Outcomes following severe septic shock in a cohort of Aboriginal and Torres Strait Islander people: a nested cohort study from the ADRENAL trial

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The inequality of health outcomes for Aboriginal and Torres Strait Islander peoples is a national health and social priority.¹ While the contribution of chronic disease to the reduced life expectancy in Aboriginal and Torres Strait Islander communities has been extensively investigated,² little has been published regarding outcomes for Aboriginal and Torres Strait Islander people presenting with critical illness,^{3–6} particularly those with sepsis. Sepsis, a life-threatening dysregulated host response to infection, is recognised as a global health priority.⁷ It has an in-hospital mortality of up to 27% in Australia⁷ and has long term implications for quality of life and function.⁸ The population-based incidence of sepsis among Aboriginal and Torres Strait Islander people has been shown to be substantially higher than that among non-Indigenous populations.^{9,10}

A recent review of the Australian and New Zealand Intensive Care Society Adult Patient Database identified 9509 intensive care unit (ICU) admissions for Aboriginal or Torres Strait Islander patients nationwide for the period 2017–2018, representing 3.9% of all ICU admissions.¹¹ Compared with non-Indigenous Australians, Aboriginal and Torres Strait Islander patients were more likely to be admitted to the ICU with sepsis, and had a higher severity of illness at presentation, but had similar in-hospital outcomes.¹¹ Very little has been published regarding the outcomes for Aboriginal and Torres Strait Islander patients with sepsis specifically.¹² With regard to Aboriginal and Torres Strait Islander patients with septic shock — the most severe form of sepsis with persisting hypotension and impaired circulatory perfusion despite resuscitation⁷ — we are not aware of any published data on mortality outcomes or the associated long term health-related quality-of-life outcomes.

The recently completed Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic

ABSTRACT

Objective: To describe the pattern of acute illness and 6-month mortality and health-related quality-of-life outcomes for a cohort of Aboriginal and Torres Strait Islander patients presenting with septic shock.

Design: Nested cohort study of Aboriginal and Torres Strait Islander participants recruited to a large randomised controlled trial of corticosteroid treatment in patients with septic shock.

Setting: Royal Darwin Hospital, Northern Territory.

Participants: All Aboriginal and Torres Strait Islander patients recruited to the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial at Royal Darwin Hospital were compared with a non-Indigenous cohort drawn from the same site, and a cohort matched for age, sex and severity of disease.

Main outcome measures: Mortality at 90 days and 6 months, time to shock resolution, mechanical ventilation requirement, renal replacement therapy requirement, and five-domain, five-level EuroQol questionnaire (EQ-5D-5L) score at 6 months.

Results: Aboriginal and Torres Strait Islander patients had significantly reduced risk of death at 90 days when compared with non-Indigenous patients recruited to ADRENAL at Royal Darwin Hospital (12/60 v 23/62; adjusted odds ratio, 0.40 [95% CI, 0.17 to 0.94]) which was robust to additional adjustment for baseline covariates (odds ratio, 0.35 [95% CI, 0.14 to 0.90]). When compared with the matched population drawn from the broader ADRENAL cohort, there was no significant difference in 90-day mortality (12/60 v 16/61; adjusted odds ratio, 1.43 [95% CI, 0.60 to 3.39]; $P = 0.42$). Only nine Aboriginal and Torres Strait Islander patients provided 6-month health-related quality-of-life data.

Conclusions: Aboriginal and Torres Strait Islander patients had reduced risk of death at 90 days when compared with non-Indigenous patients recruited to the ADRENAL trial at Royal Darwin Hospital, which was robust to adjustment for covariates, but similar outcomes when compared with a cohort matched for age, sex and severity of disease.

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Shock (ADRENAL) trial was a high quality, international, investigator-initiated, blinded randomised controlled study comparing 7 days of intravenous hydrocortisone (200 mg/day) against placebo in critically ill patients with septic shock who required mechanical ventilation.¹³ The largest number of Aboriginal and Torres Strait Islander patients was recruited to the trial from Royal Darwin Hospital — a 360-bed referral hospital in Darwin, Northern Territory. The Royal Darwin Hospital ICU admits about 1000 patients per year, about 50% of whom identify as Aboriginal or Torres Strait Islander. Similarly, on average, 101 patients are admitted to this ICU annually with a diagnosis of septic shock, of whom 51 identify as Aboriginal or Torres Strait Islander.

The aim of this nested cohort study was to describe the pattern of acute illness, mortality rates and health-related quality-of-life outcomes for a cohort of Aboriginal and Torres Strait Islander people presenting with septic shock by using data collected from the ADRENAL trial.

Methods

The ADRENAL trial recruited 3800 severely ill patients with septic shock from Australia (45 sites), the United Kingdom (12 sites) New Zealand (eight sites) Saudi Arabia (three sites) and Denmark (one site).¹³ Recruited patients were those who were admitted to the ICU with suspected sepsis and required invasive mechanical ventilation and haemodynamic support with intravenous vasopressors or inotropes.¹³ The primary outcome for this study was 90-day mortality; secondary outcomes included 6-month mortality and health-related quality of life,¹³ measured using the five-domain, five-level EuroQol questionnaire (EQ-5D-5L).¹⁴ Detailed descriptions of the study methods have been published.^{15,16} The only site recruiting large numbers of Aboriginal or Torres Strait Islander people was Royal Darwin Hospital.

The medical records of all patients who were enrolled into the ADRENAL trial from Royal Darwin Hospital were reviewed to identify those patients who identified as Aboriginal or Torres Strait Islander and consented to data use. Using data collected in the ADRENAL trial, this cohort was described and compared with two populations: the non-Indigenous patients recruited to the trial from Royal Darwin Hospital, and a cohort of patients drawn from the remaining ADRENAL cohort (recruited from other sites worldwide) who were matched for sex, age and severity of disease.

Given the prospectively recognised small size of the Aboriginal and Torres Strait Islander cohort, differences in baseline demographics between this population and the two comparison populations were described as standardised differences of means rather than using a test of statistical difference.¹⁷ A standard difference larger than 0.1 suggests that there is a difference between two groups.

The primary and secondary outcomes of the ADRENAL trial were described for this cohort and compared with the two comparison populations. The mortality outcomes for this cohort — including odds ratio (OR) for death at 28 days, 90 days and 6 months — were described and compared between cohorts using logistic regression models with adjustment for treatment and admission type as a fixed effects, and with additional covariates including treatment, admission type, sex, age (as a continuous variable), severity of illness (defined by an Acute Physiology and Chronic Health Evaluation [APACHE] II¹⁸ score at randomisation as a continuous variable), time from onset of shock to randomisation (as a continuous variable) and use of renal replacement therapy in the 24 hours preceding randomisation as fixed effects. The secondary outcomes of the ADRENAL trial were used to describe the pattern of acute illness, including the time to shock resolution, requirement for mechanical ventilation and renal replacement therapy, and the recurrence of bacteraemia or fungaemia. EQ-5D-5L scores measured at 6 months were also described for the Aboriginal and Torres Strait Islander and comparison groups, by reporting the proportions responding to each of the domains; between-group comparisons for these data were then conducted by describing standard differences. Similarly, the mean utility scores and mean visual analogue scale scores from the EQ-5D-5L for each population were described.

The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, which included members of the Aboriginal Ethics Sub-Committee (HREC: 2020-3616). The study's authorship group includes Aboriginal and Torres Strait Islander researchers, and the study design and manuscript preparation incorporated feedback from the George Institute for Global Health's Aboriginal and Torres Strait Islander health program. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹⁹

Results

From 123 patients recruited to the ADRENAL trial from Royal Darwin Hospital between March 2013 and February 2017, a cohort of 61 patients who identified as Aboriginal and/or Torres Strait Islander and consented to data use was identified. The characteristics and baseline demographics of this cohort at enrolment into the ADRENAL trial are described in Table 1 and the Online Appendix (Supplementary Table 1).

Baseline characteristics

When compared with non-Indigenous patients presenting to Royal Darwin Hospital, Aboriginal and Torres Strait

Table 1. Baseline characteristics of a cohort of Aboriginal and Torres Strait Islander patients compared with a cohort of non-Indigenous patients recruited at RDH and a cohort matched for age, sex and APACHE II score

Variable	Aboriginal and Torres Strait Islander cohort (n = 61)	Non-Indigenous RDH cohort (n = 62)	Standard difference	Matched cohort (n = 61)	Standard difference
Age, mean $\pm$ SD	51.8 $\pm$ 11.5	59.6 $\pm$ 13.3	0.64	51.9 $\pm$ 11.4	0.00
Men, number/total (%)	26/61 (43%)	38/62 (61%)	0.38	28/61 (46%)	0.07
Weight (kg), mean $\pm$ SD	77.3 $\pm$ 21.3	77.2 $\pm$ 20.9	0.01	89.1 $\pm$ 31.3	0.44
Admission type, number/total (%)*					
Non-operative	52/61 (85%)	46/62 (74%)	0.28	47/61 (77%)	0.21
Operative	9/61 (15%)	16/62 (26%)	0.28	14/61 (23%)	0.21
Admission source					
Emergency department	39/61 (64%)	27/62 (44%)	0.42	24/61 (39%)	0.51
Hospital wards	5/61 (8%)	15/62 (24%)	0.44	12/61 (20%)	0.34
Transfer from another ICU	0/61	0/62	—	2/61 (3%)	0.26
Transfer from another hospital (except from another ICU)	8/61 (13%)	6/62 (10%)	0.11	8/61 (13%)	—
Admitted from theatre following emergency surgery	9/61 (15%)	13/62 (21%)	0.16	13/61 (21%)	0.17
Admitted from theatre following elective surgery	0/61	1/62 (2%)	0.18	2/61 (3%)	0.26
First site of infection identified, number/total (%)					
Pulmonary	37/61 (61%)	31/62 (50%)	0.22	26/61 (43%)	0.37
Intra-abdominal	1/61 (2%)	18/62 (29%)	0.82	4/61 (7%)	0.25
Blood	6/61 (10%)	3/62 (5%)	0.19	12/61 (20%)	0.28
Skin	11/61 (18%)	6/62 (10%)	0.24	5/61 (8%)	0.29
Urinary	3/61 (5%)	4/62 (6%)	0.07	4/61 (7%)	0.07
Gut	0/61	0/62	—	3/61 (5%)	0.32
Endocarditis	0/61	0/62	—	2/61 (3%)	0.26
Other	3/61 (5%)	0/62	0.32	5/61 (8%)	0.13
Pulmonary v non-pulmonary primary site of sepsis, number/total (%)					
Pulmonary	43/61 (70%)	38/62 (61%)	0.20	34/61 (56%)	0.31
Non-pulmonary	18/61 (30%)	24/62 (39%)	0.20	27/61 (44%)	0.31
APACHE II score†					
Median (interquartile range)	25 (22–30)	24 (20–29)	—	25 (22–30)	—
Grouped, number/total (%)†					
< 25	28/61 (46%)	31/62 (50%)	0.08	28/61 (46%)	—
≥ 25	33/61 (54%)	31/62 (50%)	0.08	33/61 (54%)	—
Physiological variables at randomisation, mean $\pm$ SD or number/total (%)					
Temperature (°C)	37.5 $\pm$ 1.2	37.5 $\pm$ 1.1	0.02	37.4 $\pm$ 1.2	0.03

(Continues)

Table 1. Baseline characteristics of a cohort of Aboriginal and Torres Strait Islander patients compared with a cohort of non-Indigenous patients recruited at RDH and a cohort matched for age, sex and APACHE II score (*continued*)

Variable	Aboriginal and Torres Strait Islander cohort (n = 61)	Non-Indigenous RDH cohort (n = 62)	Standard difference	Matched cohort (n = 61)	Standard difference
Heart rate (beats/min)	98.5 ± 19.8	102.1 ± 24.1	0.17	100.7 ± 20.5	0.11
Central venous pressure (mmHg)	11.7 ± 4.7	11.3 ± 4.0	0.08	12.2 ± 4.8	0.11
Mean arterial pressure (mmHg)	71.9 ± 7.0	72.1 ± 6.8	0.03	74.3 ± 8.9	0.30
Respiratory rate > 22 breaths/min	61/61 (100%)	62/62 (100%)		61/61 (100%)	
Paco ₂ < 32 mmHg	33/61 (54%)	23/62 (37%)	0.35	30/61 (49%)	0.10
Lowest Pao ₂ :Fio ₂ ratio	157.8 ± 92.1	159.3 ± 93.8	0.02	168.7 ± 82.8	0.12
Selected therapies at baseline					
Any inotrope or vasopressor use	61/61 (100%)	66/66 (100%)	—	61/61 (100%)	—
Total catecholamine dose ≥ 15 µg/min	30/61 (49%)	30/62 (48%)	0.02	29/61 (48%)	0.03
Mechanically ventilated	61/61 (100%)	54/56 (96%)	0.11	61/61 (100%)	—
Antimicrobials commenced	61/61 (100%)	62/62 (100%)	—	61/61 (100%)	—
RRT commenced	20/61 (33%)	12/62 (19%)	0.31	16/61 (26%)	0.14
RRT for chronic renal failure	4/61 (7%)	2/62 (3%)	0.15	4/61 (7%)	—
Time from commencement of inotrope/vasopressor use to random assignment in ADRENAL trial					
Hours, mean ± SD	13.0 ± 0.6	12.1 ± 7.4	0.10	17.0 ± 15.8	0.30
Grouped, number/total (%)					
▶ < 6 hours	18/61 (30%)	14/62 (23%)	0.16	10/60 (17%)	0.31
▶ 6 to < 12 hours	18/61 (30%)	21/62 (34%)	0.09	15/60 (25%)	0.10
▶ 12 to < 18 hours	12/61 (20%)	14/62 (23%)	0.07	20/60 (33%)	0.31
▶ ≥ 18 hours	13/61 (21%)	13/62 (21%)	0.01	15/60 (25%)	0.09
ADRENAL treatment group					
Placebo	28/61 (46%)	37/66 (56%)	0.21	36/61 (59%)	0.26
Hydrocortisone	33/61 (54%)	27/62 (44%)	0.21	25/61 (41%)	0.26
Open label steroid for sepsis	4/61 (7%)	4/61 (7%)	—	6/58 (10%)	0.14

ADRENAL = Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock. APACHE = Acute Physiology and Chronic Health Evaluation. Fio₂ = fraction of inspired oxygen. ICU = intensive care unit. Paco₂ = partial pressure of carbon dioxide, arterial. Pao₂ = partial pressure of oxygen, arterial. RDH = Royal Darwin Hospital. RRT = renal replacement therapy. SD = standard deviation. * Operative admissions were defined as those where patients were admitted to the ICU from the operating theatre or the recovery room; all other admissions were defined as non-operative. † APACHE scores range from 0 to 71, with higher scores reflecting a higher risk of death. ‡ An APACHE II score of ≥ 25 is associated with a higher risk death.

Islander patients with septic shock were younger (mean age, 51.8 v 59.6 years; standard difference, 0.64) and more likely to be female (57% v 39%; standard difference, 0.38). Aboriginal and Torres Strait Islander patients were more likely to be admitted directly from the emergency

department (64% v 44%; standard difference 0.42) and to have a pulmonary source of sepsis (70% v 61%; standard difference, 0.20), and they were substantially less likely to have an intra-abdominal source of sepsis as the first site of infection identified (2% v 29%; standard difference, 0.82)

or an operative admission type (15% v 26%; standard difference, 0.28).

When compared with a cohort drawn from the remaining ADRENAL recruiting sites that was matched for sex, age and severity of disease, the Aboriginal and Torres Strait Islander patients were again more likely to be admitted with a non-operative diagnosis (85% v 77%; standard difference, 0.21) and more likely to be admitted with a pulmonary source of sepsis (70% v 56%; standard difference, 0.31).

At presentation with septic shock, Aboriginal and Torres Strait Islander patients had similar APACHE II scores (median, 25 v 24) and severity of shock (total catecholamine dose ≥ 15 $\mu\text{g}/\text{min}$, 49% v 48%; standard difference, 0.02) when compared with the Royal Darwin Hospital non-Indigenous cohort. Aboriginal and Torres Strait Islander patients had a higher mean creatinine level at presentation (271.2 $\mu\text{mol}/\text{L}$) than patients in the non-Indigenous cohort (211.6 $\mu\text{mol}/\text{L}$; standard difference, 0.22) and those in the matched cohort (209.6 $\mu\text{mol}/\text{L}$; standard difference, 0.27). They were also more likely to require renal replacement therapy (33%) than patients in the non-Indigenous cohort (19%; standard difference, 0.31) and those in the matched cohort (26%; standard difference, 0.14), which was not accounted for solely by chronic dialysis requirement.

A higher proportion of patients in the Aboriginal and Torres Strait Islander cohort were randomly assigned to receive hydrocortisone (54%) than in either comparison population (non-Indigenous cohort, 44% [standard difference, 0.21]; matched cohort, 41% [standard difference, 0.26]). Time from commencement of inotrope or vasopressor use to random assignment in the ADRENAL trial (mean, 13.0 hours) was similar to that for the non-Indigenous cohort (mean, 12.1 hours; standard difference, 0.10) but shorter than that for the matched cohort (mean, 17.0 hours; standard difference, 0.30).

Outcomes

Mortality outcomes are shown in Table 2 and Table 3. Aboriginal and Torres Strait Islander patients had reduced risk of death at 90 days when compared with non-Indigenous patients recruited to ADRENAL at Royal Darwin Hospital (12/60 v 23/62; adjusted OR, 0.40 [95% CI, 0.17 to 0.94]; $P = 0.03$). This difference in 90-day mortality was not changed after adjustment for additional covariates (adjusted OR, 0.35 [95% CI, 0.14 to 0.90]; $P = 0.03$). Mortality at 6 months for these cohorts was 14/59 v 25/61 (adjusted OR, 0.40 [95% CI, 0.18 to 0.90]; $P = 0.03$). Comparing the Aboriginal and Torres Strait Islander patients with those from the matched population drawn from the broader ADRENAL cohort, there was no difference in mortality (90-day mortality, 12/60 v 16/61; adjusted OR, 1.43 [95% CI, 0.60 to 3.39]; $P = 0.42$).

There were differences in secondary outcomes in favour of Aboriginal and Torres Strait Islander patients when compared with non-Indigenous patients recruited at Royal Darwin Hospital (Table 4). Aboriginal and Torres Strait Islander patients had more days alive and free of mechanical ventilation (mean 69.0 v 53.2, $P = 0.03$), and more days alive and free of ICU (mean, 64.8 v 50.6; $P = 0.05$). No significant differences in secondary ADRENAL outcomes were demonstrated when compared with the matched cohort. The incident requirement for renal replacement therapy in Aboriginal and Torres Strait Islander patients (62%) was not significantly different to that for either comparison population. Median time to shock resolution did not differ between groups.

Health-related quality-of-life data were provided by nine Aboriginal and Torres Strait Islander patients (15%). These patients reported better quality of life across all domains than patients in the comparison populations (Online Appendix, Supplementary Table 2).

Discussion

In this nested cohort study of patients with severe septic shock admitted to the Royal Darwin Hospital ICU, Aboriginal and Torres Strait Islander patients had similar outcomes at 90 days compared with a matched population drawn from the entire ADRENAL cohort. Despite a similar severity of illness to non-Indigenous patients at presentation, Aboriginal and Torres Strait Islander patients had a lower risk of death at 90 days when compared with non-Indigenous patients admitted at the same site. Aboriginal and Torres Strait Islander patients had a higher mean serum creatinine level and were more likely to have been commenced on renal replacement therapy at presentation, but their overall incident requirement for renal replacement therapy was not significantly different to that for either comparison population. To our knowledge, this is the first study to describe the pattern of acute illness and 6-month outcomes for a cohort of critically ill Aboriginal and Torres Strait Islander people with septic shock.

The demographics of this cohort reflect findings from other single centre studies and registry-based studies¹¹ — Aboriginal and Torres Strait Islander patients were younger and more likely to be admitted directly from the emergency department than the operating theatre. As has been noted previously, given the younger age of the Aboriginal and Torres Strait Islander cohort, the apparently equivalent APACHE scores at presentation likely reflect more significant physiological perturbation and organ failure at presentation when compared with the non-Indigenous comparison population.¹¹ The observed high rates of pulmonary source of sepsis have been described in other populations of

Table 2. Mortality outcomes for a cohort of Aboriginal and Torres Strait Islander patients compared with a cohort of non-Indigenous patients recruited at RDH

Variable	Aboriginal and Torres Strait Islander cohort (n = 61)	Non-Indigenous RDH cohort (n = 62)	Odds ratio (95% CI)	P
Mortality at 90 days				
Unadjusted	12/60 (20%)	23/62 (37%)	0.42 (0.19–0.97)	0.04
Adjusted for stratification variables*			0.40 (0.17–0.94)	0.03
Adjusted for additional covariates†			0.35 (0.14–0.90)	0.03
Mortality at 28 days				
Unadjusted	8/61 (13%)	22/62 (35%)	0.27 (0.11–0.69)	0.005
Adjusted for stratification variables*			0.25 (0.10–0.63)	0.003
Mortality at 6 months				
Unadjusted	14/59 (24%)	25/61 (41%)	0.45 (0.20–0.99)	0.05
Adjusted for stratification variables*			0.40 (0.18–0.90)	0.03

APACHE = Acute Physiology and Chronic Health Evaluation. RDH = Royal Darwin Hospital. * Analysis adjusted for stratification variables is a logistic regression including treatment and admission type as fixed effects and study site as a random effect. † Additional analysis including additional covariates is a logistic regression including treatment, admission type, sex, age (as a continuous variable), APACHE II score at randomisation (as a continuous variable), time from onset of shock to randomisation (as a continuous variable) and use of renal replacement therapy in the 24 hours preceding randomisation (yes/no) as fixed effects.

Table 3. Mortality outcomes for a cohort of Aboriginal and Torres Strait Islander patients compared with a cohort matched for age, sex and APACHE II score

Variable	Aboriginal and Torres Strait Islander cohort (n = 61)	Matched cohort (n = 61)	Odds ratio (95% CI)	P
Mortality at 90 days				
Unadjusted	12/60 (20%)	16/61 (26%)	1.42 (0.60–3.36)	0.42
Adjusted for stratification variables*			1.43 (0.60–3.39)	0.42
Adjusted for additional covariates†			1.48 (0.61–3.64)	0.38
Mortality at 28 days				
Unadjusted	8/61 (13%)	15/61 (25%)	2.16 (0.83–5.61)	0.11
Adjusted for stratification variables*			2.20 (0.84–5.75)	0.10
Mortality at 6 months				
Unadjusted	14/59 (24%)	18/59 (31%)	1.41 (0.62–3.22)	0.41
Adjusted for stratification variables*			1.46 (0.64–3.36)	0.37

APACHE = Acute Physiology and Chronic Health Evaluation. * Analysis adjusted for stratification variables is a logistic regression including treatment and admission type as fixed effects and study site as a random effect. † Additional analysis including additional covariates is a logistic regression including treatment, admission type, sex, age (as a continuous variable), APACHE II score at randomisation (as a continuous variable), time from onset of shock to randomisation (as a continuous variable) and use of renal replacement therapy in the 24 hours preceding randomisation (yes/no) as fixed effects.

Table 4. Secondary outcomes for a cohort of Aboriginal and Torres Strait Islander patients compared with a cohort of non-Indigenous patients recruited at RDH and a cohort matched for age, sex and APACHE II score

Outcome	Aboriginal and Torres Strait Islander cohort (n = 61)	Non-Indigenous RDH cohort (n = 62)	Mean difference (95% CI) or odds ratio (95% CI)	P	Matched cohort (n = 61)	Mean difference (95% CI) or odds ratio (95% CI)	P
Time to shock resolution (days), median (IQR)	4 (2–7)	4 (2–10)	—	—	4 (3–8)	—	—
Time to discharge from the ICU (days), median (IQR)	12 (7–18)	14 (7–90)	—	—	13 (6–67)	—	—
Time alive and free of ICU (days), mean $\pm$ SD	64.8 $\pm$ 28.2	50.6 $\pm$ 38.2	14.20 (0.31 to 28.08)	0.05	55.5 $\pm$ 35.4	–9.70 (–23.68 to 4.27)	0.18
Time to discharge from the hospital (days), median (IQR)	38 (22–65)	52 (23–90)	—	—	33 (24–90)	—	—
Time alive and free of hospital (days), mean $\pm$ SD	41.6 $\pm$ 27.8	35.2 $\pm$ 33.2	7.13 (–5.60 to 19.86)	0.26	39.8 $\pm$ 32.2	–6.83 (–19.6 to 6.03)	0.30
Time alive and free of mechanical ventilation (days), mean $\pm$ SD	69.0 $\pm$ 29.5	53.2 $\pm$ 40.2	16.70 (1.65 to 31.74)	0.03	59.4 $\pm$ 36.1	–11.36 (–25.81 to 3.08)	0.13
Incident RRT requirement, number/total (%)	37/60 (62%)	30/62 (48%)	1.30 (0.34 to 4.95)	0.71	30/61 (49%)	0.19 (0.03–1.48)	0.12
Time alive and free of RRT (days), mean $\pm$ SD	63.8 $\pm$ 37.3	56.6 $\pm$ 40.4	12.09 (–3.19 to 27.37)	0.12	59.7 $\pm$ 37.9	–8.34 (–24.43 to 7.74)	0.31
New onset bacteraemia/fungaemia, number/total (%)	0/61	1/62 (2%)	—	—	7/61 (11%)	—	—
Blood transfusion requirement, number/total (%)	21/61 (34%)	19/62 (31%)	0.61 (0.17 to 2.16)	0.44	31/61 (51%)	1.56 (0.45 to 5.46)	0.49

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range. RDH = Royal Darwin Hospital. RRT = renal replacement therapy. SD = standard deviation.

Aboriginal and Torres Strait Islander people,^{4,20} as have the low rates of intra-abdominal infection.⁹

The outcomes for this population of critically ill Aboriginal and Torres Strait Islander patients differ to those reported previously. Using linked datasets from South Australia, it was found that Aboriginal and Torres Strait Islander patients admitted to an ICU (with any diagnosis) had lower crude mortality rates at 12 months following discharge than non-Indigenous patients (OR, 0.69 [95% CI, 0.59 to 0.80]), but after adjustment for confounders this difference reversed and showed higher mortality at 12 months (adjusted OR, 1.14 [95% CI, 1.03 to 1.26]) and 8 years (adjusted OR, 1.23 [95% CI, 1.13 to 1.35]).⁶ In contrast, the cohort of

Indigenous patients with sepsis we describe had a difference in outcome (with crude rates of death at 90 days almost half that for the non-Indigenous cohort) that was robust to adjustment. While the unadjusted difference may have been contributed to by a relatively high 90-day mortality rate among the non-Indigenous cohort (37% [23/62]) — higher than that for the overall ADRENAL trial cohort (28.3% [1037/3658])¹³ — this difference in outcome remained significant after adjustment for several predictors of death.

Given the small study population and focus on a single recruiting site, the possibility of a type 1 error cannot be discounted and the observed difference in outcome must

be regarded as hypothesis-generating, thus warranting further exploration. Given that this study reports outcomes for those admitted to an ICU and recruited to a clinical trial, there is a potential for selection bias driven by differences in access to critical care services, or recruitment to critical care clinical trials. The slightly higher proportion of Indigenous patients assigned to the hydrocortisone arm is unlikely to explain such a profound difference in mortality rates given that the main study did not show a treatment effect with hydrocortisone.¹³

Health-related quality-of-life follow-up data for Aboriginal and Torres Strait Islander participants in the ADRENAL trial were very limited. While only nine participants were able to provide EQ-5D-5L data at 6 months, mortality data were available for 59 participants at the same time point. This likely relates to the availability of mortality data from a range of alternative sources, whereas EQ-5D-5L data required an interview administered in a potentially limited number of languages.

Study strengths and limitations

This study had several strengths. Data collection was prospective, and independently monitored as part of a double blind randomised controlled trial. Also, it included a comparison to a matched cohort drawn from the entire ADRENAL trial, adding significantly to this study's value. In addition, follow-up rates for mortality data were high, with 6-month data for 59 of 61 patients being available.

This study also had some limitations. The availability of follow-up data on health-related quality of life at 6 months was very limited, so it is difficult to draw conclusions regarding long term quality-of-life outcomes for this population, which was an aim of the study. Also, the high proportion of pulmonary sepsis in the Indigenous cohort, together with the slightly higher proportion assigned to the hydrocortisone arm, may have introduced a confounder, although evidence for steroids providing benefits in pneumonia is mixed,²¹ and this was felt to be unlikely to explain the significant difference in mortality outcomes. Finally, microbiological results were not available, so differences in causative organism between groups could not be assessed.

Implications for future research

Our findings have implications for future research. In particular, the role of access to critical care services and critical care clinical trials in driving these apparent differences in outcome must be urgently explored.

Similarly, while the EQ-5D-5L instrument has recently been validated for use in Aboriginal and Torres Strait Islander communities²² and has previously been validated for use in Māori populations,²³ it is important to address

barriers²⁴ to full contribution of health-related quality-of-life data for Aboriginal and Torres Strait Islander participants to ensure full reciprocity for trial participation. Such barriers may include access to appropriate translation of the survey tools, and a dependence on telephone follow-up, rather than in-person, in-community discussion.

In addition, given the high prevalence of chronic kidney disease in Aboriginal and Torres Strait Islander communities,²⁵ and the high incident renal replacement therapy requirement reported in this cohort, the rate of recovery from acute kidney injury or progression to dependence on dialysis in Aboriginal and Torres Strait Islander people with sepsis warrants further exploration.

Finally, with increasing recognition of the differing phenotypes of physiological response to sepsis,²⁶ the potential for differences in genomic and physiological sepsis responses in this population could be explored with appropriate community engagement.²⁷

Conclusion

In this nested cohort study of patients with septic shock, Aboriginal and Torres Strait Islander people had lower mortality rates out to 6 months following ICU admission when compared with non-Indigenous patients presenting to the Royal Darwin Hospital. Access to quality-of-life survey instruments for Aboriginal and Torres Strait Islander people was very limited.

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Competing interests

All authors declare that they do not have any potential conflict of interest in relation to this manuscript.

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