Heliyon 10 (2024) e23480

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Association between hospital spending and in-hospital mortality of patients with sepsis based on a Japanese nationwide medical claims database study

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ARTICLE INFO

Keywords:
Hospital spending
Sepsis
Diagnosis procedure combination
Medical cost
Critical care

ABSTRACT

Background: The effect of hospital spending on the mortality rate of patients with sepsis has not yet been fully elucidated. We hypothesized that hospitals that consume more medical resources would have lower mortality rates among patients with sepsis.
Methods: This retrospective study used administrative data from 2010 to 2017. The enrolled hospitals were divided into quartiles based on average daily medical cost per sepsis case. The primary and secondary outcomes were the average in-hospital mortality rate of patients with sepsis and the effective cost per survivor among the enrolled hospitals, respectively. A multiple regression model was used to determine the significance of the differences among hospital categories to adjust for baseline imbalances.
Results: Among 997 hospitals enrolled in this study, the crude in-hospital mortality rates were 15.7% and 13.2% in the lowest and highest quartiles of hospital spending, respectively. After adjusting for confounding factors, the highest hospital spending group demonstrated a significantly lower in-hospital mortality rate than the lowest hospital spending group (coefficient = −0.025, 95% confidence interval [CI] −0.034 to −0.015; $p < 0.0001$). Similarly, the highest hospital spending group was associated with a significantly higher effective cost per survivor than the lowest hospital spending group (coefficient = 77.7, 95% CI 73.1 to 82.3; $p < 0.0001$). In subgroup analyses, hospitals with a small or medium number of beds demonstrated a consistent pattern with the primary test, whereas those with a large number of beds or academic affiliations displayed no association.

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https://doi.org/10.1016/j.heliyon.2023.e23480
Received 25 August 2023; Received in revised form 1 December 2023; Accepted 5 December 2023
Available online 10 December 2023
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Conclusions: Using a nationwide Japanese medical claims database, this study indicated that hospitals with greater expenditures were associated with a superior survival rate and a higher effective cost per survivor in patients with sepsis than those with lower expenditures. In contrast, no correlations between hospital spending and mortality were observed in hospitals with a large number of beds or academic affiliations.

1. Introduction

Sepsis, a condition with a high mortality rate, affects millions of individuals worldwide [1,2]. As its prevalence rises, so do the associated medical costs [3,4]. Managing sepsis demands substantial resources including specialized staff, intensive care units (ICUs), and artificial organ support [5–7]. Consequently, a judicious allocation of limited resources across hospitals is imperative to maintain fiscal equilibrium.

While it has been theorized that increased medical resource utilization leads to improved clinical outcomes, evidence in patients with chronic heart failure or acute myocardial infarction has not consistently supported this notion [8,9]. Likewise, an analysis encompassing over 300 U.S. institutions focusing on sepsis patients found no discernible link between hospital expenditure and enhanced outcomes [10].

Given disparities in economic conditions and healthcare systems across countries [6], the association between hospital expenditures and clinical outcomes may vary. Japan's implementation of universal health insurance ensures equal access to medical care for all citizens. This unique context prompts the investigation of whether a substantial allocation of medical resources contributes to improved clinical outcomes in sepsis. However, there is a dearth of similar investigations in the sepsis population.

Therefore, this study hypothesizes that hospitals with greater medical resource consumption will yield higher survival rates and greater cost-effectiveness in managing sepsis. The aim of this study is to examine the impact of in-hospital costs on the management of sepsis in hospitals, utilizing the Japanese nationwide medical claims database from 2010 to 2017.

2. Materials and methods

2.1. Study setting and subjects

We conducted a retrospective study using a national administrative database in Japan, the Diagnosis Procedure Combination (DPC) [11]. The DPC records comprehensive information about medical procedures, medical tests, drugs, laboratory tests, and surgery, as well as medical costs during hospitalization. According to previous reports [12,13], sepsis is defined as a presumed serious infection and life-threatening organ dysfunction. To extract patients with sepsis from the registered patients in the DPC database, we screened patients with blood cultures and infusion of antibiotics for at least 4 days. In patients who were administered antibiotics, blood cultures were performed 2 days before or after administration. Organ dysfunction was defined based on the following conditions: vasopressor use, oxygen support, ventilation support, renal replacement therapy (RRT), or diagnostic codes related to kidney dysfunction, hepatic disorder, thrombocytopenia/coagulopathy, or metabolic acidosis. Patients aged <20 years were excluded. To focus on the patients with sepsis who were treated in the acute phase, we only included patients whose length of stay was 30 days or less [14–16]. Other exclusion criteria were: 1) length of stay <4 days, 2) outliers in medical costs (top and bottom 5% of the enrolled patients), 3) hospital-acquired infection, and 4) patients who were transferred to other hospitals as previously described [17–20]. In this study, we performed a hospital-based analysis using a database of patients with sepsis after excluding hospitals that managed fewer than 10 cases per year and outliers based on visual inspection of the histogram [21,22].

The Institutional Review Board of Chiba University Graduate School of Medicine approved this study (approval number: 3429) and, due to its retrospective nature, waived the obligation of obtaining written consent from the patients in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

2.2. Patients and hospital data

The following patient information was collected from the database: age, sex, chronic diseases (malignant tumors, hypertension, diabetes mellitus, heart failure, cerebrovascular disease, ischemic heart disease, chronic respiratory disease, or chronic renal failure), site of infection (respiratory, abdominal, urogenital, skin, soft tissue, neurological, blood, heart, or unknown), medical procedures, medical costs, ICU admission, and length of hospital stay. According to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, we documented admission diagnoses, comorbidities, and complications during the hospital stay as codes (Supplementary material: Table S1). Patients with multiple codes for the "site of infection" and those with missing data (n = 765,460) were classified as "multiple" and "unknown", respectively. Patients with repeat admissions were excluded from the analysis. We defined patients whose cultures or antibiotics were initiated within 48 h of hospital admission as having community-acquired sepsis.

The number of hospital beds, academic affiliations, and census regions were recorded as hospital information. The average number of hospitalized patients per institution was used as a surrogate measure for the number of hospital beds. We categorized the number of hospital beds into small (<200), medium (200–499), and large (>499), according to a previous report [23]. The census regions were

Hokkaido/Tohoku, Kanto, Chubu, Kansai, Chugoku/Shikoku, and Kyushu/Okinawa (Supplementary material: Fig. S1).

2.3. Medical costs

The representative value of medical costs was calculated from the reference prices of drugs, examinations, laboratory tests, radiological tests, and surgical procedures. Medical fees were mostly reimbursed based on the most common payment diagnosis and medical procedures performed during the hospital stay, namely, on a bundled payment basis; therefore, actual medical costs were different from the representative value that we used in this study. To estimate the cost-effectiveness of each institution, we calculated the effective cost per survivor as the sum of the medical costs of all patients/number of survivors per year [4]. To account for annual changes in consumer price index, we adjusted the representative value using the consumer index price in each year. After standardization, the price was converted from Japanese yen to U.S. dollars on January 15, 2023 (127.88 yen = 1 USD).

2.4. Hospital categories according to medical spending

We calculated the average daily medical cost per person for each hospital. According to in-hospital costs, the enrolled hospitals were divided into quartiles. We also used in-hospital costs as continuous variables in other analyses.

2.5. Statistical analysis

The primary outcome was the average in-hospital mortality rate of sepsis patients in the enrolled hospitals. The secondary outcome was effective cost per survivor. Significant differences among hospital categories according to medical expenditures were determined

Table 1
Hospital characteristics in the cohort.

	Total (n = 997)	In-hospital cost quartile[a]				p-value
		Q1 (n = 249)	Q2 (n = 249)	Q3 (n = 250)	Q4 (n = 249)	
Daily medical costs per person ($)						<0.0001
Mean (SD)	361 (37)	318 (11)	345 (6)	370 (8)	411 (23)	
Median (IQR)	357 (334–385)	320 (312–327)	345 (340–351)	369 (363–376)	404 (395–423)	
Demographics						
Annual number of sepsis patients						<0.0001
Mean (SD)	64 (60)	34 (27)	53 (42)	78 (59)	92 (79)	
Median (IQR)	45 (23–89)	26 (15–43)	40 (23–68)	65 (36–102)	73 (31–131)	
Number of hospital beds						0.47
<200 (small)	578 (58.0)	137 (55.0)	59 (23.7)	19 (7.6)	12 (4.8)	
200–499 (medium)	227 (22.8)	111 (44.6)	180 (72.3)	172 (68.8)	115 (46.2)	
>499 (large)	192 (19.3)	1 (0.4)	10 (4.0)	59 (23.6)	122 (49.0)	
Teaching hospitals, *n* (%)	65 (6.5)	0 (0)	1 (0.4)	21 (8.4)	43 (17.3)	<0.0001
Census regions						<0.0001
Hokkaido/Tohoku, *n* (%)	113 (11.3)	23 (9.2)	36 (14.5)	21 (8.4)	33 (13.3)	
Kanto (%), *n*	245 (24.6)	41 (16.5)	60 (24.1)	62 (24.8)	82 (32.9)	
Chubu (%), *n*	200 (20.1)	74 (29.7)	52 (20.9)	41 (16.4)	33 (13.3)	
Kansai (%), *n*	177 (17.8)	41 (16.5)	44 (17.7)	51 (20.4)	41 (16.5)	
Chugoku/Shikoku, *n* (%)	108 (10.8)	28 (11.2)	24 (9.6)	26 (10.4)	30 (12.0)	
Kyushu/Okinawa, *n* (%)	154 (15.4)	42 (16.9)	33 (13.3)	49 (19.6)	30 (12.0)	
Clinical characteristics						
Age, years	78 (76–80)	80 (78–81)	79 (77–81)	77 (75–79)	76 (73–77)	<0.0001
Male, *n* (%)	54.4 (50.5–58.1)	52.1 (47.9–55.3)	52.7 (49.3–56.9)	55.1 (51.3–58.6)	56.7 (54.2–60.0)	<0.0001
Chronic diseases						
Cancer, *n* (%)	21.6 (16.1–27.9)	17.0 (12.3–21.8)	20.0 (15.4–25.1)	22.9 (17.5–29.3)	27.5 (21.7–33.6)	<0.0001
Hypertension, *n* (%)	27.3 (21.2–33.6)	27.2 (20.1–33.7)	27.2 (21.7–34.7)	28.0 (20.3–34.6)	26.9 (21.5–32.3)	0.93
Diabetes mellitus, *n* (%)	20.7 (17.7–23.8)	19.4 (16.7–23.0)	20.8 (17.1–23.9)	21.2 (18.0–24.4)	21.3 (18.6–23.7)	<0.0001
Heart failure, *n* (%)	15.4 (12.2–18.9)	16.1 (12.7–20.2)	15.9 (12.3–19.1)	15.4 (12.0–18.6)	14.4 (11.9–17.5)	0.006
Stroke, *n* (%)	10.0 (7.3–13.7)	11.8 (8.8–15.6)	11.0 (8.3–14.3)	9.4 (6.7–13.0)	8.0 (6.1–10.8)	<0.0001
Ischemic heart disease, *n* (%)	8.1 (5.9–10.8)	7.1 (5.0–9.7)	7.7 (5.5–10.8)	8.6 (6.5–10.8)	9.1 (6.9–11.9)	<0.0001
Chronic respiratory disease, *n* (%)	10.9 (8.3–13.7)	11.5 (8.7–15.2)	10.7 (7.8–13.3)	10.8 (8.7–13.8)	10.5 (8.1–13.3)	0.040
Chronic renal failure, *n* (%)	2.6 (1.6–3.8)	2.4 (1.4–3.4)	2.5 (1.4–3.7)	2.6 (1.6–3.8)	3.0 (2.1–4.1)	<0.0001
ICU admission[b], *n* (%)	2.9 (0–9.4)	0 (0–0)	0 (0–6.9)	5.8 (0.7–10.4)	8.7 (4.0–16.0)	<0.0001
Therapeutic interventions						
Vasopressor therapy[b] (%)	5.1 (3.2–8.2)	4.7 (2.9–7.5)	4.7 (2.8–7.4)	5.5 (3.5–8.5)	5.4 (3.5–8.9)	<0.0001
Mechanical ventilation[b] (%)	6.8 (4.5–9.1)	5.4 (3.6–7.8)	6.1 (4.4–8.3)	7.4 (4.9–9.5)	7.9 (5.7–10.8)	<0.0001
RRT[b] (%)	1.2 (0.6–2.2)	0.8 (0.0–1.9)	1.1 (0.5–2.0)	1.4 (0.7–2.3)	1.7 (1.0–2.6)	<0.0001
In-hospital mortality[b] (%)	14.1 (11.5–17.3)	15.7 (11.7–19.4)	14.5 (12.0–17.7)	13.9 (11.5–16.4)	13.2 (11.0–15.9)	<0.0001

SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; RRT, renal replacement therapy.
[a] The cohort was quartiled according to daily medical costs per person: Q1, 284–334 ($); Q2, 335–356 ($); Q3, 357–384 ($); Q4, 385–476 ($).
[b] Data are presented as median percentage (IQR).

using a multiple regression model to adjust for baseline imbalances. Normal distribution of the variables was examined using regression diagnostics. Potential confounding factors included the annual number of patients with sepsis, number of hospital beds, academic affiliation, census region, ICU admission, and proportion of therapeutic interventions (vasopressor therapy, mechanical ventilation, and RRT).

Using the average daily medical cost per person as a continuous variable, the significance of the association between in-hospital spending and mortality was determined using fractional polynomials. Furthermore, we used restricted cubic splines (4 knots) to examine the nonlinear association between medical costs and mortality. For the sensitivity analysis, we investigated the cohort excluding uppermost and lowest 2% of the enrolled patients according to the average daily medical cost per person, instead of 5% in the primary analysis, to validate the consistency of the primary test. We also conducted subgroup analyses according to the number of hospital beds, academic affiliations, and census regions to explore the subpopulations that manifested different effects.

Categorical variables were expressed as numbers and percentages and analyzed using Pearson's chi-square test. Continuous variables were expressed as mean (standard deviation) or median (interquartile range [IQR]), as appropriate and analyzed using Student's *t*-test or Mann–Whitney *U* test according to the normality of distribution. One-way analysis of variance was performed to estimate differences among more than two groups. The data were manipulated and analyzed using SQL (mariadb v10.4.17), and pandas (v1.0.5), scipy (v1.7.3), numpy (v1.21.4), seaborn (v0.11.2), matplotlib (v3.5.1), and statsmodels (v0.13.2) in Python (v3.9.0).

3. Results

3.1. Baseline patient and hospital characteristics

Among the patients registered in the DPC database, 538,370 had sepsis according to its definition and the inclusion criteria in our study (Supplementary material: Fig. S2). The median patient age was 77 (67–85) years. The most common source of infection was the respiratory tract (Supplementary material: Table S2). After applying these criteria, 997 hospitals were selected from the database (Supplementary material: Fig. S3, Fig. S4). The enrolled hospitals were divided into quartiles according to the average daily medical cost per person in each institution. In the four categories, the median daily medical cost per person was $320 (312–327) in Q1, $345 (340–351) in Q2, $369 (363–376) in Q3, and $404 (395–423) in Q4. The proportion of hospitals with a large number of beds was 0.4% in Q1, 4.0% in Q2, 23.6% in Q3, and 49.0% in Q4. The median percentage of ICU admissions was 0% (0-0) in Q1, 0% (0–6.9) in Q2, 5.8% (0.7–10.4) in Q3, and 8.7% (4.0–16.0) in Q4 (Table 1).

3.2. Association between hospital spending and in-hospital mortality or cost-effectiveness

The median crude in-hospital mortality rate was 15.7% (11.7–19.4) in Q1, 14.5% (12.0–17.7) in Q2, 13.9% (11.5–16.4) in Q3, and 13.2% (11.0–15.9) in Q4 (Table 2). There was an inverse correlation between in-hospital mortality and daily medical costs per person among hospitals (coefficient = −0.0002, 95% confidence interval [CI] −0.0003 to −0.0001; $p < 0.0001$) (Fig. 1). After adjusting for baseline imbalances, the highest hospital spending in Q4 demonstrated significantly lower in-hospital mortality than the lowest hospital spending in Q1 (coefficient = −0.025, 95% CI –0.034 to −0.015; $p < 0.0001$). Moreover, in-hospital mortality in Q3 was lower than in Q1 (coefficient = −0.015, 95% CI –0.023 to −0.006; $p < 0.0001$) (Table 2). Similarly, the highest hospital spending in Q4 was associated with a significantly higher effective cost per survivor than the lowest hospital spending in Q1 (coefficient = 77.7, 95% CI 73.1 to 82.3; $p < 0.0001$) (Table 3).

Analyses with fractional polynomials showed that the daily medical costs per person among hospitals were significantly associated with reduced adjusted in-hospital mortality ($p < 0.0001$) (Fig. 2A). Restricted cubic splines also showed correlation patterns similar to those of the fractional polynomials between daily medical costs per person among hospitals and in-hospital mortality (Fig. 2B). The adjusted effective cost per survivor was significantly associated with the daily medical costs per person in the fractional polynomials ($p < 0.0001$) (Fig. 2C).

Table 2
Multivariable regression analysis for in-hospital mortality[a,b].

Hospital spending categories	Coefficient[c]	95% CI	p-value
Q1	Reference		
Q2	−0.006	−0.013 to 0.001	0.11
Q3	−0.015	−0.023 to −0.006	<0.0001
Q4	−0.025	−0.034 to −0.015	<0.0001

CI, confidence interval.

[a] The cohort was quartiled according to daily medical costs per person: Q1, 284–334 ($); Q2, 335–356 ($); Q3, 357–384 ($); Q4, 385–476 ($).

[b] The independent variable was adjusted for the annual number of patients with sepsis, number of hospital beds, academic affiliation, census regions, age, sex, chronic diseases, intensive care unit admission, and proportion of therapeutic interventions (vasopressor therapy, mechanical ventilation, and renal replacement therapy).

[c] 100 × coefficient shows percent change in in-hospital mortality.

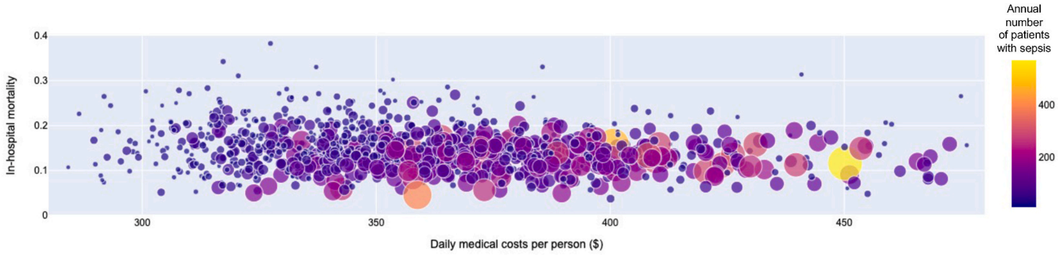

Fig. 1. Relationship between the annual number of sepsis patients per hospital, daily medical costs per day, and in-hospital mortality. Each balloon illustrates the volume of hospitals (annual number of sepsis patients per hospital) with gradient colors from blue (lower) to yellow (higher). The scatter plot shows the relationship between the daily medical costs per person on the x-axis and in-hospital mortality on the y-axis. The coefficient of daily medical costs per person is −0.0002 (95% confidence interval −0.0003 to −0.0001; $p < 0.0001$).

Table 3
Multivariable regression analysis for cost-effectiveness[a,b].

Hospital spending categories	Coefficient[c]	95% CI	p-value
Q1	Reference		
Q2	21.8	18.3 to 25.1	<0.0001
Q3	42.4	38.5 to 46.1	<0.0001
Q4	77.7	73.1 to 82.3	<0.0001

CI, confidence interval; IQR, interquartile range.

[a] The cohort was quartiled according to daily medical costs per person: Q1, 284–334 ($); Q2, 335–356 ($); Q3, 357–384 ($); Q4, 385–476 ($).

[b] The independent variable was adjusted for the annual number of patients with sepsis, number of hospital beds, academic affiliation, census regions, age, sex, chronic diseases, intensive care unit admission, and proportion of therapeutic interventions (vasopressor therapy, mechanical ventilation, and renal replacement therapy).

[c] The coefficient shows change in the effective cost per survivor

3.3. Subgroup analysis

In the subgroup analysis based on the number of hospital beds, hospitals with a small or medium number of beds demonstrated comparable patterns of correlation with the primary test, whereas those with a large number of hospital beds displayed no association (Fig. 3A–C, Supplementary material: Fig. S5). With regard to academic affiliation, teaching hospitals demonstrated no association between in-hospital mortality and daily medical costs per person (Supplementary material: Fig. S6). In the subgroup of census regions, only Kanto and Kansai displayed significant inverse correlations, indicating geographical variations in this relationship (Supplementary material: Fig. S7).

3.4. Sensitivity analysis

The significant association between the hospital spending and in-hospital mortality among hospitals was consistent after excluding the highest and lowest 2% of the enrolled patients according to daily medical costs per person (Supplementary material: Table S3A). Lower in-hospital mortality was also associated with hospital expenditures in the cohort without the exclusion of outlier hospitals based on daily medical costs per person (Supplementary material: Table S3B).

4. Discussion

In this study, we demonstrated that higher hospital spending, represented as daily medical costs per person, was associated with lower in-hospital mortality and higher effective cost per survivor in patients with sepsis. Among the enrolled hospitals, those with a large number of beds and academic affiliations exhibited inconsistent results in the primary test.

The beneficial effects of hospital spending on mortality may be attributed to an abundance of medical resources. According to a previous report that enrolled patients with sepsis in U.S. hospitals, medical costs increased with higher mortality according to the severity level; however, the association between medical costs and mortality was not clearly demonstrated in this report or in other studies [24]. A cross-sectional study attempted to identify the relationship between hospital expenditure and mortality in patients with sepsis; however, no associations were found between higher medical expenses and better survival [10]. In other fields, greater resource utilization was not associated with an increase in mortality or other clinical outcomes in patients with acute myocardial infarction, chronic heart failure, or durable left ventricular devices, suggesting that high expenditures would not be efficient for hospitals striving for optimal medical allocation [8,9,21]. Conversely, only one study demonstrated that higher hospital spending intensity was associated with lower mortality in a mixed cohort of patients with acute myocardial infarction, chronic heart failure, hip fracture, and

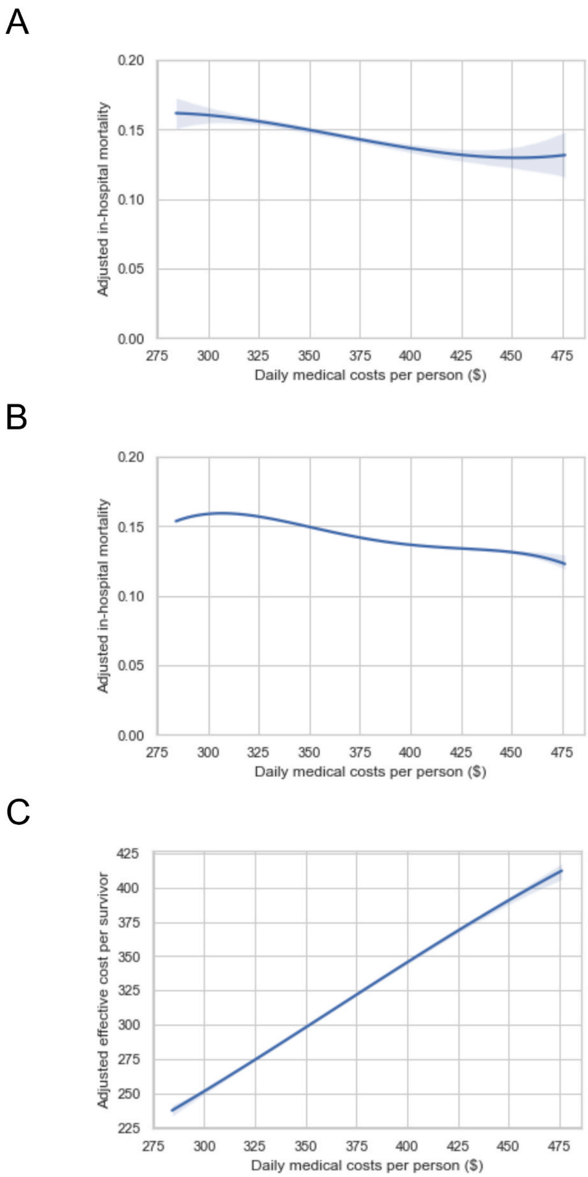

Fig. 2. Association between daily medical costs per person and in-hospital mortality.
The polynomial regression plot (A) shows the relationship between daily medical costs per sepsis case on the x-axis and adjusted in-hospital mortality on the y-axis. The coefficient of daily medical costs per person is −0.0002 (95% confidence interval [CI] −0.0003 to −0.0001; $p < 0.0001$). The cubic spline restriction plot (4 knots) (B) depicts the relationship between daily medical costs per sepsis case on the x-axis and adjusted in-hospital mortality on the y-axis. The polynomial regression plot (C) shows the relationship between daily medical costs per sepsis case on the x-axis and effective cost per survivor on the y-axis. The effective cost per survivor was calculated for each institution as the sum of the medical costs of all patients divided by the number of survivors per year. The coefficient of daily medical costs per person is 0.95 (95% CI 0.91 to 0.98; $p < 0.0001$). The 95% CI is illustrated with the depicted regression line.

colon cancer [20]. In our study, we demonstrated a significant association between higher medical expenditure and decreased mortality in the sepsis population; however, the causal relationship remains to be ascertained owing to the limitations of this observational study. The divergent findings of previous studies can be attributed to disparate study designs, variations in healthcare infrastructure, and different pathologies. However, we must be cautious about the possibility that hospitals with lower mortality rates are more likely to treat patients who are eligible for therapeutic interventions based on their age and background characteristics.

To estimate the efficiency of hospital spending in healthcare, the cost-effectiveness is used as a representative economic indicator also in the medical field [25]. As sepsis requires substantial medical resources, including medications, artificial organ support, and experienced staff, we should be cautious about the cost-effectiveness of sepsis care to prevent deterioration in the balance of the fiscal budget [6]. Additionally, the optimal allocation of medical resources should be considered based on the cost-effectiveness of medical

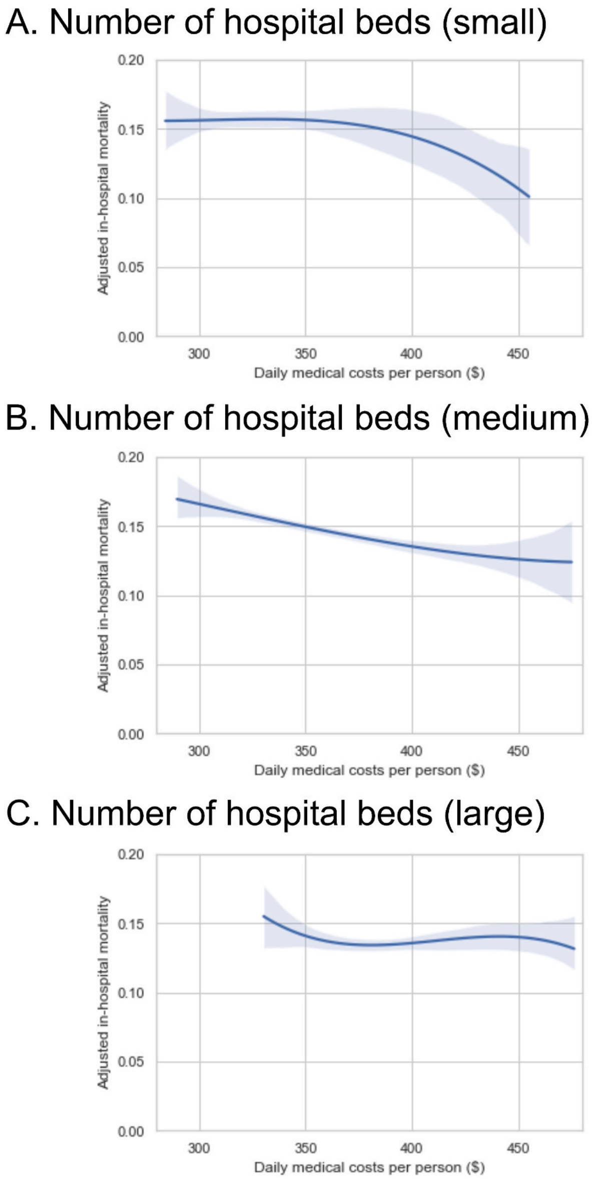

Fig. 3. Subgroup analyses according to the number of hospital beds.

The polynomial regression plot shows the relationship between daily medical costs per sepsis case on the x-axis and adjusted in-hospital mortality on the y-axis in hospitals with (A) <200 (small), (B) 200–499 (medium), and (C) >499 (large) hospital beds. The coefficient of daily medical costs per person is (A) −0.0001 (95% confidence interval [CI] −0.0004 to 0.0002; $p = 0.40$), (B) −0.0003 (95% CI –0.0004 to −0.0002; $p < 0.0001$), and (C) −0.0001 (95% CI –0.0003 to 0.0001; $p = 0.22$). The line depicts the trinomial regression according to the parameters with the 95% CI.

policies and treatments. Encouragingly, the cost-effectiveness of sepsis has gradually improved over the course of 8 years despite the increasing number of patients with sepsis and medical costs, possibly due to an increased rate of adherence to sepsis guidelines and advanced quality of sepsis management [4,26,27]. In this study, the effective cost per survivor was higher in the highest hospital spending group, suggesting that cost-effectiveness did not improve despite the lower mortality. As the median age of the highest hospital spending group was lower than that of the other groups, higher hospital spending might contribute to enhancing clinical outcomes in the working-age population. In future investigations, detailed analyses with quality-adjusted life years, estimating health-related quality of life, are expected to clarify promising tactics to enhance economic outcomes as well as improve clinical consequences in the sepsis population [28,29].

Variations in medical costs among hospitals have been reported for several diseases [8,14,21,22]. In the present study, we found some variations in the influence of the number of hospital beds, teaching hospitals, and census regions on in-hospital mortality. As the mortality of patients with sepsis was reportedly lower in hospitals with a higher case volume because of greater availability of medical resources and a larger number of experienced staff [30–33], a plausible explanation for the relationship between higher hospital spending and lower mortality could be a higher proportion of large hospitals. However, the results of the subgroup analysis denied the possibility of this speculation. Given that hospitals with a large number of beds potentially provide medical care that exceeds the standard of practice through more experienced medical staff and higher adherence to evidence-based practices [34–36], further improvement might be difficult to obtain with additional hospital spending. Similarly, teaching hospitals showed no correlation between the two variables, suggesting that hospitals with abundant medical resources would not yield disparate clinical outcomes, even if more substantial medical resources were allocated to sepsis management. Considering that hospitals with a small or medium number of beds demonstrated results consistent with the primary results, a small or medium number of hospital beds could improve patient outcomes through the additional allocation of medical resources. Other potential approaches for enhancing outcomes in these hospitals include encouraging adherence to sepsis protocols and optimal timing of transportation to large hospitals [5,37]. Although we excluded transferred patients to analyze medical costs in our study, the timely transport of patients with sepsis would likely enhance their survival rate. Conversely, initial resuscitation would have a substantial impact on clinical outcomes, and medical staff should be cautious about the significance of initial resuscitation and the timing of transportation [38,39].

Geographical variations in medical costs and quality of care have been reported for a range of conditions, including myocardial infarction, heart failure, surgery, trauma, and sepsis [15,40–48]. With regard to trauma, the distance between the scene of the accident and the nearest hospital has been found to have a negative correlation with clinical outcomes [45,46], as critical interventions such as transfusion, tracheal intubation, and surgical procedures are likely to be delayed in accordance with the arrival time. Likewise, clinical outcomes in patients with sepsis may worsen as the length of transportation increases [38,39]. Given that early recognition and prompt intervention are vital for improving the survival of patients with sepsis [38,39], geographical factors are strongly associated with early intervention. A previous report that examined regional disparities in access to plastic surgery in Japan revealed high coverage rates in the Kanto, Chubu, and Kansai areas [49], with regional variations similar to our findings. This regional disparity, potentially arising from distinctions in resident demographics and a gap in access to hospitals, could have affected the various relationships between in-hospital costs and mortality. A more comprehensive understanding of the differences among census regions can be obtained through a detailed analysis of the distribution of hospitals and medical resources.

This study has several limitations. First, the data were collected retrospectively. Second, a selection bias might have remained in the cohort despite the meticulous selection of patients and hospitals, which could represent the acute phase of sepsis treatment. Third, detailed medical costs for sepsis treatment were not collected from the database. Fourth, the medical spending investigated in this study differed from medical bills reimbursed on a bundled payment basis. Fifth, a prominent causal relationship was not shown in this study. Such a limitation may go beyond the design of observational studies, whereas randomized controlled studies attempting to show the positive effect of higher medical expenses on mortality would have some difficulties with their implementation in patients with sepsis. Sixth, long-term outcomes or parameters concerning the quality of life were not obtained from the database. As it would be highly challenging to extract such information from one database, future investigations should link other databases to the current database.

5. Conclusions

Using a Japanese nationwide medical claims database, this study suggests that hospitals with higher expenditures are associated with a better survival rate and a higher effective cost per survivor among sepsis patients than those with lower spending. Conversely, no association was detected between hospital spending and mortality in hospitals with a large number of beds or academic affiliations.

Funding

TO received grants from Chiba Foundation for Health Promotion & Disease Prevention. 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 received no specific funding for this work.

Data availability statement

Data associated with our study are not deposited into a publicly available repository. The datasets used and analyzed in our study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Takehiko Oami: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Toshikazu Abe:** Writing – review & editing, Validation, Supervision, Methodology. **Taka-aki Nakada:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Conceptualization. **Taro Imaeda:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Tuerxun Aizimu:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Nozomi Takahashi:** Writing – review & editing, Validation, Conceptualization. **Yasuo Yamao:** Writing – review & editing, Methodology, Data curation. **Satoshi Nakagawa:** Writing – review & editing, Validation, Supervision. **Hiroshi Ogura:** Writing – review & editing, Validation, Supervision. **Nobuaki Shime:** Writing – review & editing, Validation, Supervision. **Yutaka Umemura:** Writing – review & editing, Validation, Supervision. **Asako Matsushima:** Writing – review & editing, Validation, Supervision. **Kiyohide Fushimi:** Writing – review & editing, Validation, Supervision, Resources, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Takehiko Oami reports financial support was provided by Chiba Foundation for Health Promotion and Disease Prevention. 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 received no specific funding for this work.

Acknowledgements

We would like to thank all contributors to the Japan Sepsis Alliance study group. The study group is a joint research organization, which consisted of the Japanese Society of Intensive Care Medicine, the Japanese Association of Emergency Medicine, and the Japanese Society of Infectious Diseases, holds sepsis seminars and public lectures calling for the prevention, early detection and early treatment of sepsis in Japan.

Abbreviations

ICU	intensive care unit
DPC	diagnosis procedure combination
RRT	renal replacement therapy
IQR	interquartile range
CI	confidence interval

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23480.

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