ISSN 0030-6096

OSAKA CITY MEDICAL JOURNAL

Vol. 71
No. 1

2025

PUBLISHED BY
OSAKA CITY MEDICAL ASSOCIATION
OSAKA JAPAN

Osaka City Medical Journal
Vol. 71, No. 1, June 2025

CONTENTS

Osaka City Med. J. Vol. 71, 1-11, 2025

Overcoming Afferent Limb Failure: The Impact of a Modified Rapid Response System and Educational Program

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Abstract

Background

Rapid response systems (RRSs) and rapid response teams (RRTs) have been widely implemented to manage patients at risk of deterioration and reduce unexpected serious adverse events including cardiac arrest. However, their effectiveness remains controversial due to afferent limb failure (ALF), especially in hospital settings with hierarchical structures. This study evaluated the effectiveness of a modified RRS and an education program, aiming to break barriers of ALF.

Methods

This retrospective single-center cohort study compared cases requiring medical emergency team (MET)/RRT call and outcomes in 2-year periods pre- and post-implementation of them at a Japanese university hospital. Data were collected on MET/RRT calls, the timing and frequency of unexpected cardiac arrest (UCA) cases, and mortality rates.

Results

The number of MET/RRT calls increased from 8.30 to 11.68 per 100000 admission days ($p=0.082$). UCA cases did not significantly decrease (from 6.14 to 5.93, $p=0.90$), while non-cardiac arrest cases significantly increased (from 2.17 to 5.74, $p<0.01$). The mortality rate for all MET/RRT calls showed no significant improvement (57% vs 44%, $p=0.24$). There were 19 cases (56%) in the pre-period and 22 cases (71%) in the post-period where patients either did not meet the early warning criteria within 10 minutes to 24 hours, or met the criteria within 4 hours ($p=0.30$).

Conclusions

The introduction of a modified RRS and educational program significantly increased MET/RRT calls for non-cardiac arrests, improving early intervention and consultation. It was considered a useful approach for addressing ALF. Further improvements are needed to enhance outcomes and optimize resources.

Received September 4, 2024; accepted November 26, 2024.

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Key Words: Intensive care unit; Rapid response team; Medical emergency team; In-hospital cardiac arrest; Psychological safety

Introduction

Rapid response teams (RRTs) or medical emergency teams (METs) have been implemented widely across both U.S.[1] and Japanese hospitals[2] to identify patients at risk of deterioration and reduce unexpected serious adverse events (SAEs) including cardiac arrest. In 2017, the Japan Council for Quality Health Care, a third-party organization that evaluates medical institutions in Japan, added "having a system for identifying deteriorating patients" as one of its evaluation items. To meet this criterion, hospitals in Japan are urged to introduce some sort of rapid response system (RRS).

The effectiveness of RRT/METs is, however, controversial. Although meta-analyses have reported decreased rates of cardiac arrest outside intensive care units (ICUs) after the implementation of RRT/METs[3,4], robust evidence to support their effectiveness in reducing hospital mortality has not been reported[5]. The only cluster randomized controlled study, the Medical Early Response Intervention and Therapy (MERIT) trial, did not demonstrate decreased rates of cardiac arrest and mortality[6].

One of the reasons advocated to explain this result is "afferent limb failure" (ALF). The RRS is composed of an afferent limb and efferent limb. The detection of at-risk patients and early activation of RRT/METs for them by using a set of predetermined criteria constitutes the afferent limb of a RRS[7]. That study reported that the MET was called for only 30% of patients who fulfilled the calling criteria and were subsequently admitted to the ICU. An inverse relationship between such ALF and unexpected death and SAE in hospitals with RRT/METs has recently been suggested[8-11]. The causes of ALF are a lack of recognition of the signs of deterioration and cultural and behavioral barriers associated with inter-professional hierarchies in the clinical area[12,13]. Fear of criticism was identified as an important barrier to activation of the MET/RRT[13,14], and these barriers are particularly common among junior and inexperienced ward staff members[15-17].

As one reason for making the potential benefits of RRS unclear, ALF might be a considerably large problem in Japanese hospitals, in which the doctor-in-charge system for patient care is still common, and each department may care for their seriously ill patients in the ICU.

Aiming to prevent unexpected SAE, we started a modified RRS in 2015. Unlike the typical RRS, which relies on calling RRT once the patient meets certain criteria, the modified RRS incorporates a process that encourages staff to recognize early warning signs and promptly consult with senior staff. This proactive approach enables immediate reporting and consultation when staff notice any abnormal signs. Additionally, from the outset, we developed and implemented a dedicated education program as part of a comprehensive package to overcome ALF and enhance the quality of care provided by doctors and nurses who detect patient deterioration. This study evaluated the effectiveness of this attempt continued for three years by analyzing RRT/MET calls and the rates of unexpected cardiac arrest (UCA) before and after implementation of the them.

Methods

Clinical setting

Osaka City University Hospital (currently Osaka Metropolitan University Hospital) has 980 beds, handles over 20000 admissions annually, and employs approximately 500 full-time doctors. The Code Blue system has been implemented mainly for responding to cardiac arrests since before 2014. The

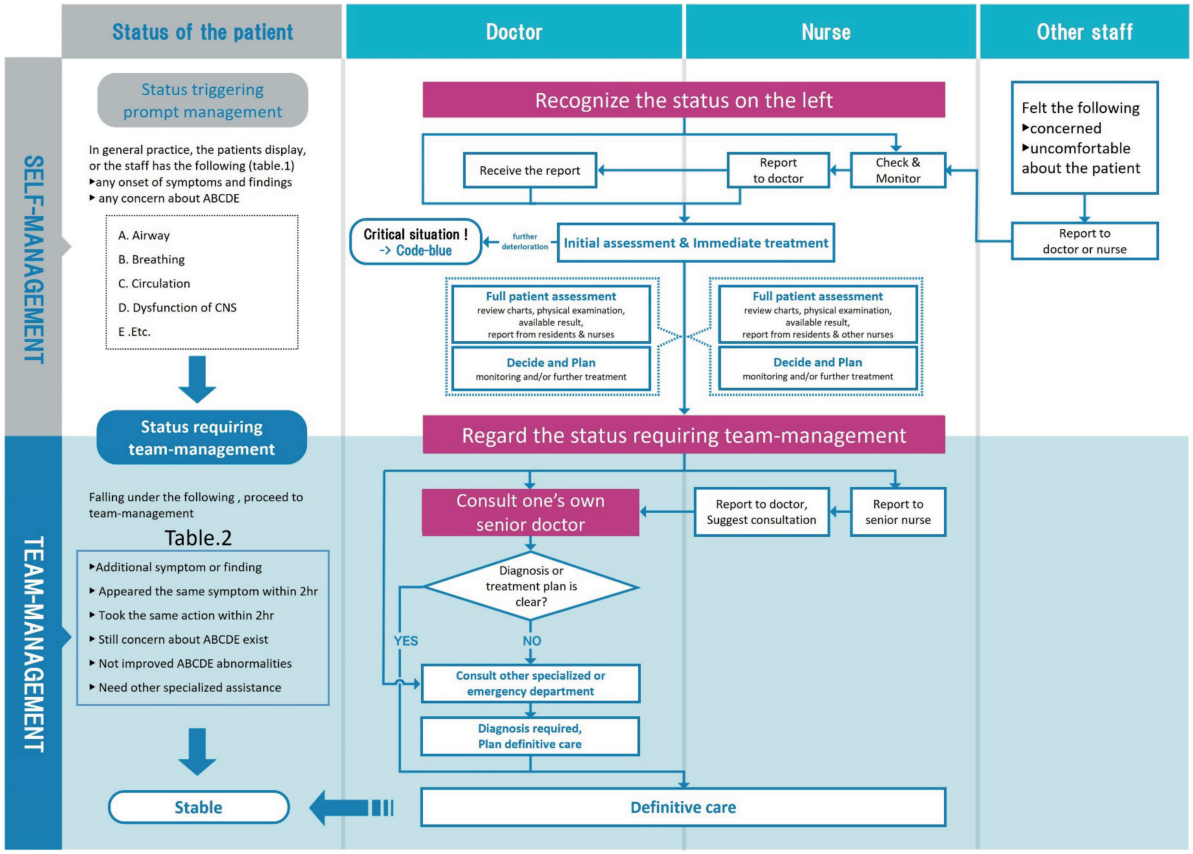

Figure 1. Resource management flowchart for doctors and nurses in non-critical-care wards.

MET for code-blue calls consists of doctors and nurses of the tertiary emergency medical care center.

In 2014, the Patient Safety Management Committee in our hospital investigated successive code blue cases during a 30-month period. They revealed that 10 of 94 (11%) cases were avoidable if antecedents prior to severe deterioration had been promptly identified and adequately treated. Those cases had two features: 1) the inability to assess antecedents—although most staff had been aware of the symptoms or signs, they could not assess them correctly, and 2) the absence of clear rules to speak up to their seniors—the junior staff did not promptly consult with their senior staff. These issues arose when young doctors, who are particularly third-year residents and tend to avoid asking seniors for help, were on night duty.

Implementation of RRS and education program

In 2015, to eliminate preventable SAE, a working group was established under our Department of Quality and Safety Management that comprised doctors, nurses, and pharmacists, and all of the authors were included in it. Within this group, we developed new system procedures and an educational program[18].

First, we created a flowchart based on the standards: recognizing the signs of severe illness and unsafe situations, sharing information, and consulting about patients' prolonged or recurring symptoms (Fig. 1) with senior team members or the RRT, whose role was expanded from that of the conventional MET.

The flowchart indicates that the doctors and nurses in general wards should perform a "self-management" response, that is, a quick assessment and early detection of antecedents. They should

Table 1. Early warning criteria (Criteria #1)

In general practice, the patient shows, or the staff have observed, the following: - any onset of new symptoms and findings - any concerns regarding ABCDE	
Airway	Obstructed
	Stridor
	Retractive breathing
	Excessive secretions
Breathing	Orthopnea
	Accessory muscles used
	Respiratory rate <10/min or >25/min
	SpO_2 <93%
Circulation	Heart rate <50/min or >120/min
	Systolic blood pressure <90 mm Hg or >180 mm Hg
	Diastolic blood pressure >120 mm Hg
	Shock index >1
	Urine output <50 mL in 4 h
Dysfunction of CNS	Acute change of mental status
	Agitated or delirious
	New pain
Others	New uncontrollable bleeding anywhere
	New unilaterality or numbness of limbs

CNS, central nervous system.

act effectively when any of the objective early warning criteria listed as criteria #1 in Table 1 are identified in the patients. Furthermore, by following a "team-management" approach, staff members are strongly encouraged to speak up to their senior staff and/or call the RRT when any of criteria #2 in Figure 1 are fulfilled such as 1) the presence of any additional symptoms or findings, 2) appearance of the same symptom within 2 hours, 3) taking the same action within 2 hours, 4) concerns about ABCDE still remain, 5) no improvement of criteria #1 abnormalities, and 6) the need for other specialized assistance. We distributed the flowchart so that all doctors and nurses in the wards could refer to it.

In addition, the working group developed a new educational program and tools based on our new standards and named it "Early Awareness & Rapid Response Training in Hospitals (EARRTH)"[19]. The EARRTH educational program comprises two types of training: general training, which targets all employees, and practical training, which is an additional program targeting junior doctors and junior nurses with five years' experience or less[18].

In the general training that began in June 2016, participants audit an animated film and attend a short lecture that aim to enhance adherence to the new standards and system. The animated film is based on SAE that occurred in our hospital and explains the philosophy of EARRTH[20].

Subjects, data collection, and definitions

The patients in the adult general wards who required a MET/RRT call in each of the 2-year periods before and after implementation were selected. A retrospective review of the medical records and data of these patients was carried out. The pre-period and post-period were defined as being from April 2013 to March 2015 and from April 2018 to March 2020, respectively. This study was approved by the Ethics Committee of Osaka City University (no. 2023-033).

As suggested by the Utstein-style scientific statement, we analyzed cases of MET/RRT calls by reviewing their medical charts. We compared the numbers of UCA in both periods and the existence and timing of physiological instability of the patients meeting criteria #1 in the period of 10 minutes to 24 hours prior to the UCA. "Do not attempt resuscitation" cases were excluded.

Statistical analyses

Categorical variables were compared with the chi-square test or Fisher's exact test, and continuous variables were compared with the Mann-Whitney U test. A p-value <0.05 was considered statistically significant. Statistical analysis was carried out using EZR (Easy R)[21], which is a graphical user interface for R. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Cases requiring MET/RRT calls

The total numbers of MET/RRT calls in each period were 46 and 61 (8.30 and 11.68 per 100000 admission days, odds ratio [OR] 1.41, 95% confidence interval [CI] 0.94-2.11, p=0.082). The mortality rates of MET/RRT cases were 57% vs 44% (pre vs post; p=0.24) (Table 2).

MET/RRT calls for UCA

The MET/RRT calls included 34 and 31 UCA cases (6.14 and 5.93 per 100000 admission days, OR 0.97, 95% CI 0.59-1.57, p=0.90). Most patients experienced cardiac arrests during weekends and holidays (56%) in the pre-period, whereas in the post-period, 81% of arrests occurred on weekdays (p <0.01), with a significant concentration occurring during weekday nights (55%; $p<0.01$). The 24-hour mortality rates of cases requiring a MET/RRT call for UCA were 26% versus 55% (pre vs post; p= 0.025) (Table 3).

There were 19 cases (56%) in the pre-period versus 22 cases (71%) in the post-period where patients either did not meet criteria #1 within 10 minutes to 24 hours prior to their UCA, or met the criteria within 4 hours. Although this represents an increase, the difference was not statistically significant (p=0.30) (Table 4, Fig. 2). In the post-period, the clinical antecedents in 7 (47%; p=0.025) patients occurred during the weekday daytime (Table 4).

Table 2. Characteristics of patients requiring MET/RRT call

	MET/RRT call			
	Pre-period n=46	Post-period n=61	OR (95% CI)	p-Value
Number of calls				
per 1000 admissions	1.22	1.39	1.14 (0.77-1.71)	0.56
per 100000 admission days	8.30	11.68	1.41 (0.94-2.11)	0.082
Male sex	34 (74%)	31 (51%)		**0.026**
Age, mean±SD	66.8±11.5	66.8±12.3		0.71
Mortality	26 (57%)	27 (44%)	0.61 (0.26-1.42)	0.24
24-hour	10 (22%)	18 (30%)	1.50 (0.57-4.13)	0.39
7-day	14 (30%)	22 (36%)	1.29 (0.53-3.19)	0.68
28-day	22 (48%)	25 (41%)	0.76 (0.33-1.76)	0.56

SD, standard deviation; MET, medical emergency team; RRT, rapid response team; OR, odds ratio; and CI, confidence interval.

Table 3. Mortality rates of patients requiring MET/RRT call for unexpected cardiac arrest

	MET/RRT call for unexpected cardiac arrest (In-hospital cardiac arrest)			
	Pre-period	Post-period	OR (95% CI)	p-Value
Number of calls	34 (74%)	31 (51%)		**0.018**
per 1000 admissions	0.90	0.71	0.79 (0.47-1.32)	0.38
per 100000 admission days	6.14	5.93	0.97 (0.59-1.57)	0.90
Male sex	25 (74%)	20 (65%)		0.59
Age, mean±SD	66.8±11.5	66.8±12.3		0.71
Time period of MET/RRT call				
Weekday	15 (44%)	25 (81%)		<**0.01**
Daytime	8 (24%)	8 (26%)		1
Nighttime	7 (21%)	17 (55%)		<**0.01**
Weekends & holidays	19 (56%)	6 (19%)		<**0.01**
Daytime	6 (18%)	1 (3%)		0.14
Nighttime	13 (38%)	5 (16%)		0.087
Witnessed arrest	25 (74%)	23 (74%)		1
Initial cardiac arrest rhythm				
Shockable	8 (24%)	7 (23%)		0.27
Asystole	4 (12%)	15 (48%)		<**0.01**
PEA	11 (32%)	4 (13%)		0.12
Unknown/others	11 (32%)	5 (16%)		0.22
ROSC	31 (91%)	22 (71%)		0.076
Mortality	22 (65%)	21 (68%)	1.14 (0.36-3.66)	1
24-hour	9 (26%)	17 (55%)	3.31 (1.60-10.93)	**0.025**
7-day	13 (38%)	19 (61%)	2.52 (0.84-7.85)	0.084
28-day	18 (53%)	20 (65%)	1.60 (0.53-4.95)	0.45

SD, standard deviation; MET, medical emergency team; RRT, rapid response team; Daytime, 8:30 AM to 4:59 PM; Nighttime, 5:00 PM to 8:29 AM; PEA, pulseless electrical activity; and ROSC, return of spontaneous circulation.

MET/RRT calls for non-cardiac arrest

There were 12 and 30 MET/RRT calls for non-cardiac arrests (2.17 and 5.74 per 100000 admission days, OR 2.65, 95% CI 1.32-5.69, $p<0.01$). The mortality rates were 33% versus 20% (pre vs post; $p=0.61$) (Table 5).

There were 12 cases (100%) in the pre-period versus 22 cases (73%) in the post-period where patients either did not meet criteria #1 within 10 minutes to 24 hours prior to the calls or met the criteria within 4 hours ($p=0.080$) (Table 5). In the pre-period, 2 patients (17%) met criteria #1 within 10 minutes to 4 hours before the calls, compared to 11 patients (37%) in the post-period (Table 6). In 6 of 30 cases, the time when the patients met criteria #1 before the call was more than 12 hours (Fig. 3).

Discussion

Through the introduction of the modified RRS and educational program, MET/RRT calls for non-cardiac arrest significantly increased by approximately two times, which is a most remarkable result. However, there was no significant reduction in the calls for UCA, and the overall mortality rate for MET/RRT calls did not show a significant reduction either.

The two-fold increase of MET/RRT calls for non-cardiac arrest can be attributed to the

Table 4. MET/RRT calls for cardiac arrest meeting criteria #1 before cardiac arrest

	MET/RRT call for unexpected cardiac arrest (In-hospital cardiac arrest)		
	Pre-period n=34	Post-period n=31	p-Value
Number of patients meeting criteria #1 within 10 min-24 h before cardiac arrest			
Never or <4 h	19 (56%)	22 (71%)	0.304
≧4 h, <24 h	15 (44%)	9 (29%)	
Time when patient met criteria #1 within 10 min-24 h before cardiac arrest			
Minutes, median (IQR)	486 (268.25, 863.5)	550 (163.5, 877)	0.845
Time period of meeting criteria #1			
Weekday	12 (63%)	12 (80%)	0.451
Daytime	2 (11%)	7 (47%)	**0.025**
Nighttime	10 (53%)	5 (33%)	0.314
Weekend & holiday	7 (37%)	3 (20%)	0.451
Daytime	3 (16%)	1 (7%)	0.613
Nighttime	4 (21%)	2 (13%)	0.672

MET, medical emergency team; RRT, rapid response team; IQR, interquartile range; Daytime, 8:30 AM to 4:59 PM; and Nighttime, 5:00 PM to 8:29 AM.

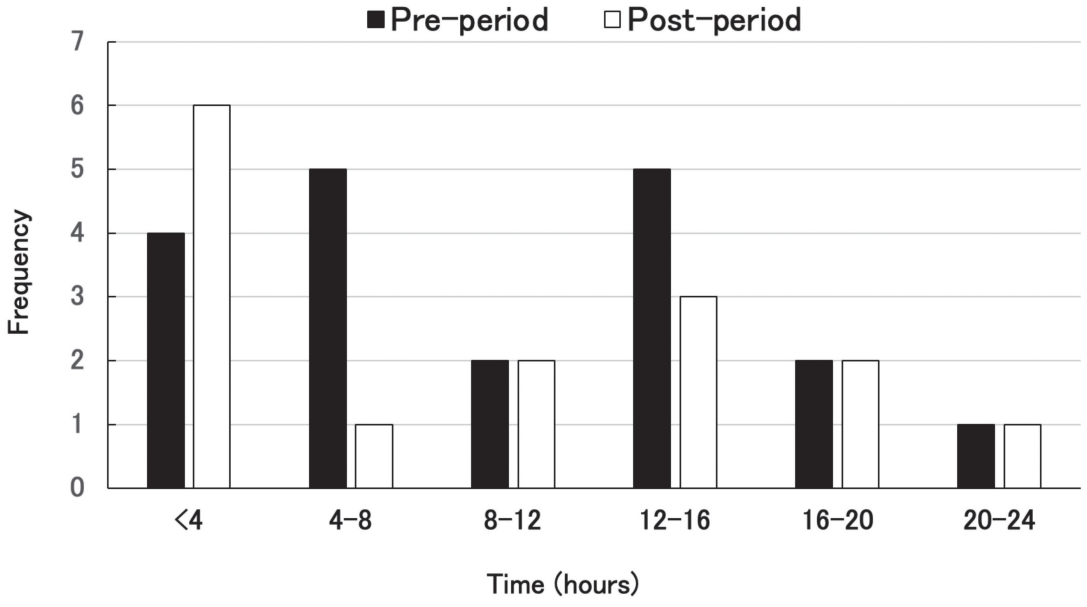

Figure 2. Time between patient meeting criteria #1 within 10 min to 24 h before unexpected cardiac arrest.

implementation of the new RRS procedures and accompanying educational program. Specifically, we have held the two education initiatives, a monthly scenario-based training for young doctors and nurses starting in 2015, and a number of educational lectures using an animated cartoon beginning in 2016[18-20]. In these sessions, the trainers teach how to detect early signs of patient deterioration, explain that our hospital has a system in place for reporting and consultation without being criticized, and recommend that participants call the MET/RRT without hesitation if they have any concerns. As

Table 5. Characteristics of patients requiring MET/RRT call for non-cardiac arrest

	MET/RRT call for non-cardiac arrest			
	Pre-period	Post-period	OR (95% CI)	p-Value
Number of calls	12 (26%)	30 (49%)		**0.018**
per 1000 admissions	0.32	0.68	2.16 (1.70-4.62)	0.029
per 100000 admission days	2.17	5.74	2.65 (1.32-5.69)	<**0.01**
Male sex	6 (50%)	20 (69%)		0.48
Age, mean±SD	60.2±20.7	61.2±16.3		0.24
Time period of MET/RRT call				
Weekday	8 (67%)	18 (60%)		0.96
Daytime	3 (25%)	10 (33%)		0.87
Nighttime	5 (42%)	8 (27%)		0.56
Weekend & holiday	4 (33%)	12 (40%)		0.96
Daytime	4 (33%)	4 (13%)		0.29
Nighttime	0 (0%)	8 (27%)		0.12
Primary problem for call				
Airway threatened	1 (8%)	3 (10%)		1
Respiratory problem	4 (33%)	6 (20%)		0.43
Hemodynamic abnormality	3 (25%)	8 (27%)		1
Neurologic derangement	2 (17%)	13 (43%)		0.16
Other	2 (17%)	0 (0%)		0.077
Transferred to				
ICU	3 (25%)	9 (30%)		1
ECU/HCU/CCU	2 (17%)	5 (17%)		1
General ward	7 (58%)	16 (53%)		1
Mortality	4 (33%)	6 (20%)	0.51 (0.09-3.10)	0.61
24-hour	1 (8%)	1 (3%)	0.39 (0.01-32.46)	1
7-day	1 (8%)	3 (10%)	1.22 (0.089- 69.89)	1
28-day	4 (33%)	5 (17%)	0.41 (0.07-2.59)	0.44

SD, standard deviation; MET, medical emergency team; RRT, rapid response team; Daytime, 8:30 AM to 4:59 PM; Nighttime, 5:00 PM to 8:29 AM; ICU, Intensive Care Unit; ECU, Emergency Care Unit; HCU, High Care Unit; and CCU, Cardiac Care Unit.

a result, the educational program led to a significant reduction in "perceived barriers to speaking up" and "negative attitudes toward voicing opinions in the healthcare team" scores among participating nurses (from 3.20 to 3.00, $p<0.01$, and from 2.47 to 2.29, $p<0.01$, respectively) and junior doctors (from 3.34 to 2.51, $p<0.01$, and from 2.42 to 2.11, $p<0.01$, respectively), as measured on a 5-point Likert scale, where 1 indicates "strongly disagree" and 5 indicates "strongly agree."[18] Given these circumstances, it is considered that these efforts have increased the frequency of realizing antecedents, reduced the burden of calling the MET/RRT, and ultimately led to the two-fold increase in non-cardiac arrest calls.

Although the reduction in the number of calls for UCA was not statistically significant, it is reasonable to infer that early consultation and intervention were effective. The time at which patients with UCA, i.e., in-hospital cardiac arrest (IHCA), met criteria #1 was most frequently 4-8 hours and 12-16 hours before arrest in the pre-period. However, in the post-period, it was mostly less than 4 hours before arrest. This suggests that in the pre-period, a lack of timely intervention in response to patient deterioration led to the UCA. Conversely, in the post-period, UCA cases with

Table 6. MET/RRT call for non-cardiac arrest meeting criteria #1 before call

	MET/RRT call for non-cardiac arrest		
	Pre-period n=12	Post-period n=30	p-Value
Number of patients meeting criteria #1 within 10 min-24 h before call			
Never or <4 h	12 (100%)	22 (73%)	0.080
≧4 h, <24 h	0 (0%)	8 (27%)	
Time when patient met criteria #1 within 10 min-24 h before call			
Minutes, median (IQR)	28, 84 (-)	775 (61, 984.5)	
Time period of meeting criteria #1			
Weekday	0 (0%)	4 (36%)	0.31
Daytime	0 (0%)	1 (9%)	1
Nighttime	2 (100%)	3 (27%)	0.61
Weekend & holiday	0 (0%)	7 (64%)	0.16
Daytime	0 (0%)	2 (18%)	1
Nighttime	0 (0%)	5 (45%)	0.3

MET, medical emergency team; RRT, rapid response team; Daytime, 8:30 AM to 4:59 PM; and Nighttime, 5:00 PM to 8:29 AM.

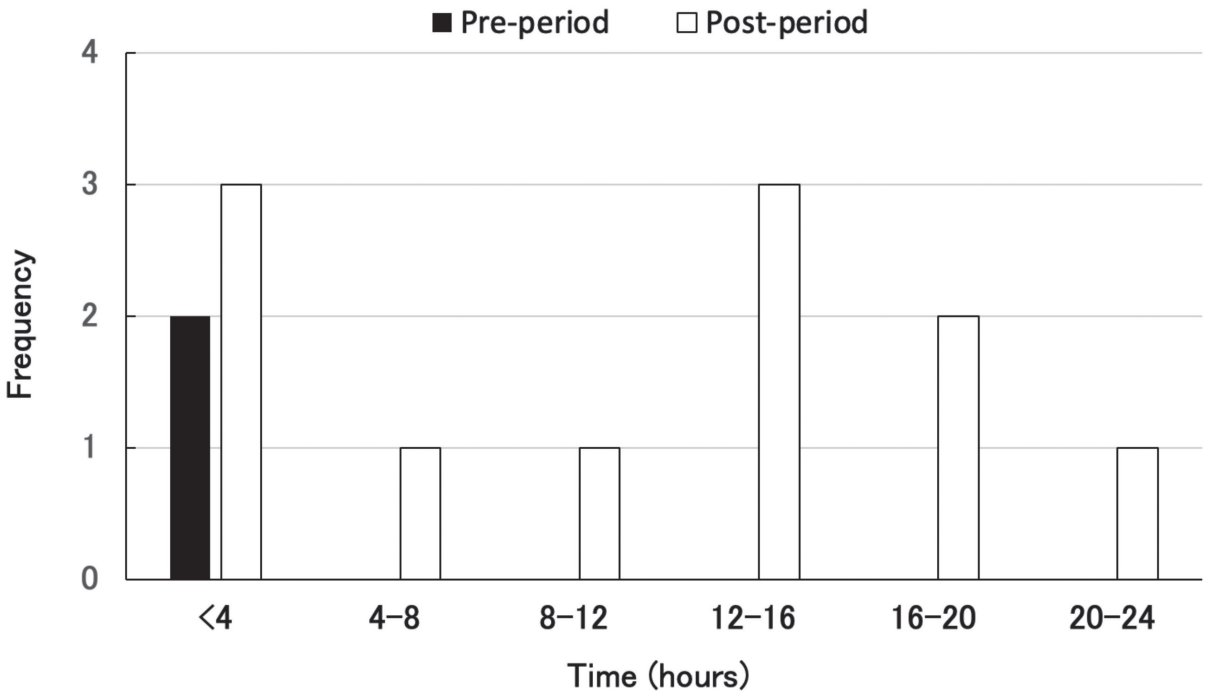

Figure 3. Time between patient meeting criteria #1 within 10 min to 24 h before call for non-cardiac arrest.

delayed intervention decreased, indicating that early consultation and intervention helped to prevent IHCA.

A significant reduction in the mortality rates after MET/RRT calls (pre 57% vs post 44%) was not found in the present study. This is influenced by the fact that the mortality rate of UCA cases did not decrease. However, considering that UCA cases in the post-period mostly deteriorated within 4 hours

before arrest and that the 24-hour mortality rate increased, it is unlikely that the arrests could have been prevented. According to the observational cohort study using a national administrative inpatient database for more than 1600 acute-care hospitals covering about 50% of all acute-care hospital beds in Japan, the mortality rates after IHCA were 87.3% in the period from 2011 to 2017[22], indicating that the mortality rates in our study cannot be considered high.

ALF is still a major issue even in well-established hospitals with a RRS. Removing the barriers is mainly a matter of education[20]. Moreover, as Davies et al emphasized, the current methods of staff education using lectures, orientation sessions, and posters are not effective[23]. An in-situ simulation training program is required that familiarizes staff with how to recognize critical patient deterioration, when and how to trigger the RRS, and how to hand off to the responder team[23,24]. The modified RRS and educational program in this study appear to have reduced hesitation and fear of criticism, encouraging staff to consult more promptly, and are thought to have effectively removed barriers associated with ALF.

There are some limitations in our study. First, we did not evaluate the number, details, and outcomes of consultations with senior staff within the same clinical department and wards. These factors could significantly influence the outcomes of the modified RRS, and their lack from this analysis may limit the comprehensiveness of our findings. Second, the early warning criteria adopted in this study were based on the single parameter criteria, which was the mainstream approach at the time of implementation. In recent years, comparative studies between single parameter criteria and aggregated weighted scores have been conducted; however, no standardized criteria have been established internationally.

In the non-arrest cases, 6 of 30 cases met criteria #1 more than 12 hours before the MET/RRT call, which is noteworthy. This finding underscores the importance of fully and effectively utilizing the resources available at our hospital to improve the quality of interventions after patients meet criteria #1. To better address the challenges identified in this study, it is essential to continue refining our RRS and educational strategies. Future efforts should include a more detailed analysis of intra-departmental consultations and their impact on patient outcomes, as well as the development of targeted interventions to further reduce the incidence of UCAs. By addressing these challenges, we can enhance the safety net provided by the RRS and improve overall patient care.

The safety net, consisting of the modified RRS and the educational program we introduced, appears to have contributed to the improvement of ALF, even though there was no significant reduction in unexpected cardiac arrests. However, the trends observed, particularly in early recognition and intervention, suggest that the system holds clinical value in enhancing patient safety. As Japanese hospitals have cultural and behavioral barriers associated with inter-professional hierarchies also remain, it is important to establish safety nets and evaluate them in accordance with the actual situation at each hospital.

Acknowledgements

All authors have no COI to declare regarding the present study.

We appreciate all members of the EARRTH Project for their contributions. NH acquired the data, performed the statistical analysis, and drafted the manuscript. EN-Y and YM participated in the design of the study and its coordination and helped to draft the manuscript. NH, EN-Y, AS, SE, TN, and YM participated in implementation of the RRS and education program.

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Osaka City Med. J. Vol. 71, 13-26, 2025

No Improvement in 30-day Mortality after Initial Higher-than-standard Beta-lactam doses among ICU Patients with Renal Failure: A Japanese Nationwide Database Study

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Abstract

Background

Some clinicians prescribe higher-than-standard doses of beta-lactams for patients in intensive care unit with increased distribution volumes and renal clearance, yet data on patients' clinical outcomes are limited.

Methods

Using a Japanese nationwide administrative database, we assessed clinical outcomes of patients in the intensive care unit who had renal failure and were administered beta-lactams requiring dose increase or decrease based on their renal clearance. The patients were categorized by their total daily dose of beta-lactams: standard, higher-than-standard, and lower-than-standard. The standard dose was defined as total daily doses converted from the recommendations in the Sanford Guide Web Edition. Cox proportional hazards regression model was employed to assess the association between the dose categories of beta-lactam and clinical outcomes of mortality within 30 days from the initial administration of beta-lactams. Inverse probability of treatment weighting method was used to control for potential confounding. An interaction analysis was conducted to explore how specific patient characteristics modify the effects of beta-lactam dose.

Results

The analysis included 925 patients. No statistically significant difference was found in association between the primary outcome and dose-categories of beta-lactam (hazard ratio 1.15, 95% confidence interval 0.75-1.77, p=0.510). In the interaction analysis, no significant interactions were observed between higher-than-standard dose and any covariates.

Received August 23, 2024; accepted November 26, 2024.
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Conclusions

Our study indicates that higher-than-standard doses of beta-lactams yield no statistically significant improvement in clinical outcomes of intensive care unit patients with renal failure. This finding underscores the need for further research to optimize dosing strategies for these patients.

Key Words: Beta-lactam; Higher-than-standard dose; ICU; Clinical outcome; Inverse probability of treatment weighting

Introduction

Bacterial infections are a major cause of mortality in patients who were admitted to the intensive care unit (ICU)[1]. Therefore, optimizing antibiotic treatment strategies—including dose, timing, and type of antibiotics—is crucial for improving clinical outcomes in these patients. In particular, the effectiveness of beta-lactams, which are the most commonly administered antibiotics in ICUs, profoundly influences these outcomes[2].

The therapeutic efficacy of beta-lactams correlates with the percentage of time that the blood-free concentration of the drug in the blood exceeds the minimum inhibitory concentration of the pathogen over a 24-h period[3,4]. The study 'Defining Antibiotic Levels in Intensive Care Unit Patients' provided critical insights into the impact of achieving the pharmacokinetic targets on the clinical outcomes of ICU patients, reporting that 16% of patients treated for infections failed to meet these targets, resulting in a 32% lower probability of achieving favorable clinical outcomes[5]. The findings suggest that the potentially increased volume of distribution and renal clearance in ICU patients hinder the achievement of pharmacokinetic targets when administering beta-lactams[6,7].

Given the pharmacokinetic challenges, therapeutic drug monitoring has been highlighted as a potential strategy to improve clinical outcomes by optimizing doses to achieve pharmacokinetic targets. Despite its promising benefits, the widespread implementation of therapeutic drug monitoring is hindered by several factors, such as limited equipment accessibility, a lack of substantial clinical evidence, and insufficient proof of cost-effectiveness[8].

Generally, doses of beta-lactams, which are mainly renally excreted, require an increase or decrease to meet standard doses for renal clearance to ensure therapeutic efficacy and avoid toxicity. In contrast, for ICU patients with potentially increased volume distribution and renal clearance, some clinicians select higher-than-standard doses of beta-lactams, which are simple to administer and serve as a practical option to overcome the difficulty in achieving pharmacokinetic targets; yet, their benefits and toxicity remain unevaluated in detail.

In a single-center study in Brazil, Camargo et al examined the clinical outcomes of ICU patients with renal failure treated with higher-than-standard and standard doses of antibiotics, including beta-lactams[9]. Patients who received higher-than-standard doses experienced significantly lower treatment failure and mortality than those who received standard doses. This study, among the few assessing dose-related clinical outcomes in ICU settings, offered valuable insights. Yet, the reported ICU mortality of 62.5% differs from 6.3% mortality rate in Japan among severe ICU cases[10]. Potential causes for this difference include differences in factors such as healthcare practices, patient demographics, and resource access between the two countries. Therefore, the effectiveness of higher-than-standard doses in Japanese ICU patients remains uncertain. Consequently, we evaluated these effects using a large nationwide database in Japan.

Methods

Study design and data source

This was a retrospective, multicenter observational study that utilized administrative claims data and laboratory data provided by Medical Data Vision (MDV) Ltd. This nationwide database in Japan includes data from about 29 million inpatients and outpatients across 389 hospitals as of September 2019. Patient data include age, sex, primary diagnosis, comorbidities, complications (International Classification of Diseases, 10th Revision [ICD-10] codes), treatment details including surgeries, daily drug administration, instrument usage, admission and discharge dates, discharge status, and laboratory data[11,12]. The availability of clinical laboratory data was determined by individual hospital policies, independent of the patient information in the database.

Study patients

We included ICU patients who were treated with beta-lactams requiring dose increase or decrease based on renal clearance, as per the Sanford Guide Web Edition, January 30, 2024[13]. The beta-lactams studied were ampicillin, ampicillin-sulbactam, cefazolin, cefepime, cefotaxime, ceftazidime, doripenem, imipenem-cilastatin, meropenem, penicillin G, piperacillin, and piperacillin-tazobactam. We established the following five exclusion criteria: (1) patients aged under 18 years, considering pharmacokinetic complexities associated with the growth and development stages and the absence of well-defined dose guidelines. (2) Patients who underwent surgery the day before or on the day they initially received a beta-lactam, to exclude those receiving it for postoperative infection prevention. (3) Patients lacking essential data (age, sex, height, or weight) required for the 3-variable Japanese equation to estimate the glomerular filtration rate (eGFR). (4) Despite using the latest ICU-obtained serum creatinine levels to fill subsequent missing data, patients lacking these measurements on the day they initially received a beta-lactam in the ICU were also excluded. (5) Patients not requiring dose reductions of administered beta-lactams were excluded, as this study focused on those with renal failure needing dose reductions. The study flowchart is detailed in Figure 1.

Definition of High-dose, Standard-dose, and Low-dose

Based on the Sanford Guide Web Edition as of January 30, 2024, we converted the recommendations to per day dose of beta-lactams, stratified by renal clearance, thereby setting our standard doses[13]. We used eGFR as the measure for renal clearance and classified the beta-lactam doses as standard, higher-than-standard, and lower-than-standard, which were defined respectively as Standard-dose, High-dose, and Low-dose. For example, patients with an eGFR of 40 mL/min have a standard meropenem dose of 2g per day[13]. Assume a patient with an eGFR of 40 mL/min was administered 3g per day of meropenem; according to our definition, this patient would be categorized as High-dose. The index day was defined as the day a patient initially received a beta-lactam in the ICU. Dose categorization on the index day depended on the time of the initial administration and thus was based on the doses administered both on the index day and the following day. Patients who received higher-than-standard doses on the index or following day were categorized as High-dose. Those not in High-dose who received standard doses on these days were categorized as Standard-dose. All remaining patients were defined as Low-dose. Patients who died, received dialysis, or were discharged from the ICU or hospital on the index day or the following day were excluded from our analysis due to the inability to categorize them. We specifically excluded patients who received dialysis for several reasons: First, the amount of drug removal varies depending on dialysis conditions, making it difficult to consistently categorize these patients. Second, the Sanford Guide,

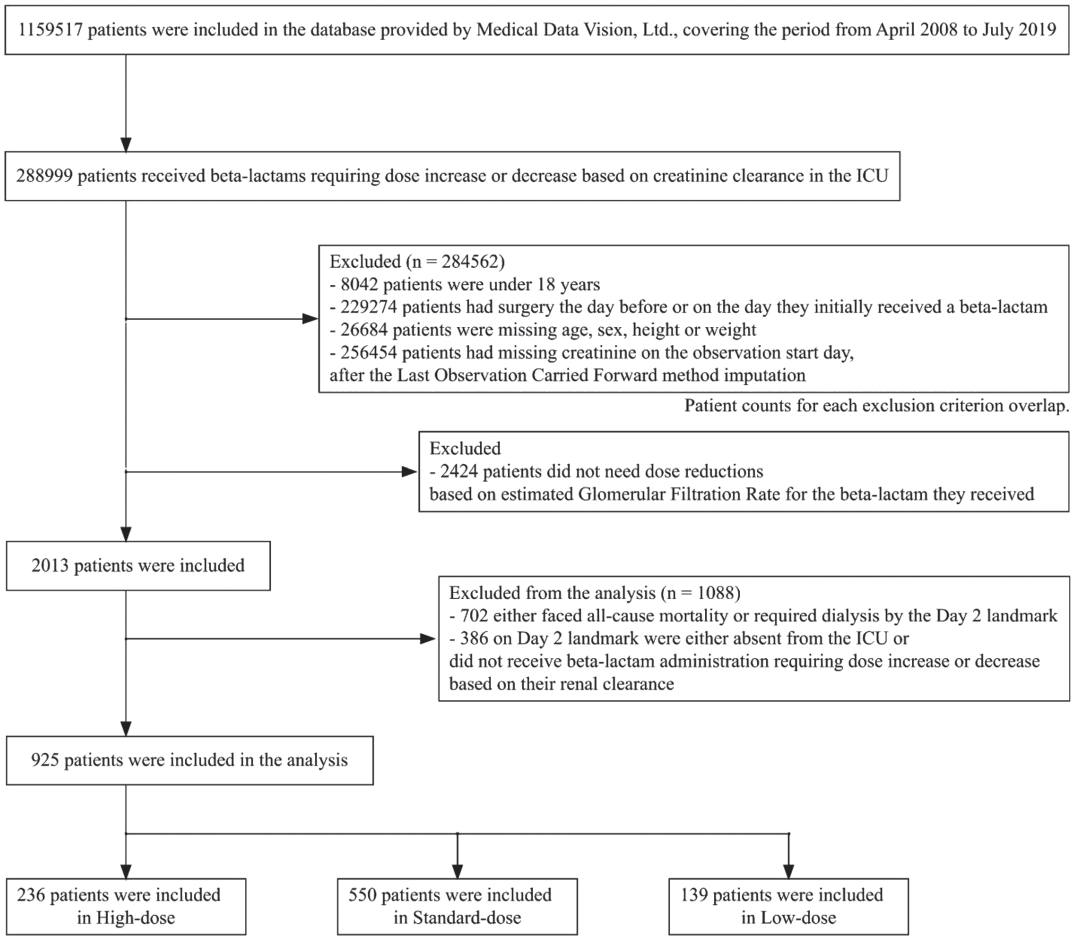


Figure 1. Study flowchart.

which we referenced for standard dose, assumes dialysis environments that differ from those in Japan.

Patient characteristics

Patients baseline data were collected at the baseline, defined at the day after the index day, including age, sex, body mass index (BMI), Charlson comorbidity index, mechanical ventilation, noradrenaline administration, total daily crystalloid volume, eGFR, platelet count, white blood cell count, albumin, C-reactive protein, hemoglobin, potassium, sodium, urea nitrogen, lactate dehydrogenase, and total bilirubin[14]. The Charlson comorbidity index was calculated based on the definition developed by Quan et al[15,16]. These covariates were used to calculate weights for the inverse probability of treatment weighting (IPTW)[17]. Additionally, as our database did not contain microbiological test results, we investigated the causative pathogens based on the infectious disease names classified according to the ICD-10 codes recorded from admission to the index day. We also reported the usage percentages of broad-spectrum antibiotics such as carbapenems or piperacillin/tazobactam by dose categories. To describe detailed profiles of the patients under study, we aggregated the principal diagnoses, which were the diseases that led to hospitalization based on ICD-10 codes.

Inverse probability treatment weighting, IPTW application

We utilized IPTW with a generalized propensity score to balance patient characteristics between

Standard-dose and both High- and Low-dose. This approach allowed us to estimate the effects of receiving High- or Low-dose beta-lactams by comparing them to the outcomes if Standard-dose patients had received these doses. The generalized propensity score was calculated as the probability of categorizing each patient into dose categories using a multinomial logistic regression model with cubic root-transformed covariates. This transformation was applied to better align the data with a normal distribution and improve the fit of the model. Missing values were addressed using multiple imputation by chained equations. The number of imputations approximated the percentage of incomplete cases, based on a rule of thumb[18]. The imputation model ran for up to 50 iterations. The differences in patient characteristics between each pair of dose categories after IPTW were assessed using absolute standardized mean differences (ASMD). Covariates with an ASMD below 0.1 were considered balanced between the dose categories.

Outcomes

All outcomes were assessed from the day of initial beta-lactam administration in the ICU. The primary outcome was defined as mortality within 30 days from the initial administration of beta-lactams. Secondary outcomes included: (1) mortality in the ICU, (2) mortality during hospitalization, (3) mortality, (4) median length of ICU stay, and (5) median length of hospital stay.

Interaction analyses

To gain insights for developing individualized treatment regimens, we conducted interaction analyses with the following covariates: age, sex, BMI, mechanical ventilation, noradrenaline administration, total daily crystalloid volume, albumin, and eGFR. We included interaction terms between each dose category and these covariates in our model. In this model, binary covariates (sex, mechanical ventilation, and noradrenaline administration) were analyzed using IPTW with calculated subgroup weights, while continuous covariates (age, BMI, total daily crystalloid volume, albumin, and eGFR) were assessed at baseline with multivariable analyses using restricted cubic splines. These interaction analyses were not post-hoc assessments dependent on the results of the primary outcome; they were planned and implemented in advance.

Statistical analyses

Continuous variables were summarized as medians with interquartile ranges, and categorical variables as frequencies and percentages (%). Using Cox proportional hazards regression models, we estimated the hazard ratio (HR) and 95% confidence interval (CI) for High- and Low-dose compared with Standard-dose. Each patient was followed from the index day until the first occurrence of all-cause mortality. For outcomes in the ICU, within 30 days from the index day, or during hospitalization, we censored patients who survived past these periods or were discharged alive within them. We assessed the median lengths of ICU stay and hospital stay using a competing risks analysis with the Fine and Gray model, treating discharge alive as the event and mortality as the competing risk. Robust variance estimation was performed for the IPTW analysis to account for the induced correlation between observations[19].

All statistical analyses used a two-sided significance level of 5%. Analyses were conducted using R 4.3.1 (https://www.r-project.org/foundation/).

Ethics

Since Japanese ethical guidelines for Medical and Health Research Involving Human Subjects do not apply to studies using anonymized secondary data, the present study did not require approval from an institutional review board or research ethics committee.

Results

Study patients and IPTW

From September 2019 to November 2022, the MDV database recorded 288999 ICU patients treated with beta-lactams requiring dose adjustments based on eGFR. Among the 2013 eligible patients, 1088 could not be categorized into defined dose categories and were excluded, leaving 925 for analysis (Fig. 1). Of these 925 patients, 236 were categorized into High-dose category, 550 into Standard-dose, and 139 into Low-dose. The usage percentage of patients who received carbapenems or piperacillin/tazobactam was 78.4% (185/236 cases) in High-dose category, 46.5% (256/550 cases) in Standard-dose category, and 79.9% (111/139 cases) in Low-dose category. Given that 431 of the 925 cases (46.6%) had missing values, we conducted 50 multiple imputations. Table 1 shows baseline patient characteristics before and after applying IPTW. Before weighting, the median eGFR was 20.8 mL/min (interquartile range [IQR]: 15.0-31.7 mL/min) in the High-dose, 23.3 mL/min (IQR: 15.8-31.2 mL/min) in the Standard-dose, and 32.0 mL/min (IQR: 23.9-40.1 mL/min) in the Low-dose. The results indicated that renal function was better in the Low-dose compared to the other two categories, while it was the worst in the High-dose. Subsequently, after weighting, all covariates were balanced between High- and Standard-dose. Although the ASMDs between Low- and Standard-dose, as well as between High- and Low-dose, were greater than 0.1, the application of IPTW improved balance, shown in Figure 2. Based on the ICD-10 codes recorded from admission to the index day, it was mostly not possible to identify the causative pathogens from the classified infectious disease names (Table 2). Additionally, Table 3 summarizes the principal diagnoses of the study patients by dose category.

Outcome analyses

Table 4 summarizes event incidences for each outcome, and Table 5 presents the HRs. For the primary outcome of mortality within 30 days from the index day, incidences were 28.4% (67/236 cases) in High-dose, 22.2% (122/550 cases) in Standard-dose, and 19.4% (27/139 cases) in Low-dose, with no significant HR differences observed between dose categories (Table 4). Similarly, for ICU mortality, the secondary outcome, incidences were 7.2% (17/236 cases) in High-dose, 8.2% (45/550 cases) in Standard-dose, and 4.3% (6/139 cases) in Low-dose, with no significant HR differences observed between dose categories (Table 4). Additionally, no significant differences in HRs for any secondary outcomes were observed between dose categories for either outcome (Table 5). The survival curves for all outcomes defined in this study are shown in Figure 3. The median length of ICU stay was 5 days for all dose categories. The median hospital length of stay was 21 days for High-dose, and it was 20 days for both Standard- and Low-dose. Additionally, no significant differences in HRs for any secondary outcomes were observed between dose categories for either outcome (Table 5). In the interaction analyses, no significant differences were observed among the subgroups for binary covariates (sex, mechanical ventilation, noradrenaline administration), nor were there significant interactions between these covariates and each dose category (Fig. 4). Similarly, for continuous covariates (age, BMI, total daily crystalloid volume, albumin, and eGFR), no significant interactions with dose categories were found (Fig. 5).

Discussion

We determined whether higher-than-standard doses of beta-lactams improve clinical outcomes in ICU patients with renal failure, using a large nationwide database in Japan. The ICU mortality of

Table 1. Baseline patient characteristics before and after inverse probability of treatment weighting (IPTW)

	Before IPTW						After IPTW					
Variables	High-dose N=236	Standard-dose N=550	Low-dose N=139	ASMD[a]	ASMD[b]	ASMD[c]	High-dose N=534	Standard-dose N=550	Low-dose N=615	ASMD[d]	ASMD[e]	ASMD[f]
Age, years (median [IQR])	76 [67.8, 83.0]	79 [70.0, 85.0]	80 [71.5, 85.0]	0.237	0.039	0.276	78 [69.0, 83.9]	79 [70.0, 85.0]	79 [69.7, 84.7]	0.049	0.007	0.044
Females, % (freq)	45.8 (108)	46.4 (255)	40.3 (56)	0.012	0.123	0.111	44.8 (239.2)	46.4 (255.0)	45.8 (281.7)	0.031	0.012	0.02
Body mass index, kg/m^2 (median [IQR])	21.5 [19.5, 24.6]	21.6 [19.2, 24.4]	21.1 [18.4, 24.0]	0.011	0.118	0.131	20.8 [19.2, 24.0]	21.6 [19.2, 24.4]	21.9 [19.1, 24.2]	0.095	0.019	0.079
Charlson Comorbidity Index, (median [IQR])	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.018	0.059	0.076	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.026	0.077	0.051
Albumin, g/dL (median [IQR])	2.3 [1.9, 2.7]	2.5 [2.1, 2.9]	2.5 [2.1, 2.8]	0.315	0.047	0.284	2.5 [2.1, 2.9]	2.5 [2.1, 2.9]	2.4 [2.1, 3.0]	0.04	0.055	0.017
C-reactive protein, mg/dL (median [IQR])	17.5 [7.5, 24.3]	10.8 [5.7, 18.9]	16 [8.1, 22.0]	0.391	0.319	0.068	10.8 [5.9, 19.8]	10.6 [5.6, 18.5]	10.8 [1.9, 17.6]	0.076	0.136	0.21
Estimated glomerular filtration rate, mL/min (median [IQR])	20.8 [15.0, 31.7]	23.3 [15.8, 31.2]	32 [23.9, 40.1]	0.004	0.647	0.625	19.8 [14.9, 30.8]	23.3 [15.7, 31.2]	21.6 [11.0, 30.8]	0.043	0.15	0.104
Hemoglobin, g/dL (median [IQR])	10.2 [8.7, 11.7]	10.2 [8.8, 11.5]	10.4 [8.7, 11.7]	0.029	0.027	0.185	10.4 [9.1, 11.8]	10.3 [8.8, 11.5]	10.7 [8.6, 12.4]	0.079	0.117	0.039
Lactate dehydrogenase, U/L (median [IQR])	326 [227, 533]	326 [236, 500]	324 [216, 496]	0.002	0.09	0.146	345 [225, 541]	316 [233, 498]	286 [215, 456]	0.011	0.056	0.05
Platelet count, ×10000/μL (median [IQR])	14.4 [8.1, 20.1]	15.1 [9.7, 21.0]	15.1 [10.0, 19.2]	0.04	0.024	0.101	14.1 [9.5, 20.0]	14.7 [9.1, 20.4]	15.5 [8.6, 20.7]	0.009	0.092	0.101
Potassium, mEq/L (median [IQR])	4.2 [3.8, 4.5]	4.1 [3.8, 4.6]	4.1 [3.8, 4.5]	0.055	0.08	0.121	4.2 [3.8, 4.6]	4.1 [3.7, 4.5]	4.2 [3.9, 4.6]	0.047	0.112	0.061
Sodium, mEq/L (median [IQR])	140 [137, 144]	141 [137, 145]	140 [136, 143]	0.086	0.161	0.176	140 [136, 144]	141 [137, 145]	141 [137, 145]	0.012	0.037	0.021
Total bilirubin, mg/dL (median [IQR])	0.7 [0.5, 1.4]	0.7 [0.5, 1.2]	0.7 [0.5, 1.0]	0.127	0.139	0.25	0.7 [0.4, 1.1]	0.7 [0.5, 1.2]	0.6 [0.4, 1.1]	0.08	0.085	0.153
Urea nitrogen, mg/dL (median [IQR])	43.6 [28.4, 63.2]	42.8 [28.8, 62.4]	34.5 [24.0, 44.2]	0.001	0.474	0.478	44 [29.5, 64.3]	43.7 [29.4, 63.7]	45.2 [33.8, 64.8]	0.002	0.015	0.013
White blood cell count, /μL (median [IQR])	12,055 [8,843, 17,525]	10,315 [7,685, 15,323]	11,310 [8,050, 14,615]	0.226	0.026	0.192	10,800 [8,000, 14,508]	10,600 [7,800, 15,570]	13,168 [8,481, 16,036]	0.022	0.077	0.101
Crystalloids administration, mL/day (median [IQR])	1,820 [725, 3,050]	780 [323, 1,594]	900 [375, 1,840]	0.429	0.04	0.438	756 [337, 1,940]	780 [320, 1,583]	819 [350, 1,411]	0.015	0.133	0.136
Mechanical ventilation, % (freq)	58.5 (138)	53.6 (295)	49.6 (69)	0.098	0.08	0.178	57.7 (308)	53.6 (295)	51.4 (316)	0.083	0.046	0.128
Noradrenaline administration, % (freq)	50.4 (119)	26.9 (148)	28.8 (40)	0.498	0.042	0.454	25.5 (136)	26.9 (148)	39.1 (241)	0.033	0.262	0.295
Year of index day, % (freq)	2016 [2015, 2017]	2015 [2013, 2017]	2015 [2013, 2017]	0.46	0.064	0.501	2015 [2014, 2017]	2015 [2013, 2017]	2015 [2014, 2017]	0.068	0.118	0.058

ASMD, Absolute Standardized Mean Difference; and IQR, Interquartile Range

The ASMD was the difference in means or proportions divided by the standard deviation

a: Absolute Standardized Mean Difference between Standard-dose and High-dose before IPTW. b: Absolute Standardized Mean Difference between Standard-dose and Low-dose before IPTW.

c: Absolute Standardized Mean Difference between High-dose and Low-dose before IPTW. d: Absolute Standardized Mean Difference between Standard-dose and High-dose after IPTW.

e: Absolute Standardized Mean Difference between Standard-dose and Low-dose after IPTW. f: Absolute Standardized Mean Difference between High-dose and Low-dose after IPTW.

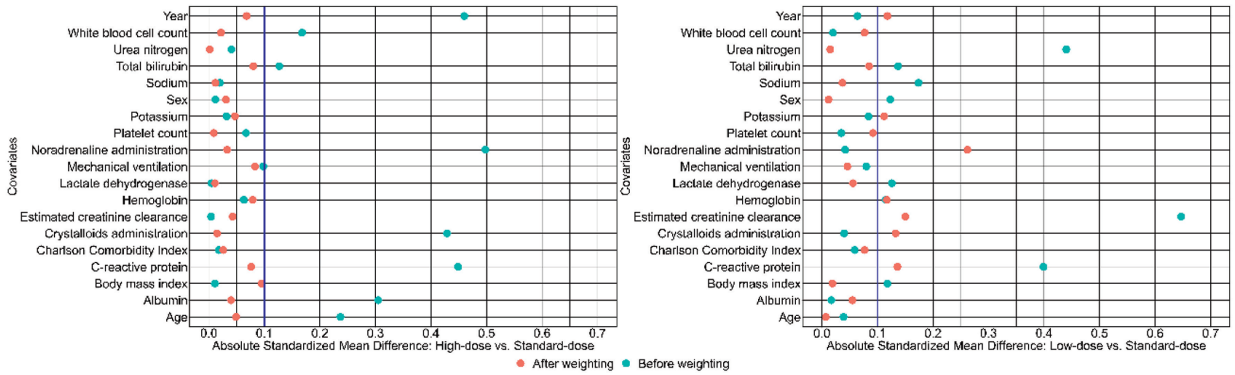


Figure 2. Balance of covariates before and after applying the inverse probability of treatment weighting method for comparisons between Standard-dose and High-dose (left) and between Standard-dose and Low-dose (right).

Table 2. Causative pathogens of infectious diseases based on ICD-10 diagnosis codes

Causative pathogens of infectious diseases	High-dose N=236	Standard-dose N=550	Low-dose N=139	ASMD[a]	ASMD[b]	ASMD[c]
Unspecified, % (freq)	99.5 (547)	99.2 (234)	97.8 (136)	0.036	0.140	0.039
Clostridium difficile, % (freq)	8.9 (49)	10.2 (24)	7.9 (11)	0.043	0.036	0.079
Other Gram-negative bacteria, % (freq)	5.6 (31)	12.7 (30)	8.6 (12)	0.247	0.117	0.108
Other Streptococcus species, % (freq)	5.5 (30)	8.9 (21)	7.9 (11)	0.134	0.099	0.035
Other Staphylococcus species, % (freq)	5.1 (28)	9.3 (22)	5.0 (7)	0.164	0.003	0.137
Staphylococcus aureus, % (freq)	5.3 (29)	8.5 (20)	5.0 (7)	0.127	0.011	0.167
Hemophilus influenzae, % (freq)	0.7 (4)	0.8 (2)	1.4 (2)	0.014	0.069	0.056
Klebsiella pneumoniae, % (freq)	0.5 (3)	0.0 (0)	0.7 (1)	0.105	0.022	0.120
Pseudomonas species, % (freq)	0.5 (3)	1.7 (4)	0.7 (1)	0.109	0.022	0.089
Salmonella species, % (freq)	0.0 (0)	0.4 (1)	0.7 (1)	0.092	0.120	0.132

ICD-10 codes, International Classification of Diseases, 10th Revision codes; and ASMD, Absolute Standardized Mean Difference. The ASMD was the difference in means or proportions divided by the standard deviation.

a: Absolute Standardized Mean Difference between Standard-dose and High-dose. b: Absolute Standardized Mean Difference between Standard-dose and Low-dose. c: Absolute Standardized Mean Difference between High-dose and Low-dose.

7.4% in this study was close to the previously reported 6.3% among severe ICU patients in Japan, suggesting a similar patient population[10]. Using the IPTW method with generalized propensity scores enabled us to address potential confounders and compare the effects of standard doses of beta-lactams with both higher-than-standard and lower-than-standard doses. Higher-than-standard beta-lactam doses did not significantly improve outcomes, including mortality within 30 days from index day and ICU mortality. Additionally, no significant interactions were observed between dose categories and covariates.

The mortality risk of ICU patients with infections and renal failure is influenced not only by antibiotic treatment but also by the effectiveness of comprehensive patient care, including circulatory

Table 3. Principal diagnoses of analyzed patients based on ICD-10 codes

Principal diagnosis	High-dose N=236	Standard-dose N=550	Low-dose N=139	ASMD[a]	ASMD[b]	ASMD[c]
Cardiovascular diseases, % (freq)	42.4 (233)	16.9 (40)	37.4 (52)	0.579	0.101	0.473
Respiratory diseases, % (freq)	18.9 (104)	23.7 (56)	21.6 (30)	0.118	0.067	0.051
Septicemia, % (freq)	6.0 (33)	13.6 (32)	9.4 (13)	0.257	0.126	0.132
Malignant neoplasms, % (freq)	2.5 (14)	6.8 (16)	3.6 (5)	0.202	0.061	0.144
Kidney diseases, % (freq)	2.9 (16)	1.7 (4)	0.7 (1)	0.081	0.165	0.089
Degenerative diseases of the nervous system, % (freq)	0.2 (1)	0.0 (0)	0.0 (0)	0.060	0.060	<0.001
Chronic liver diseases, % (freq)	0.4 (2)	0.0 (0)	0.0 (0)	0.085	0.085	<0.001
Others, % (freq)	26.7 (147)	37.3 (88)	27.3 (38)	0.228	0.014	0.214

ICD-10 codes, International Classification of Diseases, 10th Revision codes; and ASMD, Absolute Standardized Mean Difference. The ASMD was the difference in means or proportions divided by the standard deviation.

a: Absolute Standardized Mean Difference between Standard-dose and High-dose. b: Absolute Standardized Mean Difference between Standard-dose and Low-dose. c: Absolute Standardized Mean Difference between High-dose and Low-dose.

Table 4. Frequency of each outcome

Outcome	High-dose N=236	Standard-dose N=550	Low-dose N=139
Mortality in the ICU	7.2 (17)	8.2 (45)	4.3 (6)
Mortality within 30 days	28.4 (67)	22.2 (122)	19.4 (27)
Mortality during hospitalization	38.1 (90)	32.5 (179)	29.5 (41)
Mortality	44.9 (106)	43.3 (238)	36.7 (51)

ICU, intensive care uni.

Numbers outside the parentheses represent the percentage, while those inside the parentheses indicate the number of patients.

and respiratory management. Therefore, regional factors such as clinical practices, medical resource availability, and healthcare systems likely affect these patients' mortality risks[20,21]. Consequently, the impact of higher-than-standard doses of beta-lactams on clinical outcomes in ICU patients might vary depending on the region where care is provided. Thus, the difference between the results of this study and those of Camargo et al in Brazil should not be seen as refuting the potential benefits of higher-than-standard doses of beta-lactams. Our results suggest that the subtle yet potentially important benefits of administering higher-than-standard doses of beta-lactams may not have been captured in Japanese ICU settings. The interaction analysis, including covariates affecting volume distribution and renal clearance, was conducted to gain insights that could lead to the development of individualized treatment regimens. No interaction effects were observed between dose categories and any covariates. This result suggests that modifications based on specific patient characteristics may not be necessary, while also possibly indicating that the impact of beta-lactam dose on ICU patient outcomes might be limited compared to other treatments. Future studies on dosing optimization strategies to improve clinical outcomes for ICU patients in Japan may need to consider patient

Table 5. Summary of hazard ratios for each outcome

Outcome	Comparison	Crude HR (95% CI)	p value	IPTW-adjusted HR	p value
Mortality in the ICU	High-dose vs Standard-dose	0.75 (0.42-1.32)	0.316	0.95 (0.44-2.06)	0.894
	Low-dose vs Standard-dose	0.46 (0.19-1.09)	0.075	0.40 (0.13-1.27)	0.118
	High-dose vs Low-dose	1.65 (0.64-4.22)	0.294	2.35 (0.64-8.66)	0.193
Mortality within 30 days	High-dose vs Standard-dose	1.28 (0.95-1.73)	0.101	1.15 (0.75-1.77)	0.510
	Low-dose vs Standard-dose	0.84 (0.55-1.28)	0.423	1.13 (0.61-2.11)	0.699
	High-dose vs Low-dose	1.55 (1.06-2.26)	0.024	1.12 (0.62-2.01)	0.709
Mortality during hospitalization	High-dose vs Standard-dose	1.21 (0.94-1.56)	0.139	1.16 (0.82-1.64)	0.401
	Low-dose vs Standard-dose	0.78 (0.56-1.10)	0.161	1.03 (0.62-1.72)	0.888
	High-dose vs Low-dose	1.52(0.98-2.38)	0.064	1.02 (0.50-2.09)	0.954
Mortality	High-dose vs Standard-dose	1.19 (0.95-1.51)	0.128	1.00 (0.71-1.39)	0.982
	Low-dose vs Standard-dose	0.79 (0.58-1.07)	0.122	0.93 (0.59-1.47)	0.768
	High-dose vs Low-dose	1.52 (1.08-2.14)	0.016	1.07 (0.62-1.84)	0.817
Survival to ICU discharge	High-dose vs Standard-dose	0.89 (0.75-1.05)	0.164	0.97 (0.79-1.21)	0.816
	Low-dose vs Standard-dose	0.91 (0.75-1.12)	0.382	1.04 (0.77-1.39)	0.798
	High-dose vs Low-dose	0.97 (0.77-1.22)	0.799	0.94 (0.67-1.31)	0.709
Survival to discharge	High-dose vs Standard-dose	0.85 (0.70-1.04)	0.114	0.98 (0.75-1.26)	0.854
	Low-dose vs Standard-dose	0.94 (0.75-1.18)	0.577	0.98 (0.67-1.44)	0.936
	High-dose vs Low-dose	0.91 (0.70-1.18)	0.490	0.94 (0.75-1.18)	0.577

ICU, intensive care unit; HR, hazard ratio; CI, confidence interval; and IPTW, inverse probability of treatment weighting.

characteristics in more detail.

The strength of our study lies in using the large nationwide database in Japan, which enabled us to include a larger patient cohort, enhancing statistical power and producing more generalizable findings. Furthermore, this study is crucial as conducting randomized controlled trials to test the same hypothesis poses ethical challenges.

This study has some limitations. First, the definition of exposure was based on the total daily dose of beta-lactams. Prolonged or continuous beta-lactam administration, rather than intermittent administration, has been reported to increase clinical cure rates by enhancing the possibility of achieving the pharmacokinetic targets[22,23]. Moreover, with a fixed total daily dose, even with intermittent administration, the likelihood of achieving pharmacokinetic targets may vary with

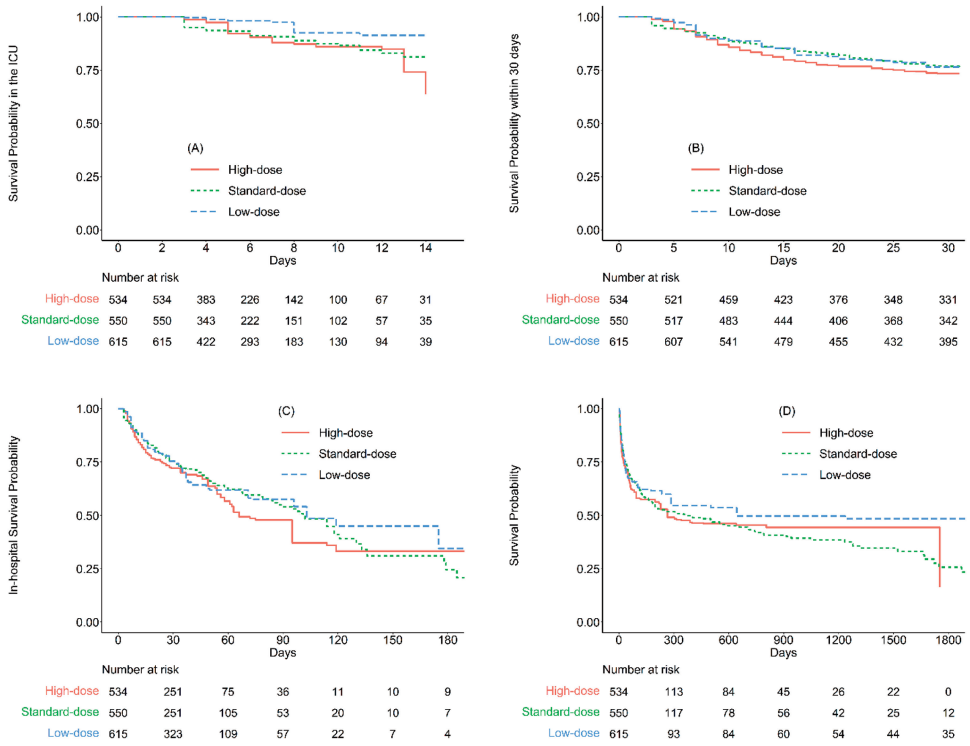
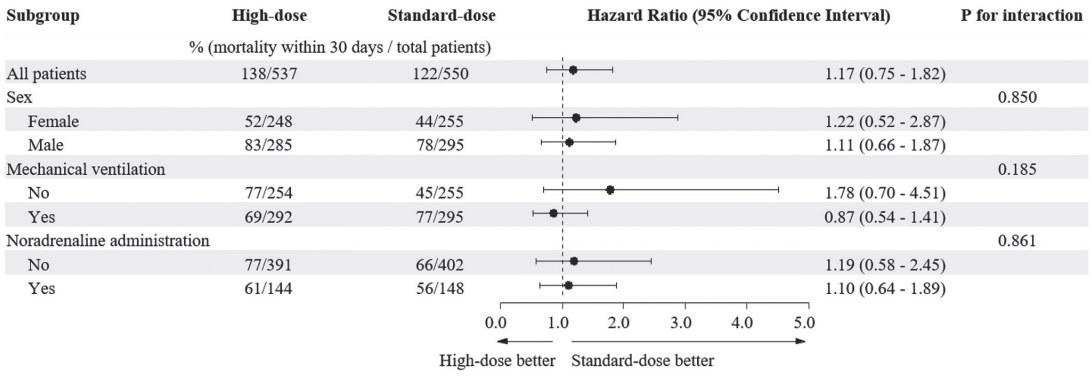


Figure 3. Survival curves starting from the initial administration of beta-lactams in the intensive care unit (ICU) for (A) mortality in the ICU, (B) mortality within 30 days, (C) mortality during hospitalization, and (D) Mortality.



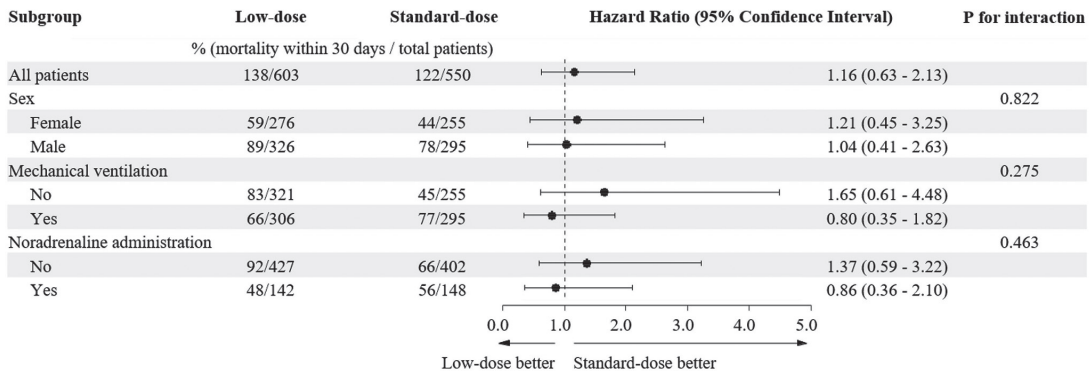


Figure 4. Forest plot of mortality within 30 days from index day based on subgroups, comparing Standard-dose and High-dose (top) and Standard-dose and Low-dose (bottom).

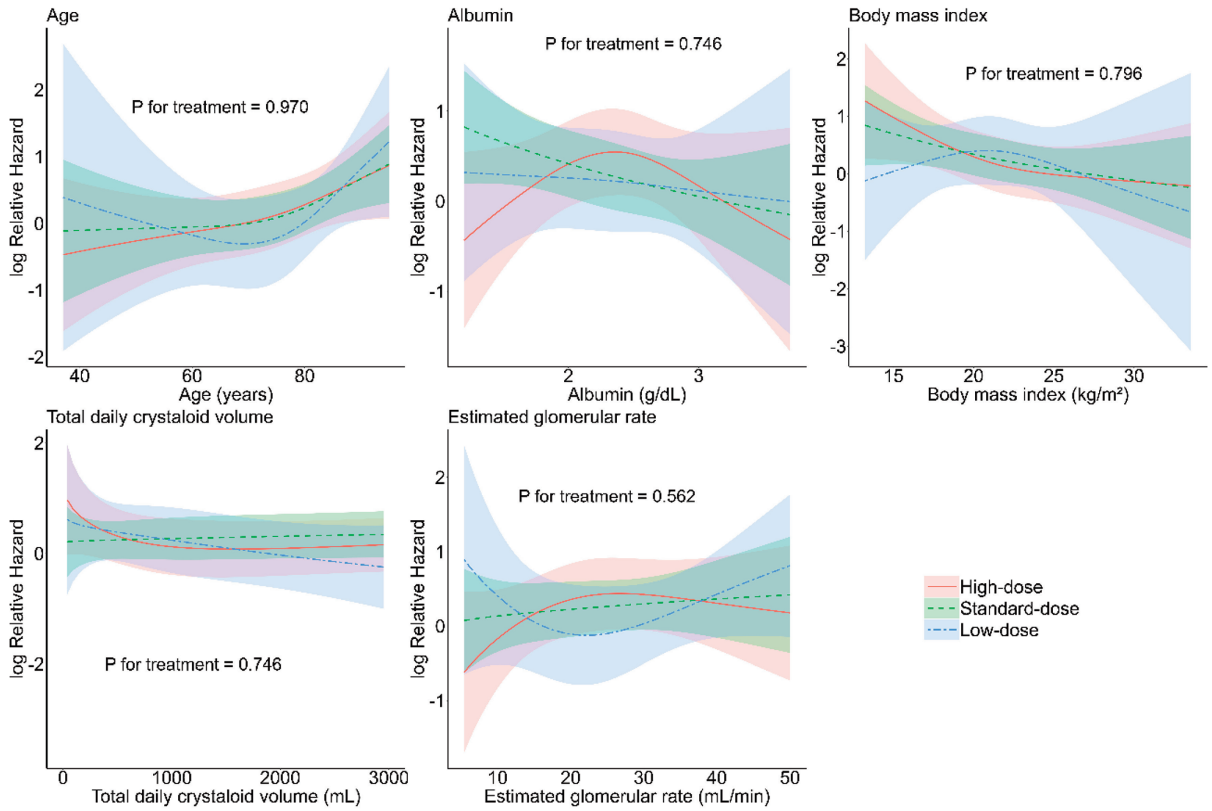


Figure 5. Relationship between age, albumin, body mass index, total daily crystalloid volume, or estimated glomerular filtration rate and their log relative hazard for mortality within 30 days. The graph represents the log relative hazard as a function of age, total daily crystalloid volume, or estimated creatinine clearance. Each point on the curve indicates the log relative hazard for a specific value.

administration frequency. In the Japanese medical setting, prolonged and continuous administration of beta-lactams is not yet common. Because beta-lactams are administered at equal intervals within a 24-h period, the options for dosing intervals are limited. Specifically, these intervals can be every 4, 6, 8, or 12 h. Therefore, with a constant total daily dose, differences in achieving pharmacokinetic targets with these options are likely minor compared to prolonged or continuous administration. Consequently, the definition of exposure using the total daily doses would not substantially impact our study results. Second, recognized ICU severity scores such as the Sequential Organ Failure Assessment score, the Simplified Acute Physiology Score, or the Acute Physiology and Chronic Health Evaluation score were unavailable from our database. Consequently, we could not ascertain patient severity accurately[24-26]. We had concerns that these unmeasured confounders could affect our study results. To address these concerns, we considered severity-associated factors such as mechanical ventilation, noradrenaline administration, and total daily crystalloid volume. Given these limitations, future studies should include more detailed analyses considering the illness severity of ICU patients. Third, microbiological test results were not available from our database. It is common for microbiological test results to be unavailable at the time of initial beta-lactam administration in ICU patients. Nevertheless, selecting the optimal beta-lactams for each patient based on microbiological test results is believed to impact clinical outcomes. In light of this limitation, our findings should be interpreted with caution. Fourth, in this study, the dose category was defined based on the total daily dose of beta-lactams administered on the day a patient initially received them in the ICU and the

following day, without accounting for any subsequent changes. Dose increases or decreases are frequently made in clinical practice beyond the initial two days as culture results become available and patient conditions evolve. Nevertheless, our study utilized DPC data, which does not allow us to accurately capture the reasons for these shifting dose categories. Therefore, we were unable to account for the dose categories beyond the third day.

In conclusion, using a large nationwide database in Japan, our study found that higher-than-standard doses of beta-lactams did not improve the mortality in ICU patients with renal failure within 30 days. Future studies into dosing optimization strategies to improve clinical outcomes for ICU patients with renal failure in Japan should more comprehensively consider patient characteristics and the details of the ICU care setting.

Acknowledgements

All authors have no COI to declare regarding the present study.

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Osaka City Med. J. Vol. 71, 27-36, 2025

Oxidative Stress and Antioxidant Capacity in Women with Anorexia Nervosa: Effects of Overeating and Vomiting

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Abstract

Background

Oxidative stress and antioxidant capacity have been linked to physical diseases; however, reports on these factors in patients with anorexia nervosa are limited. This study aimed to compare an oxidative stress marker—diacron-reactive oxygen metabolites—and an antioxidant marker—biological antioxidant potential—between patients with anorexia nervosa and healthy controls and to assess the impact of overeating and self-induced vomiting on diacron-reactive oxygen metabolites and biological antioxidant potential in patients with anorexia nervosa.

Methods

Participants included 26 women hospitalized with anorexia nervosa and 31 healthy women. The Bulimia Investigatory Test, Edinburgh, assessed the frequency of overeating and vomiting. Plasma diacron-reactive oxygen metabolites and biological antioxidant potential were compared between the patients with anorexia nervosa and healthy controls. The effects of overeating, vomiting, illness duration, age, and body mass index on diacron-reactive oxygen metabolites and biological antioxidant potential were analyzed using multiple regression.

Results

Diacron-reactive oxygen metabolites were significantly lower in the patients with anorexia nervosa than in the healthy controls ($p=0.013$); biological antioxidant potential showed no significant difference. Regression analysis revealed that biological antioxidant potential was positively associated with overeating frequency and negatively with vomiting frequency.

Conclusions

Severely underweight patients with anorexia nervosa may exhibit reduced oxidative stress. Since overeating boosts antioxidant capacity while vomiting decreases it, advising patients to first reduce vomiting frequency may help alleviate the physical burden.

Received August 28, 2024; accepted November 26, 2024.
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Key Words: Anorexia nervosa; Oxidative stress; Antioxidant; Overeating; Vomiting

Introduction

Anorexia nervosa (AN) is a subclass of eating disorder characterized by a severely low body weight, a distorted body image, and an intense fear of weight gain[1]. AN has two subtypes: AN restricting type (AN-R), wherein weight loss results from anorexia or excessive exercise, and AN binge eating/ purging type (AN-BP), involving binge eating and compensatory behaviors to prevent weight gain, like self-induced vomiting or abuse of laxatives and diuretics. Transitions between subtypes are common. AN is prevalent among young women but is often chronic, refractory[2], and associated with a high mortality rate[3,4].

Oxidative stress occurs when there is excessive production of free radicals and reactive oxygen species. Antioxidant capacity refers to the ability to neutralize oxidative stress through antioxidants that inhibit reactive oxygen species (ROS) and aid in repairing cellular damage. The imbalance between oxidative stress and antioxidant capacity leads to cellular damage, including lipid peroxidation, protein oxidation, nucleic acid damage, and abnormal cell signaling[5,6]. Oxidative stress has been linked to chronic diseases such as diabetes, endocrine and metabolic disorders, cardiovascular diseases, cognitive decline, and aging[6-10]. Oxidative stress is increased by external factors such as smoking and ultraviolet radiation[11].

Because ROS, which indicate oxidative stress, have a short half-life and are difficult to measure directly, relatively stable and easy-to-use oxidative stress marker, like diacron-reactive oxygen metabolites (d-ROMs), known for their high sensitivity and reproducibility is widely employed. In addition, antioxidant marker, biological antioxidant potential (BAP) which is easily measured and reflects the total antioxidant capacity of various substances, including ascorbic acid and proteins, is widely used[10,12-15].

It has been reported in AN that oxidative stress markers such as Advanced Oxidation Protein Products (AOPP) and Advanced Glycation End products (AGEs) show higher oxidative stress compared to healthy controls and antioxidant markers such as Total Antioxidant Capacity show lower antioxidant capacity. However, results have been inconsistent, and to our knowledge, d-ROMs and BAP have not been reported in AN[16-20]. Re-alimentation and weight gain in AN improve oxidative stress status[17]. Oxidative stress in AN is also linked to impaired mitochondrial function[21] and inflammatory responses[22]. However, it remains unclear which factors of AN clinical presentation influence oxidative stress. Patients with AN often present with starvation, overeating, and vomiting, but compensatory behaviors vary, with some patients engaging in overeating followed by excessive exercise or fasting, but not necessarily vomiting. The illness duration in AN has been related to oxidative stress levels[18], as a longer illness duration increases the psychological and physical burden, leading to more severe symptoms[23]. Overeating and vomiting in AN are associated with physical disorders[24]. In addition, pregnant women with Nausea and Vomiting of Pregnancy (NVP) have higher levels of oxidative stress and lower antioxidant capacity than healthy pregnant women[25,26]. However, to our knowledge, no studies have reported the effects of overeating and vomiting on oxidative stress and antioxidant capacity in AN.

In this study, we aimed to determine the oxidative stress levels and antioxidant capacity in hospitalized patients with AN using d-ROMs and BAP, compare them to healthy controls, and assess the effects of overeating and self-induced vomiting on these parameters. We predicted that d-ROMs

would be higher and BAP lower in patients with AN than in the healthy controls. We also predicted that d-ROMs would increase and BAP decrease as overeating and vomiting increased.

Method

Participants

The study included 30 women with AN who were admitted to the Department of Neuropsychiatry, Osaka Metropolitan University Hospital, between April 2022 and May 2024 for physical management or weight gain, who consented to participate (AN group), and healthy women (control group). The diagnosis of AN and its subtypes, AN-R and AN-BP, were made based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition[27]. Exclusion criteria for the AN group included heavy drinking, smoking, pregnancy, and a history of inflammatory disease. A total of 26 patients with AN (13 AN-R, 13 AN-BP) were included after excluding four based on these criteria. The control group consisted of 31 women recruited through our Center for Clinical Research and Innovation. Exclusion criteria for the control group were body mass index (BMI) less than 17.5 kg/m^2 or greater than 25 kg/m^2, heavy drinking, smoking, pregnancy, a history of inflammatory disease, and use of psychotropic drugs or oral contraceptives. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of Osaka Metropolitan University Graduate School of Medicine and conducted following the principles of the Declaration of Helsinki and its amendments.

Measures

Physical measurements of patients with AN and responses to a self-administered questionnaire were recorded on the day of admission. The frequency of overeating and vomiting used in this study was extracted from the responses to the Bulimia Investigatory Test, Edinburgh (BITE) on the day of admission. BITE is a self-administered questionnaire used to evaluate eating disorders, consisting of a 30-item symptom scale and a 3-item severity scale[28]. The 30-item symptom scale is scored as 1 (yes) or 0 (no), with the total score representing the number of points. A symptom scale score of 9 or less is considered low, 10-19 is medium, and 20 or more is high. A severity scale totals the frequency of behaviors like overeating, vomiting, and laxative use. A score of 5 or higher on this scale is clinically significant, while a score of 10 or higher indicates high severity. For the frequency of overeating, responses to question 27, "If you do binge, how often is this?" ("1. Hardly ever", "2. Once a month", "3. Once a week", "4. 2-3 times a week", "5. Daily", "6. 2-3 times a day") were used. No overeating was defined as 0, with responses expressed as 0-6. For the frequency of vomiting, responses to question 7, "Do you do any of the following to help you lose weight (make yourself vomit)?" ("0. Never", "2. Occasionally", "3. Once a week", "4. 2-3 times a week ", "5. Daily", "6. 2-3 times a day", "7. more than five times a day") were used, expressed as 0-7 (excluding 1). Both were treated as continuous variables.

Measurement of d-ROMs Levels and BAP Levels

Blood samples were collected early in the morning, the day after hospital admission, following a period of fasting. The samples were centrifuged to separate plasma, which was then stored frozen after processing within 24 hours of collection. Before measurements, samples were thawed at room temperature (approximately 10-20℃). d-ROMs measure the blood concentration of hydroperoxides via a color reaction, which are acidic denaturants of lipids, proteins, and nucleic acids oxidized by ROS. Higher d-ROMs levels indicate increased oxidative stress.

The results are expressed in arbitrary units (U. Carr), where one unit corresponds to 0.8 mg/L of hydrogen peroxide. BAP measures the ability of antioxidants to reduce trivalent iron ions to divalent iron ions via a color reaction. Higher BAP levels indicate greater antioxidant capacity, with results expressed in μmol/L. A free radical analyzer (Wismerll Company FREE carpe diem, Tokyo, Japan) was used to measure d-ROMs and BAP in plasma[29-31].

Statistics analysis

Statistical analysis was conducted using SPSS software (version 28.0.1; IBM Corp. NY, USA). Student's *t*-test or the Mann-Whitney U-test was used to compare continuous variables, depending on whether parametric test assumptions were met. The association of d-ROMs and BAP in the AN group was estimated using multivariate analysis, controlling for other factors such as age, BMI, illness duration, overeating and vomiting). The multivariate analysis employed the enter method. Two-sided tests were used, and a p-value of less than 0.05 was considered statistically significant.

Result

Table 1 compares sociodemographic characteristics between the AN group and control group. All participants were women; 26 were in the AN group, with 13 classified as AN-R and 13 as AN-BP. The mean age of the AN group was 21.4±4.0 years, which was not significantly different from the control group. The mean BMI of the AN group was 13.5±1.9 kg/m^2, significantly lower than that of the control group ($p<0.001$). All AN-BP patients experienced both overeating and vomiting, with the median frequency of overeating 5.0 (Interquartile Range (IQR): 3.5-6.0) and the median frequency of vomiting being 6.0 (IQR: 2.0-6.5). The average BUN/Cre ratio in the AN group was 22.8±9.1, and the average immunoreactive insulin (IRI) was 3.1±2.0 μU/mL. Table 2 compares d-ROMs and BAP levels between the AN and control groups. The median d-ROMs level in the AN group was 242.5 U.CARR (IQR: 197.8-311.8 U.CARR), while in the control group, the median was 301.0 U.CARR (IQR: 266.0-321.0 U.CARR). The difference was statistically significant ($p=0.013$). However, there was no statistically significant difference in BAP levels between the AN and control groups ($p=0.053$).

Table 3 and Table 4 present the results of multiple regression analyses with d-ROMs and BAP as dependent variables and age, BMI, illness duration, frequency of overeating, and frequency of vomiting as independent variables. None of the independent variables—age, BMI, illness duration, frequency of overeating, or frequency of vomiting—had a significant effect on d-ROMs (Table 3). However, BAP was positively associated with overeating frequency (standardized coefficient (β)= 1.941; $p<0.001$) and negatively associated with vomiting frequency (standardized coefficient (β)= −2.039; $p<0.001$). (adjusted $R^2=0.419$) (Table 4).

Discussion

In this study, we examined oxidative stress and antioxidant capacity in patients with AN and found two important findings. First, d-ROMs, which indicates the level of oxidative stress, were lower in the AN group compared to the control group. Second, BAP, a measure of antioxidant capacity, was similar between the AN group and control group. However, in a multiple regression analysis examining the effects of age, illness duration, BMI, frequency of overeating, and frequency of vomiting, BAP was positively associated with the frequency of overeating and negatively associated with the frequency of vomiting. To our knowledge, this is the first study to examine the effects of abnormal eating behaviors such as overeating and vomiting on oxidative stress and antioxidant

Table 1. Sociodemographic characteristics of the participants

	AN-R group (N=13)	AN-BP group (N=13)	AN group (N=26)	Contorol group (N=31)	p value	
Female sex, n (%)	13 (100)	13 (100)	26 (100)	31 (100)		
Age (years)	20.5±4.0	22.5±4.0	21.4±4.0	23.2±2.6	0.5	a
BMI kg/m^2	12.8±1.4	14.2±2.1	13.5±1.9	19.8±1.3	<0.001*	a
Illness duration (years)	2.5±1.7	5.9±5.3	4.2±2.8	-		
BITE symptom scale score, median (IQR)	5.0 (9.0-13.0)	21.0 (16.5-25.5)	14.5 (8.8-21.3)	3.0 (2.0-9.0)	<0.001*	b
BITE severity scale score, median (IQR)	0.0 (0.0-1.0)	11.0 (9.5-14.0)	3.5 (0.0-11.3)	0.0 (0.0-1.0)	<0.001*	b
Frequency of overeating, median (IQR)	0.0 (0.0-0.5)	5.0 (3.5-6.0)	0.0 (0.0-5.3)	0.0 (0.0-0.0)	0.002*	b
Frequency of vomiting, median (IQR)	0.0 (0.0-0.0)	6.0 (2.0-6.5)	0.0 (0.0-6.0)	0.0 (0.0-0.0)	<0.001*	b
BUN/Cre ratio	27.8±9.1	17.9±6.1	22.8±9.1	-		
Na (mmol/L)	139.8±2.5	139.8±3.0	139.8±2.7	-		
K (mmol/L)	3.9±0.4	3.7±0.8	3.8±0.6	-		
Cl (mmol/L)	103.7±3.4	99.8±6.5	101.7±5.5	-		
IRI (μU/mL)	2.4±1.5	3.9±2.1	3.1±2.0	-		

Data are presented as mean±standard deviation (SD), unless otherwise indicated.

Patients with AN group and controls were compared using two-sided Student's t-test. To compare non-normally distributed data, Mann-Whitney U-test was used. a: Student's *t*-test, b: mann-Whitney U-test. *statistically significant

Abbreviations: AN, Anorexia Nervosa; AN-R, Anorexia Nervosa restricting type; AN-BP, Anorexia Nervosa binge eating/purging type; BMI, body mass index; BITE, Bulimia Investigatory Test, Edinburgh; IRI, immunoreactive insulin; and IQR, interquartule range.

Table 2. Comparison of d-ROMs and BAP in AN and healthy control groups

	AN group (N=26)	Control group (N=31)	p value
d-ROMs (U.CARR.)	242.5 (197.8-311.8)	301.0 (266.0-321.0)	0.013*
BAP (μmol/L)	2461.6 (2325.6 -2632.8)	2577.6 (2445.0-2694.5)	0.053

Data are presented as median (IQR).

To compare patients and controls, the Mann-Whitney U-test was used for data that werenot normally distributed data. *statistically significant.

Abbreviations: AN, Anorexia Nervosa; BAP, biological antioxidant potential; d-ROMs, diacron-reactive oxygen metabolites; and IQR, interquartule range.

Table 3. Results of multiple regression analysis showing predictors of d-ROMs in AN group (N=26)

Dependent variable:d-ROMs (U.CARR)					
Independent Variable	Coef. (β)	SE	Std. Coef. (β)	t value	p value
Age (years)	−4.271	4.371	−0.218	−0.977	0.34
BMI (kg/m^2)	13.826	11.067	0.331	1.249	0.226
Illness duration (year)	−4.372	7.557	−0.156	−0.578	0.569
Frequency of overeating	12.197	19.09	0.406	0.639	0.53
Frequency of vomiting	−5.304	17.26	−0.195	−0.307	0.762
Adjusted R^2	0				

Abbreviations: AN, Anorexia Nervosa; BMI, body mass index; Coef. (β), Coefficient (β); d-ROMS, diacron-reactive oxygen metabolites; Std. Coef. (β), Standardized Coefficient (β); and SE, standard error.

Table 4. Results of multiple regression analysis showing predictors of BAP in AN group (N=26)

Dependent variable: BAP (μmol/L)					
Independent Variable	Coef. (β)	SE	Std. Coef. (β)	t value	p value
Age (years)	−10.787	39.887	−0.046	−0.27	0.79
BMI (kg/m^2)	87.11	100.996	0.174	0.863	0.399
Illness duration (year)	39.339	68.968	0.117	0.57	0.575
Frequency of overeating	697.8	174.215	1.941	4.005	<0.001*
Frequency of vomiting	−664.067	157.514	−2.039	−4.216	<0.001*
Adjusted R^2	0.419				

*statistically significant.

Abbreviations: AN, anorexia nervosa; BAP, biological antioxidant potential; BMI, body mass index; Coef. (β), coefficient (β); SE, standard error; and Std. Coef. (β), standardized coefficient (β).

capacity.

d-ROMs was lower in the AN group than in the control group. Several studies have reported on oxidative stress levels in patients with AN. These studies, using oxidative stress markers such as Apolipoprotein B (a cardiovascular risk marker associated with oxidative stress), AOPP (an indicator of protein oxidation), and AGEs (formed through the glycation of proteins by sugars), have reported higher oxidative stress levels in patients with AN with a mean BMI of 14.5 kg/m^2 or higher compared to healthy controls[18,20,32]. However, Thiobarbituric Acid Reactive Substances (TBARS), an indicator of lipid oxidation, was similar between patients with AN and healthy controls[18]. Conversely, Rodrigues et al[33] reported lower oxidative stress levels in patients with AN using TBARS, although BMI was not shown, similar to the findings of this study.

In extremely underweight patients with AN with a BMI of 14 kg/m^2 or less, as in this study, decreased lipoprotein synthesis[34] may lead to reduced production of lipid peroxides and hydroperoxides, resulting in lower oxidative stress. Additionally, reduced catabolism due to malnutrition and frequent hypothyroidism may have contributed to the decreased oxidative stress. Regarding the impact of body weight on oxidative stress, studies using various oxidative stress markers, including d-ROMs, have noted higher oxidative stress levels in obesity[35-38]. For underweight individuals, Rigaud et al[34] reported that oxidative stress levels were lower in severely underweight patients with AN with a BMI below 14 kg/m^2 compared to those with a BMI above 14 kg/m^2. If d-ROM levels positively correlate with body weight, this would align with our findings. In addition, the AN group is known to have a higher smoking rate than healthy controls[11]. This study excluded current smokers to eliminate the confounding effect of smoking on d-ROMs levels[37,39], which may explain the differences from previous studies.

Previous studies have suggested that overeating increases oxidative stress via postprandial hyperglycemia[40]. However, in this study, no significant effect of overeating frequency on d-ROMs was observed. This might be because the severely underweight patient group did not exhibit elevated blood glucose levels even after eating[41,42].

It has been reported that pregnant women with NVP have high levels of oxidative stress[25,26], it is possible that vomiting is related to oxidative stress. However, the present results showed no significant association, suggesting that the frequency of vomiting may not affect d-ROMs.

Regarding the antioxidant capacity in patients with AN, several studies have reported higher

antioxidant markers in patients with AN compared to healthy controls[17]. Conversely, most reports indicate that the antioxidant capacity in AN is low[18,32,43,44]. In this study, we observed a trend toward lower BAP in the AN group compared to control group ($p=0.053$), but the difference was not statistically significant.

Overeating in AN is often followed by vomiting to avoid weight gain. However, the frequency of overeating and vomiting does not always coincide, as weight gain in AN may be compensated by overactivity, laxative abuse, or other behaviors. Therefore, in this study, overeating and vomiting were examined separately, revealing that BAP was positively associated with overeating frequency and negatively associated with vomiting frequency. One factor that may have contributed to the positive association between overeating frequency and BAP in AN could be the effect of insulin secretion. Insulin has been suggested to regulate and promote antioxidant enzymes such as Superoxide Dismutase and catalase. Insulin secretion is typically reduced in patients with AN due to chronic hypoglycemia[41,42], while the average IRI for the AN group in this study was 3.1 μU/mL, and was relatively stable. overeating, particularly of carbohydrate-rich foods like bread, may promote insulin secretion and affected BAP. Another possible explanation is the intake of exogenous antioxidants through food. Overeating may involve consuming foods high in antioxidants, which could increase antioxidant capacity. Nutritional intake and weight gain are crucial indicators in the treatment of AN[45] and even overeating might play an important role in improving nutritional intake in severely underweight patients with AN.

The first factor contributing to the negative association of vomiting frequency and BAP observed in this study may be the loss of electrolytes and dehydration. In this study, the average BUN/Cre ratio, an indicator of dehydration, and the electrolyte levels in the AN group were each within the reference range, however, the direct relationship between frequency of vomiting and electrolyte abnormalities or dehydration has not been investigated. Chronic vomiting often leads to electrolyte abnormalities, such as hypokalemia and dehydration. Potassium deficiency has also been suggested to decrease the antioxidant capacity, including a decrease in antioxidant proteins[46,47]. It was also reported that the Total Antioxidant Status of antioxidant marker was lower in the group with dehydration than in the control group[48]. As the severity of electrolyte abnormalities and dehydration correlates with the frequency of vomiting[49,50], the high frequency of vomiting may have contributed to the lower antioxidant capacity. Second, there was a decrease in antioxidant intake due to vomiting. The concentration of carotenoids, which are exogenous antioxidants, was higher in the AN group than in the healthy group. It is speculated that the intake of vegetables and fruits was higher in patients with AN[51]. Frequent vomiting may decrease the absorption of fruits and vegetables.

This study has several limitations, including a small sample size. Psychiatric disorders such as anxiety and depression, or antidepressants may influence oxidative stress[52-54], but these factors were not considered in this study. Additionally, while the frequency of overeating and vomiting was self-reported by patients, an objective assessment of these behaviors may have provided more accurate data. The AN-R and AN-BP groups present different eating behaviors, however, they were analyzed as the AN group in this study, so the subtypes were not considered. A study of each subtype is expected.

To our knowledge, this is the first study to demonstrate that the frequency of overeating or vomiting affects oxidative stress and antioxidant capacity in patients with AN. The study revealed that patients with AN had significantly lower levels of the oxidative stress marker d-ROMs compared

to healthy controlsz. Overeating frequency was positively associated with BAP levels, an antioxidant marker, but negatively associated with vomiting frequency. These findings suggest that prioritizing the reduction of vomiting over the reduction of overeating in patients with AN may help reduce their physical burden.

Acknowledgements

All authors have no COI to declare regarding the present study.

We are grateful to the professors in the Department of Medical Statistics at Graduate School of Medicine, Osaka Metropolitan University, for their guidance and encouragement.

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Osaka City Med. J. Vol. 71, 37-43, 2025

Spinal Cord Infarction Induced by Vertebral Artery Dissection after Cervical Massage: A Case Report

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Abstract

Spinal cord infarction is a rare vascular disease, often caused by aortic lesions that obstruct the Adamkiewicz artery. Herein, we report a patient with spinal cord infarction who developed gait disturbance with worsening neck pain on the day after cervical massage. Neurological examination revealed left-dominant tetraparesis with right thermohypesthesia and hypoalgesia. Cervical magnetic resonance imaging revealed bilateral spinal cord infarction at the C2-3 level. Computed tomography angiography revealed a double lumen at the V4 segment of the right vertebral artery. The patient was diagnosed with anterior spinal artery infarction caused by vertebral artery dissection and received antiplatelet therapy. Gait disturbance and incontinence improved thereafter. Vertebral artery dissection should not be missed in the differential diagnosis of spinal cord infarction.

Key Words: Anterior spinal artery; Trauma; Incontinence; Tetraparesis; Angiography

Introduction

Spinal cord infarction is a rare vascular disease frequently caused by hypotension, aortic diseases, adjacent vertebral diseases, spinal and aortic surgery, vasculitis, vertebral artery dissection (VAD), and other rare etiologies[1-3]. The spinal cord is supplied by one anterior and two posterior spinal arteries, which extend longitudinally. These arteries receive supply from the radicular arteries, i.e., the C3 radicular artery originating from the vertebral artery, the C6 from the cervical ascending artery, the T7 from the intercostal artery, and most frequently, the T9-12 (Adamkiewicz artery) from the intercostal or the lumbar artery[4-7]. Rostrally, they originate from the V4 segment of the vertebral artery[4,6,7].

VAD is a common cause of stroke in young adults, causing ischemia in the brainstem, cerebellum, and occipital lobe[8]. Although the vertebral artery supplies the rostral part of the cervical spinal cord, VAD-associated spinal cord infarction has been reported in only a few case reports[1,9-14]. Herein, we report a rare case of spinal cord infarction presenting as anterior spinal artery syndrome caused by VAD, which was induced by cervical massage.

Received June 26, 2024; accepted November 26, 2024.
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Case Report

A 74-year-old Japanese male was transferred to our hospital from a nearby community hospital for gait disturbance and the development of urinary retention. Seven days prior to admission, he experienced a throbbing pain in the posterior neck after using a massage chair for 5 minutes. Along with the persistent neck pain experienced the following morning, he developed an unsteady gait and visited a nearby orthopedic clinic. On his way home, he started to lean to the left and finally collapsed on the sidewalk. He was transferred to the nearby hospital, where he was treated for a suspected stroke with aspirin and clopidogrel. On the next day after admission, he developed urinary retention, requiring a catheter retained in the bladder, and he became constipated. Magnetic resonance imaging (MRI) of the cervical spine revealed a spinal cord infarction, and he was transferred to our hospital. He had no medical history of vascular diseases. He smoked 20 cigarettes per day for 50 years and quit 6 years ago. He had no family history of stroke or any specific vascular diseases.

Upon admission, the following parameters were recorded: height, 165.3 cm; weight, 64.4 kg; body mass index, 23.6; blood pressure, 147/82 mm Hg; and pulse rate, 98/min and regular. Physical examination revealed no carotid bruit on either side and no cardiac murmurs. A neurological examination revealed that the patient was right-handed. He was conscious, alert, and well-oriented. His speech was fluent. He had no cranial nerve abnormalities. He had left-dominant tetraparesis, with manual muscle test 5 to 5^- on the right and 5^- on the left. The deep tendon reflexes were increased in all extremities, especially on the left side. The jaw reflex was barely induced. Pathological reflexes, including Hoffmann, Trömner, Babinski, and Chaddock reflexes, were all positive bilaterally. The tactile sensation was normal, although he presented with thermohypesthesia and hypoalgesia below the shoulder level (C4) on the right. Vibration sense was impaired on the left, whereas sense of position was maintained. The coordination tests revealed no ataxia, although clumsiness due to weakness was noted.

Laboratory tests revealed the following results: white blood cell, 5500/μL; red blood cell, 489×10^4/μL; hemoglobin level, 15.8 g/dL; platelet count, 19.3×10^4/μL; D-dimer level, $<$0.5 μg/mL; blood urea nitrogen, 17 mg/dL; creatinine, 0.79 mg/dL; low-density lipoprotein level 126 mg/dL; HbA1c level 5.7%; brain natriuretic peptide, $<$5.8 pg/mL; vitamin B12, 217 pg/mL; and human T-cell lymphotropic virus types 1 antibody (−). Cerebrospinal fluid tests yielded the following results: opening pressure, 8.5 cmH_2O; cells, 2/μL; protein, 70 mg/dL; IgG index, 0.51; and Oligoclonal band (−).

Brain MRI on the day of admission revealed no abnormal lesions (Fig. 1). Diffusion-weighted images revealed no acute-phase lesions in the brainstem, cerebellum, and occipital lobes (Fig. 1A). Magnetic resonance angiography revealed that the left vertebral artery was dominant, whereas the right vertebral artery was hypoplastic (Fig. 1B). No stenosis, obstruction, or irregularity of the vessel wall was noticed in major arteries in the cranium.

A cervical spinal cord MRI on the day of admission found no abnormal lesions. Two days after hospital admission, a high-intensity lesion was noted at the C2 to C3 level in the sagittal section of the T2-weighted image (Fig. 2A). Axial sections at the C2/3 level and the C3 level showed high-intensity lesions dominantly in the left spinal cord and right spinal cord, respectively (Figs. 2B and 2C). Eight days after hospital admission, the lesion reduced its size and intensity (Figs. 2D-2F).

Computed tomography angiography seven days after the neurological manifestation revealed an interruption of the right vertebral artery (arrow, Fig. 3A). The original image before the 3D reconstruction revealed a double lumen, a hallmark of arterial dissection, at the interrupted vertebral

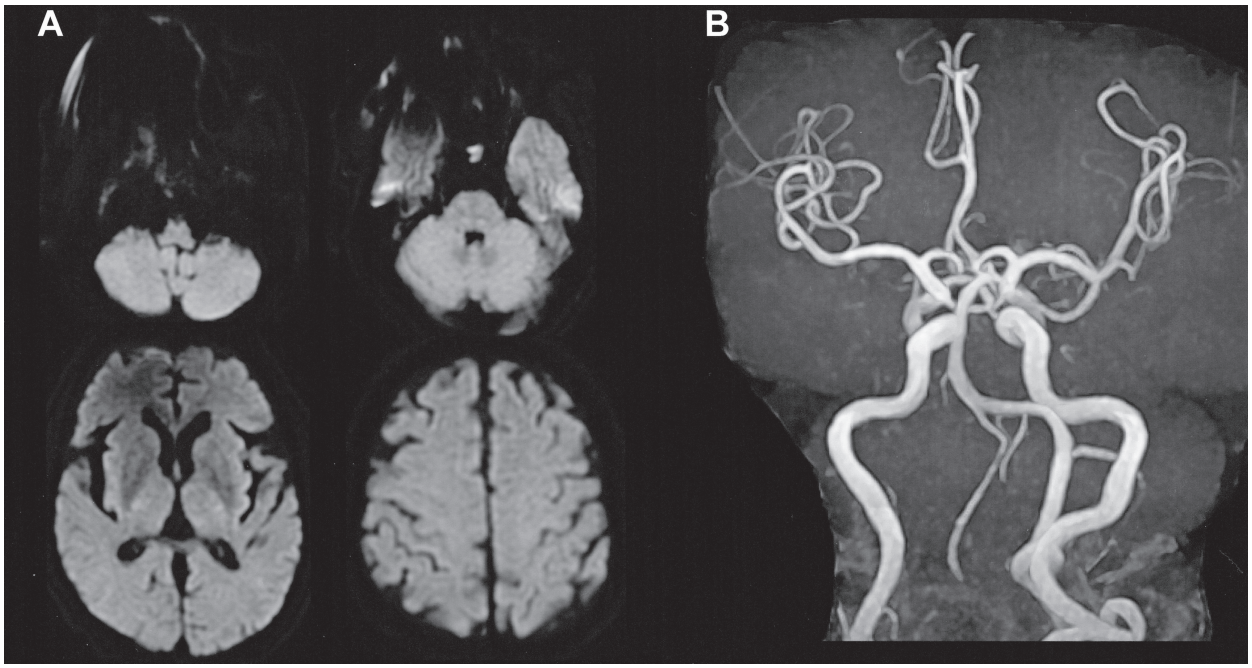

Figure 1. Brain magnetic resonance (MR) images on the day of developing neurological manifestation. A: Diffusion-weighted images show no acute-phase lesions in the brainstem, cerebellum, and occipital lobes. B: Magnetic resonance angiography reveals that the left and right vertebral arteries are dominant and hypoplastic, respectively. No stenosis can be observed upon imaging.

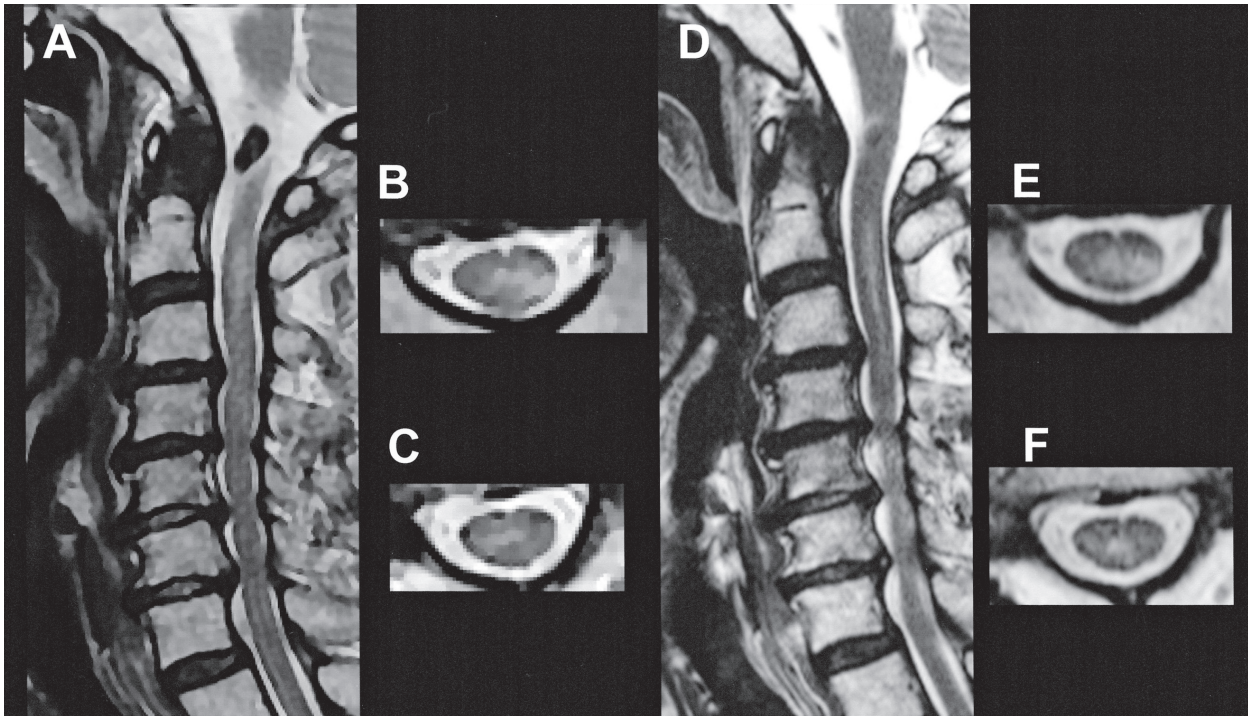

Figure 2. Magnetic resonance imaging (MRI) T2-weighted images of the cervical spinal cord at days two (A-C) and eight (D-F) after the onset of neurological symptoms. A: Sagittal image showing a lesion with high signal intensity extending from the C2 to C3 level. B: Axial image at the C2/3 level showing that the lesion extends from the center of the spinal cord to the left lateral column. C: Axial image at the C3 level showing that the lesion extends from the center to the right lateral column. D: Sagittal image showing that the lesion reduces in size and intensity six days later. E: The lesion at the C2/3 level remains unaltered. F: The lesion at the C3 level reduces in size and is localized in the center of the spinal cord.

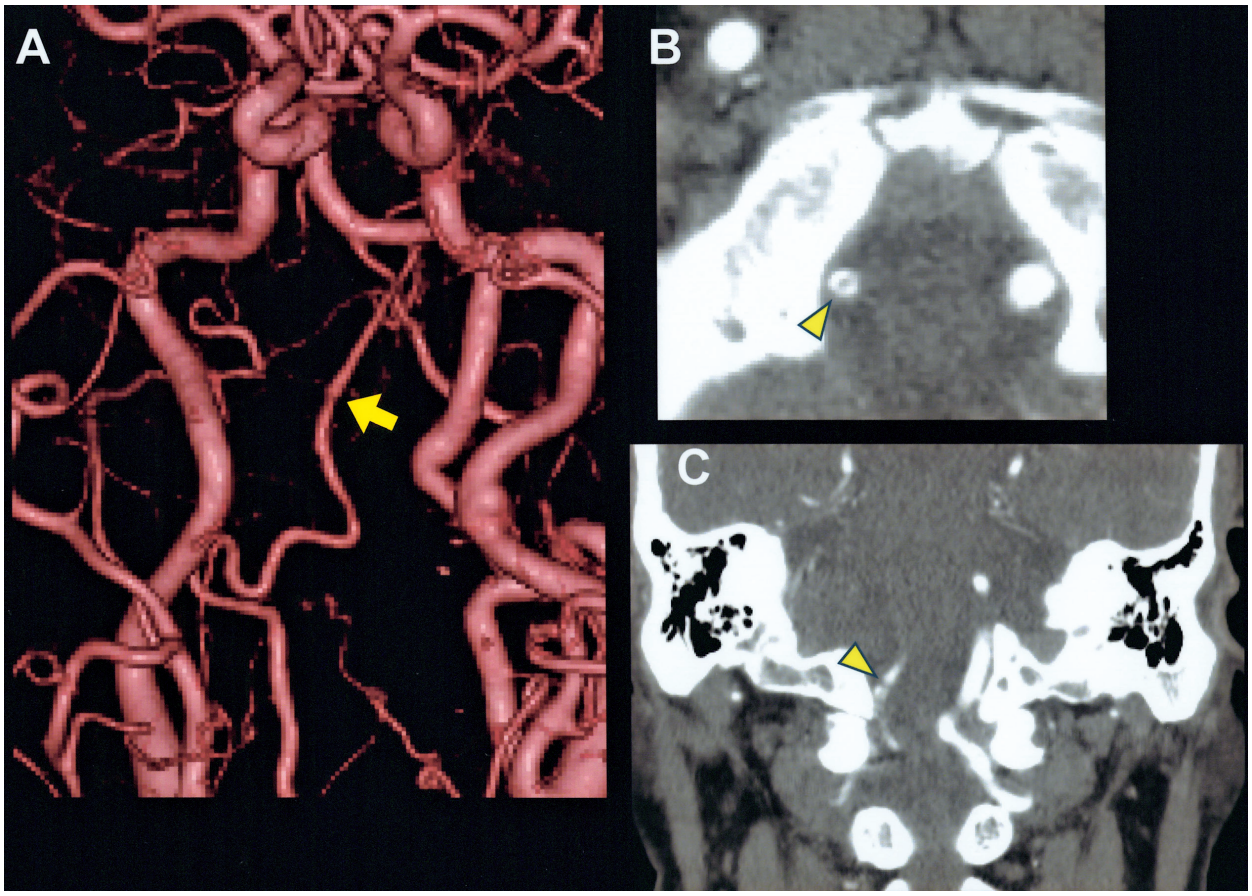

Figure 3. Computed tomography angiography images seven days after the neurological manifestation showing vertebral artery dissection. A: Reconstructed angiography image shows interruption of the right vertebral artery (arrow). B: Axial scan before the reconstruction shows a double lumen in the right vertebral artery (arrowhead). C: Coronal scan of the right vertebral artery shows interruption (arrowhead).

artery (arrowhead, Figs. 3B and 3C). The patient was diagnosed with VAD, which may have been induced by carotid massage. Dissection of the aorta was not observed.

Based on the clinical course, neurological findings, and neuroimaging findings, the patient was diagnosed with spinal cord infarction caused by VAD. The dual antiplatelet therapy with aspirin and clopidogrel initiated in the previous hospital was continued.

After admission to our hospital, weakness and sensory disturbance improved rapidly. One week after transfer, urinary incontinence was improved, such that control was possible without a catheter. Gait disturbance improved steadily with rehabilitation. The patient walked home independently thereafter and had no recurrent attacks for eight months.

Discussion

VAD is induced by a damage to the intima of the vertebral artery, allowing blood to flow into the media which may block branching vessels and cause infarction[15]. Mechanical forces, including cervical manipulative therapy and sudden neck movement, are the frequent triggers of VAD whereas underlying genetic conditions, such as Ehlers-Danlos syndrome and Marfan syndrome, may rarely be involved[15]. Posterior neck pain develops in half and ischemic symptoms in more than 90 percents of VAD patients[15]. Ischemic regions involve the brain stem, the thalamus and the cerebral or cerebellar

hemispheres[8] whereas isolated ischemia of the cervical spinal cord is an uncommon but increasingly recognized complication of VAD[16-18]. Treatments for cerebral or spinal cord infarction with VAD include antiplatelet therapy although the risk for subarachnoid hemorrhage should be considered. As most dissections of the vertebral arteries heal spontaneously, surgical or endovascular treatment should be reserved for patients who have persistent symptoms of ischemia[15].

In the current case report, the patient developed gait disturbance, sensory impairment, and bladder-bowel dysfunction with neck pain on the following day after a cervical massage. Neuroimaging confirmed a clinical diagnosis of cervical spinal cord infarction caused by VAD.

As neurological manifestations, the patient experienced left-dominant quadriparesis, accompanied by increased tendon reflexes and positive pathological reflexes bilaterally. The jaw reflex was not increased, suggesting damage to the pyramidal tracts at the rostral cervical spine or lower brainstem. The more severe findings on the left than on the right are suggestive of greater damage to the left pyramidal tract located at the lateral column than the right. Right thermohypesthesia and hypoalgesia below the level of the shoulder suggest the presence of a lesion at the left spinothalamic tract located at the anterior column of the rostral cervical spinal cord. Furthermore, bladder bowel dysfunction is indicative of a lesion of the bilateral spinal cord. Collectively, the focal diagnosis suggests that the main lesion includes the left anterior column and the lateral column, extending to the right lateral column, which was confirmed by MRI.

Differential diagnosis of an intramedullary spinal cord lesion with acute onset and rapid progress includes spinal cord infarction, arterio-venous malformation[19], acute disseminated encephalomyelitis, multiple sclerosis, neuromyelitis optica, vasculitis, and Sjögren syndrome[4]. The lesion was not observed on the day of neurological manifestation and was first noted two days later on T2-weighted MRI, suggesting the spinal cord infarction[3,20]. Inflammatory and demyelinating diseases were excluded based on the laboratory data.

The anterior spinal artery supplies the anterior two-thirds of the spinal cord. The spinal sulcal artery arises from the anterior spinal artery and penetrates the medulla of the anterior spinal cord[7,13,21]. As supply of the spinal sulcal artery is usually unilateral, obstruction of the artery causes unilateral spinal cord infarction[7,21,22]. In the present case, the distribution of spinal cord infarction suggests that the left spinal sulcal artery at the C2/3 level was more severely injured, while the right spinal sulcal artery at the C3 level was mildly injured, resulting in rapid recovery of symptoms associated with the right lesion. Multiple lesions in the present case suggest arterial thromboembolism induced by the proximal VAD as a mechanism of the infarction.

The cervical spinal cord is supplied by the vertebral artery, whereas the intercostal arteries from the aorta supply the thoracic spinal cord. Superior cervical segment of the spinal anterior artery receives blood flow from the intracranial vertebral arteries whereas the middle segment is supplied by two or three radicular arteries from the extracranial vertebral artery. Causes of vertebral artery impairment include VAD, atherosclerosis, vasculitis, vascular anomaly, iatrogenic obstruction by operation or angiography, and cervical disc hernia. In the current case, neck pain after cervical massage preceding the neurological manifestation is strongly suggestive of VAD. Indeed, VAD was confirmed at the V4 segment of the right vertebral artery which is thought to have released arterial thrombi into the rostral end of the anterior spinal artery obstructing distally the spinal sulcal arteries, dominantly on the left. As, shown in Figure 1, the posterior circulation is dominantly supplied by the left vertebral artery, cerebral infarction may have been prevented. Although proximal

extension of VAD into V2 can obstruct the C3 radicular artery causing spinal infarction at C2 or 3 level[4,7,13], no imaging findings confirmed this mechanism in the present case.

Hsu et al reviewed 17 cases of spinal cord infarction following VAD[1]. The average patient age was 40.5 years. The patients presented with a sensory level (76%) or Brown-Sequard syndrome (53%). The most common regions of dissection were at V1 or proximal V2 segments, and the infarction was mainly located at the C2-C5 levels. Spinal sulcal artery infarction was noted in 42%, posterior spinal artery infarction in 29%, and anterior spinal artery watershed infarction in 29%. In the present case, the age and dissection segment differ from the typically observed patterns, which could be explained by the ageing population and ethnicity.

In conclusion, VAD should not be missed in the differential diagnosis of spinal cord infarction.

Acknowledgments

All authors have no COI to declare regarding the present study.

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Osaka City Med. J. Vol. 71, 45-49, 2025

Catatonia in a Male Patient with Anorexia Nervosa

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Abstract

Catatonia has historically been classified as a subtype of schizophrenia but is now recognized as a syndrome that can manifest in various physical and psychiatric conditions. Its core feature is pronounced psychomotor disturbance characterized by immobility, mutism, and stupor. Although catatonia can be accompanied by diverse illnesses, its co-occurrence with eating disorders remains under-reported. A 31-year-old man with anorexia nervosa was admitted due to severe malnutrition. Upon admission, his body mass index was 11.2 kg/m^2. Initially, his refusal to eat and dramatic behavior were attributed to his eating disorder. However, symptoms such as immobility, mutism, and stupor gradually became apparent. A benzodiazepine challenge test was positive, leading to a diagnosis of catatonia. Thereafter, his catatonia symptoms responded rapidly to lorazepam treatment, and he was discharged with steady weight gain. Patients with eating disorders are vulnerable to catatonia due to their physical and psychological fragility. Nevertheless, catatonia is often overlooked because eating disorder behaviors can mimic its symptoms, such as withdrawal, histrionics, and muteness. Prompt diagnosis and treatment are crucial to prevent fatal outcomes. Clinicians should maintain a high index of suspicion of catatonia in these patients.

Key Words: Catatonia; Eating disorders; Negativism; Mannerisms; Mutism

Introduction

Catatonia is a distinct dyskinetic syndrome closely linked to mood, emotional, and cognitive disorders. Its core feature is pronounced psychomotor disturbance. Catatonia, established as a disease entity by Kahlbaum in the 19th century[1] was initially classified as a schizophrenia subtype. Subsequently, its occurrence in other psychiatric conditions, such as mood and autism spectrum disorders, as well as in physical ailments, such as encephalitis and metabolic disturbances, has been documented. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[2], it is described as a syndrome that can occur in the course of various physical illnesses and psychiatric disorders. Despite affecting over 10% of psychiatric inpatients[3,4] and responding well to treatment, catatonia remains underdiagnosed due to the DSM-5's non-specific diagnostic criteria, as highlighted by Fink and Taylar[5]. In addition, anorexia nervosa (AN) is a psychiatric disorder that presents with significantly low body weight owing to decreased food intake and is characterized by a fear of obesity,

Received August 28, 2024; accepted November 26, 2024.
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desire to lose weight, and body image disorders[2]. Malnutrition is often complicated by various physical problems such as electrolyte abnormalities, associated arrhythmias, and liver disorders[6,7]. However, a lack of awareness of the physical severity of the disease leads to treatment resistance, resulting in refractory disease, chronicity, and a high mortality rate. Although the association of catatonia with eating disorders has been under-reported[8,9], we present a case illustrating its occurrence in a severely malnourished patient. This case report explored the potential causes of catatonia, and factors often overlooked in eating disorders, as supported by relevant literature.

Case report

The patient was a 31-year-old man with AN. Ten years prior, at a height of 180 cm and weight of 130 kg (body mass index [BMI] 40.12 kg/m^2), he initiated a weight loss diet. Nine years prior, psychological stress intensified his anorexic tendencies, which progressed to chronic overeating, self-induced vomiting, and abuse of diuretics and stimulant laxatives. He had been receiving psychotherapy and medications, including antipsychotics and benzodiazepines, at a psychiatric clinic for 7 years. Five trips to emergency hospitals and several admissions for medical treatment have been conducted over the past two years. However, his weight had plummeted to 38 kg a year prior, prompting him to visit our hospital. Despite outpatient treatment over the following year, his condition deteriorated significantly, marked by frequent falls, leading to voluntary hospitalization at 36.5 kg (BMI 11.2 kg/m^2). Physical examination revealed bedsores on the buttocks, skin ecchymosis, and abrasions. Laboratory tests indicated severe electrolyte imbalance (sodium 122 mEq/L, potassium 2.0 mEq/L, and chloride 55 mEq/L), and electrocardiography (ECG) revealed pronounced conduction disturbances (QTc 748 ms). Neither hypophosphatemia nor significant impairment of hepatic and thyroid function was observed. While conscious and responsive, the patient exhibited minimal spontaneous speech and limited awareness of eating disorders. Therefore, it was difficult to convince him that he needed to gain weight.

Upon admission, intensive care, including electrolyte correction, re-nutrition (1300 kcal paste diet), and frequent monitoring was initiated. Psychotropic medication was discontinued because of ECG abnormalities and the risk of falls associated with lightheadedness and muscle weakness. Despite adequate food intake, the patient developed treatment-resistant behavior on the third day, characterized by repeated questioning, agitated behavior, and insomnia. While electrolyte imbalances improved and neurological examinations were unremarkable (including a normal cranial computed tomography scan), the patient's condition worsened on the sixth day with severe agitation and refusal to eat, necessitating nasogastric feeding. On the seventh day, he became immobile, mute, and stuporous, with catalepsy and muscle rigidity. Neuroimaging (magnetic resonance imaging and electroencephalography [EEG]) revealed mild cranial atrophy with high-amplitude slow waves in the bilateral frontal to parietal regions, but epilepsy and encephalitis were ruled out. On the ninth day, a subsequent benzodiazepine challenge test confirmed catatonia (i.e., 30 s after intravenous diazepam 5 mg, the patient responded to questions and showed body movements, and 3 min later, the patient became somnolent and was unable to speak again), and treatment with lorazepam 1.5 mg/day led to rapid symptom resolution. The patient's speech gradually improved, he became conversant, and slowly tolerated oral feeding. By the 14th day of the disease (five days after treatment initiation), the catatonia symptoms had disappeared. Since then, psychological resistance to food intake has decreased, and the need for weight gain has gradually increased. The patient ultimately gained

weight through behavioral therapy and was discharged on the 103rd day, weighing 48 kg.

Discussion

A 31-year-old man with AN developed catatonia during hospitalization for weight gain. Treatment resistance and rejection observed on the third hospital day marked the onset of catatonia, which was confirmed on the ninth day. Lorazepam treatment prevented prolonged catatonia, resolving by the 14th day.

AN is characterized by significantly low body weight owing to decreased food intake caused by psychological factors. The binge eating and purging type, a subtype of AN, is associated with overeating and compensatory behaviors to prevent weight gain, such as self-induced vomiting and abuse of laxatives and diuretics[2]. AN is often chronic. Prolonged malnutrition, habitual overeating, and self-induced vomiting often lead to physical complications, such as electrolyte abnormalities (hypokalemia, hyponatremia, liver dysfunction, and hypothyroidism)[7,10,11]. However, AN often involves a lack of awareness regarding the severity of low body weight and treatment resistance. Despite understanding the risks of significant weight loss, our patient had limited motivation for eating disorder treatment. Initially, uncooperative and rejecting behaviors were attributed to the pathology of eating disorders.

The DSM-5 classification criteria include symptoms such as catalepsy, posturing, and stereotypies, as emphasized by Fink and Taylar[5], as well as immobility, mutism, stupor, waxy flexibility, negativism, mannerisms, agitation, reduced responsiveness, grimacing, and echophenomena. In this case, the patient transitioned from food and treatment refusal to a generalized refusal of activities, accompanied by mutism, immobility, stupor, catalepsy, and muscle rigidity, prompting the diagnosis of catatonia. Catatonia is typically associated with physical complications. In cases with fever and autonomic symptoms, the prognosis is considered poor; in the past, it was referred to as fatal catatonia. However, since catatonia can improve with appropriate treatment and physical management, it is now diagnosed as malignant catatonia rather than fatal; moreover, early diagnosis and treatment are required. Differentiating between deliberate eating disorder behaviors (such as food or treatment refusal) and catatonic symptoms (such as negativism, mannerisms, or mutism) can be challenging[12]. Careful observation of rejection behaviors and core catatonic symptoms (immobility, mutism, and stupor) is crucial for the accurate diagnosis and identification of potential comorbidities. Early diagnosis and therapeutic intervention are important to reduce the risk of developing physical problems.

Among acute inpatients in psychiatric wards, mood disorders were the most common background condition for catatonia (46%), followed by psychotic disorders (26%), general physical illnesses (20%), and other psychiatric disorders (8%)[13]. It has been noted that the disease tends to occur in patients with severe illnesses and has a high affinity with hospitalized patients[14]. This means that in severely ill patients requiring hospitalization, psychiatric disorders, and physical illnesses can be background conditions for catatonia, indicating a wide range of illnesses. Extreme thinness and electrolyte abnormalities were considered potential factors in the development of catatonia in this patient. The patient had an extremely low body weight, with a BMI of 11.2 kg/m^2. Additionally, the patient was male, and the severity of his thinness may have been greater than that of a female patient with the same BMI[15]. Research suggests that decreased blood flow to the parietal lobes, associated with starvation and weight loss common in AN, can contribute to catatonia[16-19]. The patient's EEG

indicated frontal-parietal hypofunction, a known catatonia trigger. Hyponatremia is also reported to trigger catatonia[20-23], and this patient had significant electrolyte imbalances, particularly hyponatremia, before admission. This may have contributed to his condition. Although sodium levels were corrected to 138 mEq/L by the fifth day of hospitalization, his rejective behavior persisted, and catatonia symptoms gradually worsened. This progression aligns with previous case reports[24-26].

Psychological stress is another recognized risk factor for catatonia[27,28]. Inpatient treatment for AN can be highly stressful because of imposed restrictions and treatment plans. The patient exhibited difficulty adapting to the environment and a persistent demeanor, possibly indicative of a subthreshold autistic spectrum disorder. These factors may have contributed to the onset of catatonia. Close attention to patient anxiety is crucial in such cases.

Antipsychotic drugs have been recommended for the pharmacological treatment of catatonia as catatonia is considered a subtype of schizophrenia. However, their use is now contraindicated owing to the risk of catatonia exacerbation by antipsychotics and the development of malignant syndromes. Benzodiazepines and electroconvulsive therapy (ECT) are first-line treatments for catatonia. Although there was no significant difference in efficacy between benzodiazepines and ECT, considering the degree of invasiveness, benzodiazepines should be administered first, and ECT should be considered for treatment-resistant cases. In this patient, lorazepam was effective in resolving symptoms after the definitive diagnosis of catatonia. The patient had been prescribed benzodiazepine receptor agonists by his physician for several years prior to admission to our hospital. Therefore, we cannot rule out the possibility that the discontinuation of bromazepam after hospital admission caused catatonia withdrawal. In addition, the benzodiazepine challenge test is sometimes used to confirm the diagnosis of catatonia and was effective in this patient. Since catatonia can occur in the context of various diseases, and atypical symptoms such as negativism, mannerisms, and agitation may be central to catatonia rather than typical symptoms such as immobility, muteness, and stupor, a benzodiazepine challenge test should be actively considered when catatonia is suspected.

In conclusion, catatonia overlaps with eating disorder symptoms, often leading to diagnostic oversight. Clinicians should maintain a high index of suspicion of catatonia and consider early benzodiazepine treatment because of its potentially fatal course. Future case reports are likely to elucidate additional mechanisms underlying catatonia in this population.

Acknowledgements

All authors have no COI to declare regarding the present study.

I would like to thank Tsuneo Yamauchi for his significant contributions to the manuscript preparation.

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Publisher : Osaka City Medical Association,
Graduate School of Medicine, Osaka Metropolitan University,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan