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Differences in mortality when treatment is withheld in older patients experiencing septic shock

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Abstract

***Objective*: The incidence of sepsis in older adults has been increasing with the general aging of the Japanese population. However, it has been shown that age is a critical factor in determining both the risk for sepsis and subsequent vital outcomes; aggressive treatment is often discouraged in this vulnerable patient group. This study aimed to determine whether aggressive therapeutic interventions were associated with mortality in older Japanese patients experiencing septic shock.**

***Design*: Single-center retrospective cohort study.**

***Setting*: Medical Intensive Care Unit of a city hospital (Kishiwada Tokushukai Hospital) in Japan between January 2020 and September 2021.**

***Patients*: Patients diagnosed with septic shock at the time of admission and older patients over 65 years of age were included and divided into two groups: a withholding group that received only minimal peripheral infusion and antibiotic therapy and a treatment group (non-withholding group) that received intensive care, such as vasopressor use or mechanical ventilator management.**

***Interventions*: None.**

***Measurements and results*: One hundred patients were included in this study. There were 13 and 87 patients in the withholding and non-withholding groups, respectively.**

There was no significant difference in 30-day mortality between the two groups (53.85% vs 39.08%, p=0.127). However, the 72-hour mortality was significantly higher in the withholding group (53.8% vs 25.3%, p=0.034).

***Conclusions*: Among older patients with septic shock, the withholding group showed a survival rate that was not significantly different from that of the non-withholding group. On the other hand, some level of survival may be expected in patients who withhold treatment after 72 hours or more. Further studies are needed to determine the impact of withholding treatment on patients, not only in terms of mortality but also in terms of long-term prognosis and activities of daily living after discharge from the hospital.**

Key words: Withholding treatment, aging, intensive care, septic shock, mortality rate.

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Introduction

It is estimated that approximately 49.9 million people worldwide develop sepsis annually, of which 11 million (22.5%) die. (1) The incidence of sepsis has increased with the aging population in Japan. The annual number of patients with sepsis increased from approximately 110,000 in 2010 (about 3% of total inpatients) to approximately 360,000 in 2017 (about 5% of total inpatients). Although the in-hospital mortality rate is declining, it remains high at 56,905 (18.3%) in 2017. (2)

Sepsis is diagnosed clinically by the presence of acute infection and new organ dysfunction. (3) A

variety of clinical variables and tools are used for sepsis screening, such as systemic inflammatory response syndrome (SIRS) criteria, quick Sequential Organ Failure Score (qSOFA) or Sequential Organ Failure Assessment (SOFA) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS). In The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020), a diagnosis of sepsis is confirmed when the Sequential Organ Failure Assessment (SOFA) score of 2 points or more acutely increases in the presence of a clear infection or suspected infection. (4) SOFA uses laboratory and clinical data to categorize organ failure by summing six scores from individual organ systems: respiratory, cardiovascular, hepatic, coagulation, renal, and neurological.

It has been shown that age is a critical factor in determining the risk for sepsis and subsequent vital outcomes. Aggressive treatment, such as mechanical ventilation or administration of vasopressors, is often discouraged in the older population. (5) Incidence rates for sepsis in humans are known to increase with age. (6) This may reflect age-related differences in immune function, such as failed antigen processing by leukocytes and altered inflammatory cytokine expression. (7,8) Very old patients (aged 80 and over) were intubated and ventilated significantly less frequently than old patients (65-79 years) (42 vs 55%, $p<0.001$). This may indicate that the decision to limit therapy was made more frequently based on age. (9)

Few studies have compared the prognostic values of aggressive interventions such as mechanical ventilation or vasopressor administration in elderly patients with septic shock. In the present study, we aimed to determine whether aggressive therapeutic intervention is associated with mortality in older patients with septic shock.

Materials and methods

Setting

This single-center, retrospective cohort study was conducted at Kishiwada Tokushukai Hospital in Japan (with 400 beds and approximately 10,000 patients transported by Emergency Medical Services [EMS] per year). This study included 14,880 patients transported to the hospital for emergency care between January 2020 and September 2021. The medical records of patients diagnosed with septic shock at the time of admission were searched. Patients with septic shock aged 65 years or older were included by referring to the World Health Organization (WHO) definition of the elderly.

In the Japanese clinical practice guidelines for the J-SSCG 2020, the severity of sepsis is classified into two categories: sepsis and septic shock, according to the Sepsis-3 definition. Septic shock is defined as a severe form of sepsis with a high mortality rate due to acute circulatory failure, which defines septic shock as a blood lactate level >2 mmol/l (18 mg/dl) and the need for vasoconstrictive drugs in addition to infusion therapy to maintain a mean arterial blood pressure of ≥65 mmHg. (3,4) Patients with septic shock meeting the definition were selected for this study.

Eligibility

Patients were included in the study if they met the following criteria: 1) Patients admitted to the hospital after emergency transport, 2) Patients with no antibiotics or other medical interventions were administered before transport, 3) Patients with suspected infection-associated organ damage, 4) Patients with failure to maintain blood pressure after an initial infusion of lactate Ringer's solution, 5) Patients with a blood lactate level >2 mmol/l (18 mg/dl) on blood test at admission.

Patients were excluded if they met the following criteria: 1) Patients transferred to another hospital, 2) Patients who had already been treated by a previous physician, 3) Patients who did not meet the diagnostic criteria per Sepsis-3, 4) Patients who were already admitted to the hospital with other diagnostics and had a complication of septic shock, 5) Patients under 65 years, 6) Patients with end-stage renal disease on dialysis maintenance.

Exposure group and control group

Patients were divided into two groups: a withholding group that received only minimal peripheral infusion and antibiotic therapy and a non-withholding group that received aggressive therapeutic interventions such as vasopressor use or mechanical ventilation management. The selection of the withholding group was determined after a discussion between the family members and the emergency department physician. Lactate Ringer's solution was used for the infusion, and the physician in charge determined which antibiotic to select. Medical intervention procedures in the non-withholding group were investigated by reviewing the medical records. Vital signs (Glasgow Coma Scale, blood pressure, heart rate, respiratory rate, saturation of percutaneous oxygen, axillary body temperature) were recorded for all patients upon arrival. Blood and various culture tests (e.g., sputum culture, urine culture, wound culture, etc.) were performed in the Emergency Room depending on the source of infection. The site of infection was extracted according to the

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, gallbladder, intestine, peritoneal cavity, gastrointestinal system), bone and soft tissue (skin and soft tissue, bone and joint, lymph tissue, breast), and unknown.

Ethical considerations

Following the Japanese guidelines, Ethical Guidelines for Medical and Health Research Involving Human Subjects, written informed consent from each individual was obtained by disclosing information on the hospital website.

This study was conducted in compliance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and was approved by the Kishiwada Tokushukai Hospital Ethics Committee (Approval No. Study 23-21).

Outcomes

The primary endpoint was the 30-day mortality rate. The secondary endpoints were 72-hour mortality, vital signs on admission, blood test results on admission, Sepsis-related Organ Failure Assessment (SOFA) score on admission, initial infusion volume, and length of stay. All patients received lactate Ringer's solution for the initial infusion.

Statistical analysis

Statistical analyses were performed using SPSS ver. 22 (IBM, the United States, Armonk). Categorical variables were expressed as numbers and percentages, and Pearson's chi-square test was used. Continuous variables are expressed as mean (standard deviation) or median (quartiles) and analyzed using the Mann-Whitney U test. The Kaplan-Meier method was used to analyze the differences in survival between the two groups. Statistical significance was set at $p<0.05$.

Results

Characteristics of the study participants

In a total cohort of 14,880 patients who were transported to our hospital for emergency care between January 2020 and September 2021, 141 were diagnosed with septic shock upon admission. Of these, 100 were eligible for inclusion. There were 13 and 87 patients in the withholding and non-withholding groups, respectively.

The baseline patient characteristics are presented in **Table 1**. Compared to the non-withholding group, the withholding group was older (88±13 years vs 82±9 years, 95% confidence interval [CI] -10.47--2.41, p=0.004) and had a lower body mass index (BMI) (16±4 kg/m^2 vs 21±5 kg/m^2, 95% CI -0.11-7.05, p=0.043). Regarding the evaluation of the quick SOFA score items (Glasgow Coma Scale [GCS), mean arterial blood pressure, and respiratory rate) at presentation, the withholding group had significantly worse GCS scores (10 vs 13, 95% CI -0.15-4.45, p=0.020) than those of the non-withholding group. The primary source of infection was not significantly different between the two groups. Both groups had the highest rates of urinary tract infections (n=6 [46.2%] vs n=44 [47.3%], p=0.652). Meropenem was the most used antibiotic in both groups (n=9 [69.2%] vs 50 [57.5%], p=0.421), and there was no significant difference in the duration of antibiotic administration (9.7 days vs 12.6 days, 95% CI -3.45-9.23, p=0.367) (**Table2**). There were also no significant differences in laboratory data or SOFA scores at the time of septic shock diagnosis (**Table 3**).

Main results

There was no significant difference in 30-day mortality between the two groups (53.85% vs 39.08%, p=0.127). However, the 72-hour mortality was significantly higher in the withholding group (53.8% vs 25.3%, p=0.034) (**Table 4**, **Figure 1**) than in the non-withholding group. There was no significant difference in the length of hospital stay (1±34 days vs 18±28 days, p=0.311), initial infusion volume at the emergency department (1357±1000 ml vs 1226±1000 ml, p=0.509), and infusion volume per body weight (35±30 ml/kg vs 25±18 ml/kg, p=0.132) between the two groups (**Table 4**).

Discussion

There is no certainty as to whether older age increases mortality in patients with septic shock. A multicenter retrospective study comparing critically ill patients with sepsis and septic shock admitted to the intensive care unit (ICU) between old (65-79 years, median [interquartile range {IQR}] 72 [8]) and very old (>79 years, median [IQR] 84 [4]) patients found a slightly higher ICU mortality rate in the very old patients, but the difference was very small and probably acceptable from a clinical perspective (38% vs 36%, adjusted odds ratio 1.50, 95% CI 1.10-2.06, p=0.01). (9) Frailty and other geriatric impairments have also been shown to correlate with worse survival and functional outcomes. (10-14) However, there is no strong evidence for this concerning age itself. (15)

In addition, the proportion of deaths that occur after a decision to limit life support varies considerably. (16) Among patients with sepsis, very old patients

over 90 years of age admitted to the ICU have been reported to have a significant increase in 30-day mortality after withholding treatment. (17) However, in patients with sepsis aged 80 years or older admitted to the ICU, there was no significant increase in mortality in the withholding group, regardless of the SOFA score. (4) There is no certainty on what happens to mortality due to treatment restriction, regardless of whether the patient is older or not, or whether the patient is severely ill with SOFA score.

However, age often limits aggressive treatment. A multicenter prospective cohort study, comparing patients hospitalized with serious illnesses associated with an average 6-month mortality rate of 50% between younger patients (<70 years, median age [25th, 75th percentile] 57 years [46, 64]) and older patients (≥70 years, median age [25th, 75th percentile] 77 years [73, 82]), found that older patients more commonly decided to withhold life-sustaining treatments. Older age was associated with higher rates of withholding ventilator support (10% vs 13.5%, p<0.001) and dialysis (3.8% vs 4.8%, p<0.05). (18,19) In a study by Hakim et al. in the USA, the rate of do-not-resuscitate orders increased with age (from 21% in patients aged < 54 years to 55% in patients aged > 84 years). (20)

In our study, the patients in the withholding group had a significantly higher mean age than those in the non-withholding group. Physicians may be reluctant to provide intensive care to very old patients. In addition, many older patients choose to avoid unnecessary prolongation of life through organ support and intensive care. Factors other than age, such as base condition (activities of daily living [ADL]), have been reported to influence the withholding of treatment, and the failure to consider these other factors in this study is a limitation. (21)

Interestingly, in this study, the 30-day mortality rate remained the same in older patients with septic shock who did not receive intensive care compared with those who did, despite no significant differences in the severity of illness, such as SOFA scores. There are scattered reports of studies on patients admitted to ICUs in which treatment limitations are associated with higher mortality.

A multicenter prospective cohort study of older patients aged ≥80 years admitted to the ICU found that limiting intensive care was associated with increased 30-day mortality (54.8% in the withholding group and 94.2% in the withdrawal group). (16)

A similar result was found in a multicenter observational cohort study conducted in France on patients admitted to the ICU, where treatment withdrawal or withholding accounted for half of all deaths. (22) In Italy, 62% of ICU deaths were reported in withholding or withdrawal groups. (23)

In contrast, others have reported that withholding treatment does not change mortality rates. A post hoc analysis of the VIP2 study, a prospective cohort study of elderly patients over 80 years of age admitted to the ICU, found no significant difference in 30-day mortality between the treatment and withholding groups, regardless of whether the SOFA score was high or low. (17) Among elderly patients who decided to withhold treatment, ICU mortality and 30-day mortality rates were only 29.1% and 53.1%, respectively. (16)

Although this study was limited to patients with septic shock, the 30-day mortality rate remained the same as that in patients who received intensive care despite no significant differences in the severity of illness, such as the SOFA score (7.5 vs 8.0, p=0.118). It is important to note that the decision to withhold treatment is not equivalent to an end-of-life decision. (16)

In this study, there was no significant difference in 30-day mortality; however, mortality was significantly higher in the withholding group than in the non-withholding group when limited to mortality within 72 h. The impact of withholding treatment on mortality is greatest in the first week of ICU treatment, depending on the type of treatment withdrawn and the number of organs failing at the time of treatment limitation. (24,25) The effect of treatment limitation on survival was discernible until 2 weeks after ICU admissions. (16)

The strongest predictor of time to death is the severity of a patient's acute illness, and this study is limited to septic shock, which applies to the most severe form of sepsis. (25) It is interesting to note that all deaths in the withholding group (7 [67.1%]) were limited to within 72 hours of admission, and conversely, all patients survived for 30 days if more than 72 hours had passed. Although the limitation is that the number of cases is quite small, some level of survival may be expected in patients who withhold treatment after a certain period.

Although this was a single-center, retrospective cohort study, it was limited to community-onset untreated septic shock cases. These data are meaningful because of the uniformity of treatment. However, this study has some limitations. First, the long-term prognosis, including the social return-to-work rate, was not mentioned. Second, the definition of older patients was set to 65 or older, based on the WHO classification; however, there is no consensus on aging. This study could not determine the mortality rate when the age setting is raised. Finally, life expectancy depends more on the underlying disease

than age; however, this was not mentioned in this report.

Conclusion

Among older patients with septic shock, the withholding group, which was limited to minimal peripheral intravenous infusion and antibiotic therapy, showed a survival rate that was not significantly different from that in the non-withholding group. On the other hand, some level of survival may be expected in patients who withhold treatment after 72 hours or more. Further studies are needed to determine the impact of withholding treatment on patients, not only in terms of mortality but also in terms of long-term prognosis and ADL after discharge from the hospital.

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Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Table 1. Baseline characteristics

	Withholding (n=13)	Non-withholding (n=87)	p-value
Age (years), median (IQR)	88 (13)	82 (9)	0.04
Male, n (%)	3 (23.08%)	40 (43.01%)	0.12
BMI (kg/m^2), median (IQR)	16 (4)	21 (5)	0.043
GCS, median (IQR)	10 (4)	13 (4.8)	0.02
MAP (mmHg), median (IQR)	68.7 (40.3)	69 (25.8)	0.826
Respiration rate (/min), median (IQR)	25 (11)	24.5 (10)	0.882
Infection focus			
- Urogenital, n (%)	6 (46.2%)	44 (47.3%)	0.651
- Respiratory, n (%)	4 (30.8%)	15 (16.1%)	0.246
- Abdominal, n (%)	2 (15.4%)	16 (17.2%)	0.792
- Bone and soft tissue, n (%)	0	6 (6.5%)	0.329
- Unknown, n (%)	1 (7.7%)	6 (6.5%)	0.916

Legend: IQR=interquartile range; BMI=body mass index; GCS=Glasgow Coma Scale; MAP=mean arterial blood pressure.

Table 2. Antibiotic data

	Withholding (n=13)	Non-withholding (n=87)	p-value
Two-drug combination, n (%)	33 (14.9%)	6 (46.2%)	0.571
Duration of antibiotic treatment (days)	12.6	9.7	0.367
Types of antibiotics			
- Ampicillin sodium, n (%)	20 (23%)	3 (23.1%)	0.994
- Sulbactam sodium/ampicillin sodium, n (%)	5 (5.7%)	0	0.375
- Tazobactam/piperacillin, n (%)	3 (3.4%)	1 (7.7%)	0.466
- Cefmetazole sodium, n (%)	19 (21.8%)	3 (23.1%)	0.92
- Ceftriaxone, n (%)	6 (6.9%)	3 (23.1%)	0.057
- Cefepime, n (%)	2 (2.3%)	0	0.581
- Meropenem, n (%)	50 (57.5%)	9 (69.2%)	0.421
- Vancomycin, n (%)	13 (14.9%)	2 (15.4%)	0.967
- Metronidazole, n (%)	1 (1.1%)	1 (7.7%)	0.116

Legend:
Sulbactam sodium/ampicillin sodium=a combination drug of ampicillin and beta-lactamase inhibitor.
Tazobactam/piperacillin=a combination drug of tazobactam and piperacillin in the ratio of 1:4.
Cefmetazole sodium=a semisynthetic cephamycin antibiotic.
Ceftriaxone=a third-generation cephalosporin.
Cefepime=a broad-spectrum fourth-generation cephalosporin.
Meropenem=a broad-spectrum carbapenem.
Vancomycin=a glycopeptide mainly used against methicillin-resistant Staphylococci.
Metronidazole=a nitroimidazole.

Table 3. Laboratory data, median (IQR)

	Withholding (n=13)	non-Withholding (n=87)	p-value
Lactate (mg/dl)	36 (19)	42.5 (54.5)	0.748
WBC (/μl)	7700 (11500)	8200 (11275)	0.442
Hb (g/dl)	11.9 (3.83)	11 (2.95)	0.786
Plt (10^4/μl)	12.9 (13.75)	15.75 (12.28)	0.727
Glucose (mg/dl)	84 (218)	122.5 (94)	0.954
T-Bil (mg/dl)	1.01 (0.56)	0.90 (0.77)	0.663
LDH (U/l)	368 (234)	301 (175.5)	0.91
Alb (g/dl)	3 (0.7)	2.9 (1.2)	0.93
Cre (mg/dl)	1.59 (1.3)	1.79 (1.5)	0.47
CRP (mg/dl)	18.73 (27.4)	11.43 (20.26)	0.922
PCT (ng/ml)	22.38 (45.32)	7.11 (27.84)	0.178
SOFA score	7.5 (3)	8.0 (4)	0.118

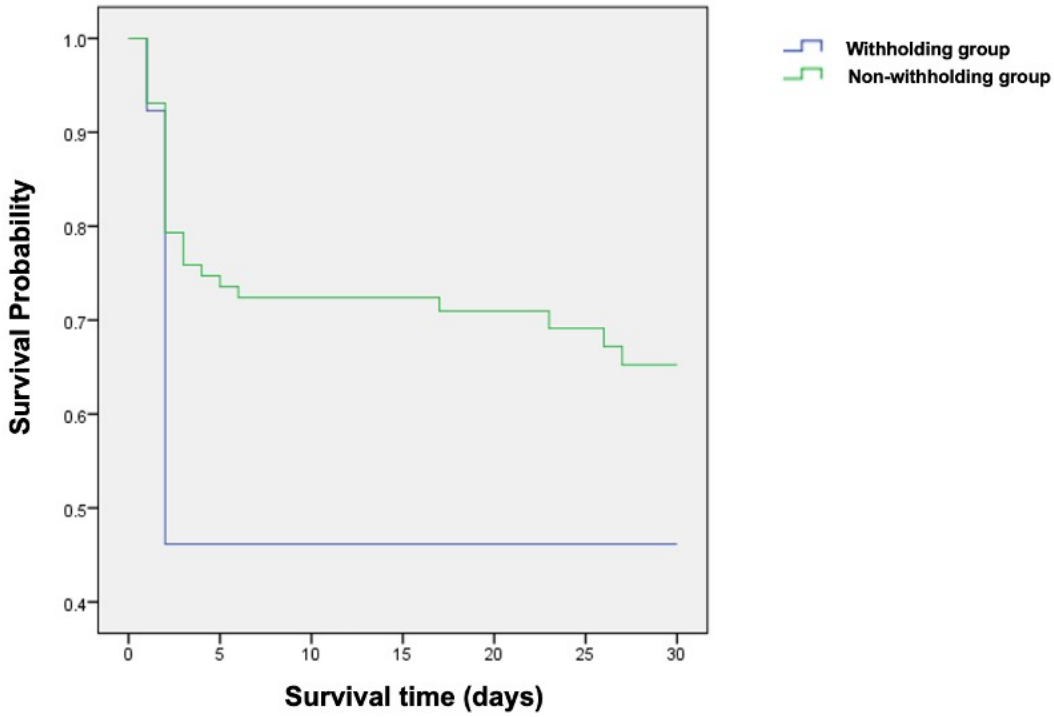
Legend: IQR=interquartile range; WBC=white blood cell; Hb=hemoglobin; Plt=platelet; T-bil=total bilirubin; LDH=lactate dehydrogenase; Alb=albumin; Cre=creatinine; CRP=C-reactive protein; PCT=procalcitonin; SOFA=Sequential Organ Failure Assessment.

Table 4. Clinical outcomes

	Withholding (n=13)	Non-withholding (n=87)	p-value
Died whithin 30 days, n (%)	7 (53.8%)	28 (30.1%)	0.127
Died whithin 72 hours, n (%)	7 (53.8%)	22 (25.3%)	0.034
Length of hospitalization (days), median (IQR)	1 (34)	18 (28)	0.311
Fluid management in first 24h - Total amount of fluid (ml), median (IQR) - Amount of fluid per kg body weight (ml/kg), median (IQR)	 1357.1 (1000) 34.67 (30)	 1226 (1000) 25 (18)	 0.509 0.132
Mechanical ventilation, n (%)		23 (26.4%)	
Vasopressor use, n (%)		87 (100%)	

Legend: IQR=interquartile range.
Vasopressor=noradrenaline or vasopressin.

Figure 1. Survival curves according to withheld treatment



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