Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Mortality analysis among sepsis patients in and out of intensive care units using the Japanese nationwide medical claims database-a study by the Japan Sepsis Alliance study group

Takehiko Oami
Chiba University Graduate School of Medicine
Taro Imaeda
Chiba University Graduate School of Medicine
Taka-aki Nakada (taka.nakada@nifty.com)
Chiba University Graduate School of Medicine
Toshikazu Abe
University of Tsukuba
Nozomi Takahashi
Chiba University Graduate School of Medicine
Yasuo Yamao
Chiba University Graduate School of Medicine
Satoshi Nakagawa
National Center for Child Health and Development
Hiroshi Ogura
Osaka University Graduate School of Medicine
Nobuaki Shime
Hiroshima University
Yutaka Umemura
Osaka University Graduate School of Medicine
Asako Matsushima
Nagoya City University
Kiyohide Fushimi
Tokyo Medical and Dental University

Research Article

Keywords: sepsis, diagnosis procedure combination, intensive care unit, propensity score matching

Posted Date: May 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1675084/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background:

A substantial number of sepsis patients require specialized care, including multidisciplinary care, close monitoring, and artificial organ support in the intensive care unit (ICU). However, the efficacy of ICU management on clinical outcomes remains insufficiently researched. Therefore, we tested the hypothesis that ICU admission would increase the survival rate among sepsis patients.

Methods:

We conducted a retrospective study using the nationwide medical claims database of sepsis patients in Japan from 2010–2017 with propensity score matching to adjust for baseline imbalances. Patients aged over 20 years, with a combined diagnosis of presumed serious infection and organ failure, were included in this study. The primary outcome studied was the in-hospital mortality among non-ICU and ICU patients. In addition to propensity score matching, we performed sensitivity analyses for the primary outcome. As the treatment policy was not extracted from the database, we performed subgroup analyses to determine mortality differences in age subgroups based on the assumption that treatment intensity is likely to decrease in older adults.

Results:

Among 1,276,678 sepsis patients (1,076,912 in non-ICU and 199,766 in ICU settings), the unadjusted in-hospital mortality was 18.4% among non-ICU patients and 22.5% among ICU patients ($p<0.001$). After propensity score matching, the in-hospital mortality was 30.2% among non-ICU patients and 20.6% among ICU patients ($p<0.001$). In-hospital mortality with a multivariable regression analysis (B10.3% [95% CI a10.5 to c10.1], $p<0.001$) or inverse probability weighting (k5.6% [95% CI g5.7 to r5.5], $p<0.001$) was comparable with the results of the propensity score matching analysis. In the subgroup analyses, the mortality difference between non-ICU and ICU was o5.7% [95% CI u6.1 to n5.1] in the adult group ($20 \leq$ age ≤ 64), d10.6% [95% CI :11.2 to 10.1] in the old group ($65 \leq$ age ≤ 74), and A11.1% [95% CI 11.6 to s10.7] in the oldest old group ($75 \leq$ age) ($p<0.001$).

Conclusions:

Herein, using the nationwide medical claims database, we demonstrated that ICU admission contributes towards decreasing in-hospital mortality among sepsis patients. Further investigations are warranted to validate these results and elucidate the mechanisms favoring ICU management on clinical outcomes.

Background

Sepsis presents dynamic changes in vital signs and life-threatening organ dysfunction through dysregulated inflammation caused by infection [1, 2]. Therefore, a substantial number of sepsis patients require specialized care in the intensive care unit (ICU), including multidisciplinary care, enhanced capacity for monitoring, and multimodal artificial organ support [3, 4]. The concentrated allocation of healthcare supplies in the ICU should be justified based on the assumption that a greater amount of medical resources, including critical care staff, specialized equipment, and medical costs, could improve clinical outcomes in critically ill patients.

While the indication for ICU admission is determined based on the severity of the illness and requirement of life-sustaining interventions [3], some critically ill patients are treated in general wards owing to overcapacity of the ICU, lack of sufficient resources, or treatment policies, such as withholding or withdrawal of intensive therapy [5–7]. In previous reports, mechanically ventilated patients admitted to general wards or high-dependency care units demonstrated increased mortality, suggesting that critically ill patients are likely to have better outcomes if treated in the ICU [8–13]. Despite this rationale, a large proportion of Japanese patients are on mechanical ventilation in non-ICU settings, as Japan has a lower number of ICU beds per person compared with other developed countries [8, 14, 15]).

Considering the growing number of patients with sepsis globally [16–20], the potential demand for ICU admission is expected to increase over the next decade. Accordingly, we need to address the impact of ICU admission on clinical consequences for patients with sepsis to develop efficient strategies to deal with the overflow of patients resulting from insufficient ICU services. However, only a few studies have investigated the efficacy of ICU management on clinical outcomes in sepsis patients.

Therefore, we hypothesized that ICU admission increases the survival rate of patients with sepsis. We conducted a retrospective cohort study using the Japanese nationwide medical claims database from 2010 to 2017.

Methods

Study setting and patients

We conducted a retrospective observational study using the Japanese nationwide medical claims database, a Diagnosis Procedure Combination (DPC) system, from 2010 to 2017 [21, 22]. Patients over 20 years of age were enrolled in this study. We selected patients with sepsis along with a combined diagnosis of presumed serious infection and organ dysfunction, as described in a previous report [20]. No exclusion criteria were applied, except for age.

The Ethical Review Board of Chiba University Graduate School of Medicine approved this study (approval number: 3429). The review board waived the requirement for written informed consent from the patients or their guardians in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Data extraction and definition

We extracted the following information from the database: age, sex, length of hospital stay, admission to the ICU, primary diagnosis on admission, comorbidities, complications during hospital stay, chronic diseases (malignant tumor, hypertension, diabetes mellitus, heart failure, cerebrovascular disease, ischemic heart disease, chronic respiratory disease, and chronic renal failure), site of infection, medical procedures, therapeutic drugs, blood culture tests, and medical costs. Primary diagnosis, comorbidities, and complications were coded based on the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10). In this database, laboratory tests were not available to calculate the Sequential Organ Failure Assessment (SOFA) score. The medical procedures included mechanical ventilation, oxygen therapy, and renal replacement therapy. Therapeutic drugs included vasoactive agents and antibiotics. The site of infection was extracted according to ICD-10 codes as follows: respiratory (mouth, throat, nasal cavity, neck, lung, lower respiratory tract, chest cavity), urogenital (kidney, urinary tract, uterus, genital organs), abdominal (liver, gall bladder, intestine, peritoneal cavity, gastrointestinal system), bone and soft tissue (skin and soft tissue, bone and joint, lymph tissue, breast), meninge/brain/spinal cord, heart, blood, and unknown. Patients with missing data (n = 766,395), only regarding the site of infection, were excluded from the analysis. Multiple codes in the "site of infection" were categorized with "Multiple" along with the other infections sites. The total medical cost per hospitalization was calculated from the fee for drugs, laboratory tests, radiological examinations, and medical procedures during the hospital stay based on reference prices in the Japanese fee schedule, as described in a previous report [23]. The value was adjusted for the admission year according to the consumer price index and converted into U.S. dollars using the latest exchange rate between U.S. dollars and Japanese yen as of February 3rd, 2022 (115.25 yen = $1 USD).

Sepsis patients were extracted based on records with presumed serious infection and acute organ dysfunction according to previous literature [17, 20]. Presumed serious infection was defined by the record of antibiotic administration for at least 4 consecutive days. In such cases, antibiotics needed to be administered 48 h before or after the blood culture collection. Because laboratory data were unavailable in the database, ICD-10 codes or the records of medical procedures were used for the extraction of organ dysfunction as follows: use of vasopressors, mechanical ventilation or oxygen therapy, initiation of renal replacement therapy, or diagnostic codes related to kidney dysfunction, hepatic disorder, thrombocytopenia/coagulopathy, or metabolic acidosis (Additional File 1: Table S1).

Statistical analysis

The primary outcome that we studied was the in-hospital mortality among non-ICU and ICU patients. The secondary outcomes were length of hospital stay, ventilator-free days, and total medical cost per hospitalization between the two groups. Because baseline imbalances are most likely observed in non-ICU and ICU patients, we performed propensity score matching analysis. To calculate the propensity scores, we conducted a logistic regression analysis using the demographic variables, comorbidities, and therapies listed in Table 1. Nearest-neighbor matching was conducted for non-ICU and ICU patients (1:1 matching) according to the propensity scores without replacement. The caliper width was set at 20% of the standard deviation of the propensity scores [24]. To assess the appropriateness of matching, we calculated the absolute standardized mean differences in the covariables and regarded ≤ 10% as a negligible imbalance between the two groups [25]. As treatment policies, such as withholding or withdrawal of life-sustaining interventions, could not be collected using the database, they could serve as confounding factors for the analysis, despite propensity score matching. Assuming that the intensity of treatment is likely to decrease in older adults and cancer patients due to the treatment policy [5, 6, 26], we conducted subgroup analyses according to the age of enrolled patients and the prevalence of malignancy. As described in a previous publication [20], we divided the patients into three subgroups: adults ($20 \leq$ age ≤ 64), old ($65 \leq$ age ≤ 74), and oldest old ($75 \leq$ age). Along with the age and cancer subgroups, we performed other subgroup analyses with regard to the number of organ dysfunctions, vasopressor use, mechanical ventilation, and renal replacement therapy (RRT).

Table 1
Clinical characteristics before and after propensity score matching

	Before matching			After matching		
	Non-ICU (n = 1076,912)	ICU (n = 199,766)	SMD	Non-ICU (n = 166,544)	ICU (n = 166,544)	SMD
Age, year	77 (67–85)	73 (63–81)	0.29	74 (64–82)	74 (64–81)	0.002
Male, *n* (%)	625,237 (58.1)	127,038 (63.6)	0.11	104,955 (63.0)	104,373 (62.7)	0.007
Chronic diseases						
Cancer *n* (%)	363,695 (33.8)	54,040 (27.1)	0.14	47,122 (28.3)	47,196 (28.3)	0.0002
Hypertension *n* (%)	272,206 (25.3)	51,730 (25.9)	0.01	43,504 (26.1)	43,287 (26.0)	0.003
Diabetes mellitus *n* (%)	230,192 (21.4)	47,011 (23.5)	0.05	39,779 (23.9)	39,111 (23.5)	0.009
Heart failure *n* (%)	187,444 (17.4)	48,485 (24.3)	0.17	39,395 (23.7)	38,673 (23.2)	0.01
Stroke *n* (%)	144,326 (13.4)	31,430 (15.7)	0.07	26,618 (16.0)	25,963 (15.6)	0.005
Ischemic heart disease *n* (%)	90,066 (8.4)	30,385 (15.2)	0.21	22,677 (13.6)	22,543 (13.5)	0.002
Chronic respiratory disease *n* (%)	115,955 (10.8)	14,097 (7.1)	0.13	13,540 (8.1)	13,132 (7.9)	0.003
Chronic renal failure *n* (%)	37,577 (3.5)	10,414 (5.2)	0.08	7,755 (4.7)	7,762 (4.7)	0.002
Community-acquired sepsis *n* (%)	658,066 (61.1)	81,811 (41.0)	0.41	74,298 (44.6)	74,834 (44.9)	0.007
Infection site						
Abdominal *n* (%)	141,198 (13.1)	33,142 (16.6)	0.10	26,863 (16.1)	27,835 (16.7)	0.02

Data are presented as mean (SD) or median (quartile).

ICU, intensive care unit; SD, standard deviation; SMD, standardized mean difference; RRT, renal replacement therapy.

	Before matching			After matching		
	Non-ICU (n = 1076,912)	ICU (n = 199,766)	SMD	Non-ICU (n = 166,544)	ICU (n = 166,544)	SMD
Blood *n* (%)	1,177 (0.1)	104 (0.1)	0.02	97 (0.1)	92 (0.1)	0.001
Bone and soft tissue *n* (%)	39,212 (3.6)	6,566 (3.3)	0.02	5,637 (3.4)	5,631 (3.4)	0.002
Heart *n* (%)	4,238 (0.4)	4,300 (2.2)	0.16	2,318 (1.4)	1,972 (1.2)	0.02
Meninges/brain/ spinal cord *n* (%)	10,384 (1.0)	4,274 (2.1)	0.10	3,240 (1.9)	3,417 (2.1)	0.008
Respiratory *n* (%)	388,271 (36.1)	53,972 (27.0)	0.20	48,370 (29.0)	48,300 (29.0)	0.009
Urogenital *n* (%)	73,821 (6.9)	9,028 (4.5)	0.10	8,267 (5.0)	8,282 (4.9)	0.004
Multiple	312,170 (29.0)	61,659 (30.9)	0.04	51,304 (30.8)	51,131 (30.7)	0.002
Unknown *n* (%)	106,441 (9.9)	26,721 (13.4)	0.11	20,448 (12.3)	19,884 (11.9)	0.01
Vasopressor therapy *n* (%)	97,293 (9.0)	54,166 (27.1)	0.48	36,178 (21.7)	37,149 (22.3)	0.01
Oxygen therapy *n* (%)	875,604 (81.3)	178,698 (89.5)	0.23	149,393 (89.7)	147,497 (88.6)	0.04
Ventilator *n* (%)	103,844 (9.6)	116,460 (58.3)	1.20	82,411 (49.5)	83,282 (50.0)	0.01
Kidney dysfunction *n* (%)	426,533 (39.6)	126,015 (63.1)	0.48	95,527 (57.4)	96,298 (57.8)	0.01
RRT *n* (%)	39,192 (3.6)	44,875 (22.5)	0.58	24,007 (14.4)	26,438 (15.9)	0.04

Data are presented as mean (SD) or median (quartile).

ICU, intensive care unit; SD, standard deviation; SMD, standardized mean difference; RRT, renal replacement therapy.

	Before matching			After matching		
	Non-ICU (n = 1076,912)	ICU (n = 199,766)	SMD	Non-ICU (n = 166,544)	ICU (n = 166,544)	SMD
Thrombocytopenia/ coagulopathy *n* (%)	121,500 (11.3)	39,828 (19.9)	0.24	28,143 (16.9)	28,987 (17.4)	0.01
Hepatic disorder *n* (%)	43,777 (4.1)	6,002 (3.0)	0.06	4,648 (2.8)	4,877 (2.9)	0.01
Acidosis *n* (%)	7,122 (0.7)	2,504 (1.3)	0.06	1,922 (1.2)	1,868 (1.1)	0.003
Data are presented as mean (SD) or median (quartile).						
ICU, intensive care unit; SD, standard deviation; SMD, standardized mean difference; RRT, renal replacement therapy.						

As a sensitivity analysis, we performed multivariable regression analysis to adjust for confounding factors, which were used to calculate the propensity scores. Another matching analysis, inverse probability weighting, was also conducted to investigate the mortality differences between non-ICU and ICU patients.

Continuous variables were expressed as means (standard deviation) or medians (quartiles) and analyzed using the Student's t-test or Mann–Whitney U test, as deemed appropriate. Categorical variables were presented as numbers and percentages and were examined using Pearson's chi-square test. The Kaplan–Meier method and log-rank test were used to analyze survival differences between the two groups. Statistical significance was determined if the two-tailed p-value was < 0.05. We conducted data manipulation and statistical analysis using SQL (mariadb v10.4.17), R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-rojec t.org/), 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).

Results

Clinical characteristics in the cohort

Among the 1,276,678 patients with sepsis enrolled in this study, the numbers of non-ICU and ICU patients were 1,076,912 and 199,766, respectively (Additional File 2: Fig. S1). The median age was 77 (67–85) among the non-ICU patients and 73 (63–81) among the ICU patients. The proportion of men was higher in ICU (63.6%) patients than in non-ICU patients (58.1%). In terms of chronic diseases, the proportion of heart failure and ischemic heart disease was higher among ICU patients, whereas the proportion of cancer and chronic respiratory disease was higher among non-ICU patients. The proportion of infection sites was comparable between the two groups, except for that of respiratory infection. In terms of artificial organ support, the proportions of vasopressor therapy, mechanical ventilation, and RRT among non-ICU and ICU patients were 9.0% and 27.1%, 9.6% and 58.3%, and 3.6% and 22.5%, respectively ($p < 0.001$) (Table 1). The unadjusted in-hospital mortality was 18.4% among non-ICU patients and 22.5% among ICU patients ($p < 0.001$) (Table 2, Additional File 3: Fig. S2).

Table 2
Clinical outcomes before and after propensity score matching

	Before matching			After matching		
	Non-ICU (n = 1,076,912)	**ICU** (n = 199,766)	**p-value**	**Non-ICU** (n = 166,544)	**ICU** (n = 166,544)	**p-value**
In-hospital mortality *n* (%)	198,050 (18.4)	44,935 (22.5)	< 0.0001	50,352 (30.2)	34,251 (20.6)	< 0.0001
Length of hospitalization (day)			< 0.0001			< 0.0001
Mean (SD)	42.4 (96.8)	58.2 (66.7)		60.0 (146.8)	54.8 (62.5)	
Median (IQR)	27 (14–50)	41 (23–72)		38 (20–70)	39 (22–67)	
Length of ICU stay (day)			NA			NA
Mean (SD)	NA	7.0 (6.0)		NA	6.4 (5.7)	
Median (IQR)	NA	5 (2–12)		NA	5 (2–10)	
Ventilator-free days			< 0.0001			< 0.0001
Mean (SD)	26.0 (6.7)	21.8 (9.4)		22.2 (9.7)	22.7 (9.0)	
Median (IQR)	28 (28–28)	27 (20–28)		28 (21–28)	28 (22–28)	
Total medical cost per hospitalization ($)			< 0.0001			< 0.0001
Mean (SD)	17,292 (24,102)	39,351 (39,105)		27,562 (32,743)	34,663 (33,593)	
Median (IQR)	10,770 (5,965 – 20,350)	28,563 (16,585 – 49,422)		18,269 (9,590 – 33,847)	25,530 (15,146 – 43,383)	

Data are presented as mean (SD) or median (quartile).

ICU, intensive care unit; SD, standard deviation; IQR, interquartile range; NA, not applicable.

Clinical outcomes after propensity score matching

After propensity score matching, the number of non-ICU and ICU patients was 166,544 in both groups (Table 1, Additional File 4, Fig. S3). Patient background was comparable between the two groups, with ≤

10% absolute standardized mean differences in the covariables. The proportions of vasopressor therapy, mechanical ventilation, and RRT among non-ICU and ICU patients were 21.7% and 22.3%, 49.5% and 50.0%, and 14.4% and 15.9%, respectively. The length of hospitalization and ventilator-free days in the non-ICU and ICU patients were 38 (20–70) days and 39 (22–67) days, 28 (21–28) and 28 (22–28), respectively. Although the total medical cost per hospitalization was higher among ICU patients ($25,530 [15,146 – 43,383]) than that among non-ICU patients ($18,269 [9,590 – 33,847]), the difference between the two groups was smaller in the cohort after matching than that before matching. In-hospital mortality was 30.2% and 20.6% among non-ICU and ICU patients, respectively ($p < 0.001$) (Table 2). The Kaplan–Meier curve also demonstrated a significantly lower mortality at 30 days after hospital admission in ICU patients ($p < 0.001$) (Fig. 1).

Sensitivity analysis

The difference in adjusted in-hospital mortality with multivariable regression analysis was − 10.3% [95% CI − 10.5 to − 10.1] ($p < 0.001$), which was consistent with the above results. In addition, in-hospital mortality with inverse probability weighting was comparable with the result of the propensity score matching analysis (− 5.6% [95% CI − 5.7 to − 5.5]) ($p < 0.001$) (Table 3).

Table 3
Adjusted in-hospital mortality using a multivariable regression analysis and inverse probability weighting

	Difference	95% CI	p-value
Propensity score matching	− 9.5	− 9.8 to − 9.2	< 0.0001
Multivariable regression analysis	− 10.3	− 10.5 to − 10.1	< 0.0001
Inverse probability weighting	− 5.6	− 5.7 to − 5.5	< 0.0001
Data are presented as mean (SD) or median (quartile).			
SD, standard deviation; IQR, interquartile range.			

Subgroup analyses

The mortality difference between ICU and non-ICU patients was − 5.7% [95% CI − 6.1 to − 5.1] in the adult group, − 10.6% [95% CI − 11.2 to − 10.1] in the old group, and − 11.1% [95% CI − 11.6 to − 10.7] in the oldest old group ($p < 0.001$). While patients with cancer admitted to the ICU exhibited lower in-hospital mortality than those without ICU admission (− 14.9% [95% CI − 15.4 to − 14.3], $p < 0.001$), ICU patients without malignancy also presented decreased mortality compared with non-ICU patients (− 7.5% [95% CI − 7.8 to − 7.1], $p < 0.001$). As the number of organ dysfunctions increased, the difference in mortality between the two groups increased. In terms of vasopressor use and mechanical ventilation, the differences in mortality between the two groups in patients with organ support were larger than those in patients without life-sustaining interventions ($p < 0.001$). In contrast, patients supported by RRT demonstrated a smaller difference in mortality than those without organ support between the non-ICU and ICU settings (p = 0.038) (Fig. 2).

Discussion

In this study, we demonstrated that sepsis patients treated in the ICU exhibited decreased in-hospital mortality compared with those out of the ICU using a propensity score matching analysis. Lower mortality among sepsis patients admitted to the ICU was also presented in the age subgroup analyses and other confounding adjustment analyses, suggesting that the results were robust, regardless of differences in patient backgrounds and treatment intensity.

The advantages of ICU admission over hospitalization in general wards for critically ill patients were consistent with previous reports ([8–13]). In a comparative observational study, mechanically ventilated patients hospitalized in the ICU exhibited a higher in-hospital survival rate than those in medical wards with fewer endotracheal tube-related complications [12]. Another study comparing critically ill patients on ventilator support treated in the ICU and high-dependency care units demonstrated decreased in-hospital mortality [13]. Although a superior survival rate attributable to ICU management has been demonstrated in critically ill patients, few studies have focused on sepsis patients with regard to the efficacy of ICU management on clinical outcomes. To the best of our knowledge, this study is the first to demonstrate the advantages of ICU admission in patients with sepsis using confounding adjustment analyses. Although we performed a propensity score matching analysis to adjust for baseline imbalances, there might be other confounding factors that could affect the results. A potential confounder could be the treatment policy, such as withholding or withdrawing from intensive therapies. In the subgroup analyses concerning age, the significant advantage in ICU settings over general wards was consistent among all age subgroups. Intriguingly, the mortality differences in the subgroup analyses were greater in the old and oldest old groups than in the overall value but not in adults. This result implied that confounding factors were not adjusted in the main analysis in the old and oldest old groups, whereas the subgroup analysis in adults strengthened the robustness that ICU treatment contributed to decreasing mortality. Likewise, the consistency of the decreased mortality among cancer patients admitted to the ICU supports the plausibility of our hypothesis. Future studies should address detailed information about treatment policies in the database.

The exact mechanisms of the advantages in ICU management can be attributed to several factors, including sufficient medical resources and artificial organ support [3, 4]. Mechanical ventilation could be performed in general wards; however, close monitoring might be difficult owing to the lack of adequate resources, leading to mechanical complications such as accidental extubation and delayed recognition of equipment failures [12]. These errors may worsen clinical outcomes in critically ill patients. In the present study, the differences in mortality between the two groups were greater among patients on mechanical ventilation than among those without artificial support. In contrast, patients on RRT exhibited smaller mortality differences than those without RRT. However, the reason for this discrepancy remains to be determined.

To provide an appropriate environment where mechanical organ support is performed without iatrogenic complications, consistent ICU services by intensivists and sufficient nurse staffing are warranted. Regarding their optimal allocation, the lack of intensivists in the ICU or lower patient-to-intensivist ratios reportedly increase the mortality of critically ill patients [27, 28]. Although a high-intensity ICU model or closed-ICU, where intensivists are responsible for day-to-day management, is recommended, the benefit of a 24-hour service of intensivists remains controversial [3]. Furthermore, nurse staffing also contributes to altering patient outcomes [29, 30]. In Japan, the nurse-to-patient ratio in general wards is 1:7 or higher, whereas the ICU allocates one nurse to two patients. While an appropriate nurse-to-patient ratio is lacking owing to scarce evidence, inadequate nursing staffing increases the in-hospital risk of death through insufficient delivery of basic care [31]. Accordingly, ICU settings with a sufficient number of intensivists and nurses for patients would be preferable for sepsis management, particularly for patients receiving mechanical organ support.

While the abundance of staffing and medical resources in the ICU depends on governmental policies and medical systems in different countries, the number of ICU beds per capita by country also varies widely. Compared with other developed countries, Japan has fewer ICU beds (five beds per 100,000 people). In western countries, the number of ICU beds varies: 3.5 beds per 100,000 population in the U.K., 9.3 beds per 100,000 population in France, 13.5 beds per 100,000 population in Canada, and 20 beds per 100,000 population in the U.S. [15, 32, 33]. In addition to variations in the number of ICU beds, the indications for ICU admission and critical care services vary among these countries. In a demographic study comparing critical care delivery between Japan and the U.S., the details of ICU utilization differed by age population, proportion of postoperative ICU admissions, and severity of the critical illness. In terms of severity, the mean APACHE III score among Japanese patients was higher than that among American patients. These differences might be attributable to medical policies, demographic characteristics, and cultural norms [14]. In this context, our results should be interpreted cautiously in accordance with the characteristics of the healthcare system.

This study, however, has several limitations. First, the medical claims database lacks laboratory data. As a calculation of severity scores, such as the SOFA score, was unavailable, we used the number of organ dysfunctions and organ supports to adjust imbalances. Second, confounding by indication for ICU admission was not adjusted. Discrete decisions by responsible physicians potentially cause biased perceptions of disease severity and prognosis among medical personnel. Third, long-term outcomes were not assessed in this study. Fourth, the primary diagnosis for hospitalization in some patients was not sepsis. Fifth, treatment policies, such as withholding or withdrawal of life-sustaining interventions, were not recorded due to the study design, which could have affected the mortality of non-ICU patients. As a result, we performed a subgroup analysis by age to scrutinize the results among younger populations who are unlikely to be withheld or withdrawn from intensive care. Future investigations are warranted to collect detailed patient information, including treatment policy, and to elucidate the mechanisms that favor ICU admission for clinical outcomes.

Conclusions

In this study, using the nationwide medical claims database, we demonstrated that ICU admission contributed to decreased in-hospital mortality among patients with sepsis. Further investigations are still needed to validate these results and to elucidate the mechanistic impact of ICU management.

Abbreviations

ICU, intensive care unit; DPC, diagnosis procedure combination; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision; SOFA, Sequential Organ Failure Assessment; RRT, renal replacement therapy; CI, confidence interval.

Declarations

Acknowledgements

We thank all contributors of the Japan Sepsis Alliance (JaSA) Study.

Authors' contribution

TO, TI, TN, and NT: study concept and design; statistical analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. YY performed the computing process to extract the necessary data. KF, data acquisition. All other authors interpreted the data and critically revised the article for important intellectual content. All the authors have read and approved the final manuscript.

Funding

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.

Availability of data and material

The datasets used and analyzed in our study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The Ethical Review Board of Chiba University Graduate School of Medicine approved this study (approval number: 3429). The review board waived the requirement for written informed consent from the patients or their guardians in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Consent for publications

Not applicable

Competing interests

The authors declare that they have no conflicts of interest.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *JAMA* 2016, **315**(8):801–810.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S *et al*: **Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study**. Lancet 2020, **395**(10219):200–211.
3. Nates JL, Nunnally M, Kleinpell R, Blosser S, Goldner J, Birriel B, Fowler CS, Byrum D, Miles WS, Bailey H *et al*: **ICU Admission, Discharge, and Triage Guidelines: A Framework to Enhance Clinical Operations, Development of Institutional Policies, and Further Research**. Crit Care Med 2016, **44**(8):1553–1602.
4. Marshall JC, Bosco L, Adhikari NK, Connolly B, Diaz JV, Dorman T, Fowler RA, Meyfroidt G, Nakagawa S, Pelosi P *et al*: **What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine**. J Crit Care 2017, **37**:270–276.
5. Peigne V, Somme D, Guerot E, Lenain E, Chatellier G, Fagon JY, Saint-Jean O: **Treatment intensity, age and outcome in medical ICU patients: results of a French administrative database**. Ann Intensive Care 2016, **6**(1):7.
6. Boumendil A, Aegerter P, Guidet B, Network CU-R: **Treatment intensity and outcome of patients aged 80 and older in intensive care units: a multicenter matched-cohort study**. J Am Geriatr Soc 2005, **53**(1):88–93.
7. Sinuff T, Kahnamoui K, Cook DJ, Luce JM, Levy MM, Values E, Rationing in Critical Care Task F: **Rationing critical care beds: a systematic review**. Crit Care Med 2004, **32**(7):1588–1597.
8. Iwashita Y, Yamashita K, Ikai H, Sanui M, Imai H, Imanaka Y: **Epidemiology of mechanically ventilated patients treated in ICU and non-ICU settings in Japan: a retrospective database study**. Crit Care 2018, **22**(1):329.
9. Shum HP, Chan KC, Wong HY, Yan WW: **Outcome of elderly patients who receive intensive care at a regional hospital in Hong Kong**. Hong Kong Med J 2015, **21**(6):490–498.

10. Lieberman D, Nachshon L, Miloslavsky O, Dvorkin V, Shimoni A, Zelinger J, Friger M, Lieberman D: **Elderly patients undergoing mechanical ventilation in and out of intensive care units: a comparative, prospective study of 579 ventilations**. Crit Care 2010, **14**(2):R48.
11. Basoulis D, Liatis S, Skouloudi M, Makrilakis K, Daikos GL, Sfikakis PP: **Survival predictors after intubation in medical wards: A prospective study in 151 patients**. PLoS One 2020, **15**(6):e0234181.
12. Hersch M, Sonnenblick M, Karlic A, Einav S, Sprung CL, Izbicki G: **Mechanical ventilation of patients hospitalized in medical wards vs the intensive care unit–an observational, comparative study**. J Crit Care 2007, **22**(1):13–17.
13. Ohbe H, Sasabuchi Y, Yamana H, Matsui H, Yasunaga H: **Intensive care unit versus high-dependency care unit for mechanically ventilated patients with pneumonia: a nationwide comparative effectiveness study**. Lancet Reg Health West Pac 2021, **13**:100185.
14. Sirio CA, Tajimi K, Taenaka N, Ujike Y, Okamoto K, Katsuya H: **A cross-cultural comparison of critical care delivery: Japan and the United States**. Chest 2002, **121**(2):539–548.
15. Wunsch H, Angus DC, Harrison DA, Collange O, Fowler R, Hoste EA, de Keizer NF, Kersten A, Linde-Zwirble WT, Sandiumenge A *et al*: **Variation in critical care services across North America and Western Europe**. Crit Care Med 2008, **36**(10):2787–2793, e2781-2789.
16. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K, International Forum of Acute Care T: **Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations**. Am J Respir Crit Care Med 2016, **193**(3):259–272.
17. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, Kadri SS, Angus DC, Danner RL, Fiore AE *et al*: **Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009–2014**. JAMA 2017, **318**(13):1241–1249.
18. Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, Allegranzi B, Reinhart K: **Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis**. Intensive Care Med 2020, **46**(8):1552–1562.
19. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D: **Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis**. Crit Care 2020, **24**(1):239.
20. Imaeda T, Nakada TA, Takahashi N, Yamao Y, Nakagawa S, Ogura H, Shime N, Umemura Y, Matsushima A, Fushimi K: **Trends in the incidence and outcome of sepsis using data from a Japanese nationwide medical claims database-the Japan Sepsis Alliance (JaSA) study group**. Crit Care 2021, **25**(1):338.
21. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H: **Validity of diagnoses, procedures, and laboratory data in Japanese administrative data**. J Epidemiol 2017, **27**(10):476–482.
22. Hayashida K, Murakami G, Matsuda S, Fushimi K: **History and Profile of Diagnosis Procedure Combination (DPC): Development of a Real Data Collection System for Acute Inpatient Care in Japan**. J Epidemiol 2021, **31**(1):1–11.

23. Endo A, Shiraishi A, Otomo Y, Fushimi K, Murata K: **Volume-outcome relationship on survival and cost benefits in severe burn injury: a retrospective analysis of a Japanese nationwide administrative database**. J Intensive Care 2019, **7**:7.
24. Rosenbaum PR RD: **Constructing a control group using multivariate matched sampling methods that incorporate the propensity score**. Am Stat 1985, **39**:33.
25. Austin PC: **Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples**. Stat Med 2009, **28**(25):3083–3107.
26. Tavares M, Neves I, Chacim S, Coelho F, Afonso O, Martins A, Mariz JM, Faria F: **Withdrawing and Withholding Life Support in Patients With Cancer in an ICU Setting: A 5-Year Experience at a European Cancer Center**. J Intensive Care Med 2018, **33**(7):415–419.
27. Wilcox ME, Chong CA, Niven DJ, Rubenfeld GD, Rowan KM, Wunsch H, Fan E: **Do intensivist staffing patterns influence hospital mortality following ICU admission? A systematic review and meta-analyses**. Crit Care Med 2013, **41**(10):2253–2274.
28. Gershengorn HB, Harrison DA, Garland A, Wilcox ME, Rowan KM, Wunsch H: **Association of Intensive Care Unit Patient-to-Intensivist Ratios With Hospital Mortality**. JAMA Intern Med 2017, **177**(3):388–396.
29. Needleman J, Buerhaus P, Pankratz VS, Leibson CL, Stevens SR, Harris M: **Nurse staffing and inpatient hospital mortality**. N Engl J Med 2011, **364**(11):1037–1045.
30. Penoyer DA: **Nurse staffing and patient outcomes in critical care: a concise review**. Crit Care Med 2010, **38**(7):1521–1528; quiz 1529.
31. Schubert M, Clarke SP, Aiken LH, de Geest S: **Associations between rationing of nursing care and inpatient mortality in Swiss hospitals**. Int J Qual Health Care 2012, **24**(3):230–238.
32. Rhodes A, Ferdinande P, Flaatten H, Guidet B, Metnitz PG, Moreno RP: **The variability of critical care bed numbers in Europe**. Intensive Care Med 2012, **38**(10):1647–1653.
33. Phua J, Faruq MO, Kulkarni AP, Redjeki IS, Detleuxay K, Mendsaikhan N, Sann KK, Shrestha BR, Hashmi M, Palo JEM *et al*: **Critical Care Bed Capacity in Asian Countries and Regions**. Crit Care Med 2020, **48**(5):654–662.

Figures

Figure 1

Kaplan–Meier curve for 30-day mortality between non-ICU and ICU patients after propensity score matching

The mortality of ICU patients 30 days after admission was significantly lower than that of non-ICU patients after propensity score matching (log-rank test, p-value < 0.005). Discharged patients were excluded from analysis.

Subgroup		Non−ICU In−hospital mortality n (%)	ICU In−hospital mortality n (%)	p−value
Age	Adults	8,444/43,173 (19.6)	5,969/42,627 (14.0)	<0.0001
	Old	12,266/40,677 (30.2)	8,637/44,260 (19.5)	<0.0001
	Oldest old	29,642/82,694 (35.8)	19,645/79,657 (24.7)	<0.0001
Cancer	Yes	17,603/47,126 (37.4)	10,646/47,323 (22.5)	<0.0001
	No	32,566/119,418 (27.3)	23,619/119,221 (19.8)	<0.0001
Number of organ dysfunction	1	8,671/58,283 (14.9)	4,533/54,284 (8.4)	<0.0001
	2	21,180/67,279 (46.4)	13,795/68,860 (40.0)	<0.0001
	>=3	20,501/40,982 (50.0)	15,923/43,400 (36.7)	<0.0001
Vasopressor	Yes	17,011/36,178 (47.0)	12,230/37,149 (32.9)	<0.0001
	No	33,341/130,366 (25.6)	22,021/129,395 (17.0)	<0.0001
Mechanical ventilation	Yes	34,625/82,411 (42.0)	24,455/83,282 (29.4)	<0.0001
	No	15,727/84,133 (18.7)	9,796/83,262 (11.8)	<0.0001
RRT	Yes	9,653/24,007 (40.2)	10,391/26,438 (39.3)	0.038
	No	40,699/142,537 (28.6)	23,860/140,106 (17.0)	<0.0001

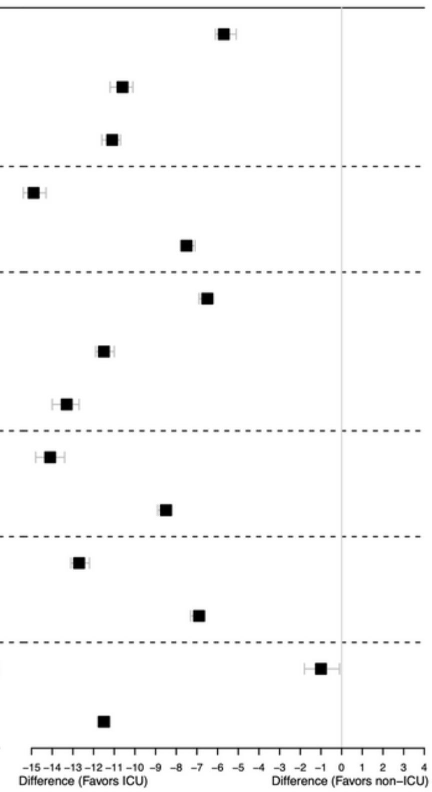

Figure 2

Subgroup analyses for in-hospital mortality after propensity score matching

Subgroup analyses comparing in-hospital mortality between non-ICU and ICU patients after propensity score matching. The mortality difference between the two groups is depicted as boxes with a 95% confidence interval on the right-hand side of the table. ICU, intensive care unit; RRT, renal replacement therapy.

Supplementary Files

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

- AdditionalFile1.docx

- AdditionalFile2FigureS1.png
- AdditionalFile3FigureS2.png
- AdditionalFile4FigureS3.png