Received: 19 May 2023 | Revised: 22 September 2023 | Accepted: 15 May 2024

DOI: 10.1002/hsr2.2162

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Comparison of clinical characteristics and outcomes of patients with sepsis identified by the Sepsis-3 criteria by blood and urine culture results: A multicentre retrospective cohort study

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Funding information

None

Abstract

Background and Aims: Blood and urine are the most common culture testing for sepsis patients. This study aimed to compare clinical characteristics and outcomes of sepsis patients by blood and urine culture positivity and to identify factors associated with positive cultures.

Methods: This retrospective study included patients aged ≥16 years with sepsis identified by the Sepsis-3 criteria presenting to the emergency department at four hospitals between 2017 and 2019 in Australia. Patient clinical outcomes were in-hospital mortality, intensive care unit (ICU) admission, hospital length of stay, and representation following discharge. Four culture groups were defined based on the positivity of blood cultures (BC) and urine cultures (UC) ordered within 24 h of triage.

Results: Of 4109 patient encounters with sepsis, 2730 (66%) were nonbacteremic, urine culture-negative (BC−UC−); 767 (19%) nonbacteremic, urine culture-positive (BC−UC+); 359 (9%) bacteremic, urine culture-negative (BC+UC−); and 253 (6%) bacteremic, urine culture-positive (BC+UC+). Compared with BC−UC− patients, BC+UC− patients had the highest risk of ICU admission (adjusted odds ratio [AOR] 95% CI: 1.60 [1.18–2.18]) while BC−UC+ patients had lowest risk (adjusted odds ratio [AOR]: 0.56 [0.41–0.76]). BC+UC− patients had the highest risk of 3-day representation (AOR: 1.51 [1.02–2.25]) and second longest hospital stay (adjusted relative risk 1.17 [1.03–1.34]). Antibiotic administration before sample collection for culture was associated with lower odds of positive blood or urine culture results (AOR: 0.38, $p < 0.0001$).

Conclusions: Enhanced clinical care should be beneficial for nongenitourinary sepsis patients (BC+UC−) who had the highest comparative risk of adverse clinical outcomes. Every effort needs to be made to collect relevant culture samples before antibiotic administration, to follow up on culture results, and tailor treatment accordingly.

KEYWORDS

blood culture, critical care outcomes, hospital mortality, pathology, sepsis, urine

1 | INTRODUCTION

Sepsis carries significant morbidity and mortality worldwide despite recent scientific and therapeutic advances. Each year sepsis affects an estimated 50 million people globally and is associated with 20% of all deaths worldwide.[1] It is of great clinical importance, being responsible for more than a third of all hospital admissions, approximately half of all intensive care unit (ICU) admissions,[2] and with sepsis patients having 11 times higher mortality rate than other hospitalized patients.[3]

Sepsis, defined as "a life-threatening organ dysfunction due to a dysregulated host response to infection" (Sepsis-3),[4] can develop from a diverse range of microorganisms. Culture-negative sepsis has been reported in an estimated 49%–58% of sepsis patients,[5–7] and 29%–43% of septic shock cases.[5,8–10] Studies investigating the mortality associated with culture-negative sepsis have reported mixed results, demonstrating comparable,[11–13] lower,[5] or higher[14] mortality than culture-positive sepsis. It is therefore of interest to compare clinical characteristics and patient outcomes between culture-negative and culture-positive sepsis cases.

Blood and urine culture tests are the most common microbiological testing ordered from emergency departments (EDs).[15] Previous studies examining factors associated with culture positivity have mostly restricted inclusion to blood culture.[16–20] This study aimed (1) to compare the characteristics of sepsis patients by blood and urine culture positivity and examine the association between culture positivity and patient clinical outcomes and (2) to identify factors associated with positive blood or urine culture results.

2 | METHODS

2.1 | Study design and setting

This was a multicentre retrospective observational study in four large Australian hospitals with a combined >200,000 ED visits per year. The overall study period was from January 1, 2017 to November 30, 2019, and the starting date varied across the sites depending on the availability of electronic medication systems—one since 2017, two since 2018, and one since 2019.

2.2 | Study population and data source

We included all adult patients (aged ≥16 years) who presented to a participating ED during the study period with a culture sample taken within 24 h of triage (Figure 1). *Patient encounters with sepsis* were identified as meeting the following Sepsis-3 criteria: (i) suspected infection based on Sepsis-3 criteria[21] with an antibiotic administered either within 24 h before or 72 h after the first culture order; and (ii) a modified Sequential Organ Failure Assessment (SOFA) score[22,23] of two or greater within 3 h of triage. We assumed a baseline SOFA score of zero given that the information on patients' pre-existing organ dysfunction is unknown. Patient hospital encounters included their ED and hospital stay if they were admitted to hospital from the ED. Patients with more than three encounters in any year were excluded as they were likely to have complicated health conditions. Further exclusion criteria for the Aim (1) analysis were patient encounters (i) with antibiotics before first blood or urine culture and (ii) with only blood or urine culture. Patient demographic and clinical data related to these encounters, including ED presentations, antibiotic administrations, laboratory testing, ICU admissions, and hospital discharge status, were extracted from hospital electronic health record systems.

2.3 | Culture positivity groups

Four culture positivity groups were defined: (i) bacteremic and urine culture-positive (*BC+UC+*), (ii) bacteremic and urine culture negative (*BC+UC−*), (iii) nonbacteremic and urine culture-positive (*BC−UC+*), and (iv) nonbacteremic and urine culture-negative (*BC−UC−*). Findings for likely contaminants or commensals in the pathology description were excluded and any remaining pathogens used to categorize culture positivity.

2.4 | Patient outcomes

Six patient outcomes were analyzed, including in-hospital mortality, ICU admission, patient hospital length of stay in hospital, and representation to ED for any reason within 3, 7, and 30 days following discharge. Our analysis also included the composite of in-hospital mortality and/or ICU admission as it was used in the study for assessing clinical criteria for Sepsis-3.[21]

2.5 | Statistical analysis

Patients' demographic and clinical characteristics were assessed by the four culture positivity groups. To examine the association between culture positivity and patient outcomes (Aim 1), multilevel logistic regression models were used for all binary outcomes, and multilevel linear regression for log-transformed hospital length of stay. All multilevel models accounted for the correlation of multiple encounters for the same patients and adjusted for patient demographics and clinical factors, including patient sex, age group, triage category, immunosuppressant usage, hospital, and worst SOFA score within 3 h of triage. Patients who died during their hospital stay were excluded from the models for hospital length of stay and representation analyses, while ICU admission was included in these models in addition to the above-listed patient and clinical factors. The factors associated with the outcome of a positive blood culture result (Aim 2) were examined using multilevel logistic regression models, adjusting for antibiotic administration before the first blood culture, patient demographics, and clinical factors as specified above. The same

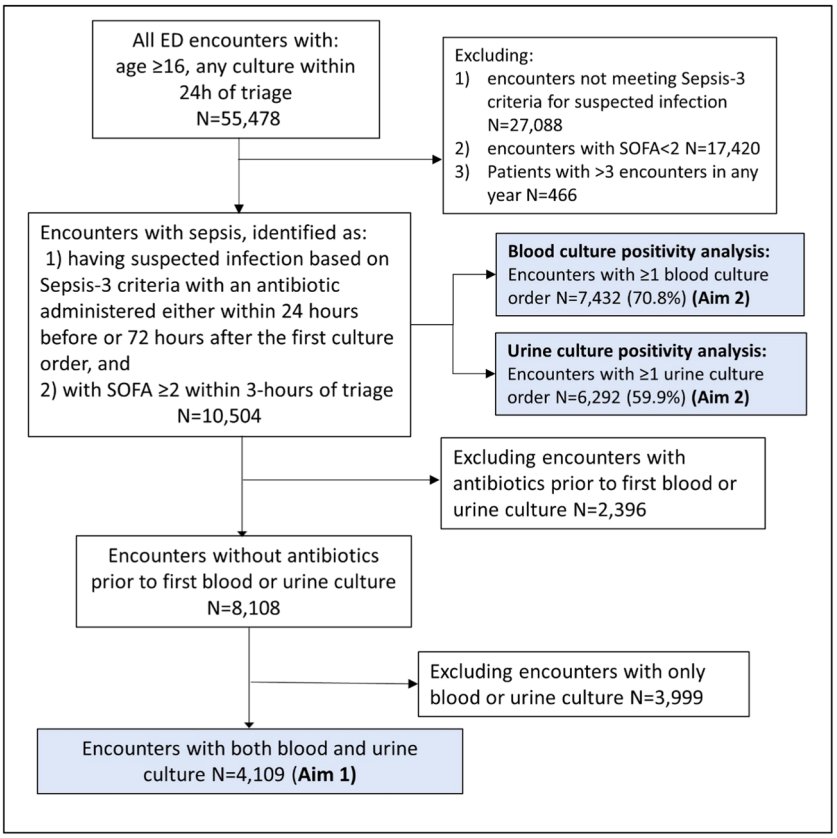

FIGURE 1 Selection of study population. ED, emergency department; SOFA, Sequential Organ Failure Assessment.

analysis was conducted for urine culture. All analyses were performed using SAS Enterprise Guide version 8.2.

3 | RESULTS

3.1 | Patient characteristics and culture ordering

A total of 10,504 patient encounters were identified as sepsis cases based on Sepsis-3 criteria (Figure 1). Overall, 7432 (70.8%) of these patient encounters had at least one blood culture and 6292 (59.9%) had one or more urine culture. The median turnaround time for culture results was 5.20 days (interquartile range [IQR]: 5.11–5.28 days) for blood cultures and 1.01 days (IQR: 0.61–1.57) for urine cultures.

A total of 4109 patient encounters were included to examine the association between culture positivity and patient outcomes. Two-thirds of these encounters ($n = 2730$, 66.44%) had no positive results for either blood or urine culture recorded (Table 1). Encounter characteristics and outcomes were compared among the four culture groups. A SOFA score of six and above (in 12.26%) and assignment to the highest priority triage category (Category 1, in 7.24%) were most frequently observed in the BC+UC− group. In comparison, the BC −UC+ group had the lowest proportion in these presenting categories (6.13% and 4.56%, respectively). A positive urine culture (UC+) was more common in female patients aged ≥75 years and in those with immunosuppressant usage.

Infection source was only recorded in 28.11% ($n = 1155$) of patient encounters. Among those recorded sources, genitourinary was the most common among the UC+ groups and pulmonary was the most common among the BC−UC− group. Systemic disturbance symptoms such as fever, lethargy, and malaise were the most common presenting problem among all groups, especially in the BC +UC+ group (53.36%). Respiratory symptoms dominated among the BC−UC− group (19.23%), and mental disturbance such as drowsiness, headache, and altered mental status were most common in the BC −UC+ groups (12.91%).

3.2 | Patient outcomes and culture positivity (Aim 1)

The BC+UC− group had the highest observed rates of in-hospital mortality, ICU admission, representation within three- and 7-days following discharge, and the longest median hospital length of stay among the four groups. Overall, bacteremic patients appeared to have worse patient outcomes than nonbacteremic cases (Table 1).

There was a statistically significant association between culture group and the primary outcome (in-hospital mortality/ICU admission, $p = 0.001$). Compared with the BC−UC− group (the reference group), the BC + UC− group had the greatest risk of in-hospital mortality/ICU admission (adjusted odds ratio [AOR] 1.47, 95% CI 1.11-1.95) while the BC−UC+ had the lowest risk (AOR 0.72, 95%CI 0.56-0.94) after adjusting for relevant patient and clinical factors (Table 2). There were

TABLE 1 Patient characteristics and outcomes by culture group ($N = 4109$); *N* (col %) unless stated otherwise.

Characteristic	Bacteremic, urine culture positive BC+, UC+	Bacteremic, urine culture negative BC+, UC−	Nonbacteremic, urine culture positive BC−, UC+	Nonbacteremic, urine culture negative BC−, UC−
N (row %)	253 (6.16)	359 (8.74)	767 (18.67)	2730 (66.44)
Sex				
Female	162 (64.03)	157 (43.73)	471 (61.41)	1164 (42.64)
Male	91 (35.97)	202 (56.27)	296 (38.59)	1566 (57.36)
Age median (IQR) years	74 (66–83)	73 (61–83)	77 (66–85)	73 (60–83)
Age group				
16–44	12 (4.74)	28 (7.8)	64 (8.34)	285 (10.44)
45–59	27 (10.67)	53 (14.76)	74 (9.65)	365 (13.37)
60–74	89 (35.18)	108 (30.08)	207 (26.99)	785 (28.75)
75+	125 (49.41)	170 (47.35)	422 (55.02)	1295 (47.44)
Triage category				
1 (highest)	12 (4.74)	26 (7.24)	35 (4.56)	177 (6.48)
2	147 (58.1)	219 (61)	379 (49.41)	1489 (54.54)
3	79 (31.23)	99 (27.58)	291 (37.94)	894 (32.75)
4–5 (lowest)	15 (5.93)	15 (4.18)	62 (8.08)	170 (6.23)
Worst 3 h SOFA				
2 (lowest)	88 (34.78)	95 (26.46)	358 (46.68)	1206 (44.18)
3	68 (26.88)	100 (27.86)	188 (24.51)	666 (24.4)
4	46 (18.18)	81 (22.56)	107 (13.95)	412 (15.09)
5	28 (11.07)	39 (10.86)	67 (8.74)	230 (8.42)
6–13 (highest)	23 (9.09)	44 (12.26)	47 (6.13)	216 (7.91)
On immunosuppressants	7 (2.77)	5 (1.39)	20 (2.61)	48 (1.76)
Number of blood culture orders within 24 h of triage				
1 blood culture orders	131 (51.78)	191 (53.2)	637 (83.05)	2146 (78.61)
2 blood culture orders	85 (33.6)	111 (30.92)	104 (13.56)	473 (17.33)
3–7 blood culture orders	37 (14.62)	57 (15.88)	26 (3.39)	111 (4.07)
Infection source recorded?				
No	156 (61.66)	254 (70.75)	543 (70.8)	2001 (73.3)
Yes	97 (38.34)	105 (29.25)	224 (29.2)	729 (26.7)
Infection source if recorded				
Genitourinary	44 (45.36)	22 (20.95)	118 (52.68)	94 (12.89)
Other	40 (41.24)	59 (56.19)	58 (25.89)	214 (29.36)
Pulmonary	13 (13.4)	23 (21.9)	43 (19.2)	406 (55.69)
Soft tissue	0 (0)	1 (0.95)	5 (2.23)	15 (2.06)
Presenting problem				
Mental disturbance	27 (10.67)	30 (8.36)	99 (12.91)	308 (11.28)
Other	40 (15.81)	60 (16.71)	158 (20.60)	455 (16.67)
Pain, abdominal	14 (5.53)	23 (6.41)	35 (4.56)	152 (5.57)
Pain, other	20 (7.91)	24 (6.69)	49 (6.39)	205 (7.51)

TABLE 1 (Continued)

Characteristic	Bacteremic, urine culture positive BC+, UC+	Bacteremic, urine culture negative BC+, UC−	Nonbacteremic, urine culture positive BC−, UC+	Nonbacteremic, urine culture negative BC−, UC−
Respiratory	17 (6.72)	32 (8.91)	84 (10.95)	525 (19.23)
Systemic disturbance	135 (53.36)	190 (52.92)	342 (44.59)	1085 (39.74)
In-hospital death	16 (6.32)	27 (7.52)	46 (6.00)	153 (5.60)
ICU admission	39 (15.42)	87 (24.23)	62 (8.08)	421 (15.42)
In-hospital death or ICU admission	53 (20.95)	102 (28.41)	102 (13.3)	524 (19.19)
Hospital length of stay (days)	Median 6.82, IQR 3.87–11.00	Median 6.91, IQR 3.60–14.00	Median 4.85, IQR 1.85–9.07	Median 5.21, IQR 2.42–10.04
Representation within 3 days following discharge	19 (7.51)	32 (8.91)	33 (4.30)	158 (5.79)
Representation within 7 days following discharge	24 (9.49)	41 (11.42)	57 (7.43)	261 (9.56)
Representation within 30 days following discharge	46 (18.18)	73 (20.33)	153 (19.95)	583 (21.36)

Abbreviations: BC, blood culture; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; UC, urine culture.

TABLE 2 Association between patient adverse outcomes and culture group among suspected sepsis patients with both blood and urine culture and without antibiotics before culture based on multivariable regression models—adjusted odd ratios (95% CI) compared to nonbacteremic and urine culture negative group (BC−UC−) and adjusted relative risk for hospital length of stay.

Patient outcomes	Bacteremic, urine culture positive BC+, UC+	Bacteremic, urine culture negative BC+, UC−	Nonbacteremic, urine culture positive BC−, UC+	*p* Value
In-hospital death	0.96 (0.56–1.66)	1.19 (0.77–1.83)	1.07 (0.75–1.54)	0.9
ICU admission	1.09 (0.71–1.68)	1.60 (1.18–2.18)	0.56 (0.41–0.76)	<0.0001
In-hospital death/ ICU admission	1.16 (0.81–1.65)	1.47 (1.11–1.95)	0.72 (0.56–0.94)	0.001
Hospital length of stay (days)	0.95 (0.86–1.04)	1.17 (1.03–1.34)	1.19 (1.04–1.37)	0.002
Representation within 3 days following discharge	1.26 (0.75–2.11)	1.51 (1.02–2.25)	0.74 (0.50–1.10)	0.045
Representation within 7 days following discharge	0.99 (0.63–1.56)	1.19 (0.84–1.69)	0.79 (0.59–1.08)	0.3
Representation within 30 days following discharge	0.77 (0.54–1.09)	0.91 (0.69–1.21)	0.91 (0.74–1.12)	0.4

Abbreviations: BC, blood culture; CI, confidence interval; ICU, intensive care unit; UC, urine culture.

similar findings for the outcome of ICU admission among the four culture groups ($p < 0.0001$) while no statistically significant association between culture group and in-hospital mortality was observed ($p = 0.9$).

Compared with the reference group (BC−UC−), the BC−UC+ group stayed 19% longer on average (adjusted relative risk [ARR] 1.19, 95% CI: 1.04-1.37), followed by the BC+UC− group (ARR: 1.17, 95% CI: 1.03–1.34) (Table 2). The BC+UC− groups were most likely to represent within 3 days of discharge (AOR: 1.51), compared with the reference BC−UC− group. The risk of representation within 7 or 30 days was comparable between all four groups ($p = 0.3$ and 0.4, respectively).

3.3 | Factors associated with positive culture (Aim 2)

Prior antibiotic administration was associated with significantly lower odds of a positive result for both blood (AOR: 0.38, 95% CI: 0.28–0.53, $p < 0.0001$; Table 3) and urine cultures (AOR: 0.38, 95% CI: 0.33–0.44, $p < 0.0001$; Table 4). Patient sex and age also appeared to be linked with both blood and urine culture results. There was an association between a higher SOFA score and greater likelihood of a positive blood culture.

TABLE 3 Factors associated with positive blood culture results ($n = 7432$ encounters including those with and without antibiotics prior culture taken).

Characteristic	OR (95% CI)	*p* Value
Antibiotic timing		
Before first blood culture	0.38 (0.28–0.53)	<0.0001
After first blood culture	Ref	
Male versus female	0.72 (0.63–0.84)	<0.0001
Age group		<0.0001
16–44	0.74 (0.56–0.98)	0.03
45–59	1.15 (0.93–1.43)	0.2
60–74	1.17 (0.99–1.39)	0.06
75+	Ref	
Worst 3 h SOFA		<0.0001
2 (lowest)	Ref	
3	1.86 (1.53–2.25)	<0.0001
4	2.10 (1.69–2.60)	<0.0001
5	2.19 (1.70–2.82)	<0.0001
6–13 (highest)	3.04 (2.39–3.88)	<0.0001

Abbreviations: CI, confidence interval; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

TABLE 4 Factors associated with positive urine culture results ($n = 6292$ encounters including those with and without antibiotics prior culture taken).

Characteristic	OR (95% CI)	*p* Value
Antibiotic timing		
Before first blood culture	0.38 (0.33–0.44)	<0.0001
After first blood culture	Ref	
Male versus female	0.44 (0.39–0.50)	<0.0001
Age group		<0.0001
16–44	0.60 (0.48–0.76)	<0.0001
45–59	0.65 (0.53–0.80)	<0.0001
60–74	0.94 (0.82–1.07)	0.35
75+	Ref	

Abbreviations: CI, confidence interval; OR, odds ratio.

4 | DISCUSSION

This is the first study to our knowledge to compare adverse hospital outcomes by blood and urine culture positivity among sepsis patients. We found in-hospital mortality comparable between patients with positive and negative blood/urine cultures. This is consistent with findings from several other studies examining outcomes for culture-positive versus negative sepsis.[11–13] For other adverse hospital outcomes, the group with the highest risk of ICU admission, representation within 3 days following discharge, and the longest hospital length of stay were bacteremic and urine culture-negative (BC+UC−), *representing nongenitourinary sepsis*. This was closely followed by bacteremic and urine culture-positive cases (BC+UC+), representing genitourinary infection that may have spread to the bloodstream.

Nonbacteremic sepsis cases with positive urine cultures (BC−UC+) had significantly lower risk of ICU admission compared with all other groups. This group *represents genitourinary infections* likely presenting early in the course of infection, as pathogens were not suspected by clinicians or detected in the bloodstream. As such, they may be easier to treat than genitourinary infections presenting later in the course of infection, or other sources of infection. On the other hand, higher proportion of bacteremic patients present with systemic symptoms (Table 1) and were more likely to be severely ill. Previous studies show that sepsis patients with BC+ were likely to die in-hospital than those with BC− or UC+.[24,25] It is therefore possible that bacteremic and urine culture-negative (BC+UC−) had more severe conditions in hospital and were more likely to be admitted to ICUs than other sepsis patients.

It is interesting that cases without either positive blood or urine cultures (BC−UC−) did not have the lowest risk of adverse hospital events. Rather, compared with nonbacteremic urine culture-positive cases (BC−UC+), they had significantly higher risk of ICU admission. The relatively higher rates of triage category 1, SOFA ≥ 6, and adverse hospital outcomes in this group suggest that it may include culture-negative suspected sepsis (CNSS) patients (Table 1). Given the higher rates of presentation with respiratory symptoms, it is likely to comprise a higher proportion of respiratory infections than the blood culture-positive groups. Respiratory infections are commonly treated with antibiotics in the community, which may result in a lack of detectable pathogens in blood and other cultures if they later present to hospital. Severe respiratory infections are more commonly culture-negative, with studies finding an association between CNSS and higher rates of respiratory infection.[10,11] Approximately 40% of patients admitted to ICU for pneumococcal community-acquired pneumonia are bacteremic,[26,27] and one recent study of ICU patients showed that the blood culture status had no influence on mortality outcomes.[28]

The rate of bacteremia-positive sepsis in our ED cohort is 8%, approximately half of the 17% found in a study set in an ICU and

three general wards combined,[5] and substantially lower than the 51% found in another ICU-only study.[6] As patients transferred to ICU have already had a deteriorating condition identified, this highlights the important role of the ED in triage and investigation of the diverse patient groups presenting with suspected sepsis.

Among our cohort presenting to the ED with sepsis based on the Sepsis-3 defintion,[4] 29% of cases did not have a blood culture ordered within 24 h of triage. The Sepsis Six Care Bundle and Clinical Excellence Commission Adult Sepsis Pathway in Australia recommend obtaining two sets of blood cultures before commencing antibiotics within an hour from triage in cases of suspected sepsis.[29,30] Although there is allowance in this Australian guideline for administering antibiotics first if it is difficult to obtain cultures, it is still unusual that no blood cultures were obtained later within the 24-h period for these cases. Another study has also found low compliance with the Sepsis Six Care Bundle.[31] Further investigation would be useful to elucidate reasons for noncompliance with guidelines.

We found evidence that prior antibiotic administration within the ED was associated with 62% of lower odds of a positive blood or urine culture (AOR: 0.38), or 2.6 times higher chance of a negative culture result. This supports findings from previous studies indicating that antibiotic administration before obtaining cultures is associated with a significant loss of pathogen detection.[6,7] As initial antibiotic treatment is incorrectly matched to the causative pathogen in an estimated third of cases,[32] it is crucial to identify pathogens and their susceptibilities wherever possible in suspected sepsis, by obtaining blood and other relevant cultures before commencing antibiotics as per sepsis pathway guidelines.[29,30]

Our findings have several important implications for clinical practice. Firstly, it is important to identify nongenitourinary sepsis cases as bacteremic urine culture-negative patients (BC+UC−) had a higher risk of ICU admission and prolonged hospital length of stay. It also emphasizes the importance of following up on blood and other culture results, checking antibiotic appropriateness, and undertaking closer monitoring of bacteremic patients with sepsis in hospital. Although most laboratories notify clinicians about critical results such as a positive blood culture before they are finalized in the system, it may still take days for blood culture results to become available. Therefore, it is important to follow up on blood culture results even if the patient has been discharged before they become available. Bacteremic patients were also at higher risk of representation within 3 days following discharge, highlighting the importance of community care and follow-up for these patients in the days after discharge. Secondly, our findings reinforce the importance of timing the collection of blood and other relevant cultures to precede antibiotic administration, while also observing guidelines to administer antibiotics within 1 h of presentation.[29] This is a requirement to optimize pathogen detection and tailor antibiotic therapy accordingly, which has significant impact on patient outcomes.[33] Lastly, it is worth further investigation into barriers to compliance with guidelines that recommend collection of two sets of blood cultures in suspected sepsis cases.

This study has several limitations. We examined sepsis patients presenting to ED in four hospitals from one local health district in Australia, which may limit the generalizability of our findings to other settings. We assumed a baseline SOFA score of zero given that the information on patients' pre-existing organ dysfunction was unknown. Although this was recommended by the Sepsis-3 criteria,[4] this could lead to the inclusion of some patients without an acute change in total SOFA score ≥2 points (with pre-existing organ dysfunctions) as being septic. Hence, the mortality rates from our study cohort were slightly low (5%–7%). However, the in-hospital mortality rates reported in our study were close to those in other ED studies using slightly different definitions to identify sepsis patients, for example, 8% by Sørensen et al.[34] and Tarabichi et al.[35] (using Sepsis-3), 8.5% by Gaieski et al.[36] (using ICD-10 coding), and 5.7% by Berger et al.[37] (using two or more SIRS criteria and clinical suspicion of infection). We included the two most common culture types ordered from EDs as nearly 75% of all cultures ordered at study sites during the study period were BC and urine culture. Future research into other culture types and testing results, for example, sputum, would increase our understanding on culture positivity and the risk of adverse patient outcomes. Potential unidentified confounders may have been missed in our data as this is a retrospective observational study. Information about prehospital antibiotic usage, and site of infection were not available. However, this is a multicentre study with a large sample size, demonstrating a strength of our study that is difficult to achieve with prospective designs. Furthermore, comprehensive analytical approaches were applied with adjustment for important patient characteristics, clinical, and hospital factors. The inclusion of sepsis patients was based on internationally accepted criteria, which would support generalization and comparison with other studies.

In conclusion, our findings show significant differences in presentation profiles and risk of adverse patient outcomes by blood and urine culture positivity among sepsis cases presenting to the ED. Nongenitourinary sepsis cases (BC+UC−) had the highest comparative risk of ICU admission, prolonged hospital length of stay, and representation within 3 days following discharge. Antibiotic administration before sample collection for culture was associated with a greater than two-fold higher rate of negative blood or urine culture results. Every effort needs to be made to collect relevant culture samples before antibiotic administration in ED, to follow up on culture results, and tailor treatment accordingly.

AUTHOR CONTRIBUTIONS

Ling Li: Conceptualization; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing—original draft; writing—review and editing. **Jannah Baker**: Formal analysis; writing—original draft; writing—review and editing. **Aldo Saavedra**: Data curation; writing—review and editing. **Carl Suster**: Data curation; writing—review and editing. **Michelle Moscova**: Data curation; writing—review and editing. **Jonathan Iredell**: Conceptualization; writing—review and editing. **Amith Shetty**:

Conceptualization; data curation; investigation; project administration; writing—review and editing.

ACKNOWLEDGMENTS

Open access publishing facilitated by Macquarie University, as part of the Wiley - Macquarie University agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are not publicly available due to data containing information that could compromise research participant privacy. The aggregated data are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study was approved by the Human Research Ethics Committee at the Western Sydney Local Health District, Sydney, Australia (HREC2014/3/5.3(3939) AU RED LNR/14/WMED/66). Research has been conducted in accordance with the ethics approval, and the relevant guidelines and regulations. The requirement for informed consent of individual patient was waived by the Human Research Ethics Committee at the Western Sydney Local Health District, Sydney, Australia because of the retrospective nature of the study.

TRANSPARENCY STATEMENT

The lead author Ling Li affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Li L, Baker J, Saavedra A, et al. Comparison of clinical characteristics and outcomes of patients with sepsis identified by the Sepsis-3 criteria by blood and urine culture results: a multicentre retrospective cohort study. *Health Sci Rep*. 2024;7:e2162. doi:10.1002/hsr2.2162