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

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Research

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

Posted Date: November 9th, 2019

DOI: https://doi.org/10.21203/rs.2.17038/v1

Abstract

Background: To estimate the clinical and economic impact of intensive care unit-acquired bloodstream infections in Taiwan. Methods: The first episodes of intensive care unit-acquired bloodstream infections in patients ≥ 20 years of age in the Taiwanese population were identified in the National Health Insurance Research Database and in the Taiwan Nosocomial Infections Surveillance (2007-2015) dataset. 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. 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.

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.

Funding

This work was supported by a grant from the National Health Research Institutes [Grant no. 108-0324-01-19-06] and Tri-Service General Hospital [TSGH-C107-099]. The sponsors had no role in the study design; collection, analysis, or interpretation of data; writing of the report; or the decision to submit the article for publication.

Author contributions

YCW, YTC, and SCK contributed to the conception and design. YCW was a major contributor in drafting and revising the manuscript. SMS and YTC contributed to the data collection and data analysis. SCK and CAH revised the manuscript with important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Prowle JR, Echeverri JE, Ligabo EV, Sherry N, Taori GC, Crozier TM, et al. Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. Crit Care 2011; 15: R100.
2. Garrouste-Orgeas M, Timsit JF, Tafflet M, Misset B, Zahar JR, Soufir L, et al. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a re-appraisal. Clin Infect Dis 2006; 42: 1118-26.
3. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired bloodstream infections. J Hosp Infect 2006; 63: 124-32.
4. Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill 2016; 21: pii=30319.
5. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to nosocomial enterococcal bacteremia: a controlled study. Am J Infect Control 1989; 17: 323-9.
6. Ong DS, Bonten MJ, Safdari K, Spitoni C, Frencken JF, Witteveen E, et al. Epidemiology, management, and risk-adjusted mortality of ICU-acquired enterococcal bacteremia. Clin Infect Dis 2015; 61: 1413-20.
7. Kramer TS, Remschmidt C, Werner S, Behnke M, Schwab F, Werner G, et al. The importance of adjusting for Enterococcus species when assessing the burden of vancomycin resistance: a cohort study including over 1000 cases of enterococcal bloodstream infections. Antimicrob Resist Infect Control 2018; 7: 133.

8. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018; 18: 318-27.
9. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan. London J Prim Care (Abingdon) 2010; 3: 115-9.
10. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007; 357: 1393-402.
11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; 45: 613-9.
12. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18: 268-81.
13. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. JAMA 1994; 271: 1598-601.
14. Laupland KB, Zygun DA, Davies HD, Church DL, Louie TJ, Doig CJ, et al. Population-based assessment of intensive care unit-acquired bloodstream infections in adults: incidence, risk factors, and associated mortality rate. Crit Care Med 2002; 30: 2462-7.
15. Barnett AG, Page K, Campbell M, Martin E, Rashleigh-Rolls R, Halton K, et al. The increased risks of death and extra lengths of hospital and ICU stay from hospital-acquired bloodstream infections: a case-control study. BMJ Open 2013; 3: e003587.
16. Marra AR, Camargo LF, Pignatari AC, Sukiennik T, Behar PR, Medeiros EA, et al. Nosocomial bloodstream infections in Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide surveillance study. J Clin Microbiol 2011; 49: 1866-71.
17. Lemos EV, de la Hoz FP, Einarson TR, McGhan WF, Quevedo E, Castañeda C, et al. Carbapenem resistance and mortality in patients with Acinetobacter baumannii infection: systematic review and meta-analysis. Clin Microbiol Infect 2014; 20: 416-23.
18. Schwab F, Geffers C, Behnke M,Gastmeier P. ICU mortality following ICU-acquired primary bloodstream infections according to the type of pathogen: a prospective cohort study in 937 Germany ICUs (2006-2015). PloS One 2018; 13: e0194210.
19. Caballero-Granado FJ, Becerril B, Cuberos L, Bernabeu M, Cisneros JM, Pachón J. Attributable mortality rate and duration of hospital stay associated with enterococcal bacteremia. Clin Infect Dis 2001; 32: 587-94.
20. Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis 2005; 41: 1591-8.
21. Tseng SH, Lee CM, Lin TY, Chang SC, Chuang YC, Yen MY, et al. Combating antimicrobial resistance: antimicrobial stewardship program in Taiwan. J Microbiol Immunol Infect 2012; 45: 79-89.

22. Howard D, Cordell R, McGowan JE, Jr., Packard RM, Scott RD 2nd, Solomon SL, et al. Measuring the economic costs of antimicrobial resistance in hospital settings: summary of the Centers for Disease Control and Prevention-Emory Workshop. Clin Infect Dis 2001; 33: 1573-8.
23. Mauldin PD, Salgado CD, Hansen IS, Durup DT, Bosso JA. Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant gram-negative bacteria. Antimicrob Agents Chemother 2010; 54: 109-15.
24. Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 2009; 48: 1695-703.
25. Dimopoulos G, Ntziora F, Rachiotis G, Armaganidis A, Falagas ME. Candida albicans versus non-albicans intensive care unit-acquired bloodstream infections: differences in risk factors and outcome. Anesth Analg 2008; 106: 523-9.
26. Moran C, Grussemeyer CA, Spalding JR, Benjamin DK Jr, Reed SD. Comparison of costs, length of stay, and mortality associated with Candida glabrata and Candida albicans bloodstream infections. Am J Infect Control 2010; 38: 78-80.
27. Gong X, Luan T, Wu X, Li G1, Qiu H2, Kang Y, et al. Invasive candidiasis in intensive care units in China: risk factors and prognoses of Candida albicans and non-albicans Candida infections. Am J Infect Control 2016; 44: e59-63.
28. Pfaller M, Neofytos D, Diekema D, Azie N, Meier-Kriesche HU, Quan SP. Epidemiology and outcomes of candidemia in 3648 patients: data from the prospective antifungal therapy (PATH Alliance®) registry, 2004-2008. Diagn Microbiol Infect Dis 2012; 74: 323-31.
29. Barchiesi F, Orsetti E, Gesuita R, Skrami E, Manso E; Candidemia Study Group. Epidemiology, clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy from 2010 to 2014. Infection 2016; 44: 205-13.
30. Nelson RE, Samore MH, Jones M, Greene T, Stevens VW, Liu CF, et al. Reducing time-dependent bias in estimates of the attributable cost of health care-associated Methicillin-resistant Staphylococcus aureus infections: a comparison of three estimation strategies. Med Care 2015; 53: 827-34.
31. Kuo SC, Shih SM, Hsieh LY, Lauderdale TY, Chen YC, Hsiung CA, et al. Antibiotic restriction policy paradoxically increased private drug consumptions outside Taiwan's National Health Insurance. J Antimicrob Chemother 2017; 72: 1544-5.
32. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative data. JAMA 2012; 307: 1433-5.

Tables

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

Characteristics	ICU 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: ICU = intensive care unit; BSI = bloodstream infection; SD = standard deviation.

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

	Full cohort			Matched cohort		
Outcomes	**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, 26,131)	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.*

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)	5,605 (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.*

Additional File Legends

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.

Figures

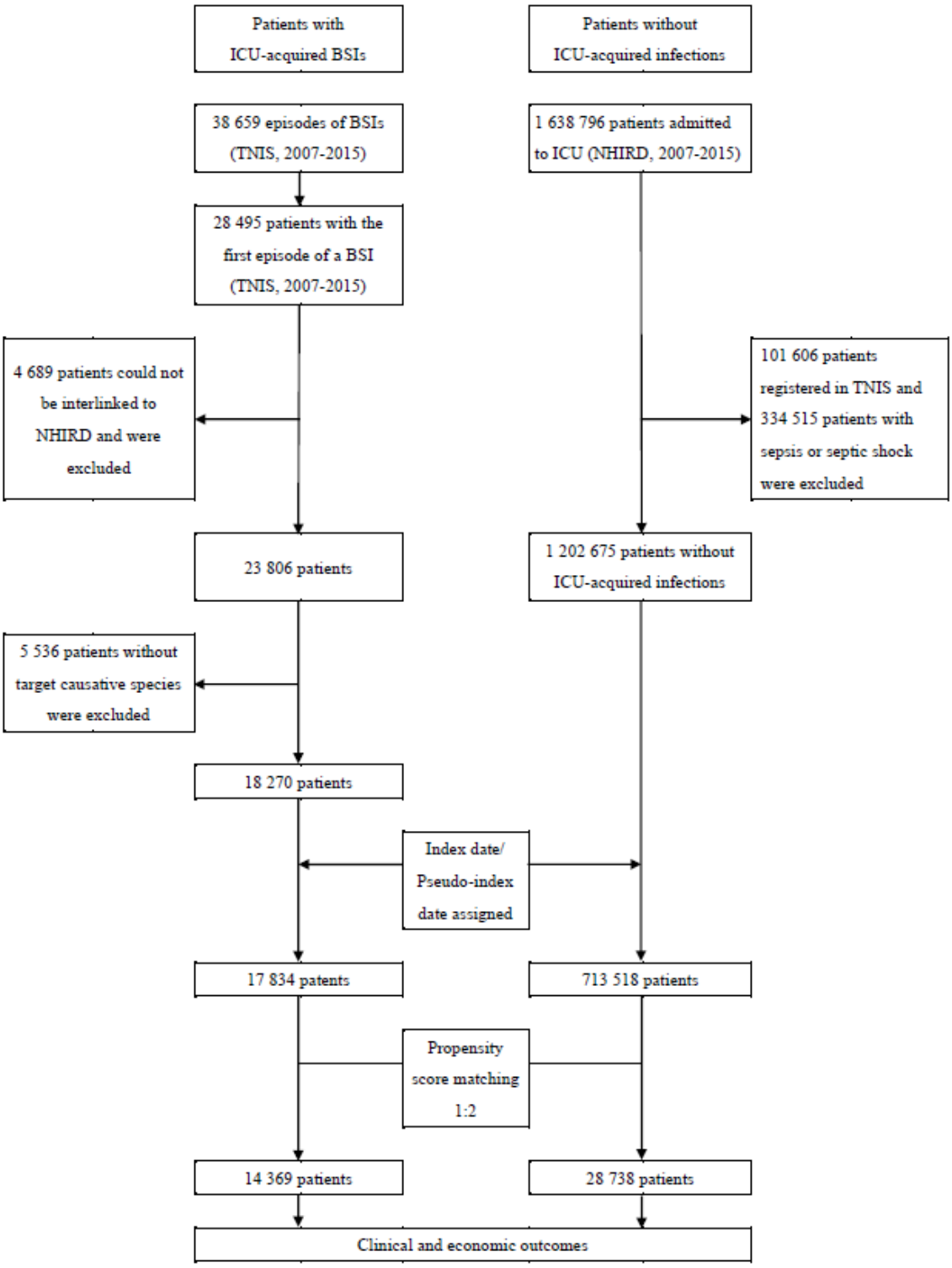

Figure 1

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

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable0928.pdf