Trends in the Incidence and Outcome of Sepsis Using Data from a Japanese Nationwide Medical Claims Database -the Japan Sepsis Alliance (JaSA) Study Group-

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Abstract

Background: Trends in the incidence and outcomes of sepsis using a Japanese nationwide database were investigated.

Methods: This was a retrospective cohort study. Adult patients, who had both presumed serious infections and acute organ dysfunction, between 2010 and 2017 were extracted using a combined method of administrative and electronic health record data from the Japanese nationwide medical claim database, which covered 71.5% of all acute care hospitals in 2017. Presumed serious infection was defined using blood culture test records and antibiotic administration. Acute organ dysfunction was defined using records of diagnosis according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, and records of organ support. The primary outcome variables were the annual incidence of sepsis and death in sepsis per 1,000 inpatients. The secondary outcome variables were in-hospital mortality rate and length of hospital stay in patients with sepsis.

Results: The analyzed dataset included 50,490,128 adult inpatients admitted between 2010 and 2017. Of these, 2,043,073 (4.0%) patients had sepsis. During the 8-year period, the annual proportion of patients with sepsis significantly increased (slope=+0.30%/year, $P<0.0001$), accounting for 4.9% of the total inpatients in 2017. The annual death rate of sepsis per 1,000 inpatients significantly increased (slope=+1.8/1,000 inpatients year, $P=0.0001$), accounting for 8.4 deaths per 1,000 inpatients in 2017. The in-hospital mortality rate and mean length of hospital stay significantly decreased ($P<0.001$) over the study period and were 18.3% and 41.9 days in 2017, respectively.

Conclusions: The Japanese nationwide data indicate that the annual incidence of sepsis and death in inpatients with sepsis significantly increased; however, the annual mortality rates and length of hospital stay in patients with sepsis significantly decreased. The increasing incidence of sepsis and death in sepsis appear to be a significant and ongoing issue.

Background

It is estimated that, annually, approximately 48.9 million people worldwide develop sepsis, and of these, 11 million (22.5%) die [1]. Multicenter studies have revealed the characteristics and outcomes of Sepsis-3 [2–4]; however, limited epidemiological investigational studies using a nationwide database have been performed [5]. Japan, which has universal public health care, developed a comprehensive reimbursement system of medical cost, named the Diagnosis Procedure Combination (DPC) system, in 2003 [6]. The claims-based database has data on diagnosis, examination, and treatment and covered 71.5% of all acute care hospitals in 2017; data from this database have been used in epidemiological studies of brain, orthopedic, and abdominal diseases and cancer [7–10], but no studies have used these data with regard to sepsis.

Between 1979 and 2012 in North America and Europe, epidemiological sepsis studies documented that mortality decreased; however, the proportion of patients with sepsis across all inpatients and the number

of deaths in sepsis increased [11–14]. In contrast, a recent Global Burden of Diseases study in the period of 1990–2017 reported a decreased fraction of sepsis in total inpatients and decreased number of deaths in sepsis [1], which is inconsistent with previous studies. Recent trends in sepsis may be changing. The purpose of the current study was to reveal the latest trends in sepsis based on the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [15] using the updated datasets.

Thus, we tested the hypothesis that there is a trend for an increased incidence of sepsis and death in sepsis in the aging society of Japan using a large nationwide claims-based database including data on over 50 million inpatients in 2010–2017. The primary outcome variables were annual incidence of sepsis and death in sepsis per 1,000 inpatients.

Materials And Methods

Study cohorts

This retrospective cohort study used Japanese nationwide data from the medical reimbursement system for acute care, DPC. Our DPC data, which were obtained from 1,237 acute care hospitals, is the largest nationwide acute care dataset in Japan; it covered 71.5% of the total acute care hospitals in 2017 [6]. Adult patients, who aged ≥ 20 years as previously reported [3], admitted to hospitals between 2010 and 2017 were enrolled. The Institutional Review Board of Chiba University Graduate School of Medicine has approved the study (approval number, 3429). Because data were anonymized, the requirement to obtain any informed consent from individual patients was waived.

Data Collection And Definitions

Data available in the database included patient's age, sex, admission and discharge dates, discharge status (death/survival), ICU admission (including emergency room and coronary care unit); primary diagnosis on admission, comorbidities on admission, and post-hospitalization complications coded using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (**Additional file 1: Table S1**) [16]; procedures including mechanical ventilation, oxygen therapy, and renal replacement therapy; therapeutic drugs used during hospitalization including vasoactive agents including dopamine, dobutamine, norepinephrine, or epinephrine, and antimicrobial, on a daily basis; examinations such as blood culture collection. Blood culture results (positive or negative) and laboratory data to calculate SOFA score were not included. The focus of infection was extracted by referring to ICD-10 codes for presumed foci of infection (**Additional file 1: Table S2**) [17]. All clinical data were recorded by the attending physicians at the time of hospital discharge.

Sepsis

Based on a previous epidemiological study in the United States (US) after the publication of Sepsis-3 [3], we extracted septic patients who had both presumed serious infections and acute organ dysfunction using a combined method of administrative and electronic health record data from the Japanese nationwide medical claim database (Fig. 1; **Additional file 2: Fig. S1**).

As previously reported [3], presumed serious infections were defined through blood culture collection records and administration of new antibiotics for four or more days. The first day of antibiotic administration was required to occur within ± 2 calendar days of blood culture collection. Four or more antibiotic days, including at least one intravenous antibiotic, were required. Fewer than 4 days of antibiotic administration duration were allowed if death occurred before the 4 days elapsed.

Information regarding acute organ dysfunction was extracted using diagnostic data from the ICD-10 codes (**Additional file 1: Table S3**) [18] as well as data regarding organ support including initiation of vasopressors, mechanical ventilation/oxygen therapy, or renal replacement therapy. We excluded maintenance dialysis in patients with end-stage renal disease from renal replacement therapy.

Statistical analysis

The primary outcome variables were the annual proportion of patients with sepsis across the total inpatient population and deaths in sepsis per 1,000 inpatients overall (hereafter referred to as deaths in sepsis per 1,000 inpatients) [12]. The secondary outcome variables were in-hospital mortality rate and length of hospital stay in patients with sepsis. Regarding to the definition of in-hospital death from sepsis, we did not use specific cut-offs like 28 days or 90 days. Individual persons were used as the unit of analysis for in-hospital mortality and deaths in sepsis per 1,000 inpatients; the hospital admission was used as the unit of analysis for length of hospital stay in patients with sepsis and proportion of patients with sepsis. The annual changes were analyzed using linear regression or the Cochran–Armitage test for trends in categorical data. The annual changes were analyzed using linear regression or the Cochran–Armitage test for trends in categorical data. The methods of trend analysis applied to the 8 individual calendar years. Subgroup analyses were conducted in three age groups: 20–64, 65–74, and 75 years and older for primary outcomes; the age split criteria were based on previous reports [19–21].

Variables such as length of hospital and ICU stay were expressed as both mean/ standard deviation (SD) and median/interquartile range (IQR) to compare with those in previous reports. Non-normally distributed variables such as age and the hospital day of the blood culture draw were expressed as median/IQR. *P*-values < 0.05 were considered statistically significant. SQL (mariadb v10.4.17) and pandas (v1.0.5) in Python (v3.9.0) and Prism software (GraphPad Prism 8; GraphPad Software Inc., San Diego, CA, USA) were used for data manipulation and statistical analysis.

Results

The analyzed dataset included 50,490,128 adult inpatients in total during the 8-year period between 2010 and 2017. Of these, 2,043,073 (4.0%) patients had sepsis (Table 1; **annual data**, **Additional file 1: Table**

S4). Major comorbidities included malignant tumors (34.9%), hypertension (26.3%), and diabetes mellitus (21.8%). Respiratory infections were the most common source of infection (41.0%) (**annual data**, **Additional file 1: Table S4 and S5**). The median (IQR) length of hospital stay was 29 (16–55) days and the in-hospital mortality rate was 19.1%.

Table 1
Demographics and clinical characteristics of patients with sepsis

Screened total inpatients, n	**50,490,128**
Extracted sepsis, n	2,043,073
Age, yr [a]	76 (66–84)
Female, n (%)	884,831 (41.4)
Comorbidity	
Malignant tumor, n (%)	712,219 (34.9)
Hypertension, n (%)	537,818 (26.3)
Diabetes mellitus, n (%)	445,438 (21.8)
Heart failure, n (%)	376,676 (18.4)
Cerebrovascular disease, n (%)	292,637 (14.3)
Ischemic heart disease, n (%)	215,868 (10.6)
Chronic respiratory disease, n (%)	179,898 (8.8)
Chronic renal failure, n (%)	79,362 (3.9)
Focus of infection [b] (n = 1,275,988)	
Respiratory, n (%)	523,057 (41.0)
Urogenital, n (%)	194,799 (15.3)
Abdominal, n (%)	147,409 (11.6)
Bone and soft tissue, n (%)	70,577 (5.5)
Blood, n (%)	3,560 (0.3)
Other, n (%)	336,587 (26.4)
The hospital day of the blood culture draw, day [a]	1 (1–2)
Length of antibiotic treatment, days	
Mean (SD)	18.7 (21.4)

[a] The data shown represent the median value along with the interquatile range.

[b] The number of cases in which an infected focus could be inferred from the Diagnosis Procedure Combination data

ICU: intensive care unit; SD: standard deviation; IQR: interquartile range

Screened total inpatients, n	50,490,128
Median (IQR)	12 (8–21)
Length of hospital stay, days	
Mean (SD)	45.7 (104.9)
Median (IQR)	29 (16–55)
ICU admission, n (%)	350,365 (17.1)
Length of ICU stay, days	
Mean (SD)	6.9 (6.2)
Median (IQR)	5 (2–11)
In-hospital mortality, n (%)	390,215 (19.1)
[a] The data shown represent the median value along with the interquatile range.	
[b] The number of cases in which an infected focus could be inferred from the Diagnosis Procedure Combination data	
ICU: intensive care unit; SD: standard deviation; IQR: interquartile range	

The annual proportion of patients with sepsis across inpatients significantly increased (R^2 = 0.98, slope = + 0.30%/year, P < 0.0001; Fig. 2). The annual number of patients with sepsis was 355,833 (4.9% of total inpatients) in 2017 (Fig. 2; **Additional file 3: Fig. S2**). The annual deaths in sepsis per 1,000 inpatients significantly increased (R^2 = 0.90, slope = + 1.8/1,000 inpatients year, P = 0.0003; Fig. 2). The annual number of deaths in patients with sepsis was 56,905 (7.8 deaths per 1,000 inpatients) in 2017 (a 2.3-fold increase compared to 2010) (Fig. 2; **Additional file 3: Fig. S2**).

The in-hospital mortality rate and length of hospital stay in sepsis significantly decreased (R^2 = 0.95, slope=-0.95%/year, P < 0.0001 and R^2 = 0.92, slope=-1.70days/year, P = 0.0002, respectively; Fig. 3). In 2017, the in-hospital mortality rate was 18.3%, and the mean length of hospital stay was 41.9 days in 2017. Repeating analysis in the age subgroups revealed that the decreased in the in-hospital mortality rate and hospital stay were significant in all age subgroups (P < 0.0001 and P < 0.01, respectively; Fig. 4a and 4b).

Discussion

In the present nationwide sepsis study, the annual incidence of sepsis and death in inpatients with sepsis significantly increased during the 8-year study period (2010–2017) in Japan. The in-hospital mortality rate and length of hospital stay significantly decreased during this period.

A US nationwide study documented that fraction of patients with sepsis in inpatients increased from 0.99–2.38% during 2000–2007 [12] and from 1.2–2.7% during 2005–2014 [22]. Similar trends have been reported in studies from European and Asian countries [23–25]. In accordance with these results, we found the proportion of sepsis inpatients significantly increased from 2.9–4.9% between 2010 and 2017.

Previous studies of severe sepsis, using the definition prior to the publication of “Sepsis-3” reported an increased number of deaths in sepsis. In 2011, Kumar et al. reported an increase in the number of deaths in inpatients with sepsis between 2000 and 2007 (8 years) in the US, from 4.0 deaths/1,000 inpatients in 2000 to 6.5 deaths/1,000 inpatients in 2007; the annual absolute number of deaths increased 1.8 times (213,124 deaths in 2007) [12]. In 2012, Lagu et al. reported an increased number of deaths between 2003 and 2007 (5 years) in the US, from 4.9 deaths/1,000 inpatients in 2003 to 6.3 deaths/1,000 inpatients in 2007; the annual absolute number of deaths increased 1.3 times (207,427 deaths in 2007) [12, 26]. In accordance with these results, we found a significant increase in the number of annual deaths in inpatients with sepsis (Slope = + 1.8/1,000 inpatients year, $P = 0.0003$), an absolute increase of 2.3 times (56,905 deaths in 2017). In contrast, a recent Global Burden of Disease study, which extracted sepsis using the ICD codes, showed a decreased number of deaths in sepsis worldwide [1]. Different regions (worldwide vs. Japan) or different extraction methods (diagnosis data only vs. diagnosis plus examination plus treatment data) may yield different results.

Substantial studies reported that the annual mortality of sepsis decreased. A meta-analysis of 36 multicenter trials of severe sepsis showed a decrease in mortality from 46.9% between 1991 and 1995 to 29% between 2006 and 2009 [27]. A US nationwide study showed decreased mortality of severe sepsis from 39–27% during 2000–2007 [12]. In accordance with these findings, we found that rate of mortality in sepsis decreased from 25.0–18.3% between 2010 and 2017; the length of hospital stay also decreased during the study period. In an epidemiological study of sepsis in Spain, the length of hospital stay decreased from 15.7 to 14.0 days during 2000–2013 [28]. In US studies, the length of hospital stay decreased from 14.0 to 12.5 days during 2000–2007 [12] and 16.1 to 10.7 days during 2005–2014 [22]. In accordance with these findings, we found that the length of hospital stay decreased from 51.3 days to 41.9 days between 2010 and 2017. These improvements in mortality and length of hospital stay in sepsis may be attributed to the widespread use of the international and Japanese sepsis guidelines, which potentially contribute to improvements in the recognition of sepsis, faster treatment, and improvement in care for critically ill patients [29–32].

We acknowledge that our study has some limitations. First, since Sepsis-3 was from 2016 and the data were collected before that date, the current study is retrospective. This is a limitation to the correct recruitment of patients. Second, the DPC data did not include laboratory data. Since the definition of sepsis requires laboratory data, including blood levels of creatinine and bilirubin and platelet counts, our extraction approach using diagnosis coding and treatment data on organ supports may underestimate the incidence compared to a more stringent extraction approach using laboratory data according to Sepsis-3. Third, due to the unavailability of blood lactate data, we could not analyze septic shock according to Sepsis-3.

Conclusions

The in-hospital mortality rate and length of hospital stay in patients with sepsis significantly improved between 2010 and 2017; however, the incidence of sepsis and death in inpatients with sepsis has been increasing annually in Japan. Sepsis appears to be a significant and ongoing issue. Health systems may consider countermeasure for reduce sepsis incidence.

Abbreviations

DPC: Diagnosis Procedure Combination; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision; IQR: interquartile range; SD: standard deviation; Sepsis-3: third International Consensus Definitions for Sepsis and Septic Shock; US: United States

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Chiba University Graduate School of Medicine has approved the study (approval number, 3429). Because data were anonymized, the requirement to obtain any informed consent from individual patients was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available with the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The authors received no specific funding for this work. TN is the CEO of Smart119 Inc. and owns stock. YY owns stock of Smart119 Inc. Smart119 Inc. had no role in the study design, data analysis, or preparation of the manuscript. Other authors declare that they have no conflicts of interest to report.

Authors’ contribution

TI and TN contributed to study conception, data acquisition, data interpretation, manuscript drafting, and critical revision of the manuscript for important intellectual content. NT, YY, SN, HO, NS, YU, AM, and KF contributed to study conception, data interpretation, and critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Figures

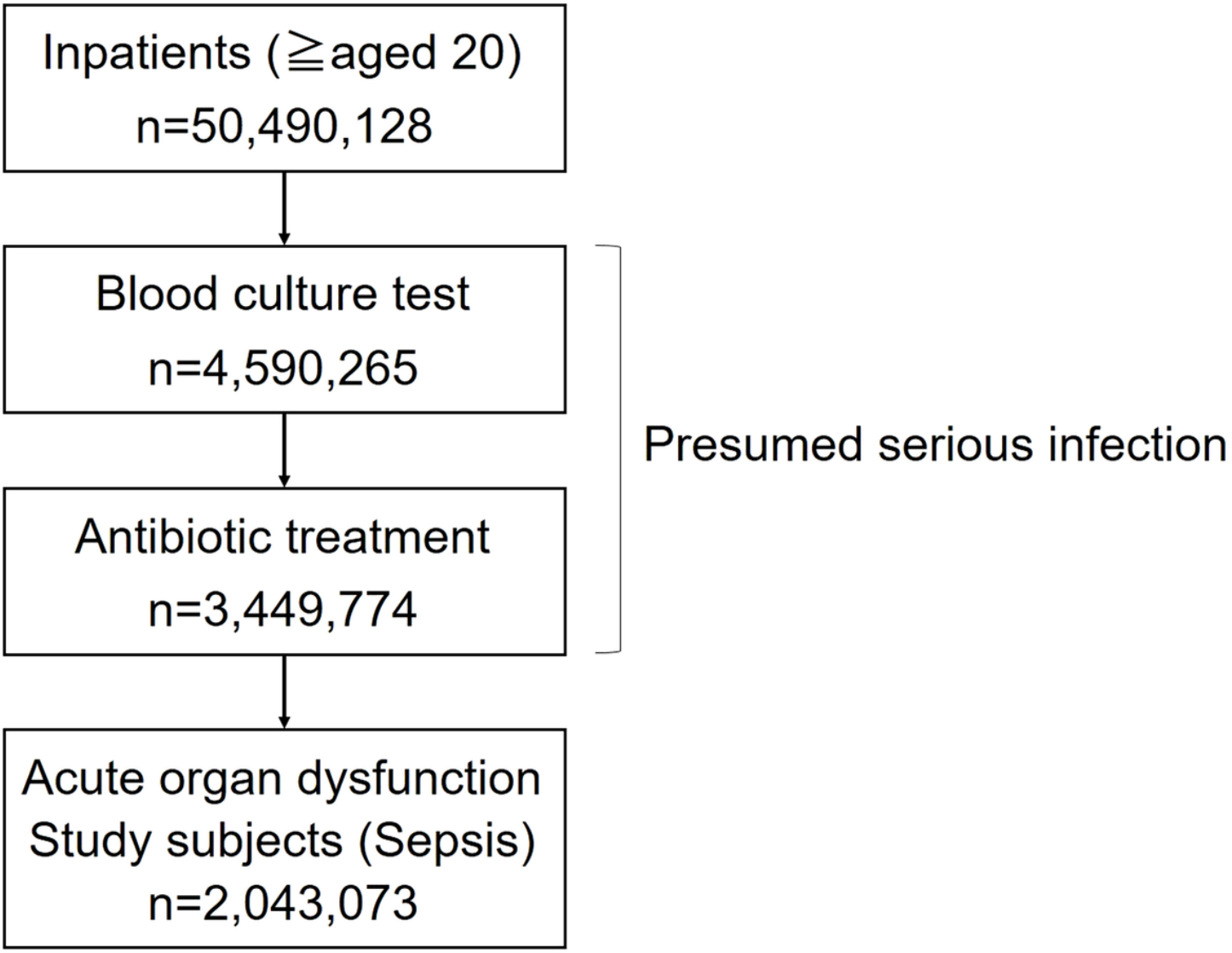

Figure 1

Flow diagram of the study population In total, 50,490,128 inpatients were enrolled in the study between 2010 and 2017. Of those, 4,590,265 patients underwent a blood culture test. Of these, 3,449,774 patients received antibiotic treatment for ≥4 days within ±2 calendar days of the blood culture draw. Of these, 2,043,073 patients had acute organ dysfunction; these patients were analyzed as study subjects (sepsis).

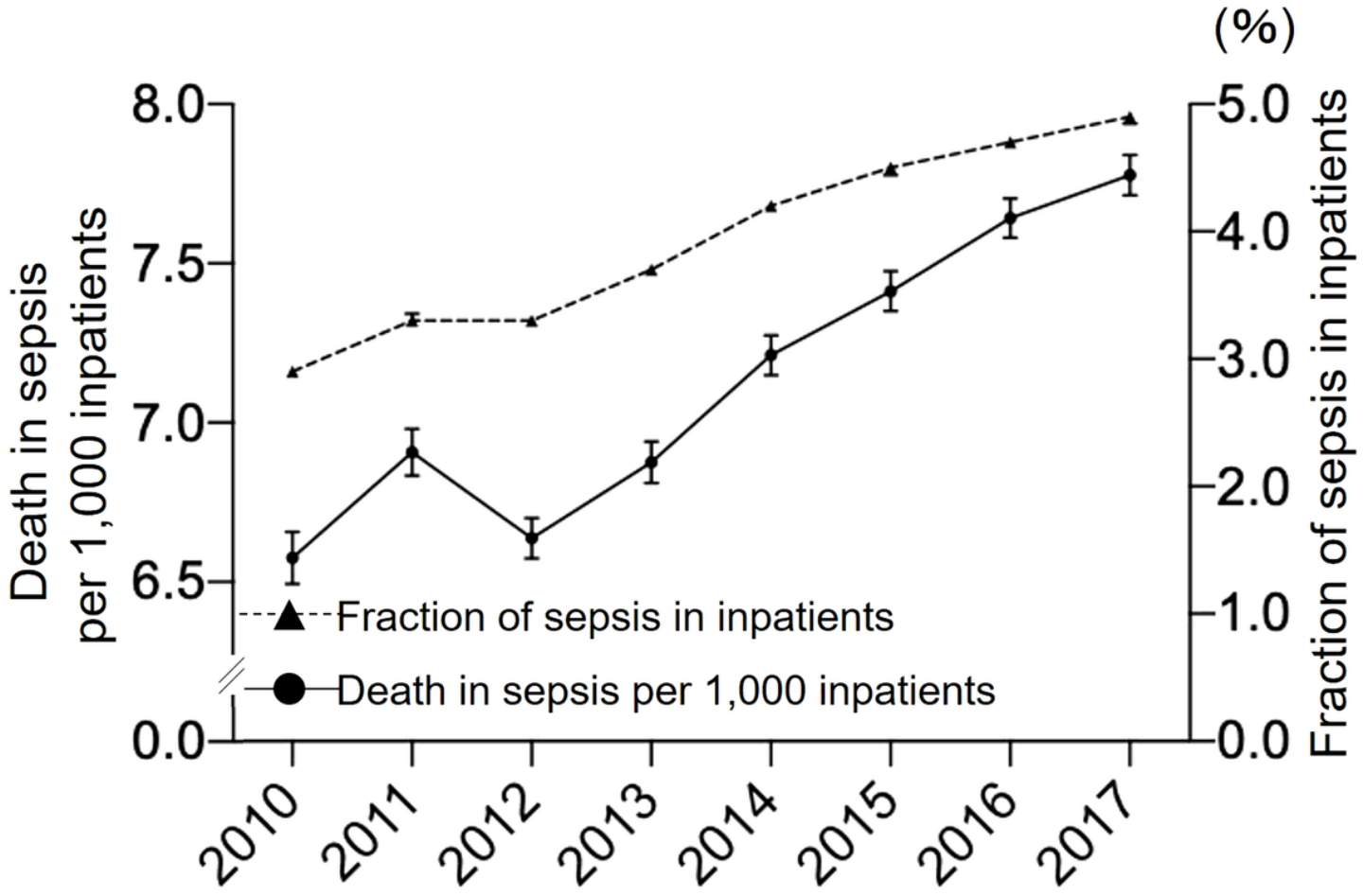

Figure 2

Annual change in deaths per 1,000 inpatients and proportion of patients with sepsis across all inpatients Deaths per 1,000 inpatients: +1.8/y [95% CI, +1.2 to +2.3], R2=0.90, P=0.0003 Fraction of sepsis in inpatients: +0.30%/y [95% CI, +0.25 % to +0.34 %], R2=0.98, P<0.0001 Error bars indicate 95% CI. CI: confidence interval

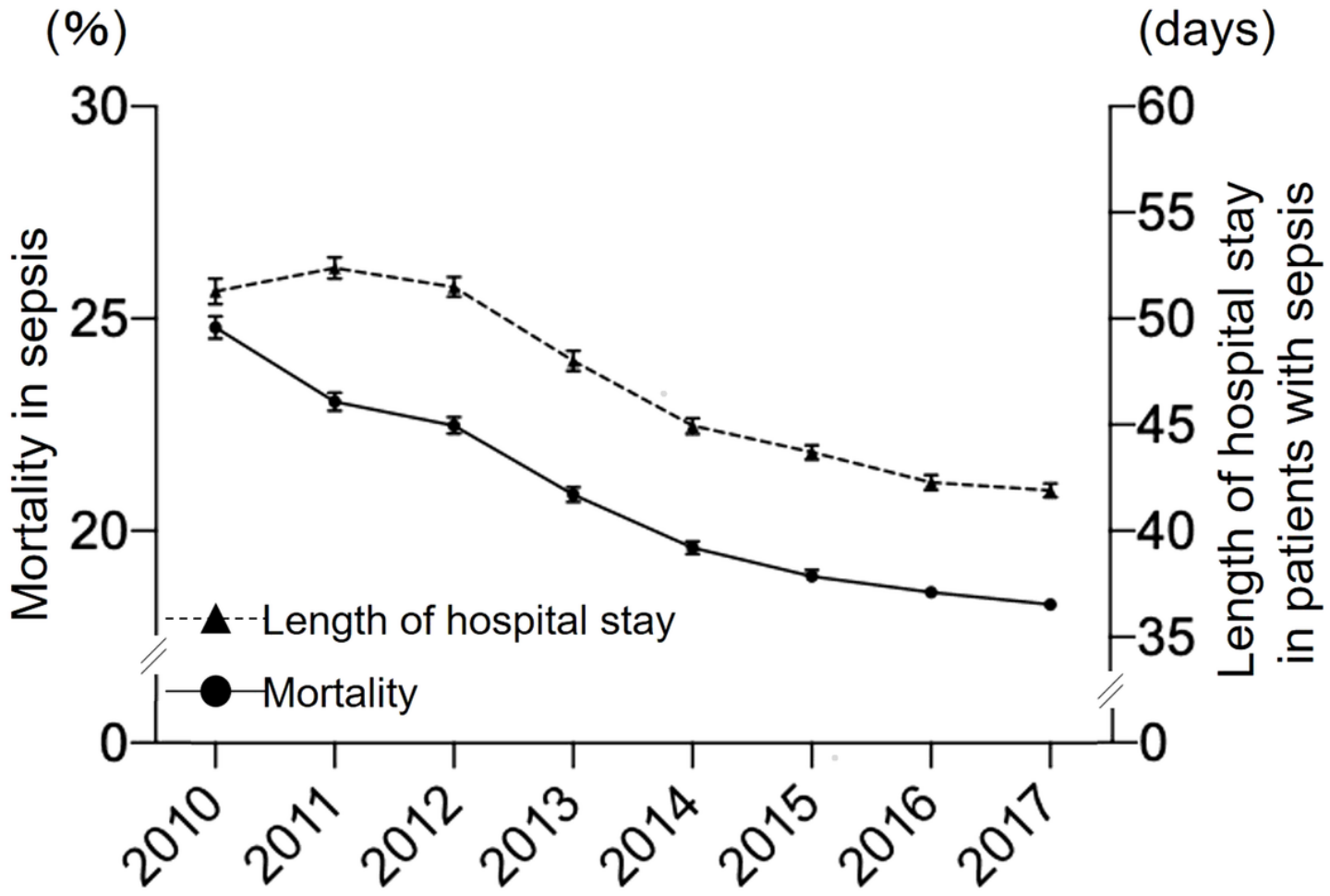

Figure 3

Annual change in the in-hospital mortality rate and mean length of hospital stay In-hospital mortality: -0.95%/y [95% CI, -1.17% to -0.73%], R2=0.95, P<0.0001 Length of hospital stay: -1.70days/y [95% CI, -2.21 to -1.19], R2=0.92, P=0.0002 Error bars indicate 95% CI. CI: confidence interval

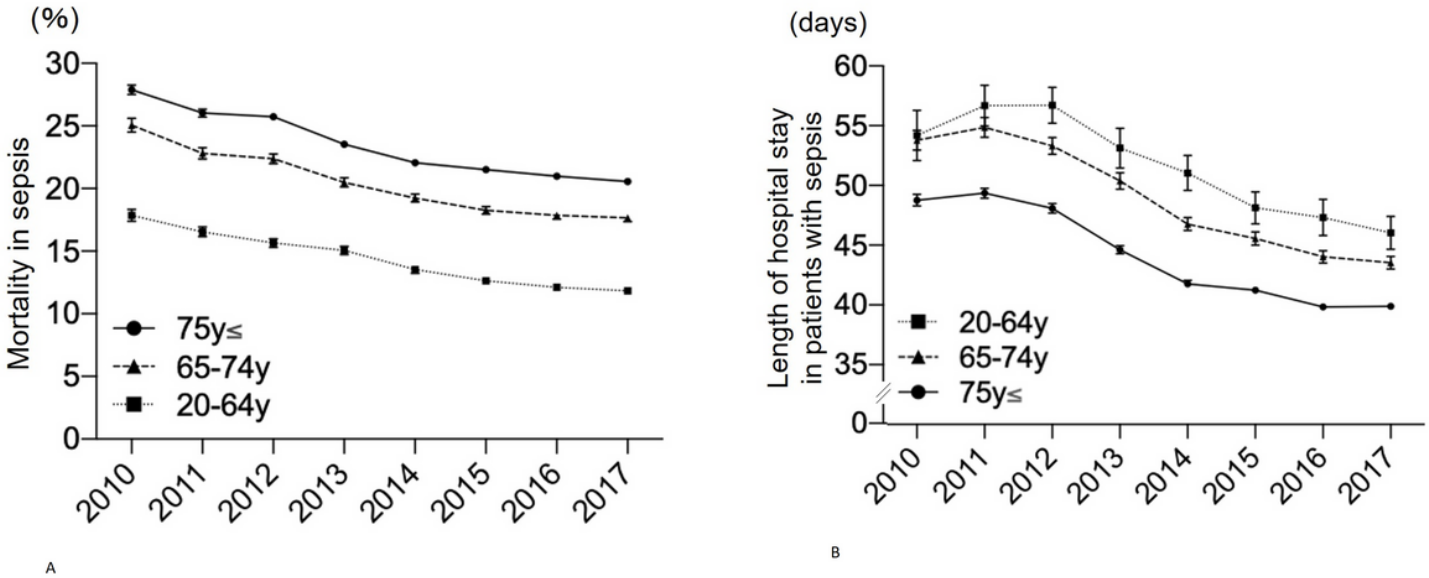

Figure 4

a. Annual change in the in-hospital mortality rate according to the age subgroups ≥75 years: -1.08%/y [95% CI, -1.33% to -0.82%], R2=0.95, P<0.0001 65–74 years: -1.08%/y [95%CI, -1.34% to -0.81%], R2=0.94, P<0.0001 20–64 years: -0.89%/y [95%CI, -1.04% to -0.75%], R2=0.98, P<0.0001 Error bars indicate 95% CI. CI: confidence interval b. Annual change in the length of hospital stay according to the age subgroups ≥75 years: -1.58%/y [95% CI, -2.06% to -1.11 %], R2=0.92, P=0.0002 65–74 years: -1.82%/y [95% CI, -2.31% to -1.33 %], R2=0.93, P=0.0001 20–64 years: -1.57%/y [95% CI, -2.24% to -0.89%], R2=0.84, P=0.0013 Error bars indicate 95% CI. CI: confidence interval

Supplementary Files

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

- Additionalfile1.docx
- Additionalfile2.pdf
- Additionalfile3.pdf