Proof Only

The Applicability of Commonly Used Severity of Illness Scores to Tropical Infections in Australia

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Abstract. Many patients with leptospirosis, melioidosis, and rickettsial infection require intensive care unit (ICU) admission in tropical Australia every year. The multi-organ dysfunction associated with these infections results in significantly elevated severity of illness (SOI) scores. However, the accuracy of these SOI scores in predicting death from these tropical infections is incompletely defined. This retrospective study was performed at Cairns Hospital, a tertiary-referral hospital in tropical Australia. All patients admitted to ICU with laboratory-confirmed leptospirosis, melioidosis, and rickettsial disease between January 1, 1999 and June 30, 2020, were eligible for the study. The ability of Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, Simplified Acute Physiology Scores (SAPS) II, and Sequential Organ Failure Assessment (SOFA) scores to predict death before ICU discharge was evaluated. Overall, 18 (12.1%) of the 149 included patients died: 15/74 (20.3%) with melioidosis, 2/54 (3.7%) with leptospirosis and 1/21 (4.8%) with rickettsial disease. However, the APACHE II, APACHE III, SAPS II, and SOFA scores significantly overestimated the case-fatality rate of all the infections; the disparity between the predicted and observed mortality was most marked in the cases of leptospirosis and rickettsial disease. Commonly used SOI scores significantly overestimate the case-fatality rate of melioidosis, leptospirosis, and rickettsial infections in Australian ICU patients. This may be at least partly explained by the unique pathophysiology of these infections, particularly leptospirosis and rickettsial disease. However, SOI scores may still be useful in facilitating the comparison of disease severity in clinical trials that examine patients with these pathogens.

INTRODUCTION

Sepsis causes approximately 20% of deaths globally and is more common in tropical low- and middle-income countries (LMIC).^{1–3} The incidence of sepsis in tropical Australia is also far greater than in the temperate regions of the country.^{4,5} Most presentations with sepsis in tropical Australia are due to pathogens—such as *Staphylococcus aureus* or *Escherichia coli*—that also cause disease in temperate settings.^{4,6} However, several classical tropical pathogens are also encountered. These include *Burkholderia pseudomallei* (which causes melioidosis), spirochetes of the genus *Leptospira* (which cause leptospirosis) and the rickettsiae *Orientia tsutsugamushi* and *Rickettsia australis* (which cause scrub typhus and Queensland tick typhus [QTT] respectively).^{4,7–9}

These tropical pathogens can lead to multi-organ involvement with concurrent—sometimes dramatic—derangement in clinical and laboratory indices.^{10–12} This results in significant elevation of the severity of illness (SOI) scores that are routinely calculated to estimate mortality risk in the critical care population.¹³ While SOI scores have no role in the management of individual patients, they permit quantitative assessment of an intensive care unit's (ICU) performance, allowing comparison between institutions. Severity of illness scores are also used in clinical trials to measure disease severity, facilitating comparison within and between cohorts, providing a benchmark to monitor the success of interventions.¹⁴

Globally, the most commonly used SOI scores are the Acute Physiology and Chronic Health Evaluation (APACHE) scores,^{15,16} the Sequential Organ Failure Assessment (SOFA) score,¹⁷ and the Simplified Acute Physiology Scores (SAPS).¹⁸ These SOI scores are neither organ nor disease

specific, but they are strong predictors of mortality in patients admitted to the ICU with sepsis.^{19–23} However, there are limited data about the predictive ability of SOI scores in patients with melioidosis, leptospirosis, and rickettsial diseases.^{24,25} This is important as the case-fatality rate of these pathogens can vary significantly in different parts of the world.³ It can be challenging to determine whether this is due to differences in patient demographics and comorbidities, to differences in the pathogens' virulence, or simply to disparities in access to optimal care.^{24,26} The routine use of SOI scores in studies of patients with these infections could standardize assessment of disease severity, enabling multi-center trials evaluating the efficacy of different management strategies of these important pathogens.

The region of Far Northern Queensland in tropical Australia has the highest incidence of leptospirosis in Australia and has a significant—and increasing—incidence of melioidosis and rickettsial disease.^{8,9,27} Given the local—and global—burden of life-threatening sepsis from these pathogens, this study was performed to determine the ability of commonly used SOI scores to predict death in patients with these infections.^{28–30} This might validate the use of these scores in the comparison of cohorts of patients affected by these pathogens in different parts of the world.

METHODS

This retrospective study was performed at Cairns Hospital, a 531-bed tertiary hospital located in Far North Queensland, tropical Australia. The hospital is the main referral center for a population of approximately 280,000 people who live across an area of 380,000 km², in the Northeastern tip of Australia.

Adults (≥18 years old) admitted to the Cairns ICU between January 1, 1999 and June 30, 2020, with a laboratory-

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confirmed diagnosis of melioidosis, leptospirosis, or rickettsial infection were included in the study. Patients were identified using the hospital's electronic pathology reporting system. A case of melioidosis was defined as a positive culture of *B. pseudomallei*. The Australian case definition for confirmed leptospirosis— isolation of pathogenic *Leptospira*, a 4-fold or greater rise in *Leptospira* agglutination titer between acute and convalescent phase sera or a single *Leptospira* micro agglutination titer ≥ 400 supported by a positive enzyme-linked immunosorbent assay IgM result—was used for cases of leptospirosis.³¹ Rickettsial infection was diagnosed if there was a clinical diagnosis of *O. tsutsugamushi* or *R. australis* infection accompanied by a positive polymerase chain reaction (PCR), a 4-fold rise in titers of paired serological samples (confirmed infection) or a single serological titer ≥ 128 with a clinically compatible syndrome (two or more of fever, rash, eschar, myalgia, or headache with no convincing alternative diagnosis) (probable infection).¹²

Demographic, clinical, and laboratory data were collected from electronic and paper medical records. The study's primary endpoint was death before ICU discharge. The APACHE II, APACHE III, SOFA, and SAPS II scores were calculated using the worst values in the first 24 hours of admission.^{15–18} The scores and associated risk of death was provided by the Australian New Zealand Intensive Care Society (ANZICS) database. Cases that occurred prior to the establishment of the ANZICS database were calculated manually using online calculators.^{32–34}

Severity of illness scores and case-fatality rates of other ICU-based studies of patients with melioidosis, leptospirosis, and rickettsial disease were collected for comparison. An electronic search was performed using MEDLINE® (1999–Present), PubMed (1999–Present), and Google Scholar. The search strategy included the terms “intensive care,” “disease severity score,” “severity of illness score” “prediction score,” the names of the individual scores, the diseases, and their etiological agents. The reference lists of the articles were also reviewed. Pediatric series, case series with < 20 patients and studies where the ICU status of the patients was incompletely defined were excluded.

To compare the performance of SOI scores in the melioidosis, leptospirosis, and rickettsial disease with their performance in patients with sepsis due to other infections, the APACHE III scores of other patients admitted to the Cairns Hospital ICU with a primary admission diagnosis of sepsis (APACHE III-J diagnostic codes 501–504: nonurinary sepsis, urinary sepsis, nonurinary sepsis with shock, and urinary sepsis with shock respectively) were also examined. The APACHE III scores of the patients with other causes of sepsis, their expected risk of death, and their observed case-fatality rate were provided by the ANZICS database.

STATISTICAL ANALYSIS

Data were de-identified, entered into an electronic database (Microsoft Excel), and analyzed using statistical software (Stata version 14.2). Groups were analyzed using the Kruskal–Wallis, the χ^2 tests, and Fisher's exact test, where appropriate. The scores' ability to predict death was determined by comparing the scores' predicted mortality—stratified into quartiles—with the observed case-fatality rate.

Ethics statement Ethics approval was provided by the Far North Queensland Human Research Ethics Committee (HREC/2020/QCH/64424–1442). As the data were retrospective and de-identified, the Committee waived the requirement for informed consent.

RESULTS

Patient characteristics. A total of 149 cases were identified: this included 74 (49.7%) cases of melioidosis, 54 (36.2%) cases of leptospirosis, and 21 (14.1%) cases of rickettsial disease (12 cases of scrub typhus and nine cases of QTT). The demographics of the patients, the ICU support they received, and their case-fatality rates are presented in Table 1.

Case-fatality rate of predictive ability of severity of illness scores. Overall, patients with melioidosis had a higher case-fatality rate (15/74 (20.3%) than those with leptospirosis (2/54 [3.7%], $P = 0.007$); the difference between the case-fatality rate of patients with melioidosis and those with rickettsial disease (1/21 [4.8%], $P = 0.11$) did not reach statistical significance. In the first 5 years of the study period, 5/8 (62.5%) patients with melioidosis died compared with 3/30 (10.0%) in the last 5 years ($P = 0.005$). The small number of fatal cases of leptospirosis and rickettsial disease during the study precluded analysis of the trend in the case-fatality rate of these infections over time (Figure 1).

However, regardless of the pathogen, all four SOI scores overestimated the patients' case-fatality rate (Table 2, Figures 2–5). The disparity between the predicted and the observed case-fatality rate was most marked in the patients with leptospirosis and rickettsial disease.

Comparison with other patients admitted to ICU with sepsis. The APACHE III scores of patients admitted to the ICU with melioidosis, leptospirosis, and rickettsial disease were compared with those of patients with sepsis due to other pathogens. The APACHE III scores also overestimated the case-fatality rates of patients admitted to the hospital's ICU with the other pathogens: the mean (95% CI) APACHE III score of these 2,092 patients was 75 (74–76). Their overall mean (95%) predicted case-fatality rate was 32 (31–24%) compared with the observed case-fatality rate of 301/2092 (14%). The degree to which the APACHE III score overestimated the case-fatality rate among these 2,092 patients with

TABLE 1
Selected demographics, supportive care, and outcomes of the cohort stratified by infection

	Number	Male n (%)	Age (mean [95% CI])	Mechanical ventilation, n (%)	RRT, n (%)	Vasopressor support, n (%)	Case-fatality rate, n (%)
Melioidosis	74	52 (70.3)	55 (52–58)	48 (64.9%)	23 (31.1%)	61 (82.4%)	15 (20.3%)
Leptospirosis	54	47 (87.0)	47 (42–52)	25 (46.3%)	19 (35.2%)	34 (63.0%)	2 (3.7%)
Rickettsial infection	21	11 (52.4)	51 (44–58)	10 (47.6%)	5 (23.8%)	13 (61.9%)	1 (5.3%)
Total	149	110 (73.8)	51 (49–54)	83 (55.7%)	46 (30.9%)	108 (72.5%)	18 (12.1%)

Association between severity of illness scores and outcome.

FIGURE 1. This figure appears in color at www.ajtmh.org.

sepsis—while similar to that seen in patients with melioidosis—was far greater degree in the cases of leptospirosis and rickettsial disease (Figure 6).

DISCUSSION

Commonly used SOI scores significantly overestimated the case-fatality rate of patients admitted to ICU with melioidosis, leptospirosis, and rickettsial disease at this center in

tropical Australia. This is likely to be at least partly linked to the distinctive pathophysiology of these infections—particularly leptospirosis and rickettsial disease—whose multi-organ involvement results in significant derangement of multiple parameters, inflating the scores, and exaggerating the risk of death. This adds to other limitations of SOI scores, whose performance tend to deteriorate over time.^{35,36} Furthermore, SOI scores perform best in the population in which the score was originally derived and as all

TABLE 2

Severity of illness scores' prediction of case-fatality rate compared with the observed case-fatality rate of patients admitted to Cairns Hospital ICU between 1999 and 2020

Disease	Observed case-fatality rate	Severity of illness score	Mean (95% CI) score	Mean (95% CI) predicted case-fatality rate (%)
Meliodosis	15/74 (20.2%)	APACHE II	22 (20–24)	44.8 (39.5–50.0)
		APACHE III	82 (75–90)	37.6 (31.4–43.7)
		SAPS2	43 (38–48)	34.5 (27.2–41.7)
		SOFA	9 (8–10)	36.0 (28.1–44.0)
Leptospirosis	2/54 (3.7%)	APACHE II	20 (17–23)	38.6 (31.0–46.3)
		APACHE III	76 (66–87)	33.7 (25.4–42.0)
		SAPS2	37 (30–43)	30.0 (20.9–39.3)
		SOFA	12 (10–14)	53.0 (43.4–62.6)
Rickettsial disease	1/21 (4.8%)	APACHE II	20 (16–23)	36.0 (26.8–45.1)
		APACHE III	79 (66–93)	33.9 (21.7–46.1)
		SAPS2	39 (31–48)	29.0 (16.3–41.6)
		SOFA	8 (6–10)	29.0 (15.3–42.7)

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; SAPS = Simplified Acute Physiology Scores; SOFA = Sequential Organ Failure Assessment.

four scores were derived in well-resourced referral ICUs in large cities in temperate regions, they are likely to be less applicable to patients in the ICUs in locations where melioidosis, leptospirosis, and rickettsial diseases are more commonly seen.^{15–18,25,37,38}

The design of the various SOI scores will tend to accentuate different physiological derangements. A patient's serum creatinine, their oxygen requirement, their bilirubin, and their platelet count, for example, are used to determine four of the SOFA score's six components.¹⁷ The systemic inflammatory response seen in leptospirosis particularly affects the microcirculation and in severe cases can lead to renal failure, respiratory failure, abnormal liver function tests, and thrombocytopenia; it may be unsurprising to see that the patients with leptospirosis in this cohort had the highest SOFA scores.^{9,39} However, this resulted in a significant overestimation of the case-fatality rate in the cohort, which the SOFA score predicted to be 53% (95% CI: 43–63%) compared with the observed figure of 3.7%. A similar pattern was observed in patients suffering from the rickettsial diseases of scrub typhus and QTT, conditions where endothelial infection and inflammation also commonly result in thrombocytopenia and hepatic and renal impairment.^{40,41} The SOFA scores of the patients with rickettsial disease predicted a case-fatality rate in the cohort of 29% (95% CI: 15–43%) compared with the observed figure of 4.8%.

The disparity between the predicted and observed case-fatality rate among patients with leptospirosis and rickettsial disease may be related to the tendency of cases with severe disease to involve multiple systems concurrently resulting in—sometimes dramatic—derangement in clinical and laboratory indices, as opposed to other causes of critical illness where fewer organ systems may be involved.⁴² Furthermore, although thrombocytopenia and derangement of liver function tests are common in cases of severe leptospirosis and rickettsial disease, neither have strong independent prognostic utility in either condition.^{43–46}

Although patients admitted to ICU with melioidosis also commonly have multi-organ involvement, their clinical presentation has a closer resemblance to the sepsis caused by more familiar bacterial pathogens.⁴⁷ Patients present most frequently with pneumonia, while 74% have septic shock.¹⁰ As the SOI scores were derived predominantly in North American and European referral centers—where pneumonia

FIGURE 2. This figure appears in color at www.ajtmh.org.

FIGURE 3. This figure appears in color at www.ajtmh.org.

and septic shock are a common cause of ICU admission—this may explain why there was less discrepancy between the SOI scores' predicted mortality in patients with melioidosis and their observed case-fatality rate.

The specific issues highlighted with using SOI scores in the patients with the tropical infections in this cohort, add to the scores' well-recognized general limitations. Severity of illness scores are almost universally derived and validated in general ICU patients in well-resourced, metropolitan referral centers in Europe and North America, their predictive ability has been shown to vary in different geographical regions.^{48,49} The scores' performance also differs in different patient populations. The APACHE II score, for instance,

FIGURE 4. This figure appears in color at www.ajtmh.org.

underestimated mortality in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),⁴² while overestimating mortality in obstetric patients.⁵⁰ Meanwhile, patients transferred from other hospitals have a case-fatality rate that is higher than predicted by the APACHE II score and this lead time bias may be seen in other SOI scores.³⁷ Finally, with improvements in critical care, the performance of SOI scores tends to deteriorate over time, the APACHE and SAPS scores have therefore been revised to improve their calibration and discrimination, although these newer iterations are more complex to calculate.^{51,52} This is relevant because a SOI score's ease of use is an important virtue, particularly in resource-limited settings where it can be challenging to collect many of the variables.^{25,36} It was notable that in this cohort the APACHE III score also overestimated

FIGURE 5. This figure appears in color at www.ajtmh.org.

the case-fatality rate of patients admitted to the Cairns Hospital ICU—which has a similar SMR to comparable ICUs in Australia—with more common causes of sepsis (Figure 6, Supplemental Figure 1).

However, while acknowledging these limitations and deficiencies, there may still be a role for SOI scores in stratifying disease severity in clinical trials of patients with melioidosis, leptospirosis, and rickettsial diseases. These pathogens have a global distribution and there is a marked geographic disparity in the case-fatality rate of each of the infections (Tables 3–5).^{28,29,76} For example, a cohort of patients with severe leptospirosis managed in well-resourced ICUs in France had a median (IQR) SAPS II score of 40 (28–58) and a case-fatality rate of 8.8%.⁵⁶ Meanwhile, a cohort of patients with severe leptospirosis managed in a single ICU on

FIGURE 6. This figure appears in color at www.ajtmh.org.

Réunion Island—which also had access to advanced supportive care including extracorporeal membrane oxygenation—had a median (IQR) SAPS II score of 38 (27–50) and a case-fatality rate of 5.9%.⁵⁵ In contrast, in a Moroccan cohort with lower SAPS II scores (24 ± 11.5), the case-fatality rate was greater at 23%.⁵⁸ The case-fatality rate was even higher in series from Brazil, India, and Sri Lanka, but SOI scores were not reported in most of these studies (Table 3).^{60–64,77} There is a similar geographic disparity in outcomes in cohorts of patients with melioidosis and rickettsial diseases in different jurisdictions (Tables 4 and 5). While these differences are almost certainly—at least partly—explained by access to optimal supportive care, which varies enormously between—

TABLE 3

Severity of illness scores and case-fatality rates of patients with leptospirosis, admitted to the ICU in other case series

Study	Study Period	Country	Setting	Cases	APACHE II	APACHE III	SAPS2	SOFA	ICU case-fatality Rate %
Cedano et al. ⁵³	2010–2016	Colombia	Single ICU	30	Not reported	Not reported	Not reported	Not reported	3.3%
Ajjimarungsri et al. ⁵⁴	2006–2016	Thailand	Single ICU	23	Not reported	Not reported	Not reported	10 (7–13)	4.3%
Delmas et al. ⁵⁵	2004–2015	Réunion Island	Single ICU	134	Not reported	Not reported	38 (27–50)	10 (8–12)	5.9%
Mialhe et al. ⁵⁶	2012–2016	France	Multiple ICU	160	Not reported	Not reported	40 (28–58)	11 (8–14)	8.8%
Tubiana et al. ⁵⁷	2008–2011	New Caledonia	Two Hospitals, Single ICU	71	Not reported	Not reported	Not reported	Not reported	14.1%
Abidi et al. ⁵⁸	2017	Morocco	Single ICU	100	12.5 (6.1 – 18.9)	Not reported	24 (12.5–35.5)	Not reported	23.0%
Vandroux et al. ⁵⁹	2004–2017	Réunion Island	Single ICU	39*	Not reported	Not reported	54 (42–70)	12 (10–17)	23.0%
De Francesco	2016	Brazil	Single ICU	83	Not reported	Not reported	Not reported	Not reported	23.5%
Daher et al. ⁶⁰	2002–2005	Brazil	Single ICU	33†	26 (24.8–27.2)‡	Not reported	Not reported	Not reported	39.4%
Weeratunga et al. ⁶²	2011–2014	Sri Lanka	Single ICU	45	24.5 (23.1–25.9)	Not reported	Not reported	Not reported	44.4%
Vieira and Brauner. ⁶³	1990–2000	Brazil	Two ICU	35	20.1 ± 4.2§	Not reported	Not reported	Not reported	51.4%
Chawla et al. ⁶⁴	2002–2003	India	Single ICU	31	Not reported	Not reported	Not reported	Not reported	51.7%
Marotto et al. ⁶⁵	1994–1997	Brazil	Single ICU	42	Not reported	Not reported	Not reported	Not reported	54.7%

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; SAPS = Simplified Acute Physiology Scores; SOFA = Sequential Organ Failure Assessment. Scores reported median (IQR) unless specified.

* Leptospirosis with ARDS.

† Comparison of renal replacement therapy regimens.

‡ Mean (standard error of mean).

§ Mean (standard deviation).

|| The scores of the entire cohort were not presented, but those with an APACHE II score > 18 had a case fatality rate of 85.7%.

and even within—the countries where these infections are seen, routine reporting of SOI scores would provide more evidence to support this contention.^{3,24,78}

Routine reporting of SOI scores—and their correlation with molecular characteristics of the pathogen—may also help determine the effect of geographic variation in the organisms' virulence on outcome. Phylogenetic analysis of melioidosis shows a clear distinction between Australian and South East Asian isolates and this may explain at least some of the difference in melioidosis-related mortality in the two continents.⁷⁹ Similarly, it has been postulated that differences in strains of *O. tsutsugamushi* contribute to the significant variation in clinical presentation of cases of scrub typhus.⁸⁰ Specific serogroups are not believed to explain the different clinical presentations of leptospirosis, although some studies have suggested that particular serovars are more likely to cause severe disease.^{9,81,82} While the pathogens' virulence is likely to have a relatively modest effect on

outcomes compared with access to optimal care, this issue remains incompletely defined.^{83,84}

The reporting of SOI scores may also assist with the evaluation of therapeutic interventions in different cohorts. With advances in critical care, the mortality from sepsis continues to fall and this is also the case with many tropical infections.² In a 24-year study of melioidosis in the Northern Territory of Australia, the case-fatality rate fell from 92.3% in 1989–1997 to 25.7% in 2005–2013, which was attributed to changes in management strategies which included an intensivist-led model of care and the empiric use of meropenem.¹⁰ The reporting of SOI scores in this Northern Territory study facilitated an understanding of the severity of the cohort's illness and, therefore, the implications for other ICU with a significant burden of melioidosis. In addition, while there is a significant global burden of melioidosis, leptospirosis, and rickettsial disease, most of the published literature to examine these conditions are single-center studies; randomized controlled trials

TABLE 4

Severity of illness scores and case-fatality rates of patients with melioidosis admitted to the ICU in other case series

Study	Study Period	Country	Setting	Cases	APACHE II	APACHE III	SAPS2	SOFA	ICU case-fatality Rate %
Stephens et al. ¹⁰	1989–2013	Australia	Single ICU	207	23 ± 8.7*	Not reported	Not reported	8 (5–11)	33.8%
Churuangsuk et al. ⁶⁶	2002–2011	Thailand	Single ICU	25	Not reported	Not reported	Not reported	Not reported	48%
Chan et al. ⁶⁷	1996–2002	Singapore	Multiple ICU	27	27 (9–47)	Not reported	Not reported	Not reported	48.1%
Tang et al. ⁶⁸	2013–2017	Malaysia	Single ICU	21	Not reported	Not reported	Not reported	Not reported	52.2%

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; SAPS = Simplified Acute Physiology Scores; SOFA = Sequential Organ Failure Assessment. Scores reported median (IQR) unless specified.

* Mean (standard deviation).

TABLE 5

Severity of illness scores and case-fatality rates of patients with rickettsial infection admitted to the ICU in other case series

Study	Study Period	Country	Setting	Cases	APACHE II	APACHE III	SAPS2	SOFA	ICU Case-fatality Rate %
Sahoo et al. ⁶⁹	2013–2014	India	Single ICU	55	13.03 ± 6.46	Not reported	Not reported	6.64 ± 3.72	7.3%
Moon et al. ⁷⁰	2004–2014	South Korea	Single ICU	70	14.9 ± 4.8	Not reported	Not reported	6 ± 2.7	14.3%
Adhikari et al. ⁷¹	2016–2017	Nepal	Single ICU	120	Not reported	Not reported	Not reported	Not reported	20.0%
Griffith et al. ⁷²	2008–2010	India	Single ICU	116	19.6 ± 8.2	Not reported	Not reported	10.5 ± 3.9	24.1%
Lee et al. ⁷³	2000–2006	South Korea	Single ICU	33*	16.9 ± 6.2	Not reported	Not reported	Not reported	30.3%
					8.3 ± 4.8				
Lee et al. ⁷⁴	2001–2006	South Korea	Single ICU	23†	11.37 ± 5.1	Not reported	Not reported	Not reported	39.1%
					6.94 ± 4.2				
Moon et al. ⁷⁵	2004–2016	South Korea	Single ICU	91	15.4 ± 6.1	Not reported	Not reported	6.1 ± 3.1	Not reported

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; SAPS = Simplified Acute Physiology Scores; SOFA = Sequential Organ Failure Assessment. Scores reported as mean (standard deviation).

* Non-survivors and non-survivors.

† Hypoalbuminemic and non-hypoalbuminemic patients.

are rare. This results in poorly powered, often retrospective studies whose conclusions are necessarily speculative.^{11,55} The use of SOI scores that stratify disease severity may help standardize recruitment of patients in multi-center trials that assess interventions more robustly.

This retrospective, single-center study has several important limitations. A relatively long, 22-year study period was used, but the sample size was small, limiting the study's power. The study only reflects clinical management strategies used at this center which evolved significantly over the study period.^{11,12} There were only 21 cases with rickettsial disease, and this group included patients with both scrub typhus and QTT, conditions caused by different pathogens. Some rickettsiologists may take issue with this approach. However, the infections have similar pathogenesis, presentation, and treatment and hence, from a pragmatic, clinical perspective we felt that it was reasonable to consider them together, although the findings may not be applicable to other rickettsial diseases.^{8,30} A minority of the patients with rickettsial disease had a diagnosis confirmed by PCR or a 4-fold rise in serology; most (8/21, 62%) were diagnosed with a single serological titer. However, patients were only included in the study if they satisfied pre-specified, conservative criteria, similar to those used in the international literature.^{85–87} The hospital's ICU was expanded in 2016 to admit high dependency patients, which may have reduced the case-fatality rate seen in the cohort. However, as the SOI scores of these high dependency patients would tend to be lower as well, this would therefore not change the study's main finding. It could be argued that the study should have examined more contemporary scoring systems—such as the APACHE IV—which predicts mortality more accurately than the APACHE III.⁵³ However, this score is not used in Australia and, as it uses 129 variables, it is unlikely to be calculated in the locations where melioidosis, leptospirosis, and rickettsial disease are seen most frequently.²⁶ Finally, the scores were evaluated in Australia's well-resourced public health system and may not overestimate mortality to the same degree in less-resourced LMIC ICUs. However, this study provides a useful reference for researchers examining melioidosis, leptospirosis, and rickettsial disease in other locations and wishing to relate the outcomes seen in their cohorts to disease severity.²⁵ As Tables 3–5 demonstrate the reporting of SOI scores in studies examining these pathogens is inconsistent, hindering understanding of geographical differences in the outcomes.

CONCLUSION

Commonly used SOI scores overestimated the case-fatality rate of patients admitted to this Australian ICU with melioidosis, leptospirosis, and rickettsial disease. This may be at least partly explained by the distinctive pathophysiology of these infections, which inflates the scores, exaggerating the risk of death. However, there may still be utility in reporting SOI scores in clinical studies of these infections as comparison between cohorts may facilitate understanding of the relative contributions of host, pathogen, and access to care in the outcome of these globally important pathogens.

Received June 2, 2021. Accepted for publication August 31, 2021.

Published online October 18, 2021.

Note: Supplemental figure appears at www.ajtmh.org.

Acknowledgments: We would like to acknowledge all the clinicians involved in the care of the patients in this study and the support of the Australian New Zealand Intensive Care Society (ANZICS) who provided much of the raw data for the study.

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