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Association between heart rate on admission and in-hospital mortality among general inpatients

Insights from Japan Adverse Drug Events (JADE) study

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Abstract

Association between heart rate (HR) and in-hospital mortality in general patients irrespective of underlying diseases were not well scrutinized. We assessed the relationship between HR on admission and in-hospital mortality among general inpatients.

We used data from Japan Adverse Drug Events (JADE) study, a prospective cohort study. One tertiary care hospital in Japan with 13 medical and 12 surgical wards, and an intensive care unit (ICU). Patients (n = 2360) were ≥12 years old and admitted to this hospital within 3 months; and pregnant women were excluded. We assessed the relationship between HR and mortality in five (<60, 60–79, 80–99, 100–119, ≥120 beats per minutes [bpm]) groups. We also compared the five HR groups according to the age (<70 years; ≥70 years) and wards (medical; surgical; ICU).

We enrolled 2360 patients (median age, 71 [interquartile range (IQR) 58–81] years) including 1147, 1068, and 145 patients in the medical and surgical wards, and the ICU, respectively. The median (IQR) HR on admission was 78 (68–91) bpm. Ninety-five patients died during hospitalization. Mortalities in the <60, 60–79, 80–99, 100–119, and ≥120 bpm groups were 2.9% (5/175), 2.7% (28/1047), 3.4% (26/762), 8.2% (24/291), and 14.3% (12/84), respectively ($P < .001$). The adjusted odds ratios of in-hospital mortality was 3.64 (95% CI 1.88–7.05, $P < .001$) when HR was ≥100 bpm in the medical ward; and 5.69 (95% CI 1.72–18.82, $P = .004$) when HR ≥120 bpm in the surgical ward. There was no statistically significant relationship with the ICU.

In conclusion, higher HR should be associated with in-hospital mortality among patients with general diseases. Even with less severe condition or outside ICU, HR should be directed attention to and patients with high HR on admission should be taken additional therapy to reduce the further risk of deterioration.

Abbreviations: bpm = beats per minutes, HR = heart rate, ICU = intensive care unit, IQR = interquartile range, JADE study = Japan Adverse Drug Events study, OR = odds ratio.

Keywords: heart rate, Japan Adverse Drug Events (JADE) study, mortality

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1. Introduction

High heart rate (HR) is associated with cardiovascular mortality and all-cause mortality in the general population.[1–3] A recent meta-analysis reported the relative risk of having 10 beats per minutes (bpm) resting HR as 1.08 (95% CI 1.06–1.10) for cardiovascular mortality among the general population.[1] The association between HR and in-hospital mortality has also been reported in patients with cardiovascular comorbidities.[4] Patients with acute ischemic stroke and HR ≥83 bpm on admission had higher risk of in-hospital mortality with adjusted odds ratio (OR) of 4.42.[4] However, the association between HR and in-hospital mortality in general patients irrespective of underlying diseases were not well scrutinized.

With any relationship between HR and in-hospital mortality, or any threshold to trigger it, the risk in such patients could be addressed to reduce mortality efficiently. In addition, any intervention aimed at reducing HR, or the sympathetic nervous system, might offer supplementary therapy for patients with abnormal HR on admission. Thus, we analyzed data from a prospective cohort study to clarify the association between HR and in-hospital mortality among general patients.

2. Methods

2.1. Study design and patient population

The Japan Adverse Drug Events (JADE) study involves series of cohort studies conducted to evaluate adverse drug events and medication errors in Japan.[5–8] In this study, we used the data from a tertiary care hospital. There were 13 medical and12 surgical wards, and an intensive care unit (ICU). We included patients aged ≥12 years old, admitted to this hospital during a 3-month period from September through November 2013, while excluding pregnant women; because they were generally considered healthy people. Those aged <12 years were excluded because the median HR among them was higher than those ≥12 years.[9] Patients were followed-up until transfer, discharge, or death. The study protocol complied with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labor, and Welfare in Japan.

The institutional review board of the hospital approved the study and the board waived the requirement of informed consent because all data were obtained as part of daily routine practice.

2.2. Data collection and definitions

In the JADE study, data on all clinical symptoms and signs as well as laboratory data were extracted from the electronic medical record from the admission to the discharge. Because patients were admitted due to a number of diseases or medical conditions, we categorized the primary diseases on admission into 15 groups by the International Classification Diseases 10th revision.[10]

The study primary endpoint was in-hospital mortality, and HR at admission was compared with in-hospital mortality. HR was treated as a continuous variable or categorized into five (<60, 60–79, 80–99, 100–119, ≥120 bpm) groups; because we hypothesized that there was threshold to the risk of mortality. We analyzed the relationship between HR and mortality as a whole, stratified by the age (<70 years; ≥70 years) and wards (medical; surgical; ICU). The threshold of age was determined by the median value. The missing values were treated as missing without imputations and we analyzed the data without the missing variables.

2.3. Statistical analyses

The descriptive statistics were shown as median (interquartile range [IQR]) for continuous variables, and as numbers and percentages for categorical variables. We used Wilcoxon rank sum test or chi-square test to compare patients' characteristics between "died" and "survived" patients. We compared HR groups and mortalities by chi-square test.

To assess the association between HR on admission and in-hospital mortality adjusted for possible confounders, we constructed multivariable logistic regression models including the following independent variables; age, gender, systolic blood pressure, hemoglobin, total protein, creatinine, and white blood cell count as well as HR. Because there were a number of diseases or medical conditions, we could not adjust for such comorbidities, rather, we stratified by wards and adjusted the surrogates, which were associated with the severity in patients. We constructed four models by treating HR as continuous or dichotomized variable with different thresholds. We conducted all analyses using JMP 13.1 (SAS Institute Inc., Cary, NC, USA) software. Two tailed P-values $< .05$ were considered statistically significant.

3. Results

We enrolled 2360 patients among the 3120 patients who were admitted during the study period. We excluded 365 patients with pregnancy or pregnancy complications, and another 395 patients who were <12 years old. The median age was 71 (IQR, 58–81) years; and men accounted for 54% (1266) (Table 1). The median HR was 78 (IQR 68–91) bpm. The missing values occurred in two patients with HR, and were generally observed in <100 patients for other variables, aside respiratory rate (1031), total bilirubin (108), γ-glutamyltranspeptidase (760), lactate dehydrogenase (272), alkaline phosphatase (538), and creatinine kinase (854). Common diseases or medical conditions included the circulatory system (26.7%), neoplasms (21.8%), and digestive system (19.4%) in the medical wards; neoplasms (33.2%), injury, poisoning, and certain other consequences of external causes (19.9%); and digestive system (13.2%), in the surgical wards; and injury, poisoning, and certain other consequences of external causes (38.6%), respiratory system (15.2%), and circulatory system (12.4%), in the ICU (Table 2).

During the hospital stay, the 95 patients who died were older than those who survived (median: 83 vs 70 years, $P < .001$). Median HR among dead patients was higher than those who survived (92 vs 78 bpm, $P < .001$) (Table 1). Patients who died during the hospital stay had significantly lower blood pressure, lower hemoglobin level, higher white blood cell count, higher urea nitrogen level, and higher lactate dehydrogenase level (Table 1).

Overall, in-hospital mortality was significantly elevated when the HR increased (Fig. 1A). Among patients with age less than 70 years, mortality in the ≥120 groups was 12.1% (4/33) ($P < .001$; Fig. 1B), whereas those ≥70 years, mortality in the 100–119 and ≥120 groups were 12.2% (20/164) and 15.7% (8/51) ($P < .001$; Fig. 1C), respectively.

In terms of wards, significant associations were observed in the medical and surgical wards (Fig. 2A and B, respectively). Mortalities in the <60, 60–79, 80–99, 100–119, and ≥120 groups were 0% (0/90), 2.3% (11/484), 3% (11/367), 10.7% (18/169), and 10.8% (4/37) in the medical wards, respectively ($P < .001$; Fig. 2A). In the surgical wards, for the ≥120 group, this was 14.8% (4/27) ($P = .009$; Fig. 2B). Although mortalities in the <60 and ≥120 groups were relatively high in the ICU (30% [3/10] and 20% [4/20]), the difference was not statistically significant ($P = .31$; Fig. 2C).

Multivariable logistic regression model showed that the adjusted OR for one increment in HR was 1.03 (95% CI 1.01–1.04, $P < .001$) in the medical ward and 1.02 (95% CI 1.00–1.04, $P = .03$) in the surgical ward, but not statistically significant in the ICU (Table 3, Model 1). With HR ≥100 bpm, adjusted OR for this category compared to HR <100 bpm was 3.64 (95% CI 1.88–7.05, $P < .001$) in the medical ward; however, this was not statistically significant in the surgical wards ($P = .10$) and ICU ($P = .30$) (Table 3, Model 2). Similarly, at HR ≥120, adjusted OR was 5.69 (95% CI 1.72–18.82, $P = .004$) compared to HR <120 bpm in surgical ward, but not statistically significant in medical ward ($P = .10$) or ICU ($P = .70$) (Table 3, Model 3). There was no association between HR <60 bpm and in-hospital mortality either in the medical ($P = .81$) or surgical wards ($P = .80$), or ICU ($P = .30$) (Table 3, Model 4).

Table 1

Patient characteristics.

Variables	All patients (n = 2360)	Died (n = 95)	Survived (n = 2265)	*P*-value
Age (years), median (IQR)	71 (58–81)	83 (74–89)	70 (57–80)	<.001
Male, n (%)	1266 (54)	53 (56)	1213 (54)	.70
Heart rate (beats per minute), median (IQR)	78 (68–91)	92 (77–109)	78 (68–90)	<.001
Systolic blood pressure (mm Hg), median (IQR)	127 (112–145)	121 (99–146)	127 (112–145)	.03
Diastolic blood pressure (mm Hg), median (IQR)	74 (65–85)	70 (59–83)	74 (65–85)	.007
Respiratory rate (/min), median (IQR)	19 (16–23)	22 (18–26)	19 (16–23)	<.001
Hemoglobin (g/dL), median (IQR)	12.7 (11.0–14.1)	11.2 (8.7–13.1)	12.7 (11.1–14.1)	<.001
Hematocrit (%), median (IQR)	37 (32.6–40.7)	32.9 (25.9–38.5)	37.1 (32.9–40.7)	<.001
White blood cell (/μL), median (IQR)	6510 (5000–9098)	9040 (6310–13050)	6440 (4970–8945)	<.001
Platelet ($\times 10^4$/μL), median (IQR)	19.5 (15.6–24.2)	16.8 (11.7–22.5)	19.6 (15.8–24.3)	.002
Serum glucose concentration (mg/dL), median (IQR)	112 (97–139)	127 (101–193)	112 (97–138)	.006
Na (mmol/L), median (IQR)	139.2 (136.9–140.8)	136.7 (133.8–140.5)	139.2 (137.1–140.8)	.001
K (mmol/L), median (IQR)	4.1 (3.8–4.4)	4.2 (3.5–4.7)	4.1 (3.8–4.4)	.50
Cl (mmol/L), median (IQR)	103.0 (100.5–104.9)	100.0 (96.5–104.1)	103.0 (100.7–104.9)	<.001
Urea nitrogen (mg/dL), median (IQR)	15.2 (11.9–20.8)	28.1 (19.1–45.4)	15.0 (11.8–20.2)	<.001
Creatinine (mg/dL), median (IQR)	0.78 (0.63–0.98)	1.02 (0.75–1.62)	0.77 (0.63–0.96)	<.001
Total protein (g/dL), median (IQR)	6.8 (6.4–7.2)	6.3 (5.6–6.8)	6.8 (6.4–7.2)	<.001
Total bilirubin (mg/dL), median (IQR)	0.7 (0.5–1.0)	0.7 (0.5–1.2)	0.7 (0.5–1.0)	.06
Aspartate aminotransferase (U/L), median (IQR)	22 (17–31)	36 (24–91)	22 (17–30)	<.001
Alanine aminotransferase (U/L), median (IQR)	17 (12–26)	23 (14–47)	16 (12–25)	<.001
γ-Glutamyltranspeptidase (U/L), median (IQR)	26 (16–52)	34 (18–113)	26 (16–50)	.03
Lactate dehydrogenase (U/L), median (IQR)	212 (179–264)	317 (257–465)	209 (178–257)	<.001
Alkaline phosphatase (U/L), median (IQR)	243 (190–313)	320 (222–516)	242 (189–310)	<.001
Creatine kinase (U/L), median (IQR)	77 (50–131)	86 (36–200)	77 (50–130)	.50
Estimated glomerular filtration rate (mL/min/1.73 m^2), median (IQR)	68.6 (53.1–83.5)	46.5 (31.0–66.3)	69.4 (54.0–84.0)	<.001

IQR = interquartile range.

4. Discussion

Similar to previous reports in the general population or among patients with specific diseases, we found higher HR was associated with higher in-hospital mortality among general in patients. This association was statistically significant in the medical and surgical wards with adjusted ORs of one bpm increment of 1.03 and 1.02, respectively. The threshold in this cohort was 100 bpm in the medical and 120 bpm in the surgical wards. However, such thresholds, either higher or lower ones, were not apparent in the ICU, although some lower and higher threshold values were graphically implied.

Recent meta-analysis showed that the general people with resting HR of ≥80 bpm had higher risk of cardiovascular and all-cause mortality with relative risks of 1.33 and 1.45, respectively.[2] Another meta-analysis showed that the resting HR was an independent predictor of coronary artery disease (hazard ratio:

Table 2

Conditions on admission.

Conditions on admissions	All patients, n (%) (n = 2360)	Medical wards, n (%) (n = 1147)	Surgical wards, n (%) (n = 1068)	Intensive care unit, n (%) (n = 145)
Certain infectious diseases	76 (3.2)	55 (4.8)	4 (0.4)	17 (11.7)
Neoplasms	605 (25.6)	250 (21.8)	355 (33.2)	0 (0)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	19 (0.8)	13 (1.1)	5 (0.5)	1 (0.7)
Endocrine, nutritional and metabolic diseases	62 (2.6)	43 (3.7)	7 (0.7)	12 (8.3)
Mental and behavioral disorders	51 (2.2)	42 (3.7)	2 (0.2)	7 (4.8)
Diseases of the nervous system	48 (2.0)	26 (2.3)	13 (1.2)	9 (6.2)
Diseases of the eye and adnexa	45 (1.9)	1 (0.1)	44 (4.1)	0 (0)
Diseases of the ear and mastoid process	19 (0.8)	1 (0.1)	18 (1.7)	0 (0)
Diseases of the digestive system	364 (15.4)	222 (19.4)	141 (13.2)	1 (0.7)
Diseases of the circulatory system	417 (17.7)	306 (26.7)	93 (8.7)	18 (12.4)
Diseases of the respiratory system	194 (8.2)	112 (9.8)	60 (5.6)	22 (15.2)
Diseases of the genitourinary system	109 (4.6)	35 (3.1)	73 (6.8)	1 (0.7)
Diseases of the skin and subcutaneous tissue	32 (1.4)	13 (1.1)	19 (1.8)	0 (0)
Diseases of the musculoskeletal system and connective tissue	28 (1.2)	6 (0.5)	21 (2.0)	1 (0.7)
Injury, poisoning, and certain other consequences of external causes	291 (12.3)	22 (1.9)	213 (19.9)	56 (38.6)

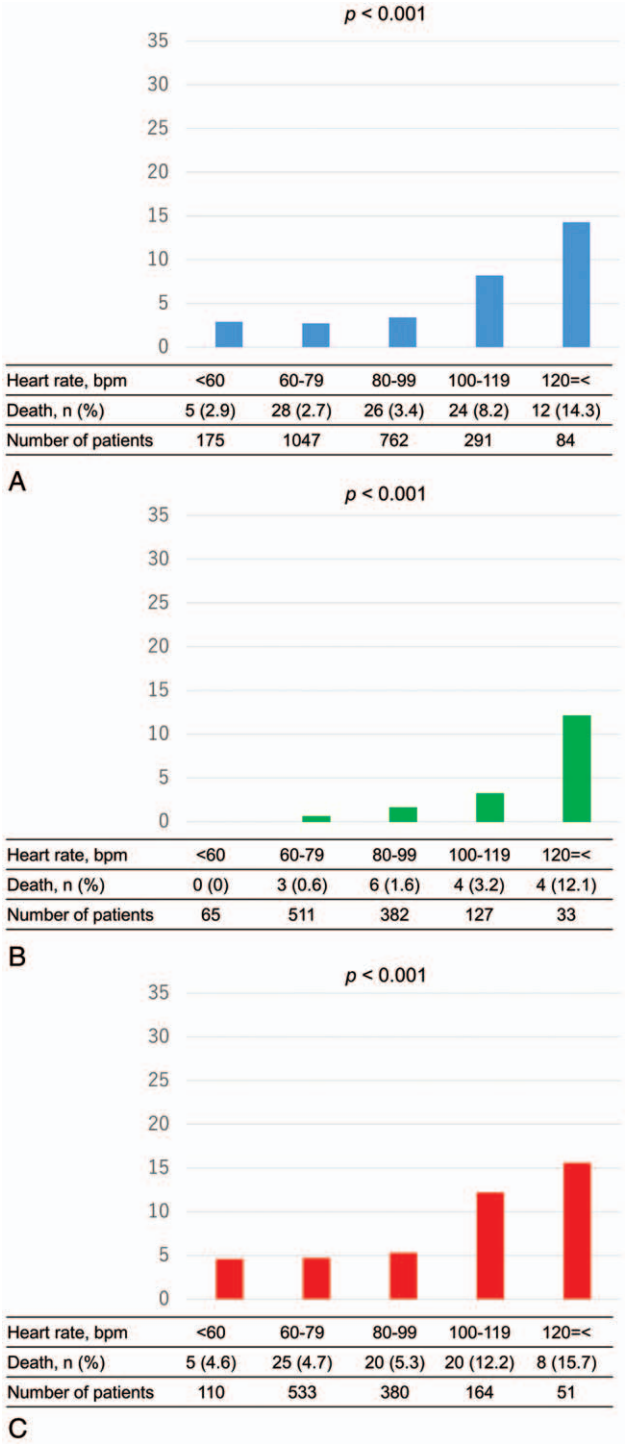

Figure 1. Heart rate on admission and in-hospital mortality in total cohort and according to age. (A) All patients; (B) patients younger than 70 years old; (C) patients equal to or older than 70 years old.

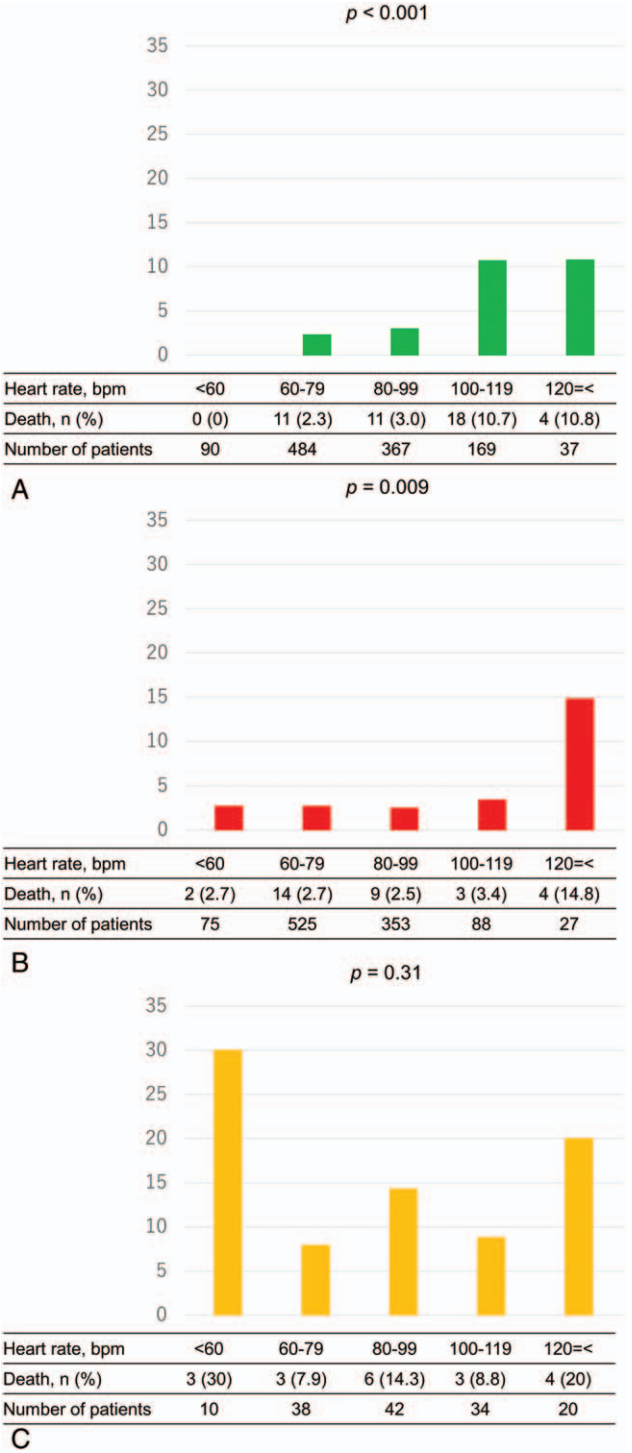

Figure 2. Heart rate on admission and in-hospital mortality according to ward. (A) Medical wards; (B) surgical wards; (C) intensive care unit.

1.12), stroke (HR, 1.05), all cancer types (hazard ratio, 1.09), and other diseases (hazard ratio, 1.25).[2] Long-term follow-up cohort from the Framingham Heart Study also reported the association between higher HR and cardiovascular events with hazard ratio of 1.15 for 11 bpm increment in the baseline HR during a median follow-up of 19 years.[11] The hazard ratio (1.32) for the same increment in HR was also reported for heart failure.[11] These observations were derived from epidemiological studies among the general population, but other reports also suggested the associations among inpatients similar to our reports.

The association between baseline HR and in-hospital mortality has been reported in patients with cardiovascular diseases. HR on

Table 3

Multivariable model for the effect of heart rate on in-hospital mortality.

	Medical ward (n = 1147)			Surgical ward (n = 1068)			Intensive care unit (n = 145)		
	Adjusted odds ratio	95% confidence interval	*P*-value	Adjusted odds ratio	95% confidence interval	*P*-value	Adjusted odds ratio	95% confidence interval	*P*-value
Model 1									
Heart rate (bpm)	1.03	1.01–1.04	< .001	1.02	1.00–1.04	.03	0.99	0.97–1.02	.50
Age (years)	1.06	1.03–1.10	< .001	1.04	1.01–1.08	.009	1.12	1.04–1.22	.01
Men	1.08	0.55–2.10	.80	2.44	1.09–5.48	.03	4.21	1.02–17.42	.05
Systolic blood pressure (mm Hg)	0.98	0.97–0.997	.02	1.01	0.995–1.02	.20	0.997	0.98–1.02	.70
Hemoglobin (g/dL)	0.90	0.78–1.04	.10	0.82	0.68–0.99	.04	0.74	0.51–1.04	.09
Total protein (g/dL)	0.66	0.45–0.97	.04	0.84	0.47–1.53	.60	0.30	0.11–0.69	.01
Creatinine (mg/dL)	1.12	0.92–1.30	.20	1.17	0.75–1.60	.40	1.05	0.60–1.70	.90
White blood cell (/μL)	1.00	0.999–1.00	.30	1.00	0.999–1.00	.20	1.00	0.999–1.00	.30
Model 2									
Heart rate ≥100 bpm	3.64	1.88–7.05	< .001	2.04	0.78–5.31	.10	0.52	0.14–1.95	.30
Age (year)	1.06	1.03–1.10	< .001	1.04	1.01–1.08	.01	1.13	1.05–1.24	.01
Men	1.10	0.56–2.15	.80	2.17	0.98–4.77	.06	4.38	1.04–18.43	.04
Systolic blood pressure (mm Hg)	0.98	0.97–0.997	.02	1.01	0.997–1.03	.10	0.997	0.98–1.02	.80
Hemoglobin (g/dL)	0.9	0.78–1.03	.10	0.84	0.69–1.01	.06	0.74	0.51–1.05	.10
Total protein (g/dL)	0.65	0.44–0.95	.03	0.68	0.39–1.20	.20	0.30	0.11–0.69	.01
Creatinine (mg/dL)	1.12	0.91–1.30	.20	1.18	0.76–1.60	.40	1.03	0.59–1.68	.90
White blood cell (/μL)	1.00	0.999–1.00	.30	1.00	0.999–1.00	.20	1.00	0.999–1.00	.30
Model 3									
Heart rate ≥120 bpm	2.56	0.80–8.19	.10	5.69	1.72–18.82	.004	1.37	0.28–6.66	.70
Age (year)	1.06	1.03–1.10	< .001	1.04	1.01–1.08	.01	1.11	1.04–1.21	.01
Men	1.02	0.53–1.99	.90	2.19	0.992–4.84	.05	3.80	0.92–15.7	.06
Systolic blood pressure (mm Hg)	0.98	0.97–0.995	.008	1.01	0.997–1.03	.10	0.998	0.98–1.02	.80
Hemoglobin (g/dL)	0.90	0.79–1.04	.20	0.83	0.69–1.00	.06	0.71	0.48–1.02	.08
Total protein (g/dL)	0.60	0.41–0.87	.009	0.71	0.40–1.26	.20	0.31	0.12–0.71	.01
Creatinine (mg/dL)	1.11	0.91–1.29	.20	1.17	0.74–1.59	.40	1.07	0.62–1.73	.80
White blood cell (/μL)	1.00	0.999–1.00	.20	1.00	0.999–1.00	.10	1.00	0.999–1.00	.30
Model 4									
Heart rate <60 bpm	–	–	–	0.81	0.18–3.66	.80	2.73	0.43–17.24	.30
Age (year)	1.07	1.03–1.10	< 0.001	1.04	1.01–1.08	.01	1.11	1.04–1.21	.01
Men	0.98	0.51–1.91	1.00	2.27	1.03–4.97	.04	3.76	0.92–15.41	.07
Systolic blood pressure (mm Hg)	0.98	0.97–0.99	.006	1.01	0.997–1.03	.10	0.998	0.98–1.02	.80
Hemoglobin (g/dL)	0.91	0.79–1.05	.20	0.84	0.70–1.02	.08	0.73	0.50–1.02	.07
Total protein (g/dL)	0.61	0.41–0.89	.01	0.66	0.37–1.18	.20	0.30	0.11–0.69	.01
Creatinine (mg/dL)	1.12	0.92–1.29	.20	1.17	0.75–1.59	.40	1.08	0.62–1.76	.80
White blood cell (/μL)	1.00	0.999–1.00	.20	1.00	0.999–1.00	.10	1.00	0.999–1.00	.30

admission was associated with in-hospital mortality with hazard ratio of 4.42 for 10 bpm increment in HR, in patients with acute ischemic stroke. The recalculated OR for 10 bpm increment in HR in the medical wards in our study was 1.33, and the effect was smaller than that reported in patients with acute ischemic stroke. The reason for this discrepancy is probably because our study enrolled all patients including relatively healthier ones and thus the effect of HR was diluted by such patients.[4] Not only HR on admission, but high HR 24–36 h after admission was also associated with in-hospital mortality in patients with heart failure.[12] Although we did not find any relationship between HR on admission and in-hospital mortality in patients in ICU, mortality was reported to decrease in such patients when HR was kept less than 100 bpm within the first admission day.[13] Thus, to the best of our knowledge, there has been no report to suggest the existence of a relationship between HR and in-hospital mortality among the general patients; and our study is the first to address this important clinical issue.

The association between HR and mortality was well documented, but the reasons for this association were not well clarified.[14] Several explanations were proposed such as low physical fitness, higher blood pressure, or reduced variability in HR, and diminished baroreceptor sensitivity in those with high HR.[1,2,14] The immune or endocrine systems are impaired by the dysregulation of the autonomic nervous system in patients with chronic diseases, and HR variability is the indicator for the autonomic nervous system.[15–18] However, these explanations could not fully account for the pathophysiology of higher mortality, especially, within the context of short-term effect, observed among inpatients.

Association between baseline HR and in-hospital mortality should shed light on the effective risk stratification of inpatient care, among patients with cardiovascular diseases and the general inpatients. Patients with such elevated HR and with no apparent reasons for the high HR should be closely investigated to determine the reasons, and be monitored to prevent the deterioration of underlying diseases. This strategy could be more effective in the general medical or surgical wards, due to the apparent trend of in-hospital mortality in our study. On the other hand, this approach might not be effective in ICU, because ICU patients are being closely monitored due to their serious conditions already. Another approach is the use of medications,

which weakens the sympathetic nervous tone and decreases the HR. Such medications could be used as supplementary treatment to avoid fatality, in addition to therapy, targeting the underlying diseases. The effectiveness of beta-blockers in non-cardiac surgery patients remains controversial,[19] however, supportive treatments in this direction, should be investigated.

Several limitations must be addressed in this study. First, there were a number of diseases with significantly varied severity, in this cohort; because we enrolled all admitted adult patients. Mortality was primarily associated with underlying diseases and their severity. Because it was unrealistic to adjust for all disease categories in the multivariate models, we adjusted for the surrogate markers of mortalities such as blood pressure or critical laboratory parameters. Second, the number of patients were relatively small, especially in the ICU; therefore, the relationship, other than the categories used, might not have been well scrutinized. In addition, there were no statistically significant associations with the ICU. Third, we utilized the HR on admission only. HR changes over time and the first measurement of HR on the admission day might not be a precise indicator. However, there were no distinct rules to determine which timing of HR measurement is best for use as an indicator; therefore, it was inevitable to use the first measurement to stratify the patients' risk. Finally, the JADE study only enrolled Japanese patients; and this analysis utilized the data from just one hospital. To generalize and validate our results, it is necessary to conduct similar study with enough sample size in several settings.

5. Conclusion

We confirmed that higher HR was associated with higher in-hospital mortality among patients with general diseases in the medical and surgical wards. Even with less severe condition or outside ICU, HR should be directed attention to and patients with high HR on admission should be taken additional therapy to reduce the further risk of deterioration. Our findings should be attested to by further studies in other settings, or studies using interventional designs.

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RESEARCH ARTICLE Open Access

Clinical characteristics of pyogenic spondylitis and psoas abscess at a tertiary care hospital: a retrospective cohort study

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Abstract

Background: Psoas abscess and pyogenic spondylitis are intractable diseases that require long-term treatment, but the clinical characteristics and causative organisms have not been fully investigated. Herein, we describe the clinical characteristics of these diseases and evaluate the factors associated with in-hospital mortality and the presence of gram-negative rods as causative microorganisms.

Methods: All patients diagnosed with pyogenic spondylitis or psoas abscesses at a tertiary hospital were included. We retrieved the clinical data (age, sex, outcome, length of hospital stay, disease, bacteria, medication, comorbidities, and treatment status), vital signs (blood pressure, heart rate, and body temperature), and laboratory test results (blood cell count, liver function, renal function, electrolytes, blood sugar, and C-reactive protein) of all patients. The outcomes were in-hospital deaths and positive cultures of gram-negative rods.

Results: We analyzed 126 patients consisting of 69 (55%) men with a population mean age of 72 years. Seventy-two patients had pyogenic spondylitis and 54 had psoas abscesses. Eleven patients (8.3%) died during admission. The causative bacteria were gram-positive cocci in 63 patients (50%) and gram-negative bacteria in 19 patients (15%). The multivariate logistic model showed that blood urea nitrogen (BUN) (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02–1.06) and cardiovascular diseases (OR 7.02, 95% CI 1.55–31.8) were associated with in-hospital mortality. Platelets less than 150,000/μL (OR 3.14, 95% CI 1.02–9.65) and higher aspartic aminotransferase (OR 1.02, 95% CI 1.00–1.03) were associated with gram-negative rods.

Conclusions: Patients with suspected psoas abscesses or pyogenic spondylitis having a high BUN level and a history of cardiovascular diseases have a higher risk of mortality.

Keywords: Pyogenic spondylitis, Psoas abscess, Mortality

Background

Pyogenic spondylitis and psoas abscesses are caused by *Staphylococcus aureus*, often in areas with a low prevalence of tuberculosis [1–3]. Patients often have underlying diseases such as malignancies, diabetes mellitus, chronic renal failure, and cirrhosis, as well as long-term corticosteroid use [4–8]. These diseases are diagnosed using a combination of imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) and specimen cultures; however, diagnosis may often be difficult if the patient has few symptoms.

While some studies have reported the underlying diseases associated with pyogenic spondylitis and psoas abscesses [4–8], few have discussed the risk factors for a poor prognosis. It is also important to decide whether to administer antibiotics targeting gram-negative rods because bacteria other than *Staphylococcus* should be considered in some circumstances. Because clinical characteristics and risk factors associated with mortality or bacterial strains have not been well investigated, we described the clinical characteristics of patients with pyogenic spondylitis and psoas abscesses and investigated the factors associated with in-hospital deaths and the presence

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of gram-negative rods at the time of diagnosis. In addition, we compared the differences in clinical characteristics and outcomes between pyogenic spondylitis and psoas abscess, if any.

Methods

Study design and patients

We conducted a historical cohort study of all patients diagnosed with pyogenic spondylitis or psoas abscesses from 2000 to 2014 at Shimane Prefectural Central Hospital, a tertiary care hospital in Japan. Inclusion criteria were (1) patients who were diagnosed with pyogenic spondylitis or psoas abscesses by the physician in charge, (2) confirmation of the clinical diagnosis by radiological images, and (3) no apparent other causes that may mimic pyogenic spondylitis or psoas abscesses. There were no exclusion criteria. The diagnosis of pyogenic spondylitis and psoas abscess was confirmed using either CT or MRI. Bacteria associated with lesions or blood cultures were identified. Surgical interventions, such as percutaneous drainage, surgical drainage, and laminectomy, were determined by the physician in charge. The antimicrobial treatment was determined by the physician in charge based on the culture results and sensitivity analyses. Until the culture results were available or if the causative species could not be determined, empirical treatments based on established guidelines were administered.

We retrieved clinical data, vital signs, and laboratory test results of the patients from the Integrated Intelligent Management System database of Shimane Prefectural Central Hospital between August 1998 and August 2014. The Institutional Review Board of Shimane Prefectural Central Hospital approved this study. Since all data were obtained as part of our routine daily practice, informed consent was waived by the institutional review board.

Measurements

Clinical data included age, sex, the primary complaint, days from admission to diagnosis of pyogenic spondylitis or psoas abscess, and comorbidities (diabetes, hypertension, hyperlipidemia, cardiac disease, cerebrovascular disease, neurological disease, liver disease, renal disease, malignancy, and surgical history).

We also collected data regarding patient vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, and body temperature) and laboratory test results (white blood cell count [WBC], hemoglobin, platelet cell count [Plt], C-reactive protein [CRP], aspartic aminotransferase [AST], alanine aminotransferase [ALT], blood sugar, serum albumin [Alb], total bilirubin, lactate dehydrogenase [LDH], blood urea nitrogen [BUN], creatinine [Cr], sodium, and potassium) at the time of diagnosis.

We also collected data regarding treatment modalities (intravenous antimicrobial use and surgical treatments), as well as in-hospital deaths and the length of time in the hospital.

Statistical analyses

Continuous variables are presented as the mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables as numbers and percentages. We compared continuous variables with the Student's t test or the Wilcoxon rank-sum test on the basis of the distributions. We compared categorical variables with the χ^2 test when appropriate; otherwise, we used Fisher's exact test. To explore the factors associated with in-hospital mortality and the presence of gram-negative rods, we constructed multivariate logistic regression models. We analyzed all patients to identify factors associated with in-hospital mortality but selected only culture-positive patients to investigate the factors associated with gram-negative rods.

Included continuous variables were unmodified; however, the units for WBCs and Plts were 100 and 10,000, respectively. For convenience, platelets were only analyzed if less than 150,000/μL. Potential variables were the measured clinical variables described above, and final models were determined after backward selection. Associations are expressed as odds ratio [OR] and 95% confidence intervals [CI]. All statistical analyses were performed using Stata12. All reported p values were two-tailed, and p values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 126 patients (72 with pyogenic spondylitis [57%] and 54 with psoas abscesses [43%]) (Table 1) were studied. Their mean age was 72 ± 11 years (range 37–95 years). The number of male patients was 69 (55%). Lumbago or back pain was more frequent in pyogenic spondylitis (49 [68%] vs. 23 [43%], $p = 0.004$), whereas shock was more frequent in psoas abscesses (9 [17%] vs. 2 [2.8%], $p = 0.009$) (Table 1).

All 126 patients received antibiotic treatment. One patient received only oral antibiotics. A total of 54 (43%) patients received invasive interventions, and they were more frequent in psoas abscesses (29 [54%] vs. 25 [35%], $p = 0.045$). The invasive interventions included 50 percutaneous drainage (40%), 4 laminectomy (3.2%), and 2 surgical drainage (1.6%). Two patients received multiple treatments, one patient received percutaneous drainage and laminectomy, another patient received percutaneous drainage and surgical drainage.

There were 11 in-hospital deaths (8.7%). Although there was one death (0.8%) within 14 days and 10 deaths (7.9%) 14 days after admission, these were not statistically significant ($p = 0.82$). When we compared the

Table 1 Patients characteristics

	All *n* = 126	Pyogenic spondylitis *n* = 72	Psoas abscess *n* = 54	*p* value
Variables	*n* (%) or mean ± SD or median [IQR]			
Male	69 (55)	38 (53)	31 (57)	0.61
Age, year	72 ± 11	74 ± 10	70 ± 11	0.07
Length of stay, days	60 [39–97]	60 [41–106]	58 [36–94]	0.06
In-hospital death	11 (8.7)	3 (4.1)	8 (15)	0.05
Invasive interventions	54 (43)	25 (35)	29 (54)	0.045
Percutaneous drainage	50 (40)	21 (29)	29 (54)	0.006
Operation	6 (4.8)	5 (6.9)	1 (1.9)	0.24
Laminectomy	4 (3.2)	4 (5.6)	0 (0.0)	0.13
Surgical drainage	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Days after admission to diagnosis, day	0 [0–11]	0 [0–5]	2 [0–20]	0.0167
Days after admission to diagnosis, day ≥ 14 days	28 (22)	10 (14)	18 (33)	0.016
Antibiotics use, days	28 [17–42]	28 [18–42]	30 [15–42]	0.79
Over 6 weeks	38 (30)	23 (32)	15 (28)	0.70
Symptoms				
Lumbago or back pain	72 (57)	49 (68)	23 (43)	0.004
Fever	51 (40)	32 (44)	19 (35)	0.30
Shock	11 (8.7)	2 (2.8)	9 (17)	0.009
Classification				
Type A*	–	33 (46)	–	–
Type B*	–	18 (25)	–	–
Type C*	–	21 (29)	–	–
Multiple abscesses	–	–	30 (56)	–
Co-morbidities	102 (81)	56 (78)	46 (85)	0.36
Hospitalized for comorbidity	57 (45)	27 (38)	30 (56)	0.044
Hospitalized for other infections	17 (13)	6 (8.3)	11 (20)	0.07
Bacterial detection	84 (67)	45 (63)	39 (72)	0.34
Gram-positive cocci	63 (50)	35 (49)	28 (52)	0.72
Gram-negative rods	19 (15)	8 (11)	11 (20)	0.15
Mycobacterium	2 (1.6)	2 (2.8)	0 (0.0)	0.51
Vital signs				
SBP, mmHg	132 ± 31	137 ± 28	127 ± 35	0.10
DBP, mmHg	75 ± 18	78 ± 15	70 ± 20	0.0151
Body temperature, °C	37.3 ± 1.1	37.4 ± 1.1	37.2 ± 1.1	0.27
Heart rate, /min	89 ± 19	88 ± 19	89 ± 19	0.30
Laboratory data				
WBC, $\times 10^2$/μL	113 ± 51	106 ± 41	122 ± 61	0.07
Hb, g/dL	11.3 ± 2.2	11.7 ± 1.8	10.7 ± 2.5	0.0116
Plt, $\times 10^4$/μL	22.8 ± 11.8	24.8 ± 11.5	20.0 ± 11.9	0.0234
CRP, mg/dL	11.1 ± 9.8	9.4 ± 8.4	13.3 ± 11.0	0.0233
T-bil, mg/dL	0.8 ± 0.5	0.8 ± 0.4	0.8 ± 0.5	0.75
Alb, g/dL	3.3 ± 0.6	3.4 ± 0.6	3.1 ± 0.7	0.0045
AST, IU/L	33 ± 30	31 ± 28	37 ± 31	0.26

Table 1 Patients characteristics *(Continued)*

	All *n* = 126	Pyogenic spondylitis *n* = 72	Psoas abscess *n* = 54	*p* value
ALT, IU/L	26 ± 23	26 ± 25	24 ± 19	0.73
LDH, IU/L	261 ± 123	239 ± 88	290 ± 153	0.0233
Blood sugar, mg/dL	152 ± 71	141 ± 66	165 ± 76	0.06
BUN, mg/dL	25.6 ± 22.8	20.9 ± 10.6	32.0 ± 32.0	0.0069
Cr, mg/dL	1.3 ± 1.7	1.0 ± 0.8	1.7 ± 2.5	0.0178
Na, mmol/L	137.0 ± 5.0	137.2 ± 5.1	136.7 ± 4.8	0.57
K, mmol/L	4.0 ± 0.6	4.0 ± 0.5	3.9 ± 0.7	0.42

*Classification by Pola et al. [17]

number of deaths before, and 60 days after admission, there were 6 deaths (4.8%) and 5 deaths (4.0%), respectively.

The number of patients who had comorbidities was 102 (81%), including 36 (29%) with hypertension, 32 (25%) with a surgical history, 21 (17%) with malignancies, 19 (15%) with diabetes, 15 (12%) with neurological diseases, 18 (14%) with cardiac disease, and 15 (12%) with cerebrovascular disease (Table 2).

Laboratory testing and physical examinations indicated that CRP (13.3 ± 11.0 vs. 9.4 ± 8.4 mg/dL, $p = 0.02$), LDH (290 ± 153 vs. 239 ± 88 IU/L, $p = 0.02$), BUN (32.0 ± 32.0 vs. 20.9 ± 10.6 mg/dL, $p = 0.007$), and Cr (1.7 ± 2.5 vs. 1.0 ± 0.8 mg/dL, $p = 0.02$) were higher in psoas abscess cases (Table 1).

Hospital courses

The median time from admission to diagnosis was 0 days (IQR 0–11, minimum 0 and maximum 185). In many cases, hospitalization occurred after the diagnosis of pyogenic spondylitis and psoas abscess (Table 1). The number of patients diagnosed with these diseases ≥ 14 days after hospitalization was 28 (22%) (median 31 days; IQR 21–50, minimum 14 and maximum 185). These patients developed pyogenic spondylitis or psoas abscesses during the course of hospitalization. There were 57 patients who were admitted for other comorbidities: medical department (40 patients) and surgical department (17 patients). Hospitalization for other infections were 17 patients. Comorbidities between pyogenic spondylitis and psoas abscess patients were generally similar (Table 2). Pyogenic spondylitis was diagnosed more rapidly than psoas abscesses (14% in ≥ 14 days vs. 33%, $p = 0.016$). The duration of antibiotics use was a median of 28 days (IQR 17–42, minimum 0 and maximum 206). Thirty-eight patients (30%) received intravenous antibiotics for 6 weeks. There was no statistical difference in the long-term use of antibiotics among patients ($p = 0.70$).

The median length of hospitalization was 60 days (IQR 39–97, minimum 4 and maximum 429). Eleven (8.7%) patients died during the hospitalization period.

Factors associated with in-hospital deaths included a lower SBP (110 ± 35 vs. 134 ± 30 mmHg, $p = 0.02$), a lower DBP (62 ± 19 vs. 76 ± 17 mmHg, $p = 0.03$), lower Alb (2.9 ± 0.8 vs. 3.3 ± 0.6 mg/dL, $p = 0.02$), higher AST (40 ± 19 vs. 33 ± 31 IU/L, $p = 0.02$), higher ALT (29 ± 11 vs. 25 ± 23 IU/L, $p = 0.04$), higher LDH (327 ± 114 vs. 254 ± 122 IU/L, $p = 0.01$), higher BUN (53.5 ± 45.3 vs. 22.9 ± 17.5 mg/dL, $p = 0.02$), and higher Cr (1.7 ± 0.9 vs. 1.3 ± 1.8 mg/dL, $p = 0.005$) (Table 3). The multivariate logistic model showed that BUN (OR 1.04, 95% CI 1.02–1.06) and cardiovascular disease (OR 7.02, 95% CI 1.55–31.8) were associated with in-hospital mortalities (Table 4).

Microbiological examinations

Causal microorganisms were identified in 85 patients (67%), including gram-positive bacteria in 63 patients (50%), gram-negative rods in 19 patients (15%), and others or undetermined (Table 5).

Factors associated with gram-negative rods included lower Plts (15.8 ± 9.6 vs. 22.9 ± 12.3 × 10,000/μL, $p = 0.0134$; Plt < 1.5×10^4/μL, 11 [58%] vs. 20 [30%], $p = 0.034$) and higher ASTs (57 ± 57 vs. 32 ± 23 IU/L, $p = 0.0236$) (Table 6). The multivariate logistic model showed that platelets less than 150,000/μL (OR 3.14, 95% CI 1.02–9.65) and higher aspartic aminotransferase (OR 1.02, 95% CI 1.00–1.03) were associated with gram-negative rods (Table 7).

Discussion

We showed the epidemiology of pyogenic spondylitis and psoas abscesses, as well as the factors associated with in-hospital mortality and the presence of gram-negative rods in patients' cultures at a single center. The factors associated with mortality were an elevated BUN and a history of cardiovascular disease. The factors associated with a positive culture of gram-negative rods included higher AST and lower Plt laboratory results.

Previous studies have reported that the predisposing factors for bacterial spondylitis or psoas abscesses were diabetes mellitus, malnutrition, substance abuse, human immunodeficiency virus infection, malignancy, long-term

Table 2 Co-morbidities of patients and status at hospitalization

	All	Pyogenic spondylitis	Psoas abscess	*p* value
	n = 126	*n* = 72	*n* = 54	
Variables	*n* (%)			
Co-morbidities	102 (81)	56 (78)	46 (85)	0.36
Diabetes	19 (15)	10 (14)	9 (17)	0.80
Hypertension	36 (29)	23 (31)	13 (24)	0.43
Hyperlipidemia	7 (5.6)	5 (6.9)	2 (3.7)	0.70
Cardiac diseases	18 (14)	8 (11)	10 (18)	0.31
Cerebrovascular disease	15 (12)	6 (8.3)	9 (17)	0.17
Neurological disease	15 (12)	8 (11)	7 (13)	0.79
Dementia	4 (3.2)	4 (5.6)	0 (0.0)	0.13
Alcoholism	4 (3.2)	1 (1.4)	3 (5.6)	0.31
Neurosis	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Schizophrenia	2 (1.6)	0 (0.0)	2 (3.7)	0.18
Mental retardation	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Depression	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Epilepsy	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Parkinson's disease	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Pulmonary disease	7 (5.6)	3 (4.2)	4 (7.4)	0.46
Liver disease	7 (5.6)	4 (5.6)	3 (5.6)	1.00
Renal disease	8 (6.3)	3 (4.2)	5 (9.3)	0.29
Malignancy	21 (17)	9 (13)	12 (22)	0.16
Operation	32 (25)	17 (24)	15 (28)	0.68
Others	30 (24)	17 (24)	13 (24)	1.00
Osteoporosis	5 (4.0)	4 (5.6)	1 (1.9)	0.39
Pancreatitis	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Thyroid disease	3 (2.4)	1 (1.4)	2 (3.7)	0.58
Inguinal hernia	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Malignant syndrome	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Hypoadrenalism	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Gastrointestinal ulcer	4 (3.2)	2 (2.8)	2 (3.7)	1.00
Glaucoma	3 (2.4)	2 (2.8)	1 (1.9)	1.00
Discitis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Cholecystitis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Pemphigoid	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Spinal stenosis	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Rheumatoid arthritis	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Reflux esophagitis	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Ureteral stent placement	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Common bile duct stone	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Status at hospitalization				
Hospitalized for comorbidity	57 (45)	27 (38)	30 (56)	0.044
Medical department*	40 (32)	19 (26)	21 (39)	0.18
Surgical department**	17 (13)	8 (11)	9 (17)	0.43
Hospitalized for other infections	17 (13)	6 (8)	11 (20)	0.07
Urinary tract infection	7 (5.6)	1 (1.4)	6 (11)	0.042
Sepsis	4 (3.2)	2 (2.8)	2 (3.7)	1.00
Pneumonia	2 (1.6)	0 (0.0)	2 (3.7)	0.19
Cholangitis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Liver abscess	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Pulmonary tuberculosis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Infectious arthritis	1 (0.8)	1 (1.4)	0 (0.0)	1.00

*Comorbidities treated at medical department: blood stream infection 1, cardio-pulmonary arrest 1, cerebral infarction 1, cholangitis 1, congestive heart failure 2, diabetes 1, drug eruption 1, fever of unknown origin 2, gastric ulcer 1, leukemia 1, liver abscess 1, lumbago 2, malignant lymphoma 1, myeloma 2, neuralgia 1, Paget disease 1, pneumonia 3, pulmonary tuberculosis 1, renal failure 3, schizophrenia 1, sepsis 3, skin damage 1, transient ischemic attack 1, urinary tract infection 7

**Comorbidities treated at the surgical department: abdominal trauma 1, burn injury 1, colon cancer 2, fall trauma 1, gastric cancer 2, hip pain 1, ileus 3, infectious arthritis 1, internal iliac artery aneurysm 1, knee pain 1, normal pressure hydrocephalus 1, subarachnoid hemorrhage 2

steroid use, chronic renal failure, liver cirrhosis, and sepsis [4–8]. Some reports have showed that CRP or WBCs were associated with recovery [9, 10], although our study showed that CRP was also associated with gram-negative rods.

Staphylococcus was found in 50–88% of patients in prior studies [3, 11, 12], and our study showed a similar percentage (60%). Among gram-negative bacteria identified in our study, *Escherichia coli* was found in 5.6%, which was slightly higher than the 2.8% reported in previous studies [11, 13]. *Mycobacterium tuberculosis* is a frequent cause of psoas abscesses in regions where tuberculosis is common (e.g., southern China) [1, 2]; however, the proportion of patients with tuberculosis among pyogenic spondylitis cases decreased to about 24% in these areas [3]. Tuberculosis is common in Japan, yet there was only one case of tuberculosis in our study, which may reflect an early diagnosis before progression to severe tuberculosis or before the incidence of tuberculosis decreased in Japan [14].

In previous studies, delay of treatment, old age, sepsis, and *E. coli* infection were reported as mortality risk factors [11, 15]. There were no differences in mortality between patients with and without gram-negative rods and between elderly and younger patients in our study. We assumed that all patients were promptly treated after the diagnosis. If the treatment was delayed, this factor might be associated with mortality. A previous report revealed an association between endocarditis and pyogenic spondylitis [16]; however, there were no cases of endocarditis

Table 3 Factors associated with in-hospital mortality

	Death ($n = 11$)	Alive ($n = 115$)	p value
Variables	n (%) or mean ± SD or median [IQR]		
Male	7 (64)	62 (54)	0.75
Age, year	73 ± 10	72 ± 11	0.80
Length of stay, days	57 [34–86]	60 [39–98]	0.68
Diseases			
Psoas abscess	8 (73)	46 (40)	0.038
Invasive interventions	6 (55)	48 (42)	0.31
Percutaneous drainage	6 (55)	44 (38)	0.23
Operation	1 (9.1)	5 (4.3)	0.43
Laminectomy	0 (0.0)	4 (3.5)	1.00
Surgical drainage	1 (9.1)	1 (0.9)	0.17
Co-morbidities	9 (82)	93 (81)	1.00
Diabetes	1 (9.1)	18 (16)	1.00
Hypertension	4 (36)	32 (28)	0.51
Hyperlipidemia	1 (9.1)	6 (5.2)	0.48
Cardiac diseases	4 (36)	14 (12)	0.05
Cerebrovascular disease	1 (9.1)	14 (12)	1.00
Neurological disease	2 (18)	13 (11)	0.62
Pulmonary diseases	0 (0.0)	7 (6.1)	1.00
Liver disease	0 (0.0)	7 (6.1)	1.00
Renal disease	1 (9.1)	7 (6.1)	0.53
Maligancy	2 (18)	19 (17)	1.00
Operation	1 (9.1)	31 (27)	0.29
Others	2 (18)	28 (24)	1.00
Bacteria			
Gram-positive cocci	7 (64)	56 (49)	0.53
Gram-negative rods	0 (0.0)	19 (17)	0.21
Unknown	3 (27)	38 (33)	1.00
Vital signs			
SBP, mmHg	110 ± 35	134 ± 30	0.0196
DBP, mmHg	62 ± 19	76 ± 17	0.0310
Body temperature, ℃	36.9 ± 1.1	37.4 ± 1.1	0.12
Heart rate, /min	93 ± 13	89 ± 19	0.33
Labo data			
WBC, $\times 10^2/\mu L$	115 ± 56	113 ± 51	0.88
Hb, g/dL	10.2 ± 2.8	11.4 ± 2.1	0.07
Plt, $\times 10^4/\mu L$	20.4 ± 18.8	23.0 ± 11.0	0.17
CRP, mg/dL	17.8 ± 12.2	10.4 ± 9.3	0.06
T-bil, mg/dL	1.1 ± 0.7	0.8 ± 0.5	0.11
Alb, g/dL	2.9 ± 0.8	3.3 ± 0.6	0.0220
AST, IU/L	40 ± 19	33 ± 31	0.0245
ALT, IU/L	29 ± 11	25 ± 23	0.0376
LDH, IU/L	327 ± 114	254 ± 122	0.0134
Blood sugar, mg/dL	156 ± 42	151 ± 73	0.26
BUN, mg/dL	53.5 ± 45.3	22.9 ± 17.5	0.0197
Cr, mg/dL	1.7 ± 0.9	1.3 ± 1.8	0.0053
Na, mmol/L	134.6 ± 10.0	137.3 ± 4.2	0.86
K, mmol/L	4.0 ± 0.5	4.0 ± 0.6	0.68

in our study. Psoas abscesses are generally reported to have higher morbidity and mortality. One study reported that the mortality rate of primary and secondary abscesses was 2.4% and 19%, respectively, and may approach 100% in untreated cases [1]. Our study had a similar mortality rate (15%), including primary and secondary psoas abscesses, although we could not differentiate them.

When the causative microorganism could not be identified, clinicians must administer an empirical treatment. The empirical treatment policy of the institution was following: (1) vancomycin ± cefazolin in general and (2) meropenem or similar antibiotics when gram-negative bacteria was likely in the setting of previous organism or infections of other sites. Those patients with an elevated BUN or cardiovascular comorbidity were at a higher risk of mortality. Therefore, such patients should receive broad-spectrum antibiotics as well as aggressive drainage and other intensive supportive therapies. The factors associated with gram-negative rods should also be a guide for empirical treatments. The prevalence of gram-negative rods was low, but those with lower platelet counts or elevated ASTs may be at a higher risk of gram-negative rod infections. These patients should receive antibiotics that target gram-negative rods as an initial therapy.

A new classification of pyogenic spondylodiscitis has been reported [17]. The new classification was based on clinical symptoms and radiological findings and associated with recurrence rate and mortality. Since our study had a retrospective design, we could not obtain the information necessary to reclassify our patients and our risk factors should be re-evaluated in future studies incorporating the new classification.

In this study, BUN and a history of cardiovascular disease were associated with in-hospital deaths. Low Plts

Table 4 Multivariate logistic model for death

	Odds ratio	95% confidence interval
BUN, mg/dL	1.04	1.02–1.06
Cardiovascular diseases	7.02	1.55–31.8

Table 5 Causative bacteria

Bacteria	All ($n = 126$)
	n (%)
Identified	85 (67)
Gram-positive cocci	63 (50)
Staphylococci	51 (40)
MSSA	28 (22)
MRSA	12 (9.5)
CNS	11 (8.7)
Enterococci	3 (2.4)
Streptococci	8 (6.3)
Gram-negative rods	19 (15)
Escherichia coli	7 (5.6)
Klebsiella	3 (2.4)
Prevotella	3 (2.4)
Proteus mirabilis	2 (1.6)
Citrobacter koseri	1 (0.8)
Bacteroides	4 (3.2)
Mycobacterium	2 (1.6)
Tuberculosis	1 (0.8)
Nontuberculosis	1 (0.8)
Other bacteria	2 (1.6)
Unknown	41 (33)

MSSA methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*; *CNS* coagulase-negative *Staphylococcus*; *Enterocucci Enterococcus faecium* 1, *Enterococcus faecalis* 2; *Streptcocci* alpha-hemolytic *Streptococcus* 1, *Streptococcus agalactiae* (type B group) 3, *Streptococcus intermedius* 1, *Streptococcus sanguinis* 1, *Streptococcus pneumoniae* 2; *Klebsiella Klebsiella pneumoniae* 2, *Klebsiella oxytoca* 1; *Prevotella Prevotella oris* 1, *Prevotella melaninogenica* 1, unidentified 1; *Bacteroides Bacteroides fragilis* 3, *Bacteroides thetaiotaomicron* 1; other bacteria: Corynebacterium sp. 1

(< 150,000/μL) and high ASTs were associated with gram-negative rods after performing multivariate analyses. For the group with a higher risk of in-hospital mortality, aggressive drainage should be considered in addition to intensive antimicrobial combination therapy. Although the frequency of gram-negative rods was low, the use of wide-spectrum antibiotics should be considered for the group with a high probability of having gram-negative rods based on these risk factors.

This study has some limitations. First, since our study had a retrospective design, we were unable to measure all factors. Second, we investigated a total of 126 patients, and this sample size is insufficient for robust multivariate analyses. We also could not break down into small homogenous group due to small sample size. However, our primary purpose was to describe the general picture of patients who were diagnosed in daily practice. Third, since we focused solely on patients with pyogenic spondylitis or psoas abscesses and did not analyze all patients who presented with fever and lower

Table 6 Factors associated with gram-negative rods

	GNR ($n = 19$)	Others ($n = 66$)	*p* value
Variables	*n* (%) or mean ± SD or median [IQR]		
Male	13 (68)	33 (50)	0.20
Age, year	71 ± 9	72 ± 12	0.41
Psoas abscess	11 (58)	29 (44)	0.31
In hospital death	0 (0.0)	8 (12)	0.19
Invasive intervention	11 (58)	35 (53)	0.80
Percutaneous drainage	10 (53)	33 (50)	1.00
Operation	2 (11)	3 (4.5)	0.31
Laminectomy	2 (11)	2 (3.0)	0.22
Surgical drainage	0 (0.0)	1 (1.5)	1.00
Co-morbidities	15 (79)	52 (79)	1.00
Diabetes	3 (16)	9 (14)	0.73
Hypertension	5 (26)	12 (18)	0.52
Hyperlipidemia	2 (11)	3 (4.5)	0.31
Cardiac diseases	4 (21)	9 (14)	0.48
Cerebrovascular disease	5 (26)	8 (12)	0.15
Neurological disease	3 (16)	9 (14)	0.73
Pulmonary disease	0 (0.0)	4 (6.1)	0.57
Liver disease	1 (5.3)	4 (6.1)	1.00
Renal disease	0 (0.0)	4 (6.1)	0.57
Malignancy	1 (5.3)	12 (18)	0.28
Operation	6 (32)	17 (26)	0.77
Others	6 (32)	12 (18)	0.22
Vital signs			
SBP, mmHg	124 ± 27	131 ± 32	0.40
DBP, mmHg	75 ± 18	72 ± 16	0.58
Body tempereture, ℃	37.7 ± 1.3	37.4 ± 1.1	0.59
Heart rate, /min	91 ± 17	91 ± 20	0.83
Laboratory			
WBC, $\times 10^2/\mu L$	138 ± 69	120 ± 49	0.42
Hb, g/dL	11.8 ± 2.0	11.1 ± 2.1	0.16
Plt, $\times 10^4/\mu L$	15.8 ± 9.6	22.9 ± 12.3	0.0134
Plt < $1.5 \times 10^4/\mu L$	11 (58)	20 (30)	0.034
CRP, mg/dL	17.1 ± 9.5	12.6 ± 9.8	0.07
T-bil, mg/dL	1.0 ± 0.6	0.8 ± 0.4	0.18
Alb, g/dL	3.2 ± 0.6	3.2 ± 0.6	0.70
AST, IU/L	57 ± 57	32 ± 23	0.0236
ALT, IU/L	31 ± 23	27 ± 25	0.22
LDH, IU/L	292 ± 126	264 ± 108	0.37
Blood sugar, mg/dL	147 ± 83	157 ± 73	0.23
BUN, mg/dL	26.9 ± 14.9	25.2 ± 20.6	0.19
Cr, mg/dL	1.3 ± 1.2	1.3 ± 1.7	0.24
Na, mmol/L	136.9 ± 3.7	137.0 ± 4.7	0.86
K, mmol/L	4.0 ± 0.6	3.8 ± 0.5	0.66

GNR gram-negative rods

Table 7 Multivariate logistic model for gram-negative rods

	Odds ratio	95% confidence interval
Plt < 1.5×10^4/μL	3.14	1.02–9.65
AST, IU/L	1.02	1.00–1.03

back pain, there is a possibility of missed cases. However, considering that our institution is a teaching hospital with easy access to imaging technology, we believe that the number of missed cases is low. Fourth, bacteria were not identified in all cases. Therefore, factors related to gram-negative bacteria should be interpreted with caution. Fifth, there were no established protocols for antibiotics and surgical treatments because this study was a retrospective observational study. The effect of treatment modalities on mortality should be considered. Sixth, we could not classify the psoas abscesses as primary and secondary. If we had been able to differentiate between primary and secondary psoas abscesses, we might have indicated another risk factor for mortality as reported in the previous study. Seventh, there were many variables we compared between pyogenic spondylitis and psoas abscess. The issue of multiple comparisons and the resultant significance should be considered to interpret the results.

Conclusion

In clinical practice, pyogenic spondylitis and psoas abscesses are likely to be severe in the presence of low blood pressure, malnutrition, liver failure, and kidney dysfunction. When deciding which antibiotic to use, the possibility of gram-negative bacteria should be considered in patients with low Plts and liver dysfunction.

Abbreviations

Alb: Albumin; ALT: Alanine aminotransferase; AST: Aspartic aminotransferase; BUN: Blood urea nitrogen; CI: Confidence interval; CNS: Coagulase-negative Staphylococcus; Cr: Creatinine; CRP: C-reactive protein; CT: Computed tomography; DBP: Diastolic blood pressure; GNR: Gram-negative rods; IQR: Interquartile range; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-sensitive Staphylococcus aureus; OR: Odds ratio; Plt: Platelet cell count; SBP: Systolic blood pressure; SD: Standard deviation; WBC: White blood cell count

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author by request.

Authors' contributions

TN and TM designed the study and analyzed the datasets. TN, KoK, YY, JM, and KiK performed the data collection. TN and TM wrote and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Review Board of Shimane Prefectural Central Hospital (R14–060). Since all data were obtained as part of our routine daily practice, informed consent was waived by the institutional review board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Publisher's Note

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Effect of baseline renal and hepatic function on the incidence of adverse drug events: the Japan Adverse Drug Events study

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Abstract

Background: The impact of renal and hepatic dysfunction on the morbidity and mortality of inpatients with adverse drug events (ADEs) is uncertain in daily clinical practice. The objective of this study was to investigate the effect of renal and hepatic function on ADEs and inpatients' morbidity and mortality.

Methods: The Japan Adverse Drug Events (JADE) study was a prospective cohort study carried out at three tertiary-care teaching hospitals in Japan. Participants were consecutive inpatients (n = 3459) aged 15 years or older. We evaluated the effect of renal and hepatic function on the occurrence of ADEs, and assessed how they affected length of hospital stay (LOS) and in-hospital mortality. We used the estimated glomerular filtration rate to quantify renal function and categorized patients into three groups (normal, ≥60 mL/min/1.73 mm; moderate, ≥30 and <60 mL/min/1.73 mm; severe, <30 mL/min/1.73 mm). We defined patients as having hepatic dysfunction when at least one data point (total bilirubin, aspartate aminotransferase, alanine aminotransferase, or gamma glutamyltransferase) was beyond a cutoff value.

Results: We analyzed the laboratory data of 2508 patients. There was a significant difference in the occurrence of ADEs among the three GFR categories (normal, 20%; moderate, 26%; severe, 22%; p = 0.02). More ADEs occurred in patients with hepatic dysfunction (25% vs. 20%, p = 0.01). LOS was significantly longer in those with ADEs stratified either by renal or by hepatic dysfunction (p < 0.0001). ADEs were independently associated with in-hospital mortality, adjusting for renal and hepatic function (p < 0.0001).

Conclusions: Inpatients' organ dysfunction increased ADEs, and ADEs were associated with both LOS and in-hospital mortality independently, irrespective of renal and hepatic function.

Keywords: adverse drug events; hepatic function; JADE study; patient safety; renal function.

Introduction

Adverse drug events (ADEs) are injuries from medication usage [1, 2] and are a cause of morbidity, mortality, and hospitalization [1, 3]. Many inpatients with acute or chronic diseases need to take multiple medications for treatment. Because all medications pass through the processes of absorption, distribution, metabolism, and excretion (ADME), declines in ADME functions of organs with aging, injury, and disease influence the safety of medications [4–6]. In daily clinical practice, multi-medication therapies are used for patients with comorbidities or complications. However, we know little about how many ADEs occur in such patients in daily clinical practice, including patients with renal or hepatic dysfunction, except what we learn from clinical trials. Furthermore, the influence of ADEs on in-hospital mortality or on the length of hospital stay (LOS) of patients with organ dysfunction has not been reported.

In our previous Japan Adverse Drug Events (JADE) study, we evaluated the incidence of ADEs among 3459 hospitalized patients and found that 726 patients had 1010 ADEs during hospitalization, and 6.5% of these ADEs were life-threatening [7]. We are interested in how renal and hepatic dysfunction affects the morbidity and mortality of patients with ADEs in daily clinical practice. Therefore, we investigated how inpatients' renal and hepatic function was related to the occurrence of ADEs. We also investigated the influence of ADEs on in-hospital mortality and on LOS, taking renal and hepatic dysfunction into account.

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Materials and methods

Study design and patient population

The JADE study was a prospective cohort study of 3459 patients aged 15 years or older who were admitted to three tertiary-care hospitals in Japan from January to June 2004. These patients were admitted to 15 medical and surgical wards and three intensive care units in these hospitals [7]. Patients were followed until transfer, discharge, or death.

Ethics approval and consent to participants

The study protocol complied with the Declaration of Helsinki and the guidelines for epidemiological studies issued by the Ministry of Health, Labour, and Welfare in Japan. The institutional review boards of the three participating hospitals (St. Luke's International Hospital, Rakuwakai Otowa Hospital, and Aso Iizuka Hospital) and the Ethics Committee of the Kyoto University Graduate School of Medicine approved the study (E-15). Informed consent was waived because all data were collected in daily clinical practice. This waiver was approved by the institutional review boards.

Data collection and review process

The data collection method was based on that described in a previous report [2]. An ADE was defined as any unintended injury related to medication usage, regardless of existing errors [2, 8]. In the first step, trained research assistants reviewed all practice data (such as medical charts, laboratories, prescription data, incident reports, and prescription queries). They also collected the patient characteristics. Comorbidity in the patients was quantified using the Charlson Comorbidity Index [9].

In the second step, two independent physician reviewers evaluated and classified all data collected by the research assistants as either ADEs or exclusion.

Interrater reliabilities were assessed using κ statistics. The κ scores regarding presence of an ADE between reviewers were 0.75 (ADE vs. potential ADE or exclude) and 0.77 (exclude vs. ADE or potential ADE). The κ for preventability was 0.86 (preventable vs. nonpreventable), whereas κ scores for severity were 0.31 (life-threatening vs. serious or significant) and 0.64 (significant vs. serious or life-threatening) [1].

Renal and hepatic dysfunction

Laboratory data were collected on admission. We calculated the estimated glomerular filtration rate (eGFR) from serum creatinine on admission and divided the patients into the following three categories according to the Japanese CKD guideline [10]. We considered those with eGFR ≥60 mL/min/1.73 mm as having normal renal function, those with ≥30 and <60 mL/min/1.73 mm as having moderate dysfunction, and those with <30 mL/min/1.73 mm as having severe dysfunction.

We used total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyltransferase (GGTP) as measurements of hepatic function. We defined hepatic dysfunction as having at least one of the four laboratory data points of the hepatic function data beyond a cutoff value. Cutoff values were set from the classification criteria for the seriousness of adverse drug reactions to medications, developed by the Ministry of Health and Welfare in Japan [11]: total bilirubin ≥3.0 mg/dL, AST ≥100 IU/L, ALT ≥100 IU/L, GGTP ≥105 IU/L (male), and GGTP ≥45 IU/L (female).

Statistical analyses

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), and categorical variables are shown as numbers and percentages. Relationships between patient's demographic data and ADEs were assessed using the Wilcoxon rank-sum test when the data were continuous and the χ^2 test when the demographic data were categorical. We compared the occurrence of ADEs between patients with and without renal dysfunction, and patients with and without hepatic dysfunction. We compared the occurrence of ADEs between patients with less than five medications on admission and those with five or more medications on admission, and counterpart stratified the test by renal and hepatic dysfunction. We divided the number of medications used into two categories (<5 and ≥5) based on our previous report from the JADE study [7].

We compared LOS and in-hospital mortality between those with ADEs and those without ADEs, stratified by renal or hepatic dysfunction. We also conducted sensitivity analyses excluding the patients who died within 2 days after admission because such patients showed renal or hepatic dysfunction on admission and their abnormal laboratory data and poor prognosis were not associated with ADEs or longer LOS. We finally developed a logistic regression model to assess the effect of renal and hepatic dysfunction on in-hospital mortality, adjusting for age, presence of ADEs, and the number of medications used on admission in the sensitivity analysis cohort. Two-tailed p-values <0.05 were considered statistically significant.

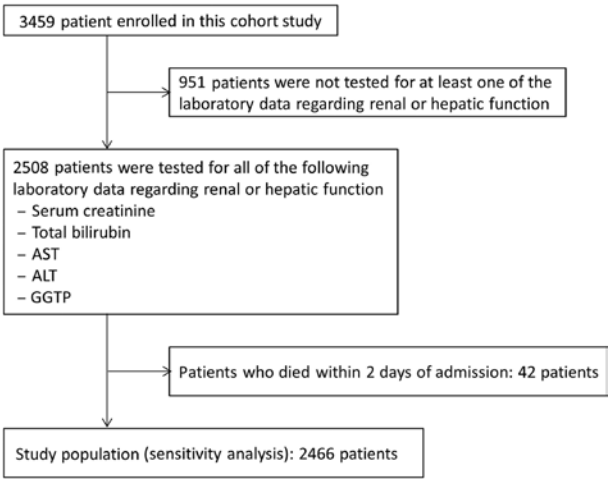

Figure 1: Flowchart of patients.

Table 1: Characteristics and demographics of patients on admission.

Characteristics	Total (n = 2508)	With ADEs (n = 546)	Without ADEs (n = 1962)	p-Value
Age, years, mean ± SD	66.1 ± 16.9	70.3 ± 14.1	64.9 ± 17.4	<0.0001
Men, n (%)	1441 (58)	309 (57)	1132 (58)	0.6
Body mass index, mean ± SD	22.3 ± 4.0	21.4 ± 4.0	22.5 ± 3.9	<0.0001
Wards, n (%)				0.001
Surgical	1132 (45)	261 (48)	871 (44)	
Medical	1022 (41)	233 (43)	789 (40)	
ICUs	354 (14)	52 (10)	302 (15)	
Charlson index score, median (25%–75%)	3 (1–5)	3 (1–5)	2 (1–5)	<0.0001
SBP (mmHg), mean ± SD	131.8 ± 24.3	133.0 ± 25.9	131.4 ± 23.9	0.4
DBP (mmHg), mean ± SD	73.4 ± 14.1	73.7 ± 13.6	73.3 ± 14.2	0.9
Renal function, n (%)				0.01
Normal renal function	1664 (66)	336 (62)	1328 (68)	
Moderate renal dysfunction	584 (23)	152 (28)	432 (22)	
Severe renal dysfunction	260 (10)	58 (11)	202 (10)	
Hepatic function, n (%)				0.01
Normal hepatic function	1716 (68)	349 (64)	1367 (70)	
Hepatic dysfunction	792 (32)	197 (36)	595 (30)	
Drug, n (%)				
Antibiotics	797 (32)	188 (34)	609 (31)	0.13
Antitumor agents	63 (3)	12 (2)	51 (3)	0.59
Diuretics	391 (16)	81 (15)	310 (16)	0.58
Antihypertensive	661 (26)	148 (27)	513 (26)	0.65
Antiarrhythmic	57 (2)	12 (2)	45 (2)	0.89
Cardiovascular	466 (19)	98 (18)	368 (19)	0.67
Anticoagulants	279 (11)	58 (11)	221 (11)	0.67
Dyslipidemic agents	142 (6)	30 (5)	112 (6)	0.85
Antidiabetics	287 (11)	67 (12)	220 (11)	0.49
Antiasthmatics	96 (4)	21 (4)	75 (4)	0.98
Peptic ulcer drugs	890 (35)	202 (37)	688 (35)	0.40
Laxatives	427 (17)	110 (20)	317 (16)	0.028
Antidepressants	30 (1)	7 (1)	23 (1)	0.83
Sedatives	955 (38)	225 (41)	730 (37)	0.087
Antipsychotics	149 (6)	44 (8)	105 (5)	0.018
Antiseizure	69 (3)	19 (3)	50 (3)	0.24
Anti-Parkinson's drugs	38 (2)	10 (2)	28 (1)	0.49
Muscle relaxant	70 (3)	17 (3)	53 (3)	0.61
NSAIDs	569 (23)	151 (28)	418 (21)	0.0017
Other analgesics	666 (27)	156 (29)	510 (26)	0.23
Corticosteroids	145 (6)	41 (8)	104 (5)	0.051
Antihistamines	83 (3)	20 (4)	63 (3)	0.60
Electrolytes or fluids	1338 (53)	284 (52)	1054 (54)	0.48
Experimental drugs	1 (0.04)	1 (0.2)	0 (0)	0.058
Others	1547 (62)	342 (63)	1205 (61)	0.60

ICUs, intensive care units; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSAIDs, nonsteroidal antiinflammatory drugs.

We carried out all analyses using the JMP 11.2 software (SAS Institute Inc., Cary, NC, USA).

Results

Laboratory data of both renal and hepatic function were available for 2508 of the 3459 patients enrolled (Figure 1). After excluding 42 patients who died within 2 days who had no ADE, the data of 2466 patients were used in the sensitivity analysis.

Among the 2508 patients, 546 had ADEs. The mean age was significantly higher in patients with ADEs than in those without (70.3 vs. 64.9 years, $p < 0.0001$). The mean Charlson index score was also significantly higher in patients with ADEs (3 vs. 2, $p < 0.0001$), whereas

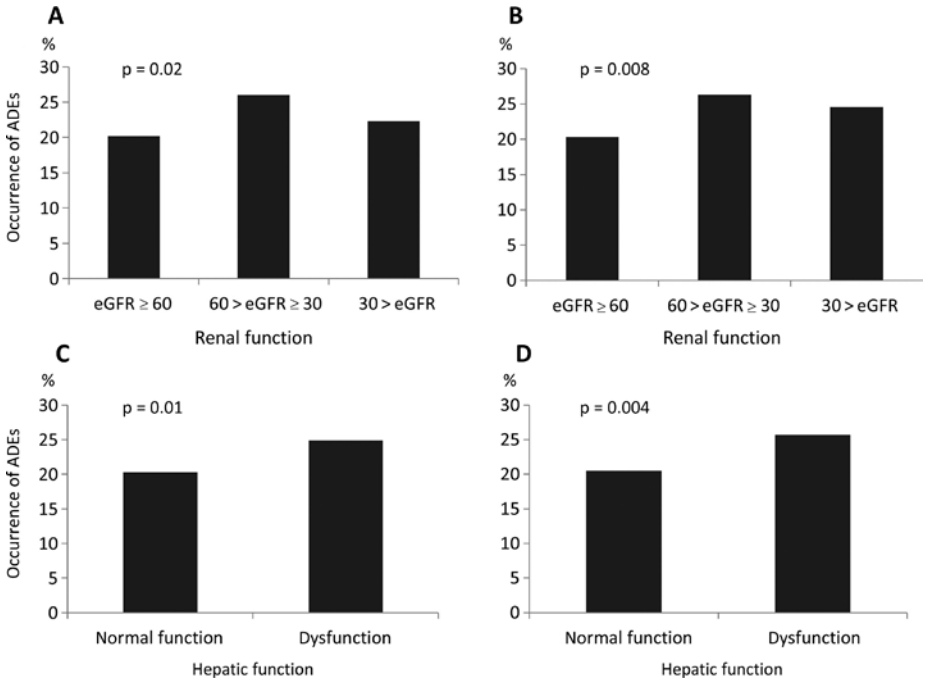

Figure 2: Effect of organ function on ADEs.
(A) The occurrence of ADEs in patients stratified by eGFR category (<30; ≥30 and <60; ≥60 mL/min/1.73 mm). (B) Sensitivity analysis of the occurrence of ADEs in patients in the three eGFR categories. (C) The occurrence of ADEs in patients with normal hepatic function and hepatic dysfunction. (D) Sensitivity analysis of the occurrence of ADEs in patients with normal hepatic function and hepatic function abnormalities.

body mass index was significantly lower (21.4 vs. 22.5, $p < 0.0001$). The categories of renal and hepatic function were also significantly different between the two groups (Table 1).

Effect of renal and hepatic dysfunction on ADEs

The occurrence of ADEs was significantly different among eGFR categories [normal function, 20% (n = 336); moderate dysfunction, 26% (n = 152); and severe dysfunction, 22% (n = 58); p = 0.02] (Figure 2A). The occurrence of ADEs was also significantly different between hepatic function categories [normal function, 20% (n = 349); dysfunction, 25% (n = 197); p = 0.01] (Figure 2C). The sensitivity analyses, excluding patients who died within 2 days, showed similar results [normal renal function, 20%, (n = 336); moderate renal dysfunction, 26% (n = 152); and severe renal dysfunction, 25% (n = 58); p = 0.008; and normal hepatic function, 20% (n = 349); dysfunction, 26% (n = 197); p = 0.004] (Figure 2B and D). Among the 792 patients with hepatic dysfunction, the occurrence of ADEs was higher in the elderly [≥65 years old, 28% (n = 131) vs. 20% (n = 66); p = 0.007].

Effect of number of medications used on ADEs

Among those with normal renal function, ADE occurrence was significantly higher in patients to whom five or more medications were prescribed on admission than in those who were prescribed less than five [25% (n = 143) vs. 18% (n = 193), p = 0.0005] (Figure 3A). However, these effects were not observed among those with moderate or severe renal dysfunction [moderate dysfunction, 25% (n = 60) vs. 27% (n = 92), p = 0.5; severe dysfunction, 23% (n = 35) vs. 22% (n = 23), p = 0.8]. Among those with normal hepatic function, ADE occurrence was also significantly higher in patients to whom five or more medications were prescribed on admission than in those who were prescribed less than five [24% (n = 159) vs. 18% (n = 190), p = 0.007] (Figure 3C). This effect was also not observed among those with hepatic dysfunction. The results of the sensitivity analyses were similar [normal renal function, 25% (n = 143) vs. 18% (n = 193), p = 0.0005; moderate renal dysfunction, 25% (n = 60) vs. 27% (n = 92), p = 0.5; severe renal dysfunction, 24% (n = 35) vs. 25% (n = 23), p = 0.9; and normal hepatic function, 24% (n = 159) vs. 18% (n = 190), p = 0.008; hepatic dysfunction, 27% (n = 79) vs. 25% (n = 118), p = 0.4] (Figure 3B and D).

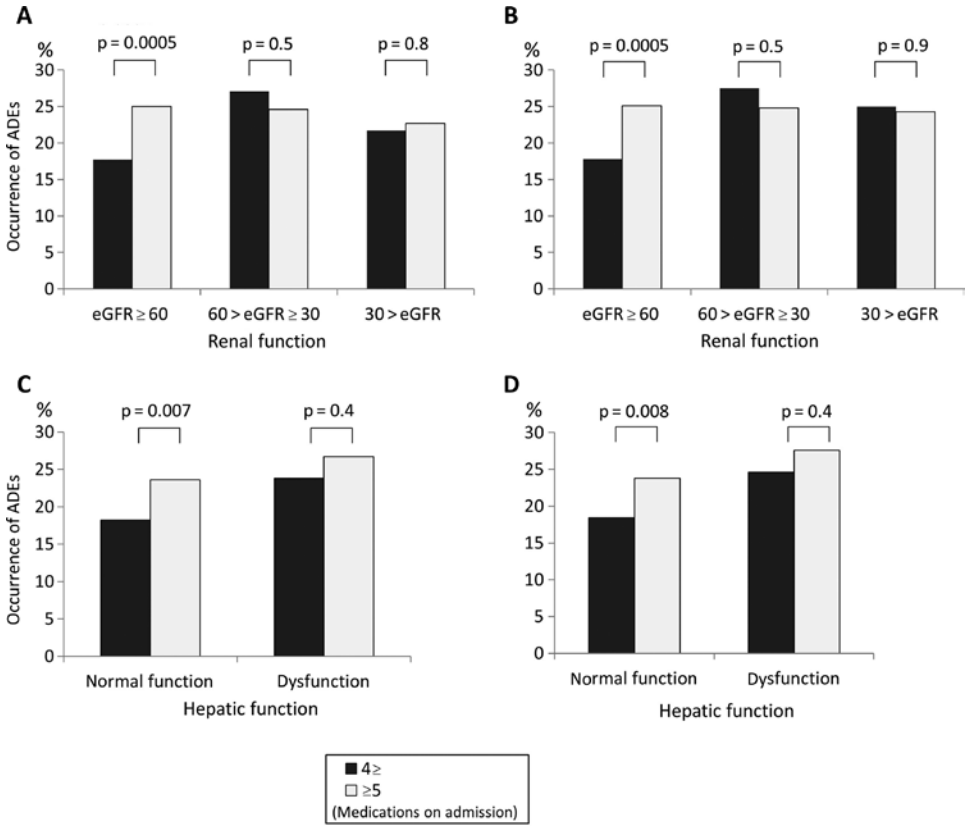

Figure 3: Effect of the number of medications used on ADEs, stratified by organ function.
(A) The occurrence of ADEs in patients in the three eGFR categories (<30; ≥30 and <60; ≥60 mL/min/1.73 mm), stratified by the number of medications used. (B) Sensitivity analysis of the occurrence of ADEs in patient in the three eGFR categories, stratified by the number of medications used. (C)The occurrence of ADEs in patients with normal hepatic function and hepatic dysfunction, stratified by the number of medications used. (D) Sensitivity analysis of the occurrence of ADEs in patients with normal hepatic function and hepatic dysfunction, stratified by the number of medications used. Black bars, the number of medications used is four or less; white bars, the number of medications used is five or more.

Effect of ADEs on LOS

The median LOS of patients with ADEs was longer than that of patients without ADEs, among those with normal renal function (20 vs. 7 days, $p < 0.0001$) and those with renal dysfunction (moderate renal dysfunction, 26 vs. 9 days, $p < 0.0001$; severe renal dysfunction, 22 vs. 6 days, $p < 0.0001$). It was also longer among those with normal hepatic function (21 vs. 7 days, $p < 0.0001$) and those with hepatic dysfunction (23 vs. 8 days, $p < 0.0001$). The results of the sensitivity analyses were similar.

Effect of ADEs on in-hospital mortality

In-hospital mortality was higher in patients with ADEs than in patients without ADEs, among patients with normal renal function and moderate renal dysfunction [normal renal function, 13.7% (n = 46) vs. 3.9% (n = 52), $p < 0.0001$; moderate renal dysfunction, 15.1% (n = 23) vs. 8.3% (n = 36), $p = 0.02$] (Figure 4A). However, these effects were not observed among those with severe renal dysfunction [24.1 (n = 14) vs. 20.8 (n = 42), $p = 0.6$]. In the sensitivity analysis, in-hospital mortality showed the same tendencies in the normal renal function and moderate renal dysfunction groups. However, in this analysis, in-hospital mortality was also higher in patients with ADEs among those with severe renal dysfunction [24.1 (n = 14) vs. 10.1 (n = 18), $p = 0.01$] (Figure 4B). Similarly, in-hospital mortality was higher in patients with ADEs among those with normal hepatic function [13.2 (n = 46) vs. 4.8 (n = 65), $p < 0.0001$] and hepatic dysfunction [18.8% (n = 37) vs. 10.9% (n = 65), $p = 0.006$] (Figure 4C). The hepatic function results of the sensitivity analyses were similar (Figure 4D).

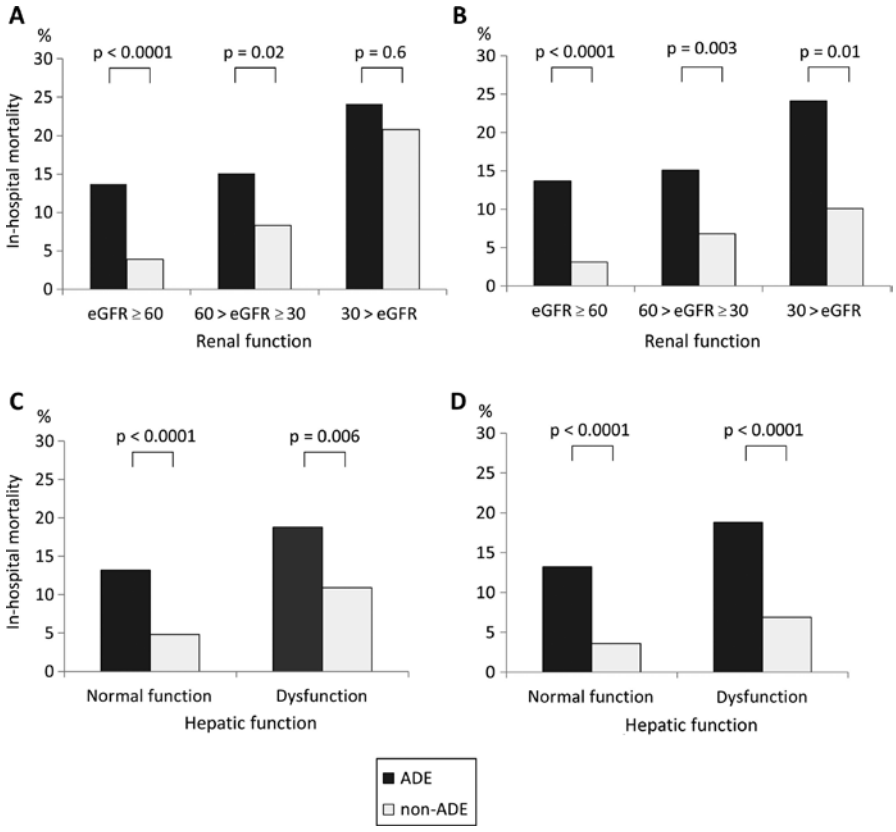

Figure 4: Effect of ADEs on in-hospital mortality, stratified by organ functions.
(A) In-hospital mortality in patients in the three eGFR categories (<30; ≥30 and <60; ≥60 mL/min/1.73 mm), stratified by ADE occurrence. (B) Sensitivity analysis of in-hospital mortality in patients in each eGFR category, stratified by ADE occurrence. (C) In-hospital mortality in patients with normal hepatic function and hepatic dysfunction, stratified by ADE occurrence. (D) Sensitivity analysis of in-hospital mortality in patients with normal hepatic function and hepatic dysfunction, stratified by ADE occurrence.

Effect of renal and hepatic dysfunction on in-hospital mortality

The multivariate logistic regression model showed moderate and severe renal dysfunction were significantly associated with in-hospital mortality [odds ratio (OR) of moderate relative to normal, 1.49 (95% confidence interval, CI, 1.04–2.12); OR of severe relative to normal, 4.12 (95% CI, 2.81–6.02)]. Hepatic dysfunction was also significantly associated with in-hospital mortality (OR, 2.08; 95% CI, 1.55–2.79). The occurrence of ADEs was also independently associated with in-hospital mortality, adjusting

Table 2: Effect of renal and hepatic dysfunction on in-hospital mortality by univariate and multivariate analysis.

Variables	Univariate		Multivariate	
	OR		OR	
	(95% CI)	p-Value	(95% CI)	p-Value
ADEs	2.53 (1.88–3.39)	<0.0001	2.36 (1.74–3.20)	<0.0001
Age ≥65 years	2.05 (1.48–2.83)	<0.0001	1.67 (1.19–2.37)	0.0029
Renal dysfunction (eGFR, mL/min/1.73 mm)				
≥60	1 (reference)		1 (reference)	
≥30 and <60	1.29 (0.94–1.77)	0.12	1.49 (1.04–2.12)	0.029
<30	3.66 (2.61–5.12)	<0.0001	4.12 (2.81–6.02)	<0.0001
Hepatic dysfunction	2.13 (1.61–2.84)	<0.0001	2.08 (1.55–2.79)	<0.0001
No. of medications ≥5	1.34 (0.78–1.38)	0.81	0.83 (0.61–1.12)	0.23

for renal and hepatic dysfunction (OR, 2.36; 95% CI, 1.74–3.20) (Table 2).

Discussion

We found that approximately 30% of unselected inpatients in acute-care hospitals had renal or hepatic dysfunction, and that the risk of ADEs in such patients was significantly higher than in patients with normal organ function. We also found that the variables associated with increased occurrence of ADEs, such as being elderly, having renal dysfunction, and having hepatic dysfunction, were also independently associated with in-hospital mortality.

However, the occurrence of ADEs with severe renal dysfunction was smaller than the occurrence with moderate renal dysfunction. In-hospital mortality was significantly associated with renal dysfunction. Therefore, more patients with renal dysfunction would die before experiencing ADEs during the hospital stay. Indeed, the occurrence of ADEs with severe renal dysfunction increased when patients who died within 2 days were excluded.

Our findings were consistent with those from a previous study, which showed that a substantial proportion (7.5%–10.4%) of patients admitted to acute-care hospitals experienced ADEs, with some of them being fatal [12].

Prevention of ADEs is expected to improve the prognosis of patients. In the United States, ADEs contribute to as many as 140,000 deaths annually, occurring in about 1 of 16 hospitalized patients. An estimated 28% to 56% of ADEs are preventable, and most preventable ADEs are due to errors during prescription [12]. A UK study showed that 12% of all primary-care patients may be affected by a prescribing or monitoring error over the course of a year, increasing to 38% in those aged 75 years and older and 30% in patients receiving five or more drugs during a 12-month period. Overall, about 5% of prescriptions are believed to have prescribing errors [13]. The WHO has provided a list of 10 key actions that are likely to have the most impact on improving safety in primary care, and one of them is to focus on those at a higher risk of safety incidents [14]. Our study showed that ADEs occurred significantly more in patients with organ dysfunction. Thus, intensive monitoring of such patients would contribute to reducing the incidence of ADEs, morbidity, and mortality.

In patients with normal renal or hepatic function in this study, the occurrence of ADEs increased when the number of medications increased. However, this tendency was not observed in patients with renal or hepatic dysfunction. Field et al. [15] reported that the risk of ADEs increased when the number of regularly scheduled medications was more than five in patients with normal renal and hepatic function, and our results were consistent with this report. Generally, drugs and their metabolites are excreted in the urine after polarization by a drug metabolism process in the liver [5]. If patients have hepatic or renal dysfunction, then this metabolism or excretion process has deteriorated. The relationship between the number of medications and occurrence of ADEs was not observed in patients with renal or hepatic dysfunction because of the decreased metabolism and excretion function. Even with only a few drugs administered, the blood concentration of these drugs or their metabolites increases causing enhanced drug sensitivity in patients with renal or hepatic dysfunction [16–22]. We suggested that the risk of ADEs depends on the number of medications in patients with normal metabolism, whereas the risk of ADEs was high even with a small number of medications in patients with decreased metabolism.

The efficiency of renal and hepatic function changes with age [23–25], and mean age on admission was 70 years in patients with ADEs in our study. Budnitz et al. [26] reported in a US study that there were an estimated 99,628 emergent hospitalizations for ADEs in adults aged 65 years or older each year from 2007 to 2009. Nearly half of these hospitalizations were reported for adults aged 80 years or older, and nearly two thirds of those were due to unintentional overdoses. In the same study, two thirds of the ADEs involved drugs such as warfarin, insulin, oral antiplatelet agents, and oral hypoglycemic agents. More caution during prescription is needed because many medications could cause renal or hepatic dysfunction [27–31]. In contrast, Dreischulte et al. [32] reported in a Scotland study that a complex intervention combining professional education, informatics, and financial incentives reduced the rate of high-risk prescribing of antiplatelet medications and nonsteroidal antiinflammatory drugs. The proper use and dose of medications are more important for elderly patients with renal or hepatic dysfunction because our results indicated that being elderly and having renal or hepatic dysfunction and ADEs were independently associated with in-hospital mortality. Furthermore, monitoring of renal and hepatic function should be approached with more attention in cases of multiple medication therapy.

Several limitations must be addressed regarding this study. First, the number of all medications were not available during the hospitalization. The changes in laboratory data after admission were also not assessed. Although the

primary purpose of this study was to estimate the risk of ADEs and in-hospital mortality based on the renal and hepatic functions on admission, the changes in medication use and laboratory data could be incorporated to risk stratification. Second, we also did not assess the established indicators of hepatic function, which are widely used for the prognosis of liver disease, such as the Child–Pugh score [33]. Therefore, the effect of renal and hepatic function on the occurrence of ADEs might be different if we used different indicators. Third, we did not consider pharmacogenomics or pharmacokinetic/pharmacodynamic studies to estimate the risks of ADEs in this study because such tests were not used in all patients in daily practice. We focused on the risk of ADEs based on renal and hepatic function, which are measured in all patients on admission. However, the risk stratification ability should be improved if we used such tests in the future. Finally, the JADE study only enrolled Japanese patients, and the study was conducted in 2004, with data that seem relatively old. To generalize our results globally, we need to study the effect of renal and hepatic function on the occurrence of ADEs in other countries to evaluate their effects among different ethnic groups and also in different healthcare systems, which can affect decision-making by healthcare professionals. However, as the medications used in this study have not been changed for decades, our findings and their clinical implication should be considered relevant in the present.

Conclusions

We found that renal and hepatic dysfunction increased the occurrence of ADEs, and that ADEs were associated with longer LOS and higher mortality in patients with both normal and decreased renal or hepatic function. Therefore, the appropriate and careful use of medication should be promoted, especially in patients with renal or hepatic dysfunction. Systems to confirm the necessity of organ function tests depending on the medications that a patient is taking, and to increase the timely identification and interception of ADEs according to renal or hepatic function, should be implemented to ensure the safer use of medication.

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ORIGINAL ARTICLE

Improving the assessment of adverse drug reactions using the Naranjo Algorithm in daily practice: The Japan Adverse Drug Events Study

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Abstract

It is difficult to determine adverse drug reactions (ADRs) in daily complicated clinical practice in which many kinds of drugs are prescribed. We evaluated how well the Naranjo Algorithm (NA) categorized ADRs among suspected ADRs. The Japan Adverse Drug Events (JADE) study was a prospective cohort study of 3459 inpatients. After all suspected ADRs were reported from research assistants, a single physician reviewer independently assigned an NA score to each. After all NA score of suspected ADRs were scored, two physician reviewers discussed and determined ADRs based on the literature. We investigated the sensitivity and specificity of NA and each component to categorize ADRs among suspected ADRs. A total of 1579 suspected ADRs were reported in 962 patients. Physician reviewers determined 997 ADRs. The percentage of ADRs was 94% if the total NA score reached 5. The modified NA consisted of 5 components that showed high classification abilities; its area under the curve (AUC) was 0.92 for categorizing ADRs, the same as the original. When we set the total NA score cut-off value to 5, specificity was 0.95 and sensitivity was 0.59. When we reclassified NA components as binary variables, the specificity increased to 0.98 with a cut-off value of 4 and yielded an AUC of 0.93. In conclusion, we showed that both NA and modified NA could categorize ADRs among suspected ADRs with a high likelihood in daily clinical practice.

KEYWORDS
adverse drug reactions, categorization, daily practice, JADE study, modification, Naranjo Algorithm, patient safety, pharmacovigilance, sensitivity, specificity

1 | INTRODUCTION

Discriminating adverse drug events (ADRs) from various symptoms in daily practice is important in order for physicians to take action to mitigate the adverseness and prevent recurrence. However, patients are usually treated with many kinds of drugs, which make it difficult to identify an ADR in daily practice. A tool to categorize ADRs

Abbreviations: ADRs, adverse drug reactions; AUC, area under the curve; JADE, The Japan Adverse Drug Events; NA, Naranjo Algorithm; ROC, receiver operating characteristic.

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among complicated suspected symptoms could be useful for healthcare professionals to take action proactively as well as to confirm the probability of ADRs retrospectively.

Naranjo et al proposed a tool to evaluate the probability of true ADRs from suspected ADRs,[1,2] and it has been widely used as the Naranjo Algorithm (NA).[3-6] In addition to the NA, several assessment tools have been developed, such as the Liverpool adverse drug reaction causality assessment tool[7] and the French Causality Assessment Method.[8] These tools are used to evaluate the probability of an ADR rather than to screen ADRs from suspected ADRs prospectively to take action. While the NA is a traditional tool, it consists of 10 components, and it is complicated to calculate the total score and would require time to utilize it in a daily clinical setting. To save time and resources, a convenient tool to categorize ADRs with high specificity is needed.

We recently conducted the Japan Adverse Drug Events (JADE) study, which evaluated the incidence of ADRs and medication errors among Japanese hospitalized inpatients.[9-14] In the present study, we evaluated the usefulness of the NA to categorize ADRs among suspected ADRs using the JADE database and tried to modify it into a convenient tool to use in daily clinical practice.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

The JADE study was a multicenter prospective cohort study that included 3459 inpatients aged ≥15 years. The study site was three urban tertiary care hospitals in Japan, patients admitted at 15 randomly selected medical and surgical wards as well as three intensive care units from January through June 2004 were eligible for this study.[9] The institutional review boards of the three participating hospitals approved the study. Informed consent was waived because all data were collected in daily practice.

2.2 | Naranjo Algorithm

The NA consists of 10 components assessing the likelihood of ADRs.[1,2] Each component is scored from −1 to +2 based on the findings of each event, including (1) previous conclusive reports, (2) time course, (3) improvement after withdrawal or treatment, (4) re-emergence after re-challenge, (5) other causative conditions of symptoms, (6) response to placebo if used, (7) evidence in blood of toxicity, (8) dose response, (9) similar reactions before, and (10) other objective evidence.

2.3 | Data collection and review process

Research assistants, who were trained nurses or nursing students, reviewed all medical charts, along with laboratory results, incident reports, and prescription queries by pharmacists with the standardized form daily. They reported any suspected ADRs that might be potential ADRs in a standard manner.[15] After all suspected ADRs were reported from research assistants, a single physician reviewer independently assigned an NA score to each suspected ADR. After all NA score of suspected ADRs were scored, two independent physician reviewers evaluated all suspected ADRs and classified them as confirmed ADRs or not. If discordance happened, such discordance was resolved through discussion to reach consensus.

2.4 | Statistical analyses

A continuous variable is presented as the mean ± standard deviation (SD) and categorical variables are shown as numbers and percentages. We expressed the distribution of NA scores in each component as the percentage of confirmed ADRs among suspected ADRs for each score in each component. We evaluated the percentage of confirmed ADRs among suspected ADRs for each total NA score. ADRs which are confirmed by physician reviewers are considered as true positive. All suspected ADRs were categorized as positive or negative based on the NA score; then sensitivity and specificity were calculated by these figures. We constructed a receiver operating characteristic (ROC) curve for the summed score of all and selected NA components to compare the categorization abilities of original and modified NA scores. To simplify the NA for convenient use, we reclassified NA components as binary variables. For example, an NA component that had three possible scores, such as +2, 0, and −1 or +1, 0, and 1, were converted to +1 and 0 in which the positive score was converted to +1 and the 0 and negative scores were summarized as 0. We carried out all analyses using JMP 11.2 (SAS Institute Inc., Cary, NC, USA) software.

3 | RESULTS

There were 1579 suspected ADRs occurring in 962 patients from among 3459 patients enrolled (Figure 1). Physician reviewers finally concluded that 997 actual ADRs occurred from among the suspected ADRs. Among the 962 patients with NA scores, 517 (54%) were men and the mean age was 70 (SD 15) years. The medical and surgical wards and the ICUs admitted 437 (45%), 410 (43%), and 115 (12%) patients, respectively. Comorbidities based on the Charlson index are summarized in Table 1. Medications that were the most frequently associated with ADRs were electrolytes or fluids (n = 623, 62%), followed by antibiotics (n = 569, 57%) and peptic ulcer drugs (n = 463, 46%) (Table 2).

3.1 | Distribution of NA score and percentage of ADRs by each component

NA components 6 through 10 (response to placebo if used, evidence in blood of toxicity, dose response, similar reactions before, and other objective evidence) classified more than 95% of suspected ADRs with a specific score; in which 99.8% (n = 1576) of suspected ADRs were classified with a score 0 (do not know) for component 6, and 99.9% of suspected ADRs were classified with a score 0 (no or do not know) for component 7. Thus, components 6 through 10 did

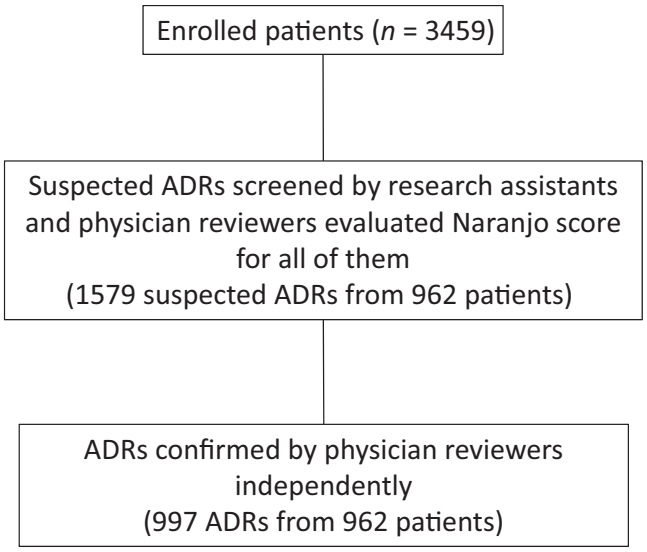

FIGURE 1 Evaluation process for adverse drug events (ADRs). ADRs were evaluated using 3 steps. Research assistants suggested suspected ADRs from potential drug-related incidents. A physician reviewer scored each suspected ADR independently using the NA. Two physician reviewers identified ADRs based on consensus of an expert panel

not show sufficient categorization in identifying ADRs in this cohort. On the other hand, components 1 through 5 (previous conclusive report, time course, improvement after withdrawal or treatment, re-emergence after re-challenge, and other causative conditions of symptoms) showed good categorization in identifying ADRs from among suspected ADRs for each component; in which 64% (n = 1002) of suspected ADRs were classified with a + 1 score (yes) and 37% (n = 577) of suspected ADRs were classified with a 0 score (no or do not know) for component 1 (Table 3).

TABLE 1 Characteristics and demographics of patients on admission

Characteristic	Mean ± SD or n (%) n = 962
Age (years)	70.0 ± 14.8
Male sex	517 (54)
Race (Japanese)	957 (99.5)
Admitting ward	
Medical	437 (45)
Surgical	410 (43)
Intensive care units	115 (12)
Comorbidity	
Myocardial infarction	67 (7)
Heart failure	141 (15)
Peripheral vascular disease	54 (6)
Cerebrovascular disease	136 (14)
Dementia	143 (15)
Chronic obstructive pulmonary disease	122 (13)
Rheumatologic	38 (4)
Peptic ulcer	247 (26)
Liver diseases	177 (18.4)
Diabetes	163 (16.9)
Chronic kidney disease	61 (6)
Any tumor	377 (39.2)

Most parameters are duplicated to a certain degree, as many patients experienced multiple medical events.

TABLE 2 Medications suspected to induce adverse drug reactions (ADRs)

Medication	n (%) n = 997
Electrolytes or fluids	623 (62)
Antibiotics	569 (57)
Peptic ulcer drugs	463 (46)
Sedatives	360 (36)
Antihypertensive	302 (30)
Laxatives	254 (25)
Diuretics	221 (22)
Cardiovascular	202 (20)
NSAIDs	194 (19)
Anticoagulants	170 (17)
Antidiabetics	139 (14)
Antipsychotics	119 (12)
Dyslipidemic agents	73 (7)
Analgesics	42 (4)

NSAIDs, nonsteroidal anti-inflammatory drugs.

Each NA component 1 to 5 had relatively high sensitivity or specificity for categorizing ADRs among suspected ADRs. With component 1, 86% (n = 866) of suspected ADRs were confirmed as ADRs among 1002 suspected ADRs assigned a + 1 score (Yes), and 23% (n = 131) of suspected ADRs were confirmed as ADRs among 577 suspected ADRs assigned a 0 score (No/Do not know) (Figure 2). Since the NA has a "Do not know" classification, we simply could not calculate specificity. When we classified "do not know" as "no", the sensitivity was 0.87 and specificity was 0.77 for component 1. Similarly, the approximate sensitivity and specificity were 0.99 and 0.68, respectively, for component 2; 0.31 and 0.97, respectively, for component 3; 0.27 and 0.93, respectively, for component 4; and 0.71 and 0.91, respectively, for component 5.

3.2 | Relationship between total NA score and ADRs percentage of suspected ADRs

The total NA score calculated for each suspected ADR ranged from −2 to 11. The most frequent total NA score was 0 (n=403) followed by 5 (n=280). The percentage of ADRs was 56% if the total NA score was 1, and it gradually increased to 94% if the total NA score reached 5 (Figure 3). We did not show the total NA scores of −2 and −1 since only 2 and 0 suspected ADRs, respectively, were assigned these scores.

TABLE 3 Distribution of the Naranjo Algorithm (NA) score for each component

	Component	Score			
		+2	+1	0	−1
1	Are there previous conclusive reports on this reaction?	—	1002 (64)	577 (37)	—
2	Did the adverse event appear after the suspected drug was administered?	1172 (74)	—	400 (25)	7 (0.4)
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	—	322 (20)	1257 (80)	—
4	Did the adverse reaction reappear when the drug was readministered?	309 (20)	—	1040 (66)	230 (15)
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	761 (48)	—	422 (27)	396 (25)
6	Did the reaction reappear when a placebo was given?	—	3 (0.2)	1576 (99.8)	0 (0)
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	—	2 (0.1)	1577 (99.9)	—
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	—	24 (2)	1555 (98)	—
9	Did the patient have a similar reaction on the same or similar drugs in any previous exposure?	—	35 (2)	1544 (98)	—
10	Was the adverse event confirmed by any objective evidence?	—	53 (3)	1526 (97)	—

Data expressed as n (%).

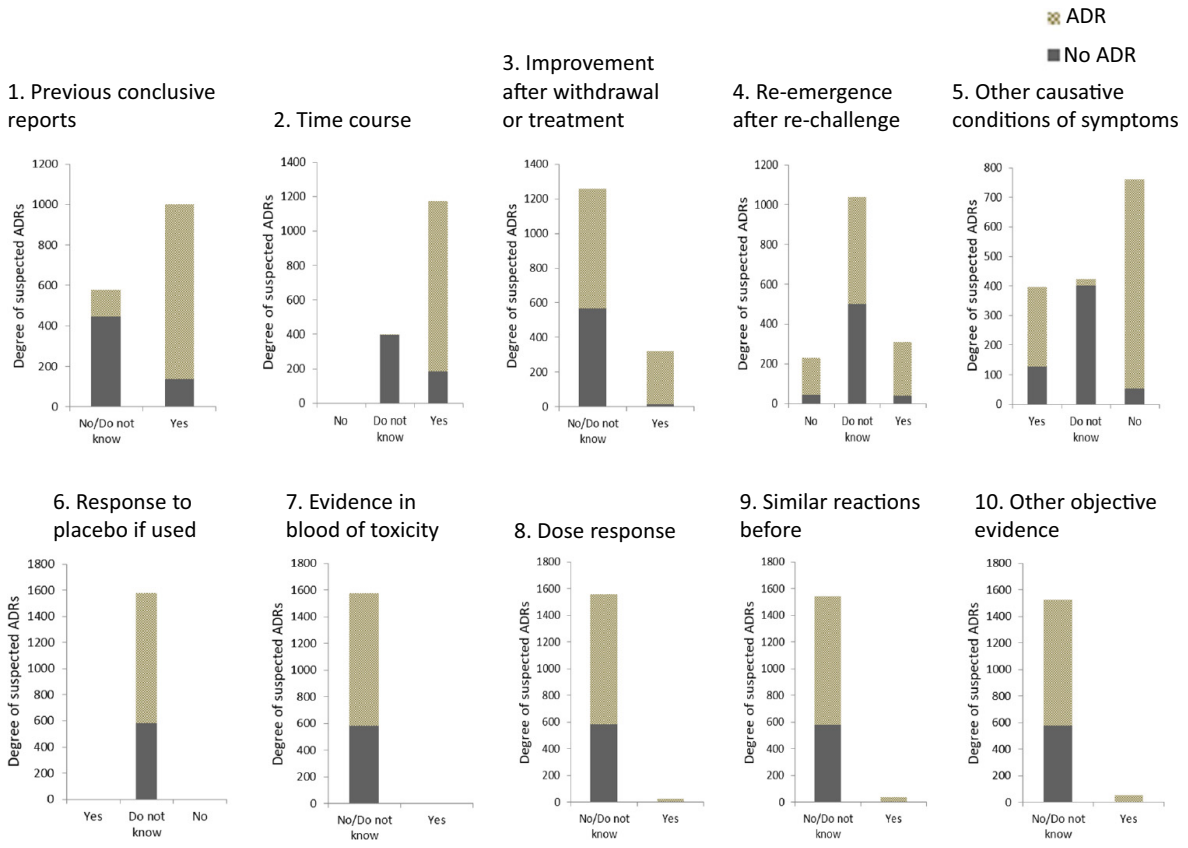

FIGURE 2 Distribution of adverse drug reactions (ADRs) by each Naranjo Algorithm (NA) component. The distribution of ADRs identified by physician reviewers for scored suspected ADRs by each NA component is shown. A total of 10 components, each consisting of 2 or 3 classifications were evaluated

3.3 | Sensitivity and specificity of the NA to determine ADRs

The area under the curve (AUC) to confirm ADRs was 0.92 (95% confidence interval [CI]: 0.91-0.94) based on the total NA sore; the specificity was 0.94 and the sensitivity was 0.61 if the cut-off value was set at 5 (Figure 4A). Since more than 97% of suspected ADRs were assigned a score of 0 for components 6 through 10, we considered that these components were not useful in the real-world setting. We generated a modified NA that consisted of components 1

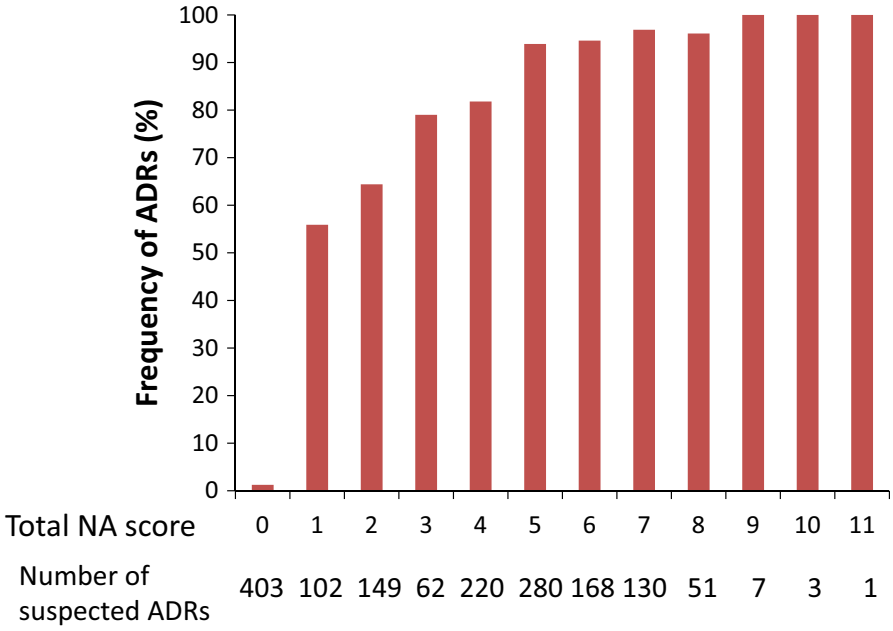

FIGURE 3 Relationship between the total Naranjo Algorithm (NA) score and the percentage of identified adverse drug events (ADRs) among suspected ADRs. The percentage of confirmed ADRs among suspected ADRs are expressed for each total NA score (0 through 11)

through 5. This modified NA confirmed ADRs with an AUC of 0.92 (95% CI: 0.91-0.94), which was the same AUC as the original NA (Figure 4B). If the cut-off value was set at 5, the specificity was 0.95 and sensitivity was 0.59. In the modified NA, we reclassified NA components 2, 4, and 5 into binary variables, which increased the specificity to 0.98 and sensitivity of 0.34 with an AUC of 0.93 (95% CI: 0.91-0.94) if the cut-off value was set at 4 (Figure 4C). We further modified the NA to consist of components 2 through 5 as binary variables. This simplest NA confirmed ADRs with an AUC of 0.92 (95% CI: 0.90-0.93) and showed a specificity of 0.97 and sensitivity of 0.40 if the cut-off value was set at 3 (Table 4, Figure 4D).

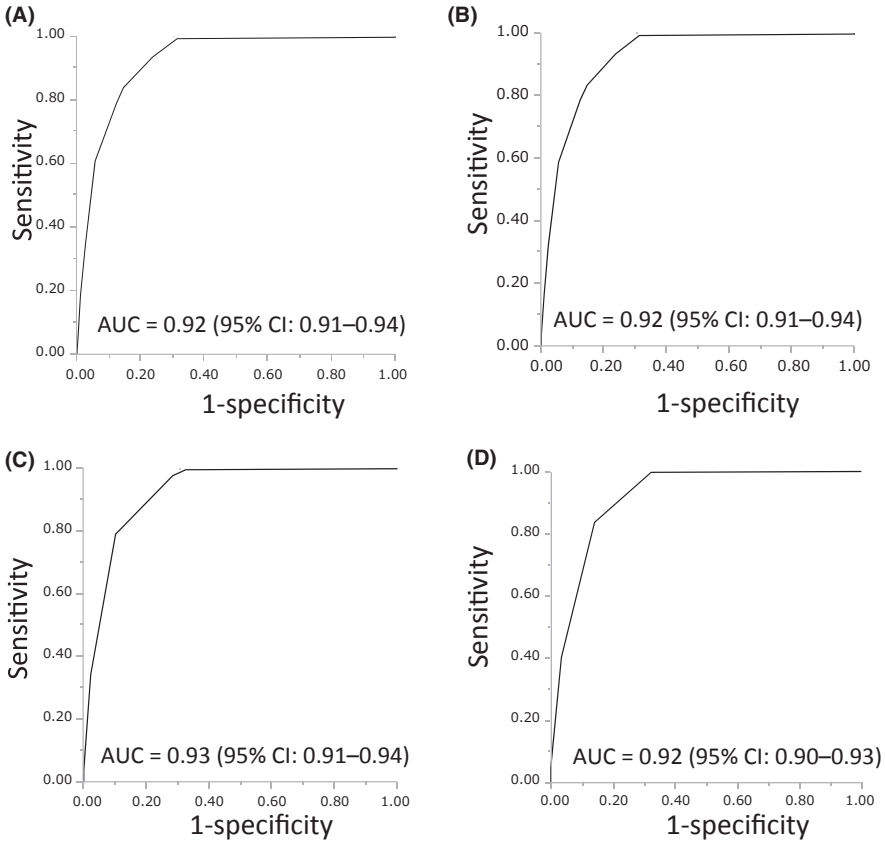

FIGURE 4 Receiver operating characteristic curve for adverse drug events (ADRs) and total Naranjo Algorithm (NA) score. A, The AUC for the sum of all NA components. B, The AUC for selected NA components (1-5). C, The AUC for selected NA components (1-5) converted to binary scores (0 or 1). D, The AUC for selected NA components (2-5) converted to binary scores (0 or 1)

TABLE 4 Modified Naranjo Algorithm (NA)

	Component	Score	
		Yes	No/Do not know
2	Did the adverse event appear after the suspected drug was administered?	+1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0
4	Did the adverse reaction reappear when the drug was readministered?	+1	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	0	+1

4 | DISCUSSION

We showed that the NA was able to categorize ADRs among suspected ADRs efficiently in daily clinical practice using the large-scale JADE database,[9] which was independent with a consensus panel by physicians' reviewers. While each NA component showed relatively high sensitivity or specificity, we evaluated the sensitivity or specificity for the total NA score, since healthcare professionals usually make a decision from multiple factors in the actual clinical setting. We also showed that the modified NA, consisting of components 1 through 5, also effectively categorized ADRs with a high likelihood. We further modified the NA to include all binary scores for components 1 through 5 and found that this algorithm determined ADRs with high likelihood, also similar to the original. In addition, we removed component 1 because this component required sufficient knowledge of ADRs for each suspected drug. We considered that the modified NA with binary scores for components 2 through 5 was the most reasonable in terms of the practical use in daily clinical practice and its effectiveness in determining ADRs with a high likelihood, similar to the original index and all of the other modified NAs.

In previous studies, the NA was utilized retrospectively to evaluate the probabilities of ADRs in a specific case or cohort.[3-6] In this study, however, we showed that the NA had high predictive accuracy for determining true ADRs among suspected ADRs, which could contribute to safety monitoring activities by healthcare professionals or pharmaceutical manufacturers. If the modified NA score is simultaneously reported with a suspected ADR, a health authority or pharmaceutical manufacturers could evaluate the suspected ADR more easily and quickly and could allocate time and resources more effectively. For example, pharmaceutical manufacturers could start an intensive survey giving priority to a suspected ADR with a high modified NA score. Additionally, healthcare professionals could start preclinical studies to clarify the mechanism of ADRs focusing on a high modified NA score. Thus, the modified NA score could help healthcare professionals or pharmaceutical manufacturers take their own action in preventing ADRs as early as possible before health authorities issue a warning or guidance.

NA was reported to show poor performance for causality assessment of hepatic adverse reactions.[16,17] On the other hand, NA and modified NA were able to categorize ADRs among suspected ADRs including hepatic adverse reactions in the current study. However, the number of hepatic adverse reactions was limited in the current study, the reliability to assess such hepatic adverse reactions was uncertain. Further studies which address the accuracy of NA and modified NA against hepatic adverse reaction should be considered.

Other than the NA, Gallagher et al reported the usefulness of the Liverpool adverse drug reaction causality assessment tool.[7] Although this tool also tried to simplify the NA and increase its credibility, their study had different objectives. It takes time to evaluate one case and provide an outcome (possible, probable, or definite) using the probability tree in the Liverpool tool. Additionally, this tool does not provide any score to be evaluated for sensitivity and specificity, similar to the NA. Also WHO-UMC causality assessment could be another simple tool to categorize ADR.[18] While this tool takes number of assessment criteria into consideration to categorize ADRs and each assessment criteria are similar to NA, it does not provide any score to be evaluated for sensitivity and specificity as well. Thus, there have been few reports proposing a tool that could be used to take action to mitigate adverseness and to prevent recurrence proactively rather than merely confirming the probability of ADRs retrospectively. We think our modified NA will not jeopardize the spontaneous ADR reporting but increase the awareness of ADR reporting with simple tool. It is still challenge for medical professionals to report suspected ADRs spontaneously because the importance of ADR reporting could not be understood well and medical professionals do not have an effective trigger tool to report ADRs. We are convinced that simple ADR assessment tools including our modified NA can introduce more frequent ADR reporting among medical professionals and can be used as a trigger tool to report ADRs.

Our study has several limitations. First, the JADE study only enrolled inpatients. Therefore, the modified NA score in this study might not be applicable in outpatients. Pharmacovigilance for inpatient should be different from usual pharmacovigilance situation of spontaneous reporting. Further studies are needed to clarify whether our findings could be applicable in outpatient settings and to generalize the modified NA for use in a pharmacovigilance system. Second, we removed components 6-10 in the modified NA model. For drugs in which the blood level should be known, such as vancomycin or theophylline, component 7 could be useful for detecting ADRs. However, only 2 cases were given a score of +1 for that component in this study, which shows that measuring blood levels of suspected drugs is not frequent in daily clinical practice. Third, the same independent physician reviewer classified the ADR and scored NA at different times, which might have led to a connection between ADR classification and NA scoring and subsequently to misclassification of the NA based on the reviewer's background or knowledge. Fourth, the JADE study only enrolled Japanese patients. To generalize the results globally, we need to study the modified NA in other countries to evaluate its ability to categorize ADRs among various races

and in different healthcare systems, which affect decision-making by healthcare professionals. Fifth, the JADE study was conducted in 2004 and the data used seemed relatively old. However, NA was developed in 1981 and still used for clinical settings. The drug used in this study and spontaneous ADR reporting system has not been changed for decades. Thus, the findings and clinical implication of this study should be valid at present time. Finally, we focused on the most suspected drug among all drugs administered when symptoms occurred in this study. Therefore, we could not exclude the possibility of synergistic effects of multiple drugs and drug-drug interaction.

In conclusion, we assessed the categorization abilities of the original and modified NAs in daily practice and found that the modified NA could be easily used to categorize actual ADRs among suspected ADRs with high predictive accuracy. Therefore, use of the modified NA could help to save time and resources and categorize ADRs more effectively and promptly in daily clinical practice. Additionally, utilizing this tool for a pharmacovigilance system could be useful to enable professionals take prompt action in developing a strategy to prevent and mitigate the adverseness of ADRs.

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DISCLOSURES

H. Murayama and Y. Takahashi: Employees of Novartis Pharma KK; M. Sakuma and T. Morimoto: None Declared.

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原　著

島根県中病医誌 43
17頁 ～ 22頁

外来患者への適切な投薬指示のための臨床決断支援システム

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大谷　真紀[4)]　小阪　真二[2,5)]　森本　剛[2,6)]

概　要：【背景・目的】島根県立中央病院の臨床決断支援システムの１つとして入院患者における腎機能別の推奨投与のシステムを開発したところ有用であった。同様のシステムを外来患者に導入し、有効性を評価した。

【方法】既存の入院患者向けシステムでは、入院患者の腎機能を自動計算し推奨投与量を画面上で医師に示したうえで、医師が最終的に用量を選択できる。同システムを元に、腎機能に基づいた抗微生物薬処方の臨床決断支援システムを外来患者用に開発した。2017年10月よりシステムを導入し、2018年９月時点では実際にカルテ画面には出さず介入前のバックグラウンドの状況で稼働中である。開始から2018年７月までの10か月間の抗微生物薬処方内容を調査し、システム本稼働後の実際の効果を予測した。

【結果】腎機能で調整が必要な薬剤は薬品単位で35,594件であった。腎機能が測定されていなかった患者における処方は、5,675件（16％）であった。腎機能測定されていた場合に、腎機能から計算された適切な処方は27,852件（78％）で、適切でないと判断された処方は、2,067件（６％）だった。

【結語】システム本稼働後は腎機能の測定の増加と適切でない処方の減少が期待される。

索引用語：決断支援システム、腎機能、抗微生物薬、抗微生物薬適正使用

Clinical decision support system for appropriate medication orders in outpatient service

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Maki OTANI[4)]　Shinji KOSAKA[2,5)]　and Takeshi MORIMOTO[2,6)]

Abstract：**Objectives;** We had developed a clinical decision support system, which enabled physicians to order any medication with recommended doses based on the updated renal function of each inpatient at Shimane Prefectural Central Hospital. We launched the same system into outpatient settings, and evaluated them.

Methods; We developed the clinical decision support system which automatically recommended appropriate doses for any medication which needed to be adjusted for renal function for inpatients. Recommended doses were displayed on the screen for inpatients, the physician could finally select the clinical dose. Since October 2017, we installed the system in outpatients, but the recommended doses were not displayed on the screen and ran in the background to measure the baseline data. We measured the antimicrobial prescription contents for 10 months until July 2018 to predict the actual effect after system

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operation.

Results; We obtained 35,594 drugs regulated by renal function orders for outpatients during the study period. Patients who ordered 5,675 medications（16%）did not have renal function test which was needed. In addition, 2,067 orders（6%）were incorrect dose（over or under）.

Conclusion; The clinical decision support system equipped with recommended antibiotics dose by renal function were useful for outpatients to reduce the inappropriate dose.

Key words：decision support system, renal function, antibiotics, antimicrobial stewardship

背　　景

現在の医療において医療安全は最優先の重要な分野である[1)]。また、指示を行う医師、指示を受ける看護師などは人間であり、エラーは避けられない[2)]。薬剤の中には腎機能等によって調整するべき薬剤がある。しかし、用量調整の必要な全ての薬剤について忙しい臨床医が把握した上で、もれなく調整を行うことは難しい。用量調整がうまくいかなければ過剰投与や過少投与となり副作用発現や治療不全をきたしうることが危惧される。さらに抗微生物薬適正使用の面からも適切な抗微生物薬処方が重要である[3)]。

島根県立中央病院は島根県東部に位置する臨床研修病院である。統合情報システム（IIMS: Integrated Intelligent Management System）を開発し、1999年より稼働している[4)]。IIMS内には、現在入院患者を対象とした抗微生物薬処方時における用量調整を行う臨床決断支援システムが2011年12月より組み込まれ、運用されている。今回は外来患者における同様のシステムの有用性を検討する。2018年９月現在ではツールは画面上に現れていない状態であり、どの程度の影響をもって稼働し、支援しうるかを検証するために、ツールの実行前のデータを検討した。

方　　法

＜概　要＞

入院患者に対する既存のシステムは腎機能を自動計算し、それによる推奨投与量を画面上で医師に示し、医師は最終的に用量を選択することができ、医学的理由から推奨された用量以外の用量を選択することもできるものである。抗微生物薬に関連するものとしては、医師が使用する抗微生物薬を選択した時点で腎機能による推奨の投与量を画面上に表示し、医師が画面から選択できるものである（図１）。これを応用し腎機能に基づいた投薬指示の臨床決断支援システムを外来患者用に開発した。Crや身長が測定されていな

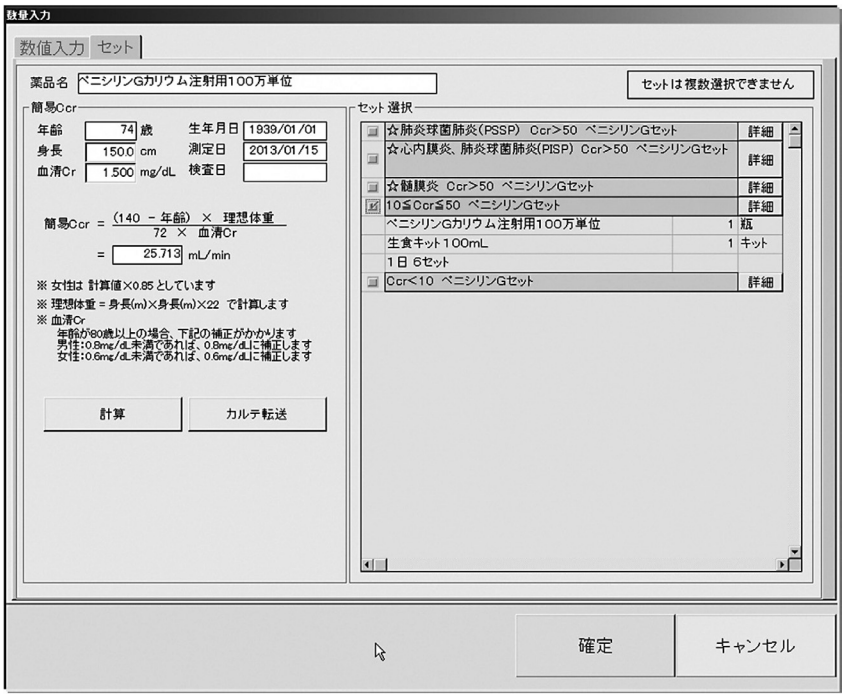

図1　現在の処方画面（入院患者用）
入院患者の注射指示の画面の例である。薬剤「ペニシリンGカリウム」を選択した後に図に示す画面が現れる。年齢、身長、血清クレアチニン値を自動取得し、簡易クレアチニンクリアランスを自動計算する。その簡易クレアチニンクリアランスをもとに推奨する用量のセットを色の変化で示す。病態などで他の処方を選択することも可能である。最終的に指示する処方セットをチェックしてオーダーを発行する。身長などが測定されていない場合は空欄となり自動計算は行わない。その場合は空欄に直接に値を打ち込んで「計算」ボタンを押してオーダーを発行する事も可能である。

ければメッセージが表示される機能を追加することとした。2017年10月よりシステムは稼働しているが、2018年９月時点では実際に画面には出さずバックグラウンドで稼働中である

＜対　象＞

2017年10月から2018年７月までの10か月間。島根県立中央病院で処方された全外来処方のうち、腎機能で調整が必要な処方を行ったものを対象とした。

<推奨投与量＞

推奨投与量は、腎機能で調整が必要な薬剤に対して島根県立中央病院薬剤局が中心となって、主にクレアチニンクリアランスに基づいた腎機能による推奨投与量を定めている（付表）。そのうち抗微生物薬に関しては島根県立中央病院の抗菌薬適正使用支援チーム（AST: Antimicrobial Stewardship Team）および感染制御チーム（ICT: Infection Control Team）が、PK/PD理論をもとに定めた投与量を推奨投与量とした。推奨投与量範囲内（Correct dose）とは、その推奨投与量の範囲内にあるものであり、推奨投与量範囲外（Incorrect dose）とは、推奨投与量範囲内にないもので、過量投与・過少投与と考えられる処方である。

＜データ抽出＞

病院関連の情報は、島根県立中央病院の年報データより抽出した。抽出項目は、2017年のデータで、病床数、職員数、入院患者（総数、性別、年齢）、外来患者（来院部署、来院方法）、外来患者の総処方箋数。

システムに関連するデータの抽出は、島根県立中央病院情報システム管理室において情報処理を専門とする職員が抽出した。抽出項目は、腎機能で調整が必要な処方薬の薬品単位での処方数、抗微生物薬の内容、３か月以内の腎機能測定有無、腎機能が測定されていた場合は推奨投与量範囲内外である。

＜解　析＞

得られたデータをもとに記述統計を行う。数と割合（%）または中央値［四分位値］で表記する。単変量解析において、カテゴリー変数はカイ二乗検定を行った。統計解析は、Stata15を用いて行った。

付表：推奨投与を行う腎機能により調整が必要な薬剤のリスト（主成分のみ）

アテノロール	セフカペン　ピボキシル
アマンタジン	セフジトレン　ピボキシル
アモキシシリン	セフジニル
アログリプチン	セフタジジム
アロプリノール	セフメタゾール
アンピシリン	タゾバクタム・ピペラシリン
アンピシリン・スルバクタム	ダビガトラン
イミペネム・シラスタチン	チアプリド
エナラプリル	テノホビル
エノキサパリン	トラネキサム酸
エプレレノン	ドリペネム
エムトリシタビン・テノホビル	ピオグリタゾン
エリスロマイシン	ピペラシリン
オセルタミビル	ピルシカイニド
オロパタジン	ファモチジン
クラリスロマイシン	フェキソフェナジン
グリクラジド	フェソテロジン
グリベンクラミド	ブシラミン
グリメピリド	フルコナゾール
ソリフェナシン	フレカイニド
ジゴキシン	フロモキセフ
ジソピラミド	ベザフィブラート
シタグリプチン	ベンジルペニシリン
シタフロキサシン	ベンラファキシン
シプロフロキサシン	ホスホマイシン
シベンゾリン	ミノドロン酸
シロドシン	メチルジゴキシン
スルタミシリン	メトホルミン
スルファメトキサゾール・トリメトプリム	メトロニダゾール
	メロペネム
セチリジン	ラコサミド
セファゾリン	ラニチジン
セファレキシン	リセドロン酸
セフェピム	リバーロキサバン
セフォタキシム	レボセチリジン
セフォチアム	ロスバスタチン

＜倫理・COI＞

この研究は、島根県立中央病院の臨床研究・治験審査委員会の承認を受けている（R16-064）。政策科学総合研究事業（臨床研究等ICT基盤構築・人工知能実装研究事業）「安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究」の研究費を用いて実施した。

結　　果

＜病院統計＞

2017年の島根県立中央病院の病床数は634床、医師数は167名で全職員1,180名のうち14%であった（表

表１　Hospital characteristics（2017）

Shimane Prefectural Central Hospital from 1940 Tertiary educational medical hospital, Japan 1999- Integrated intelligent management system	
Contents	no（%）
Number of beds	634
Medical staff	1,180
Doctors	167（14）
Nurses	687（58）
Paramedical	205（18）
Clerk	121（10）
Patients	
Inpatients	12,340
Age, years, median [IQR]	67 [38-80]
Male	6,197（50）
In hospital death	511（4）
Outpatients	249,733
Emergency Room	21,838（9）
Ambulance	4,068（19）
Doctor helicopter	490（2）
Walking	227,895（91）
Prescription	
Inpatients prescription count	97,466
June, 2017	8,051
Outpatient prescription count	108,223
June, 2017	9,088

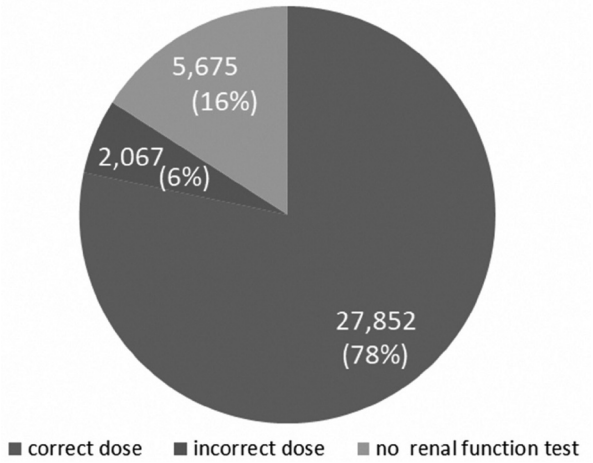

図２　外来処方内容（2017年10月から2018年７月）
10か月間で腎機能での調整が必要な抗微生物薬等の処方は合計35,594処方であった。そのうち5,675（16%）は腎機能が測定されていなかった。腎機能が測定された処方の内、27,852（78%）は腎機能での推奨投与量範囲内であった。2,067（６%）は推奨投与量範囲外であった。

表２　Drugs regulated by renal function

Total drugs	All antibiotics	Oral antibiotics
29,919	7,766（26）	6,495（22）

１）。入院患者数は12,340人で、年齢の中央値は67歳（四分位範囲38-80歳、最小０歳-最大107歳）、男性は6,197人（50%）、院内死亡は511人（４%）であった。外来患者数は249,733名で、救急受診は21,838人（９%）であった。救急受診の内、救急車での来院は4,068名（19%）、ドクターヘリ利用は490名（２%）であった。総処方数は入院で97,466件、外来で108,223件、６月の１か月当たりではそれぞれ8,051件、9,088件であった。

＜処方薬＞

研究期間中における腎機能で調整が必要な薬品数は、薬品単位で35,594件であった（図２）。腎機能が測定されていなかったものは、5,675件（16%）であった。腎機能が測定されていた処方は29,919件（84%）で、腎機能から計算された適切な処方は27,852件（78%）で、適切でないと判断された処方は、2,067件（６%）だった。

腎機能が測定された処方29,919件のうち、抗微生物薬は7,766件（26%）、そのうち経口抗微生物薬は6,495件（22%）であった（表２）。抗微生物薬の推奨投与量範囲内の処方は7,064件（91%）で、推奨投与量範囲外は702件（９%）であった（表３）。抗微生物薬以外の腎機能で調整が必要な薬品の推奨投与量範囲内の処方は20,788件（94%）で、推奨投与量範囲外は1,365件（６%）であった。抗微生物薬処方の方が推奨投与量範囲外の割合が高かった（$p<0.001$）。

経口の抗微生物薬の中では第３世代セフェム系薬の推奨投与量範囲外の割合が36%と高かった（表４）。次いでキノロン剤が８%であった。第３世代セフェムと同系統のβラクタム系でも第１世代セフェムおよび同ペニシリン系は推奨投与量範囲外の割合は３%と第３世代セフェムの十分の一以下であった。マクロライド・ST合剤・その他の抗微生物薬は１-３%であった。抗微生物薬の種別による推奨投与量範囲外の割合には差が認められた（$p<0.001$）。

考　　察

今回我々は腎機能で調整が必要な薬品に対するシステムのベースラインでの稼働状況を解析することによ

表３　Univariate analysis Antibiotics and other drugs regulated by renal function

Classification	All drug	Correct dose	Incorrect dose	*p*-value
Antibiotics	7,766	7,064（91）	702（9）	<0.001
Other	22,153	20,788（94）	1,365（6）	

表４　Breakdown of oral antibiotics

Classification	All antibiotics	Correct dose	Incorrect dose
β-lactam			
Penicillin	1,839	1,787（97）	52（3）
1st Cephem	502	489（97）	13（3）
3rd Cephem	1,509	969（64）	540（36）
Macrolide	1,362	1,346（99）	16（1）
ST	757	734（97）	23（3）
Quinolon	244	224（92）	20（8）
Other	187	183（98）	4（2）
Total	6,495	5,818（90）	677（10）

$p<0.001$

り、システムの有用性について検討した。

病院の特性に関しては、同様の規模の全国の平均とほぼ差がないと考えられた[5]。すなわち、全国の500床以上の平均ベッド数は618、2017年６月の１か月平均入院処方数は8,434、2017年６月の１か月平均外来処方数は11,236、平均医師数は194、医師一人当たりの１か月平均入院処方数は43.5、医師一人当たりの１か月平均外来処方数は57.9との報告に対し、島根県立中央病院ではそれぞれ634、8,051、9,088、167、49.1、55.4であり、同等と考えられる。したがって今回のデータは全国の病院でも応用できる可能性がある。

腎機能で調整が必要な薬品のうち約1/4が抗微生物薬であった。また、抗微生物薬は他の腎機能で調整が必要な薬品よりも推奨投与量範囲外が多かった。過去の研究でもガイドラインで推奨されたアミノグリコシド系抗菌薬投与量の研究[6]、ICUでの腎機能に応じた抗微生物薬量の検討[7]、などにおいても過量投与の調整が必要とされており、抗微生物薬は緊急に処方されることも多いので慎重な処方が検討される。

内服抗微生物薬では第３世代セフェム系薬およびキノロン剤で推奨投与量範囲外が多かった。先行研究では数種類の抗微生物薬での腎機能による決断支援システムはあるが[8]、今回の研究のように65種類以上の薬剤を対応するシステムではないので処方内容の比較は困難ではある。ただ、第３世代セフェム系薬およびキノロン剤は、薬剤耐性（AMR）対策アクションプランでも減量が目標として挙げられており[9]、薬剤の選択の問題のみならず用量でも問題がある傾向にあると考えられた。第３世代セフェム系薬に関しては、他のβラクタム系のペニシリン系・第１世代セフェムが推奨投与量範囲内が多いことを比べて考えると、第３世代セフェム系薬は十分に吟味されずに使用されている可能性がある。今後は用量のみならず、より適切に薬剤の選択ができる方法が望まれる。

今回の研究ではいくつかの限界が挙げられる。１つ目は、単一での施設での状況であること。ただし、同様の病院と処方数などが大きくずれていないのでおおむね同等の規模の病院では当てはまると考えられる。２つ目は、腎機能のみで他の問題（肝障害・アレルギーなど）は検討されていないこと。また一般的には腎機能低下時に用量を下げることは検討されるが、肥満などに対しての用量増量に関してはシステムに組み込まれていないので今後の検討が必要である[10]。３つ目は、今回はベースラインでの検討なので実際の効果は不明で、オーバードーズに関する方策などの対策が今後必要となってくる[11]。これは実際に画面上で表示してからの効果で再検討の必要がある。

結　　語

腎機能による抗微生物薬投与量推奨ツールは臨床決

断支援システムとして有用であり、外来患者に対しても安全に投与するツールとなりうる。

謝　　辞

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ORIGINAL RESEARCH ARTICLE

Differences in Adverse Drug Events Among Pediatric Patients With and Without Cancer: Sub-Analysis of a Retrospective Cohort Study

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Abstract

Objectives This study investigated the differences in the incidence and severity of adverse drug events (ADEs) in pediatric patients with and without cancer.

Methods We used data from the Japan Adverse Drug Events Study for pediatrics, a cohort study enrolling pediatric inpatients at two tertiary care teaching hospitals in Japan. ADEs were identified by on-site review of all medical charts, incident reports, and prescription queries by pharmacists. Two independent physicians reviewed all potential ADEs and classified ADEs in terms of severity and class of causative medication. We compared the incidence and characteristics of ADEs between pediatric cancer patients and non-cancer patients.

Results We enrolled 1189 patients during the study period, 27 with cancer and 1162 without cancer. We identified 480 ADEs in 234 patients (20%): 191 ADEs among 21 cancer patients and 289 ADEs among 213 non-cancer patients (7.1 per patient vs. 0.25 per patient, respectively; $p < 0.0001$). The most common medications associated with ADEs in cancer patients were antitumor agents; in contrast, medications associated with fatal or life-threatening ADEs in cancer patients were most often sedatives (25%) and blood products (25%). Medications associated with fatal or life-threatening ADEs among non-cancer patients were most often sedatives (15%). The percentages of fatal or life-threatening ADEs in cancer patients and non-cancer patients were 2.1 and 4.5%, respectively.

Conclusions Pediatric patients with cancer have a higher risk for ADEs. Although the overall severity was similar between patients with and without cancer, the most common classes of causative medication and medications associated with a higher rate of severe ADEs differed. Application of this information may help minimize the impact of ADEs in pediatric patients.

Key Points

Adverse drug events occurred in pediatric patients with cancer 28 times more frequently than in those without cancer.

As expected, the medications most commonly associated with adverse drug events in pediatric patients with cancer were antitumor agents, but fatal or life-threatening events due to such medications were rare (0.7%).

The category of causative medication and severity of adverse drug events differed between pediatric patients with cancer and without cancer.

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1 Introduction

Adverse drug events (ADEs) are injuries due to medication use. ADEs represent a serious problem in healthcare because they are the most frequent cause of injuries due to medical care in hospitals in developed countries [1, 2]. In Japan, the JADE (Japan Adverse Drug Events) study, a multicenter cohort study, was conducted to estimate the epidemiology of ADEs in several settings [3]. In both Japan and in Western countries, ADEs have been associated with substantial increases in morbidity and mortality [1, 3–5]. Patients who need chemotherapy often experience ADEs as the result of antitumor agents [6]. Pediatric inpatients are vulnerable to ADEs because they often cannot describe their symptoms and have small metabolic reserves [7, 8]. In particular, pediatric cancer patients receiving antitumor agents are at high risk for ADEs because of the nature of the patients and drugs involved [9, 10].

To examine the epidemiology of ADEs in pediatric inpatients, we conducted the JADE study for pediatric patients [11]. As a sub-study, we analyzed differences in ADEs between pediatric patients with and without cancer and evaluated the causes, symptoms, and severity of the ADEs.

2 Methods

2.1 Study Design and Patient Population

This study was based on the data from the JADE study for pediatric inpatients, which was a historical cohort study performed in two tertiary care teaching hospitals in Japan. The details of the study have been described elsewhere [11]. Briefly, we included all patients aged ≤15 years admitted to any ward, including the neonatal intensive care unit (NICU) and pediatric intensive care unit (ICU), and patients aged >15 years admitted to any pediatric ward over a 3-month period in 2009. Because some adult patients with congenital or metabolic diseases were cared for by pediatricians from a young age, such patients were included in this cohort study based on the protocol. We excluded neonates in well-baby nurseries from this study because they were healthy and not cared for by pediatricians. If neonates had a problem such as temporary dyspnea or mild cyanosis of the limbs at birth, they were admitted to the NICU and cared for by neonatologists. We included these neonates in this study. We categorized the age groups as follows: neonates (aged <1 month), infants (1 month to <1 year), preschoolers (1 year to <7 years), school-aged children (7 to <13 years), teenagers (13 to <19 years), and adults (≥19 years).

The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, the institutional review boards waived the need for informed consent.

2.2 Definitions

The primary outcome of the study was the occurrence of ADEs, which we compared between pediatric patients with and without cancer. Cancer patients were defined as those who were diagnosed with any malignant tumor or those who had a tumor and were receiving antitumor agents. Non-cancer patients included those with benign or other tumors. We used validated methodology for the classification of ADEs [12]. An ADE was defined as a health injury occurring because of medication use. For example, nausea or vomiting in a patient receiving an antitumor agent was considered an ADE. We categorized the severity of ADEs as follows: fatal (resulting in death), life-threatening (requiring transfer to the ICU or causing anaphylactic shock), serious (neutropenia requiring a special protective environment, cutaneous lesions requiring therapy, gastrointestinal bleeding, altered mental status, excessive sedation, increased creatinine level, or decreased blood pressure), or significant (rash, diarrhea, or nausea). Categories of ADE symptoms included bleeding; central nervous system; allergic or skin reaction; liver or metabolic dysfunction; cardiovascular; gastrointestinal; renal; respiratory; bone marrow suppression or cytopenia; and other.

We categorized medications as follows: antihistamines, antibiotics, antitumor agents, adrenaline/anticholinergics, blood products, hematopoietic drugs, anticoagulants, diuretics/cardiovascular agents, antipyretic analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, sedatives, antipsychotics, diagnostic drugs/electrolytes and fluids/others, antitussives, ophthalmic/otolaryngologic/dermatologic drugs, laxatives, local anesthetics, corticosteroids, hormones/insulin, aminophylline, and peptic ulcer drugs. Antitussives did not include codeine but did include expectorants, and sedatives did not include narcotics or opiates. Because doses for pediatric patients were generally determined by body weight, and the standard doses varied between drugs, we did not account for dose in the analyses.

2.3 Data Collection and Review Process

Trained reviewers based at each participating hospital reviewed all medical charts, laboratory results, incident reports, and prescription queries from pharmacists. The trained reviewers included a board-certified pediatrician,

pediatric nurses, and a dietitian; the pediatrician trained all reviewers in a standard manner, as reported elsewhere [12]. Reviewers collected the characteristics and administrative data for all patients enrolled in the cohort and identified potential ADEs and associated details, such as detailed symptoms and drug name, dose, route, and class.

After data collection, two independent physician reviewers assessed, in a standard manner, whether any potential ADEs should be classified as ADEs [12]. Briefly, the reviewers summarized and discussed many aspects, including preceding drugs, other causative conditions occurring during hospitalization, previous literature reports, alleviation after discontinuation of drug, repeated symptoms when the same drug was re-introduced, and so on. They classified the severity, symptoms, and class of medication involved in ADEs. When disagreement arose over classification of an event, the reviewers reached consensus through discussion. Uncertain symptoms or those for which consensus was not reached were excluded from the ADEs.

2.4 Statistical Analyses

Categorical variables regarding patient characteristics are reported as numbers and percentages. A Chi squared test was used to compare patients with and without cancer. We also constructed a logistic regression model for cancer patients who developed ADEs, adjusting for the age group and admission to an ICU. The likelihood of ADEs was expressed as an odds ratio (OR) and its 95% confidence interval (CI). The ADE rate per 100 patients, ADE severity, and ratio of ADE severity for each drug were compared between cancer and non-cancer patients; the Chi squared test was used for categorical variables.

We carried out all analyses using JMP 12.0 software (SAS Institute Inc., Cary, NC, USA). Two-tailed p values <0.05 were considered statistically significant.

3 Results

3.1 Patient Characteristics

Among the 1189 patients included in the JADE study for pediatrics, 480 ADEs occurred in 234 (20%) patients. Among the different age categories, there were 252 (21%) neonates, 174 (15%) infants, 465 (39%) preschoolers, 189 (16%) school-aged children, 98 (8%) teenagers, and 11 (1%) adults (Table 1). The age of adults ranged from 20 to 42 years.

Antibiotics (61%), antipyretic analgesics/NSAIDs (32%), adrenaline/anticholinergics (26%), and antitussives (26%) were the three most frequent classes of prescribed medication on admission.

3.2 Comparison of Cancer Patients and Non-Cancer Patients

In all, we included 27 cancer patients and 1162 non-cancer patients in this study. One patient with teratoma and another with optic glioma were categorized as cancer patients because they received chemotherapy during the hospitalization. Patients with cancer had more operations and received antitumor agents or anticoagulants more often than those without cancer (Table 1). On the other hand, patients without cancer more often received adrenaline/anticholinergics and antipyretic analgesics/NSAIDs. Overall, 191 ADEs occurred in 21 cancer patients and 289 ADEs occurred in 213 non-cancer patients. The ADE rate per 100 patients in cancer patients was 707 compared with 25 in non-cancer patients ($p < 0.0001$). The adjusted OR of ADEs among patients with cancer was 12.3 (95% CI 4.9–31.1) compared with patients without cancer.

The severity of ADEs in cancer patients was similar to that in non-cancer patients ($p = 0.13$). The percentages of fatal or life-threatening ADEs in cancer patients and non-cancer patients were 2.1 and 4.5%, respectively (Fig. 1).

Among 191 ADEs in cancer patients, 149 (78%) were associated with antitumor agents, 13 (7%) with corticosteroids, ten (5%) with antibiotics, and eight (4%) with sedatives. In contrast, among 289 ADEs in non-cancer patients, 135 (47%) were associated with antibiotics, 52 (18%) with sedatives, 21 (7%) with corticosteroids, and 13 (4%) with antipyretic analgesics/NSAIDs (Fig. 2).

In contrast to all ADEs, medications with a high frequency of fatal or life-threatening ADEs among cancer patients included sedatives (25%) and blood products (25%); those among non-cancer patients included anticoagulants (50%), sedatives (15.4%), and hormones/insulin (50%), although the sample size was small (Fig. 3).

3.3 Adverse Drug Events (ADEs) Due to Antitumor Agents

Among the 27 cancer patients, 149 ADEs occurred in 18 patients due to antitumor agents, for a rate of 552 per 100 patients. Analysis of the severity of ADEs due to antitumor agents showed there was one (0.7%) life-threatening ADE, 43 (29%) serious ADEs, and 105 (70%) significant ADEs. Symptom categories of ADEs due to antitumor agents included five (3%) bleeding, eight (5%) central nervous system, 11 (8%) allergic or skin reaction, 17 (11%) liver or metabolic dysfunction, one (0.7%) cardiovascular, 58 (39%) gastrointestinal, four (3%) renal, one (0.7%)

Table 1 Patient characteristics

Characteristics	All ($n = 1189$)	Cancer patients ($n = 27$)	Non-cancer patients ($n = 1162$)	p value
Age				
Neonate (<1 month)	252 (21)	0 (0)	252 (22)	0.02
Infant (1 month to <1 year)	174 (15)	5 (19)	169 (15)	
Preschooler (1 to <7 years)	465 (39)	12 (44)	453 (39)	
School-aged (7 to <13 years)	189 (16)	4 (15)	185 (16)	
Teenager (13 to <19 years)	98 (8)	6 (22)	92 (8)	
Adult (≥19 years)	11 (1)	0 (0)	11 (1)	
Sex				
Male	649 (55)	18 (67)	631 (54)	0.2
Surgery during hospitalization	294 (25)	14 (52)	280 (24)	0.001
Drug after admission				
Antihistamines	244 (21)	8 (30)	236 (20)	0.24
Antibiotics	727 (61)	19 (70)	708 (61)	0.32
Antitumor agents	4 (0.3)	3 (11)	1[a] (0.1)	<0.0001
Adrenaline/anticholinergics	309 (26)	1 (4)	308 (27)	0.006
Blood products	28 (2)	0 (0)	28 (2)	1.0
Hematopoietic drugs	24 (2)	0 (0)	24 (2)	1.0
Anticoagulants	86 (7)	6 (22)	80 (7)	0.002
Diuretics/cardiovascular agents	119 (10)	2 (7)	117 (10)	1.0
Antipyretic analgesics/NSAIDs	383 (32)	3 (11)	380 (33)	0.02
Anticonvulsants	173 (15)	7 (26)	166 (14)	0.09
Sedatives	69 (6)	4 (15)	65 (6)	0.07
Antipsychotics	13 (1)	0 (0)	13 (1)	1.0
Diagnostic drugs/electrolytes and fluids/others	967 (81)	21 (78)	946 (81)	0.63
Antitussives	305 (26)	3 (11)	302 (26)	0.12
Ophthalmic/otolaryngologics/dermatologics	154 (13)	2 (7)	152 (13)	0.56
Laxatives	191 (16)	6 (22)	185 (16)	0.38
Local anesthetics	39 (3)	2 (7)	37 (3)	0.22
Corticosteroid	138 (12)	6 (22)	132 (11)	0.08
Hormones/insulin	24 (2)	2 (7)	22 (2)	0.1
Aminophylline	67 (6)	0 (0)	67 (6)	0.4
Peptic ulcer drugs	111 (9)	2 (7)	109 (9)	1.0

Data are presented as n (%) unless otherwise indicated

ADEs adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] One patient without cancer received an antitumor agent to treat a non-malignant condition

respiratory, 37 (25%) bone marrow suppression or cytopenia, and seven (5%) other.

4 Discussion

The rate of ADEs in pediatric patients with cancer was higher than in those without cancer—cancer patients had seven ADEs on average. Although the sample size of cancer patients was small, the overall severity of the ADEs seemed similar between cancer and non-cancer patients. While most of the ADEs for cancer patients were caused by antitumor agents, most of the fatal or life-threatening ADEs were caused by sedatives and blood products. The classes of drugs causing fatal or life-threatening ADEs seemed to differ between pediatric patients with cancer and those without.

Data on ADEs among pediatric patients with cancer are sparse. For example, Takata et al. [13] found that pediatric patients with cancer more frequently experienced ADEs and that hematology and oncology wards had a higher incidence of ADEs. In this study, while we found that

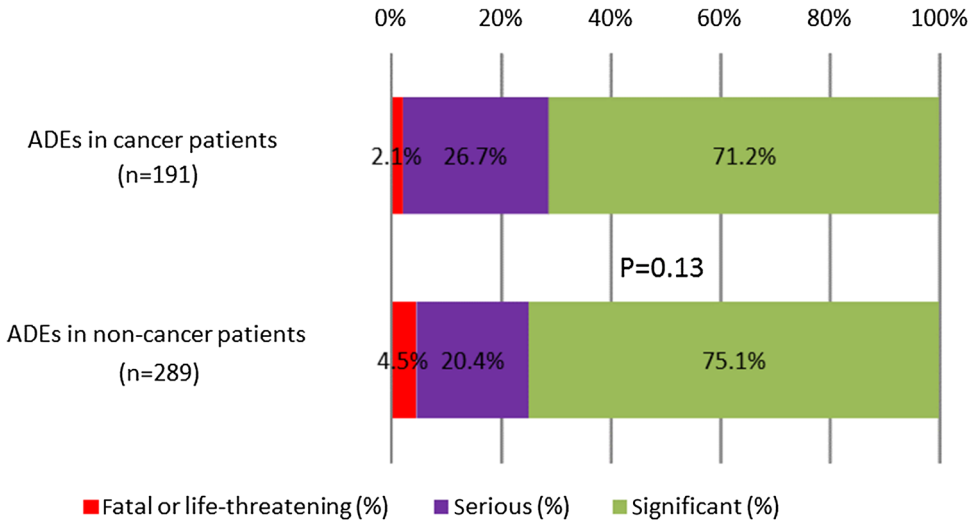

Fig. 1 Comparison of adverse drug event severity between cancer patients and non-cancer patients. *ADEs* adverse drug events

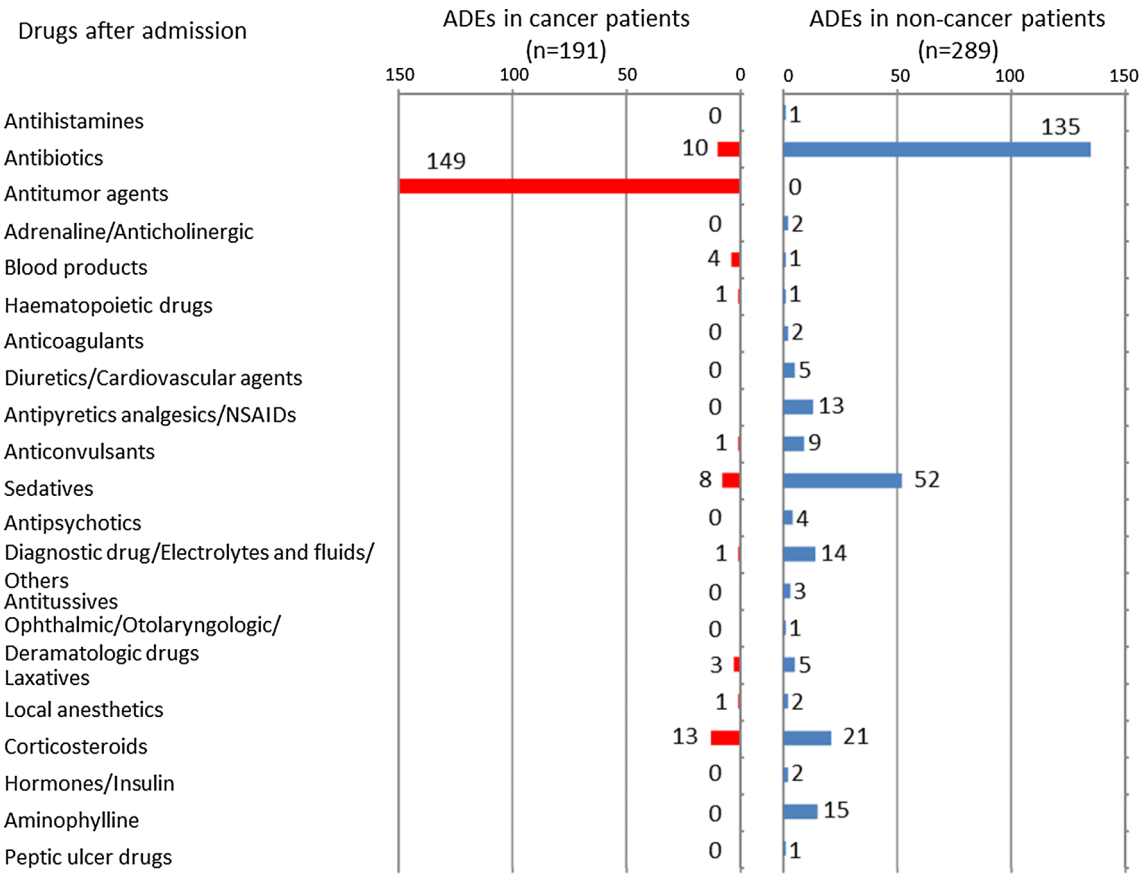

Fig. 2 Causative drugs of adverse drug events. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

ADEs occurred frequently in pediatric cancer patients, the rate of fatal or life-threatening ADEs was much lower (2.1%). A systematic review of studies in pediatric patients with leukemia reported treatment-related mortality (which should be considered an ADE) of 3.6% [14], which is similar to the rate in our data. The higher incidence of all ADEs but comparable risk for fatality in the current study might be because we proactively collected all ADEs in a standard manner, and most ADEs were minor injuries.

The prevalence of ADEs by medication classes differs between settings. For example, one study in hospitalized adults found that 32% of ADEs due to antitumor agents were fatal [15]. Moreover, another study [16] in patients with unplanned cancer admissions found that 13% had

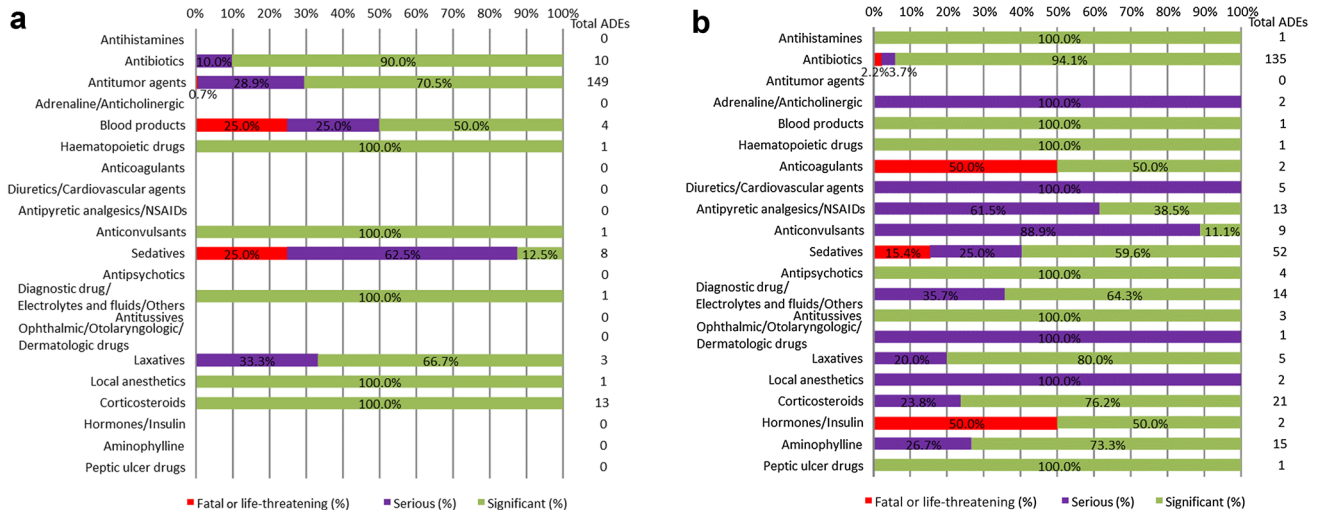

Fig. 3 Severity of adverse drug events in **a** cancer and **b** non-cancer patients. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

ADEs. Furthermore, Nazer et al. [15] reported that, among oncology patients, the medications most commonly associated with an ADE requiring ICU admission were antitumor agents, analgesics, and anticoagulants. In contrast, in the current study in the pediatric setting, only one (0.7%) fatal or life-threatening ADE due to antitumor agents occurred, although the number of patients evaluated was small.

As sepsis from febrile neutropenia (FN) sometimes causes a fatal ADE, it is an important type of ADE due to antitumor agents. Admittance for FN has been reported to be 4.4 per 100 oncology admissions [16], with an annual incidence of 19.4 cases of FN per 1000 oncology admissions [17]. Because we classified such symptoms as bone marrow suppression rather than FN, the incidence of bone marrow suppression was higher, at 205 per 100 cancer patients. This provides additional evidence that antitumor agents as a class are most commonly associated with ADEs.

We must recognize that drugs with great benefit generally have a high rate of ADEs. Moreover, differences were apparent between the drug classes causing ADEs in cancer patients compared with in non-cancer patients. Such differences should be noted to assist with awareness and proper monitoring when these drugs are administered. Although the frequency of ADEs due to antitumor agents was high, the high risk for fatal or life-threatening ADEs with other drugs, namely blood products and sedatives, should also be considered for pediatric patients with cancer.

Our study has several limitations. First, the number of pediatric patients with cancer was much smaller than that without cancer, so we could not draw definitive conclusions. On the other hand, this study was conducted at a daily clinical setting, and the findings reflect real-world data. Second, we conducted this pediatric study at two tertiary care teaching hospitals. Therefore, the results are not generalizable to non-tertiary care teaching hospitals, in which most children receive medical care in Japan. Third, some ADEs may not have been noted in the charts and may thus not have been detected, potentially resulting in underestimation of ADEs. In addition, because many ADEs due to antitumor agents are well-known and noticeable, other ADEs in cancer patients might have been overlooked. However, more robust alternatives to measure ADEs have not yet been developed. Finally, the classification of ADEs seemed arbitrary, and many symptoms were difficult to classify as ADEs or other conditions. However, we determined the most likely causative drug based on the historical evidence from the literature, and this method is the best one currently available.

5 Conclusion

Pediatric patients with cancer had more frequent ADEs than did those without cancer. While most ADEs in cancer patients were caused by antitumor agents, other medications caused the greatest proportion of fatal or life-threatening ADEs. The overall severity of ADEs in patients with and without cancer was similar. Nonetheless, knowing which medication classes have higher risks for ADEs in pediatric patients with and without cancer may help providers more carefully use those medications and monitor patients, which may in turn help to minimize the impact of ADEs in pediatric patients overall.

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Compliance with Ethical Standards

Informed consent The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, the institutional review boards waived the need for informed consent.

Conflict of interest Drs. Koizumi, Ohta, Sakuma, Okamoto, Matsumoto, and Morimoto have no conflicts of interest. Dr. Bates received equity from Intensix, which makes software to support clinical decision making in intensive care; is named as co-inventor on patent no. 6029138 held by Brigham and Women's Hospital (Boston, MA, USA) on the use of decision-support software for medical management licensed to the Medicalis Corporation; holds a minority equity position in Medicalis, which develops web-based decision support for radiology test ordering; consults for EarlySense, which makes patient safety monitoring systems; has received equity and cash compensation from QPID Inc., a company focused on intelligence systems for electronic health records; has received cash compensation from CDI (Negev) Ltd., a not-for-profit incubator for health IT startups; and has received equity from Enelgy, which makes software to support evidence-based clinical decisions, from Ethosmart, which makes software to help patients with chronic diseases, and from MDClone, which takes clinical data and produces de-identified versions of it.

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Ethical approval This study was approved by all institutional review boards at all participating hospitals and was conducted in accordance with the provisions of the Declaration of Helsinki and the ethical guidelines for clinical studies in Japan.

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RESEARCH ARTICLE Open Access

The epidemiology of adverse drug events and medication errors among psychiatric inpatients in Japan: the JADE study

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Abstract

Background: Knowledge of the epidemiology of adverse drug events (ADEs) and medication errors in psychiatric inpatients is limited outside Western countries. The nature of ADEs and medication errors are important for improving the quality of care worldwide; therefore, we conducted the Japan Adverse Drug Events Study, a series of cohort studies at several settings in Japan.

Methods: This report included 448 inpatients with 22,733 patient-days in a psychiatric hospital and psychiatric units at a tertiary care teaching hospital over 1 year. Four psychiatrists and two other physicians reviewed all medical charts and related documents to identify suspected incidents. The physicians later classified those incidents into ADEs, potential ADEs, medication errors, or exclusions and evaluated the severity and preventability if the incidents were events.

Results: During the study period, we identified 955 ADEs and 398 medication errors (incidence: 42.0 and 17.5 per 1000 patient-days, respectively). Among ADEs, 1.4 %, 28 %, and 71 % were life-threatening, serious, and significant, respectively. Antipsychotics were associated with half of all ADEs. The incidence of medication errors was higher in medical care units than in acute and nursing care units (40.9, 15.6, and 17.4 per 1000 patient-days, respectively). The monitoring and ordering stages were the most common error stages (39 % and 34 % of all medication errors, respectively), and 76 % of medication errors with ADEs were found at the monitoring stage. Non-psychiatric drugs were three times as likely to cause ADEs with errors compared to psychiatric drugs.

Conclusions: Antipsychotic use, inadequate monitoring, and treatment of physical ailments by psychiatrists may contribute to the high incidence of medication errors and ADEs among psychiatric inpatients in Japan. Psychiatrists should be cautious in prescribing antipsychotics or unfamiliar medications for physical problems in their psychiatric patients, and should monitor patients after medication administration.

Keywords: Adverse drug event, Medication error, Epidemiology, Psychiatry, Patient safety

Abbreviations: ADE, Adverse drug event; CI, Confidence interval; IQR, Interquartile range; SD, Standard deviation

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Background

Adverse drug events (ADEs) are drug-related injuries resulting from medical intervention [1–3]. ADEs are generally the most frequent cause of injuries due to medical care in hospitals [4, 5]. Psychiatric inpatients are at high-risk for these injuries because pharmacotherapy plays a central role in psychiatric treatment [6, 7]. In addition, many psychiatric patients present with comorbid medical disorders that require treatment with non-psychiatric drugs, and when these conditions are treated in psychiatric hospitals, this puts patients at further risk for ADEs and medication errors [7, 8].

There is a need for more epidemiological data concerning appropriate medication use in order to provide safer and more effective pharmacological treatment for psychiatric inpatients. Previous studies, however, have noted the complexities of identifying ADEs and medication errors in psychiatric settings because it is difficult to distinguish ADEs caused by drugs from symptoms related to mental disorders; in addition, it can be difficult to define medication errors in these settings, as psychiatric pharmacotherapy often deviates from standard treatment [9, 10]. In fact, there have been notably few comprehensive studies on this topic, especially regarding ADEs [7, 11–13]. Furthermore, the studies that have been conducted all took place in Western countries, meaning that their results cannot be generalized to clinical settings in other countries without first assessing local data [14], because mental health services differ between countries. For example, longer hospital stays and lower staff ratios are two characteristics of Japanese psychiatric care [15], while many African countries suffer from a critical lack of psychiatrists and pharmacists [16]. To this end, we conducted a historical cohort study in psychiatric settings to estimate the incidence and nature of ADEs and medication errors among psychiatric inpatients in Japan.

Methods

Study design and patient population

This historical cohort study was conducted as part of a multicenter cohort study known as the Japan Adverse Drug Events (JADE) Study [17, 18]. As part of the JADE study series, we collected information using the standard JADE protocol. [3, 17, 18] Data were collected from the psychiatric inpatient units at one psychiatric hospital and one tertiary care teaching hospital. There were a total of 438 psychiatric inpatient beds between these two hospitals, including beds in acute care units, nursing care units, and medical care units. The acute care unit comprises the main section of a psychiatric department in which patients with an acute mental disorder receive targeted mental care. Psychiatric patients who have recovered from the acute stage of their condition but who still require nursing care are admitted to nursing care units. Medical care units are specialized sections within a psychiatric department that provide treatment to psychiatric patients with physical medical conditions. Both hospitals included in this study used electronic medical records.

At the tertiary care teaching hospital, patients were treated both by attending psychiatrists and by resident psychiatrists, who have <3 years of training after obtaining their medical license. Resident psychiatrists practiced under the supervision of attending psychiatrists and primarily ordered medications. In contrast, most of the psychiatrists at the psychiatric hospital were attending psychiatrists. Both hospitals admitted patients to the acute care or medical care units within the psychiatry department if psychiatric disorders were the main presenting problem and the patients' physical problems were considered to be mild; internists provided medical consultations as needed. Conversely, if patients' physical complications were considered to be more severe than their psychiatric problems, or if patients required intensive care (for example, as a result of myocardial infarction or femoral fracture, or if they required intubation), they were discharged from the psychiatric department and transferred to non-psychiatric wards for subsequent care.

Data were collected from all psychiatric inpatients who were admitted to and discharged from the acute, nursing and medical care units from April 1, 2010 through March 31, 2011. The main measures that were evaluated were patient-days and the number of admissions. The study was approved by the institutional review boards of the Kyoto Prefectural University of Medicine and by the institutional review boards of the two participating hospitals. The need for informed consent was waived because all data were collected as part of the hospitals' daily practices.

Definitions

The primary outcome measured in this study was the number of ADEs, defined as drug-related injuries resulting from medical intervention [1, 2]. The term ADE has a wide spectrum of definitions, including harm caused by drugs at a usual dosage (adverse drug reactions: ADRs) or at an unusual dosage, and also including harm from dose reduction and discontinuation of drug therapy [19]. For example, an extrapyramidal symptom, such as akathisia, occurring after a patient receives antipsychotics, and with no other apparent cause, is considered to be an ADE. Rebound insomnia that occurs following discontinuation of sedatives is another example of an ADE. An ADE was then categorized by severity as fatal, life-threatening, serious or significant. Fatal ADEs were those that resulted in death. Life-threatening ADEs were those that caused such issues as respiratory depression or suicidal behavior. Serious ADEs included gastrointestinal bleeding, falls, or a

decrease in blood pressure. Significant ADEs included cases with milder symptoms, such as diarrhea, constipation, extrapyramidal symptoms or drowsiness.

A secondary outcome that was measured in this study was medication errors. Medication errors could occur at any step of the medication use process (ordering, transcribing, dispensing, administering or monitoring), and medication errors may or may not cause ADEs. If a medication error was found, the type of error and the stage in the process where it occurred were classified. The medication use process included the following stages: ordering by psychiatrists or other physicians; transcription by nurses; dispensing by pharmacists (or by psychiatrists and nurses, as was the case during the night shift and on weekends in the psychiatric hospital); administration by nurses or by patients; and monitoring by psychiatrists, other health professionals or by patients themselves.

ADEs were categorized as either preventable or non-preventable. An ADE was considered to be preventable if it resulted from a medication error or was otherwise ameliorable by available means (e.g., switching to a different drug or cautious monitoring after administration). An ADE that occurred in the absence of a medication error was defined as a non-preventable ADE. For example, a rash that occurred due to lamotrigine use in a patient without a history of lamotrigine-induced rash would not be considered a preventable ADE, but it would be considered as a preventable ADE if the patient had a history of such a rash.

We also classified ADEs according to their potential for causing injury. A potential ADE was an error that had the potential for injury but did not actually result in injury, either because of specific circumstances, chance, or because the error was intercepted. For example, if hypnotics were administered several hours earlier than prescribed, this would constitute a medication error and potential ADE, even if no negative effects were observed because hypnotics may cause immediate somnolence. On the other hand, early administration of anti-dementia drugs would be classified as a medication error but not a potential ADE because the drug rarely causes acute side effects.

Data collection and classification

The definitions and methods used in this study were consistent with those from prior studies on this topic [3, 17, 18]. In this study, four psychiatrists and two physicians, all with experience in the classification of ADEs as a result of previous research on this topic, reviewed all patient charts from each participating hospital, along with laboratory results, incident reports and prescription queries. Research assistants used patient charts to compile demographic characteristics and administrative data for all enrolled patients in the cohort.

Once all data were collected from participating hospitals, the reviewers independently classified relevant incidents as an ADE, potential ADE or medication error, while also recording the details of those incidents. This included information about the name, dose, route and class of the drugs, the details of symptoms resulting from ADEs, and the details related to medication errors such as type, stage and persons who were in charge at the time the error occurred. The reviewers also independently classified all incidents according to their severity and preventability. After all suspected incidents were collected, the reviewers met to confirm the final classification for each incident. When the reviewers disagreed on the classification of an incident, they reached a consensus through discussion.

Statistical analyses

The incidences per 1000 patient-days, crude rates per 100 admissions, and 95 % confidence intervals (CIs) were calculated as a whole and by unit types (acute care unit, nursing care unit, and medical care unit). Continuous variables are presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs), and categorical variables are shown as numbers and percentages. We used the χ^2 test to assess the relationship between drug classes and preventable ADEs. We calculated inter-rater reliabilities using k statistics. Kappa scores between reviewers regarding the presence of an ADE were 0.96 (ADE v. potential ADE or exclude). The kappa for preventability was 0.95 (preventable v. non-preventable), while the kappa for severity was 0.43 (significant v. serious or life-threatening). These values were similar to those published in previous reports by Rothschild et al. (2007) and Morimoto et al. (2011). We performed all analyses using JMP V.11.2 (SAS Institute, Cary, North Carolina, USA) software.

Results

There were a total of 448 admissions with 22,733 patient-days during the study period. The ages of the included patients ranged from 13 to 97 years old, and the mean age was 56 (SD 22) years. Forty-one (185/448) percent of patients were aged ≥65 years, and 247 (55 %) were female. The median hospital stay was 32 (interquartile range 15–75) days. The acute care, nursing care and medical care units admitted 341 (76 %), 75 (17 %), and 32 (7 %) patients, respectively (Table 1). Of all admissions, approximately 42 % were involuntary admissions. The most common reasons for admission were schizophrenic disorders and dementia, and the median number of medications patients were taking on admission was 6 (range 4–8) (Table 1).

Adverse drug events

We identified 1234 suspected incidents, and through reviews and discussions of these suspected incidents, we identified 955 ADEs among 283 patients (63 %) (Fig. 1). The incidence of ADEs was 42.0 [95 % CI 39.4–44.6] per

Table 1 Demographic data for the study population

Factors	No. of patients
	Total (*n* = *448*)
Age ≥ 65 years, *n* (%)	185 (41)
Female, *n* (%)	247 (55)
Admitting unit, *n* (%)	
Acute	341 (76)
Nursing	75 (17)
Medical	32 (7)
Admission pathway, *n* (%)	
Scheduled admission	247 (55)
Emergency admission	201 (45)
Nonresident physician in charge, *n* (%)	379 (85)
Involuntary admission, *n* (%)	186 (41.5)
Number of prescribed medications on admission, median (quartile)	6 (4–8)
Primary diagnosis,[a] *n* (%)	
Dementia	97 (21.7)
Other organic disorders	19 (4.2)
Mental or behavioral disorder due to substance use	48 (10.7)
Schizophrenia and other psychotic disorders	113 (25.2)
Mood disorders	84 (18.8)
Depression	38 (8.5)
Mania, Bipolar disorder	32 (7.1)
Other mood disorders	14 (3.1)
Neurotic, stress-related and somatoform disorders	40 (8.9)
Anorexia	17 (3.8)
Mental retardation	11 (2.5)
Development disorder	12 (2.7)
Other	7 (1.6)

[a]Diagnoses based on the International Classification of Diseases, Tenth Revision [24]

1000 patient-days, and the crude rate was 213 [95 % CI 184–243] per 100 admissions (Table 2). Significant ADEs accounted for 71 % (677 events in 263 patients) of all events, followed by serious ADEs (28 %, 265 in 124) and life-threatening ADEs (1.4 %, 13 in 12). There were no fatal ADEs that occurred during the study.

The most common class of drugs associated with ADEs was atypical antipsychotics (34 %, 323/955), and almost half of ADEs (46.9 %, 448/955) were associated with typical and atypical antipsychotics. Non-psychiatric drugs accounted for 16 % (124/789) of non-preventable ADEs, but were associated with 42 % (69/166) of all preventable ADEs. In other words, the proportion of preventable ADEs to all ADEs associated with non-psychiatric drugs (69 per 193 ADEs; 36 %) was higher compared to psychiatric drugs (97 per 762 ADEs; 13 %) ($P < 0.001$) (Table 3).

When ADEs were assessed by organ system, central nervous system symptoms (including falls, over-sedation and extrapyramidal symptoms) were the most frequent symptoms, accounting for 44 % (415/995) of all ADEs, followed by gastrointestinal symptoms (including diarrhea and constipation) (34 %, 326/955), allergic or skin symptoms (including drip leakage) (6 %, 58/955) and metabolic or liver dysfunction (5 %, 49/955).

Medication errors and potential adverse drug events

We identified 398 medication errors among 174 patients (39 %). The incidence was 17.5 [95 % CI 15.8–19.2] per 1000 patient-days, and the crude rate was 88.8 [95 % CI 72.9–105] per 100 admissions. Among the 398 medication errors, 166 actually resulted in ADEs and were therefore classified as preventable ADEs, whereas 186 had the potential to cause injury but did not result in observed harm (Fig. 1). The incidence and crude rates were approximately two times higher in the medical care units compared to the other units. Furthermore, the

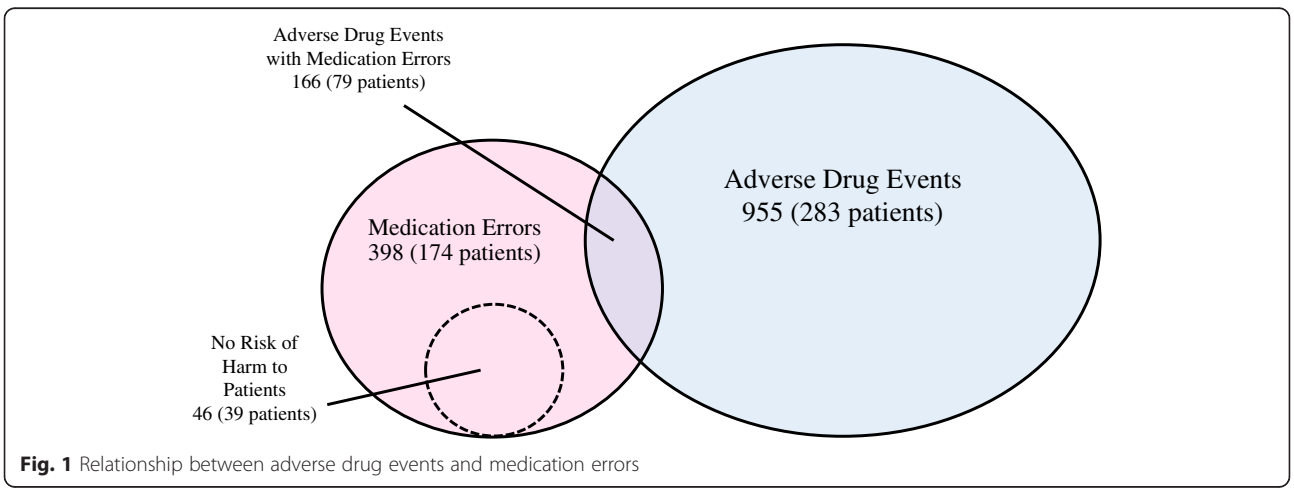

Fig. 1 Relationship between adverse drug events and medication errors

Table 2 Incidences of adverse drug events, medication errors and preventable adverse drug events

Unit	*n*	Patient-days	ADEs	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	725	43.1	40.0–46.1	213	179–246
Nursing	75	4480	157	35.0	29.7–40.4	209	144–275
Medical	32	1419	73	51.4	40.0–62.9	228	88.6–368
Total	448	22733	955	42.0	39.4–44.6	213	184–243
Unit	*n*	Patient-days	Medication Errors	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	262	15.6	13.7–17.4	76.8	62.0–91.7
Nursing	75	4480	78	17.4	13.6–21.2	104	56.3–152
Medical	32	1419	58	40.9	30.6–51.2	181	73.4–289
Total	448	22733	398	17.5	15.8–19.2	88.8	72.9–105
Unit	*n*	Patient-days	Preventable ADEs	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	86	5.1	4.0–6.2	25.2	16.4–34.1
Nursing	75	4480	38	8.5	5.8–11.2	50.7	17.5–83.8
Medical	32	1419	42	29.6	20.8–38.4	131	35.9–227
Total	448	22733	166	7.3	6.2–8.4	37.1	25.8–48.3

ADEs adverse drug events, *CI* confidence interval
[a]Per 1000 patient-days
[b]Per 100 admissions

incidence of preventable ADEs in the medical care units (29.6) was much higher compared to the acute care units (5.1) and nursing care units (8.5) (Table 2).

The incidence of preventable ADEs and non-preventable ADEs was 7.3 [95 % CI 6.2–8.4] and 34.7 [95 % CI 32.3–37.1] per 1000 patient-days, respectively. Thus, 17.4 % (166/955) of ADEs were considered preventable. The incidence of potential ADEs was 8.2 [95 % CI 7.0–9.4] per 1000 patient-days. Forty-six medication errors were determined to carry no risk of injury to patients, so these errors were not considered to be potential ADEs. Twelve percent of potential ADEs (23 cases) were intercepted before a drug was administered and were thus classified as intercepted potential ADEs. Medication errors were most frequently associated with the monitoring stage (39 %, 155/398) and ordering stage (34 %, 134/398) of treatment. In addition, 76 % (126/166) of preventable ADEs occurred during the monitoring stage. Potential ADEs occurred most frequently during the ordering stage, accounting for 46 % (86/186) of all potential ADEs, followed by the administering stage (36 %, 67/186).

Discussion

We determined that ADEs and medication errors were common in Japanese psychiatric inpatient settings. ADEs were observed in 63 % of psychiatric inpatients with an incidence of 42 per 1000 patient-days, and medication errors were observed in 39 % of inpatients with an incidence of 17.5 per 1000 patient-days. Most of these ADEs were not preventable (83 % of ADEs), and 29 % of ADEs were classified as serious or life-threatening. In addition, we identified frequent medication errors at the monitoring stage (39 % of all medication errors), and this was more evident for preventable ADEs (76 % of all preventable ADEs occurred at this stage).

Comparison with findings from previous studies in psychiatric settings

Although there have been several previous studies on ADEs (or ADRs) and medication errors in psychiatric settings, comparisons between the previous studies were difficult because they used different designs and denominators [20]. In addition, among studies utilizing the same denominator but with different study designs, there were significant differences in the reported rates of medication errors (e.g., 0.79 potential ADEs per 1000 patient-days based on a reporting system [21] vs. 1516 medication errors per 1000 patient-days on a retrospective chart review [8]). Therefore, in order to compare our findings with those of previous studies in different settings, we adopted the same definition and methodology used in the study performed by Rothschild et al., which took place in psychiatric settings in the USA [7], as well as those of other studies in general settings in the USA [2] and Japan [17]. In comparison with the present study, Rothschild et al. reported one-quarter incidence of ADEs (10 per 1000 patient-days) and one-third medication errors (6.3 per 1000 patient-days). The difference become even more evident regarding the crude rate of ADEs per 100 admissions (213 v. 10.2) and medication errors (88.8 v. 6.4); this is likely a result of the fact that the mean length of stay is much longer in Japan compared to the USA (50.7 v. 10.3 days).

Table 3 Frequency of adverse drug events according to drug class

Drug Class	ADEs, *n* (%) (*n = 955*)	Preventable ADEs, *n* (%) (*n = 166*)	Non-preventable ADEs, *n* (%) (*n = 789*)	Potential ADEs, *n* (%) (*n = 186*)	Intercepted potential ADEs, *n* (%) (*n = 23*)	Non-intercepted potential ADEs, *n* (%) (*n = 163*)
Antibiotics	10 (1.0)	0 (0)	10 (1.3)	2 (1.1)	0 (0)	2 (1.2)
Antihypertensives	14 (1.5)	3 (1.8)	11 (1.4)	7 (3.8)	1 (4.3)	6 (3.7)
Cardiovascular drugs	8 (0.8)	1 (0.6)	7 (0.9)	12 (6.5)	2 (8.7)	10 (6.1)
Anticoagulants	9 (0.9)	2 (1.2)	7 (0.9)	1 (0.5)	0 (0)	1 (0.6)
Antihyperlipidemics	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Antidiabetics	10 (1.0)	2 (1.2)	8 (1.0)	9 (4.8)	1 (4.3)	8 (4.9)
Peptic ulcer drugs	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Laxatives	40 (4.2)	10 (6.0)	30 (3.8)	7 (3.8)	0 (0)	7 (4.3)
NSAIDs	6 (0.6)	0 (0)	6 (0.8)	7 (3.8)	0 (0)	7 (4.3)
Antiallergic agents	2 (0.2)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)
Electrolytes or fluids	58 (6.1)	50 (30.1)	8 (1.0)	21 (11.3)	1 (4.3)	20 (12.3)
Chinese herbal medicines	2 (0.2)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)
Sedatives (benzodiazepine)	66 (6.9)	28 (16.9)	38 (4.8)	53 (28.5)	0 (0)	53 (32.5)
Sedatives (other)	15 (1.6)	4 (2.4)	11 (1.4)	5 (2.7)	1 (4.3)	4 (2.5)
Anxiolytics	31 (3.2)	6 (3.6)	25 (3.2)	5 (2.7)	2 (8.7)	3 (1.8)
Antidepressants (SSRI, SNRI, NaSSA)	58 (6.1)	2 (1.2)	56 (7.1)	4 (2.2)	3 (13.0)	1 (0.6)
Antidepressants (other)	62 (6.5)	6 (3.6)	56 (7.1)	1 (0.5)	1 (4.7)	0 (0)
Mood stabilizers	45 (4.7)	14 (8.4)	31 (3.9)	4 (2.2)	2 (8.7)	2 (1.2)
Antipsychotics (atypical)	323 (33.8)	32 (19.3)	291 (36.9)	34 (18.3)	6 (26.1)	28 (17.2)
Antipsychotics (typical)	125 (13.1)	4 (2.6)	121 (15.3)	1 (0.5)	0 (0)	1 (0.6)
Anticonvulsants	8 (0.8)	1 (0.6)	7 (0.9)	3 (1.6)	0 (0)	3 (1.8)
Anti-parkinsonian drugs	24 (2.5)	0 (0)	24 (3.0)	1 (0.5)	0 (0)	1 (0.6)
Anti-dementia medicines	5 (0.5)	0 (0)	5 (0.6)	1 (0.5)	1 (4.3)	0 (0)
Other drugs	32 (3.4)	1 (0.6)	31 (3.9)	8 (4.3)	2 (8.7)	6 (3.7)
Psychiatric drugs[a]	762 (79.8)	97 (58.4)	665 (84.3)	112 (60.2)	16 (69.6)	96 (58.9)
Non-psychiatric drugs[b]	193 (20.2)	69 (41.6)	124 (15.7)	74 (39.8)	7 (30.4)	67 (41.1)
All drugs	955 (100)	166 (100)	789 (100)	186 (100)	23 (100)	163 (100)

ADEs adverse drug events, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRI* selective serotonin reuptake inhibitor; *SNRI* serotonin-noradrenaline reuptake inhibitor, *NaSSA* noradrenergic and specific serotonin antidepressants

[a]Psychiatric drugs include: sedatives (benzodiazepine), sedatives (other), anxiolytics, antidepressants (SSRI, SNRI, NaSSA), antidepressants (other), mood stabilizers, antipsychotics (atypical), antipsychotics (typical), anticonvulsants, anti-parkinsonian drugs and anti-dementia medicines

[b]Non-psychiatric drugs include: antibiotics, antihypertensives, cardiovascular drugs, anticoagulants, antihyperlipidemics, antidiabetics, peptic ulcer drugs, laxatives, NSAIDs, antiallergic agents, electrolytes or fluids, Chinese herbal medicines and other drugs

The reasons for the higher incidence of ADEs in the present study may result from differences inpatient characteristics between this study and the USA study. The most common diagnosis in the USA study was mood disorders (66.4 %), while schizophrenic disorder (25 %) followed by dementia (22 %) were the most common disorders in the present study. In accordance with this finding, Schmidt et al. (1984) reported a similar rate of ADRs (346 per 100 admissions) in a previous study performed in Germany in which schizophrenic disorder was the most common diagnosis (37 %) [11], and Hermesh et al. (1985) reported that elderly patients with organic brain disorders were at high risk of ADRs [12].

Differences of the medical system in the treatment of physical complications in psychiatric inpatients may be another possible reason for the discrepancy between our findings and prior reports on this topic. Patients in psychiatric settings in Japan tend to receive more extensive treatments for physical complications compared to patients in the USA, where patients with severe physical complications are commonly transferred to a general-care setting, especially in cases that require electrocardiographic monitoring or a continuous intravenous drip [7]. As a result, patients in Japanese inpatient psychiatric units may be at higher risk of ADEs and medication errors, as prescribing unfamiliar drugs is associated with

medication errors due to lack of experience and knowledge for practitioners in both psychiatric and general settings [7, 22]. In the present study, the proportion of preventable ADEs associated with non-psychiatric drugs was three times higher compared to psychiatric drugs (36 % v. 13 %, respectively), and the incidence of preventable ADEs was higher in the medical care units compared to acute and nursing care units (27.5 v. 5.1 v. 9.2 per 1000 patient-days, respectively).

Comparison to general-care settings in Japan

Compared with a previous study on ADEs in general-care settings in Japan [17], we also found a higher incidence of ADEs (42.0 v. 17.0 per 1000 patient-days) and medication errors (17.5 v. 8.7 per 1000 patient-days). The higher incidence of ADEs and medication errors in psychiatry units may result from the specific complexities of the medications used to treat psychiatric patients. Our results demonstrated that almost half of ADEs were associated with antipsychotics, which is in accordance with previous studies that also found that antipsychotics were the drug class most frequently associated with ADEs [7, 11, 13]. Antipsychotics are prescribed for many patients—not only for the treatment of schizophrenia but also for sedation in agitated patients—and they may cause a wide range of ADEs, including neurological, gastrointestinal, cardiovascular, metabolic and endocrine symptoms. The frequency and intensity of ADEs resulting from the use of antipsychotics (especially when used at high dosages for patients with severe mental disorders) may contribute to the high incidence of ADEs in psychiatric units. In addition, psychiatric patients with severe mental disorders may lack self-awareness, and as a result, they may not be able to fully report their symptoms due to ADEs to medical staff. Furthermore, if they unexpectedly refuse to take their medications, this may cause more frequent medication errors. Finally, monitoring errors may occur due to a combination of lack of experience and knowledge regarding the management of physical complications on the part of psychiatrists as well as inadequate staffing in psychiatric units [15].

Clinical implications

Psychiatrists usually regard ADEs like constipation from antipsychotics and drowsiness from sedatives as common and unavoidable consequences of medication, and believe that such ADEs seldom cause serious outcomes. However, serious ADEs are not rare, even though only a small percentage of ADEs are serious because ADEs occur frequently in medical care. According to the results of this research, life-threatening and serious ADEs accounted for 1.4 % (13 events in 12 patients) and 28 % (265 events in 124 patients) of events, respectively. Psychiatrists sometimes have to decide whether or not to continue administering medications associated with ADEs to treat patients with serious mental conditions; therefore, it is important to identify ADEs at an earlier stage to prevent serious events or to ameliorate their severity.

Moreover, as demonstrated by the results of the present study, psychiatrists were likely to make medication errors with ADEs during physical treatments, especially during the monitoring stage. This may be because psychiatrists focus on psychiatric problems and are less likely to treat physical problems, especially in psychiatric settings. Physicians usually tend to keep psychiatric inpatients at a distance, and psychiatrists in Japan may thus have to treat physical complications, with the exception of very severe physical conditions. Fragmentation of the physical and mental health systems is one of the barriers that hinders patients from receiving adequate care; [23] therefore, fixing the fragmented systems and increasing communication between physicians and psychiatrists could improve patients' physical health and minimize injury from medications among psychiatric inpatients in Japan and other countries.

Study limitation and strengths

Our study had several limitations. First, we conducted this study at one psychiatric hospital and one tertiary care teaching hospital. Therefore, our results may not represent other hospitals, although we attempted to mitigate this limitation by including both a psychiatric hospital and a tertiary care teaching hospital to represent a wide range of psychiatric settings. Second, we could not estimate the incidence and nature of ADEs and medication errors caused by doctors with other specialties in psychiatric settings because almost all medications were prescribed by psychiatrists in this study. Third, some ADEs and medication errors may have been missed, which would mean that our results underestimate the true incidence. However, we were able to precisely evaluate and collect data on confirmed incidents, especially physical symptoms due to ADEs; this was because internists with experience in the classification of ADEs as a result of previous research on this topic [17, 18] played a leading role in this study. In addition, more robust alternatives for measuring ADEs and medication errors have not yet been developed, and the approach we used is the approach that is currently used most widely, suggesting that the figures obtained in this study are the best that are currently available.

Conclusions

We found high incidences of ADEs and medication errors in general psychiatric settings and identified some risk factors for ADEs, including prescription of antipsychotics and treatment during the monitoring stage after drugs are administered. Therefore, clinicians should be

cautious in prescribing antipsychotics and while monitoring patients after administration, especially when patients are unable to report their symptoms due to a severe mental condition. Furthermore, because of the higher risk of ADEs and medication errors during the treatment of physical complications, consultation with physicians in other departments is essential when psychiatrists are considering prescribing unfamiliar medications for physical problems in their psychiatric patients.

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Availability of data and materials
We do not wish to share the datasets because only a portion of the datasets was used in the reported study, and we are going to conduct a secondary analysis using the datasets. We will share the datasets if the datasets have been entirely processed.

Authors' contributions
All authors were involved in the design of the study. NA, MS, TM, TK, KW, and JN collected the data. NA analyzed the data under the technical supervision of MS and TM. NA and JN interpreted study results, and NA wrote the first draft of the manuscript. All authors reviewed the manuscript, provided substantive intellectual contributions, and approved the final version of the manuscript for publication.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the institutional review boards of the Kyoto Prefectural University of Medicine. The need for informed consent was waived because all data were collected as part of the hospitals' daily practices.

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