Temporal trend and survival impact of infection source among patients with sepsis: a nationwide study

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ABSTRACT

Background: To determine the temporal trends of incidence and outcome based on different sources of sepsis using a nationwide administrative database.

Methods: From 2002 to 2012, the entire Taiwan's health insurance claims data of emergency-treated and hospital-treated sepsis were analysed for incidence and mortality trends. The information about patients with sepsis and sources of sepsis was identified using a set of validated International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes. The 30-day all-cause mortality was verified by linked death certificate database.

Results: A total of 1 259 578 episodes of sepsis were identified during the 11-year study period. Lower respiratory tract infection is the most common source of sepsis in patients, with the highest mortality rate. The incidence of genitourinary tract infection has the fastest growing rate. The sepsis mortality was declining at different rates for each source of sepsis. Co-infections in patients with sepsis are associated with higher mortality rate.

Conclusion: The temporal trends of sepsis incidence and mortality varied among different sources of sepsis, with lower respiratory tract being the highest burden among patients with sepsis. Furthermore, sources of sepsis and the presence of co-infection are independent predictors of mortality. Our results support source-specific preventive and treatment strategies for future sepsis management.

Crit Care Resusc 2020; 22 (2): 126-132

Sepsis is a dysregulated host response to infection with the presence of organ dysfunction.[1] The incidence of sepsis is rising worldwide.[2-5] It is a major cause of death and the most expensive condition to treat, accounting for 6.2% of all inpatient hospital costs in the United States in 2013.[5,6] Despite its final pathway leading to organ dysfunction via dysregulated host response, the underlying causes that incite these aberrant responses differ among patients with sepsis. Identifying the underlying causes of sepsis is important as treatments differ, with some causes being potentially preventable. For example, pneumonias can be prevented by vaccination and restriction of off-label use of proton pump inhibitors or antipsychotics,[7,8] and bloodstream infections and urinary tract infections can be prevented by aseptic technique and early removal of catheters.

The temporal trends of sources of sepsis with its implications on the prognosis of sepsis have not been comprehensively reported. A few studies have investigated if the underlying causes of sepsis and the burden of co-infection may have strong implications regarding prognosis of sepsis, but the results were discordant.[9-12]

A population-based study addressing the temporal trends of sources of sepsis with their corresponding mortality can provide important information for intensive care resource allocation, public health prevention and research priorities. We hypothesise that the sources of sepsis and the burden of co-infection have strong implications on the outcome of patients with sepsis. Based on a nationwide temporal data over 11 years, we seek to address the following three aims. First, we aim to report the temporal trends of the incidence for each specific source of sepsis and their corresponding prognosis in a large population-wide administrative database in Taiwan. Second, we aim to investigate the independent role of co-infections on the outcome of sepsis. Lastly, we aim to investigate the independent impact of underlying diagnosis or source of infection as a determinant of outcome in sepsis.

Methods

Study design

We adopted a cross-sectional design for temporal trends analysis and a cohort design for survival impact analysis. We analysed the entire National Health Insurance (NHI) claims database of Taiwan between 1 January 2002 and 31 December 2012. Since this study was based on an anonymous electronic database, patient consent was not required. Our study was approved by the institutional review board of the National Taiwan University Hospital.

Source of data

The NHI claims database was developed as part of the National Health Informatics Project (NHIP) sponsored by the Ministry of Health and Welfare of Taiwan. The NHI of Taiwan is a government-operated, mandatory health insurance system that covers 99.7% of the entire 23 million residents of Taiwan. More than 95% of the Taiwanese population are Han Chinese, and the second largest ethnic group is of Austronesian ancestry (around 2%).

Identification of patients with sepsis

The Sepsis-3 consensus defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.[13] The coding system used in this study conformed to Sepsis-3 definition, which was validated by Angus and colleagues.[14] Sepsis cases were identified by selecting all cases with both bacterial or fungal infection (Online Appendix; supplementary appendix 1) and a diagnosis of acute organ or system dysfunction using International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes (Online Appendix, supplementary methods). The source of sepsis includes lower respiratory, genitourinary tract, intra-abdominal, skin and skin structure, musculoskeletal, biliary tree, and systemic fungal infection. The source of sepsis information was gathered by using ICD-9-CM codes (Online Appendix; supplementary appendix 1). Index date was defined as the first day of emergency department visit or hospital admission of sepsis. Demographic data, pre-existing comorbidity, and outcome were collected for analysis. The comorbidity information was obtained one year before the sepsis index date. The method for obtaining comorbidity information was based on ICD-9-CM codes and validated by Gangne and colleagues.[15] Other information was abstracted from the index hospitalisation claims records. Mortality was defined as 30-day all-cause mortality verified by a linked national death certificate database.

Statistical analysis

Patients with sepsis were divided into subgroups according to different sources of sepsis. Categorical variables were presented as frequency and percentage, and continuous variables were presented as mean (standard deviation [SD]). For each group, the crude incidence of sepsis was calculated as the number of incident sepsis episodes divided by the number of years followed for each person, and the crude mortality rate was calculated by the number of deaths divided by the total number of sepsis cases in each group. If a patient was admitted due to sepsis more than once in the same calendar year, only the first admission due to sepsis was included for analysis. The temporal trends were all presented with line graphs. We calculated the overall and average annual percentage change in the hospitalisation and mortality of sepsis and specific source of infection between 2002 and 2012. Since NHI claims database of Taiwan allows capture of all cases of sepsis, there is minimal possibility of chance variation. Therefore, confidence intervals (CIs) were not presented in all incidence and mortality estimates. To evaluate the impact of co-infection and source of sepsis on the survival of patients with sepsis, we used a multivariable Cox proportional hazard model adjusting for age, sex, and comorbidity measures (Online Appendix, supplementary table 2). We tested the proportional hazard assumption by examining the parallel log–log transformation curves of hazards over time between two groups in comparison, and tested the significance of interaction term between time and covariates. We used the entire study period for this regression analysis to ensure adequate power to make reliable estimates of risk. Two-sided $P < 0.05$ was considered statistically significant for all analyses. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA).

Results

The NHI database began in 1997. We used the data between 2002 and 2012 for this analysis. In this time frame, a total of 230 154 807 patients were enrolled, of which 228 853 139 patients were excluded since they did not fulfil the working definition of sepsis in this study. In addition, 42 090 patients were further excluded because they were aged less than 18 years. Finally, a total of 1 259 578 adult patients with sepsis were identified in the 11-year period. Table 1 shows the proportion, mortality rate and readmission rate of seven sources of sepsis. Overall, among patients with sepsis, lower respiratory tract infection (LRTI) was the most common source of sepsis (54.0%, n = 680 324), followed by genitourinary tract infection (GUTI) (33.9%), intra-abdominal infection (IAI) (5.8%), skin and skin structure infection (5.0%), systematic fungal infection (2.4%), musculoskeletal infection (1.5%), and biliary tract infection (1.1%). With respect to mortality, LRTI (25.8%) and IAI (25.1%) were associated with the worst outcome, followed by GUTI (15.1%), biliary tract infection (13.6%), skin and skin structure infection (13.4%), musculoskeletal infection (11.9%), and systematic fungal infection (11.8%).

The distribution of demographics and source of sepsis by year are shown in the Online Appendix (supplementary table 1). Men comprised more than half of sepsis cases, and the proportion of male patients ranged between 58.1% and 59.9% in the study period. The average age of patients with sepsis gradually increased over time, from 67.3 years in 2002 to 70.7 years in 2012. LRTI was the most common source of sepsis accounting for more than half of the sepsis cases. GUTI was the second leading source of sepsis. Taken together, these two sources accounted for most sources of sepsis.

Table 1. Population incidence, 30-day mortality, and readmission rate of specific infection source among patients with sepsis

	Incidence *n* (%)	30-day mortality *n* (%)	Readmission *n* (%)
Lower respiratory tract infection	607 746 (48.3%)	142 456 (23.4%)	108 786 (17.9%)
Genitourinary tract infection	252 168 (20.0%)	29 352 (11.6%)	89 338 (14.7%)
Intra-abdominal infection	53 658 (4.3%)	13 881 (25.9%)	46 796 (7.7%)
Skin and skin structure infection	27 207 (2.2%)	3300 (12.1%)	64 421 (10.6%)
Systematic fungal infection	11 714 (0.9%)	2000 (17.1%)	75 968 (12.5%)
Musculoskeletal infection	8565 (0.7%)	1263 (14.8%)	72 321 (11.9%)
Biliary tract infection	7683 (0.6%)	973 (12.7%)	23 702 (3.9%)
Other	290 837 (23.1%)	85 506 (29.4%)	64 481 (10.61%)

Table 2 shows the changes in population incidence of specific source of sepsis. Most sources of sepsis showed constant increasing incidence, with GUTI having the fastest growing rate (annual increase 3.2%). On the contrary, biliary tract infection as the source of sepsis did not show increased incidence (annual decrease 0.1%), as opposed to other sources, which all showed to have an annual growth rate between 2% and 2.8%.

The temporal trends of mortality rate for each source of sepsis are described in Table 3. Mortality rates for every source of sepsis were all declining, with sepsis due to biliary tract infection having the fastest declining rate (annual decrease 3.15%), followed by skin and skin structure infection (annual decrease 2.87%) and GUTI (annual decrease 2.07%). Systemic fungal infection as the source of sepsis had the slowest declining rate for mortality (annual decrease 0.92%). Sepsis due to LRTI and IAI had the highest mortality rate, with sepsis due to IAI having higher mortality rate initially (29.6% *v* 28.7% in 2002). However, sepsis due to lower respiratory infection had a slower declining mortality rate, causing the mortality of sepsis from lower respiratory infection to surpass that of IAI since 2007.

Figure 1 and Table 4 show the effect of co-infections on mortality in patients with sepsis. The presence of co-infection in patients with sepsis caused significantly higher mortality rate. Patients with three co-existing infections had a 90-day mortality of 25.7% compared with 22.1% in patients with a single source of sepsis. The effect remained significant after adjusting for age, gender, comorbidities, health care utilisation, and co-medication. Compared with patients with a single source of sepsis, patients co-infected by two sources were associated with a 36% increase in 30-day mortality (hazard ratio [HR], 1.36; 95% CI, 1.31–1.42; $P < 0.001$), while those co-infected by three sources were associated with a 20% increase in 30-day mortality (HR, 1.20; 95% CI; 1.14–1.26; $P < 0.001$). The covariates included in the Cox model with corresponding HR and 95% CI are shown in the Online Appendix (supplementary table 2).

Table 2. Population incidence of specific source of sepsis — the incidence is presented by events per 100 000 population

	Total number of events											Annual change
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
Lower respiratory tract infection	323.8	326.0	347.7	371.0	364.9	372.3	384.8	388.0	411.8	430.9	425.3	2.8%
Genitourinary tract infection	202.0	209.7	215.3	225.6	224.3	235.8	243.1	250.8	263.4	261.3	272.8	3.2%
Intra-abdominal infection	37.0	37.4	36.9	37.2	37.3	39.6	41.8	43.3	44.7	45.6	45.5	2.1%
Skin and skin structure infection	30.8	30.7	31.2	33.0	32.8	34.5	35.1	36.4	39.8	39.3	40.3	2.8%
Systematic fungal infection	16.7	15.7	14.6	14.7	15.6	16.5	17.4	17.9	19.0	19.3	20.3	2.0%
Musculoskeletal infection	8.8	7.8	7.1	6.6	7.4	10.9	8.0	8.0	9.0	8.5	11.1	2.3%
Biliary tract infection	8.5	10.0	11.0	10.1	10.8	7.5	10.9	9.8	13.4	12.1	8.4	-0.1%

Table 3. Thirty-day mortality rate and annual change of mortality rate over the 11-year period in patients with different sources of sepsis

	30-day mortality rate											Annual change
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
Lower respiratory tract infection	28.7%	27.4%	25.8%	25.5%	24.9%	24.4%	24.7%	24.3%	24.0%	24.4%	24.5%	-1.34%
Genitourinary tract infection	18.0%	17.3%	16.2%	15.7%	14.8%	14.5%	14.3%	14.3%	13.6%	13.5%	13.9%	-2.07%
Intra-abdominal infection	29.6%	28.0%	26.6%	26.0%	25.1%	13.2%	24.3%	23.9%	23.1%	22.6%	23.2%	-1.96%
Skin and skin structure infection	16.9%	12.8%	12.5%	12.4%	11.5%	24.0%	11.5%	10.9%	11.0%	10.8%	11.6%	-2.87%
Systematic fungal infection	14.2%	16.1%	15.4%	13.6%	13.7%	11.7%	12.5%	11.7%	10.8%	11.7%	12.7%	-0.92%
Musculoskeletal infection	14.0%	11.5%	11.6%	11.0%	11.6%	11.3%	11.3%	11.6%	10.6%	12.6%	11.9%	-1.39%
Biliary tract infection	17.2%	14.9%	14.3%	17.3%	12.7%	13.9%	12.6%	11.7%	11.2%	12.1%	11.3%	-3.15%

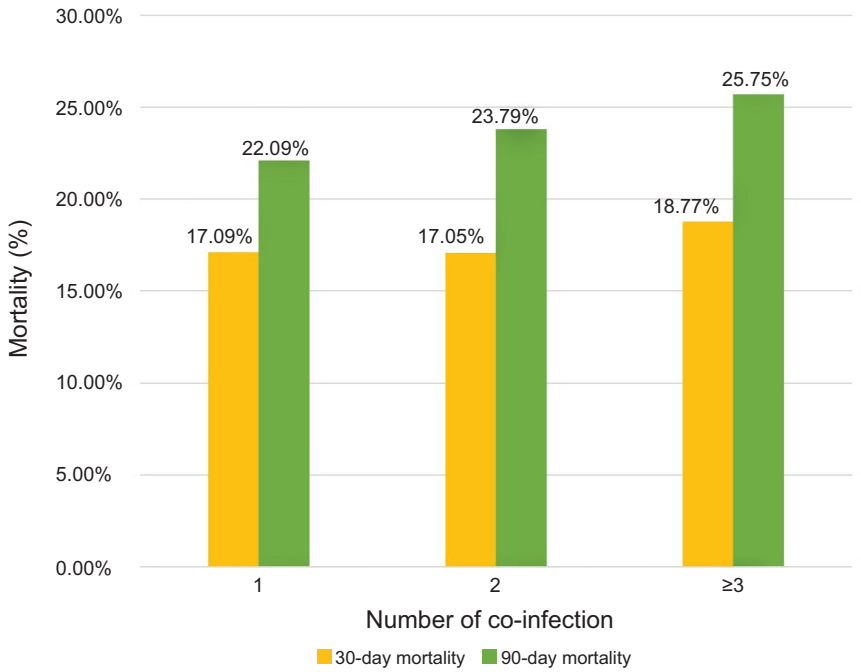
Figure 2 shows the independent survival impact of individual sources of sepsis. Using GUTI as a reference, sepsis with skin and skin structure infection or biliary tract infection had comparable mortality, while sepsis with other sources of infection were associated with increased mortality. Compared with sepsis with GUTI, sepsis with IAI had the highest impact on mortality (HR, 1.82; 95% CI; 1.67–1.99), followed by LRTI (HR, 1.59; 95% CI, 1.52–1.66), musculoskeletal infection (HR, 1.54; 95% CI, 1.31–1.80), and systemic fungal infection (HR, 1.43; 95% CI, 1.23–1.66).

Discussion

The current study provides data on incidence and mortality of sepsis according to sepsis source in a large population over a prolonged (11 years) study duration. The database had an impressive coverage of the Taiwanese population and the linkage to the mortality data was robust. At 2012, LRTI is the most common source of sepsis with the highest mortality rate in the Taiwanese population, comprising more than half of patients with sepsis and a mortality rate approaching 25%. The incidence was increasing at different speed in most sources of sepsis, with GUTI having the fastest growing rate. The mortality rates were decreasing at different speed in every source of sepsis, with sepsis due to biliary tract infection having the fastest decline and systemic fungal infection having the slowest. Furthermore, co-infection in patients with sepsis is associated with a higher mortality rate. Lastly, among all the sources of infection, IAI had the highest HR for mortality in patients with sepsis.

Previously, few studies had reported the effect of infection source on sepsis prognosis but with heterogeneous results, which may be attributed to diverse study design and different population.[16] Our results showed that, after adjusting for demographics, comorbidities, and health care utilisation, the source of sepsis had significant impact on sepsis mortality. In this 11-year cohort, IAI had the highest mortality rate in patients with sepsis. This result was consistent with findings of prior studies.[10,17] A study conducted by Zahar and colleagues[11] reported that the source of sepsis was not independently associated with mortality in patients with severe sepsis. They used a database from 12 French intensive care units from 1996 to 2009 that included 4006 severe sepsis episodes. After adjusting for severity, comorbidities and early appropriate antimicrobials, they found no association between source of sepsis and mortality in patients with severe sepsis. Their approach, by controlling for severity, may be controversial because severity as reflected by organ dysfunctions is the downstream event after the initial infection. Adjusting for downstream events may cause intermediate bias or overadjustment bias. We did not include severity in our model because different sources of sepsis are associated with different incidence of organ dysfunction and severity. We think the differential prognostic information of different

Figure 1. Thirty- or 90-day mortality of patients with sepsis according to number of co-infections



sources of sepsis is crucial to frontline clinicians, such as emergency physicians, because patients with sepsis with different source of infection may have a similar presentation in the early phase. The knowledge of high risk infection source may heighten their awareness for early assessment of organ dysfunction and initiate evidence-based bundle care earlier.

Our study showed a steady decline in the mortality rate of sepsis, which is similar to the results of the study conducted by Kaukonen and colleagues[18] in the same time frame in the Australian and New Zealand population.[18] The rise in incidence and the decrease in mortality may be due to earlier recognition, earlier treatment and more advances in sepsis treatment during the study period. However, there was a strong debate that the observed increase in the incidence of sepsis was coding or reporting bias over time. Namely, the incidence of sepsis was artificially inflated due to the upcoding practice. For example, implementation of health insurance incentive for sepsis bundle care may have increased the documentation of organ dysfunction and hence the diagnosis of sepsis.[3,5,19,20] We could not totally exclude this possibility in our study because there were continuing national education activities of the Surviving Sepsis Campaign guideline in Taiwan and the increased awareness of sepsis over time may increase the diagnosis of sepsis. However, unlike the US and several European countries, there was no health insurance incentive for quality improvement in Taiwan to promote the upcoding of sepsis. Contrary to most studies using claims-based analysis on sepsis which showed significant increased incidence and decreased mortality,[3,5,19,20] a study conducted by Rhee et al[21] using electronic health records from 409 hospitals in the US showed that the incidence and outcome of sepsis did not change significantly between 2009 and 2014. However, this potential coding bias could not explain the different trends for sepsis incidence and mortality among different sources of sepsis found in the present study. Therefore, we believe that the trends observed in the present study are valid.

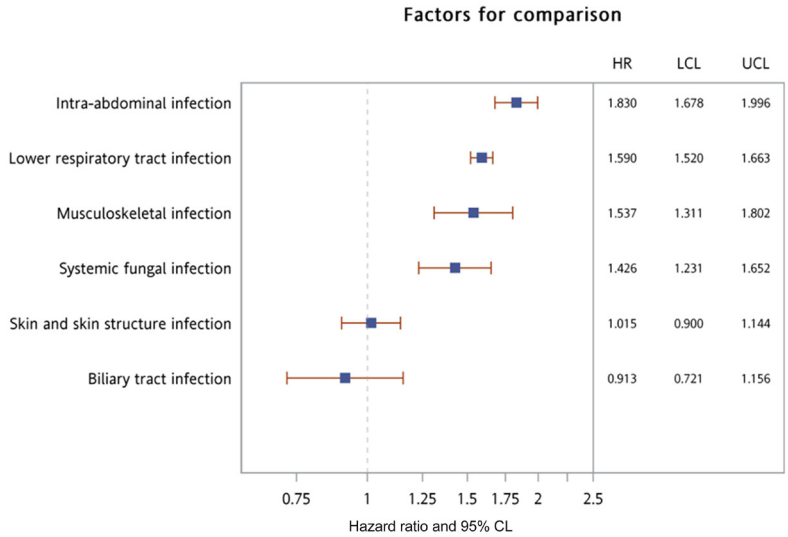
Our study confirmed lower respiratory infection as the greatest burden of sepsis due to its high incidence and high mortality. Lower respiratory infection is the fifth leading cause of death, with high morbidity worldwide.[22] However, LRTI is largely preventable. Several preventive measures had been proposed that include decreasing air pollution,[23] smoking cessation,[24] and increased coverage of influenza and pneumococcal vaccines.[25] Nursing home residents are prone to LRTI due to their poor functional status, swallowing

Table 4. Crude and adjusted hazard ratios of 90-day mortality according to number of co-infections

Number of co-infections	Crude mortality rate	Crude hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
1	202 448/916 469 (22.09%)	Reference	Reference
2	71 048/298 646 (23.79%)	1.46 (1.41–1.52)†	1.36 (1.31–1.42)†
≥ 3	11 431/44 463 (25.71%)	1.33 (1.27–1.39)†	1.20 (1.14–1.26)†

* Adjustment for age, gender, combined comorbidity score, health care utilisation, and co-medication.
† $P < 0.001$.

Figure 2. Survival impact of individual source of sepsis in relation to patients with genitourinary tract infections (GUTIs)*



HR = hazard ratio; LCL = lower confidence limits; UCL = upper confidence limits. * The risk estimates were adjusted for all covariates listed in the Online Appendix (supplementary table 1).

difficulties, and presence of other comorbidities;[26] several additional preventive measures had been proposed in these group of patients that include increasing oral hygiene[27] and prevention of aspiration such as elevation of the head of the bed and careful selection of patients for tube feeding.[28]

Results of this study should be interpreted in light of both strength and weakness. A major strength of this study is the use of a nationwide database. The use of population cohort minimises the risk for selection bias, with valid death outcome verified by linked national death certificate database being another merit. Previous studies based on administrative database such as nationwide inpatient sample or electronic health record database were based on in-hospital mortality which tends to underestimate the true mortality for sepsis because severe cases tend to discharge early. This study has several limitations. First, since our analysis was based on the analysis of a large administrative database, several potential confounding factors or effect modifiers may not be included, such as time to the initiation of antimicrobials and time to resuscitation. This information was lacking in the NHI database of Taiwan. However, the effect of timeliness was unlikely to vary greatly among different sources of sepsis and the misclassification errors are expected to be random, with a bias toward the null. Second, since this study was based on the Taiwanese population, which mostly comprised people of Han Chinese origin, the results might not be extrapolated to other populations. Third, an administrative database does not have any data on laboratory tests, and severity of organ dysfunction cannot be assessed. It is not known if the effect of infection source on mortality persisted after severity of organ dysfunction was adjusted.

Conclusion

The increasing incidence and the decreasing mortality of sepsis progress at different rates among different sources of sepsis. Lower respiratory infection has the highest burden among patients with sepsis. We confirmed that infection source and the presence of multiple infection sources are independent predictors of mortality. The results support source-specific preventive and treatment strategies for future sepsis management.

Acknowledgements: This study was funded by the Taiwan National Science Foundation Grant NSC 102-2314-B-002-131-MY3; National Taiwan University Hospital Grant NTUH.106-P04; Taiwan National Ministry of Science and Technology Grants MOST 104-2314-B-002-039-MY3, and MOST 106-2811-B-002-048. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interests

None declared.

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