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Research paper

Indigenous Australians critically ill with sepsis: Characteristics, outcomes, and areas for improvement

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ABSTRACT

Background: Aboriginal and Torres Strait Islander Australians have amongst the highest incidence of sepsis globally.
Objective: The objective of this study was to describe the characteristics, short- and long-term outcomes of non-Indigenous, Aboriginal Australian and Torres Strait Islander Australians admitted with sepsis to an intensive care unit (ICU) to inform healthcare outcome improvement.
Methods: A retrospective cohort study of 500 consecutive sepsis admissions to the Cairns Hospital ICU compared clinical characteristics, short-term (before ICU discharge) and long-term (2000 days post-hospital discharge) outcomes. Cohort stratification was done by voluntary disclosure of Indigenous status.
Results: Of the 442 individual admissions, 145 (33%) identified as Indigenous Australian. Indigenous and non-Indigenous Australians had similar admission Acute Physiology and Chronic Health Evaluation-3 scores (median [interquartile range]: 70 [52–87] vs. 69 [53–87], $P = 0.87$), but Indigenous patients were younger (53 [43–60] vs. 62 [52–73] years, $P < 0.001$) and were more likely to have chronic comorbidities such as type 2 diabetes (58% vs. 23%, $P < 0.001$), cardiovascular disease (40% vs 28%, $P = 0.01$), and renal disease (39% vs. 10%, $P < 0.001$). They also had more hazardous healthcare behaviours such as smoking (61% vs. 45%, $P = 0.002$) and excess alcohol consumption (40% vs. 18%, $P < 0.001$). Despite this, the case-fatality rate of Indigenous and non-Indigenous Australians before ICU discharge (13% vs. 12%, $P = 0.75$) and 2000 days post hospital discharge (25 % vs. 28 %, $P = 0.40$) was similar. Crucially, however, Indigenous Australians died younger both in the ICU (median [interquartile range] 54 (50–60) vs. 70 [61–76], $P < 0.0001$) and 2000 days post hospital discharge (58 [53–63] vs. 70 [63–77] years, $P < 0.0001$).
Conclusions: Although Indigenous Australians critically ill with sepsis have similar short and long-term mortality rates, they present to hospital, die in-hospital, and die post-discharge significantly younger. Unique cohort characteristics may explain these outcomes, and assist clinicians, researchers and policy-makers in targeting interventions to these characteristics to best reduce the burden of sepsis in this cohort and improve their healthcare outcomes.

1. Introduction

Aboriginal and Torres Strait Islander Australians—hereafter respectfully referred to as Indigenous Australians—have amongst the highest incidence of sepsis globally.[1–3] Compared to non-Indigenous Australians, they present to hospital with sepsis at a younger age, more frequently, with a greater burden of comorbidities, and more often require intensive care unit (ICU) support.[4–6] Yet, the overall case-fatality rate of Indigenous and non-Indigenous Australians remains similar.[4,5,7]

Despite this, there have been few studies with inconsistent data that describe Indigenous sepsis cohort characteristics and post-ICU discharge outcomes. One prospective cohort study in the Northern Territory study demonstrated that Indigenous Australians have an

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increased mortality risk that persists for up to 3 years,[8] whilst another cohort study in New South Wales showed no increased mortality after 1 year. Furthermore, it showed a 70% Indigenous sepsis readmission rate within that year.[9] Whilst some of these findings may be explained by well-documented inequities in the social determinants of health, which result in an increased burden of chronic disease and are exacerbated by disparities in access to, and utilisation of, culturally respectful healthcare[5,6], the relative contribution of these factors to outcomes and readmission rates remain unclear.[3] A better understanding of their impact and interplay is essential if health outcomes of Indigenous Australians are to improve. Furthermore, a hospital admission provides an opportunity to address those factors that precipitated the admission and to optimise the management of both comorbidities and health behaviours that impact on long-term outcomes.[10,11]

In the current political climate, where key decision makers seek to implement the landmark "Uluru Statement from The Heart" by enshrining an Indigenous voice to parliament and as the Australian Government's "Closing The Gap" strategic policy to reduce disadvantage among Indigenous Australians by improving Indigenous Australian life expectancy by 2031, of which sepsis contributes to significantly, healthcare research to guide future approaches to improve Indigenous healthcare outcomes is critical.[12,13]

Far North Queensland (FNQ) is the only Australian region that is home to both Aboriginal Australians and Torres Strait Islander Australians. Although these populations face many similar challenges, they are socioculturally distinct, with different histories. Previous studies examining Indigenous health outcomes often compare Indigenous and non-Indigenous populations; however, in FNQ, there is a further opportunity to compare and contrast the characteristics and outcomes of sepsis of Aboriginal Australians and Torres Strait Islander Australians to inform a more tailored approach to sepsis in Australia's Indigenous population. Our objectives were to define key variables that may differ between non-Indigenous, Aboriginal Australian and Torres Strait Islander Australians with critical sepsis, to describe the clinical characteristic of their sepsis as well as their short- and long-term outcomes, and lastly, to hypothesise reasons for these differences. Through this, our ultimate aim was to inform both further research and future interventions that best reduce the burden of Indigenous sepsis and close the gap on healthcare outcomes.

2. Methods

2.1. Study design and setting

This retrospective cohort study was performed at Cairns Hospital, a 531-bed tertiary referral centre, which has the only ICU in the FNQ region. The region of FNQ covers an area of 204,255 km^2 and is home to approximately 290,000 people, 17% of whom identify as Indigenous Australians (9.1% identify as Aboriginal Australian, 4.7% identify as Torres Strait Islander Australian, and 3.0% identify as both).[14]

2.2. Participants and study size

The first 500 consecutive adults aged ≥18 admitted to the Cairns Hospital ICU between 01/06/2014 and 31/12/2017 with a diagnosis of sepsis were eligible for inclusion. Sepsis was defined using the Sepsis-3 definitions[15] and Acute Physiology and Chronic Health Evaluation III-J diagnostic codes 501–504: nonurinary sepsis, urinary sepsis, nonurinary sepsis with shock, and urinary sepsis with shock, respectively.[16] If patients were admitted on several occasions, only their first admission was included to avoid data skew. Removing nonsepsis cases and readmissions resulted in a total of 442 individual sepsis presentations to analyse.

2.3. Variables, data sources, and measurement

The externally validated Predisposition, Infection, Response and Outcome (PIRO) sepsis-staging model was primarily used to guide variable selection.[17] Variables found in commonly used sepsis mortality prediction models such as the Acute Physiology and Chronic Healthcare Evaluation scores and Australia and New Zealand Risk of Death score, for example, were added to the PIRO model.[3,16,18] Because no data exist on the differences in characteristics or outcomes between Aboriginal Australian and Torres Strait Islander Australians critically ill with sepsis, a more liberal approach to variable selection was implemented to facilitate hypothesis generation. The hospital electronic medical record and ICU electronic medical record of each patient was reviewed, and demographic, clinical, and laboratory variables available to clinicians during their ICU admission were placed into the PIRO sepsis-staging model, with standardised variable definitions provided (Table 1). All patients requiring care in the Queensland public health system are routinely asked at hospital admission if they identify as an Aboriginal Australian, Torres Strait Islander Australian, both, or neither. The case-fatality rate in the ICU and at 2000 days post hospital discharge were taken from linked data provided by the hospital-based corporate information system, and the age at death was documented.

2.4. Statistical methods

Data were entered into an electronic database (Microsoft Excel, Redmond, WA) and analysed with statistical software (Stata version 14.2, College Station, TX). *P*-values and confidence intervals were generated. Results were adjusted for the two comparisons per variable using Bonferroni's method to reduce the risk of family-wise type-1 error, with an adjusted p-value for significance being 0.025. Survival curves were developed using the Kaplan–Meier method. Time to death was defined as the time, in days, after the patients' initial hospital admission.

The Human Research Ethics Committee of the Cairns and Hinterland Health District provided ethical approval for the study (HREC/17/QCH/93/AMO3). As the data were retrospective, deidentified, and aggregated, the Committee waived the requirement for informed consent. One author who identifies as a Ngan'gi Aboriginal and Torres Strait Islander woman, TB, provided a cultural point of reference.

3. Results

3.1. Cohort characteristics

There were 442 individual cases admitted to the ICU during the study period. Their median age was 59 (48–70) years, and 238 (54%) were male. Among the 442 admissions, 145 (32.8%) identified as Indigenous Australians compared to 49,282 of 287,168 (17.2%) of the general FNQ population at the end of the study period ($P < 0.0001$); 94 (21%) identified as Aboriginal Australian; 36 (8%) identified as Torres Strait Islander Australians, and 15 (3%) identified as both.

3.2. Indigenous vs. non-Indigenous characteristics

Compared to non-Indigenous patients, Indigenous patients were younger (53 vs 65 years, $P < 0.001$) and were more likely to have had sepsis previously (22% vs. 10%, $P = 0.001$). They had a

Table 1
Variable definitions.

- Presumed infection: assumed when concomitant orders exist for both blood cultures and antibiotics within the time period around suspected infection 1.
- SOFA: needs a rise of >2 in SOFA score to meet inclusion criteria.[a]
- Age: must be ≥18 at the time of admission.
- Mortality: if the patient died during ICU admission episode.
- Smoker: either current, or former, with ≥10 cigarettes/day for ≥1 year.
- History of alcohol use: if patient has, or used to have, ≥4 standard drinks of alcohol/day for ≥1 year.
- From interhospital transfer: if patient admitted elsewhere and then transferred to cairns.
- From the emergency department: patient admitted to the ICU from the emergency department.
- From operating theatre: patient admitted to the ICU within 24 h after surgery.
- From hospital ward: patient admitted to the ICU from the ward (having spent at 4 h there).
- History of sepsis: any previous diagnosis of sepsis as per Australian ICU diagnostic coding (APAHCE-3j codes 501–504)
- History of cardiovascular disease [b]: ischaemic heart disease, stroke, heart failure (major adverse cardiac events).
- History of respiratory disease [c]: chronic obstructive or restrictive lung disease.
- History of renal disease [d]: chronic kidney disease or on dialysis.
- History of haematological cancer:[d] lymphoma, leukaemia, myeloma.
- History of gastrointestinal disease:[d] cirrhosis, hepatic failure.
- History of diabetes: type 1 or type 2 diabetes.
- History of metastatic cancer:[d] malignancy with metastatic disease.
- History of being immunocompromised:[d] HIV/AIDS, steroids, chemotherapy, immunosuppressant medication (e.g., methotrexate, azathioprine, etc).
- Admit night: patient admitted after 6 pm and before 8 am.
- Site of infection lungs/genitourinary/neurological/bones or joints/soft tissue/abdomen/other: primary site of suspected infection.
- Bacteraemia: positive blood cultures with grown organism.
- Recent arrest: cardiac/respiratory arrest in last 24 h s
- All clinical variables/laboratory tests/procedures: taken ± 4 h from the time of ICU admission (take closest to admission when >1 in this period)
- Albumin = calcium-corrected version obtained.
- Fibrinogen – derived fibrinogen, not clotted.
- Number of vasopressors: the number of vasopressors the patient was on 4 h from the time of ICU admission.
- Admission antibiotics: were antibiotics started either on, or within 4 h from the ICU admission.
- Arrhythmia: anything nonsinus excluding sinus bradycardia, tachycardia, Premature Atrial Contraction and Premature Ventricular Contraction.

Abbrevitions: APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment.

[a] Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315 (8):801–810.

[b] Arnott C, Li Q, Kang A et al. Sodium-Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2020; 9(3):e014908. https://doi.org/10.1161/JAHA.119.014908.

[c] Knaus WA, Draper EA, Wagner DP. Acute Physiology and Chronic Health Evaluation II: a severity of disease classification system. Crit Care Med. 1985, 13(10):818–29.

[d] Zimmerman JE, Kramer AA, McNair DS et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. Crit Care Med 2006341297–1310.

higher comorbidity burden with type 2 diabetes (58% vs 23%, $P < 0.001$), cardiovascular disease (40% vs 28%, $P = 0.01$) and renal disease (39% vs 10 , $P < 0.001$), and higher levels of hazardous healthcare behaviours such as tobacco smoking (61% vs 45%, $P = 0.002$) and excess alcohol consumption (40% vs 18%, $P < 0.001$) all of which may predispose them to sepsis and critical illness. In contrast, non-Indigenous Australians appeared to have more non-communicable disease such as metastatic cancer (10% vs 4%, $P = 0.04$).

With regards to the infection itself, Indigenous patients were more likely to have polymicrobial (23% vs 15%, $P = 0.04$) infection of the skin and soft tissue foci (28% vs 14%, $P < 0.001$) with Gram-positive blood stream infections (38% vs 28%, $P = 0.04$) such as *Streptococcus pyogenes* (11% vs 3%, $P = 0.001$). Biochemically, they had worse renal function, with higher creatinine (162 μmol/L vs 118 μmol/L, $P < 0.001$) and lower glomerular filtration rate (29 mL/min vs 49 mL/min, $P < 0.001$), as well as anaemia with a lower haemoglobin (100 g/dL vs 111 g/dL, $P = 0.007$).

Indigenous Australians had similar severity scores on ICU admission compared to non-Indigenous Australians.[3] There was no difference in rates of intervention within the ICU as intubation (19% vs. 22%, $P = 0.59$), central venous line insertion (42% vs. 41%, $P = 0.79$), arterial line insertion (84% vs. 83%, $P = 0.73$), urinary catheterisation (81% vs. 85%, $P = 0.27$), and renal replacement therapy (19 vs. 27, $P = 0.2$) were all similar.

3.3. Aboriginal Australian vs. Torres Strait Islander Australian characteristics

In a subset analysis, of the 145 patients who identified as Indigenous Australians, Aboriginal Australians were more likely than Torres Strait Islanders to be from remote areas (69% vs 40%, $P = 0.003$) and, subsequently, to require interhospital transfer (48% vs 22%, $P = 0.009$). Torres Strait Islander Australians and Aboriginal Australians both had chronic health disease risk factors; however, while Torres Strait Islanders had more diabetes mellitus (75% vs 51%, $P = 0.01$) and higher body mass index (31 vs 24, $P = 0.02$), Aboriginal Australians had higher levels of hazardous drinking (52% vs 19%, $P = 0.001$).

In terms of their infectious characteristics, Aboriginal Australians had a higher burden of respiratory sepsis than Torres Strait Islander Australians (43% vs 19%, $P = 0.02$), but Torres Strait Islander Australians had more sepsis from skin and soft tissue sources (56% vs 19%, $P < 0.001$) with a higher incidence of both *Staphylococcus aureus* (31% vs 14%, $P = 0.03$) and bacteraemia in general (56% vs 30%, $P = 0.006$). Torres Strait Islander Australians, however, had greater renal impairment with a higher creatinine (273 μmol/L vs 123 μmol/L, $P = 0.007$) and lower glomerular filtration rate (22 mL/min vs 45 mL/min, $P = 0.02$) (Table 2), a probable reflection of their higher rates of diabetes and obesity.

3.4. Cohort outcomes

The short-term ICU case-fatality rate for Indigenous and non-Indigenous Australians was similar (38/297 [13%] versus 17/145 [12%], $P = 0.75$). The difference in the ICU case-fatality rate for Aboriginal Australians and Torres Strait Islander Australians did not reach statistical significance (15/109 [14%] versus 2/36 [6%], $P = 0.24$). After 2000 days, there was no difference in mortality rate between the Indigenous and non-Indigenous patients who survived to ICU discharge (39/128 [30%] versus 70/259 [27%], $P = 0.48$). The difference in the proportion of Aboriginal Australians and

Table 2
Comparison of non-Indigenous Australians to Aboriginal and Torres Strait Islander Australians, adjusted for Bonferroni's method ($P < 0.025$).

Predisposition Variables						
Variable	ATSI n = 145	Non-ATSI n = 297	p-value (ATSI vs. non-ATSI)	AA n = 94	TSIA n = 36	p-value (AA vs. TSIA)
Age	**53 (43–60)**	**65 (52–73)**	**0.0001**	52 (41–57)	55 (44–62)	0.20
Mortality	17 (12%)	38 (13%)	0.75	14 (15%)	2 (6%)	0.23
Male gender	68 (47%)	170 (57%)	0.04	**38 (43%)**	**23 (64%)**	**0.02**
Inter-hospital transfer	56 (39%)	115 (39%)	0.98	**45 (48%)**	**8 (22%)**	**0.009**
Admitted from Emergency Department	44 (30%)	95 (32%)	0.73	25 (27%)	13 (36%)	0.29
Planned admission after surgery	3 (2%)	2 (1%)	0.34	0	2 (6%)	0.08
Admitted from hospital ward	42 (29%)	83 (28%)	0.82	24 (26%)	13 (36%)	0.23
Hazardous alcohol consumption	**58 (40%)**	**53 (18%)**	**<0.0001**	**49 (52%)**	**7 (19%)**	**0.001**
Cigarette smoker	**88 (61%)**	**134 (45%)**	**0.002**	63 (67%)	18 (50%)	0.07
History of sepsis	**32 (22%)**	**30 (10%)**	**0.001**	21 (22%)	7 (19%)	0.82
History of cardiovascular disease	**58 (40%)**	**83 (28%)**	**0.01**	34 (36%)	18 (50%)	0.15
History of respiratory disease	31 (21%)	49 (17%)	0.21	20 (21%)	10 (28%)	0.43
History of renal disease	**56 (39%)**	**29 (10%)**	**<0.0001**	32 (34%)	18 (50%)	0.09
History of haematological disease or malignancy	7 (5%)	29 (10%)	0.10	4 (4%)	1 (3%)	1.0
History of gastrointestinal disease	18 (12%)	22 (7%)	0.09	12 (13%)	3 (8%)	0.76
History of diabetes mellitus	**84 (58%)**	**67 (23%)**	**<0.0001**	**48 (51%)**	**27 (75%)**	**0.01**
History of metastatic cancer	6 (4%)	29 (10%)	0.04	4 (4 %)	1 (3%)	1.0
Immunocompromised	**9 (6%)**	**52 (18%)**	**0.001**	7 (7%)	1 (3%)	0.44
Body mass index	27 (22–33)	28 (24–33)	0.07	**24 (21–29)**	**31 (25–40)**	**0.0001**
Recent cardiorespiratory arrest	5 (3%)	9 (3%)	0.78	5 (5%)	0	0.32
Receiving statin at admission	48 (33%)	71 (24%)	0.04	**26 (28%)**	**18 (50%)**	**0.02**
Infection variables						
Variable	ATSI n = 145	Non-ATSI n = 297	p-value (ATSI vs. non-ATSI)	AA n = 94	TSIA n = 36	p-value (AA vs. TSIA)
Respiratory source	51 (35%)	97 (33%)	0.60	**40 (43%)**	**7 (19%)**	**0.02**
Genitourinary source	32 (22%)	64 (22%)	0.90	22 (23%)	6 (17%)	0.48
Bone/joint source	7 (5%)	6 (2%)	0.13	4 (4%)	1 (3%)	1.0
Central nervous system source	0 (0%)	6 (2%)	0.18	0	0	
Skin/soft tissue source	**41 (28%)**	**43 (14%)**	**0.0001**	**18 (19%)**	**20 (56%)**	**<0.001**
Abdominal source	13 (9%)	43 (14%)	0.10	11 (12%)	1 (3%)	0.12
Other source	**10 (7%)**	**47 (16%)**	**0.01**	3 (3%)	4 (11%)	0.09
Bacterial infection	103 (71%)	194 (65%)	0.23	62 (66%)	29 (81%)	0.10
Gram negative bacteria	63 (43%)	131 (44%)	0.90	38 (40%)	16 (44%)	0.68
Gram positive bacteria	55 (38%)	84 (28%)	0.04	31 (33%)	18 (50%)	0.07
Fungal infection	7 (5 %)	9 (3 %)	0.42	6 (6%)	1 (3%)	0.67
Viral infection	10 (7%)	22 (7%)	0.85	10 (11%)	0	0.06
Bacteraemia present	56 (39%)	128 (43%)	0.37	**28 (30%)**	**20 (56%)**	**0.006**
Polymicrobial	34 (23%)	46 (15%)	0.04	18 (19%)	11 (31%)	0.16
Escherichia coli isolated	15 (10 %)	44 (15 %)	0.20	9 (10%)	2 (6%)	0.73
Staphylococcus aureus isolated	26 (18%)	40 (13%)	0.22	13 (14%)	11 (31%)	0.03
Methicillin-resistant *S. aureus isolated*	7 (5%)	6 (2 %)	0.13	7 (7%)	0	0.19
Pseudomonas aeruginosa isolated	15 (10%)	28 (9%)	0.76	7 (7%)	6 (17%)	0.19
Klebsiella pneumoniae isolated	9 (6%)	15 (5%)	0.66	7 (7%)	1 (3%)	0.44
Influenza A *isolated*	5 (3%)	13 (4%)	0.80	5 (5 %)	0	0.32
Burkholderia pseudomallei isolated	8 (6%)	8 (3%)	0.17	4 (4%)	4 (11%)	0.22
Streptococcus pyogenes isolated	**16 (11 %)**	**9 (3%)**	**0.001**	7 (7%)	7 (19%)	0.06
Leptospirosis *isolated*	**0**	**11 (4%)**	**0.02**	0	0	
Streptococcus pneumoniae isolated	6 (4%)	10 (3%)	0.79	6 (6%)	0	0.19
Pneumocystis jirovecii isolated	2 (1%)	4 (1%)	1.0	2 (2%)	0	1.0
Response variables						
Variable	ATSI n = 145	Non-ATSI n = 297	p-value (ATSI vs. non-ATSI)	AA n = 94	TSIA n = 36	p-value (AA vs. TSIA)
Heart rate (beats/min)	99 (89–118)	97 (81–114)	0.28	99 (86–117)	100 (90–120)	0.59
Systolic blood pressure (mmHg)	107 (94–118)	106 (94–122)	0.42	107 (93–117)	105 (95–114)	0.86
Mean arterial pressure (mmHg)	73 (66–82)	72 (65–83)	0.50	75 (66–82)	72 (65–79)	0.56
Temperature (°C)	36.8 (36.5–37.4)	36.9 (36.5–37.3)	0.53	36.8 (36.4–37.4)	36.9 (36.5–37.5)	0.17
Respiratory rate (breaths/min)	20 (17–26)	20 (16–25)	0.99	20 (16–25)	20 (18–25)	0.60
O_2 saturations (%)	97 (95–99)	96 (94–98)	0.03	97 (95-99	97 (95–99)	0.33
Glasgow Coma Score	15 (14–15)	15 (14–15)	0.98	15 (13–15)	15 (14–15)	0.14
Glucose (mmol/L)	6.9 (5.0–9.4)	6.6 (5.4–8.5)	0.96	6 (4.8–8.6)	8.1 (5.3–9.7)	0.06
Lactate (mmol/L)	1.8 (1.1–3.0)	1.7 (1.1–2.8)	0.29	1.7 (1.1–3.0)	1.9 (1.1–3.4)	0.99
pH	7.36 (7.24–7.42)	7.37 (7.30–7.43)	0.13	7.37 (7.24–7.44)	7.36 (7.22–7.41)	0.41
paCO2 (mmHg)	34 (27–39)	34 (29–42)	0.0496	33 (26–40)	35 (29–38)	0.45
HCO3 (mmol/L)	**18 (15–21)**	**20 (17–23)**	**0.001**	18 (14–21)	19 (16–22)	0.35
Base excess (mmol/L)	**−6.2 (-10.9 to -2.8)**	**−4.5 (-8.4 to -2.2)**	**0.004**	−6.7 (−11.1–−2.8)	−5.5 (−10–−2.6)	0.57
Anion gap	9 (7–12)	9 (7–12)	0.44	9 (7–12)	9 (8–12)	0.47
Haemoglobin (g/dL)	**100 (87–122)**	**111 (93–124)**	**0.007**	98 (87–124)	99 (86–117)	0.57
White cell count (x10^9/L)	13.8 (9.3–21.9)	13.8 (7.9–22.2)	0.67	14 (8.8–21.9)	13.7 (12–22.8)	0.61
Neutrophils (x10^9/L)	10.7 (7.1–19.2)	11.6 (6.2–19.4)	0.80	10.5 (6.3–19.4)	10.6 (8.5–18.9)	0.68

(*continued on next page*)

Table 2 (*continued*)

Predisposition Variables						
Variable	ATSI n = 145	Non-ATSI n = 297	p-value (ATSI vs. non-ATSI)	AA n = 94	TSIA n = 36	p-value (AA vs. TSIA)
Platelets (x10^9/L)	170 (111–257)	1650 (101–236)	0.17	169 (110–254)	183 (107–294)	0.62
C-reactive protein (mg/L))	165 (67–295)	172 (85–286)	0.57	165 (71–259)	230 (63–337)	0.42
Troponin I (ng/mL)	0.07 (0.04–0.39)	0.11 (0.04–0.43)	0.85	0.07 (0.05–0.32)	0.07 (0.03–0.95)	0.79
Prothrombin (seconds)	16 (14–21)	16 (14–18)	0.07	16 (14–21)	16 (15–17)	0.51
APTT (seconds)	**39 (34–47)**	**36 (31–40)**	**0.0001**	41 (33–47)	39 (34–46)	0.92
INR	1.5 (1.3–1.9)	1.4 (1.3–1.6)	0.03	1.5 (1.3–1.9)	1.4 (1.3–1.5)	0.44
Fibrinogen	6.2 (4.6–8.3)	6.6 (4.9–8.2)	0.35	6.5 (4.3–8.3)	6.7 (4.7–9.1)	0.32
Total Bilirubin (μmol/L)	18 (12–31)	20 (13–31)	0.31	16 (11–29)	19 (13–35)	0.35
Albumin (g/L)	**24 (20–27)**	**25 (22–29)**	**0.007**	23 (19–26)	26 (19–29)	0.20
AST (IU/mL)	45 (21–104)	52 (27–106)	0.12	49 (21–103)	38 (21–94)	0.74
ALT (IU/mL)	**25 (12–42)**	**35 (20–65)**	**0.0001**	23 (13–38)	25 (12–55)	0.75
GGT (IU/mL)	**41 (22–65)**	**51 (26–94)**	**0.01**	42 (23–82)	38 (22–59)	0.28
ALP (IU/mL)	**91 (69–134)**	**82 (57–119)**	**0.01**	94 (70–143)	87 (53–125)	0.19
LDH (IU/mL)	333 (248–482)	329 (239–439)	0.43	321 (241–456)	345 (259–519)	0.56
Sodium (mmol/L)	**133 (131–137)**	**135 (133–138)**	**0.0004**	134 (130–137)	133 (130–136)	0.52
Potassium (mmol/L)	4.1 (3.6–4.8)	4.0 (3.7–4.5)	0.31	4.0 (3.5–4.6)	4.4 (3.7–5.0)	0.13
Chloride (mmol/L)	104 (99–109)	104 (100–108)	0.92	104 (99–109)	104 (96–106)	0.19
Creatinine (μmol/L)	**162 (87–403)**	**118 (75–190)**	**0.0003**	**123 (77–361)**	**273 (135–571**)	**0.007**
eGFR (ml/min)	**29 (11–65)**	**49 (24–80)**	**0.0002**	**45 (13–71)**	**22 (8–44)**	**0.02**
Calcium (mmol/L)	2.2 (2.1–2.3)	2.2 (2.1–2.3)	0.99	2.20 (2.07–2.31)	2.23 (2.14–2.37	0.21
Magnesium (mmol/L)	0.73 (0.66–0.87)	0.75 (0.65–0.88)	0.48	0.71 (0.64–0.87)	0.74 (0.69–0.87)	0.31
Phosphate (mmol/L)	**1.5 (1.0–2.0)**	**1.1 (0.9–1.5)**	**0.0001**	1.42 (0.97–1.82)	1.70 (1.15–2.15)	0.16
UO 4 h (ml)	**195 (43–436)**	**275 (120–530)**	**0.009**	200 (63–523)	188 (39–378)	0.52
Organ Dysfunction Variables						
Variable	ATSI n = 145	Non-ATSI n = 297	p-value (ATSI vs. non-ATSI)	AA n = 94	TSIA n = 36	p-value (AA vs. TSIA)
Vasopressors on admission	102 (70%)	204 (69%)	0.72	68 (72%)	25 (69%)	0.74
Number of vasopressors	1 (1–1)	1 (0–1)	0.89	1 (1–1)	1 (1–1)	0.29
Admission Antibiotics	142 (98%)	288 (97%)	0.56	91 (97%)	36 (100%)	0.28
Intubated	28 (19%)	64 (22%)	0.59	20 (21%)	5 (14%)	0.46
PICC line	40 (28%)	89 (30%)	0.61	24 (25%)	12 (33%)	0.37
Central venous line	61 (42%)	121 (41%)	0.79	39 (41%)	14 (39%)	0.79
Arterial line	122 (84%)	246 (83 %)	0.73	80 (85%)	29 (81%)	0.53
Indwelling urinary catheter	117 (81%)	252 (85%)	0.27	79 (84%)	27 (75%)	0.23
Renal replacement therapy	19 (13%)	27 (9%)	0.20	9 (10%)	7 (19%)	0.14

Severity score values on admission to the ICU, stratified by Indigenous status.

Variable	No. of patients	Indigenous n = 145	Non- Indigenous n = 297	p-value
APACHE 3	430	70 (52–87)	69 (53–87)	0.87
ANZROD	430	0.24 (0.10–0.44)	0.23 (0.10–0.46)	0.86

BOLD font was used for results that reached statistical significance adjusted for Bonferroni's method.
Abbreviations: AA = Aboriginal Australian; ALP = Alkaline Phosphatase; ALT = Alanine Transaminase; ANZROD = Australia and New Zealand Risk of Death score; APACHE-III = Acute Physiology, Age, Chronic Health Evaluation-III; APTT = Activated Partial Thromboplastin Time; AST = Aspartate Transaminase; eGFR = estimated Glomerular Filtration Rate; GGT = Gamma Glutamyl-Transferase; INR = International Normalised Ratio; LDH = Lactate Dehydrogenase; PICC = Peripherally Inserted Central Cather; TSIA = Torres Strait Islander Australian.

Torres Strait Islander Australians dying in the 2000 days post-ICU discharge was also similar and did not reach statistical significance (26/94 [28%] versus 13/34 [38%], $P = 0.24$) (Figs. 1–4).

The median (interquartile range) age of death in the ICU was 70 (61–76) for non-Indigenous Australians vs. 54 (50–60) in Indigenous Australians ($P = 0.0001$). Indigenous Australians suffered more deaths 2000 days post ICU discharge 41 (28%) than did non-Indigenous Australians 73 (25%) ($P = 0.0001$). The mean age of death after ICU discharge was 69 (62–75) for non-Indigenous Australians versus 56 (53–62) for Indigenous Australians ($P = 0.0001$) (Table 3).

4. Discussion

Despite having similar short-term case-fatality and 2000-day survival rates compared to non-Indigenous Australians, critically ill Indigenous Australians with sepsis present to the ICU more frequently and at a significantly younger age, and they die younger both within the ICU and after hospital discharge. They have unique demographic and clinical characteristics that help explain this observed phenomenon, namely, a greater burden of sepsis from a skin and soft tissue or respiratory source, higher rates of diabetes, renal and cardiovascular disease, and are more likely to smoke and consume alcohol in a hazardous manner. Clinicians, researchers, and policy makers may best improve Indigenous Australian sepsis outcomes by targeting these characteristics at the community level both before and after a hospital admission and at the community–hospital interface.

4.1. Pre-hospital admission

Indigenous Australians were younger on admission and had greater rates of cardiovascular disease, renal disease, and type 2 diabetes. These comorbidities account for a significant proportion of the preventable Indigenous sepsis burden and are often caused by hazardous healthcare behaviours such as excess alcohol consumption and tobacco smoking, which were also present in this cohort.[19] In combination with the findings of Davis et al. showing similar increases in comorbidities and hazardous healthcare

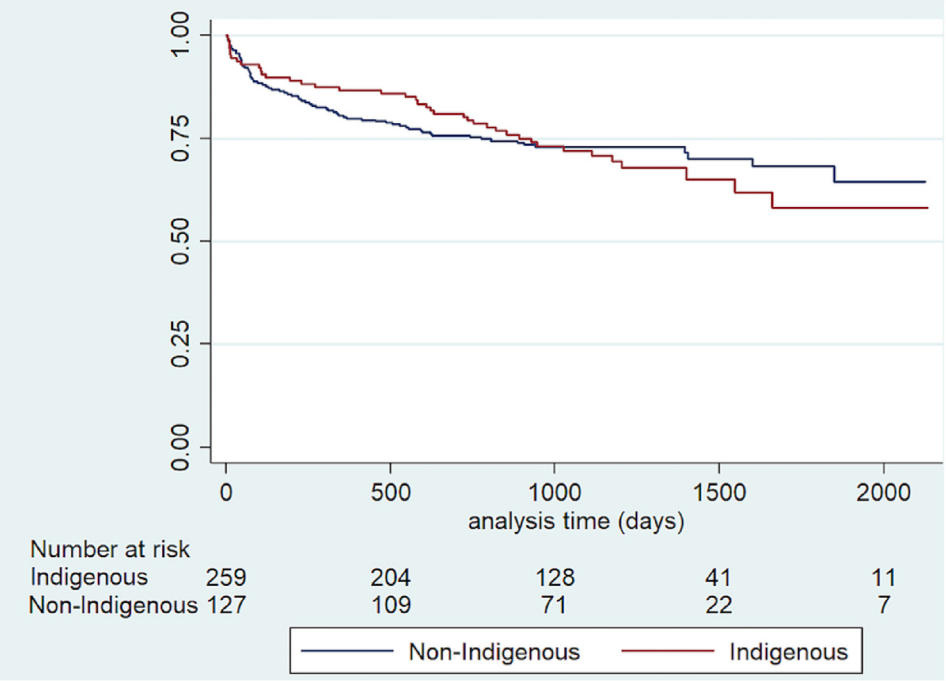

Fig. 1. Non-Indigenous versus Indigenous survival at 2000 days post ICU discharge ($P = 0.9$). Abbreviation: ICU = intensive care unit.

behaviours, this highlights a need for pragmatic policies that address these issues.[2]

A systematic review of 73 interventions in Indigenous communities found four key targets to assist in decreasing tobacco consumption: the centring of Aboriginal leadership, long-term community investments, the provision of culturally appropriate health materials, and intervention activities at the community level (including education and media campaigns), individual level (including behavioural support and incentivisation), and legislative level (including taxes and implementation of policies such as the *National Aboriginal and Torres Strait Islander Peoples' Drug Strategy 2014–2019*).[20,21]

Population-level, Indigenous-led interventions provide a practical and cost-effective way to prevent hazardous alcohol use. These include both reducing the economic availability of alcohol through implementation of a minimum unit price and reducing alcohol's

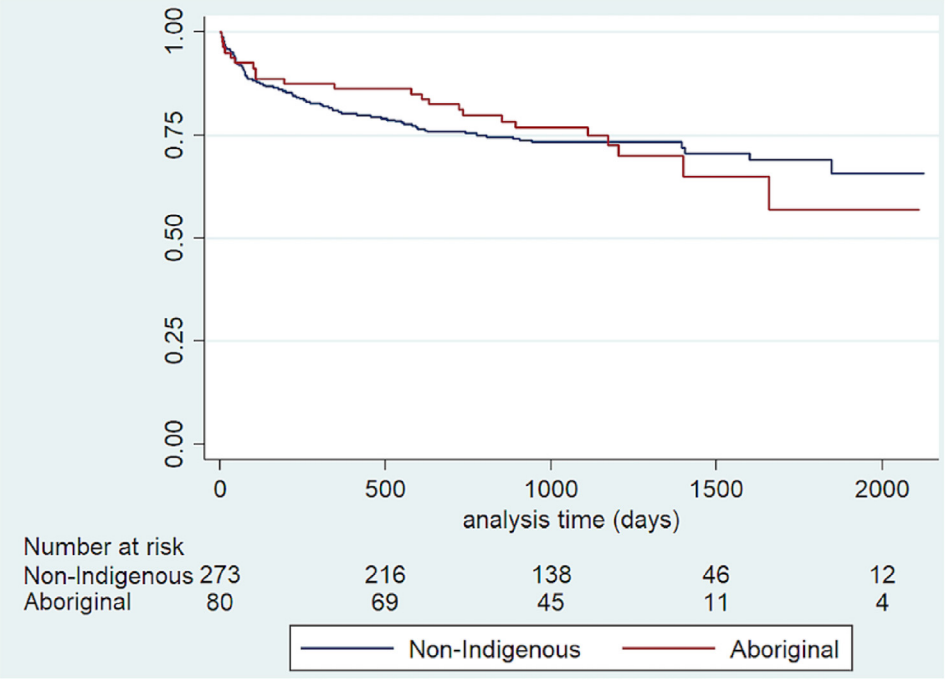

Fig. 2. Aboriginal Australian versus non-Indigenous Australian survival at 2000 days post ICU discharge (p = 0.77). Abbreviation: ICU = intensive care unit.

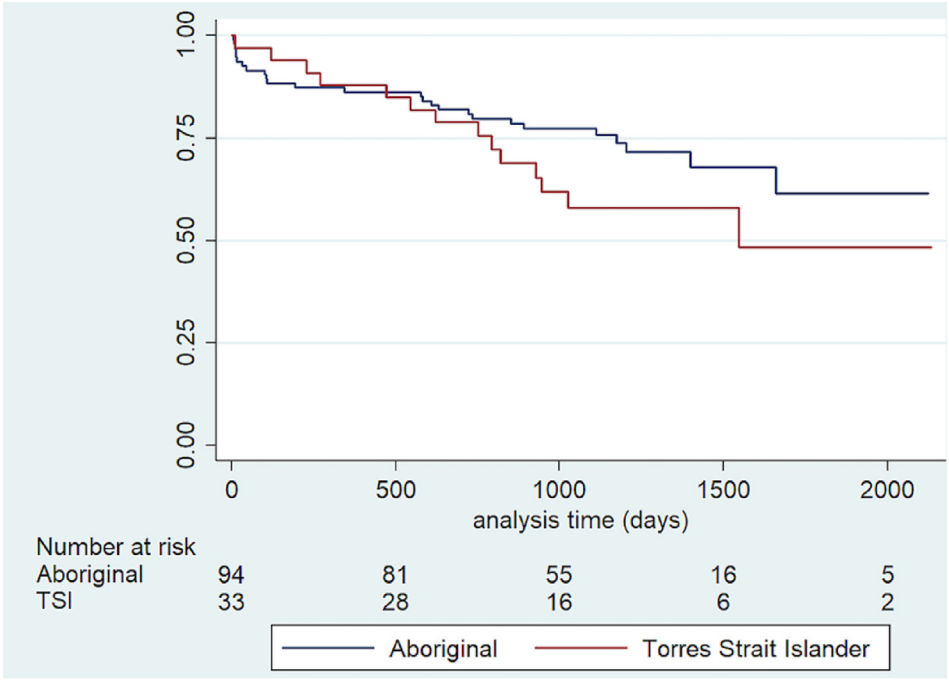

Fig. 3. Torres Strait Islander Australian versus Aboriginal Australian survival at 2000 days post ICU discharge (p = 0.26). TSI = 1 represents a patient who identifies as a Torres Strait Islander Australian.
Abbreviation: ICU = intensive care unit.

physical availability though reducing alcohol providers, trading hours, and autonomous implementation of "alcohol-controlled" communities.[22–24]

Indigenous Australians present with a high burden of skin and soft tissue sepsis, particularly *S. pyogenes*, a likely reflection of their sub-optimal living conditions, including overcrowding.[14,17] Increasing the use of soap and water to wash people, and their clothes and bedding, the introduction and use of chlorinated swimming pools, a reduction in household overcrowding, and a commitment to the funding and implementation of programs outlined in the National Indigenous Housing Guide may improve this.[25–27] The development of a Staphylococcal vaccine would be ideal.[28]

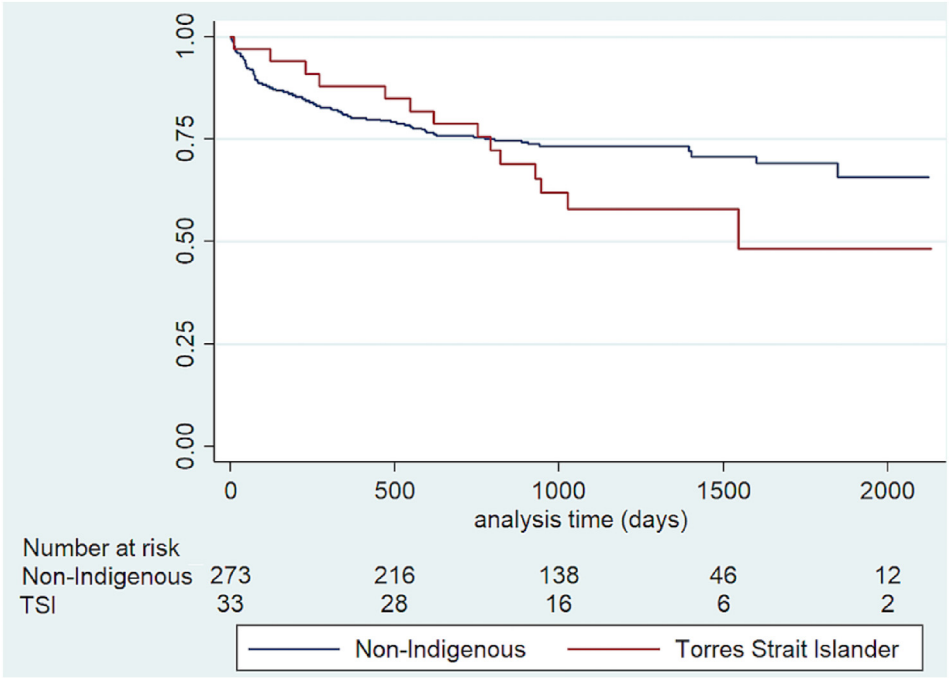

Fig. 4. Torres Strait Islander Australian versus non-Indigenous Australian survival at 2000 days post ICU discharge (p = 0.34). TSI = 1 represents a patient who identifies as a Torres Strait Islander Australian.
Abbreviation: ICU = intensive care unit.

Table 3
Cohort outcomes stratified by Indigenous status, adjusted for Bonferroni's method ($P < 0.025$).

Variable	Non-Indigenous	Indigenous	p-value (non-ATSI vs. ATSI)	AA	TSIA	p-value (AA vs. TSIA)
Number admitted	297	145	0.75	94	36	n/a
Number died in ICU	38 (13%)	17 (12%)	0.40	14 (15%)	2 (6%)	0.23
Number died post ICU discharge (2000 days)	73 (25%)	41 (28%)	0.0001	23 (24%)	15 (42%)	n/a
Age on ICU admission	65 (52–73)	53 (43–60)	0.0001	52 (41–57)	55 (44–52)	0.20
Age on ICU death	70 (61–76)	54 (50–60)	0.0001	55 (51–60)	41 (30–52)	n/a
Age on post-ICU death	70 (63–77)	58 (53–63)	0.75	56 (53–63)	63 (57–68)	n/a

AA = a patient who identifies as an Aboriginal Australian. ICU = intensive care unit. TSIA = a patient who identifies as Torres Strait Islander Australia. BOLD font was used for results that reached statistical significance adjusted for Bonferroni's method.

4.2. During hospital admission

Indigenous Australians present with sepsis to the ICU equally as sick but are significantly younger. Despite being at a relatively higher risk of mortality at ICU admission, the ICU case-fatality rate for sepsis did not differ between Indigenous and non-Indigenous Australians. The frequency of interventions performed during an ICU admission was also similar. This suggests that the public health factors underlying the presentation are more important than the ICU admission itself. If the aim is to improve outcomes of Indigenous sepsis outcomes; there must be a greater focus on what happens before and after an ICU admission.

Whilst reassuring that the crude ICU mortality is similar for Indigenous and non-Indigenous patients, any gains achieved in hospital are futile if the circumstances that precipitated their presentation are unaddressed.[29] An episode of critical illness can provide an opportunity to address the trajectory of a patients' health.[30] In hospital, Indigenous patients should be screened opportunistically about their comorbidities and hazardous modifiable healthcare behaviours, such as alcohol and smoking use, and brief interventions should be offered.[13] Linking-in to appropriate services before discharge with a coordinated transitional care plan at the community–hospital interface can reduce this.[31] Indigenous healthcare workers should be used to identify and address areas of unmet socioeconomic and healthcare need.[32] Health safety and quality standards should be continuously updated to provide culturally appropriate clinical care, acknowledging the differences in Western and Indigenous concepts of health.[33,34] Culturally appropriate clinical care that reduces the bias and racism of western healthcare can be further improved through implementation of the College of Intensive Care Medicine Reconciliation Action Plan, namely, focussing on improved clinician education, the development and employment of Indigenous clinicians and fostering partnerships with Indigenous communities.[35] A national, cohesive, and structured approach to the detection and treatment of sepsis and creation of national clinical standards and coordinated follow-up services to address the needs of sepsis survivors may further help.[36]

4.3. Post hospital discharge

Fundamentally, the most critical interventions to reduce the global burden of sepsis will improve overall public health and create health benefits far beyond sepsis. Any public health initiative to reduce the burden of sepsis must consider the reduction of healthcare inequity. Neither health disparities nor the gap in life expectancy will close until access to basic health care for Indigenous Australians is improved.[35]

High levels of acute illness, higher readmission rates, and underutilisation of healthcare resources all demonstrate inequity of access to primary healthcare (PHC) for Indigenous Australians.[3,27] Early recognition and treatment of sepsis, at the PHC and community level, are priorities in Indigenous health if the over-representation of Indigenous peoples in the ICU is to be reduced.[3] PHC facilities are underused by Indigenous populations despite evidence that strengthening PHC via increased funding, regional/remote development and training, and employment of Indigenous health professionals results in fewer hospitalisations and better health outcomes. Initiatives to tackle Indigenous sepsis at the PHC level may be most effective if they are community-controlled; for example, the National Aboriginal Community Controlled Health Organisation model of care, which focuses on Indigenous disease prevention, health promotion, and addressing the social determinants of health to improve access and outcomes.[37,38] Hospitals can further support PHCs through good coordination, communication, and by providing treatment as close to home as possible through outreach clinics or telehealth. Whilst acknowledging that the burden of sepsis in Indigenous Australians is complex and multifactorial, and that solutions should be Indigenous-led, some recommendations based on our observational data are summarised in Table 4.[39]

4.4. Aboriginal Australians and Torres Strait Islander Australians

Although the two populations are frequently conflated under the term Aboriginal and Torres Strait Islander Australians, Aboriginal Australians and Torres Strait Islander Australians are ethnologically distinct, with different homelands and different histories.[40] Such conflation, and the fact that the homelands of Torres Strait Islanders are largely confined to remote Northern Australia, has limited the available data to explain their unique sepsis characteristics and outcomes. Different studies comparing the two populations have noted differences in body composition with Torres Strait Islanders having greater adiposity,[41] a greater chronic comorbidity burden in Aboriginal Australians than in Torres Strait Islanders,[42] and infections such as melioidosis being more prevalent along with more rainfall and chronic comorbidity in the Torres Strait.[43] We also found that the pattern of comorbidities and aetiology of sepsis differed between the two populations. Torres Strait Islander Australians had higher rates of type 2 diabetes, which is likely to explain their worse renal function and contribute to the higher rates of skin and soft tissue infections.[44] Aboriginal Australians, however, were more likely to present from remote locations[6] and, therefore, underwent inter-hospital transfer more frequently and often outside of standard working hours. In these same populations, Aboriginal Australians also had similar findings of both hazardous alcohol consumption and respiratory sepsis.[7] The differences in the cohort characteristics and outcomes of Aboriginal Australians and Torres Strait Islander Australians suggest that a more tailored approach to "Indigenous" sepsis is needed at all levels of the healthcare system.

Limitations included single-site data collection from 5 years ago and a moderate-sized cohort of 442 patients limiting

Table 4
Summary table of interventions to decrease the burden of sepsis, and improve outcomes, in Indigenous Australians based on our observational data.

Prehospital interventions	**Decrease smoking**	Culturally appropriate investment at the 1. Individual level (behaviour support and incentivisation) 2. Community level (education and media campaigns) 3. Legislative level (taxation and policy implementation—i.e., National Aboriginal and Torres Strait Islander Peoples' Drug Strategy).
	Decrease hazardous alcohol use	1. Implementation of minimum unit prices 2. Reducing alcohol providers and trading hours 3. Creating "alcohol-controlled" communities.
	Decrease skin and soft tissue infections	1. Washing of hands, clothes, and bedding 2. Reduce overcrowding (via implementation the National Indigenous Housing Guide) 3. Development of a staphylococcal vaccine.
Intrahospital interventions	**Opportunistic screening**	For hazardous healthcare behaviours such as excessive alcohol intake and smoking and chronic diseases such as diabetes and hypertension.
	Increase Indigenous healthcare workers	To provide culturally appropriate education, assist with treatment, encourage the reduction of hazardous health behaviours, and help with follow-up.
	Increase community–hospital interface workers	1. To encourage clear follow-up plans 2. Monitor and treat complications 3. Prevent readmissions
Posthospital interventions	**Improve access to healthcare**	Should include appropriate location, staffing, funding, resourcing, and education of primary healthcare clinics
	Invest in innovative models of care	1. National Aboriginal Community Controlled Health Organisations 2. Telehealth model (care closer to home with supports).
	Create a national cohesive sepsis approach	1. Creation of clinical standards 2. Implementation of coordinated follow up services

generalisability and increasing the risk of type-2 error. Some data from patients who live remotely were unavailable, and cohort stratification by Indigenous status may have been confounded due to systemic bias and injustice in Australian healthcare contributing to identification taboo. The retrospective nature of this review meant that long-term outcome data were limited to mortality only. Data were unadjusted for confounders to generate hypothesis; however, further research should seek to identify these complex associations. Even though surrogates for the social determinants of health, namely, hazardous healthcare behaviours, chronic disease, rurality, and statin use were investigated; more comprehensive analysis is required to establish the role that the social determinants of health play in Indigenous sepsis.

5. Conclusions

Indigenous Australians with sepsis are admitted to the ICU disproportionately and with unique demographic and clinical characteristics. Yet, they have similar ICU and long-term mortality rates. Crucially, however, they both present to hospital, and die, significantly younger. Interventions to improve their outcomes, and close the life expectancy gap, should address their unique sepsis characteristics at the community level, both before and after hospital admission, and at the community–hospital interface. Furthermore, differences in sepsis characteristics between Aboriginal Australians and Torres Strait Islander Australians may reveal opportunities for a tailored approach to improving sepsis outcomes in these distinct populations.

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Credit authorship contribution statement

Satyen Hargovan: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Roles/Writing—original draft; Writing—review and editing.

Taissa Groch: Data curation; Formal analysis; Writing—review and editing.

James Brooks: Data curation; Formal analysis; Writing—review and editing.

Sayonne Sivalingam: Data curation; Formal analysis; Writing—review and editing.

Tatum Bond: Conceptualisation; Methodology; Project administration; Supervision; Writing—review and editing.

Angus Carter: Conceptualisation; Methodology; Project administration; Supervision; Writing—review and editing.

Conflict of interest

None declared.

All authors have approved the final article and agreed to be accountable for all aspects of the work and acknowledge that all those entitled to authorship are listed as authors.

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