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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

Editor: Bernhard Schaller.

This work was supported by JSPS KAKENHI Grant Numbers JP17689022 (TM), JP21659130 (TM), JP22390103 (TM), JP23659256 (TM), JP26293159 (TM), JP18H03032 (TM), JP22790494 (MS), JP24689027 (MS), JP15K08862 (MS), JP25860484 (YO), JP15K21535 (YO), and grants from the Ministry of Health, Labor and Welfare of Japan (H26-Iryo-Ippan-012 and H28-ICT-Ippan-004) (TM). However, these funding sources had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the manuscript for publication.

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:16(e15165)

Received: 28 August 2018 / Received in final form: 27 February 2019 / Accepted: 15 March 2019

http://dx.doi.org/10.1097/MD.0000000000015165

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)

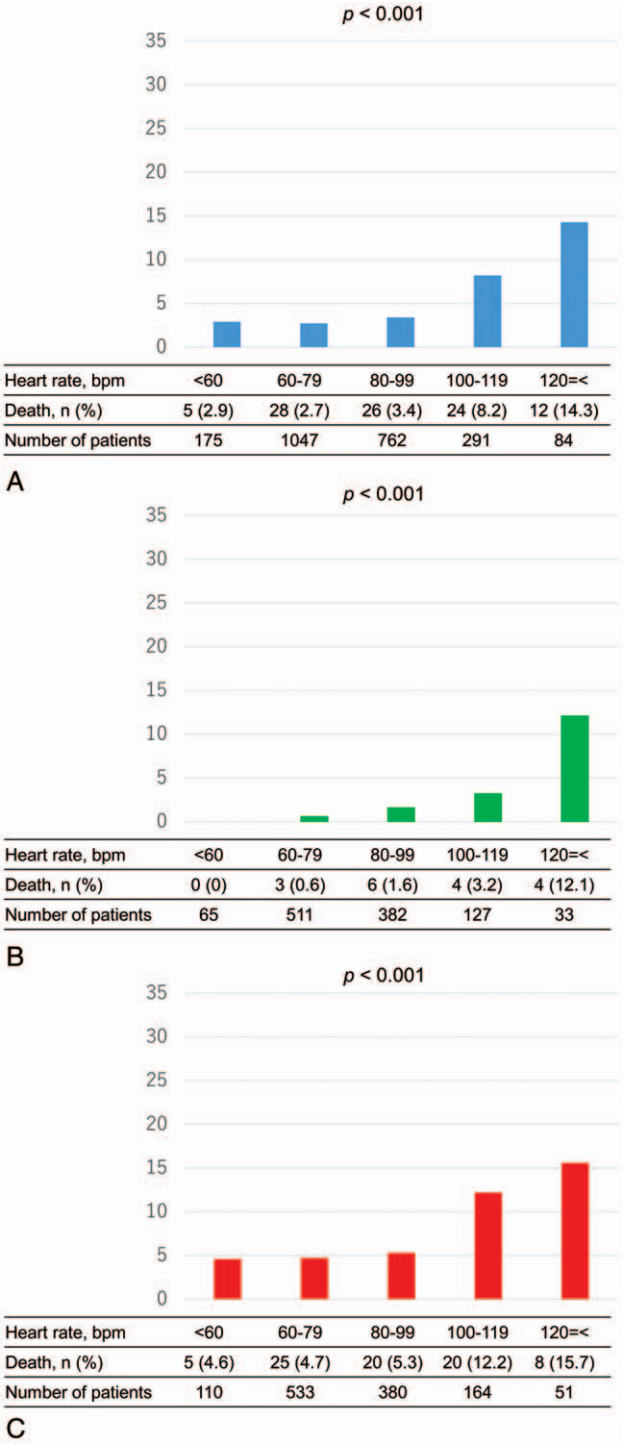

Figure 1. Heart rate on admission and in-hospital mortality in total cohort and according to age. (A) All patients; (B) patients younger than 70 years old; (C) patients equal to or older than 70 years old.

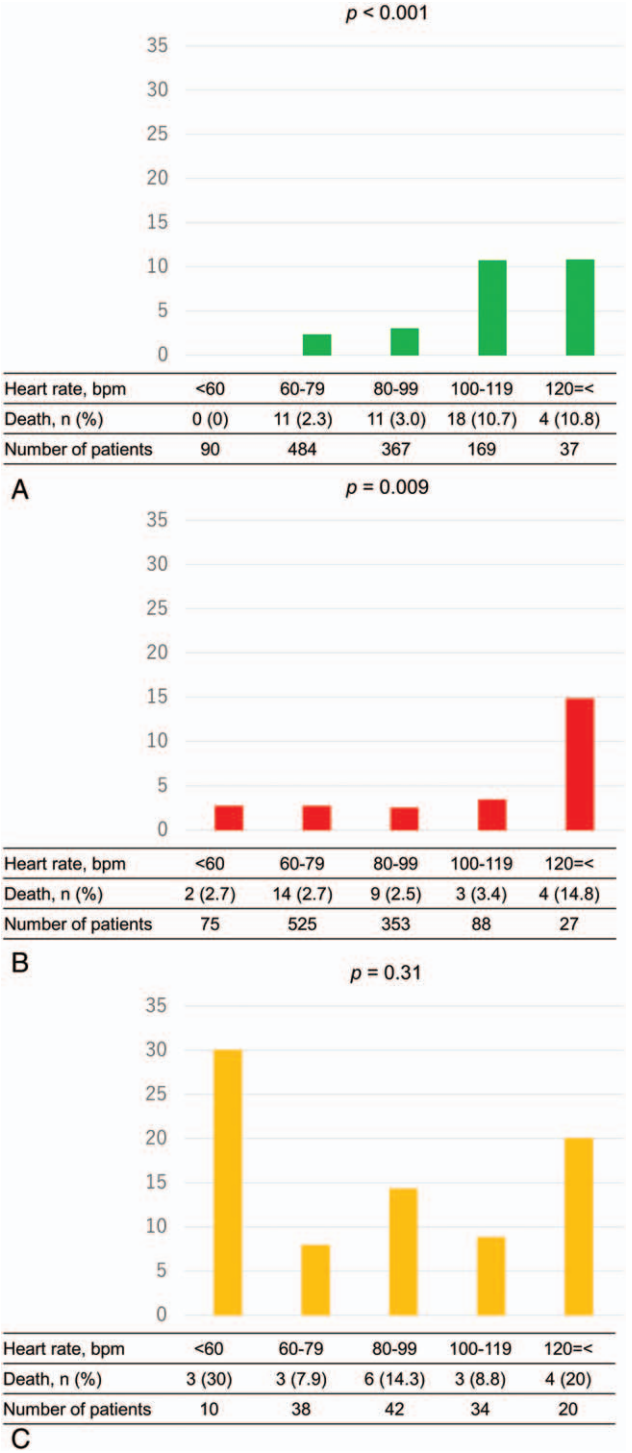

Figure 2. Heart rate on admission and in-hospital mortality according to ward. (A) Medical wards; (B) surgical wards; (C) intensive care unit.

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.

Acknowledgments

This study used part of the data from JADE Study with Decision Support. We are indebted to Dr. Shinji Kosaka, Dr. Kiyoshi Kikuchi, Dr. Tsukasa Nakamura, Mr. Eisaku Hirano, Mr. Kazuo Takeshita, Mr. Tomohiro Sonoyama, Mr. Shuichi Kurahashi, Mr. Koichiro Ichiki, and Mr. Akito Uchio for their management of JADE Study with Decision Support.

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References

[1] Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ 2016;188:E53–63.
[2] Zhang D, Wang W, Li F. Association between resting heart rate and coronary artery disease, stroke, sudden death and noncardiovascular diseases: a meta-analysis. CMAJ 2016;188:E384–92.
[3] Aune D, Sen A, O'Hartaigh B, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis 2017;27:504–17.
[4] Erdur H, Scheitz JF, Grittner U, et al. Heart rate on admission independently predicts in-hospital mortality in acute ischemic stroke patients. Int J Cardiol 2014;176:206–10.
[5] Morimoto T, Sakuma M, Matsui K, et al. Incidence of adverse drug events and medication errors in japan: the JADE study. J Gen Intern Med 2011;26:148–53.
[6] Ohta Y, Sakuma M, Koike K, et al. Influence of adverse drug events on morbidity and mortality in intensive care units: the JADE study. Int J Qual Health Care 2014;26:573–8.
[7] Sakuma M, Ida H, Nakamura T, et al. Adverse drug events and medication errors in Japanese paediatric inpatients: a retrospective cohort study. BMJ Qual Saf 2014;23:830–7.
[8] Ayani N, Sakuma M, Morimoto T, et al. The epidemiology of adverse drug events and medication errors among psychiatric inpatients in Japan: the JADE study. BMC Psychiatry 2016;16:303.
[9] Darabi KF, Ortiz V. Childbearing among young Latino women in the United States. Am J Public Health 1987;77:25–8.
[10] Jette N, Quan H, Hemmelgarn B, et al. The development, evolution, and modifications of ICD-10: challenges to the international comparability of morbidity data. Med Care 2010;48:1105–10.
[11] Ho JE, Larson MG, Ghorbani A, et al. Long-term cardiovascular risks associated with an elevated heart rate: the Framingham heart study. J Am Heart Assoc 2014;3:e000668.
[12] Lancellotti P, Ancion A, Magne J, et al. Elevated heart rate at 24–36 h after admission and in-hospital mortality in acute non-arrhythmic heart failure. Int J Cardiol 2015;182:426–30.
[13] Kara D, Akinci SB, Babaoglu G, et al. Increased heart rate on first day in intensive care unit is associated with increased mortality. Pak J Med Sci 2016;32:1402–7.
[14] Reunanen A, Karjalainen J, Ristola P, et al. Heart rate and mortality. J Intern Med 2000;247:231–9.
[15] Mancia G, Bousquet P, Elghozi JL, et al. The sympathetic nervous system and the metabolic syndrome. J Hypertens 2007;25:909–20.
[16] Abboud FM, Harwani SC, Chapleau MW. Autonomic neural regulation of the immune system: implications for hypertension and cardiovascular disease. Hypertension 2012;59:755–62.
[17] Stuckey MI, Tulppo MP, Kiviniemi AM, et al. Heart rate variability and the metabolic syndrome: a systematic review of the literature. Diabetes Metab Res Rev 2014;30:784–93.
[18] Wulsin LR, Horn PS, Perry JL, et al. Autonomic imbalance as a predictor of metabolic risks, cardiovascular disease, diabetes, and mortality. J Clin Endocrinol Metab 2015;100:2443–8.
[19] Blessberger H, Kammler J, Domanovits H, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. Cochrane Database Syst Rev 2018;3:Cd004476.

Journal of Orthopaedic Surgery and Research

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

Acknowledgments

We express appreciation to Ms. Emi Onoda, medical secretary for performing data extraction.

Funding

This work was partly supported by a grant from the Ministry of Health, Labor and Welfare of Japan (H28-ICT-004) and JSPS KAKENHI Grant Numbers 26293159 and 18H03032.

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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Received: 16 June 2018 Accepted: 15 November 2018
Published online: 28 November 2018

References

1. Mallick IH, Thoufeeq MH, Rajendran TP. Iliopsoas abscesses. Postgrad Med J. 2004;80(946):459–62.
2. Muckley T, Schutz T, Kirschner M, Potulski M, Hofmann G, Buhren V. Psoas abscess: the spine as a primary source of infection. Spine (Phila Pa 1976). 2003;28(6):E106–13.
3. Yee DKH, Samartzis D, Wong YW, Luk KDK, Cheung KMC. Infective spondylitis in Southern Chinese. A descriptive and comparative study of ninety-one cases. Spine. 2010;35:635–41.
4. Del Curling OJ, Gower DJ, McWhorter JM. Changing concepts in spinal epidural abscess: a report of 29 cases. Neurosurgery. 1990;27:185–92.
5. Sampath P, Rigamonti D. Spinal epidural abscess: a review of epidemiology diagnosis and treatment. Journal of Spinal Disorders. 1999;12:89–93.
6. Reihsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. Neurosurg Rev. 2000;23:175–204.
7. Boszcyk BM, Krause P, Bolay H, Hohmann F, Mayer HM. Spinal epidural abscess following blunt pelvic trauma. Eur Spine J. 2000;9:80–4.
8. Soehle M, Wallengang T. Spinal epidural abscesses: clinical manifestations, prognostic factors and outcomes. Neurosurgery. 2002;51:79–85.
9. Rosahl SK, Gharabaghi A, Zink P, Ml S. Monitoring of blood parameters following anterior cervical fusion. J Neurosurg. 2000;92:169–74.
10. An HS, Seldomridge A. Spinal infections Diagnostic tests and imaging studies. Clin Orthop Relat Res. 2006;444:27–33.
11. Navarro Lopez V, Ramos JM, Meseguer V, Perez Arellano JL, Serrano R, Garcia Ordonez MA, et al. Microbiology and outcome of iliopsoas abscess in 124 patients. Medicine (Baltimore). 2009;88(2):120.
12. Govender S. Spinal infection. The Bone & Joint Journal. 2005;87-B:1454–8.
13. Lin MF, Lau YJ, Hu BS, Shi ZY, Lin YH. Pyogenic psoas abscess: analysis of 27 cases. J Microbiol Immunol Infect. 1999;32(4):261–8.
14. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015;45:928–52.
15. Huang JJ, Ruaan MK, Lan RR, Wang MC. Acute pyogenic iliopsoas abscess in Taiwan: clinical features, diagnosis, treatments and outcome. J Infect. 2000; 40(3):248–55.

16. Koslow M, Kuperstein R, Eshed I, Perelman M, Maor E, Sidi Y. The unique clinical features and outcome of infectious endocarditis and vertebral osteomyelitis co-infection. Am J Med. 2014;127(7):669.e9–669.e15.
17. Pola E, Autore G, Formica VM, Pambianco V, Colangelo D, Cauda R, et al. New classification for the treatment of pyogenic spondylodiscitis: validation study on a population of 250 patients with a follow-up of 2 years. Eur Spine J. 2017;26(Suppl 4):479–88. https://doi.org/10.1007/s00586-017-5043-5. Epub 2017 Mar 21.

Rural and Remote Health James Cook University ISSN 1445-6354

ORIGINAL RESEARCH

Experience of receiving care by interns reduces psychological barrier of community residents to further care in Japan

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PUBLISHED

5 September 2018 Volume 18 Issue 3

HISTORY

RECEIVED: 14 October 2017

REVISED: 6 May 2018

ACCEPTED: 30 May 2018

CITATION

Takamura A, Morimoto T. Experience of receiving care by interns reduces psychological barrier of community residents to further care in Japan. *Rural and Remote Health* 2018; **18:** 4613. https://doi.org/10.22605/RRH4613

ABSTRACT:

Introduction: A uniform certified basic training program for interns started in Japan in 2004. Following this change, more interns chose to train in community settings, including in rural areas. Patients' experiences of and attitudes toward interns' practice might vary across communities. To examine the geographic and demographic variations linked to the new training system, a nationwide cross-sectional survey was conducted and analyzed.

Methods: Two years after the start of the new certified basic program, 2400 adults were randomly selected from all areas of Japan. Those who participated were asked about their experiences of and attitudes toward interns' practice.

The data were used to compare differences in geographic areas and by demographic factors.

Results: A total of 1109 (46%) people participated in the study. Of these, 10% (114/1109) had been treated by interns. In total, 37% (410/1084) of respondents were prepared to accept treatment from interns. Those with personal experience of receiving treatment from an intern were significantly more likely to be comfortable with the idea than those who had no personal experience (55%, $p<0.001$). This acceptance level did not vary by region or population (between urban and rural areas). People who were comfortable with interns providing treatment, and who had personal experience of care provision by interns (they or a family member had done so) were more likely to understand the importance of interns being able to practice as part of their clinical training (92% ($p<0.001$) vs 76% ($p=0.006$)). They were also more likely to believe that interns should be able to receive training at smaller hospitals (76% ($p<0.001$) vs 77% ($p=0.02$)).

Conclusions: Acceptance by patients of interns' practice was positively associated with experience of care provision by interns. However, there was no significant difference of acceptance among geographic conditions, and among the size of population. Community-based medical education could be implemented and developed independent of geographic and demographic elements in Japan.

KEYWORDS:

attitudes, community-based medical education, general public, interns, Japan, survey.

FULL ARTICLE:

Introduction

Patients often prefer to see an experienced doctor because they worry that inexperienced doctors will not be able to provide them with suitable treatment[1]. It can therefore be a challenge for junior doctors, also known as interns, to establish good relationships with patients while acquiring the necessary clinical skills through practice[2,3]. Some studies have suggested that patients' level of comfort with care provided by interns appears to differ with interns' level of involvement and competencies, as well as other factors[4-6]. It has also been reported that community-based medical education could play an important role in not only nurturing clinical skills but also understanding community health care for interns and medical students[7,8]. Recently, both urban and rural or remote communities internationally have had reported benefits in terms of medical education from community-based clinical training[9-11]. Previous investigations have shown the importance of active participation of communities in understanding not only community medicine but also the whole community itself[12]. Some past studies have also suggested that these programs can benefit in primary care settings in particular[8,13,14]. However, few studies in medical education have investigated purely geographic or demographic elements, and especially those with a community resident perspective. It is not known whether there is an association between demography or geographic region and patients' acceptance or attitudes toward care provided by interns[15].

A new internship system started in 2004 in Japan, in which interns had to complete 6 months of training in internal medicine; 3 months in emergency medicine; and at least 1 month in each of surgery, pediatrics, obstetrics and gynecology, and community medicine, in 2 years training curricula. Before this, almost 90% of interns were trained in tertiary hospitals. Since 2004, approximately 60% of interns have chosen to start their internships in community hospitals, including in rural or remote areas. Community awareness of clinical training among interns might therefore have changed in recent years.

To investigate the associated geographic elements of the practice by interns, a nationwide survey was carried out in Japan to focus on the relationships between attitudes toward care provided by interns, and patients' experience of this, and whether geographic and demographic variables affected acceptance or understanding of the need for intern training, especially following introduction of the new internship system.

Methods

Study design and participants

A nationwide survey was conducted using a representative sample of 2400 people (15–79 years) selected from the entire population of Japan in 2005. A custom research service (Nippon Research Center; http://www.nrc.co.jp/english/services/custom) was used and the inclusion criteria and sample size were fixed. Participants were selected by multistage stratified random sampling. Municipalities were selected, then specific areas within municipalities, and participants were then selected using the Japanese basic resident register. A total of 200 research assistants went door-to-door to conduct surveys with participants in March 2006. The research assistants visited each participant twice. During the initial visit, they asked participants to complete a paper questionnaire on their views on care from interns, plus demographic factors. They visited again to collect the questionnaire several days later. If the assistants could not contact the participants at the second visit, those people were considered to have declined to participate.

Questionnaire

The questionnaire was developed to measure the experience of and attitudes toward care provision by interns. Key questions addressed participants' experience with, impressions of and requirements associated with treatment by interns. Most of the questions had multiple-choice responses. Eight non-medically trained people reviewed the questionnaire prior to the survey to improve its clarity and brevity.

Measurements and statistical analysis

Data were obtained on participants' characteristics and opinions, including several on experience of and attitudes toward care provision by interns: experience of receiving care from an intern, willingness to accept care provided by interns and the reasons for this, and differences in acceptance of care from interns. Participants were also asked about the importance of nurturing the next generation of doctors and where interns should develop their clinical skills.

Anyone who had ever had a medical appointment with an intern, or whose family member had done so, was defined as having experienced care provided by an intern. Participants' spouses, parents, grandparents, siblings, children and grandchildren were included as family members. Anyone answering 'no/unsure' was defined as having no experience of care provided by interns. Acceptance of care provision by interns was classified into binary variables. Participants who answered 'I am indifferent about being seen by an intern', 'I want to be seen by an intern, if possible', or 'I would love to be seen by an intern' were considered to accept care provided by interns. Those who answered 'I absolutely do not want to be seen by an intern' or 'I do not want to be seen by an intern, if possible' were considered not to accept care from interns.

To examine whether location influenced experience and attitude toward care provision by interns, participants were gathered from almost all regions in Japan and divided into five areas (Hokkaido and Tohoku, 15.4%; Kanto, 30.8%; Chubu and Hokuriku, 20.1%; Kinki, 13.6%; Chugoku, Shikoku and Kyushu, 20.0%). The participants were from communities with a variety of population sizes: 19.2% were from the 14 most populated cities, 30.9% from municipalities with a population of more than 150 000, 22.5% from municipalities with a population of 50 000–150 000, 8% from municipalities with a population of less than 50 000 and 19.3% from rural areas. Participants were classified into age groups: 15–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years and more than 60 years.

People who had been treated by interns were asked for their impressions, and all participants were asked the reasons for their acceptance of care from interns, and for suggestions about interns' clinical training. The data on geographic elements were analyzed against these responses.

Responses on the importance of nurturing the next generation of doctors were categorised as either 'I should be willing or am willing to be examined by interns because nurturing doctors is very important' or 'I don't want to be examined by interns, but I understand the importance of nurturing doctors'. Participants' responses about where interns should train were categorised as either 'only large tertiary hospitals' or 'smaller or community hospitals'.

All responses were coded as either binary or categorical variables. The details of both accepting and non-accepting participants were analyzed by grouping them based on their experience of receiving care from interns (experienced and

inexperienced groups). Impressions about interns' care provision among participants in the experienced group were classified as 'accepting' or 'non-accepting'. Participants' acceptance was also analyzed by participant past experience of having been treated by interns, their age group, the population of their municipality of residence, and region. The difference was assessed using χ^2 or Fisher's exact tests. Statistical analyses were conducted using SPSS v20 (IBM; http://www.spss.com). Observations with missing data were eliminated from analyses and two-tailed *p*-values less than 0.05 were considered statistically significant.

Ethics approval

This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (institutional review board number E160). Informed consent was obtained from each participant.

Results

Demographics

The sample data were representative of the Japanese population (128 million residents; mean age 43 years; 49% men (2005 census)). A total of 1109 (46%) participants completed the questionnaire. The gender ratio and mean age were consistent with the 2005 Japanese census (Table 1). In total, 10.2% (114/1109) of participants had received medical care from interns, of whom 4.5% (51 respondents) had direct experience. The other 5.7% (63) had experience of care provided by interns through a family member (indirect experience). Participants' responses indicated that the situations most commonly involved hospitalization (60.5%), outpatient clinics (32.4%) or emergency room visits (5.2%).

Table 1: Study participants' characteristics

Participant characteristic (*n*=1109)	*n* (%)
Sex	
Male	557 (50.2)
Age (years)	
15–19	58 (5.2)
20–29	138 (12.4)
30–39	181 (16.3)
40–49	172 (15.5)
50–59	226 (20.4)
≥60	334 (30.1)
Region	
Hokkaido and Tohoku	171 (15.4)
Kanto	342 (30.8)
Chubu and Hokuriku	223 (20.1)
Kansai	151 (13.6)
Chugoku, Shikoku & Kyushu	222 (20.0)
Population size	
14 biggest cities	213 (19.2)
>150 000	343 (30.9)
50 000–150 000	250 (22.5)
<50 000	89 (8.0)
Rural	214 (19.3)
Experience of interns' practice	
Participants themselves	51 (4.5)
Participants' family member	63 (5.7)
Clinical conditions experienced by participants (*n*=114)	
Practice situation	
Ambulatory	37 (32)
Emergency room	6 (5)
Ward (hospitalization)	69 (61)
Other	2 (2)
Content of interns' practice	
Interview and physical examination	72 (63)
Drawing blood	18 (16)
Injection and drop infusion	28 (25)
Non-invasive examination	22 (19)
Explanation	42 (37)

Attitudes toward care provision by interns

Overall, 37.0% (410/1109) of participants were comfortable receiving care from interns. Participants who had experience of care by interns were more likely to show acceptance than those with no experience (57% (65/114) vs 35.7% (344/964), $p<0.001$). Participants in larger cities were more likely to have experienced care by interns ($p=0.04$), but there was no significant difference by region ($p=0.98$). Neither population of municipality nor region was associated with satisfaction with care provision by interns ($p=0.3$ and $p=0.5$).

Acceptance of care provision by interns was not associated with region ($p=0.8$, Fig1a), population of municipality of

residence (p=0.9, Fig1b) or age group (45.6%, 15–19 years; 43.4%, 20–29 years; 36.6%, 30–39 years; 38.2%, 40–49 years; 33.0%, 50–59 years; and 38.9%, ≥60 years; p=0.3). Those who were willing to accept care from interns were statistically more likely than others to express understanding that interns needed experience of providing care (accepting 91.6% (207/226) vs non-accepting 41.4% (143/345), p<0.001; experience 76.0% (57/75) vs no experience 59.3% (293/494), p=0.006). Participants who were willing to accept care from interns were also statistically more likely to respond that interns would have more opportunities to be trained at smaller or community hospitals than at tertiary hospitals (p<0.001, p=0.02, Fig2). This tendency was consistent across municipalities, regardless of population (57.5% for larger cities, 60.2% for municipalities with populations of over 150 000, 65.3% for municipalities with populations of 50 000–150 000, 57.1% for municipalities with populations <50 000, and 56.3% for rural areas; p=0.8). Satisfaction with care provision by interns was highest among those who had been seen in ward settings (73.9%, 51/69) and lowest in those who had been seen in an emergency room (33.3%, 2/6).

Table 2 shows reasons given by both those with experience and no experience of care provision by interns for accepting or not accepting care from interns, and the population of their home municipalities, stratified by acceptance. In total, 52% of accepting participants responded ‘because interns should have more experience’ and 29% responded ‘to further the advancement of medical science’. Among participants who would accept care provided by interns, those with experience of such care were significantly more likely to feel that interns were ‘polite’ (p<0.001) and ‘kind’ (p<0.001) than those with no experience with interns. The most common reason for non-acceptance was fear of negative aspects of care, particularly medical errors (p=0.03). There was no significant difference of acceptance among the population of the home municipality, the location of the community and any of the reasons for non-acceptance.

Table 3 shows the relationships among acceptance of care from interns, the population of the home municipality and the impressions of participants who had experienced care from interns. The following responses were significantly more common among those who accepted care provision by interns: ‘interns were polite’ (p<0.001), ‘interns’ practice was thorough’ (p<0.001), ‘interns worked very hard’ (p<0.001), ‘interns’ explanations were easy to understand’ (p<0.001), and ‘the intern seemed kind’ (p<0.001) Only one response, ‘the intern spent a lot of time’, was not positively associated with participant acceptance (p=0.3) but was associated with participants who lived in larger cities (p=0.02).

Participants with no experience of care from interns, but accepting of the concept, were more likely to respond that ‘communication between senior doctors and nurses is very important for interns’ training’ (p=0.009; supplementary table). Participants with no experience of and who were non-accepting of care provision by interns were more likely to respond that ‘interns should be educated regarding medical errors’ (p=0.004). There was an association between the population of home municipality and the response ‘I want to know who the intern is’ (p=0.049) among participants who would accept care provision by interns. This tendency was stronger in larger cities than in smaller municipalities. Non-accepting participants were also associated with the population of the home municipality for responses including ‘interns should not examine first-time patients because of the risk of misdiagnosis’ (p=0.01), ‘senior doctors, not interns, should perform invasive procedures’ (p=0.02) and ‘a senior doctor should explain to patients before interns perform invasive procedures’ (p=0.03). Those negative answers were more common in participants from larger cities than from smaller municipalities. There was no significant association between these demands and the region.

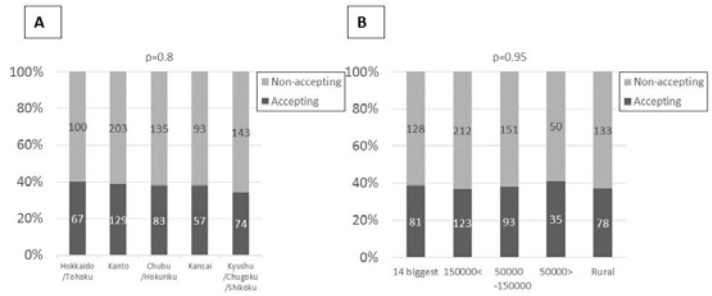

Figure 1: Acceptance of practice by interns in Japan by (a) region, (b) population of municipality.

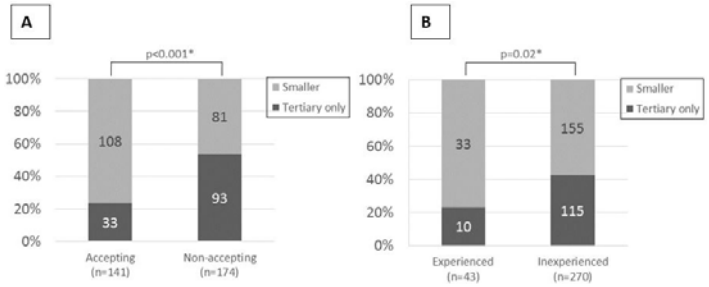

Figure 2: Perspectives of community residents on interns' training site according to (a) acceptance/non-acceptance, (b) experience/lack of experience.

Table 2: Acceptance or non-acceptance of care provision by interns, by reason

Reason for acceptance/non-acceptance	Experience with intern? (*n*)			Population size (*n*)					
	Yes	No	*p*-value†	14 biggest	>150 000	50 000–150 000	<50 000	Rural	*p*-value†
Reason (accepting)	(*n*=65)	(*n*=344)							
Interns' lack of knowledge	6	24	0.6¶	8	9	4	4	5	0.6¶
Interns' lack of skills	8	20	0.07¶	5	6	8	3	6	0.8¶
Fear of medical errors	4	14	0.5¶	5	6	2	1	4	0.7¶
It takes extra time	1	4	0.6¶	1	1	1	0	2	0.8¶
I worry whether senior doctors will examine me properly	7	14	0.06¶	7	6	4	0	4	0.4¶
Interns are unreliable	7	19	0.2¶	4	8	7	3	4	0.9¶
I feel anxious	7	32	0.7	8	10	8	7	6	0.3
My disease is too serious for interns	2	4	0.2¶	2	3	1	0	0	0.5¶
My disease is too mild for interns	9	14	0.005**¶	4	6	4	2	7	0.7¶
For further development of medical science	23	97	0.2	23	33	30	13	21	0.7
I want interns to experience more real practice	35	179	0.9	37	68	54	17	38	0.4
Interns are polite	14	14	<0.001***¶	8	5	6	4	5	0.4¶
Interns are kind	18	19	<0.001***	8	9	8	3	9	0.9
Interns examine thoroughly	18	36	0.001***	7	16	12	7	13	0.5
Interns explain thoroughly	12	30	0.03	5	13	9	5	10	0.6¶
I am being examined by a senior doctor too	16	42	0.02	14	17	13	2	13	0.5
I have never examined by interns before	1	111	<0.001***¶	25	36	28	5	19	0.4
Reason (non-accepting)	(*n*=49)	(*n*=620)							
Interns' lack of knowledge	17	308	0.05	69	94	77	22	65	0.4
Interns' lack of skills	24	326	0.7	75	110	79	23	65	0.5
Fear of medical errors	12	247	0.03	54	72	63	14	57	0.2
It takes extra time	7	52	0.2	8	22	11	5	13	0.7
I worry whether senior doctors will examine me properly	9	136	0.7	29	49	30	4	34	0.1
Interns are unreliable	20	248	1	58	81	54	21	54	0.6
I feel anxious	23	363	0.1	71	126	82	31	77	0.8
My disease is too serious for interns	3	23	0.4¶	4	8	4	1	9	0.4¶
My disease is too mild for interns	0	0	1	0	0	0	0	0	1
For further development of medical science	0	0	1	0	0	0	0	0	1
I want interns to experience more real practice	0	0	1	0	0	0	0	0	1
Interns are polite	0	0	1	0	0	0	0	0	1
Interns are kind	0	0	1	0	0	0	0	0	1
Interns examine thoroughly	0	0	1	0	0	0	0	0	1
Interns explain thoroughly	0	0	1	0	0	0	0	0	1
I am being examined by a senior doctor too	0	0	1	0	0	0	0	0	1
I have never examined by interns before	0	0	1	0	0	0	0	0	1

*$p<0.05$, **$p<0.01$, ***$p<0.001$
† Calculated by χ^2 test unless otherwise indicated.
¶ Calculated by Fisher's exact test.

Table 3: Impressions of participants who have experience of care provided by interns

Impression	Accepting of intern? (*n*)			Population size (*n*)					
	Yes (*n*=65)	No (*n*=49)	*p*-value†	14 biggest	>150 000	50 000–150 000	<50 000	Rural	*p*-value†
The intern did not introduce him/herself	7	13	0.8¶	4	10	2	3	1	0.1¶
The intern did not introduce him/herself as an intern	6	16	0.3¶	8	5	2	3	4	0.2¶
The intern was polite	31	9	<0.001***	8	12	4	7	9	0.09
The intern's appearance was inappropriate	1	0	0.2¶	1	0	0	0	0	0.4¶
The intern's examinations were thorough	32	8	<0.001***	11	11	4	3	11	0.2
The intern came every day	10	7	0.7¶	6	7	3	1	0	0.2¶
The intern was with me until late at night	3	0	0.03¶	0	2	0	1	0	0.2¶
The intern worked very hard	40	11	<0.001***	11	21	4	5	10	0.1
The intern's examinations were not smooth	4	11	0.4¶	4	6	2	2	1	0.5¶
The intern spent too much time	2	7	0.3¶	3	0	2	3	1	0.02¶
The intern's explanations were easy to understand	13	3	<0.001***¶	6	6	1	2	1	0.1¶
The intern's explanations were not easy to understand	4	13	0.2¶	5	7	3	2	0	0.2¶
The intern did not explain things	1	1	0.7¶	0	0	0	1	1	0.1¶
The intern's explanations were too long	1	1	0.7¶	1	0	1	0	0	0.6¶
The intern showed a lack of knowledge	1	6	0.2¶	3	2	1	0	1	0.6¶
The intern did not understand my explanations	0	0	1	0	0	0	0	0	1
The intern seemed kind	32	6	<0.001***	8	15	4	5	6	0.3
The intern seemed unkind	0	1	0.4¶	1	0	0	0	0	0.4¶
The intern seemed oppressive	0	1	0.4¶	1	0	0	0	0	0.4¶
The intern seemed nervous	10	8	0.1¶	6	6	1	1	4	0.4¶
The intern seemed unreliable	10	25	0.3	11	11	7	3	3	0.3
I felt anxious	6	15	0.4¶	6	6	4	3	2	0.5¶

*p<0.05, **p<0.01, ***p<0.001
† Calculated by χ^2 test unless otherwise indicated.
¶ Calculated by Fisher's exact test.

Discussion

Individuals' experiences of and attitudes toward care provision by interns were analyzed by geographic and demographic variables following a nationwide survey. The analysis showed that people who had experienced or whose family members had experienced care provided by interns were more likely to accept care from interns than those without experience. Acceptance of care provision by interns was not associated with geographic variables such as region or population of municipality. Participants who accepted and had experienced care from interns tended to respond that interns should train at both tertiary hospitals and smaller and community hospitals. People who had experience of care provided by interns, either personally or through family members, and were accepting of this, responded that interns were generally 'kind', 'polite' and 'thorough'. A few responses were associated with the population of the municipality of residence but, overall, geographic elements were not associated with the acceptance of care provision by interns.

In real-world settings, there are still sometimes difficulties in having interns examine patients, even when they have suitable qualifications[1,2]. It has been shown that patients participate in medical training largely out of altruism rather than obligation[13,16]. Several studies have shown that patients tend to accept treatment from medical students or interns when they are informed and give consent beforehand[17]. The significance of allowing interns to practice seemed to be understood by those participants who were prepared to accept medical care from interns. This suggests that dissemination of information about interns might be essential to improve patients' acceptance of interns. Training hospitals and medical schools should disseminate information about practice by interns in several ways, and provide explanations to patients before obtaining informed consent. This might increase acceptance of care provision by interns. This research shows that, in smaller communities or hospitals, the dissemination task might be easier than expected.

As in previous studies, participants in this study who had already experienced care provision by interns were more likely to accept care from them in future[18-20]. This suggests that, as more people experience care provision by interns, the overall level of acceptance will grow. There is little evidence from previous studies of any relationship between patients' acceptance of care provision by interns and geographic and demographic variables. There was a statistically significant association between the response 'the intern spent too much time' and participants who lived in larger cities, although this might vary with culture. The reason for this is still unknown but people in larger cities might tend to feel busy or feel interns are wasting their time if they take too long. If so, novice doctors might be able to take more time, and therefore benefit both themselves and the patients, in smaller cities. On most responses, the present study shows that variables such as region and population of the patients' home municipality were not important factors in patients'

acceptance and overall attitudes. These results might show that the benefits of medical education in communities result from the training content or the size of community health facilities. Participants who reported having experienced care provided by interns were more likely to live in large cities than smaller municipalities. This might be because in Japan there are more training hospitals in large cities than in smaller municipalities. Participants who were prepared to accept and had experience of care provided by interns tended to respond that they believed it was important to allow interns to provide care because of their need for clinical education.

Patients who accepted care provision by interns tended to respond that interns should be trained in both large tertiary hospitals and smaller community hospitals. This is one of the most important results because it informs medical educators in communities that residents might prefer interns to have a wider range of experience. They might therefore be ready to accept interns as a part of the advancement of community-based medical education, as a clinical educational resource. There are many smaller hospitals in smaller communities in Japan, so the use of smaller community hospitals for clinical education is a reasonable option.

Patients appreciated characteristics of interns such as being ‘kind’, ‘polite’ and ‘thorough’. Interns’ bedside manner and attitude are very important in ensuring that patients are prepared to be treated by them. However, patients are anxious about whether interns’ clinical skill or knowledge is sufficient. To increase the rate of acceptance of care provision by interns, it might therefore be helpful to inform patients that, under Japanese law, interns only practice under the supervision of senior staff. In contrast to the results in this study, several previous studies have reported that patients accepted medical students’ or interns’ involvement[15,21-24]. There are multiple issues related to care provision by interns, so further research is needed to improve acceptance. Studies should examine views of patients, interns and instructors, and those of staff in hospitals, medical schools and governments. It may also be helpful to examine factors of cultural, historical and geographic diversity.

The present study’s findings should be interpreted in light of the study limitations. First, this study did not verify whether participants or their family members had actually experienced care provision by interns. Second, as these data were gathered only in Japan, the results may be influenced by unique cultural and social factors, including aspects of the medical system. These results therefore cannot be generalized to other cultural settings. In addition, the limited sample size and response rate might result in the statistically non-significant association between attitude and geographic variation. However, because a random sample of adult Japanese living in almost all areas of Japan was surveyed, these data provide a reliable and generalizable account of the Japanese healthcare setting. Finally, this study was a cross-sectional study, so the findings were primarily based on the correlations of observations. To attest these findings, more proactive methods to assess associations between acceptance of resident practice and geographical area should be considered.

Conclusions

This study provided a comprehensive picture of the geographic and demographic factors associated with patients’ attitudes toward care provision by interns in Japan. There were no significant differences in responses on clinical education by region, population of municipality or age group, which suggests that community-based medical education could be provided anywhere in Japan. Participants who accept and have experience of care provision by interns were more likely to respond that interns would be trained better at smaller community hospitals than at tertiary hospitals. Clinical education in Japan mainly takes place in tertiary hospitals at present, but this study suggests that further research into differences in acceptance level by hospital size or role may be helpful to clarify the benefit of community- and primary care-based medical education.

Acknowledgements

The authors thank Makiko Ohtorii and Ai Mizutani for their assistance with administration and data management. They also thank Melissa Leffler from Edanz Group for editing a draft of this manuscript.

REFERENCES:

1 Waterbury J. Refuting patients' obligations to clinical training: a critical analysis of the arguments for an obligation of patients to participate in the clinical education of medical students. *Medical Education* 2001; **35(3):** 286-294. https://doi.org/10.1046/j.1365-2923.2001.00865.x PMid:11260453

2 Stacy R, Spencer J. Patients as teachers: a qualitative study of patients' views on their role in a community-based undergraduate project. *Medical Education* 1999; **33(9):** 688-694. https://doi.org/10.1046/j.1365-2923.1999.00454.x PMid:10476021

3 Santen S, Hemphill R, Spanier C, Fletcher N. 'Sorry, it's my first time!' Will patients consent to medical students learning procedures? *Medical Education2005* 39; **4(365-369).** https://doi.org/10.1111/j.1365-2929.2005.02113.x PMid:15813758

4 Graber M, Pierre J. Patient opinions and attitudes toward medical student procedures in the emergency department. *Academic Emergency Medicine* 2003; **10(12):** 1329-1333. https://doi.org/10.1197/S1069-6563(03)00554-2

5 Passaperuma K, Higgins J, Power S, Taylor T. Do patients' comfort levels and attitudes regarding medical student involvement vary across specialties? *Medical Teacher* 2008; **30(1):** 48-54. https://doi.org/10.1080/01421590701753443 PMid:18278651

6 Hubbeling D. Can patients refuse to be treated by medical students? *Medical Education* 2008; **42(7):** 747. https://doi.org/10.1111/j.1365-2923.2008.03115.x PMid:18507765

7 Hirsh D, Gaufberg E, Ogur B, Cohen P, Krupat E, Cox M, et al. Educational outcomes of the Harvard Medical School-Cambridge integrated clerkship: a way forward for medical education. *Academic Medicine* 2012; **87(5):** 643-650. https://doi.org/10.1097/ACM.0b013e31824d9821 PMid:22450189

8 Worley P, Prideaux D, Strasser R, Magarey A, March R. Empirical evidence for symbiotic medical education: a comparative analysis of community and tertiary-based programmes. *Medical Education* 2006; **40(2):** 109-116. https://doi.org/10.1111/j.1365-2929.2005.02366.x PMid:16451237

9 Kelly L, Walters L, Rosenthal D. Community-based medical education: Is success a result of meaningful personal learning experiences? *Education for Health* 2014; **27:** 47-50. https://doi.org/10.4103/1357-6283.134311 PMid:24934943

10 Ogur B, Hirsh D, Krupat E, Bor D. The Harvard Medical School-Cambridge integrated clerkship: an innovative model of clinical education. *Academic Medicine* 2007; **82(4):** 397-404. https://doi.org/10.1097/ACM.0b013e31803338f0 PMid:17414198

11 Worley P, Silagy C, Prideaux D, Newble D, Jones A. The parallel rural community curriculum: an integrated clinical curriculum based in rural general practice. *Medical Education* 2000; **34(7):** 558-565. https://doi.org/10.1046/j.1365-2923.2000.00668.x PMid:10886639

12 Takamura A, Misaki H, Takemura Y. Community and interns' perspectives on community-participatory medical education: from passive to active participation. *Family Medicine* 2017; **49(7):** 507-513. PMid:28724147

13 Walters L, Greenhill J, Richards J, Ward H, Campbell N, Ash J, et al. Outcomes of longitudinal integrated clinical placements for students, clinicians and society. *Medical Education* 2012; **46(11):** 1028-1041. https://doi.org/10.1111/j.1365-2923.2012.04331.x PMid:23078680

14 Worley PS, Prideaux DJ, Strasser RP, Silagy CA, Magarey JA. Why we should teach undergraduate medical students in rural communities. *Medical Journal of Australia* 2000; **172:** 615-617. PMid:10914111

15 Tallentire VR, Smith SE, Skinner J, Cameron HS. Understanding the behaviour of newly qualified doctors in acute care contexts. *Medical Education* 2011; **45(10):** 995-1005. https://doi.org/10.1111/j.1365-2923.2011.04024.x PMid:21916939

16 Lowe M, Kerridge I, McPhee J, Hart C. Do patients have an obligation to participate in student teaching? *Medical*

Education 2008; **42(3):** 237-241. https://doi.org/10.1111/j.1365-2923.2007.02948.x PMid:18221270

17 Howe A, Anderson J. Involving patients in medical education. *British Medical Journal* 2003; **327(7410):** 326-328. https://doi.org/10.1136/bmj.327.7410.326 PMid:12907488

18 Simons R, Imboden E, Martel J. Patient attitudes toward medical-student participation in a general internal-medicine clinic. *Journal of General Internal Medicine* 1995; **10(5):** 251-254. https://doi.org/10.1007/BF02599880

19 Jones S, Oswald N, Date J, Hinds D. Attitudes of patients to medical student participation: general practice consultations on the Cambridge community-based clinical course. *Medical Education* 1996; **30(1):** 14-17. https://doi.org/10.1111/j.1365-2923.1996.tb00711.x

20 Cooke F, Galasko G, Ramrakha V, Richards D, Rose A, Watkins J. Medical students in general practice: how do patients feel? *British Journal of General Practice* 1996; **46(407):** 361-362. PMid:8983256

21 Bishop F, Matthews FJ, Probert CS, Billett J, Battcock T, Frisby SD, et al. Patients' views on how to run hospital outpatient clinics. *Journal of the Royal Society of Medicine* 1991; **84(9):** 522-523. https://doi.org/10.1177/014107689108400906

22 Hartz M, Beal J. Patients' attitudes and comfort levels regarding medical students' involvement in obstetrics-gynecology outpatient clinics. *Academic Medicine* 2000; **75(10):** 1010-1014. https://doi.org/10.1097/00001888-200010000-00018 PMid:11031149

23 Shah-Khan M, Chowdhry S, Brand MI, Saclarides TJ. Patient attitudes toward medical students in an outpatient colorectal surgery clinic. *Diseases of the Colon & Rectum* 2007; **50(8):** 1255-1258. https://doi.org/10.1007/s10350-007-0274-x PMid:17587085

24 Tang TS, Skye EP. When patients decline medical student participation: the preceptors' perspective. *Advances in Health Sciences Education* 2009; **14(5):** 645-653. https://doi.org/10.1007/s10459-008-9145-z PMid:19011983

SUPPLEMENTARY CONTENT:

Conditions set for the acceptance of care provision by interns

Reason for acceptance/non-acceptance	Experience with intern? (*n*)			Population size (*n*)					
	Yes	No	*p*-value†	14 biggest	>150 000	50 000–150 000	<50 000	Rural	*p*-value†
Reason (accepting)	(*n*=65)	(*n*=344)							
I want to know who the intern is	39	222	0.5	57	78	66	20	40	0.049
I want to be asked for permission to be examined by intern beforehand	15	120	0.06	35	35	29	11	25	0.3
The communication between senior doctors and nurses is very important for interns' training	24	75	0.009**	21	29	25	4	20	0.4
The fee should be lower if I am examined by interns	2	31	0.1¶	7	10	6	3	7	0.98¶
I should be examined as a priority	1	5	0.96¶	1	1	3	0	1	0.6¶
Interns should accumulate more experience by seeing more patients	24	88	0.06	25	29	25	10	23	0.8
Interns should be trained in a primary care setting over longer periods of time	10	49	0.8	15	14	12	4	14	0.5
Interns should be trained in a specialty care setting over longer periods of time	0	1	0.6¶	1	0	0	0	0	0.4
Interns should not examine first-time patients	15	50	0.08	14	21	17	5	8	0.6
Interns should begin examining with easy tasks	18	69	0.2	22	19	23	11	13	0.1
Interns should examine patients under the supervision of a senior doctor	16	103	0.4	30	34	25	7	23	0.4
Interns should be checked after giving examinations by a senior doctor	22	129	0.6	36	50	28	8	29	0.1
A senior doctor should explain to patients before interns perform invasive procedures	23	110	0.6	33	43	26	11	20	0.2
Senior doctors, not interns, should perform invasive procedures	11	45	0.4	10	18	15	4	9	0.9
Interns should experience being examined as a patient	18	76	0.3	18	29	20	7	20	0.96
Interns should be educated regarding medical errors	9	35	0.4	14	9	12	3	6	0.2
The new training system for interns creates gaps and maldistribution of doctors in communities	23	91	0.1	29	29	23	10	23	0.4
Reason (non-accepting)	(n=49)	(n=620)							
I want to know who the intern is	30	431	0.03	89	148	100	36	93	0.9
I want to be asked for permission to be examined by intern beforehand	25	283	0.5	60	104	66	20	61	0.8
Communication between senior doctors and nurses is very important for interns' training	13	146	0.6	34	55	34	10	28	0.7
The fee should be lower if I am examined by interns	8	73	0.3	20	18	22	3	19	0.1
I should be examined as a priority	3	28	0.6¶	5	7	12	0	8	0.1¶
Interns should accumulate more experience by seeing more patients	8	77	0.4	20	27	16	9	14	0.5
Interns should be trained in a primary care setting over longer periods of time	7	81	0.8	17	30	19	7	16	0.98
Interns should be trained in a specialty care setting over longer periods of time	1	4	0.3¶	1	2	1	1	0	0.7¶
Interns should not examine first-time patients	14	126	0.2	35	46	17	12	32	0.012
Interns should begin examining with easy tasks	8	123	0.6	28	43	24	12	24	0.6
Interns should examine patients under the supervision of a senior doctor	19	203	0.4	49	77	38	16	43	0.1
Interns should be checked after giving examinations by a senior doctor	15	201	0.8	47	73	37	14	47	0.1
A senior doctor should explain to patients before interns perform invasive procedures	19	170	0.09	48	65	31	13	34	0.026
Senior doctors, not interns, should perform invasive procedures	9	136	0.6	41	48	25	9	24	0.018
Interns should experience being examined as a patient	9	101	0.7	23	41	17	8	22	0.3
Interns should be educated regarding medical errors	8	36	0.004**	10	14	9	5	7	0.8
The new training system for interns creates gaps and maldistribution of doctors in communities	8	141	0.3	33	45	26	12	35	0.3

*$p<0.05$, **$p<0.01$
† Calculated by χ^2 test unless otherwise indicated.
¶ Calculated by Fisher's exact test.

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

https://doi.org/10.1515/dmpt-2018-0018
Received June 28, 2018; accepted October 3, 2018; previously published online November 10, 2018

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.

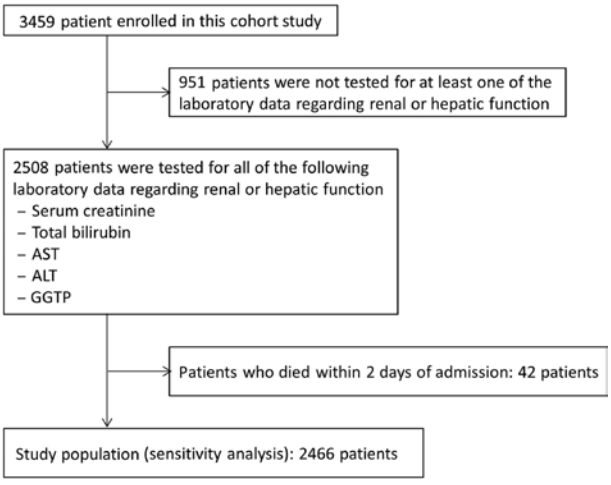

Figure 1: Flowchart of patients.

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

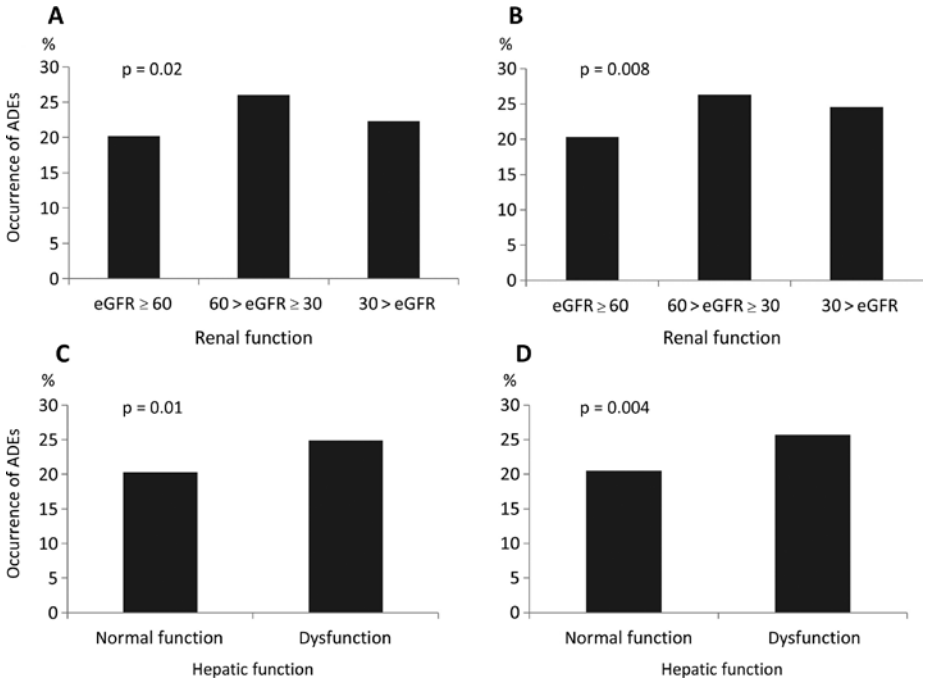

Figure 2: Effect of organ function on ADEs.
(A) The occurrence of ADEs in patients stratified by eGFR category (<30; ≥30 and <60; ≥60 mL/min/1.73 mm). (B) Sensitivity analysis of the occurrence of ADEs in patients in the three eGFR categories. (C) The occurrence of ADEs in patients with normal hepatic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

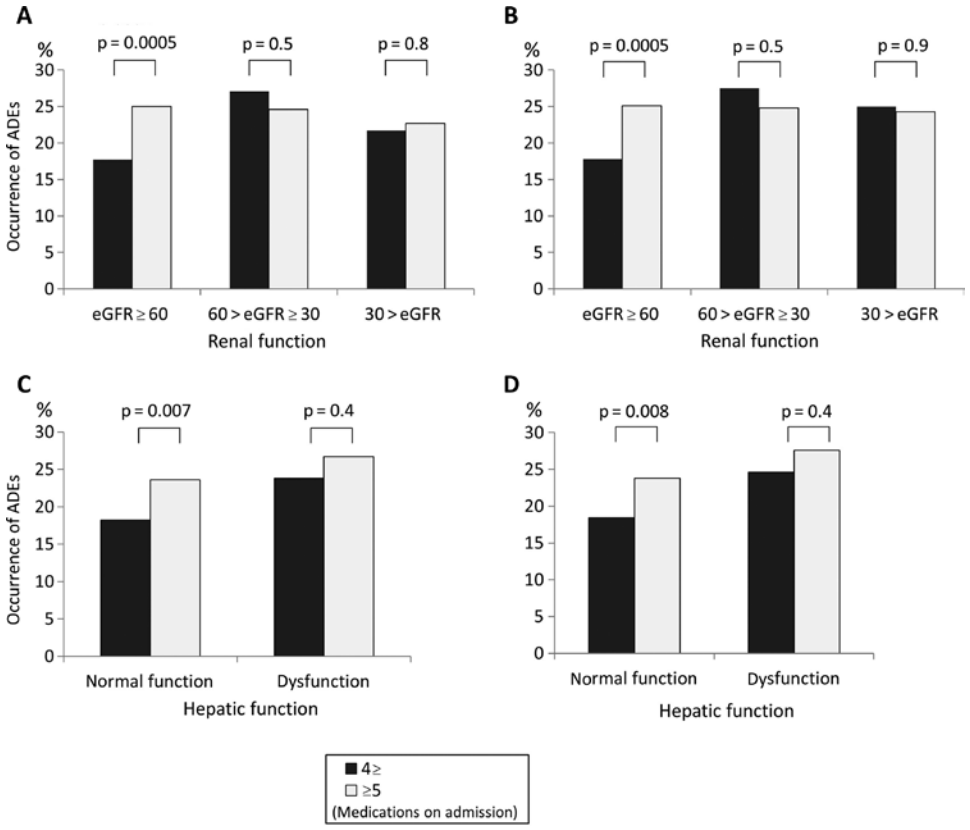

Figure 3: Effect of the number of medications used on ADEs, stratified by organ function.
(A) The occurrence of ADEs in patients in the three eGFR categories (<30; ≥30 and <60; ≥60 mL/min/1.73 mm), stratified by the number of medications used. (B) Sensitivity analysis of the occurrence of ADEs in patient 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).

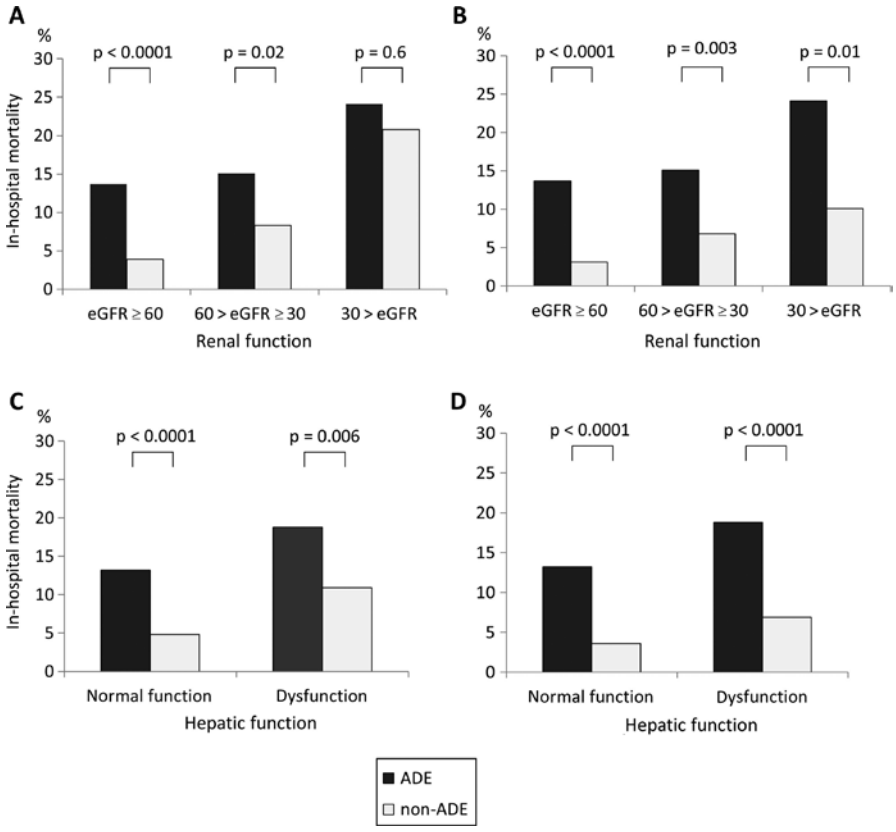

Figure 4: Effect of ADEs on in-hospital mortality, stratified by organ functions.
(A) In-hospital mortality in patients in the three eGFR categories (<30; ≥30 and <60; ≥60 mL/min/1.73 mm), stratified by ADE occurrence. (B) Sensitivity analysis of in-hospital mortality in patients in each eGFR category,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

Acknowledgments: The JADE study for adult inpatients was conducted by the following investigators: Kunihiko Matsui, MD, MPH; Nobuo Kuramoto, MD; Jinichi Toshiro, MD; Junji Murakami, MD; Tsuguya Fukui, MD, MPH; Mayuko Saito, MD, MPH; Atsushi Hiraide, MD; and David W. Bates, MD, MSc. We are also indebted to Ms. Makiko Ohtorii, Ms. Ai Mizutani, Ms. Mika Sakai, Ms. Izumi Miki, Ms. Kimiko Sakamoto, Ms. Eri Miyake, Ms. Takako Yamaguchi, Ms. Yoko Oe, Ms. Kyoko Sakaguchi, Ms. Kumiko Matsunaga, Ms. Yoko Ishida, Ms. Kiyoko Hongo, Ms. Masae Otani, Ms. Yasuko Ito, Ms. Ayumi Samejima, and Ms. Shinobu Tanaka for their data collection and management.
Author contributions: YT, MS, and TM planned this study. YT, HM, MS, and TM conducted the analysis, and wrote the draft and the final manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: This work was supported by JSPS KAKENHI (grant nos. JP17689022, JP21659130, JP22390103, JP23659256, JP26293159, JP18H03032), the grants from the Ministry of Health, Labour and Welfare of Japan (H26-Iryo-012, H28-ICT-004), the grants from the Pfizer Health Research Foundation, and the Uehara Memorial Foundation.
Employment or leadership: YT is an employee of Novartis Pharma KK. HM is an employee of Novartis Pharma KK. MS and TM have declared that they do not have any conflicts of interest pertaining to this manuscript.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Bates DW, Cullen DJ, Laird NM, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. J Am Med Assoc 1995;274:29–34.
2. Morimoto T, Gandhi TH, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004;13:306–14.
3. Al Hamid A, Ghaleb M, Aljadhey H, Aslanpour Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol 2014;78:202–17.
4. Hilmer SN. ADME-tox issues for the elderly. Expert Opin Drug Metab Toxicol 2008;4:1321–31.
5. Caldwell J, Gardner I, Swales N. An introduction to drug disposition: the basic principles of absorption, distribution, metabolism, and excretion. Toxicol Pathol 1995;23:102–14.
6. Roberts DJ, Hall RI. Drug absorption, distribution, metabolism and excretion considerations in critically ill adults. Expert Opin Drug Metab Toxicol 2013;9:1067–84.
7. Morimoto T, Sakuma M, Matsui K, Kuramoto N, Toshiro J, Murakami J, et al. Incidence of adverse drug events and

medication errors in Japan: the JADE study. J Gen Intern Med 2011;26:148–53.
8. Committee of Experts on Management of Safety and Quality in Health Care (SP-SQS). Expert Group on Safe Medication Practice. Glossary of term related to patient and medication safety. Available at: http://www.who.int/patientsafety/highlights/COE_patient_and_medication_safety_gl.pdf. Accessed: 16 Nov 2017.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
10. Evidence-based Practice Guideline for the Treatment of CKD 2013. Available at: http://www.jsn.or.jp/guideline/pdf/CKD_evidence2013/all.pdf.
11. PAB/SD Notification No. 80 issued by the Director of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992. Available at: http://www.mhlw.go.jp/shingi/2005/10/dl/s1006-4f2.pdf [in Japanese].
12. Research Priority Setting Working Group of the WHO World Alliance for Patient Safety (Allegranzi B, Angood P, Bhutta Z, Davis P, Grandt D, Hamid M, Insua J, Kaitiritimba R, Khamassi S, Madiba T, Morimoto T, Noble D, Norton P, Pang TE, Sidorchuk R, Supachutikul A, Thomas E). Summary of the evidence on patient safety: implications for research. World Health Organization. 2008.
13. Avery A, Barber N, Ghaleb M, Franklin BD, Armstrong S, Crowe S, et al. Investigating the prevalence and causes of prescribing errors in general practice: the PRACtICe study. London: General Medical Council, 2012.
14. Medication Errors by The Technical Series on Safer Primary Care in WHO. Available at: http://www.who.int/patientsafety/topics/primary-care/technical_series/en/.
15. Field TS, Gurwitz JH, Avorn J, McCormick D, Jain S, Eckler M, et al. Risk factors for adverse drug events among nursing home residents. Arch Intern Med 2001;161:1629–34.
16. Bianchetti G, Graziani G, Brancaccio D, Morganti A, Leonetti G, Manfrin M, et al. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. Clin Pharmacokinet 1976;1:373–84.
17. Maher JF. Pharmacological considerations. In: Maher JF, editor. Replacement of renal function by dialysis. Boston: Kluwer Academic Publishers, 1989.
18. Gambertoglio JG. Pharmacokietic basis for drug treatment. In: Benet LZ, Massoud N, Gambertoglio JG, editors. New York: Raven Press, 1984.
19. Haughey DB, Krafy CJ, Matzke GR, Keane WF, Halstenson CE. Protein binding of disopyramide and elevated alpha-1-acid glycoprotein concentrations in serum obtained from dialysis patients and renal transplant recipients. Am J Nephrol 1985;5:35–9.
20. Lima JJ. Disopyramide. In: Evans WE, Schentag JJ, Jusco WJ, editors. Applied pharmacokinetics. 2nd ed. WA: Applied Therapeutics, Inc., 1987.
21. Belpaire FM, Van de Velde EJ, Fraeyman NH, Bogaert MG, Lameire N. Influence of continuous ambulatory peritoneal dialysis on serum alpha 1-acid glycoprotein concentration and drug binding. Eur J Clin Pharmacol 1988;35:339–43.
22. Lam YW, Banerji S, Hatfield C, Talbert RL. Principal of drug administration in renal insufficiency. Clin Pharmacokinet 1997;32:30–57.
23. Schmucker DL. Age-related changes in liver structure and function: implication for disease? Exp Gerontol 2005;40:650–9.
24. Le Couteur DG, Warren A, Cogger VC, Smedsrød B, Sørensen KK, De Cabo R, et al. Old age and the hepatic sinusoid. Anat Rec 2008;291:672–83.
25. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. Adv Chronic Kidney Dis 2016;23:19–28.
26. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011;365:2002–12.
27. Choudhury D, Ahmed Z. Drug–associated renal dysfunction and injury. Nat Clin Pract Nephrol 2006;2:80–91.
28. Markowitz GS, Bomback AS, Perazella MA. Drug–induced glomerular disease: direct cellular injury. Clin J Am Soc Nephrol 2015;10:1291–9.
29. Izzedine H, Perazella MA. Thrombotic microangiopathy, cancer, and cancer drugs. Am J Kidney Dis 2015;66:857–68.
30. Gökmen MR, Cosyns JP, Arlt VM, Stiborová M, Phillips DH, Schmeiser HH, et al. The epidemiology, diagnosis, and management of aristolochic acid nephropathy: a narrative review. Ann Intern Med 2014;158:469–77.
31. Yuan L, Kaplowitz N. Mechanism of drug-induced liver injury. Clin Liver Dis 2013;17:507–18.
32. Dreischulte T, Donnan P, Grant A, Hapca A, McCowan C, Guthrie B. Safer prescribing – a trial education, informatics, and financial incentives. N Engl J Med 2016;374:1053–64.
33. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varice. Br J Surg 1973;60:646–9.