local data [12]. The lack of such basic data represents one of the barriers to implementing strategies to improve patient safety in ICUs, especially outside the West.

To address this knowledge gap, we evaluated the epidemiology of ADEs in the ICUs as well as their impact on morbidity and mortality. We analyzed the data of the Japan Adverse Drug Events (JADE) study, a multicenter cohort study [6], and we used the length of ICU stay as morbidity.

Methods

Study design and patient population

The JADE study was a prospective cohort study involving all adult patients aged ≥15 years who were admitted to three urban tertiary care hospitals in Japan from January through June 2004[6]. The present study was limited to the patients admitted to all ICUs in these hospitals. The total number of beds among the three ICUs was 32 including the medical and the surgical beds. Patients were followed until transfer, discharge or death. The institutional review boards of three participating hospitals approved the study. Informed consent was waived because all data were collected in the daily practice.

Data collection and classification

The data collection method was based on that described in previous reports [1, 6]. ADE was defined as any unintended injury due to a medication use regardless of existing errors [1, 13]. Investigators trained nurses and nursing students in a standard manner and placed them in the participating hospitals where they reviewed practice data such as charts, laboratories or prescription data. They collected demographic data for all patients on admission to the ICUs and identified ADEs.

Next, two independent physician reviewers evaluated all events and classified collected ADEs as ADEs or exclusion. Then, physician reviewers classified ADEs into 10 categories according to the symptoms as well as rated the severity of ADEs using a four-point scale. The categories of symptoms were bleeding, central nervous, allergic reaction, liver disorder, cardiovascular, gastrointestinal, renal, respiratory, bone marrow suppression, and sepsis. For example, symptoms of bleeding included anemia and gastrointestinal bleeding due to warfarin, antiplatelet agents or NSAIDs; central nervous symptoms included delirium and muscle weakness due to sedative agents; gastrointestinal symptoms included diarrhea, constipation, nausea and vomiting due to antibiotics or opiates; respiratory symptoms included nosocomial infections which could be related to the use of antibiotics. We defined nosocomial infections as a patient who had negative culture on admission became to have positive culture after use of antibiotics. Categories of severity were fatal, life-threatening, serious, and significant. Fatal ADEs resulted in death; life-threatening ADEs caused such issues as anaphylactic shock or cardiopulmonary arrest; serious ADEs included gastrointestinal bleeding, altered mental status, excessive sedation, increased creatinine or a decrease in blood pressure; and significant ADEs included cases with rash, diarrhea or nausea, for example. When disagreements affected the classification of an ADE and its severity, the physician reviewers reached consensus through discussion.

To assess the severity of patients on admission to ICUs, we used the sepsis-related organ failure assessment (SOFA) score, later called the sequential organ failure score because it is not restricted to sepsis, to evaluate the presence of organ dysfunctions objectively [14]. The SOFA score consists of six components of organ systems such as respiratory, coagulation, liver, cardiovascular, central nervous system and renal. Each organ system is evaluated using a score from 0 (normal) to 4 (most abnormal) depending on its severity. To evaluate the presence of each organ dysfunction in this study, we used the SOFA score. The presence of each organ dysfunction was defined as follows: respiratory dysfunction; PaO_2/FiO_2 ≤400 mmHg, coagulopathy; platelets $\leq 150 \times 10^3/\mu l$, liver dysfunction; bilirubin ≥1.2 mg/dl, hypotension; mean arterial pressure <70 mmHg, unconsciousness; Glasgow Coma Scale ≤14, and renal dysfunction; creatinine ≥1.2 mg/dl.

Statistical analyses

The ADE incidence per 1000 patient-days and rates per 100 admissions were calculated. Continuous variables are presented as means with standard deviations (SDs) or medians with interquartile ranges, and categorical variables are shown as numbers and percentages. Relationships between patients' demographic data and ADEs were assessed using the Wilcoxon rank sum test when the data were continuous and the chi-square test when the demographic data were categorical. To assess associations between ADEs and mortality, we used the chi-square test. Because patients who died soon after admission had no chance to have an ADE, we did the same comparison eliminating patients who died within 3 days after admission to the ICUs. We used the *t*-test to compare the length of ICU stay between patients with ADEs and without ADEs during the ICU stay among those who were discharged from the ICU alive. We used a Cox proportional hazard model to estimate the hazard ratios (HRs) of ADEs for the risk of mortality along with 95% confidence intervals (CIs). We also used a linear regression model to assess the effects of the ADEs on the length of ICU stay. Both models were adjusted for age and the presence of organ dysfunctions such as respiratory, coagulopathy, liver, hypotension, unconsciousness and renal variables defined using the SOFA score. Patients with missing values for any selected variables were excluded from both analyses. We carried out all statistical analyses using the JMP 8.0 (SAS Institute Inc., Cary, NC). *P* values of <0.05 were considered to be statistically significant.

Results

We enrolled 459 admissions, accounting for a total of 3231 patient-days in the ICUs. Among the 459 patients, 290 (63%) were males and the mean age was 66 (SD 16) years; 60% were 65 years and older. The medical and the surgical ICUs admitted 263 (57%) and 196 (43%) patients, respectively. Of all admissions to the ICUs, 84% were emergent. The median

number of organ dysfunctions which patients suffered from on admission to the ICUs was 2 (inter-quartile range 1–3) and respiratory dysfunction was the most frequent (67%) followed by unconsciousness (46%) (Table 1).

Adverse drug events

We identified 99 ADEs in 70 patients (15%) for an incidence of 30.6 [95% CI 24.6–36.7] per 1000 patient-days and a rate per 100 admissions of 21.6 [95% CI 17.9–25.6]. The median day of the ADE onset after admission was 3 days.

Table 1 Demographic data in study population

	Total ($n = 459$)
Age, ≥65 (years) (*n*, %)	276 (60)
Male (*n*, %)	290 (63)
Departments (*n*, %)	
Medicine	263 (57)
Surgery	196 (43)
Admission pathway (*n*, %)	
Scheduled admission	75 (16)
Emergency admission	384 (84)
Principal reason for admission to unit (*n*, %)	
Cardiac disorders	136 (30)
Vascular disorders	49 (11)
Respiratory disorders	59 (13)
Neurological disorders	50 (11)
Kidney disorders	29 (6)
Gastrointestinal disorders	19 (4)
Trauma	32 (7)
Intoxication	5 (1)
Metabolic disorders	5 (1)
Others	75 (16)
Organ dysfunction on admission (*n*, %)	
Respiratory disorders (PaO_2/FiO_2 ≤400 mmHg)	306 (67)
Coagulopathy (platelets ≤150 × $10^3/\mu l$)	88 (19)
Liver dysfunction (bilirubin ≥1.2 mg/dl)	73 (17)
Hypotension (mean arterial pressure <70 mmHg)	79 (17)
Unconsciousness (Glasgow Coma Scale ≤14)	211 (46)
Renal dysfunction (creatinine ≥1.2 mg/dl)	152 (33)
Temperature (centigrade degrees) (mean, SD)	36.6 (0.9)
History of allergy (*n*, %)	21 (5)
Past history and statement (*n*, %)	
Heart failure, NYHA = 4	253 (55)
Home oxygen therapy	17 (4)
Hemodialysis	64 (14)
The number of medications on admission (median, quartile)	5 (4–7)
Length of experienced years of a doctor in charge (median, quartile)	8 (4–16)

NYHA, New York Heart Association.

Among the 70 patients who had at least one ADE, 49 patients (70%) were 65 years and older and 21 patients (30%) were under 65, and 51 patients (73%) admitted urgently to the ICU and 19 patients (27%) did not. There was a trend for those 65 years and older to have a higher rate of ADEs compared with younger patients though this difference was not statistically significant ($P = 0.07$). Those admitted urgently to the ICU had a higher risk of ADEs ($P = 0.008$). The median age of the physician's experience among the doctors in charge who cared for patients with ADE was 6 years (inter-quartile range 3–13) while that without ADEs was 9 years (inter-quartile range 4–16). Thus, having a less experienced physician as the doctor in charge increased the ADE risk compared with having a senior physician ($P = 0.01$). Having organ dysfunction of any type at ICU admission was not associated with a higher risk of having an ADE (Figs 1 and 2). The number of medications on admission was also not significantly correlated with having an ADE [median 5 (inter-quartile range 3–7) vs. 5 (4–8); $P = 0.7$] though the median of the number of medications administered within the 24 h before an ADE was 11 (inter-quartile range 6–14).

Seven fatal or life-threatening ADEs occurred in 7 patients, which accounted for 7% of the 99 ADEs. Fatal or life-threatening ADEs included nosocomial infections caused by antibiotic use and shock associated with omitted vasopressor use. Serious ADEs and significant ADEs accounted for 34 and 59% of all ADEs, respectively.

Liver disorders and gastrointestinal disorders were the most frequent types of ADEs, accounting for 29% of all ADEs, respectively (Table 2).

Influence of ADEs on mortality and morbidity

Among the 459 patients admitted to the ICU, 73 patients (16%) died during their ICU stay. The mortalities of patients with ADE and without ADE were 17% (12/70) and 16% (61/389), respectively ($P = 0.8$). Among the 73 deaths, 38 died within 3 days of admission to the ICU. After excluding those 38 deaths, 12 deaths occurred among 70 patients (17%) who had at least one ADE during their ICU stay and 23 deaths (7%) occurred among 351 patients who had no ADEs during their ICU stay ($P = 0.003$). A Cox proportional hazard model showed that ADEs did not increase the mortality in the ICUs after adjusting for age and organ dysfunction status (HR: 0.7; 95% CI: 0.3–1.5) (Table 3).

Among the remaining 386 patients after excluding 73 patients who died during their ICU stay, the median ICU stay of those who had at least one ADE was 13 days (inter-quartile range: 6–20), while 2 days (inter-quartile range: 1–6) in those who had no ADEs ($P < 0.0001$). A linear regression model for the length of ICU stay showed that ADEs significantly increased the length of ICU stay, even after adjusting for age and organ dysfunction status (Table 3).

Discussion

We found that the presence of an ADE was associated with longer ICU stay consistent with previous studies [11, 15].

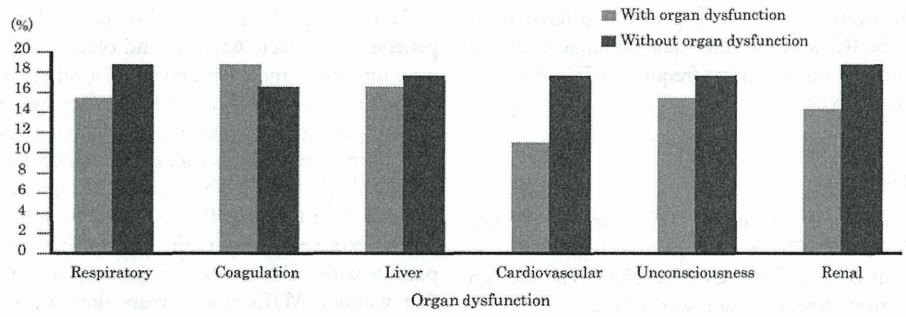

Figure 1 Comparison of the ratio of patients who had at least one ADE during their ICU stay between those who had any organ dysfunction and those without organ dysfunction.

After adjusting for the severity of illness and age, ADEs were still associated with a 10-day longer ICU stay. One interpretation of this result could be that patients with a longer ICU stay were more likely to experience an ADE. However, the median day of onset of ADEs after admission was 3 and the median length of ICU stay among those who had no ADEs was 2. This result suggests that ADEs increased the length of ICU stay rather than that longer ICU stays cause more ADEs, although both could play a role.

ADEs were not associated with increased mortality, although we had limited power to identify such an association. There were three deaths judged to be due to an ADE in this study, all of which were nosocomial infections associated with antibiotic use. Determination of cause is complex in such cases, but many such deaths have been reported previously; for example one study found that nosocomial infections in ICUs contributed to two fatal adverse events [8] and another study reported that nosocomial infections accounted for 24% of the adverse events identified in ICUs [16]. These results suggest that nosocomial infections are especially hazardous in critically ill patients.

We found that ADEs were common in ICUs in Japan, and the incidence of ADEs in ICUs was twice the rate of 16.2 per 1000 patient-days in the general wards [6]. These results were generally similar to previous studies from other countries. For example, Rothschild *et al.* [8] reported in a US study that the incidence of ADEs was 37.6 per 1000 patient-days, and Cullen *et al.* reported in another study from the USA that patients in ICUs experienced a higher rate of ADEs than non-ICU patients [9]. These results suggested that critically ill patients in ICUs are vulnerable to ADEs.

Among the factors contributing to this risk in ICU patients are likely organ dysfunction of a variety of types, the complexity of underlying disease in these patients, and the high number of medications and high-risk interventions they receive [8, 11]. Seynaeve *et al.* [17] reported that the severity of patients in ICUs was strongly associated with ADEs: the mean SOFA score was significantly higher on days when ADEs occurred than on days without ADEs (10 vs. 8). In our study, organ dysfunctions defined using the SOFA score were not related to

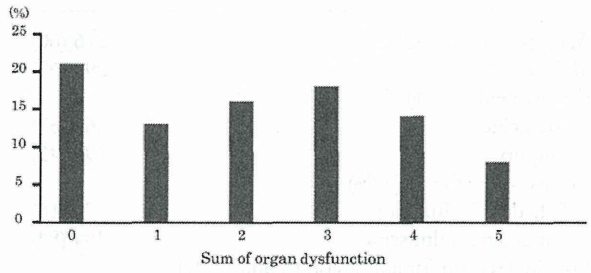

Figure 2 The percentage of patients who had at least one ADE according to the total number of organs dysfunctioning.

Table 2 Types of ADEs

Symptoms	ADEs (%)
Bleeding	5 (5)
Central nervous system	2 (2)
Allergic reaction	20 (20)
Liver disorder	29 (29)
Cardiovascular	7 (7)
Gastrointestinal	29 (29)
Kidney injury	2 (2)
Respiratory	2 (2)
Marrow depression	2 (2)
Sepsis	1 (1)

ADEs, adverse drug events.

ADEs. This could be because our assessment of the patients' severity was not sensitive enough to detect the relationship with ADEs. Because this study was based on the JADE study, which was done in both ICUs and non-ICUs, we did not perform a detailed severity assessment beyond the SOFA. Other studies have reported that a higher number of medications administered is associated with a higher ADE rate; one

Table 3 The influence of ADEs on mortality and morbidity

Variables	Mortality		Morbidity	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)
ADE	0.7 (0.3 to 1.4)	0.7 (0.3 to 1.5)	10.6 (8.0 to 13.1)	10.2 (7.6 to 12.8)
Age (≥65)	0.9 (0.4 to 2.1)	1.0 (0.5 to 2.4)	2.5 (0.5 to 4.4)	1.9 (−0.02 to 3.9)
Respiratory disorders (PaO_2/FiO_2 ≤400 mmHg)	2.6 (1.2 to 6.6)	2.4 (1.0 to 6.1)	−1.3 (−3.3 to 0.7)	−1.4 (−3.4 to 0.7)
Coagulopathy (platelets ≤150 × 10^3/μl)	1.3 (0.6 to 2.7)	1.0 (0.4 to 2.3)	0.8 (−1.7 to 3.4)	0.8 (−1.8 to 3.4)
Liver dysfunction (bilirubin ≥1.2 mg/dl)	1.7 (0.7 to 3.5)	1.6 (0.7 to 3.6)	−0.7 (−3.5 to 2.2)	−0.4 (−3.2 to 2.4)
Hypotension (mean arterial pressure <70 mmHg)	1.7 (0.6 to 4.1)	1.2 (0.4 to 3.0)	0.2 (−3.3 to 3.8)	0.3 (−3.2 to 3.8)
Unconsciousness (Glasgow Coma Scale ≤14)	2.6 (1.3 to 5.6)	1.9 (0.9 to 4.3)	−0.2 (−1.8 to 2.1)	0.2 (−1.8 to 2.3)
Renal dysfunction (creatinine ≥1.2 mg/dl)	1.6 (0.8 to 3.0)	1.4 (0.7 to 2.9)	0.6 (−1.6 to 2.8)	1.0 (−1.2 to 3.1)

HR, hazard ratio; CI, confidence interval; ADE, adverse drug event.

showed the correlation using a database during a certain period where ADEs increased when more medications were used and another study showed that the number of medications used the month before admission was associated with ADEs [10, 18]. In our study, the number of medications administered on admission was not significantly correlated with having an ADE; however, the number of medications administered within the 24 h before an ADE was 11 and it was higher than 5, which was the number of medications administered on ICU admission. Even though the number of medications among those without ADEs was not assessed, this finding might address the issue that the more medications administered would be related to higher risk of an ADE. Though we assessed the relationship between patients' demographic data evaluated on admission to ICUs and ADEs, only several factors such as urgent admission and the length of experienced year of physicians in charge were associated with a higher ADE rate. Our results suggested that early prediction and prevention of ADEs simply by assessing the patients' demographic status evaluated on admission would likely not produce groups of sufficiently varying risk to be an effective approach.

This study has several limitations. First, some ADEs may not have been noted in the charts and may thus have not been detected, which would make our estimates a lower bound. However, more robust alternatives to measure ADEs have not yet been developed, so that the approach we used is the current standard one. Secondly, our data may not be sensitive enough to evaluate the characteristics or severity of critically ill patients because the JADE study did not focus on ICUs; thus, we evaluated the presence of organ dysfunction using the original SOFA score.

In conclusion, we found that ADEs were common and occurred to patients regardless of the presence of organ dysfunction in ICUs in Japan. ADEs were significantly associated with the length of stay though not related to mortality. Earlier detection of ADEs with close monitoring might improve the morbidity in ICUs.

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Conflict of interest

D.W.B. is on the clinical advisory board for Patient Safety Systems, which provides a set of approaches to help hospitals

improve safety. He also consults for Hearst, which develops knowledge resources, and serves on the clinical advisory board for SEA Medical Systems, which makes intravenous pump technology.

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