ARISE investigators

The ARISE study was a collaboration between the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australasian College for Emergency Medicine and the Australian and New Zealand Intensive Care Research Center, Monash University. The trial was endorsed by the Irish Critical Care Trials Group and the College of Intensive Care Medicine. The trial was funded by the National Health and Medical Research Council (No. 491075 and 1021165) and coordinated by the Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne.

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