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Original Article

# Sepsis in the absence of fever: Determining the criteria for and feasibility of future therapeutic temperature management trials

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ABSTRACT

***Objective:*** The purpose of this study is to examine the occurrence, characteristics, and outcomes of intensive care unit (ICU) patients with sepsis and the absence of fever.
***Design:*** Multicentre, retrospective cohort study.
***Setting:*** Twelve ICUs in Queensland, Australia.
***Participants:*** Adults (≥18 years) admitted to the ICU with sepsis between 1 January 2015 and 31 December 2021 were eligible for inclusion. Patients admitted with seizures, traumatic brain injury, postcardiac arrest, end-of-life care, and elective surgery were excluded, as were readmissions.
***Main outcome measures:*** The primary outcome was fever deficit (defined as degree-hours under 38.3°C) during the first 72 h of ICU admission, and all-cause 30-day mortality was the key secondary outcome.
***Results:*** Of 89,117 admissions, 15,612 were included. Admission temperatures were ≥38.3°C in 1026 (6.6%), 37.5–38.2°C in 2096 (13.4%), 36–37.4°C in 9216 (59.0%), and <36°C in 3274 (21.0%). Temperatures changed rapidly over the first 12 h and, by 24 h, approached reasonably stable levels. For the admission temperature groups of ≥38.3°C, 37.5–38.2°C, 36–37.4°C, and <36°C, fever deficits were a median of 47 (interquartile range (IQR), 24 to 72), 53 (IQR, 29 to 83), 69 (IQR, 40 to 100), and 85 (IQR, 52 to 123) degree-hours, respectively, and 147 (14%), 248 (12%), 1,104 (12%), and 549 (17%) died by day 30. After controlling for confounders, a high fever deficit, defined as a fever deficit above the median, during the

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first 24 h of ICU admission, was not associated with all-cause 30-day mortality (OR 1.02, 95% CI, 0.93 −1.13; p = 0.7).

***Conclusion:*** Fever deficits were large, particularly when the initial body temperature was not febrile. Only 1 in 15 ICU patients with sepsis had an initial body temperature ≥38.3°C. Approximately 2000 adults a year with sepsis and an initial body temperature <37.5°C would potentially be eligible for a trial of therapeutic hyperthermia in our 12 ICUs.



## 1. Introduction

Patients with sepsis and the absence of fever who are admitted to intensive care units (ICUs) have been recognised for decades to have a high risk of death.[1–3] Unlike fever, which represents a physiological response to infection,[4] hypothermia is believed to be a maladaptive failure of temperature homeostasis.[5] Hypothermia may reflect depleted physiological reserve associated with a blunted inflammatory response or be a consequence of immunological resistance, resilience or resolution; these states may predispose patients to secondary infection.[5–7] Moreover, microbial growth is optimised, and antibiotic effects are attenuated when body temperature is low.[8] Accordingly, hypothermic patients are at increased risk for both developing infections and subsequent treatment failure.

There is a growing but limited body of literature examining hypothermia and outcomes among patients admitted to ICUs. We recently reported in a study of 3951 patients that a faster rate of rewarming of hypothermic patients admitted to the ICU with bloodstream infection was associated with improved survival.[9] While prompt rewarming of septic patients to treat hypothermia may be considered standard practice,[10] the observation that patients with elevated body temperature have better sepsis outcomes raises the possibility that warming hypothermic or normothermic patients to supra-normal body temperatures may be of benefit.[1,11,12]

Further information on the temperature profiles and outcomes of patients in the ICU is required to plan for future therapeutic warming trials. Thus, this study aimed to investigate the occurrence, characteristics, and outcomes of septic patients with the absence of fever admitted to ICUs to guide the design of future clinical trials.

## 2. Patients and methods

### 2.1. Study design

The study design was a retrospective cohort conducted among 12 closed models, publicly funded, ICUs in Queensland, including data from ICU admissions between 1 January 2015 and 31 December 2021. Participating sites included a range of tertiary, metropolitan, and regional ICUs. Admissions were identified using electronic health information from all sites, with linkages performed to statewide and national databases as previously described.[13] The human research ethics committee at Metro South Hospital and Health Service approved the study, and an individual waiver of consent was granted (HREC/2022/QMS/82024).

### 2.2. Enrolment criteria

All patients aged 18 years and older meeting the criteria for sepsis on the first day of ICU admission at a participating ICU during the study period were eligible for inclusion. We excluded patients admitted for palliation, readmissions to the ICU during the study period, elective surgical admissions, and those admitted following cardiac arrest or traumatic brain injury (Table S2).

### 2.3. Definitions

Unless otherwise stated, the definitions from the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD) data dictionary were used.[15] ANZICS APD diagnostic codes were used to exclude patients admitted with trauma and seizures. Previously established and validated algorithms were used to calculate the Charlson Comorbidity Index[16] (Table S1). Frailty was extracted from the APD and derived from the clinical frailty scale, with a score of four or more classified as frail.[17] An immunosuppressed state was determined either by the presence of the APACHE III-J comorbidity, 'immunosuppressed', or from the APACHE II comorbidities, 'immunosuppressive disease', or 'immunosuppressive therapy'.

Sepsis was defined according to the Third International Consensus definitions for sepsis and septic shock.[18] According to the SEPSIS-3 definition, we identified patients with a Sequential Organ Failure Assessment (SOFA) score greater than or equal to two points at ICU admission with proven or suspected infection. We assumed a SOFA score of zero before ICU admission. Where individual components of SOFA were missing, no contribution was made to the total score.[19] Given the challenges of interpreting neurological SOFA with concurrent sedation, it was not included in the total SOFA.[20] Proven or suspected infection was defined as the commencement or escalation of antimicrobial therapy and microbiological sampling within one day of the SOFA score increase.[21] An escalation of antimicrobials was defined as an increase in antimicrobial 'rank' within 1 day of diagnosis of sepsis.[22,23] As previously published, ranking corresponds to the spectrum of activity, with rank one indicating the lowest spectrum, such as first-generation cephalosporin, and rank four the highest spectrum, such as carbapenems or tigecycline.[23,24]

All hourly temperature measurements, validated within the clinical information system as accurate by clinical staff, were included during the first 72 h of ICU admission. The temperature measurement was performed according to standard clinical practice in each participating ICU. Where more than one temperature measurement was obtained during an hour of observation, the mean level for that hour was used. If a measurement was absent during an hour, the most recent temperature was carried forward until the next validated temperature was recorded. A fever was defined as ≥38.3°C and was selected based on established clinical definitions used in critical care settings and sepsis research.[14] The temperature ranges were chosen a priori to capture clinically distinct populations: hypothermic patients (<36 °C), normothermic patients (36−37.4°C), patients with low-grade fever (37.5−38.2°C), and those with established fever (≥38.3°C). Fever deficit was calculated as the number of degree-hours below 38.3°C. For example, 1 h spent with a temperature one degree below 38.3°C was defined as one degree-hour of fever deficit.

### 2.4. Outcomes

The primary outcome was the fever deficit during the first 72 h of ICU admission. Secondary outcomes included the use of vasopressors, invasive mechanical ventilation, renal replacement therapy, length of stay, and mortality.

### 2.5. Analysis

Data were managed and analysed using R (Version 4.4.1). Analysis was primarily descriptive. Medians with interquartile range (IQR) were used to describe skewed continuous variables, and group comparisons were made using Wilcoxon–Mann–Whitney tests. Means with standard deviations were used to describe normally or near-normally distributed continuous data and were compared using t-tests or one-way ANOVA for multiple group comparisons. Categorical data were reported as percentages and were compared using the chi-squared test, while group comparisons were made using the Kruskal–Wallis rank sum test. A multivariable logistic regression model was developed to examine whether a high fever deficit, defined as a fever deficit above the median value for the cohort, was independently associated with all-cause 30-day mortality. The variables used for analysis were determined a priori, reflected the clinical utility of available data, and consisted of the SOFA score at ICU admission, the Charlson comorbidity index, medical admission status, and treatment limitations at ICU admission. The results of the multivariable analysis were reported as odds ratios (OR) with 95% confidence intervals (95% CI). Furthermore, a multivariable logistic regression model was used to evaluate the high fever deficit and its association with all-cause 30-day mortality within each baseline temperature group. Given the large dataset, a two-sided p-value of <0.01 was considered statistically significant.

## 3. Results

### 3.1. Patients

Of 89,117 ICU admissions, 15,612 patients met the study eligibility criteria (Fig. S1). The median temperature at admission was 36.7°C (IQR 36.1°C–37.3°C), and 1026 (6.6%), 2096 (13.4%), 9216 (59.0%), and 3274 (21.0%) patients had admission temperatures of ≥38.3°C, 37.5–38.2°C, 36.0–37.4°C, and <36°C, respectively.

The baseline characteristics of the study cohort are displayed in Table 1. The median age of the septic cohort was 59 (IQR 45–71) years, and 6883 (44%) were female. Across the four temperature group, the age, sex distribution, and Charlson comorbidity index were comparable. Compared to other temperature groups, patients with admission temperatures <36°C had significantly higher ventilation rates, vasopressor requirements, and renal replacement therapy. The median time to ICU admission from hospital presentation was 7.7 h (IQR 1.9 to 3.2), 7.8 h (IQR 2.7 to 27), 7.4 h (IQR 2.8 to 23), and 6.5 h (IQR2.5 to 22) for patients in admission temperatures of ≥38.3°C, 37.5–38.2°C, 36.0–37.4°C, and <36°C, respectively.

### 3.2. Temperature profile

Following admission, marked temperature changes were recorded with measurements approaching a stable level within the first 24 h of ICU admission (Fig. 1). Most of the normalisation of body temperature occurred within the first 12 h of ICU admission, with all four temperature groups between 36.5 and 37.5°C. Although temperature differences became smaller over time in all groups, temperatures remained separated according to the presenting temperature group.

### 3.3. Fever deficit

Over the first three days of ICU admission, the temperature profiles and fever deficits subsequently varied by presenting temperature group (Table 2). Although a fever deficit was present among all study subjects during each of the first three days of admission, its magnitude varied directly with the presenting temperature classification group.

Patients with an admission temperature of ≥38.3°C had the smallest fever deficit, with deficits of 15, 32, and 47 degree-hours at 24, 48, and 72 h of ICU admission, respectively. Patients with an admission temperature <36°C spent the highest proportion of their time in the ICU without a fever, with 24, 47, and 54 h less than

**Table 1**
Baseline characteristics.

| Variable | Temperature on admission to the ICU | | | |
|---|---|---|---|---|
| | ≥38.3 N = 1,026[a] | 37.5–38.2 N = 2,096[a] | 36–37.4 N = 9,216[a] | <36 N = 3,274[a] |
| Age (years) | 60 (43, 71) | 58 (43, 70) | 60 (45, 71) | 60 (46, 72) |
| Female | 432 (42%) | 964 (46%) | 4080 (44%) | 1407 (43%) |
| Body mass index | 27.8 (24.7, 32.4) | 27.8 (24.6, 33.2) | 27.8 (24.2, 32.1) | 27.6 (24.2, 31.2) |
| Charlson Comorbidity Index | 3 (1, 5) | 3 (1,5) | 3 (1,5) | 3 (1,5) |
| Immunosuppressed[b] | 150 (15%) | 244 (12%) | 909 (9.9%) | 330 (10%) |
| Frail[c] | 149 (43%) | 357 (44%) | 1655 (46%) | 533 (43%) |
| Unknown | 677 | 1279 | 5584 | 2030 |
| Treatment limitation order | 93 (9.1%) | 192 (9.2%) | 879 (9.5%) | 307 (9.4%) |
| Time from hospital presentation to ICU admission (hours) | 8 (2,32) | 8 (3,27) | 7 (3,23) | 6 (2,22) |
| First recorded temperature in ICU | 38.7 (38.4, 39.1) | 37.7 (37.6, 38.0) | 36.7 (36.4, 37.0) | 35.5 (35.0, 35.7) |
| APACHE III score | 62 (46, 82) | 59 (43, 76) | 58 (43, 76) | 64 (47, 84) |
| ANZROD score, mean (SD) | 0.17 (0.23) | 0.13 (0.19) | 0.12 (0.18) | 0.17 (0.23) |
| Any ventilation[d] | 523 (51%) | 1076 (51%) | 4819 (52%) | 2393 (73%) |
| Any renal replacement therapy[d] | 51 (5.0%) | 82 (3.9%) | 442 (4.8%) | 276 (8.4%) |
| Any vasopressors[d] | 578 (56%) | 1101 (53%) | 4825 (52%) | 2139 (65%) |
| Maximum SOFA score | 6 (4,9) | 5 (4,8) | 5 (3,8) | 6 (4,8) |
| Maximum lactate (mmol/L) | 2.3 (1.5, 4.2) | 2.1 (1.4, 3.6) | 2.0 (1.3, 3.5) | 2.1 (1.3, 4.0) |

Abbreviations: ICU = intensive care unit; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.
[a] Median (Q1, Q3); n (%) unless otherwise noted.
[b] Immunosuppressed defined as either the presence of the APACHE III-J comorbidity, 'immunosuppressed', or from the APACHE II comorbidities, 'immunosuppressive disease' or 'immunosuppressive therapy'.
[c] Frail, defined as clinical frailty score ≥ 4.
[d] On day of ICU admission.

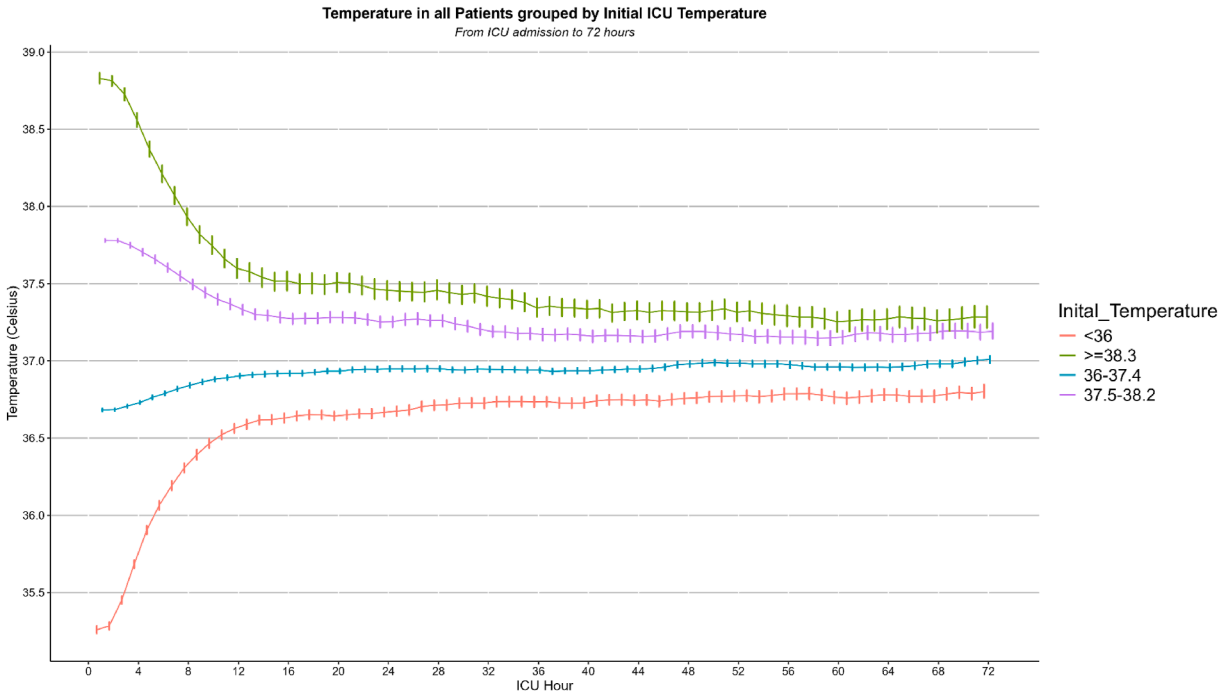


**Fig. 1.** Temperature in all patients grouped by initial ICU temperature. ICU, intensive care unit.

≥38.3°C at 24, 48, and 72 h of ICU admission, respectively. Patients admitted with a temperature of 38.2°C or less rarely had a temperature ≥38.3°C; the median proportion of time in the ICU with a temperature <38.3°C was 100% in all three temperature groups.

While the fever deficit was greatest in the first 8–12 h of ICU admission, the cumulative fever deficit continued to change by group thereafter, most notably among the hypothermic subjects (Fig. 2).

### 3.4. Outcomes

The use of vasopressors, invasive mechanical ventilation, and renal replacement therapy differed by initial temperature category

**Table 2**
Temperature profile.

| Variable | Temperature on admission to the ICU | | | |
|---|---|---|---|---|
| | ≥38.3 N = 1,026[a] | 37.5–38.2 N = 2,096[a] | 36–37.4 N = 9,216[a] | <36 N = 3,274[a] |
| Within 24 hours | | | | |
| Hours in ICU | 24 (24,24) | 24 (24,24) | 24 (24,24) | 24 (24,24) |
| Mean temperature | 37.4 (0.5) | 37.9 (0.6) | 36.3 (0.6) | 36.9 (0.5) |
| Hours with temperature <38.3 | 16 (11,19) | 24 (19,24) | 24 (22,24) | 24 (24,24) |
| Proportion of time <38.3 | 0.71 (0.48, 0.79) | 1.00 (0.88, 1.00) | 1.00 (1.00, 1.00) | 1.00 (1.00, 1.00) |
| Fever deficit, degree-hours | 15 (6, 23) | 20 (13,28) | 34 (25, 41) | 46 (36, 55) |
| Any vasopressors | 662 (65 %) | 1252 (60 %) | 5416 (59%) | 2320 (71%) |
| Any invasive ventilation | 559 (54 %) | 1126 (54 %) | 4926 (53%) | 2425 (74%) |
| Within 48 hours | | | | |
| Hours in ICU | 48 (45, 48) | 48 (39, 48) | 48 (30, 48) | 48 (28, 48) |
| Mean temperature | 37.3 (0.5) | 37.7 (0.6) | 36.4 (0.6) | 36.9 (0.5) |
| Hours with temperature <38.3 | 35 (21, 41) | 43 (29, 48) | 45 (28, 48) | 47 (27, 48) |
| Proportion of time <38.3 | 0.79 (0.60, 0.88) | 1.00 (0.88, 1.00) | 1.00 (1.00, 1.00) | 1.00 (1.00, 1.00) |
| Fever deficit | 32 (17, 50) | 40 (24, 58) | 56 (36, 75) | 70 (48, 94) |
| Any vasopressors | 696 (68 %) | 1312 (63 %) | 5597 (61%) | 2356 (72%) |
| Any invasive ventilation | 578 (56 %) | 1152 (55 %) | 5014 (54%) | 2443 (75%) |
| Within 72 hours | | | | |
| Hours in ICU | 72 (45, 72) | 69 (39, 72) | 59 (30, 72) | 58 (28, 72) |
| Mean temperature | 37.3 (0.5) | 37.6 (0.6) | 36.5 (0.6) | 36.9 (0.5) |
| Hours with temperature <38.3 | 46 (28, 62) | 54 (34, 70) | 53 (29, 72) | 54 (27, 72) |
| Proportion of time <38.3 | 0.82 (0.65, 0.90) | 1.00 (0.89, 1.00) | 1.00 (1.00, 1.00) | 1.00 (1.00, 1.00) |
| Fever deficit | 47 (24, 72) | 53 (29, 83) | 69 (40, 100) | 85 (52, 123) |
| Any vasopressors | 699 (68%) | 1325 (63%) | 5663 (61%) | 2373 (72%) |
| Any invasive ventilation | 581 (57%) | 1160 (55%) | 5063 (55%) | 2454 (75%) |
| Any steroids | 372 (36%) | 707 (34%) | 3042 (33%) | 1050 (32%) |
| Any paracetamol | 798 (78%) | 1459 (70%) | 5917 (64%) | 1893 (58%) |

Abbreviations: ICU = intensive care unit.
Fever deficit was calculated as the number of degree-hours below 38.3°C (for example, 1 h spent with a temperature one degree below 38.3°C was defined as one degree-hour of fever deficit).
[a] Median (Q1, Q3); n (%).

(Table 3). Day-30 mortality also differed significantly by initial temperature category and was highest in those with an initial temperature below 36°C. The ICU and hospital lengths of stay, ICU-free days, hospital-free days, and ventilator-free days by initial temperature category are also shown in Table 3.

### 3.5. Multivariable analysis

Table 4 presents the multivariable analysis for all-cause 30-day mortality. After controlling for confounders, a high fever deficit, defined as a fever deficit above the median, during the first 24 h of ICU admission, was not associated with all-cause 30-day mortality (OR 1.02, 95% CI 0.93–1.13; p = 0.7). However, the SOFA score on ICU admission, the Charlson comorbidity index, a medical admission, and treatment limitations were independently associated with worse outcomes.

The association between high fever deficit and all-cause 30-day mortality was examined in each temperature group (Table S3). For patients admitted with a temperature ≥38.3°C, a fever deficit deficit was independently associated with a decreased risk of all-cause 30-day mortality (OR 0.67; 95% 0.46–0.98; p = 0.04). In patients admitted with temperatures of 37.5–38.2 (OR 0.82; 95% CI, 0.62–1.09), 36.0–37.4 (0.92; 95% CI, 0.80–1.05; p = 0.2), and <36°C (OR 1.00; 95% CI, 0.82–1.22; p > 0.9), a high fever deficit was not associated with a change in risk of all-cause 30-day mortality.

## 4. Discussion

### 4.1. Statement of principal findings

In this retrospective cohort study, including more than 15,000 patients admitted to Queensland ICUs with sepsis, only 1 in 15 patients had an initial body temperature in the ICU of ≥38.3°C. Irrespective of the initial temperature, most recorded temperatures in the first 72 h in the ICU were below 38.3°C, resulting in a fever deficit in all patients. After adjusting for confounders, a high fever deficit was not independently associated with mortality overall; however, in patients admitted with a temperature ≥38.3°C, a higher deficit was associated with a lower risk of all-cause 30-day mortality.

### 4.2. Relationship to previous studies

Our findings align with our recent single-centre prospective observational study, which demonstrated high fever deficits in unplanned ICU admissions who were prescribed antimicrobials and that active warming of these patients was uncommon [CRISP Study, Under Review at CCR]. In our study, we observed that, although temperatures among groups defined by initial body temperature converged, a slight separation remained at 72 h. This may be because the febrile response is ongoing in some patients, patients in respective temperature categories have different 'normal' temperatures, or a combination of these factors.

A nationwide cohort study of 2385 adults admitted to the ICU within 24 h of ED presentation in Sweden demonstrated a median temperature on ICU admission of 37.6°C, which is comparable, though slightly higher than in our study.[25] Furthermore, consistent with our findings, the authors demonstrated that patients with higher admission temperatures had lower mortality rates than those with lower temperatures. In addition, an examination of the Medical Information Mart for Intensive Care (MIMIC) IV database, which examined over 35,000 patients admitted to the hospital with sepsis, found that the highest temperature during the first 24 h greater than 38°C occurred in less than one-in-four patients.[26] Our finding that fever on ICU admission was not the most common temperature profile has been consistently presented in the literature across multiple jurisdictions.

Prior data support the notion that low body temperature is an abnormal pathological state in sepsis[27–29] and we hypothesise that therapeutic warming to high-normal or supra-normal target levels may be beneficial. A recent meta-analysis, including 42 observational studies, demonstrated a mortality of 47% in patients

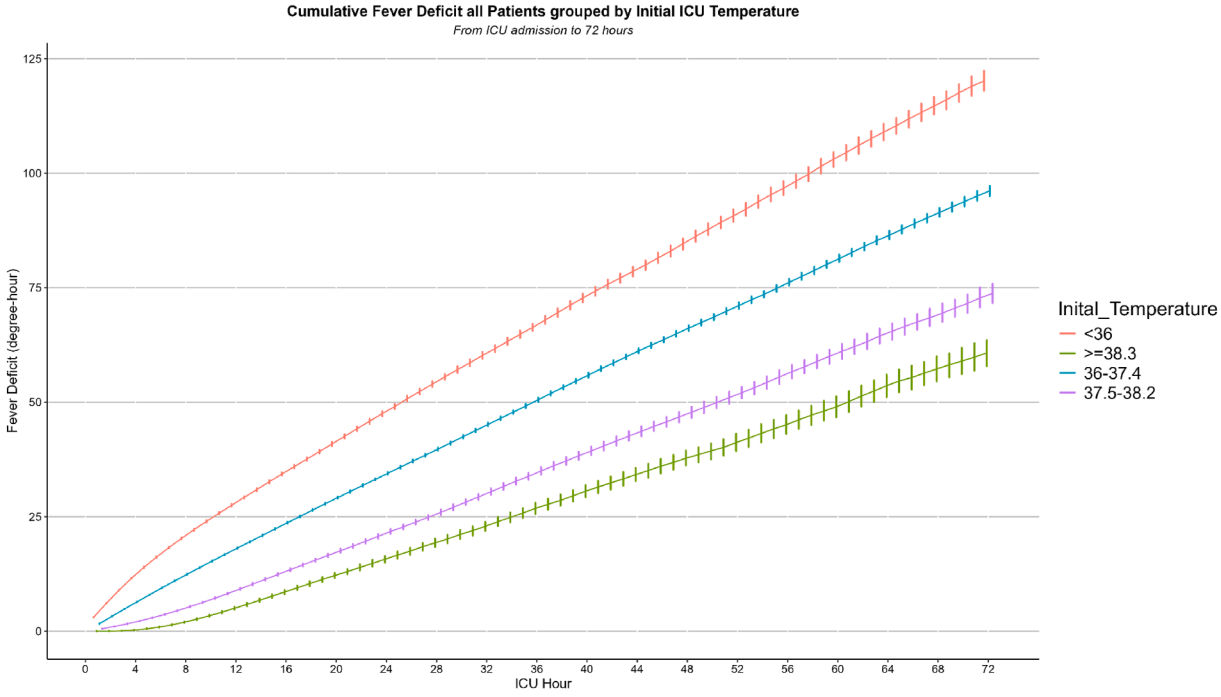


**Fig. 2.** Cumulative fever deficit all oatients grouped by initial ICU temperature. ICU, intensive care unit.

**Table 3**
Outcomes by temperature on ICU admission.

| Characteristic | Temperature on admission to the ICU | | | | |
|---|---|---|---|---|---|
| | ≥38.3 N = 1,026[a] | 37.5–38.2 N = 2,096[a] | 36–37.4 N = 9,216[a] | <36 N = 3,274[a] | p-value[b] |
| Any invasive ventilation during ICU admission | 585 (57%) | 1177 (56%) | 5116 (56%) | 2464 (75%) | <0.001 |
| Days alive and free of invasive ventilation at 30 days | | | | | <0.001 |
| Median (Q1, Q3) | 28 (22,30) | 28 (24,30) | 28 (25,30) | 28 (22,29) | |
| Mean (SD) | 23 (10) | 24 (9) | 25 (8) | 23 (9) | |
| Any vasopressors during ICU admission | 718 (70%) | 1349 (64%) | 5758 (62%) | 2407 (74%) | <0.001 |
| Days alive and free of vasopressors at 30 days | | | | | <0.001 |
| Median (Q1, Q3) | 28 (25,30) | 28 (26,30) | 28 (26,30) | 28 (24,29) | |
| Mean (SD) | 24 (9) | 25 (8) | 25 (8) | 24 (9) | |
| Any renal replacement therapy during ICU admission | 162 (16%) | 222 (11%) | 987 (11%) | 503 (15%) | <0.001 |
| Days alive and free of RRT at 30 days | | | | | <0.001 |
| Median (Q1, Q3) | 30 (28,30) | 30 (30,30) | 30 (30,30) | 30 (28,30) | |
| Mean (SD) | 26 (9) | 27 (8) | 27 (7) | 26 (9) | |
| Length of stay, ICU (days) | | | | | <0.001 |
| Median (Q1, Q3) | 4.0 (2.0, 7.0) | 3.0 (2.0, 6.0) | 3.0 (2.0, 6.0) | 3.0 (2.0, 6.0) | |
| Days alive and free of ICU at 30 days | | | | | <0.001 |
| Median (Q1, Q3) | 26 (19,27) | 26 (21,28) | 26 (22,28) | 26 (19,28) | |
| Mean (SD) | 21 (10) | 22 (9) | 22 (9) | 21 (10) | |
| Length of stay, hospital (days) | | | | | 0.008 |
| Median (Q1, Q3) | 11 (6,22) | 10 (6,19) | 10 (6,18) | 10 (6,19) | |
| Days alive and free of hospital at 30 days | | | | | <0.001 |
| Median (Q1, Q3) | 18 (1,24) | 19 (5,24) | 19 (7,24) | 17 (1,23) | |
| Mean (SD) | 14 (10) | 15 (10) | 16 (10) | 14 (10) | |
| ICU mortality | 108 (11%) | 167 (8.0%) | 666 (7.2%) | 353 (11%) | <0.001 |
| Hospital mortality | 144 (14%) | 226 (11%) | 957 (10%) | 505 (15%) | <0.001 |
| Mortality at 30 days | 147 (14%) | 248 (12%) | 1104 (12%) | 549 (17%) | <0.001 |

Abbreviations: ICU = intensive care unit.
[a] Median (Q1, Q3); n (%).
[b] Pearson's Chi-squared test; Kruskal–Wallis rank sum test.

with hypothermic sepsis compared to 22% in those with a fever.[30] Given that elevated body temperatures are very uncommon in ICU patients with sepsis, our data suggest such therapeutic warming does not appear to be a feature of current clinical practice.

### 4.3. Strengths and limitations

Although, we conducted a large multicentric study that included a detailed assessment of body temperature profiles and outcomes, we acknowledge certain limitations. First, we could not determine which therapeutic interventions that affect body temperature were used. While observed temperature changed over time, it remains unclear whether these were natural or therapeutic responses. Although there is a lack of evidence in the literature to support the treatment of fever in patients such as those included in our study,[15,16] the treatment of fever may be widespread.[31,32] We suspect that active warming is less common. Second, we did not standardise temperature measurement frequencies or methods used to measure temperature. Our results may differ from what they would be if we had dictated a standardised protocol for temperature measurement.[33] Third, we imputed some temperature values; different imputation methods would be expected to affect the description of temperature profiles; however, as we used all recorded body temperature measurements, we submit that our approach was reasonable. Fourth, our cohort was exclusively comprised of critically ill patients; therefore, our findings may not apply to the general hospital population. Fifth, we acknowledge that the 38.3°C fever threshold is somewhat arbitrary within the range of physiologically plausible values. However, this threshold was selected based on established clinical definitions of fever commonly used in critical care settings and sepsis research, providing consistency with the broader literature and clinical practice.[14] Sixth, the retrospective nature of our study and reliance on administrative data may have led to the misclassification of sepsis diagnoses. However, we used validated algorithms and established definitions consistent with SEPSIS-3 criteria to minimise this risk.[21,24] Lastly, our multivariable analysis may be subject to over-adjustment bias, as some covariates may act as mediators on the causal pathway between fever deficit and mortality rather than true confounders. However, we felt this conventional regression approach was appropriate for our descriptive study focused on trial feasibility. Future mechanistic

**Table 4**
Multivariable analysis for all-cause 30-day mortality.

| Variable | OR[a] | 95% CI[a] | p-value |
|---|---|---|---|
| High temperature deficit during first 24 h of ICU admission | 1.02 | 0.93, 1.13 | 0.7 |
| SOFA score on ICU admission | 1.09 | 1.07, 1.11 | <0.001 |
| Charlson Comorbidity Index | 1.21 | 1.19, 1.23 | <0.001 |
| Medical admission | 1.71 | 1.52, 1.94 | <0.001 |
| Treatment limitations | 2.89 | 2.54, 3.28 | <0.001 |

High temperature deficit was defined by 'fever deficit' above the median value. Fever deficit was calculated as the number of degree-hours below 38.3°C (for example, 1 h spent with a temperature one degree below 38.3°C was defined as one degree-hour of fever deficit.
The odds ratios presented represent adjusted associations conditional on the other covariates included in the model rather than independent causal effects, and their interpretation depends on model specification and the assumption of no unmeasured confounding.
[a] Abbreviations: OR = Odds Ratio, CI = Confidence Interval.

studies may benefit from formal mediation analysis or directed acyclic graph approaches to elucidate causal relationships better.

### 4.4. Implications for practice and future research

Our data suggest there may be scope within current practice to conduct a clinical trial comparing prompt rewarming of septic patients without a fever to a modest level of hyperthermia. A logical next step would be to conduct a feasibility trial to determine whether therapeutic warming effectively increases body temperature in afebrile patients with sepsis. Given that most ICU patients with sepsis are afebrile at admission, establishing the efficacy and safety of such interventions could have far-reaching public health implications. If therapeutic warming is shown to improve clinical outcomes, it could represent a transformative shift in sepsis management for a large and potentially undertreated subgroup of critically ill patients.

The observation that a greater temperature deficit in febrile patients correlates with better outcomes suggests that persistent fever may be indicative of a nonresolving infection, which is associated with a heightened risk of mortality. This finding is significant as it underscores the inherently confounded relationship between temperature profiles and outcomes, emphasising the complexity involved in their assessment.

## 5. Conclusion

In this multicentre retrospective cohort study, which included patients with sepsis admitted to Queensland ICUs, fever deficits were large, particularly in the absence of a fever. Only 1 in 15 ICU patients with sepsis had an initial body temperature $\geq$38.3°C. Approximately 2000 adults a year with sepsis and initial body temperature <37.5°C would potentially be eligible for a trial of therapeutic hyperthermia in the 12 ICUs that participated in this study.

## Author contributions

The study conception and design (KW, KL, PY, MS) data acquisition (all authors); analysis (KW); interpretation of data (all authors); article drafting (KW, KL, PY, MS); article revision for important intellectual content (all authors); final approval of the version submitted for publication (all authors); agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (KW, KL, PY, MS).

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## Conflicts of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paul Young is the acting Co-Editor-in-Chief, and Manoj Saxena is an Editorial Board member for Critical Care and Resuscitation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability statement

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data released for research under Sect. 280 of the Public Health Act 2005 requires an application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2025.100135.

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