


BMJ Open Clinical and economic impact of intensive care unit-acquired bloodstream infections in Taiwan: a nationwide population-based retrospective cohort study

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ABSTRACT

Objectives To estimate the clinical and economic impact of intensive care unit-acquired bloodstream infections in Taiwan.

Design Retrospective cohort study.

Setting Nationwide Taiwanese population in the National Health Insurance Research Database and the Taiwan Nosocomial Infections Surveillance (2007–2015) dataset.

Participants The first episodes of intensive care unit-acquired bloodstream infections in patients ≥ 20 years of age in the datasets. Propensity score-matching (1:2) of demographic data, comorbidities and disease severity was performed to select a comparison cohort from a pool of intensive care unit patients without intensive care unit-acquired infections from the same datasets.

Primary and secondary outcome measures The mortality rate, length of hospitalisation and healthcare cost.

Results After matching, the in-hospital mortality of 14 234 patients with intensive care unit-acquired bloodstream infections was 44.23%, compared with 33.48% for 28 468 intensive care unit patients without infections. The 14-day mortality rate was also higher in the bloodstream infections cohort (4323, 30.37% vs 6766 deaths, 23.77%, respectively; $p < 0.001$). Furthermore, the patients with intensive care unit-acquired bloodstream infections had a prolonged length of hospitalisation after their index date (18 days (IQR 7–39) vs 10 days (IQR 4–21), respectively; $p < 0.001$) and a higher healthcare cost (US\$16 038 (IQR 9667–25 946) vs US\$10 372 (IQR 6289–16 932), respectively; $p < 0.001$). The excessive hospital stay and healthcare cost per case were 12.69 days and US\$7669, respectively. Similar results were observed in subgroup analyses of various WHO's priority pathogens and *Candida* spp.

Conclusions Intensive care unit-acquired bloodstream infections in critically ill patients were associated with increased mortality, longer hospital stays and higher healthcare costs.

INTRODUCTION

Critically ill patients in intensive care units (ICUs) are vulnerable to various infections,

Strengths and limitations of this study

- A large number of patients obtained from Nationwide Taiwanese population from two datasets in Taiwan were included.
- Propensity score-matching was performed to select a comparison cohort.
- The mortality rate, length of hospitalisation and healthcare cost were analysed.
- Subgroup analyses of several drug-resistant pathogens were conducted.
- The retrospective design may include some unmeasurable bias.

and these can lead to increased morbidity, mortality and healthcare costs. Bloodstream infections (BSIs) are one of the most common infections acquired by ICU patients. It was reported that BSIs affected approximately 7% of patients admitted to ICUs.¹ Previous studies have shown that ICU-acquired BSIs resulted in attributable mortality of 24.8%,² extended hospital stays by 13.5 days³ and the cost of treatment was approximately US\$12 321 per case. Moreover, despite advances in medical care and the development of new therapies, the outcome of BSIs in critically ill patients is adversely affected by a greater number of vulnerable hosts and the emergence of drug-resistant pathogens.

Discrepancies regarding the impact of pathogens on mortality have been reported. However, worse clinical outcome and higher economic burden have been reported for patients with BSI caused by resistant pathogens.^{1 4} For example, BSIs involving third-generation cephalosporin-resistant Enterobacteriaceae have been shown to significantly increase mortality risk compared with BSIs involving susceptible strains.⁴

Moreover, candidemia has been associated with a four-fold increase in mortality, while *Staphylococcus aureus* BSIs doubled the risk of mortality.¹ Meanwhile, the clinical impact of enterococci remains a controversial topic.⁵⁻⁷ Therefore, it is important not only to describe the clinical and economic impact of infections, but also to decipher the impact of individual pathogens. Due to the limited number of cases and the complex clinical characteristics of critically ill patients, previous studies have reported either clinical or economic outcomes, have focused on several species of pathogens or have assessed only a limited number of pathogens. In the present study, a health insurance database and a nationwide surveillance system for healthcare-associated infections were used to estimate the clinical and economic consequences of ICU-acquired BSIs caused by different pathogens in a large number of patients in Taiwan. In addition, the impact of individual pathogens, especially antibiotic-resistant bacteria on the WHO priority list,⁸ were investigated.

METHODS

Data sources

Two datasets, the National Health Insurance Research Database (NHIRD) and the Taiwan Nosocomial Infection Surveillance (TNIS) dataset, were used in this study. Demographic data, diagnoses (according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)), procedures and medications for patients enrolled in Taiwan's national insurance system have been collected in the NHIRD since 1995.⁹ In 2007, the TNIS was launched by the Taiwan Centers for Disease Control to evaluate the epidemiologic trend of healthcare-associated infections in the ICUs in Taiwan. The latter is a web-based surveillance system which collects clinical information of patients with healthcare-associated infections from the ICUs of participating hospitals. This information includes demographic data, infection foci, causative pathogens and antimicrobial susceptibility results. Participation in TNIS is essential for hospital accreditation in Taiwan.

Both datasets were deposited in a database maintained by the Health and Welfare Data Science Center, Ministry of Health and Welfare. Individual personal identification numbers were encrypted so that data from the NHIRD and TNIS datasets could be interlinked.

Study population, data collection and propensity-score matching

This retrospective cohort study enrolled adult patients who underwent ICU hospitalisation between 2007 and 2015 in Taiwan. From the entries in the TNIS database, we identified all of the patients whose first episode of an ICU-acquired BSI occurred during the study period. Coagulase-negative staphylococci are often identified in the ICUs but a certain proportion is associated with contamination; therefore, these cases were not included in our analysis. We included species that constituted >1%

of known bloodstream pathogens (online supplemental table 1), which constituted 79.4% of all ICU-acquired BSI episodes. The index date for each case was defined as the date on which a positive blood culture result was obtained. The encrypted personal identification numbers of included patients were interlinked with NHIRD to retrieve their demographic data, comorbidities, procedures and medications.

For comparison, we identified ICU patients who did not have ICU-acquired infections registered in TNIS database. In addition, patients with a discharge diagnosis of sepsis (ICD-9-CM: 038.X, 995.91), severe sepsis (ICD-9-CM: 995.92) or septic shock (ICD-9-CM: 785.52) in the comparison cohort, but not in the BSI group, were also excluded. The pool of comparison patients was created for the selection of those with the same admission date as any patient with ICU-acquired BSI. Because the comparison patients did not have index date of acquisition of infection, they were assigned 'pseudo-index dates' during hospitalisation, which was selected from the index date of patients with the same day of hospitalisation in the BSI group. Baseline variables and those associated with ICU-acquired BSIs were first selected. Propensity scores were then calculated for the likelihood of ICU-acquired BSIs by multivariate logistic regression analysis. Variables were removed from the multivariable model in a stepwise fashion. We used 1:2 greedy matching¹⁰ within a calliper width equal to 0.1 of the SD of the logit of the propensity score (online supplemental table 2). Patient data from January 2005 were used to ensure that individuals were followed for at least 2 years prior to their selection for this study in order to confirm comorbidities¹¹ and for matching purposes. The determination of comorbidities and organ dysfunction by ICD-9-CM codes were in accordance with the previous studies.¹¹⁻¹³ The variables with missing values included monthly income and urbanisation level. Missing values were treated as a separate category by itself. The low rate of missing data (table 1) may not have a great impact on our study.

Patient and public involvement

Patients and the public were not directly involved in the planning of this study.

Outcome measurements

Clinical outcomes included in-hospital, 14-day and 28-day mortality rate after the index date/pseudo-index date. Economic outcomes included hospitalisation length after the index date/pseudo-index date and cost of overall hospitalisation. Hospitalisation length was defined as the duration of hospital stay after the index date/pseudo-index date. The overall cost of hospitalisation was calculated. The costs were standardised and presented in values from 2017.

Subgroup analysis

To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different pathogens, we

Table 1 Characteristics of the intensive care unit patients with bloodstream infections and the matched comparison cohort

Characteristics	Patients with BSI	Comparison cohort	Standardised difference
No of patients	14 234	28 468	
Year of index date			
2007	1244 (8.74%)	3474 (12.2%)	0.113
2008	1608 (11.3%)	3101 (10.89%)	0.013
2009	1714 (12.04%)	2923 (10.27%)	0.056
2010	1745 (12.26%)	3119 (10.96%)	0.041
2011	1947 (13.68%)	3107 (10.91%)	0.084
2012	1727 (12.13%)	3119 (10.96%)	0.037
2013	1496 (10.51%)	2985 (10.49%)	0.001
2014	1371 (9.63%)	3226 (11.33%)	0.056
2015	1382 (9.71%)	3414 (11.99%)	0.073
Season of in-date			
Mar–May	3564 (25.04%)	7207 (25.32%)	0.006
Jun–Aug	3577 (25.13%)	7224 (25.38%)	0.006
Sep–Nov	3519 (24.72%)	6964 (24.46%)	0.006
Dec–Feb	3574 (25.11%)	7073 (24.85%)	0.006
Males	8971 (63.03%)	17 861 (62.74%)	0.006
Age, years, mean (SD)	65.12 (21.62)	65.08 (20.60)	0.002
Length of stay before index date/pseudo-index date, days, mean (SD)	15.69 (12.14)	15.29 (11.96)	0.033
Monthly income, US\$			
Dependent	2416 (16.97%)	4813 (16.91%)	0.002
<657.33	4740 (33.3%)	9575 (33.63%)	0.007
657.33–1504.60	6324 (44.43%)	12 563 (44.13%)	0.006
>1504.60	740 (5.2%)	1484 (5.21%)	0.001
Unknown	14 (0.1%)	33 (0.12%)	0.005
Urbanisation level			
1 (urban)	3639 (25.57%)	7293 (25.62%)	0.001
2	3968 (27.88%)	7920 (27.82%)	0.001
3	2227 (15.65%)	4432 (15.57%)	0.002
4 (rural)	4389 (30.83%)	8802 (30.92%)	0.002
Unknown	11 (0.08%)	21 (0.07%)	0.001
Hospital level			
Medical centre	7168 (50.36%)	14 393 (50.56%)	0.004
Regional hospital	6125 (43.03%)	12 242 (43%)	0.001
Local hospital	940 (6.6%)	1833 (6.44%)	0.007
Charlson Comorbidity Index Score, mean (SD)			
0	2950 (20.73%)	6411 (22.52%)	0.044
1	1930 (13.56%)	3928 (13.8%)	0.007
2	2283 (16.04%)	4251 (14.93%)	0.031
≥3	7071 (49.68%)	13 878 (48.75%)	0.019
Comorbidities			
Diabetes mellitus	4840 (34%)	9642 (33.87%)	0.003
Cerebrovascular disease	3552 (24.95%)	7048 (24.76%)	0.005

Continued

Table 1 Continued

Characteristics	Patients with BSI	Comparison cohort	Standardised difference
Myocardial infarction	525 (3.69%)	1124 (3.95%)	0.014
Heart failure	2532 (17.79%)	5173 (18.17%)	0.01
Peripheral vascular disease	742 (5.21%)	1509 (5.3%)	0.004
Liver disease	2740 (19.25%)	5393 (18.94%)	0.008
Chronic kidney disease	3864 (27.15%)	7982 (28.04%)	0.02
Dyslipidaemia	2766 (19.43%)	5683 (19.96%)	0.013
Cancer	2753 (19.34%)	5635 (19.79%)	0.011
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4035 (28.35%)	8549 (30.03%)	0.037
1	6445 (45.28%)	12293 (43.18%)	0.042
2	3273 (22.99%)	6243 (21.93%)	0.026
≥3	481 (3.38%)	1383 (4.86%)	0.074
Use of inotropic agents	11 398 (80.08%)	22 858 (80.29%)	0.005
Use of steroid	9 (0.06%)	20 (0.07%)	0.003
Use of ventilator	12 493 (87.77%)	25 075 (88.08%)	0.01
Use of ventilator (>3 days)	11 668 (81.97%)	23 458 (82.4%)	0.011
Emergent renal replacement therapy	2615 (18.37%)	5370 (18.86%)	0.013
Propensity Score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

BSI, bloodstream infection.

performed analyses on patients infected with single pathogen. For example, the impact of WHO priority bacteria and *Candida* were examined separately, as was the impact of drug resistance in these bacteria. We included patients whose first episode of an ICU-acquired BSI were caused by bacteria on the WHO priority list or *Candida*. Therefore, the clinical and economic outcomes of patients with *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, common Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, and *Serratia marcescens*), *S. aureus*, *Enterococcus* species, *Candida albicans* and non-*albicans* *Candida* (*Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata*) were determined.

The definition of multiple drug resistance (MDR) of WHO priority bacteria according to the European Centre for Disease Prevention and Control was modified¹⁴ (online supplemental table 3). In this study, non-susceptibility to at least one agent in at least three antimicrobial categories in Gram-negative bacteria was defined as MDR. Oxacillin-non-susceptible and vancomycin-non-susceptible *S. aureus* and vancomycin-non-susceptible *Enterococcus* species were considered MDR Gram-positive bacteria.

Sensitivity analysis

To avoid competing risk between mortality and length of hospitalisation/healthcare cost, we included patients who survived to discharge. For these patients, the length of hospitalisation after the index date/pseudo-index date and hospitalisation costs were determined.

Statistical analysis

Descriptive statistics were used to examine baseline demographic and clinical characteristics of the ICU patients included in this study. To account for potential confounding biases among the study cohort, propensity score matching analysis was performed. Propensity scores were calculated with multivariate logistic regression. Standardised differences between the two groups with differences less than 0.1 were confirmed in order to assess baseline characteristics. The Mann-Whitney U test was used to evaluate economic outcomes and the χ^2 test was used to evaluate mortality rate. Conditional logistic regression was used to calculate ORs to evaluate risk of mortality in patients with BSI and the comparison cohort, while a generalised linear model was used to calculate β values to estimate excess costs and length of hospitalisation. Variables with a p value < 0.05 were eligible for inclusion in the model. P values less than 0.05 were considered statistically significant. All analyses were performed by using SAS statistical software (V.9.4, SAS Institute).

RESULTS

Among 38 659 episodes of ICU-acquired BSIs registered in TNIS during the 9-year study period, 28 495 patients were identified to have their first episode of a BSI. The NHIRD included 1 638 796 patients who underwent ICU hospitalisation (figure 1). After excluding patients whose

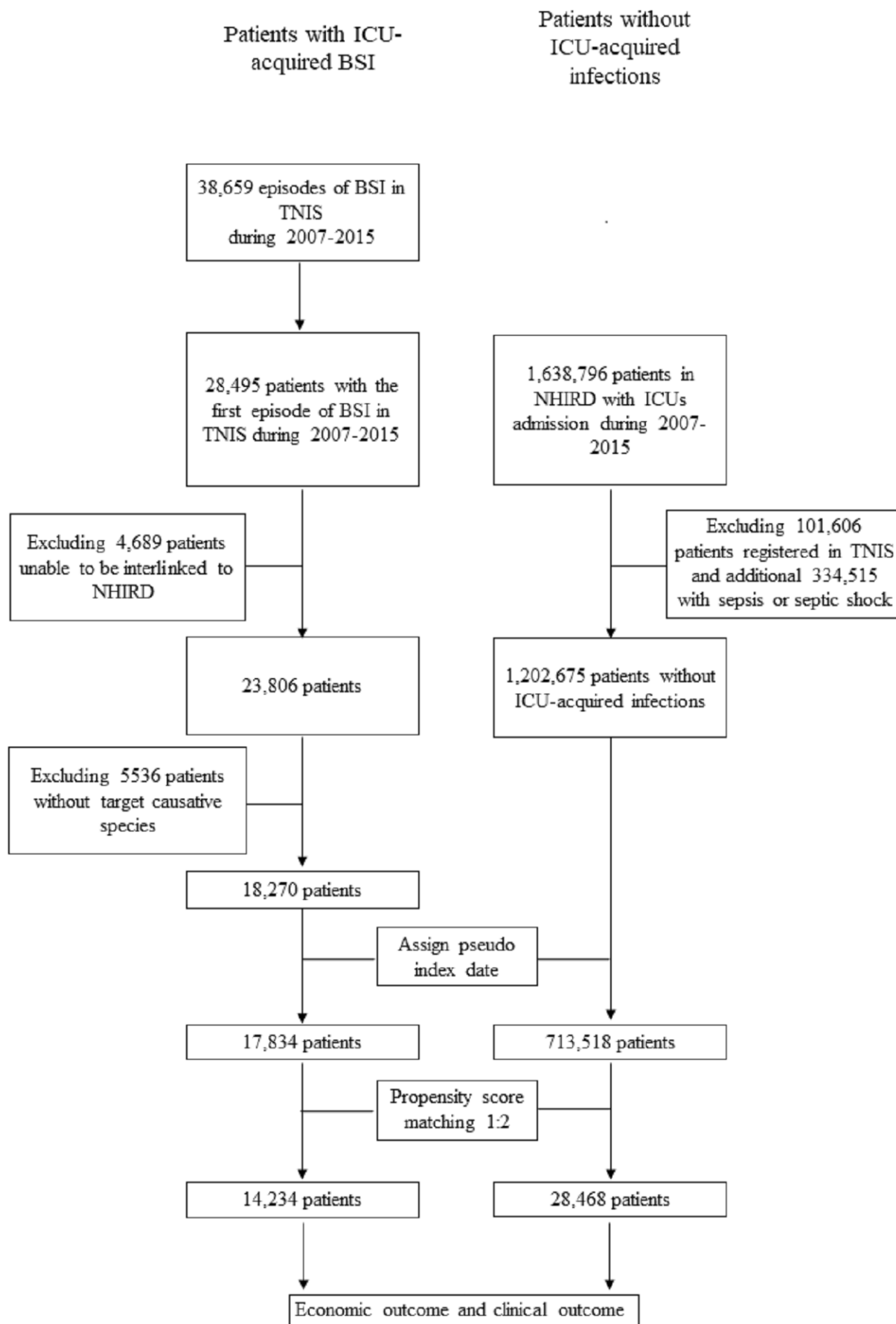


Figure 1 Flow diagram of the study design. BSI, bloodstream infection; ICU intensive care unit; NHIRD, National Health Insurance Research Database; TNIS, Taiwan Nosocomial Infections Surveillance.

Table 2 Clinical and economic outcomes among patients with bloodstream infections and the matched comparison cohort

Outcomes	Full cohort			Matched cohort		
	ICU patients with BSI	Comparison cohort	P value	ICU patients with BSI	Comparison cohort	P value
No of patients	17 834	713 518		14 234	28 468	
Clinical outcomes						
In-hospital mortality, n (%)	8639 (48.44)	65 282 (9.15)	<0.0001	6295 (44.23)	9532 (33.48)	<0.0001
14-day mortality, n (%)	5693 (31.92)	54 998 (7.71)	<0.0001	4323 (30.37)	6766 (23.77)	<0.0001
28-day mortality, n (%)	7469 (41.88)	73 552 (10.31)	<0.0001	5619 (39.48)	9189 (32.28)	<0.0001
Economic outcomes						
Length of hospitalisation after the index date/pseudo-index date, median (IQR)	18 (6–40)	6 (3–13)	<0.0001	18 (7–39)	10 (4–21)	<0.0001
Cost of hospitalisation (US\$)*, median (IQR)	18 457 (10 938–30 778)	4971 (2770–8598)	<0.0001	16 038 (9667–25 946)	10 372 (6289–16 932)	<0.0001

*The costs are standardised and presented as the values in 2017. BSI, bloodstream infection; ICU, intensive care unit.

data could not be interlinked with NHIRD or who did not have target pathogens, 14 234 patients with ICU-acquired BSIs were successfully matched to 28 468 ICU patients without ICU-acquired infections (1:2). The demographic and clinical characteristics of the patients with BSI and comparison cohort are presented in table 1. The groups had standardised differences that were <10% for all of the continuous and dichotomous categorical variables which were examined.

Table 2 lists the clinical and economic outcomes of the ICU patients with BSIs and the comparison cohort. The ICU patients with BSIs suffered a higher in-hospital mortality rate (44.23% vs 33.48%, respectively; $p<0.001$), a higher 14-day mortality rate (30.37% vs 23.77%, respectively; $p<0.001$) and a higher 28-day mortality (39.48% vs 32.28%, respectively; $p<0.001$). Logistic regression analyses showed that the OR of in-hospital mortality for the ICU patients with BSIs was 1.67 (95% CI, 1.59–1.75;

$p<0.001$), and it was 1.42 (95% CI, 1.35–1.49; $p<0.001$) for 14-day mortality and 1.41 (95% CI, 1.34–1.47; $p<0.001$) for 28-day mortality. These significant associations were also observed in the subgroup analyses performed (table 3).

The ICU patients with BSIs had a longer length of hospitalisation after the index date (18 days vs 10 days, respectively; $p<0.001$). Moreover, on average, their hospital stay was extended by 12.69 days (95% CI, 11.92–13.47; $p<0.001$). The subgroup analyses performed (table 4) showed that all of the causative pathogens shared a similar trend. Compared with the patients without ICU-acquired infections, the duration of hospitalisation after the index date for those with BSIs caused by MDR bacteria, WHO priority bacteria or *Candida* spp. was longer. In addition, hospitalisation costs of the ICU patients with BSIs were higher (16 038 vs 10 372, respectively; $p<0.001$) (table 2), with the excess cost being US\$7669 per patient (95% CI, 7380–7958; $p<0.001$).

Table 3 Clinical outcomes for the various pathogen groups

Pathogen groups (no of patients)	Odds ratio (95% CI)		
	In-hospital mortality	14-day mortality	28-day mortality
MDR Gram-negative bacteria (2232)	2.12 (1.89–2.38)	1.77 (1.57–1.99)	1.79 (1.6–2)
MDR Gram-positive bacteria (1429)	1.84 (1.59–2.12)	1.52 (1.31–1.76)	1.5 (1.3–1.72)
<i>Acinetobacter baumannii</i> (1761)	1.67 (1.47–1.91)	1.45 (1.26–1.66)	1.45 (1.27–1.66)
<i>Pseudomonas aeruginosa</i> (853)	1.69 (1.41–2.03)	1.73 (1.42–2.1)	1.47 (1.23–1.77)
Enterobacteriaceae* (3548)	1.59 (1.45–1.75)	1.28 (1.16–1.41)	1.31 (1.19–1.43)
<i>Staphylococcus aureus</i> (1721)	1.63 (1.42–1.87)	1.24 (1.07–1.44)	1.31 (1.15–1.51)
<i>Enterococcus</i> species† (1277)	1.87 (1.6–2.18)	1.69 (1.44–1.99)	1.6 (1.37–1.85)
<i>Candida albicans</i> (951)	2.04 (1.71–2.43)	1.61 (1.35–1.91)	1.68 (1.42–1.98)
Non- <i>albicans Candida</i> ‡ (703)	1.97 (1.61–2.41)	1.58 (1.29–1.95)	1.61 (1.32–1.95)

*Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes* and *Serratia marcescens*.

†*Enterococcus* species included *Enterococcus faecium*, *Enterococcus faecalis* and other *Enterococcus* species.

‡Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata*.

§Only patients with bloodstream infections involving a single pathogen were included in this analysis. MDR, multiple drug resistance.

Table 4 Economic outcomes for the various pathogen groups

Pathogen groups	Excess costs or length of hospitalisation (95% CI)	
	Length of hospitalisation after the index date (days)	Cost of hospitalisation (US\$)
MDR Gram-negative bacteria	10.41 (8.55–12.27)	7563 (6725–8401)
MDR Gram-positive bacteria	13.82 (11.38–16.27)	6342 (5500–7184)
<i>Acinetobacter baumannii</i>	9.4 (7.65–11.14)	6727 (5823–7632)
<i>Pseudomonas aeruginosa</i>	10.01 (7.83–12.19)	6761 (5609–7913)
Enterobacteriaceae*	15.05 (13.33–16.76)	7444 (6881–8007)
<i>Staphylococcus aureus</i>	14.72 (12.63–16.81)	5211 (4528–5894)
<i>Enterococcus</i> species†	10.66 (7.85–13.48)	7219 (6305–8132)
<i>Candida albicans</i>	11.37 (8.82–13.92)	8688 (7512–9864)
Non- <i>albicans Candida</i> ‡	15.13 (11.77–18.49)	11 476 (10 025–12 927)

*Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes* and *Serratia marcescens*.

†*Enterococcus* species included *Enterococcus faecium*, *Enterococcus faecalis* and other *Enterococcus* species.

‡Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata*.

§Only patients with bloodstream infections involving a single pathogen were included in this analysis.

MDR, multiple drug resistance.

Table 4 presents the higher costs associated with each of the various causative pathogens.

For the ICU patients with BSIs who survived to discharge, their length of hospitalisation and healthcare costs were increased by 19.59 days and US\$8871, respectively (online supplemental table 4) compared with the survivors without ICU-acquired infections.

DISCUSSION

This study demonstrated that ICU patients with BSIs in Taiwan had significantly worse clinical outcomes and higher economic burden than ICU patients without ICU-acquired infections from the same population. For example, the patients with BSI exhibited 1.67-fold, 1.42-fold and 1.41-fold increases in in-hospital, 14-day and 28-day mortality rates, respectively. Per case, the patients with BSI had an excess hospital stay of 12.69 days and cost of US\$7669. Furthermore, a similar clinical and economic impact was observed among all of the causative pathogens examined.

BSIs have been associated with higher mortality and morbidity, contingent on the causative pathogen involved.^{1 3 15–18} For example, worse clinical outcomes have been reported for patients with BSIs caused by *A. baumannii*,^{18 19} *P. aeruginosa*,^{17 18} *S. aureus*,^{1 4 17 18} Enterobacteriaceae^{4 18} and *Candida* spp.^{1 18 20} In contrast, controversial results have been obtained regarding the mortality of patients affected by enterococcal bacteremia. While some authors have argued that *Enterococcus* spp. represents a low virulence pathogen¹ and is not associated with increased mortality unless in the presence of endocarditis,²¹ other authors have reported contrasting results.^{5 6 18 20} In the present study, significantly higher mortality was observed for patients with enterococcal bacteremia, and this may

be due to vulnerability of the hosts examined, increased resistance and a larger study population.

The high healthcare burden of BSIs reported in previous literature^{3 15 22} and in the present study underscores the importance of preventing ICU-acquired BSIs by infection control measurements. Furthermore, the results of these studies help to assess cost effectiveness of infection control measurements in the process of policy-making. For example, patients with ICU-acquired BSIs during the 9-year period cost Taiwan an estimated US\$297 million and 492 129 days (online supplemental table 5). A policy that reduced the rate of infection by 10%²³ would translate into a savings of US\$30 million and 49 213 patient-days saved.

Drug resistance has been found to be correlated with higher medical costs due to the need for second-line antimicrobials for treatment, as well as additional diagnostic and treatment tools.^{24 25} In the present study, the costs for MDR bacteria included extra US\$84 million and 1 40 043 days over 9 years (online supplemental table 5). However, cost differences between susceptible and resistant strains were not determined in the present study. Drug-susceptible strains were not included as controls due to differences in testing methods, drugs and breakpoints for these strains which could lead to mis-assignments of drug-resistant pathogens as susceptible pathogens.

Candidemia poses a great threat to ICU patients due to its excessive medical burdens,^{18 20 22} and *C. albicans* is the most common pathogen. However, in some countries, the prevalence of non-*albicans Candida* exceeds that of *C. albicans*.²⁶ For those infected with non-*albicans Candida*, higher rates of mortality,^{26 27} longer hospitalisation stays and increased hospital costs have been described^{27–29}; although other studies have reported contradicting findings.^{30 31} These discrepancies may



be due to host factors and differences in the virulence and resistance patterns²⁶ of non-*albicans* *Candida*. In the present study, the crude 14-day and in-hospital mortality rates of 951 patients infected with *C. albicans* were 37.96% and 55.94%, respectively. In comparison, among 703 patients infected with non-*albicans* *Candida*, these rates were 34.99% and 53.06%, respectively. While the hospital costs and length of stay were higher in the non-*albicans* *Candida* group compared with the *C. albicans* group, the 95% CI overlapped for the two groups (table 4). These data suggested that the clinical and economic outcomes of these two groups did not greatly differ. However, the present study was not designed to specifically compare the outcomes of those infected with *C. albicans* versus non-*albicans* *Candida*. Therefore, additional studies with a larger number of patients, adjustment for host factors and consideration of antifungal drugs, incubation time and treatment duration are needed to clarify the impact of each *Candida* species.

The large number of patients examined in this study and the use of propensity score matching represent two major strengths of the present study. These aspects also allowed the impact of each pathogen group to be discerned. However, there were also several limitations associated with the present study which merit discussion. First, the exact cost after the index date could not be retrieved from the NHIRD. Therefore, the high total cost shown in this study may be due to costs incurred prior to the onset of a BSI. It is possible that matching of the duration before the index date and comorbidity may have reduced overestimations of healthcare costs due to time-dependent bias.³² Second, confounding factors associated with clinical impact, such as Acute Physiology and Chronic Health Evaluation II (APACHE II) or Pitt Bacteremia scores, were not included in this study. Instead, other clinical risk factors (Charlson Comorbidity Index Score, number of organ failures, use of inotropic agents and receipt of invasive procedures) were incorporated in our model. Third, our study is inherently limited by its retrospective design, which includes a dependence on the accuracy of the ICD codes used and unmeasurable bias.^{33 34} Fourth, the prolonged hospitalisation may have been due to a change in patient management in response to a BSI, rather than increased morbidity due to a BSI.¹⁷ Fifth, the number of participating hospitals varied during study period and therefore was considered in propensity score matching. Finally, the collection of personal identification numbers is not mandatory in TNIS, which resulted in failure of interlink. However, their impact on the outcome was unknown. In addition, the administrative data are inherently subjected to coding errors and changes in coding practices.³⁴

CONCLUSIONS

ICU-acquired BSIs have a negative clinical and economic impact on affected patients regardless of the causative pathogens involved. Awareness of these negative affects

is important for promoting infection control measurements and for policy-making.

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