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Article category: Original research

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 14-day mortality rate, length of hospitalization, and healthcare cost.

Results: After matching, the in-hospital mortality of 14,369 patients with intensive care unit-acquired bloodstream infections was 44.38%, compared to 33.50% for 28,738 intensive care unit patients without bloodstream infections. The 14-day mortality rate was also higher in the bloodstream infections cohort (4,367, 30.39% *vs.* 6,860 deaths, 23.87%, respectively; $p < 0.001$). Furthermore, the patients with intensive care unit-acquired bloodstream infections had a prolonged length of hospitalization after their index date (18 [IQR 7–39] *vs.* 10 days

[IQR 4–21], respectively; $p < 0.001$) and a higher healthcare cost (16,086 [IQR 9,706–26,131] *vs.* 10,731 US dollars [IQR 6,375–16,910], respectively; $p < 0.001$). The excessive hospital stay and healthcare cost per case were 12.77 days and 7,646 US dollars, respectively. Similar results were observed in subgroup analyses of various World Health Organization'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.

Keywords: bloodstream infection; healthcare costs; hospital stay; intensive care unit; mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. A large number of patients obtained from Nationwide Taiwanese population from two datasets in Taiwan were included.
2. Propensity score-matching was performed to select a comparison cohort.
3. The 14-day mortality rate, length of hospitalization, and healthcare cost were analyzed.
4. Subgroup analyses of several drug-resistant pathogens were conducted.
5. The retrospective design may include some unmeasurable bias.

BACKGROUND

Critically ill patients in intensive care units (ICUs) are vulnerable to various infections, 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 days[3] and the cost of treatment was approximately 12,321 US dollars 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 to BSIs involving susceptible strains.[4] Moreover, candidemia has been associated with a 4-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 World Health Organization (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.

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. The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Study population, data collection, and propensity-score matching

This retrospective cohort study enrolled adult patients who underwent ICU hospitalization 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. Since coagulase-negative *Staphylococci* are often associated with contamination, these cases were not included in our analysis. We included species that constituted > 1 % of known bloodstream pathogens (Supplementary 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.

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) were also excluded. The pool of comparison patients was created for 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 hospitalization, which was selected from the index date of patients with the same day of hospitalization in the BSI group. We used 1:2 greedy matching[10] within a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. Propensity scores were then calculated for the likelihood of ICU-acquired

BSIs by using baseline covariates and multivariate logistic regression analysis (Supplementary Table 2). Patient data from January 2005 were used to ensure that individuals were followed for at least two years prior to their selection for this study in order to confirm comorbidities[11] and for matching purposes.

Outcome measurements

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

Subgroup analysis

To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different pathogens, we 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 (ECDC) was modified[12] (Supplementary 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- 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 hospitalization/healthcare cost, we included patients who survived to discharge. For these patients, length of hospitalization after the index date/pseudo-index date and hospitalization 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. Standardized 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 Chi-squared test was used to evaluate mortality rate. Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of mortality in patients with BSI and the comparison cohort, while a generalized linear model was used to calculate β values to estimate excess costs and length of hospitalization. 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 (version 9.4, SAS Institute Inc., Cary, NC, USA).

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 hospitalization (Figure 1). After excluding patients whose data could not be interlinked with NHIRD or who did not have target pathogens, 14,369 patients with ICU-acquired BSIs were successfully matched to 28,738 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 standardized 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 (44.38% *vs.* 33.50%, respectively; $p < 0.001$) and a higher 14-day mortality rate (30.39% *vs.* 23.87%, respectively; $p < 0.001$). Logistic regression analyses showed that the OR of in-hospital mortality for the ICU patients with BSIs was 1.66 (95% confidence interval [CI], 1.59–1.73; $p < 0.001$), and it was 1.41 (95% CI, 1.34–1.47; $p < 0.001$) for 14-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 hospitalization after the index date

(18 *vs.* 10 days, respectively; $p < 0.001$). Moreover, on average, their hospital stay was extended by 12.77 days (95% CI, 12.02–13.52; $p < 0.001$). 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 hospitalization after the index date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp. was longer. In addition, hospitalization costs of the ICU patients with BSIs were higher (16,086 *vs.* 10,731, respectively; $p < 0.001$) (Table 2), with the excess cost being 7,646 US dollars per patient (95% CI, 7,356–7,935; $p < 0.001$). Table 4 presents the higher costs associated with each of the various causative pathogen.

For the ICU patients with BSIs who survived to discharge, their length of hospitalization and healthcare costs were increased by 19.38 days and 8,829 US dollars, respectively, (Supplementary Table 4) compared to 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 1.66-fold and 1.41-fold increases in in-hospital and 14-day mortality rates. Per case, the patients with BSI had an excess hospital stay of 12.77 days and cost of 7,646 US dollars. 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.[1,3,13-16] For example, worse clinical outcomes have been reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S. aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] 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 pathogen[1] and is not associated with increased mortality unless in the presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] 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[3,13,20] 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 298 million US dollars and 495,222 days (supplementary Table 5). A policy that reduced the rate of infection by 10%[21] would translate into a savings of 30 million US dollars and 4,952 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.[22, 23] In the present study, the costs for MDR bacteria included extra 85 million US dollars and 140,923 days over nine years (Supplementary 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,[16,18,20] and *C. albicans* is the most common pathogen. However, in some countries, the prevalence of non-*albicans Candida* exceeds that of *C. albicans*.[24] For those

infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization stays, and increased hospital costs have been described;[25-27] although other studies have reported contradicting findings.[28,29] These discrepancies may be due to host factors and differences in the virulence and resistance patterns[24] of non-*albicans Candida*. In the present study, the crude 14-day and in-hospital mortality rates of 958 patients infected with *C. albicans* were 38.10% and 56.16%, respectively. In comparison, among 704 patients infected with non-*albicans Candida*, these rates were 34.94% and 52.98%, respectively. While the hospital costs and length of stay were higher in the non-*albicans Candida* group compared to 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.[30] Second, confounding factors associated with clinical impact, such as 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.[31,32] In addition, the prolonged hospitalization may have been due to a change in patient management in response to a BSI, rather than increased morbidity due to a BSI.[15]

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.

LIST OF ABBREVIATIONS

BSI = bloodstream infection;

CI = confidence interval;

ECDC = European Centre for Disease Prevention and Control;

ICD-9-CM = international classification of diseases, 9th revision, clinical modification;

ICU = intensive care unit;

IQR = interquartile range;

MDR = multiple drug resistance;

NHIRD = National Health Insurance Research Database;

OR = odds ratio;

TNIS = Taiwan Nosocomial Infection Surveillance;

WHO = World Health Organization;

DECLARATIONS

Ethics approval and consent to participate

The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Ministry of Health and Welfare, Taiwan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ministry of Health and Welfare, Taiwan.

Competing interests

The authors declare that they have no competing interests.

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

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,369	28,738	
Males	9,060 (63.05)	18,059 (62.84)	0.004
Age, years, mean (SD)	65.21 (21.58)	65.41 (20.24)	0.010
Length of stay before index date/ pseudo-index date, days, mean (SD)	15.81 (12.51)	15.32 (12.21)	0.039
Monthly income, USD			
Dependent	2,438 (16.97)	4,837 (16.83)	0.004
< 657.33	4,794 (33.36)	9,601 (33.41)	0.001
657.33–1504.60	6,370 (44.33)	12,805 (44.56)	0.005
> 1504.60	753 (5.24)	1,465 (5.10)	0.006
Urbanization level			
1 (urban)	3,681 (25.62)	7,292 (25.37)	0.006
2	4,004 (27.87)	8,028 (27.94)	0.002
3	2,246 (15.63)	4,541 (15.80)	0.005
4 (rural)	4,427 (30.81)	8,849 (30.79)	0
Charlson Comorbidity Index score, mean (SD)	3.09 (2.80)	3.12 (2.93)	0.013
0	2,968 (20.66)	6,198 (21.57)	0.022
1	1,947 (13.55)	3,995 (13.90)	0.010
2	2,313 (16.10)	4,418 (15.37)	0.020

≥ 3	7,141 (49.70)	14,127 (49.16)	0.011
Comorbidities			
Diabetes mellitus	4,901 (34.11)	9,848 (34.27)	0.003
Cerebrovascular disease	3,592 (25.00)	7,192 (25.03)	0.001
Hypertension	8,156 (56.76)	16,334 (56.84)	0.002
Myocardial infarction	530 (3.69)	1,110 (3.86)	0.009
Heart failure	2,574 (17.91)	5,276 (18.36)	0.012
Peripheral vascular disease	755 (5.25)	1,524 (5.30)	0.002
Liver disease	2,765 (19.24)	5,573 (19.39)	0.004
Chronic kidney disease	3,905 (27.18)	8,003 (27.85)	0.015
Dyslipidemia	2,787 (19.40)	5,558 (19.34)	0.001
Cancer	2,799 (19.48)	5,689 (19.80)	0.008
Number of dysfunctional organs, mean (SD)	1.02 (0.81)	1.03 (0.86)	0.014
0	4,047 (28.16)	8,465 (29.46)	0.029
1	6,498 (45.22)	12,396 (43.13)	0.042
2	3,324 (23.13)	6,460 (22.48)	0.016
≥ 3	500 (3.48)	1,417 (4.93)	0.072
Use of inotropic agents	11,529 (80.24)	23,153 (80.57)	0.008
Use of steroid	10 (0.07)	19 (0.07)	0.001
Use of ventilator (> 3 days)	11,798 (82.11)	23,578 (82.04)	0.002
Emergent renal replacement therapy	2,680 (18.65)	5,523 (19.22)	0.014
Propensity score (SD)	0.13 (0.11)	0.13 (0.11)	0.014

Abbreviations: BSI = bloodstream infection; SD = standard deviation.

453 **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		14,369	28,738	
Clinical outcomes						
In-hospital mortality, n (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,377 (44.38)	9,627 (33.50)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,367 (30.39)	6,860 (23.87)	< 0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median (IQR)	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 39)	10 (4, 21)	< 0.0001

Cost of hospitalization (USD)[a], median (IQR)	18,457 (10,938, 30,778)	4,971 (2,770, 8,598)	< 0.0001	16,086 (9,706, 26,431)	10,731 (6,375, 16,910)	< 0.0001

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

[a]The costs are standardized and presented as the values in 2017.

Table 3. Clinical outcomes for the various pathogen groups.

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)	
	In-hospital mortality	14-days mortality
MDR Gram-negative bacteria (2,255)	1.97 (1.76, 2.21)	1.65 (1.47, 1.85)
MDR Gram-positive bacteria (1,440)	1.90 (1.64, 2.19)	1.32 (1.14, 1.53)
Acinetobacter baumannii (1,775)	1.48 (1.30, 1.68)	1.39 (1.21, 1.59)
Pseudomonas aeruginosa (861)	1.62 (1.35, 1.95)	1.74 (1.43, 2.11)
Enterobacteriaceae[b] (3,581)	1.53 (1.40, 1.68)	1.28 (1.16, 1.41)
Staphylococcus aureus (1,733)	1.69 (1.47, 1.94)	1.15 (0.99, 1.33)
Enterococcus species[c] (1,287)	1.75 (1.50, 2.04)	1.50 (1.28, 1.76)
Candida albicans (958)	2.39 (2.00, 2.85)	1.84 (1.54, 2.20)
Non-*albicans Candida*[d] (704)	1.95 (1.59, 2.38)	1.47 (1.19, 1.81)

Abbreviations: MDR = multiple drug resistance.

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

[b]Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens.*

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species.*

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

468 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Beta (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.76 (8.82, 12.70)	7,397 (6,514, 8,279)
MDR Gram-positive bacteria	13.36 (10.46, 16.25)	5,615 (4,706, 6,504)
Acinetobacter baumannii	10.14 (8.49, 11.80)	7,331 (6,401, 8,261)
Pseudomonas aeruginosa	9.68 (7.49, 11.88)	6,187 (5,043, 7,330)
Enterobacteriaceae[b]	14.96 (13.29, 16.63)	7,372 (6,784, 7,960)
Staphylococcus aureus	14.96 (12.81, 17.10)	4,847 (4,147, 5,547)
Enterococcus species[c]	10.57 (7.78, 13.35)	7,354 (6,387, 8,321)
Candida albicans	11.01 (8.6, 13.42)	9,145 (7,929, 10,361)

Non-*albicans Candida*[d]	14.19 (10.31, 18.08)	11,344 (9,850, 12,838)

Abbreviations: MDR = multiple drug resistance.

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

[b]Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Serratia marcescens*.

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species*.

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

FIGURE LEGENDS

Figure 1. Flow diagram of the study design.

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National Health Insurance Research Database.

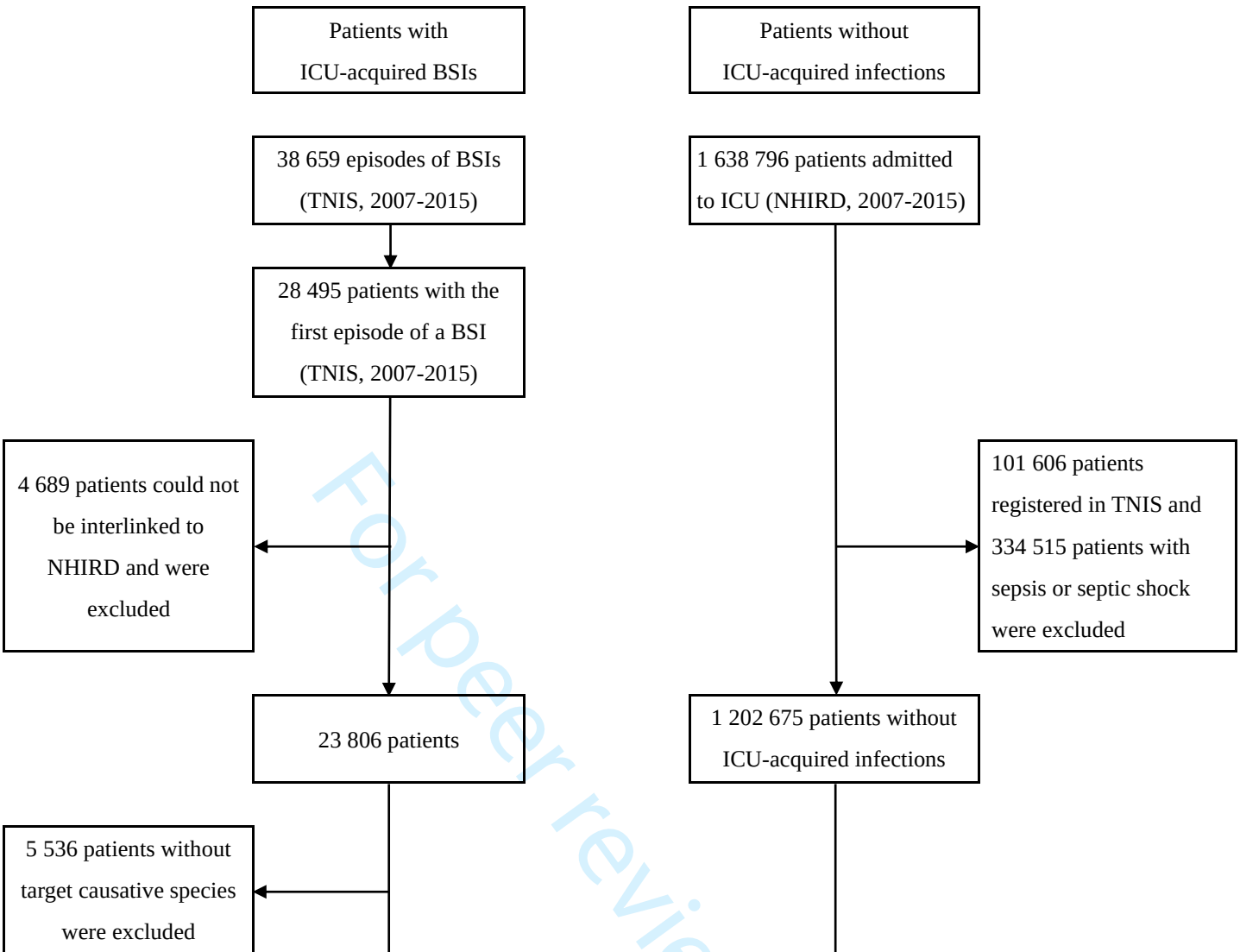
SUPPLEMENTARY FILES:

Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.



Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

	No. of BSI episodes before enrollment[a]	No. of patients after matching[b]
Acinetobacter baumannii	5,214	1,775
Staphylococcus aureus	4,382	1,733
Klebsiella pneumoniae	3,965	1,376
Pseudomonas aeruginosa	2,619	861
Candida albicans	2,554	958
Escherichia coli	2,287	850
Enterobacter cloacae	1,982	755
Enterococcus faecium	1,950	653
Stenotrophomonas maltophilia	1,599	465
Enterococcus faecalis	1,427	422
Serratia marcescens	1,239	437
Candida tropicalis	890	332
Burkholderia cepacia	808	252
Other *Enterococcus species*[c]	688	212
Elizabethkingia meningoseptica	659	177
Chryseobacterium indologenes	553	154
Candida parapsilosis	534	177
Candida glabrata	461	195
Enterobacter aerogenes	419	163

Abbreviations: BSI= bloodstream infection.

[a]The number of episodes of bloodstream infections with known pathogens was 38,659.

Coagulase-negative staphylococci was excluded from analyses due to possibility of contamination. One episode may have multiple pathogens. There were 30,697 episodes of bloodstream infections caused by the pathogens listed above.

[b]The number of patients enrolled case was 14,369 (Table 1) but only patients with bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it was 11,947. There were 2,422 patients with bloodstream infections caused by multiple pathogens.

[c]*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis.*

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Parameter	Estimate	Odds ratios	95% Confidence interval		*P*-value
			Lower	Upper	
Age, years	-0.002	0.998	0.997	1.000	0.019
Length of stay before index date/pseudo-index date, days	0.010	1.010	0.997	1.023	0.131
Year of index date					
2007	--	1.000	--	--	--
2008	0.313	1.367	1.251	1.494	< 0.0001
2009	0.474	1.606	1.468	1.758	< 0.0001
2010	0.450	1.569	1.432	1.718	< 0.0001
2011	0.553	1.739	1.579	1.915	< 0.0001
2012	0.440	1.552	1.402	1.719	< 0.0001
2013	0.335	1.398	1.254	1.558	< 0.0001
2014	0.193	1.212	1.082	1.359	0.001
2015	0.144	1.155	1.025	1.301	0.018
Month of index date					
Jan	--	1.000	--	--	--
Feb	0.015	1.015	0.919	1.122	0.768
Mar	-0.014	0.986	0.895	1.087	0.782
Apr	-0.021	0.979	0.887	1.080	0.670
May	0.034	1.034	0.936	1.142	0.507
Jun	0.083	1.087	0.983	1.202	0.104

Jul	0.054	1.056	0.955	1.167	0.287
Aug	0.097	1.101	0.997	1.217	0.058
Sep	0.112	1.118	1.010	1.238	0.032
Oct	-0.012	0.988	0.892	1.094	0.816
Nov	-0.020	0.981	0.885	1.087	0.708
Dec	-0.106	0.900	0.812	0.997	0.044
Male	0.016	1.017	0.973	1.062	0.463
Monthly income, USD					
Dependent	--	1.000	--	--	--
<657.33	0.026	1.026	0.958	1.100	0.461
657.33–1504.60	-0.013	0.987	0.920	1.059	0.721
>1504.60	0.089	1.093	0.979	1.220	0.114
Urbanization level					
1 (urban)		1.000			
2	-0.016	0.984	0.929	1.042	0.584
3	-0.042	0.959	0.894	1.028	0.239
4 (rural)	-0.019	0.982	0.927	1.039	0.522
Hospital level					
Level I (Medical center)	--	1.000	--	--	--
Level II (Regional hospital)	-0.018	0.982	0.931	1.036	0.512
Level III (Local hospital)	-0.016	0.985	0.836	1.160	0.852
Charlson Comorbidity Index score					
0	--	1.000	--	--	--

1	0.107	1.113	1.032	1.201	0.006
2	0.240	1.272	1.176	1.375	< 0.0001
≥ 3	0.293	1.340	1.222	1.469	< 0.0001
Comorbidities					
Diabetes mellitus	0.002	1.002	0.951	1.056	0.926
Cerebrovascular disease	-0.029	0.972	0.902	1.046	0.447
Hypertension	-0.001	0.999	0.950	1.049	0.953
Myocardial infarction	0.015	1.015	0.829	1.243	0.885
Heart failure	-0.037	0.964	0.883	1.052	0.408
Peripheral vascular disease	-0.018	0.982	0.891	1.082	0.713
Liver disease	-0.043	0.958	0.891	1.030	0.247
Chronic kidney disease	-0.070	0.932	0.862	1.009	0.082
Dyslipidemia	-0.017	0.984	0.919	1.053	0.634
Cancer	-0.122	0.885	0.831	0.943	< 0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.136	1.146	0.991	1.324	0.066
2	0.192	1.211	0.921	1.593	0.170
≥ 3	-0.167	0.846	0.555	1.291	0.438
Use of inotropic agents	0.103	1.109	0.883	1.393	0.374
Use of steroid	-0.001	0.999	0.454	2.197	0.998
Use of ventilator (> 3 days)	0.190	1.209	0.851	1.719	0.290
Emergent renal replacement	0.051	1.053	0.915	1.211	0.472

therapy

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Pathogens	Antimicrobial categories	Antimicrobial agents
Acinetobacter baumannii[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime
		Ceftriaxone
Pseudomonas aeruginosa[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem

		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Antipseudomonal cephalosporins	Cefepime
		Cefpirome
		Ceftazidime
Enterobacteriaceae[a] *(Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae Enterobacter aerogenes*, or *Serratia marcescens*)	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
		Ertapenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime

		Ceftriaxone
Staphylococcus aureus[b]	Glycopeptides	Vancomycin
	β-lactamase-resistant penicillins	Oxacillin
Enterococcus faecium, Enterococcus faecalis, or other *Enterococcus species*[b]	Glycopeptides	Vancomycin

[a]Drug resistance was defined as being non-susceptible to ≧1 agent in ≧3 antimicrobial categories.

[b]Drug resistance was defined as being non-susceptible to ≧1 agent.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.[a]

Clinical outcomes	beta (95% Confidence interval)[b]	*P*-value
Length of hospitalization after the index date/pseudo-index date, days	19.38 (18.57, 20.2)	< 0.0001
Cost of hospitalization, USD	8,829 (8,428, 9,231)	< 0.0001

[a]A total of 7,992 of patients with intensive care uit-acquired bloodstream infections and 19,111 comparators survived to the discharge.

[b]Adjusted imbalanced variables in Table 1.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

Pathogen groups (Numbers of patients)[a]	9-year excessive hospitalization or healthcare cost	
	Length of hospitalization after the index date (days)[b]	Cost of hospitalization (USD)[b, c]
All pathogens (38,659)	495,222	297,515,798
MDR Gram-negative bacteria (6,825)	87,428	52,524,518
MDR Gram-positive bacteria (4,176)	53,495	32,138,078
Acinetobacter baumannii (5,214)	66,791	40,126,423
Pseudomonas aeruginosa (2,619)	33,549	20,155,562
Enterobacteriaceae[d] (9,486)	121,516	73,003,307
Staphylococcus aureus (4,382)	56,133	33,723,434
Enterococcus species[e] (4,045)	51,816	31,129,916
Candida albicans (2,554)	32,717	19,655,329
Non-albicans Candida[f] (1,872)	23,980	14,406,725

Abbreviations: MDR= multiple drug resistance.

[a]The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The incluson and exclusion criteira in the method section were not applied in this Table (see Figure 1).

[b]The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s) and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was that in matched control group.

$Ave_{Hospitalization}$ per case= [(sum of hospitalization length)/the number of patients].

Excessive $Ave_{Hospitalization}$ per person= ($Ave_{Hospitalization}$ in bloodstream infection group) - ($Ave_{Hospitalization}$ in comparison group).

Total excessive hospitalization length over 9 years = (excessive $Ave_{Hospitalization}$ per person) × (total number of episodes over 9 years)

The 9-year excessive healthcare cost was calculated similarly.

[c]The costs are standardized and presented the values in 2017.

[d]*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens.*

[e]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species.*

[f]*Non-albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
Methods			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	#9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*#9-10*
Bias	9	Describe any efforts to address potential sources of bias	*#9-10*
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#11-12
		(*b*) Describe any methods used to examine subgroups and interactions	#10-11
		(*c*) Explain how missing data were addressed	#8-10
		(*d*) If applicable, explain how loss to follow-up was addressed	#8-10
		(*e*) Describe any sensitivity analyses	#11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#13
		(b) Give reasons for non-participation at each stage	#13
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#13-14
		(b) Indicate number of participants with missing data for each variable of interest	#13-14
		(c) Summarise follow-up time (eg, average and total amount)	#13-14
Outcome data	15*	Report numbers of outcome events or summary measures over time	#13-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#13-14
		(*b*) Report category boundaries when continuous variables were categorized	#13-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#13-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	#15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	#17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#20-21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Article category: Original research

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 14-day mortality rate, length of hospitalization, 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 to 33.48% for 28,468 intensive care unit patients without bloodstream infections. The 14-day mortality rate was also higher in the bloodstream infections cohort (4,323, 30.37% *vs.* 6,766 deaths, 23.77%, respectively; $p < 0.001$). Furthermore, the patients with intensive care unit-acquired bloodstream infections had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] *vs.* 10

days [IQR 4–21], respectively; $p < 0.001$) and a higher healthcare cost (16,038 US dollars [IQR 9,667–25,946] *vs.* 10,372 US dollars [IQR 6,289–16,932], respectively; $p < 0.001$). The excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars, respectively. Similar results were observed in subgroup analyses of various World Health Organization'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.

Keywords: bloodstream infection; healthcare costs; hospital stay; intensive care unit; mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. A large number of patients obtained from Nationwide Taiwanese population from two datasets in Taiwan were included.
2. Propensity score-matching was performed to select a comparison cohort.
3. The 14-day and 28-day mortality rate, length of hospitalization, and healthcare cost were analyzed.
4. Subgroup analyses of several drug-resistant pathogens were conducted.
5. The retrospective design may include some unmeasurable bias.

BACKGROUND

Critically ill patients in intensive care units (ICUs) are vulnerable to various infections, 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 days[3] and the cost of treatment was approximately 12,321 US dollars 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 to BSIs involving susceptible strains.[4] Moreover, candidemia has been associated with a 4-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 World Health Organization (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 the 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. The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Study population, data collection, and propensity-score matching

This retrospective cohort study enrolled adult patients who underwent ICU hospitalization 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 been 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 (Supplementary 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 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 hospitalization,

which was selected from the index date of patients with the same day of hospitalization 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 matching[10] within a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score. Propensity scores were then calculated for the likelihood of ICU-acquired BSIs by using baseline covariates and multivariate logistic regression analysis (Supplementary Table 2). Patient data from January 2005 were used to ensure that individuals were followed for at least two years prior to their selection for this study in order to confirm comorbidities[11] and for matching purposes.

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 hospitalization length after the index date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined as the duration of hospital stay after the index date/pseudo-index date. The overall cost of

hospitalization was calculated. The costs were standardized and presented in values from 2017.

Subgroup analysis

To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different pathogens, we 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 (ECDC) was modified[12] (Supplementary 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- 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 hospitalization/healthcare cost, we included patients who survived to discharge. For these patients, length of hospitalization after the index date/pseudo-index date and hospitalization 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. Standardized 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 Chi-squared test was used to evaluate mortality rate. Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of mortality in patients with BSI and the comparison cohort, while a generalized linear model was used to calculate β values to estimate excess costs and length of hospitalization. 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 (version 9.4, SAS Institute Inc., Cary, NC, USA).

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 hospitalization (Figure 1). After excluding patients whose 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 standardized 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% confidence interval [CI], 1.59–1.75; $p < 0.001$), and it was 1.42 (95% CI, 1.35–1.49; $p < 0.001$) for 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 hospitalization after the index date (18 *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 hospitalization after the index date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp. was longer. In addition, hospitalization 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 7,669 US dollars per patient (95% CI, 7,380–7,958; $p < 0.001$). Table 4 presents the higher costs associated with each of the various causative pathogen.

For the ICU patients with BSIs who survived to discharge, their length of hospitalization and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively, (Supplementary Table 4) compared to 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-, 1.42-, 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 7,669 US dollars. 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.[1,3,13-16] For example, worse clinical outcomes have been reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S. aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] 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 pathogen[1] and is not associated with increased mortality unless in the presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] 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[3,13,20] 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 297 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate of infection by 10%[21] would translate into a savings of 30 million US dollars 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.[22, 23] In the present study, the costs for MDR bacteria included extra 84 million US dollars and 140,043 days over nine years (Supplementary 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,[16,18,20] and *C. albicans* is the most common pathogen. However, in some countries, the prevalence of non-*albicans Candida* exceeds that of *C. albicans*.[24] For those

infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization stays, and increased hospital costs have been described;[25-27] although other studies have reported contradicting findings.[28,29] These discrepancies may be due to host factors and differences in the virulence and resistance patterns[24] 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 to 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.[30] Second, confounding factors associated with clinical impact, such as 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.[31,32] Fourth, the prolonged hospitalization may have been due to a change in patient management in response to a BSI, rather than increased morbidity due to a BSI.[15] In addition, 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 (missing data). Their impact on the outcome was unknown.

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.

LIST OF ABBREVIATIONS

BSI = bloodstream infection;

CI = confidence interval;

ECDC = European Centre for Disease Prevention and Control;

ICD-9-CM = international classification of diseases, 9th revision, clinical modification;

ICU = intensive care unit;

IQR = interquartile range;

MDR = multiple drug resistance;

NHIRD = National Health Insurance Research Database;

OR = odds ratio;

TNIS = Taiwan Nosocomial Infection Surveillance;

WHO = World Health Organization;

DECLARATIONS

Ethics approval and consent to participate

The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Ministry of Health and Welfare, Taiwan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ministry of Health and Welfare, Taiwan.

Competing interests

The authors declare that they have no competing interests.

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

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (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, USD			
Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001
Urbanization level			
1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002
Hospital level			
Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007
Charlson Comorbidity Index score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019
Comorbidities			
Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005
Hypertension	525 (3.69%)	1,124 (3.95%)	0.014
Myocardial infarction	2,532 (17.79%)	5,173 (18.17%)	0.01

Heart failure	742 (5.21%)	1,509 (5.3%)	0.004
Peripheral vascular disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Liver disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Chronic kidney disease	2,766 (19.43%)	5,683 (19.96%)	0.013
Dyslipidemia	2,753 (19.34%)	5,635 (19.79%)	0.011
Cancer	4,840 (34%)	9,642 (33.87%)	0.003
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (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%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

Abbreviations: BSI = bloodstream infection; SD = standard deviation.

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 (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.23%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.37%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.48%)	9,189 (32.28%)	<0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 39)	10 (4, 21)	< 0.0001

(IQR)						
Cost of hospitalization (USD)[a], median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,246)	(6,289, 16,932)	

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

[a]The costs are standardized and presented as the values in 2017.

Table 3. Clinical outcomes for the various pathogen groups.

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
Acinetobacter baumannii (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
Pseudomonas aeruginosa (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae[b] (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
Staphylococcus aureus (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
Enterococcus species[c] (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
Candida albicans (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non-*albicans Candida*[d] (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

Abbreviations: MDR = multiple drug resistance.

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

[b]Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens.*

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other

Enterococcus species.

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

Table 4. Economic outcomes for the various pathogen groups.

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,342 (5,500, 7,184)
Acinetobacter baumannii	9.4 (7.65, 11.14)	6,727 (5,823, 7,632)
Pseudomonas aeruginosa	10.01 (7.83, 12.19)	6,761 (5,609, 7,913)
Enterobacteriaceae[b]	15.05 (13.33, 16.76)	7,444 (6,881, 8,007)
Staphylococcus aureus	14.72 (12.63, 16.81)	5,221 (4,528, 5,894)
Enterococcus species[c]	10.66 (7.85, 13.48)	7,219 (6,305, 8,132)
Candida albicans	11.37 (8.82, 13.92)	8,688 (7,512, 9,864)

Non-*albicans Candida*[d]	15.13 (11.77, 18.49)	11,476 (10,025, 12,927)

Abbreviations: MDR = multiple drug resistance.

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

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

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species.*

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

FIGURE LEGENDS

Figure 1. Flow diagram of the study design.

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National Health Insurance Research Database.

SUPPLEMENTARY FILES:

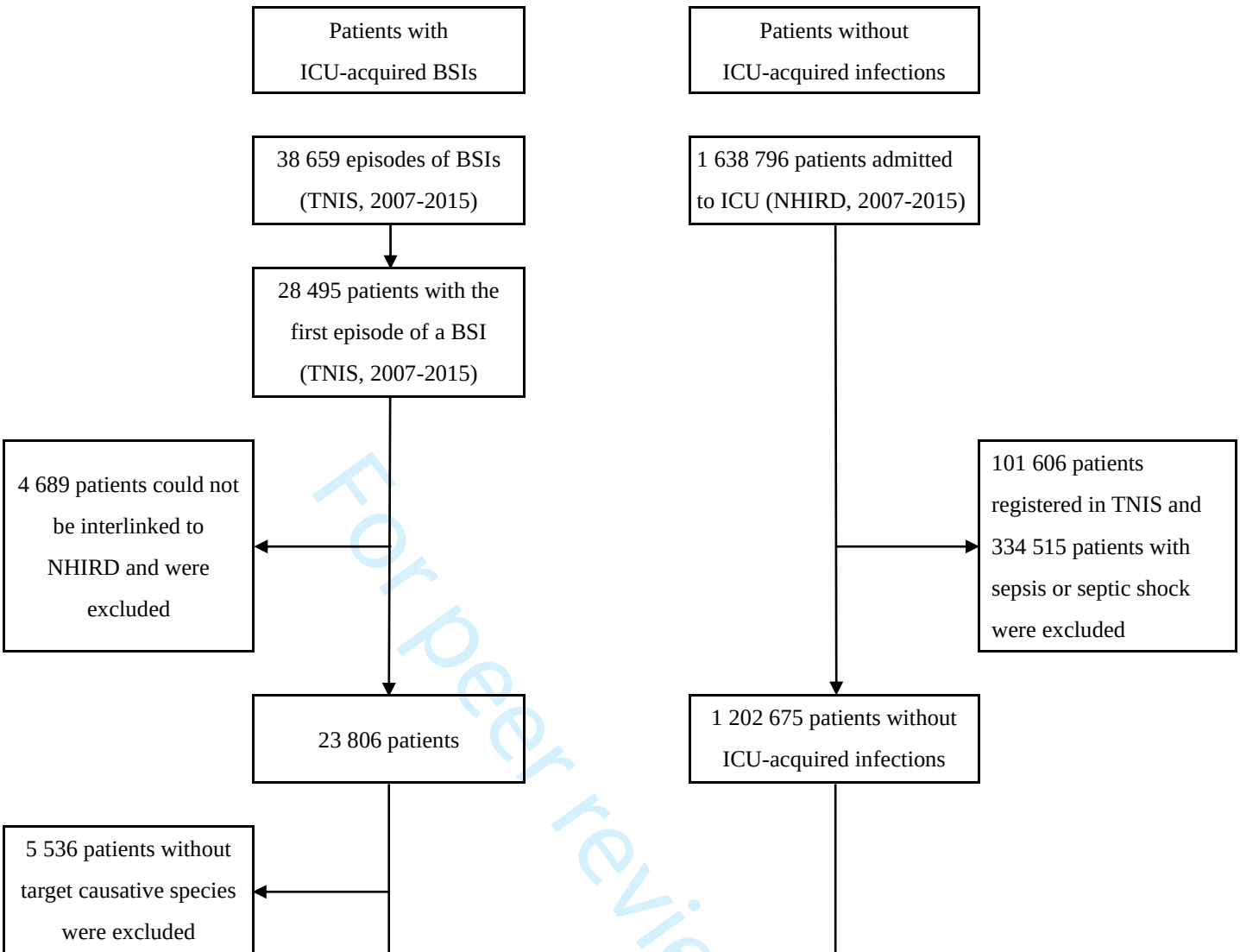
Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.



Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

	No. of BSI episodes before enrollment[a]	No. of patients after matching[b]
Acinetobacter baumannii	5,214	1,761
Staphylococcus aureus	4,382	1,721
Klebsiella pneumoniae	3,965	1,357
Pseudomonas aeruginosa	2,619	853
Candida albicans	2,554	951
Escherichia coli	2,287	843
Enterobacter cloacae	1,982	746
Enterococcus faecium	1,950	647
Stenotrophomonas maltophilia	1,599	454
Enterococcus faecalis	1,427	419
Serratia marcescens	1,239	439
Candida tropicalis	890	329
Burkholderia cepacia	808	251
Other *Enterococcus species*[c]	688	211
Elizabethkingia meningoseptica	659	173
Chryseobacterium indologenes	553	152
Candida parapsilosis	534	177
Candida glabrata	461	197
Enterobacter aerogenes	419	163

Abbreviations: BSI= bloodstream infection.

[a]The number of episodes of bloodstream infections with known pathogens was 38,659.

Coagulase-negative staphylococci was excluded from analyses due to possibility of contamination. One episode may have multiple pathogens. There were 30,697 episodes of bloodstream infections caused by the pathogens listed above.

[b]The number of patients enrolled case was 14,234 (Table 1) but only patients with bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it was 11,844. There were 2,390 patients with bloodstream infections caused by multiple pathogens.

[c]*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis.*

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Parameter	Estimate	Odds ratios	95% Confidence interval		*P*-value
			Lower	Upper	
Age, years	-0.0014	0.9986	0.9974	0.9998	0.0251
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

Dependent	--	1.000	--	--	--
<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
Urbanization level					
1 (urban)		1.000			
2	0.0093	1.0094	0.9516	1.0706	0.7560
3	-0.0006	0.9994	0.9293	1.0748	0.9872
4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
Hospital level					
Level I (Medical center)	--	1.000	--	--	--
Level II (Regional hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
Charlson Comorbidity Index score					
0	--	1.000	--	--	--
1	0.1421	1.1527	1.0681	1.2439	0.0003
2	0.2932	1.3407	1.2390	1.4508	<0.0001
≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
Comorbidities					
Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292

Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Pathogens	Antimicrobial categories	Antimicrobial agents
Acinetobacter baumannii[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime
		Ceftriaxone
Pseudomonas aeruginosa[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem

		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Antipseudomonal cephalosporins	Cefepime
		Cefpirome
		Ceftazidime
Enterobacteriaceae[a] *(Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae Enterobacter aerogenes,* or *Serratia marcescens*)	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
		Ertapenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime

		Ceftriaxone
Staphylococcus aureus[b]	Glycopeptides	Vancomycin
	β-lactamase-resistant penicillins	Oxacillin
Enterococcus faecium, Enterococcus faecalis, or other *Enterococcus species*[b]	Glycopeptides	Vancomycin

[a]Drug resistance was defined as being non-susceptible to ≧1 agent in ≧3 antimicrobial categories.

[b]Drug resistance was defined as being non-susceptible to ≧1 agent.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.[a]

Clinical outcomes	Excess costs or length of hospitalization (95% Confidence interval)[b]	*P*-value
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	< 0.0001
Cost of hospitalization, USD	8,871 (8,475, 9,268)	< 0.0001

[a]A total of 7,939 of patients with intensive care uit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

[b]Adjusted imbalanced variables in Table 1.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

Pathogen groups (Numbers of patients)[a]	9-year excessive hospitalization or healthcare cost	
	Length of hospitalization after the index date (days)[b]	Cost of hospitalization (USD)[b, c]
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
Acinetobacter baumannii (5,214)	66,374	40,003,372
Pseudomonas aeruginosa (2,619)	33,340	20,093,754
Enterobacteriaceae[d] (9,486)	120,757	72,779,438
Staphylococcus aureus (4,382)	55,783	33,620,019
Enterococcus species[e] (4,045)	51,493	31,034,454
Candida albicans (2,554)	32,512	19,595,054
Non-albicans Candida[f] (1,872)	23,831	14,362,546

Abbreviations: MDR= multiple drug resistance.

[a]The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The incluson and exclusion criteira in the method section were not applied in this Table (see Figure 1).

[b]The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s) and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was that in matched control group.

$Ave_{Hospitalization}$ per case= [(sum of hospitalization length)/the number of patients].

Excessive $Ave_{Hospitalization}$ per person= ($Ave_{Hospitalization}$ in bloodstream infection group) - ($Ave_{Hospitalization}$ in comparison group).

Total excessive hospitalization length over 9 years = (excessive $Ave_{Hospitalization}$ per person) × (total number of episodes over 9 years)

The 9-year excessive healthcare cost was calculated similarly.

[c]The costs are standardized and presented the values in 2017.

[d]*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens.*

[e]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species*

[f]*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata.*

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
Methods			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	#9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*#9-10*
Bias	9	Describe any efforts to address potential sources of bias	*#9-10*
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#11-12
		(*b*) Describe any methods used to examine subgroups and interactions	#10-11
		(*c*) Explain how missing data were addressed	#8-10
		(*d*) If applicable, explain how loss to follow-up was addressed	#8-10
		(*e*) Describe any sensitivity analyses	#11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#13
		(b) Give reasons for non-participation at each stage	#13
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#13-14
		(b) Indicate number of participants with missing data for each variable of interest	#13-14
		(c) Summarise follow-up time (eg, average and total amount)	#13-14
Outcome data	15*	Report numbers of outcome events or summary measures over time	#13-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#13-14
		(*b*) Report category boundaries when continuous variables were categorized	#13-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#13-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	#15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	#17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#20-21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Article category: Original research

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 hospitalization, 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 to 33.48% for 28,468 intensive care unit patients without bloodstream infections. The 14-day mortality rate was also higher in the bloodstream infections cohort (4,323, 30.37% *vs.* 6,766 deaths, 23.77%, respectively; $p < 0.001$). Furthermore, the patients with intensive care unit-acquired bloodstream infections had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] *vs.* 10

days [IQR 4–21], respectively; $p < 0.001$) and a higher healthcare cost (16,038 US dollars [IQR 9,667–25,946] *vs.* 10,372 US dollars [IQR 6,289–16,932], respectively; $p < 0.001$). The excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars, respectively. Similar results were observed in subgroup analyses of various World Health Organization'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.

Keywords: bloodstream infection; healthcare costs; hospital stay; intensive care unit; mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

BACKGROUND

Critically ill patients in intensive care units (ICUs) are vulnerable to various infections, 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 days[3] and the cost of treatment was approximately 12,321 US dollars 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 to BSIs involving susceptible strains.[4] Moreover, candidemia has been associated with a 4-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 World Health Organization (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 the 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. The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Study population, data collection, and propensity-score matching

This retrospective cohort study enrolled adult patients who underwent ICU hospitalization 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 (Supplementary 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 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 hospitalization,

which was selected from the index date of patients with the same day of hospitalization 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 matching [10] within a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score (Supplementary Table 2). Patient data from January 2005 were used to ensure that individuals were followed for at least two years prior to their selection for this study in order to confirm comorbidities[11] and for matching purposes.

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 hospitalization length after the index date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined as the duration of hospital stay after the index date/pseudo-index date. The overall cost of hospitalization was calculated. The costs were standardized and presented in values from

2017.

Subgroup analysis

To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different pathogens, we 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 (ECDC) was modified[12] (Supplementary 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- 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 hospitalization/healthcare cost, we included patients who survived to discharge. For these patients, length of hospitalization after the index date/pseudo-index date and hospitalization 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. Standardized 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 Chi-squared test was used to evaluate mortality rate. Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of mortality in patients with BSI and the comparison cohort, while a generalized linear model was used to calculate β values to estimate excess costs and length of hospitalization. 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 (version 9.4, SAS Institute Inc., Cary, NC, USA).

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 hospitalization (Figure 1). After excluding patients whose 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 standardized 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% confidence interval [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 hospitalization after the index date (18 *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 hospitalization after the index date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp. was longer. In addition, hospitalization 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 7,669 US dollars per patient (95% CI, 7,380–7,958; $p < 0.001$). Table 4 presents the higher costs associated with each of the various causative pathogen.

For the ICU patients with BSIs who survived to discharge, their length of hospitalization and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively, (Supplementary Table 4) compared to 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-, 1.42-, 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 7,669 US dollars. 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.[1,3,13-16] For example, worse clinical outcomes have been reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S. aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] 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 pathogen[1] and is not associated with increased mortality unless in the presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] 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[3,13,20] 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 297 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate of infection by 10%[21] would translate into a savings of 30 million US dollars 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.[22, 23] In the present study, the costs for MDR bacteria included extra 84 million US dollars and 140,043 days over nine years (Supplementary 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,[16,18,20] and *C. albicans* is the most common pathogen. However, in some countries, the prevalence of non-*albicans Candida* exceeds that of *C. albicans*.[24] For those

infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization stays, and increased hospital costs have been described;[25-27] although other studies have reported contradicting findings.[28,29] These discrepancies may be due to host factors and differences in the virulence and resistance patterns[24] 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 to 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.[30] Second, confounding factors associated with clinical impact, such as 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.[31,32] Fourth, the prolonged hospitalization may have been due to a change in patient management in response to a BSI, rather than increased morbidity due to a BSI.[15] In addition, 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 (missing data). In 2007-2015 TNIS dataset, 27,603 of 132,118 (20.9%) patients lacked personal identification numbers, compared to 4689 of 28495 (16.5%) patients with ICU-acquired BSI in this study. Patients without personal identification numbers were excluded from the analyses and therefore no further methods were applied to account for excluded data. However, their impact on the outcome was unknown.

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.

LIST OF ABBREVIATIONS

BSI = bloodstream infection;

CI = confidence interval;

ECDC = European Centre for Disease Prevention and Control;

ICD-9-CM = international classification of diseases, 9th revision, clinical modification;

ICU = intensive care unit;

IQR = interquartile range;

MDR = multiple drug resistance;

NHIRD = National Health Insurance Research Database;

OR = odds ratio;

TNIS = Taiwan Nosocomial Infection Surveillance;

WHO = World Health Organization;

DECLARATIONS

Ethics approval and consent to participate

The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Ministry of Health and Welfare, Taiwan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ministry of Health and Welfare, Taiwan.

Competing interests

The authors declare that they have no competing interests.

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

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (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, USD			
Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001
Urbanization level			
1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002
Hospital level			
Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007
Charlson Comorbidity Index score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019
Comorbidities			
Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005
Myocardial infarction	525 (3.69%)	1,124 (3.95%)	0.014
Heart failure	2,532 (17.79%)	5,173 (18.17%)	0.01

Peripheral vascular disease	742 (5.21%)	1,509 (5.3%)	0.004
Liver disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Chronic kidney disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Dyslipidemia	2,766 (19.43%)	5,683 (19.96%)	0.013
Cancer	2,753 (19.34%)	5,635 (19.79%)	0.011
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (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%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

Abbreviations: BSI = bloodstream infection; SD = standard deviation.

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 (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.23%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.37%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.48%)	9,189 (32.28%)	<0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 39)	10 (4, 21)	< 0.0001

(IQR)						
Cost of hospitalization (USD)[a], median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,946)	(6,289, 16,932)	

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

[a]The costs are standardized and presented as the values in 2017.

Table 3. Clinical outcomes for the various pathogen groups.

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
Acinetobacter baumannii (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
Pseudomonas aeruginosa (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae[b] (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
Staphylococcus aureus (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
Enterococcus species[c] (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
Candida albicans (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non-*albicans Candida*[d] (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

Abbreviations: MDR = multiple drug resistance.

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

[b]Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens*.

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other

Enterococcus species.

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

484 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,342 (5,500, 7,184)
Acinetobacter baumannii	9.4 (7.65, 11.14)	6,727 (5,823, 7,632)
Pseudomonas aeruginosa	10.01 (7.83, 12.19)	6,761 (5,609, 7,913)
Enterobacteriaceae[b]	15.05 (13.33, 16.76)	7,444 (6,881, 8,007)
Staphylococcus aureus	14.72 (12.63, 16.81)	5,221 (4,528, 5,894)
Enterococcus species[c]	10.66 (7.85, 13.48)	7,219 (6,305, 8,132)
Candida albicans	11.37 (8.82, 13.92)	8,688 (7,512, 9,864)

Non-*albicans Candida*[d]	15.13 (11.77, 18.49)	11,476 (10,025, 12,927)

Abbreviations: MDR = multiple drug resistance.

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

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

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species.*

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

FIGURE LEGENDS

Figure 1. Flow diagram of the study design.

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National Health Insurance Research Database.

SUPPLEMENTARY FILES:

Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

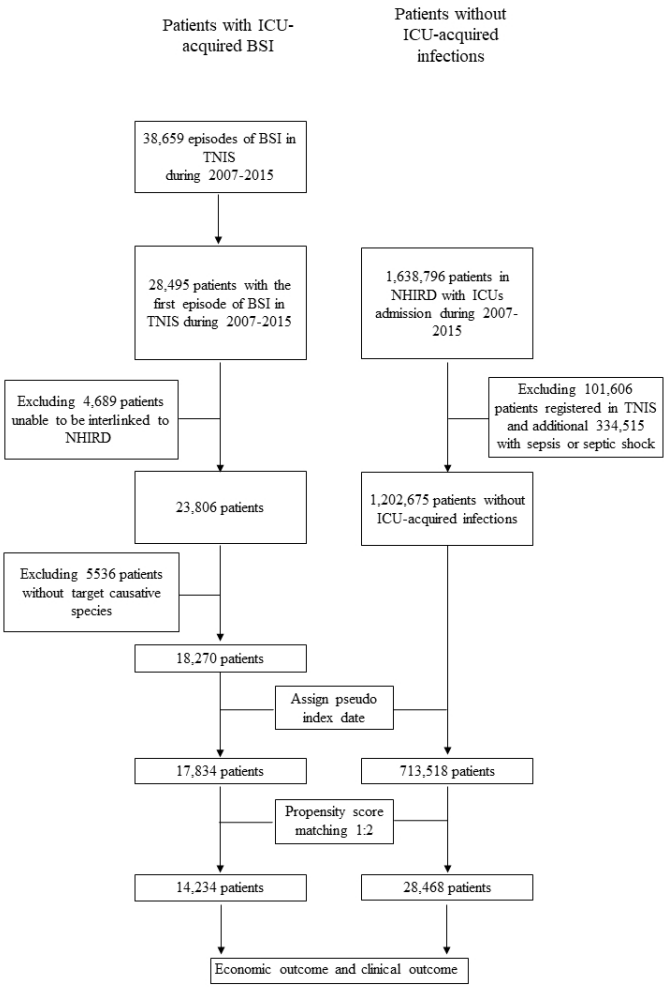

Figure 1. Flow diagram of the study design.

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Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

	No. of BSI episodes before enrollment[a]	No. of patients after matching[b]
Acinetobacter baumannii	5,214	1,761
Staphylococcus aureus	4,382	1,721
Klebsiella pneumoniae	3,965	1,357
Pseudomonas aeruginosa	2,619	853
Candida albicans	2,554	951
Escherichia coli	2,287	843
Enterobacter cloacae	1,982	746
Enterococcus faecium	1,950	647
Stenotrophomonas maltophilia	1,599	454
Enterococcus faecalis	1,427	419
Serratia marcescens	1,239	439
Candida tropicalis	890	329
Burkholderia cepacia	808	251
Other *Enterococcus species*[c]	688	211
Elizabethkingia meningoseptica	659	173
Chryseobacterium indologenes	553	152
Candida parapsilosis	534	177
Candida glabrata	461	197
Enterobacter aerogenes	419	163

Abbreviations: BSI= bloodstream infection.

[a]The number of episodes of bloodstream infections with known pathogens was 38,659.

Coagulase-negative staphylococci was excluded from analyses due to possibility of contamination. One episode may have multiple pathogens. There were 30,697 episodes of bloodstream infections caused by the pathogens listed above.

[b]The number of patients enrolled case was 14,234 (Table 1) but only patients with bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it was 11,844. There were 2,390 patients with bloodstream infections caused by multiple pathogens.

[c]*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis.*

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Parameter	Estimate	Odds ratios	95% Confidence interval		*P*-value
			Lower	Upper	
Age, years	-0.0014	0.9986	0.9974	0.9998	0.0251
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

Dependent	--	1.000	--	--	--
<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
Urbanization level					
1 (urban)		1.000			
2	0.0093	1.0094	0.9516	1.0706	0.7560
3	-0.0006	0.9994	0.9293	1.0748	0.9872
4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
Hospital level					
Level I (Medical center)	--	1.000	--	--	--
Level II (Regional hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
Charlson Comorbidity Index score					
0	--	1.000	--	--	--
1	0.1421	1.1527	1.0681	1.2439	0.0003
2	0.2932	1.3407	1.2390	1.4508	<0.0001
≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
Comorbidities					
Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292

Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Pathogens	Antimicrobial categories	Antimicrobial agents
Acinetobacter baumannii[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime
		Ceftriaxone
Pseudomonas aeruginosa[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem

		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Antipseudomonal cephalosporins	Cefepime
		Cefpirome
		Ceftazidime
Enterobacteriaceae[a] *(Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae Enterobacter aerogenes,* or *Serratia marcescens*)	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
		Ertapenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime

		Ceftriaxone
Staphylococcus aureus[b]	Glycopeptides	Vancomycin
	β-lactamase-resistant penicillins	Oxacillin
Enterococcus faecium, Enterococcus faecalis, or other *Enterococcus species*[b]	Glycopeptides	Vancomycin

[a]Drug resistance was defined as being non-susceptible to ≧1 agent in ≧3 antimicrobial categories.

[b]Drug resistance was defined as being non-susceptible to ≧1 agent.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.[a]

Clinical outcomes	Excess costs or length of hospitalization (95% Confidence interval)[b]	*P*-value
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	< 0.0001
Cost of hospitalization, USD	8,871 (8,475, 9,268)	< 0.0001

[a]A total of 7,939 of patients with intensive care uit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

[b]Adjusted imbalanced variables in Table 1.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

Pathogen groups (Numbers of patients)[a]	9-year excessive hospitalization or healthcare cost	
	Length of hospitalization after the index date (days)[b]	Cost of hospitalization (USD)[b, c]
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
Acinetobacter baumannii (5,214)	66,374	40,003,372
Pseudomonas aeruginosa (2,619)	33,340	20,093,754
Enterobacteriaceae[d] (9,486)	120,757	72,779,438
Staphylococcus aureus (4,382)	55,783	33,620,019
Enterococcus species[e] (4,045)	51,493	31,034,454
Candida albicans (2,554)	32,512	19,595,054
Non-albicans Candida[f] (1,872)	23,831	14,362,546

Abbreviations: MDR= multiple drug resistance.

[a]The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The incluson and exclusion criteira in the method section were not applied in this Table (see Figure 1).

[b]The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s) and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was that in matched control group.

$Ave_{Hospitalization}$ per case= [(sum of hospitalization length)/the number of patients].

Excessive $Ave_{Hospitalization}$ per person= ($Ave_{Hospitalization}$ in bloodstream infection group) - ($Ave_{Hospitalization}$ in comparison group).

Total excessive hospitalization length over 9 years = (excessive $Ave_{Hospitalization}$ per person) × (total number of episodes over 9 years)

The 9-year excessive healthcare cost was calculated similarly.

[c]The costs are standardized and presented the values in 2017.

[d]*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens.*

[e]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species*

[f]*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata.*

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1 and #3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
Methods			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	#9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#9-12
		(*b*) Describe any methods used to examine subgroups and interactions	#9-12
		(*c*) Explain how missing data were addressed	#19
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	#12
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#14
		(b) Give reasons for non-participation at each stage	#14
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#14
		(b) Indicate number of participants with missing data for each variable of interest	#19
		(c) Summarise follow-up time (eg, average and total amount)	#14-15
Outcome data	15*	Report numbers of outcome events or summary measures over time	#14-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#14-15
		(*b*) Report category boundaries when continuous variables were categorized	#14-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#15
Discussion			
Key results	18	Summarise key results with reference to study objectives	#16
Limitations			#18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	#16-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#22-23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan: A nationwide population-based retrospective cohort study

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Article category: Original research

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 14-day mortality rate, length of hospitalization, 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 to 33.48% for 28,468 intensive care unit patients without bloodstream infections. The 14-day mortality rate was also higher in the bloodstream infections cohort (4,323, 30.37% *vs.* 6,766 deaths, 23.77%, respectively; $p < 0.001$). Furthermore, the patients with intensive care unit-acquired bloodstream infections had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] *vs.* 10

days [IQR 4–21], respectively; $p < 0.001$) and a higher healthcare cost (16,038 US dollars [IQR 9,667–25,946] *vs.* 10,372 US dollars [IQR 6,289–16,932], respectively; $p < 0.001$). The excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars, respectively. Similar results were observed in subgroup analyses of various World Health Organization'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.

Keywords: bloodstream infection; healthcare costs; hospital stay; intensive care unit; mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. A large number of patients obtained from Nationwide Taiwanese population from two datasets in Taiwan were included.
2. Propensity score-matching was performed to select a comparison cohort.
3. The 14-day and 28-day mortality rate, length of hospitalization, and healthcare cost were analyzed.
4. Subgroup analyses of several drug-resistant pathogens were conducted.
5. The retrospective design may include some unmeasurable bias.

BACKGROUND

Critically ill patients in intensive care units (ICUs) are vulnerable to various infections, 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 days[3] and the cost of treatment was approximately 12,321 US dollars 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 to BSIs involving susceptible strains.[4] Moreover, candidemia has been associated with a 4-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 World Health Organization (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 the 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. The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Study population, data collection, and propensity-score matching

This retrospective cohort study enrolled adult patients who underwent ICU hospitalization 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 (Supplementary 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 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 hospitalization,

which was selected from the index date of patients with the same day of hospitalization 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 matching [10] within a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score. (Supplementary Table 2). Patient data from January 2005 were used to ensure that individuals were followed for at least two years prior to their selection for this study in order to confirm comorbidities[11] and for matching purposes. The variables with missing values included monthly income and urbanization 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 hospitalization length after the index date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined

as the duration of hospital stay after the index date/pseudo-index date. The overall cost of hospitalization was calculated. The costs were standardized and presented in values from 2017.

Subgroup analysis

To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different pathogens, we 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 (ECDC) was modified[12] (Supplementary 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- 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 hospitalization/healthcare cost, we included patients who survived to discharge. For these patients, length of hospitalization after the index date/pseudo-index date and hospitalization 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. Standardized 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 Chi-squared test was used to evaluate mortality rate. Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of mortality in patients with BSI and the comparison cohort, while a generalized linear model was used to calculate β values to estimate excess costs and length of hospitalization.

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 (version 9.4, SAS Institute Inc., Cary, NC, USA).

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 hospitalization (Figure 1). After excluding patients whose 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 standardized 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% confidence interval [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 hospitalization after the index date (18 *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 hospitalization after the index date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp. was longer. In addition, hospitalization 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 7,669 US dollars per patient (95% CI, 7,380–7,958; $p < 0.001$). Table 4 presents the higher costs associated with each of the various causative pathogen.

For the ICU patients with BSIs who survived to discharge, their length of hospitalization and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively, (Supplementary Table 4) compared to 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-, 1.42-, 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 7,669 US dollars. 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.[1,3,13-16] For example, worse clinical outcomes have been reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S. aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] 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 pathogen[1] and is not associated with increased mortality unless in the presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] 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[3,13,20] 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 297 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate of infection by 10%[21] would translate into a savings of 30 million US dollars 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.[22, 23] In the present study, the costs for MDR bacteria included extra 84 million US dollars and 140,043 days over nine years (Supplementary 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,[16,18,20] and *C. albicans* is the most common pathogen. However, in some countries, the prevalence of non-*albicans Candida* exceeds that of *C. albicans*.[24] For those

infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization stays, and increased hospital costs have been described;[25-27] although other studies have reported contradicting findings.[28,29] These discrepancies may be due to host factors and differences in the virulence and resistance patterns[24] 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 to 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.[30] Second, confounding factors associated with clinical impact, such as 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.[31,32] Fourth, the prolonged hospitalization may have been due to a change in patient management in response to a BSI, rather than increased morbidity due to a BSI.[15] In addition, 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.

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.

LIST OF ABBREVIATIONS

BSI = bloodstream infection;

CI = confidence interval;

ECDC = European Centre for Disease Prevention and Control;

ICD-9-CM = international classification of diseases, 9th revision, clinical modification;

ICU = intensive care unit;

IQR = interquartile range;

MDR = multiple drug resistance;

NHIRD = National Health Insurance Research Database;

OR = odds ratio;

TNIS = Taiwan Nosocomial Infection Surveillance;

WHO = World Health Organization;

DECLARATIONS

Ethics approval and consent to participate

The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Ministry of Health and Welfare, Taiwan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ministry of Health and Welfare, Taiwan.

Competing interests

The authors declare that they have no competing interests.

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

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (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, USD			
Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001
Unknown	14 (0.1%)	33 (0.12%)	0.005
Urbanization level			
1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002
Unknown	11 (0.08%)	21 (0.07%)	0.001
Hospital level			
Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007
Charlson Comorbidity Index score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019
Comorbidities			
Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005

Myocardial infarction	525 (3.69%)	1,124 (3.95%)	0.014
Heart failure	2,532 (17.79%)	5,173 (18.17%)	0.01
Peripheral vascular disease	742 (5.21%)	1,509 (5.3%)	0.004
Liver disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Chronic kidney disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Dyslipidemia	2,766 (19.43%)	5,683 (19.96%)	0.013
Cancer	2,753 (19.34%)	5,635 (19.79%)	0.011
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (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%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

Abbreviations: BSI = bloodstream infection; SD = standard deviation.

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 (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.23%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.37%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.48%)	9,189 (32.28%)	<0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 39)	10 (4, 21)	< 0.0001

(IQR)						
Cost of hospitalization (USD)[a], median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,946)	(6,289, 16,932)	

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

[a]The costs are standardized and presented as the values in 2017.

Table 3. Clinical outcomes for the various pathogen groups.

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
Acinetobacter baumannii (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
Pseudomonas aeruginosa (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae[b] (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
Staphylococcus aureus (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
Enterococcus species[c] (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
Candida albicans (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non-*albicans Candida*[d] (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

Abbreviations: MDR = multiple drug resistance.

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

[b]Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens*.

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other

Enterococcus species.

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

484 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,342 (5,500, 7,184)
Acinetobacter baumannii	9.4 (7.65, 11.14)	6,727 (5,823, 7,632)
Pseudomonas aeruginosa	10.01 (7.83, 12.19)	6,761 (5,609, 7,913)
Enterobacteriaceae[b]	15.05 (13.33, 16.76)	7,444 (6,881, 8,007)
Staphylococcus aureus	14.72 (12.63, 16.81)	5,221 (4,528, 5,894)
Enterococcus species[c]	10.66 (7.85, 13.48)	7,219 (6,305, 8,132)
Candida albicans	11.37 (8.82, 13.92)	8,688 (7,512, 9,864)

Non-*albicans Candida*[d]	15.13 (11.77, 18.49)	11,476 (10,025, 12,927)

Abbreviations: MDR = multiple drug resistance.

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

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

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species.*

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

FIGURE LEGENDS

Figure 1. Flow diagram of the study design.

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National Health Insurance Research Database.

SUPPLEMENTARY FILES:

Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

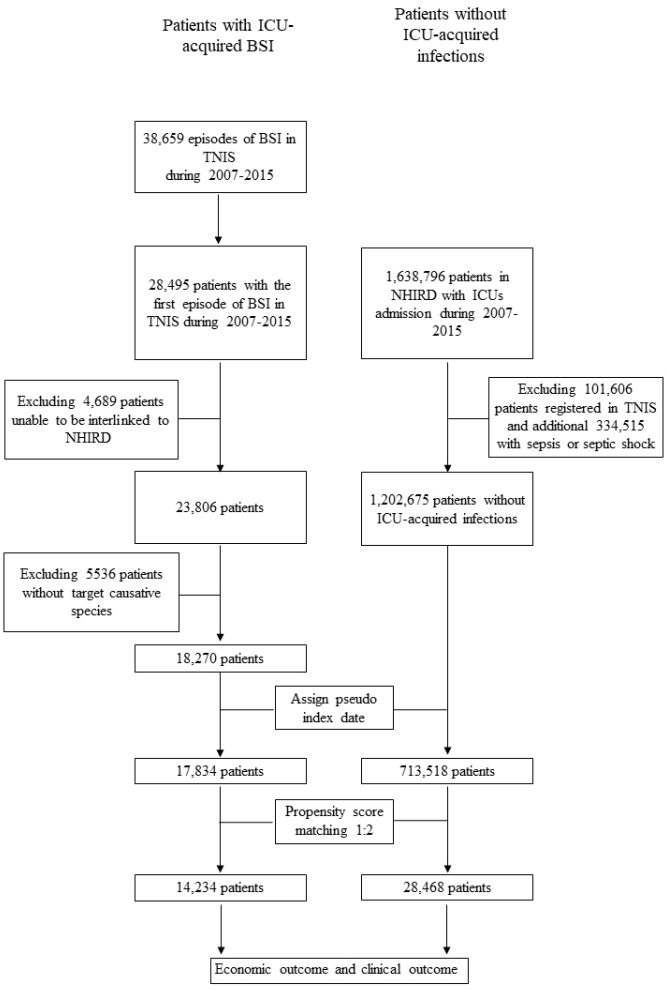

Figure 1. Flow diagram of the study design.

60x108mm (300 x 300 DPI)

Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

	No. of BSI episodes before enrollment[a]	No. of patients after matching[b]
Acinetobacter baumannii	5,214	1,761
Staphylococcus aureus	4,382	1,721
Klebsiella pneumoniae	3,965	1,357
Pseudomonas aeruginosa	2,619	853
Candida albicans	2,554	951
Escherichia coli	2,287	843
Enterobacter cloacae	1,982	746
Enterococcus faecium	1,950	647
Stenotrophomonas maltophilia	1,599	454
Enterococcus faecalis	1,427	419
Serratia marcescens	1,239	439
Candida tropicalis	890	329
Burkholderia cepacia	808	251
Other *Enterococcus species*[c]	688	211
Elizabethkingia meningoseptica	659	173
Chryseobacterium indologenes	553	152
Candida parapsilosis	534	177
Candida glabrata	461	197
Enterobacter aerogenes	419	163

Abbreviations: BSI= bloodstream infection.

[a]The number of episodes of bloodstream infections with known pathogens was 38,659.

Coagulase-negative staphylococci was excluded from analyses due to possibility of contamination. One episode may have multiple pathogens. There were 30,697 episodes of bloodstream infections caused by the pathogens listed above.

[b]The number of patients enrolled case was 14,234 (Table 1) but only patients with bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it was 11,844. There were 2,390 patients with bloodstream infections caused by multiple pathogens.

[c]*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis.*

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Parameter	Estimate	Odds ratios	95% Confidence interval		*P*-value
			Lower	Upper	
Age, years	-0.0014	0.9986	0.9974	0.9998	0.0251
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

Dependent	--	1.000	--	--	--
<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
Urbanization level					
1 (urban)		1.000			
2	0.0093	1.0094	0.9516	1.0706	0.7560
3	-0.0006	0.9994	0.9293	1.0748	0.9872
4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
Hospital level					
Level I (Medical center)	--	1.000	--	--	--
Level II (Regional hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
Charlson Comorbidity Index score					
0	--	1.000	--	--	--
1	0.1421	1.1527	1.0681	1.2439	0.0003
2	0.2932	1.3407	1.2390	1.4508	<0.0001
≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
Comorbidities					
Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292

Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Pathogens	Antimicrobial categories	Antimicrobial agents
Acinetobacter baumannii[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime
		Ceftriaxone
Pseudomonas aeruginosa[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem

		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Antipseudomonal cephalosporins	Cefepime
		Cefpirome
		Ceftazidime
Enterobacteriaceae[a] *(Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae Enterobacter aerogenes,* or *Serratia marcescens*)	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
		Ertapenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime

		Ceftriaxone
Staphylococcus aureus[b]	Glycopeptides	Vancomycin
	β-lactamase-resistant penicillins	Oxacillin
Enterococcus faecium, Enterococcus faecalis, or other *Enterococcus species*[b]	Glycopeptides	Vancomycin

[a]Drug resistance was defined as being non-susceptible to ≧1 agent in ≧3 antimicrobial categories.

[b]Drug resistance was defined as being non-susceptible to ≧1 agent.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.[a]

Clinical outcomes	Excess costs or length of hospitalization (95% Confidence interval)[b]	*P*-value
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	< 0.0001
Cost of hospitalization, USD	8,871 (8,475, 9,268)	< 0.0001

[a]A total of 7,939 of patients with intensive care uit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

[b]Adjusted imbalanced variables in Table 1.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

Pathogen groups (Numbers of patients)[a]	9-year excessive hospitalization or healthcare cost	
	Length of hospitalization after the index date (days)[b]	Cost of hospitalization (USD)[b, c]
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
Acinetobacter baumannii (5,214)	66,374	40,003,372
Pseudomonas aeruginosa (2,619)	33,340	20,093,754
Enterobacteriaceae[d] (9,486)	120,757	72,779,438
Staphylococcus aureus (4,382)	55,783	33,620,019
Enterococcus species[e] (4,045)	51,493	31,034,454
Candida albicans (2,554)	32,512	19,595,054
Non-albicans Candida[f] (1,872)	23,831	14,362,546

Abbreviations: MDR= multiple drug resistance.

[a]The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The incluson and exclusion criteira in the method section were not applied in this Table (see Figure 1).

[b]The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s) and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was that in matched control group.

$Ave_{Hospitalization}$ per case= [(sum of hospitalization length)/the number of patients].

Excessive $Ave_{Hospitalization}$ per person= ($Ave_{Hospitalization}$ in bloodstream infection group) - ($Ave_{Hospitalization}$ in comparison group).

Total excessive hospitalization length over 9 years = (excessive $Ave_{Hospitalization}$ per person) × (total number of episodes over 9 years)

The 9-year excessive healthcare cost was calculated similarly.

[c]The costs are standardized and presented the values in 2017.

[d]*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens.*

[e]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species*

[f]*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata.*

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1 and #3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
Methods			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	#9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#9-12
		(*b*) Describe any methods used to examine subgroups and interactions	#9-12
		(*c*) Explain how missing data were addressed	#10
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	#12
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#14
		(b) Give reasons for non-participation at each stage	#14
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#14 and #30-32
		(b) Indicate number of participants with missing data for each variable of interest	#19 and #31
		(c) Summarise follow-up time (eg, average and total amount)	#14-15
Outcome data	15*	Report numbers of outcome events or summary measures over time	#14-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#14-15
		(*b*) Report category boundaries when continuous variables were categorized	#14-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#15
Discussion			
Key results	18	Summarise key results with reference to study objectives	#16
Limitations			#18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	#16-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#22-23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Article category: Original research

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 14-day mortality rate, length of hospitalization, 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 to 33.48% for 28,468 intensive care unit patients without bloodstream infections. The 14-day mortality rate was also higher in the bloodstream infections cohort (4,323, 30.37% *vs.* 6,766 deaths, 23.77%, respectively; $p < 0.001$). Furthermore, the patients with intensive care unit-acquired bloodstream infections had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] *vs.* 10

days [IQR 4–21], respectively; $p < 0.001$) and a higher healthcare cost (16,038 US dollars [IQR 9,667–25,946] *vs.* 10,372 US dollars [IQR 6,289–16,932], respectively; $p < 0.001$). The excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars, respectively. Similar results were observed in subgroup analyses of various World Health Organization'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.

Keywords: bloodstream infection; healthcare costs; hospital stay; intensive care unit; mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. A large number of patients obtained from Nationwide Taiwanese population from two datasets in Taiwan were included.
2. Propensity score-matching was performed to select a comparison cohort.
3. The 14-day and 28-day mortality rate, length of hospitalization, and healthcare cost were analyzed.
4. Subgroup analyses of several drug-resistant pathogens were conducted.
5. The retrospective design may include some unmeasurable bias.

BACKGROUND

Critically ill patients in intensive care units (ICUs) are vulnerable to various infections, 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 days[3] and the cost of treatment was approximately 12,321 US dollars 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 to BSIs involving susceptible strains.[4] Moreover, candidemia has been associated with a 4-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 World Health Organization (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 the 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. The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Study population, data collection, and propensity-score matching

This retrospective cohort study enrolled adult patients who underwent ICU hospitalization 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 (Supplementary 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 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 hospitalization,

which was selected from the index date of patients with the same day of hospitalization 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 matching [10] within a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score. (Supplementary Table 2). Patient data from January 2005 were used to ensure that individuals were followed for at least two years prior to their selection for this study in order to confirm comorbidities [11] 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 urbanization 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 hospitalization length after the index date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined as the duration of hospital stay after the index date/pseudo-index date. The overall cost of hospitalization was calculated. The costs were standardized and presented in values from 2017.

Subgroup analysis

To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different pathogens, we 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 (ECDC) was modified [14]

(Supplementary 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- 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 hospitalization/healthcare cost, we included patients who survived to discharge. For these patients, length of hospitalization after the index date/pseudo-index date and hospitalization 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. Standardized 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 Chi-squared test was used to evaluate mortality rate. Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of

mortality in patients with BSI and the comparison cohort, while a generalized linear model was used to calculate β values to estimate excess costs and length of hospitalization. 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 (version 9.4, SAS Institute Inc., Cary, NC, USA).

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 hospitalization (Figure 1). After excluding patients whose 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 standardized 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% confidence interval [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 hospitalization after the index date (18 *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 hospitalization after the index date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp. was longer. In addition, hospitalization 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 7,669 US dollars per patient (95% CI, 7,380–7,958; $p < 0.001$). Table 4 presents the higher costs associated with each of the various causative pathogen.

For the ICU patients with BSIs who survived to discharge, their length of hospitalization and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively, (Supplementary Table 4) compared to 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-, 1.42-, 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 7,669 US dollars. 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 pathogen [1] 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 297 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate of infection by 10% [23] would translate into a savings of 30 million US dollars 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 84 million US dollars and 140,043 days over nine years (Supplementary 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 hospitalization 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 patterns [26] 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 to 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 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 hospitalization 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.

LIST OF ABBREVIATIONS

BSI = bloodstream infection;

CI = confidence interval;

ECDC = European Centre for Disease Prevention and Control;

ICD-9-CM = international classification of diseases, 9th revision, clinical modification;

ICU = intensive care unit;

IQR = interquartile range;

MDR = multiple drug resistance;

NHIRD = National Health Insurance Research Database;

OR = odds ratio;

TNIS = Taiwan Nosocomial Infection Surveillance;

WHO = World Health Organization;

DECLARATIONS

Ethics approval and consent to participate

The institutional review board of the National Health Research Institutes approved this study (EC1051207-R4).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Ministry of Health and Welfare, Taiwan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ministry of Health and Welfare, Taiwan.

Competing interests

The authors declare that they have no competing interests.

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

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (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, USD			
Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001
Unknown	14 (0.1%)	33 (0.12%)	0.005
Urbanization level			
1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002
Unknown	11 (0.08%)	21 (0.07%)	0.001
Hospital level			
Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007
Charlson Comorbidity Index score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019
Comorbidities			
Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005

Myocardial infarction	525 (3.69%)	1,124 (3.95%)	0.014
Heart failure	2,532 (17.79%)	5,173 (18.17%)	0.01
Peripheral vascular disease	742 (5.21%)	1,509 (5.3%)	0.004
Liver disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Chronic kidney disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Dyslipidemia	2,766 (19.43%)	5,683 (19.96%)	0.013
Cancer	2,753 (19.34%)	5,635 (19.79%)	0.011
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (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%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

Abbreviations: BSI = bloodstream infection; SD = standard deviation.

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 (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.23%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.37%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.48%)	9,189 (32.28%)	<0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 39)	10 (4, 21)	< 0.0001

(IQR)						
Cost of hospitalization (USD)[a], median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,946)	(6,289, 16,932)	

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

[a]The costs are standardized and presented as the values in 2017.

Table 3. Clinical outcomes for the various pathogen groups.

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
Acinetobacter baumannii (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
Pseudomonas aeruginosa (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae[b] (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
Staphylococcus aureus (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
Enterococcus species[c] (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
Candida albicans (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non-*albicans Candida*[d] (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

Abbreviations: MDR = multiple drug resistance.

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

[b]Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens*.

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other

Enterococcus species.

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

Table 4. Economic outcomes for the various pathogen groups.

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,342 (5,500, 7,184)
Acinetobacter baumannii	9.4 (7.65, 11.14)	6,727 (5,823, 7,632)
Pseudomonas aeruginosa	10.01 (7.83, 12.19)	6,761 (5,609, 7,913)
Enterobacteriaceae[b]	15.05 (13.33, 16.76)	7,444 (6,881, 8,007)
Staphylococcus aureus	14.72 (12.63, 16.81)	5,221 (4,528, 5,894)
Enterococcus species[c]	10.66 (7.85, 13.48)	7,219 (6,305, 8,132)
Candida albicans	11.37 (8.82, 13.92)	8,688 (7,512, 9,864)

Non-*albicans Candida*[d]	15.13 (11.77, 18.49)	11,476 (10,025, 12,927)

Abbreviations: MDR = multiple drug resistance.

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

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

[c]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species.*

[d]Non-*albicans Candida* included *Candida tropicalis, Candida parapsilosis,* and *Candida glabrata.*

FIGURE LEGENDS

Figure 1. Flow diagram of the study design.

Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National Health Insurance Research Database.

SUPPLEMENTARY FILES:

Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

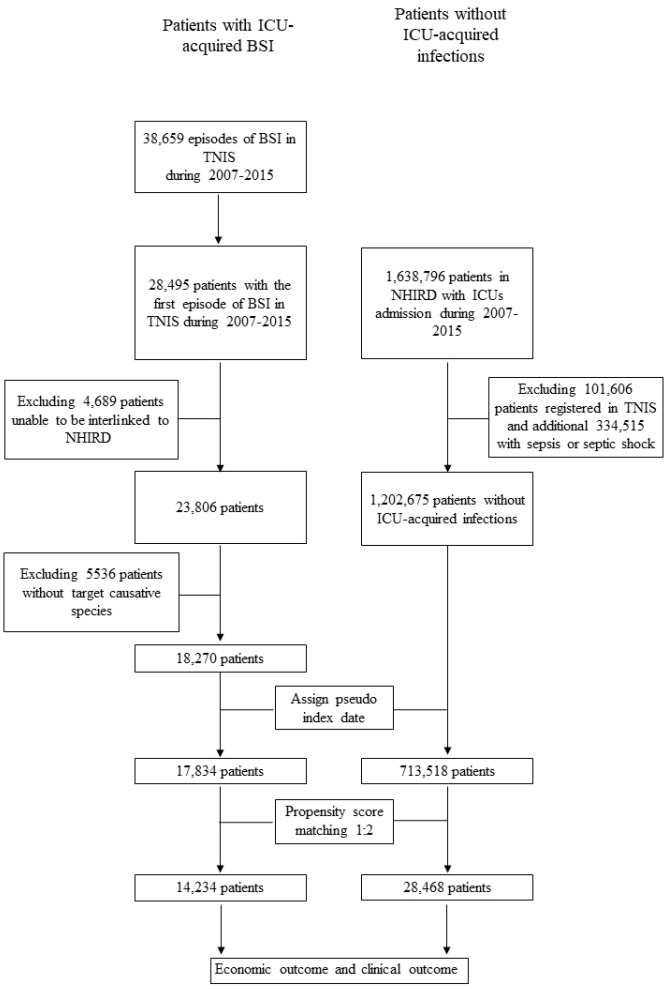

Figure 1. Flow diagram of the study design.

60x108mm (300 x 300 DPI)

Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before enrollment and the number of patients infected after matching.

	No. of BSI episodes before enrollment[a]	No. of patients after matching[b]
Acinetobacter baumannii	5,214	1,761
Staphylococcus aureus	4,382	1,721
Klebsiella pneumoniae	3,965	1,357
Pseudomonas aeruginosa	2,619	853
Candida albicans	2,554	951
Escherichia coli	2,287	843
Enterobacter cloacae	1,982	746
Enterococcus faecium	1,950	647
Stenotrophomonas maltophilia	1,599	454
Enterococcus faecalis	1,427	419
Serratia marcescens	1,239	439
Candida tropicalis	890	329
Burkholderia cepacia	808	251
Other *Enterococcus species*[c]	688	211
Elizabethkingia meningoseptica	659	173
Chryseobacterium indologenes	553	152
Candida parapsilosis	534	177
Candida glabrata	461	197
Enterobacter aerogenes	419	163

Abbreviations: BSI= bloodstream infection.

[a]The number of episodes of bloodstream infections with known pathogens was 38,659.

Coagulase-negative staphylococci was excluded from analyses due to possibility of contamination. One episode may have multiple pathogens. There were 30,697 episodes of bloodstream infections caused by the pathogens listed above.

[b]The number of patients enrolled case was 14,234 (Table 1) but only patients with bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it was 11,844. There were 2,390 patients with bloodstream infections caused by multiple pathogens.

[c]*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis.*

Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched comparison cohort.

Parameter	Estimate	Odds ratios	95% Confidence interval		*P*-value
			Lower	Upper	
Age, years	-0.0014	0.9986	0.9974	0.9998	0.0251
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

Dependent	--	1.000	--	--	--
<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
Urbanization level					
1 (urban)		1.000			
2	0.0093	1.0094	0.9516	1.0706	0.7560
3	-0.0006	0.9994	0.9293	1.0748	0.9872
4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
Hospital level					
Level I (Medical center)	--	1.000	--	--	--
Level II (Regional hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
Charlson Comorbidity Index score					
0	--	1.000	--	--	--
1	0.1421	1.1527	1.0681	1.2439	0.0003
2	0.2932	1.3407	1.2390	1.4508	<0.0001
≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
Comorbidities					
Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292

Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

Pathogens	Antimicrobial categories	Antimicrobial agents
Acinetobacter baumannii[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime
		Ceftriaxone
Pseudomonas aeruginosa[a]	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem

		Doripenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Antipseudomonal cephalosporins	Cefepime
		Cefpirome
		Ceftazidime
Enterobacteriaceae[a] *(Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae Enterobacter aerogenes,* or *Serratia marcescens*)	Aminoglycosides	Gentamicin
		Tobramycin
		Amikacin
		Netilmicin
	Carbapenems	Imipenem
		Meropenem
		Doripenem
		Ertapenem
	Fluoroquinolones	Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
	Extended-spectrum cephalosporins	Cefotaxime
		Cefepime
		Cefpirome
		Ceftazidime

		Ceftriaxone
Staphylococcus aureus[b]	Glycopeptides	Vancomycin
	β-lactamase-resistant penicillins	Oxacillin
Enterococcus faecium, Enterococcus faecalis, or other *Enterococcus species*[b]	Glycopeptides	Vancomycin

[a]Drug resistance was defined as being non-susceptible to ≧1 agent in ≧3 antimicrobial categories.

[b]Drug resistance was defined as being non-susceptible to ≧1 agent.

Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the discharge.[a]

Clinical outcomes	Excess costs or length of hospitalization (95% Confidence interval)[b]	*P*-value
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	< 0.0001
Cost of hospitalization, USD	8,871 (8,475, 9,268)	< 0.0001

[a]A total of 7,939 of patients with intensive care uit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

[b]Adjusted imbalanced variables in Table 1.

Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

Pathogen groups (Numbers of patients)[a]	9-year excessive hospitalization or healthcare cost	
	Length of hospitalization after the index date (days)[b]	Cost of hospitalization (USD)[b, c]
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
Acinetobacter baumannii (5,214)	66,374	40,003,372
Pseudomonas aeruginosa (2,619)	33,340	20,093,754
Enterobacteriaceae[d] (9,486)	120,757	72,779,438
Staphylococcus aureus (4,382)	55,783	33,620,019
Enterococcus species[e] (4,045)	51,493	31,034,454
Candida albicans (2,554)	32,512	19,595,054
Non-albicans Candida[f] (1,872)	23,831	14,362,546

Abbreviations: MDR= multiple drug resistance.

[a]The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The incluson and exclusion criteira in the method section were not applied in this Table (see Figure 1).

[b]The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s) and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was that in matched control group.

$Ave_{Hospitalization}$ per case= [(sum of hospitalization length)/the number of patients].

Excessive $Ave_{Hospitalization}$ per person= ($Ave_{Hospitalization}$ in bloodstream infection group) - ($Ave_{Hospitalization}$ in comparison group).

Total excessive hospitalization length over 9 years = (excessive $Ave_{Hospitalization}$ per person) × (total number of episodes over 9 years)

The 9-year excessive healthcare cost was calculated similarly.

[c]The costs are standardized and presented the values in 2017.

[d]*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa,* and *Serratia marcescens.*

[e]*Enterococcus species* included *Enterococcus faecium, Enterococcus faecalis,* and other *Enterococcus species*

[f]*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata.*

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1 and #3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
Methods			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	#9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#9-12
		(*b*) Describe any methods used to examine subgroups and interactions	#9-12
		(*c*) Explain how missing data were addressed	#10
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	#12
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#14
		(b) Give reasons for non-participation at each stage	#14
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#14 and #30-32
		(b) Indicate number of participants with missing data for each variable of interest	#19 and #31
		(c) Summarise follow-up time (eg, average and total amount)	#14-15
Outcome data	15*	Report numbers of outcome events or summary measures over time	#14-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#14-15
		(*b*) Report category boundaries when continuous variables were categorized	#14-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#15
Discussion			
Key results	18	Summarise key results with reference to study objectives	#16
Limitations			#18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	#16-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#22-23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.