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ORIGINAL ARTICLE

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

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Abstract

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

KEYWORDS

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

1 | INTRODUCTION

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

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

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

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

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

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

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

2.2 | Naranjo Algorithm

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

2.3 | Data collection and review process

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

2.4 | Statistical analyses

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

3 | RESULTS

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

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

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

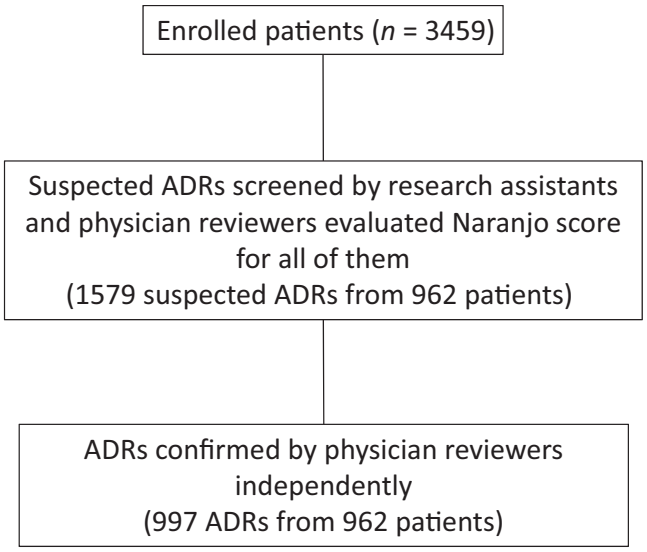

FIGURE 1 Evaluation process for adverse drug events (ADRs). ADRs were evaluated using 3 steps. Research assistants suggested suspected ADRs from potential drug-related incidents. A physician reviewer scored each suspected ADR independently using the NA. Two physician reviewers identified ADRs based on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

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

TABLE 1 Characteristics and demographics of patients on admission

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

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

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

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

NSAIDs, nonsteroidal anti-inflammatory drugs.

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

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

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

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

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

Data expressed as n (%).

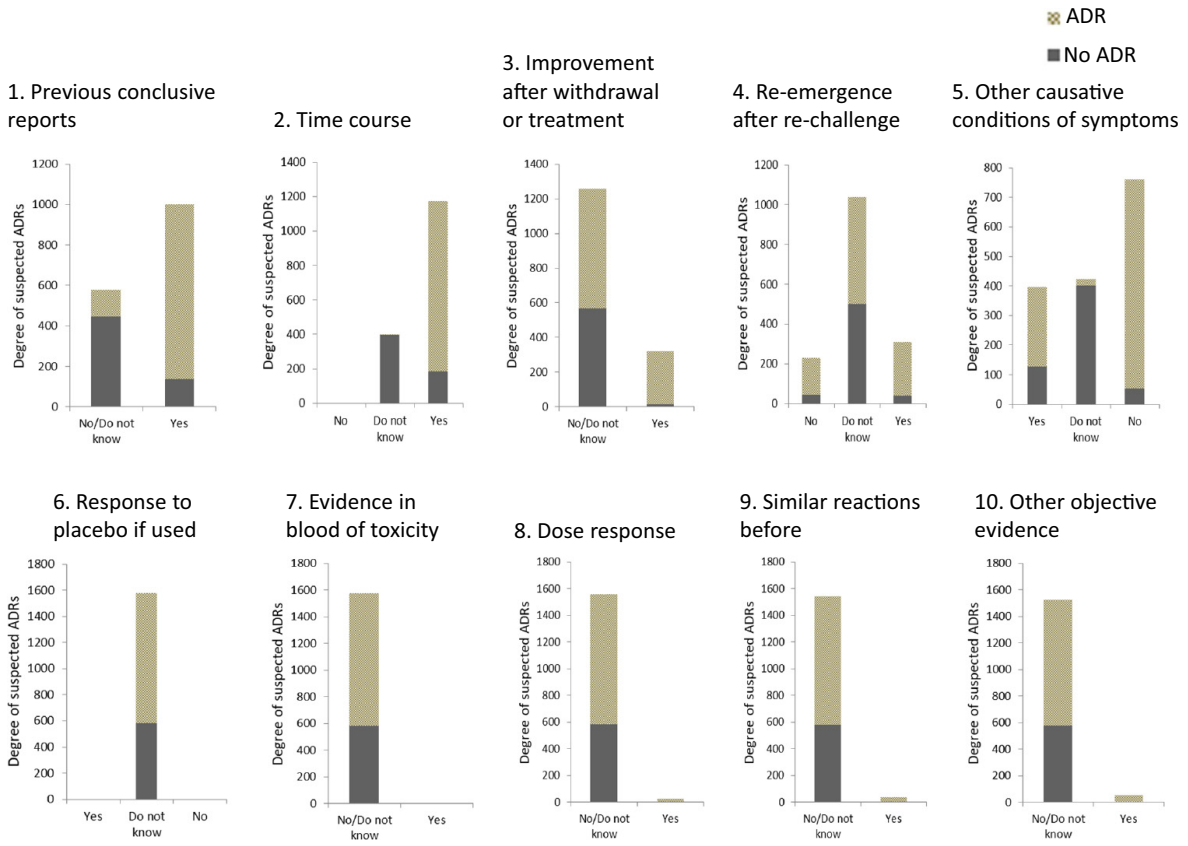

FIGURE 2 Distribution of adverse drug reactions (ADRs) by each Naranjo Algorithm (NA) component. The distribution of ADRs identified by physician reviewers for scored suspected ADRs by each NA component is shown. A total of 10 components, each consisting of 2 or 3 classifications were evaluated

3.3 | Sensitivity and specificity of the NA to determine ADRs

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

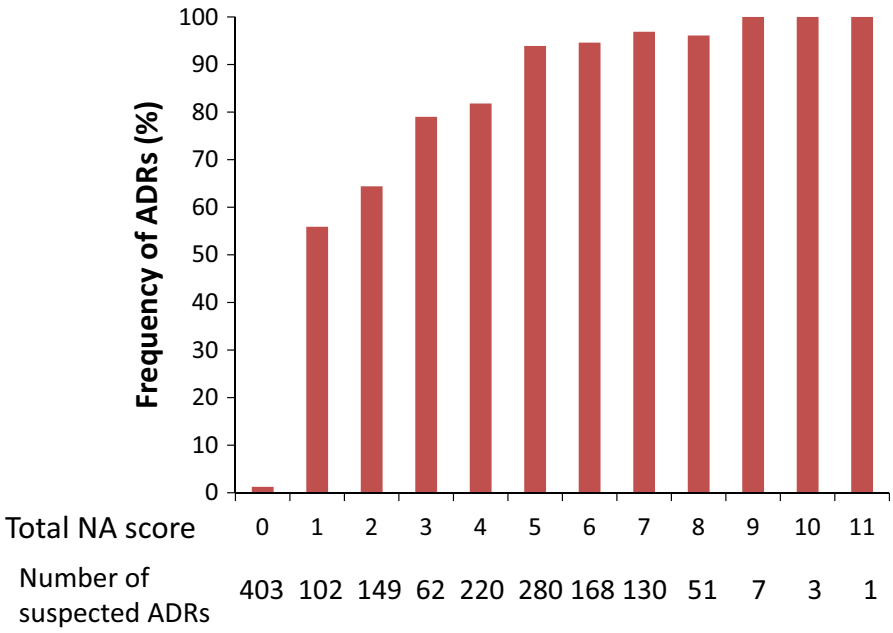

FIGURE 3 Relationship between the total Naranjo Algorithm (NA) score and the percentage of identified adverse drug events (ADRs) among suspected ADRs. The percentage of confirmed ADRs among suspected ADRs are expressed for each total NA score (0 through 11)

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

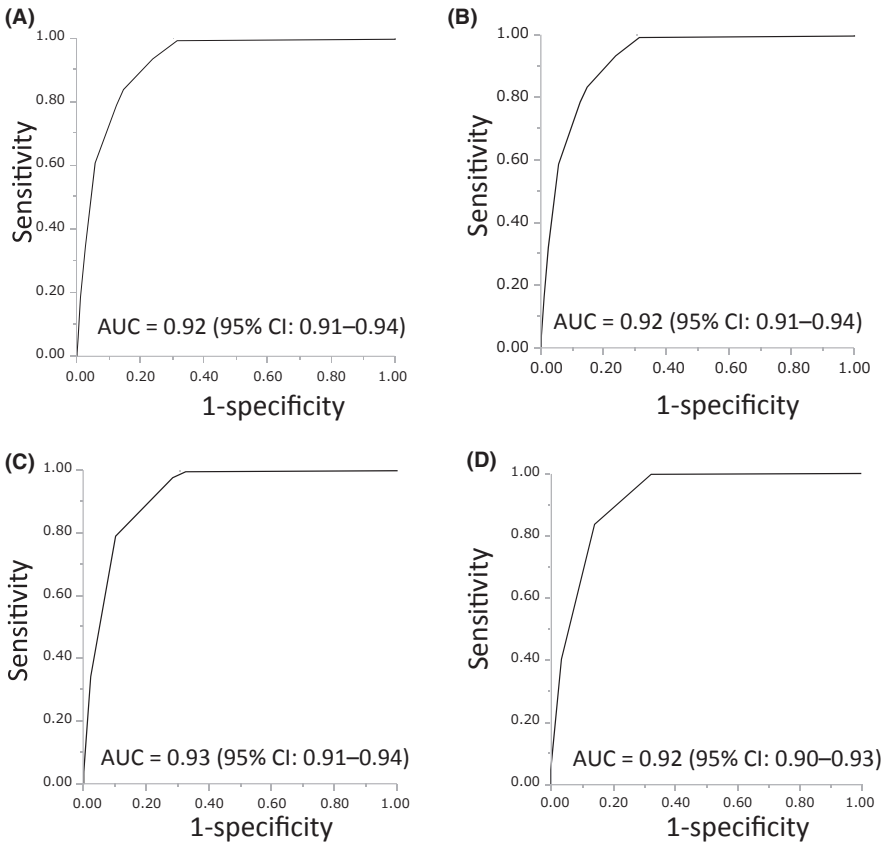

FIGURE 4 Receiver operating characteristic curve for adverse drug events (ADRs) and total Naranjo Algorithm (NA) score. A, The AUC for the sum of all NA components. B, The AUC for selected NA components (1-5). C, The AUC for selected NA components (1-5) converted to binary scores (0 or 1). D, The AUC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

TABLE 4 Modified Naranjo Algorithm (NA)

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

4 | DISCUSSION

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

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

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

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

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

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

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

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DISCLOSURES

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RESEARCH Open Access

Effect of norepinephrine dosage on mortality in patients with septic shock

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Abstract

Background: Use of high-dose norepinephrine is thought to have an immunosuppressive action that increases mortality. This study aimed to evaluate the correlation between norepinephrine dosage and prognosis of patients with septic shock.

Methods: This study was a nested cohort of the DExmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) trial. We evaluated 112 patients with septic shock and an initial Sequential Organ Failure Assessment Cardiovascular (SOFA-C) category score > 2 and initial lactate level > 2 mmol/L. We divided the patients into two groups according to the norepinephrine dosage administered over the initial 7 days: high dose (≥ 416 μg/kg/week) (H group, $n = 56$) and low dose (< 416 μg/kg/week) (L group, $n = 56$). The primary outcome of interest was 28-day mortality. Secondary outcomes were ventilator-free days, initial 24-h infusion volume, initial 24- to 48-h infusion volume, and the need for renal replacement therapy. For comparisons between the H group and L group, we used the chi-square test or Fisher's exact test for categorical variables and the *t* test or Wilcoxon rank sum test for continuous variables. For time-to-event outcomes, Cox proportional hazards models were used. Kaplan-Meier survival curves were created for graphical representation.

Results: Patient characteristics appeared to be similar between the two groups except for the SOFA-C score and fibrinogen degradation product level. The cumulative incidence of death at 28 days was 29.9% (16 patients) in the L group and 29.7% (15 patients) in the H group ($p = 0.99$). The median number of 28-day ventilator-free days was 20 (0, 25) in the L group and 16 (0, 22) in the H group ($p < 0.05$). Initial infusion volume at 0–24 h in the H group was significantly higher than that in the L group ($p = 0.004$). Infusion volume at 24–48 h in the H group was also significantly higher than that in the L group ($p = 0.03$).

Conclusions: No statistically significant difference was observed in 28-day mortality between patients with septic shock treated with high-dose norepinephrine compared with those treated with low-dose norepinephrine. However, the number of ventilator-free days in the L group was higher than that in the H group.

Trial registration: clinicaltrials.gov Identifier: NCT01760967 Date of trial registration: January 4, 2013.

Keywords: Norepinephrine, Septic shock, Ventilator-free days

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Background

Norepinephrine is the vasopressor of first choice for patients with septic shock [1]. Norepinephrine recruits unstressed volume through alpha adrenergic effects on venous and arterial vessels and might recruit volume to the macrovasculature. However, norepinephrine is also thought to have an immunosuppressive action that causes a poor prognosis [2, 3]. Previous reports showed that norepinephrine dosage was associated with intensive care unit (ICU) mortality, with an especially high mortality rate at doses above 1 μg/kg per min [2]. From this previous study, the high-dose usage of norepinephrine was thought to cause high mortality in patients with sepsis. As another problem, in the treatment strategy of septic shock, it is important to include early recognition, fluid resuscitation, and maintenance of the blood pressure. However, if massive fluid resuscitation is required, this can cause pulmonary edema and prolonged the number of ventilator days. In this study, we aimed to evaluate the correlation between norepinephrine dosage and prognosis and the number of ventilator-free days (VFD) of patients with septic shock.

Methods

Patient selection

The DExmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) trial was conducted from February 2013 to January 2016 [4]. This trial was a multicenter, randomized, controlled trial that enrolled 201 adult patients with sepsis undergoing ventilation. It was designed to assess the effects of a sedation strategy with dexmedetomidine compared with that without dexmedetomidine. The results of this trial in the 201 patients showed that treatment with dexmedetomidine vs that without dexmedetomidine did not significantly reduce the number of VFD (20 vs 18 days) or 28-day mortality (23 vs 31%, hazard ratio 0.69). This subanalysis of the 201 randomized patients included those with septic shock. Septic shock was defined as a Sequential Organ Failure Assessment (SOFA) score > 2 for the cardiovascular category and a lactate level > 2 mmol/L at randomization. We enrolled 112 patients and divided the patients into two groups according to the total dosage of norepinephrine administered over the initial 7 days: low dose (< 416 μg/kg/week) (L group, $n = 56$) and high dose (≥ 416 μg/kg/week) (H group, $n = 56$) (Fig. 1).

Treatment protocol

The treatment protocol for sepsis was based on the Guidelines for the Management of Sepsis [1]. In the resuscitation from septic shock-induced hypoperfusion, we initially administered an adequate amount of crystalloid on admission to maintain a mean arterial pressure of 65 mmHg, central venous pressure of 8–12 mmHg, and urinary output of > 0.5 mL/kg/h. Following fluid resuscitation, if the blood pressure could not be maintained, we used norepinephrine or vasopressin as the vasopressor.

Measurements

We collected data on the initial serum lactate level, SOFA score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score at randomization. White blood cell (WBC) count, levels of fibrinogen, D-dimer, fibrinogen degradation products (FDP), C-reactive protein (CRP), and procalcitonin (PCT) and norepinephrine dosage were assessed. Infusion volume was assessed on the first and second days, and the dosages of other vasopressors were assessed on the first 7 days after randomization.

The primary outcome of interest was 28-day mortality. For other outcomes, patients were followed in the hospital

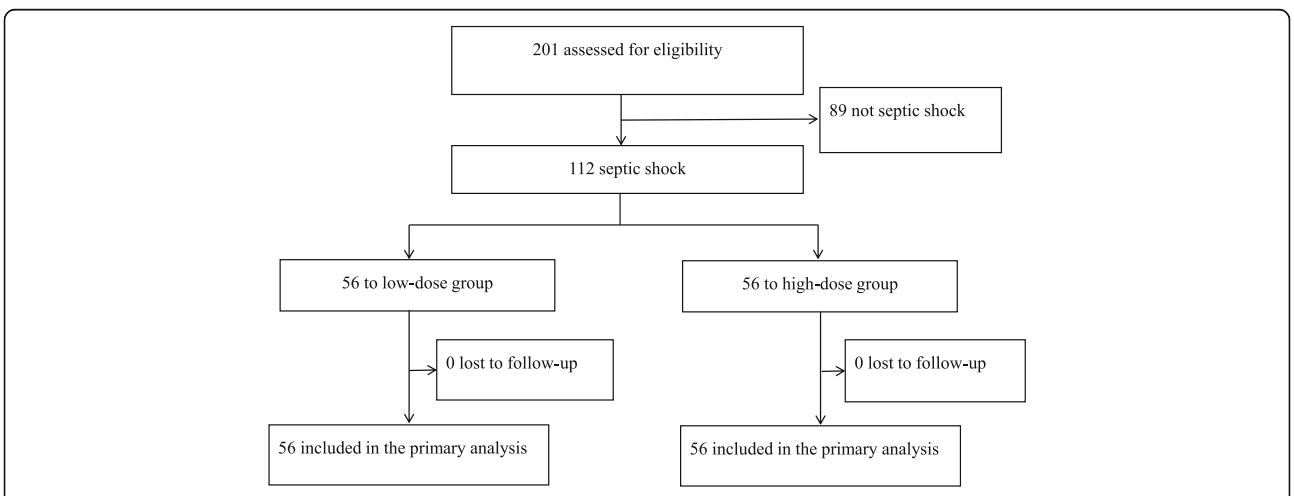

Fig. 1 Flow of participants in the norepinephrine dosage for septic shock study

from enrollment for 28 days or until discharge or death if earlier. Secondary outcomes included the number of VFD, defined as the number of days without use of a ventilator during the 28-day study period, initial 24-h infusion volume, initial 24- to 48-h infusion volume, and the need for renal replacement therapy including continuous renal replacement therapy and hemodialysis.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) or the median and interquartile range (IQR). Categorical variables are presented as numbers and percentages (%). For comparisons between the H group and L group, we used the chi-square test or Fisher's exact test for categorical variables and the *t* test or Wilcoxon rank sum test for continuous variables.

For time-to-event outcomes (time to ICU discharged death), Cox proportional hazards models were used. Kaplan-Meier survival curves were created for graphical representation of these time-to-event outcomes. When examining 28-day mortality, patients were censored at the time of last contact while alive or at 28 days from enrollment, whichever came first. Censoring for hospital discharge analyses occurred at the time of death or, rarely, at study withdrawal. To account for any effect of site and for baseline imbalances, a Cox proportional hazards regression model was used with patients nested within site, and site treated as a random effect with the following covariates included in the model: APACHE II score > 23, age > 65, emergency operation, infection site is lung, and treated with dexmedetomidine. A two-sided p value of < 0.05 was considered statistically significant, and all analyses were performed using JMP Pro software (version 12.2; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics appeared to be similar between the two groups except for the Sequential Organ Failure Assessment Cardiovascular (SOFA-C) score and FDP level (Table 1). In the H group, use of another vasopressor, such as dobutamine, and total vasopressin dosage within 7 days were significantly higher than those in the L group. Causes of sepsis were lung ($n = 29$), abdomen ($n = 52$), and others ($n = 31$).

As the primary outcome, the cumulative incidence of death at 28 days was not significantly different between the two groups: 29.9% (16 patients) in the L group and 29.7% (15 patients) in the H group ($p = 0.99$) (Fig. 2). The analysis adjusted for infusion volume over the first 24 h also did not show a significant difference ($p = 0.38$). The median 28-day VFD in the L group was significantly higher than that in the H group (20 [0, 25] vs 16 [0, 20] days: $p < 0.05$) (Fig. 3). Using the Cox proportional hazards model to adjust for all five of the covariates, VFD was incorporated into the model, with similar results compared with the primary analysis. The dose of norepinephrine used was significantly different between the two groups on each of the first 7 days. Especially, the highest dose of norepinephrine administered was in the H group on day 2 at 345.1 (170.9) μg/kg (Fig. 4).

Initial infusion volume at 0–24 h in the H group was significantly higher than that in the L group (7829 [5689, 10,676] vs 5544 [3985, 8000] mL, $p = 0.004$). Infusion volume at 24–48 h in the H group was also significantly higher than that in the L group (3530 [2382, 4612] vs 2689 [1962, 3916] mL, $p = 0.03$). Within the first 3 days after admission, 7 patients died in the H group and 9 patients died in the L group. The cumulative incidences of death at 28 days except for the patients with death within 3 days were not significantly different between the two groups: 32.8% in the L group and 28.4% in the H group ($p = 0.39$). Renal replacement therapy was performed in 32 patients in the H group and in 18 patients in the L group.

Discussion

Septic shock is defined as a subset of sepsis in which underlying abnormalities of circulatory and cellular metabolism are profound enough to substantially increase mortality [5]. Norepinephrine is the vasoactive agent of first choice for patients with septic shock after adequate volume resuscitation [1]. Our results showed that the dosage of norepinephrine did not affect the mortality of patients with septic shock, but the number of VFD was lower in the H group. The reason for the difference in the number of VFD between the two groups was that the infusion volume in the H group was significantly higher than that in the L group. Massive infusion volumes can bring about pulmonary dysfunction and cardiovascular failure. Generally, such conditions require ventilator support. Thus, we thought that the factors contributing to the lower number of VFD in the H group were the unstable circulatory status and massive infusion volume administered. A previous report showed that a norepinephrine dosage of 1 μg/kg per minute was associated with an ICU death rate of 90% and suggested that a dosage of norepinephrine greater than 1 μg/kg per minute is an independent factor associated with mortality in patients with septic shock [2]. However, the study by Martin and colleagues had a few problems related to fluid treatment for septic shock. The non-survivors group did not receive the same resuscitation infusion volume as the survivors group. Crystalloid was 1.0 L (0.0–2.5) in the 168 survivors vs 1.0 L (0.0–2.0) in the 156 non-survivors, and cumulative fluid administration was 1.5 L (0.9–3.0) in the 168 survivors vs 1.0 L (0.5–2.0) in the 156 non-survivors [2]. These results indicate that the non-survivors were not infused

Table 1 Patient characteristics

	L group ($n = 56$)	H group ($n = 56$)	p value
Age, years	70.8 ± 13.4	70.5 ± 14.4	0.92
Male sex, *n* (%)	33 (58)	36 (64)	0.56
Body weight, kg	53.9 ± 11.2	54.7 ± 11.9	0.72
COPD (%)	4 (7.1)	3 (5.3)	0.70
Soft tissue infection (%)	4 (7.1)	4 (7.1)	1.00
Emergency surgery (%)	28 (50.1)	23 (41.1)	0.34
Site of infection (%)			
Lung	16 (29)	13 (23)	
Abdomen	29 (52)	23 (41)	
Urinary tract	4 (7)	8 (14)	
Skin and soft tissue	1 (2)	6 (11)	
Others	6 (11)	6 (11)	
APACHE II score	25 (19, 33)	25 (20, 30)	0.89
SOFA score	10 (8, 12)	10 (8, 12)	0.63
SOFA-R score	2 (1, 3)	2 (1, 3)	0.65
SOFA-P score	0.5 (0, 2)	1 (0, 2)	0.23
SOFA-L score	0 (0, 1)	0 (0, 1)	0.65
SOFA-C score	3 (3, 4)	4 (3, 4)	0.007
SOFA-N score	0 (0, 3)	1 (0, 2)	0.63
SOFA-K score	1.5 (0, 3)	1 (0, 2)	0.34
Systolic BP, mmHg	109 (26)	105 (28)	0.31
Mean BP, mmHg	73 (16)	72 (18)	0.75
Lactate level, mmol/L	4.5 (3.0, 7.8)	4.4 (3.6, 6.6)	0.94
Urine output, mL/day	1240 (298, 2302)	1279 (378, 2566)	0.84
WBC, mm^3	8500 (4500, 14,109)	5000 (2250, 13,930)	0.18
FDP, μg/dL	15.8 (7.5, 28.0)	23.6 (10.5, 52)	0.02
Fibrinogen, mg/dL	337 (243, 532)	403 (271, 583)	0.26
CRP, mg/dL	11.9 (5.2, 24.4)	16.1 (5.4, 27.3)	0.76
PCT, ng/mL	29.3 (3.2, 81.5)	40.0 (12.9, 100)	0.11
Catecholamine			
Total dopamine dosage (μg/kg)	15,727 (6180, 36,150)	28,532 (12,321, 43,407)	0.15
Total dobutamine dosage (μg/kg)	6191 (3652, 14,796)	23,051 (13,931, 35,760)	0.003
Total vasopressin dosage (IU)	9.8 (5.1, 15.4)	30.2 (12, 54.2)	0.05
Hospital length of stays, days	29 (31)	33 (29)	0.12
Renal replacement therapy (%)	18 (32)	32 (57)	0.008

Data are shown as mean ± SD, number of subjects (%), or median (IQR), as appropriate

SD standard deviation, *COPD* chronic obstructive pulmonary disease, *IQR* interquartile range, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *SOFA-R* Sequential Organ Failure Assessment Respiration score, *SOFA-P* Sequential Organ Failure Assessment Coagulation score, *SOFA-L* Sequential Organ Failure Assessment Liver score, *SOFA-C* Sequential Organ Failure Assessment Cardiovascular score, *SOFA-N* Sequential Organ Failure Assessment Central nervous system score, *SOFA-K* Sequential Organ Failure Assessment Renal score, *BP* blood pressure, *WBC* white blood cell, *FDP* fibrinogen degradation products, *CRP* C-reactive protein, *PCT* procalcitonin

with an adequate amount of resuscitation volume in the initial period.

In our study, the H group received an adequate amount of resuscitation fluid compared with the L group over the initial 24 h and at 48 h. The most important treatment strategy for patients with septic shock is initial fluid resuscitation and maintenance of the blood pressure. If patients with septic shock receive adequate infusion of fluid volume, the dose of norepinephrine may not be related to patient prognosis.

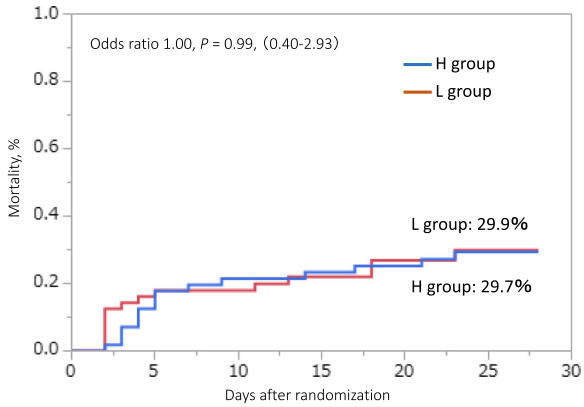

Fig. 2 Twenty-eight-day mortality between the high-dose group and low-dose group

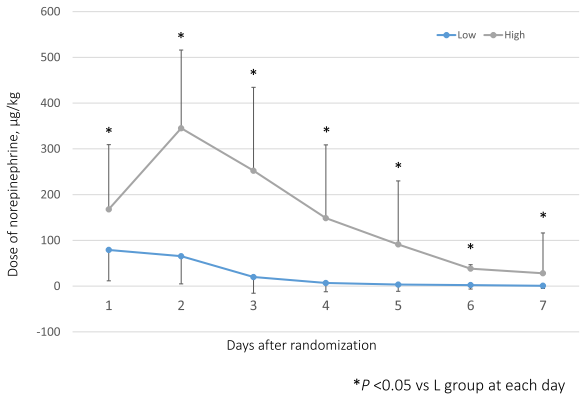

Fig. 4 Dose of norepinephrine on each day. *$p < 0.05$ vs L group at each day

In previous in vitro and animal studies, norepinephrine was shown to exert multiple anti-inflammatory actions [6, 7]. Exogenous norepinephrine infused into the portal vein of rats resulted in elevation of serum levels of IL-10 and IL-1 beta [8, 9]. Another study showed neutrophils incubated with norepinephrine displayed an immunosuppressive phenotype [10–12]. These studies indicate that epinephrine may have anti-inflammatory effects. In contrast, clinical studies have not investigated norepinephrine in relation to immunosuppressive reactions. Some studies investigating the correlation of the dosage of norepinephrine with mortality indicated that a high norepinephrine level is associated with high mortality in patients with septic shock [13]. However, no study found any correlation between the dosage of norepinephrine and immunological parameters. The blocking action of endogenous catecholamine with β-blockers has improved the prognosis in patients with sepsis [14, 15] and reduced secondary infection in pediatric burn patients [16]. These clinical studies suggested that a high catecholamine level may have led to immunoparalysis [17, 18].

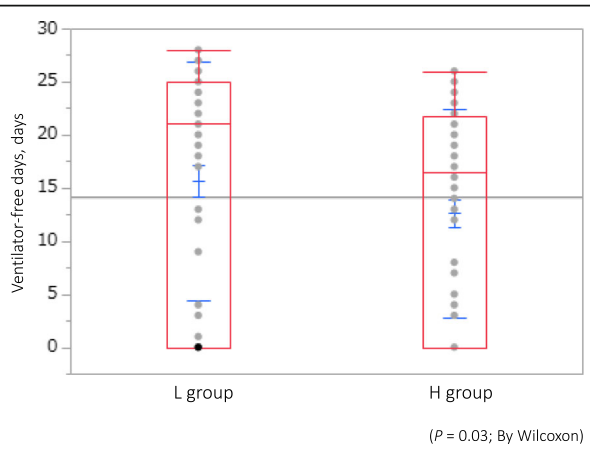

Fig. 3 Ventilator-free days between the high-dose group and low-dose group. $p = 0.03$; by Wilcoxon

In our study, some alternative vasopressors were also used to treat the patients with septic shock. More dobutamine, vasopressin, and renal replacement therapy were used in the H group than in the L group. However, mortality was not significantly different between the two groups. Our results indicated that renal replacement therapy and total dobutamine dosage also did not affect mortality. We surmise that because of the greater inflammatory action in the H group, the patients did not respond to the epinephrine effect and required the use of vasopressin and another vasopressor to maintain their blood pressure. The patients in a severe condition died earlier, and as a result, the doses of norepinephrine or another vasopressor in these patients might be smaller. We also assessed the incidence of death at 28 days after excluding the patients who died within 3 days. However, there was no significant difference between the two groups, and thus we thought that the early death of some patients had no influence on mortality.

Several adverse effects of catecholamines were reported previously, such as pulmonary edema, bowel ischemia, immunomodulation, increase cellular energy expenditure, and hyperglycemia [19–21]. Generally, we believed that a high concentration of catecholamine would increase mortality and worsen patient prognosis. However, our results were contrary to those of previous reports and did not indicate that high norepinephrine usage worsened mortality or caused organ dysfunction such as bowel ischemia and pulmonary edema although we did not measure the actual catecholamine concentration in serum. We think that high-dose norepinephrine may be used safely with no associated complications.

This study has several limitations. First, it was a nested cohort of a randomized control study, and use of a vasopressor other than norepinephrine was not allowed by

the treatment protocol. Our study concentrated on the use of noradrenaline as the initial vasopressor, and use of another vasopressor was uneven. Second, use of an alternate vasopressor other than norepinephrine was left to each physician's judgment. Third, we cannot determine to what extent the mechanism of norepinephrine contributed to the change in mortality. Also, the duration of shock was similar because there was no significant difference in initial lactate levels and APACHE II scores between the two groups. However, the initial SOFA-C score was different. We attribute this difference in SOFA-C score to the catecholamine dosage in the two groups because the initial blood pressure was not different between the groups. The early recognition and treatment of septic shock in our patients may be one factor influencing our results. However, the greater inflammatory action occurring in the H group required a high-dose vasopressor.

Conclusions

There was no statistically significant difference in 28-day mortality between the patients with septic shock treated with high-dose norepinephrine vs those treated with low-dose norepinephrine. However, the number of VFD was significantly higher in the group treated with low-dose norepinephrine than in the group treated with high-dose norepinephrine.

Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II; CRP: C-reactive protein; FDP: Fibrinogen degradation products; ICU: Intensive care unit; IQR: Interquartile range; PCT: Procalcitonin; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; SOFA-C: Sequential Organ Failure Assessment Cardiovascular; VFD: Ventilator-free days; WBC: White blood cell

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Availability of data and materials

The datasets generated during and/or analyzed during the present study are not publicly available owing to currently ongoing research studies, but the data are available from the corresponding author on reasonable request.

Authors' contributions

HY made substantial contributions in data acquisition and writing of the manuscript. HY, YO, and TM contributed to the study design, statistical analysis, interpretation of data, and final approval of the manuscript. YK, TY, and KM made equally substantial contributions in data acquisition and reviewing the manuscript. HY critically revised the manuscript for important intellectual content. TM supervised the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the institutional review boards of Wakayama Medical University and each participating institution. All patients provided necessary consent to participate in this study.

Consent for publication

No individual personal data are included in the study. All patients provided necessary consent to participate in this study.

Competing interests

Dr. Yamamura reports receipt of lecture fees from Hospira Japan, Nipro, and Asahi Kasei and educational consulting fees from Toray Industries, CSL Behring, Teijin Pharma, and Nihon Pharmaceutical. Dr. Kawazoe reports receipt of lecture fees from Hospira Japan and Pfizer Japan and a scholarship from Hospira Japan. Dr. Miyamoto reports receipt of lecture fees from Becton Dickinson and Pfizer Japan. Dr. Morimoto reports receipt of lecture fees from AbbVie, AstraZeneca, Daiichi-Sankyo, Kowa, Kyorin, Mitsubishi-Tanabe, and Pfizer Japan and consulting fees from Asahi Kasei and Boston Scientific. Dr. Tomonori Yamamoto and Dr.Yoshinori Ohta, have no competing interests. The other authors declare no competing interests.

Publisher's Note

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ORIGINAL RESEARCH ARTICLE

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

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Abstract

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

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

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

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

Key Points

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

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

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

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1 Introduction

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

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

2 Methods

2.1 Study Design and Patient Population

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

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

2.2 Definitions

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

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

2.3 Data Collection and Review Process

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

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

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

2.4 Statistical Analyses

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

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

3 Results

3.1 Patient Characteristics

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

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

3.2 Comparison of Cancer Patients and Non-Cancer Patients

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

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

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

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

3.3 Adverse Drug Events (ADEs) Due to Antitumor Agents

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

Table 1 Patient characteristics

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

Data are presented as n (%) unless otherwise indicated

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

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

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

4 Discussion

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

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

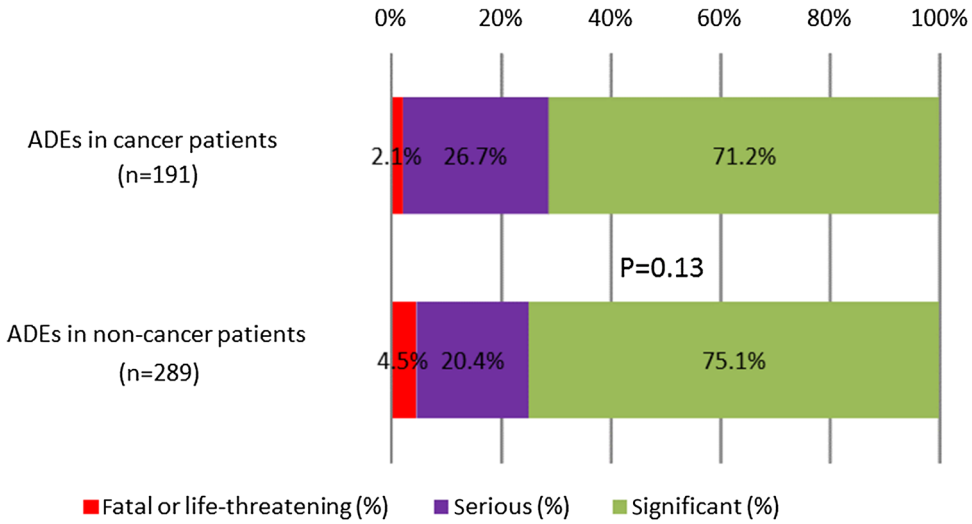

Fig. 1 Comparison of adverse drug event severity between cancer patients and non-cancer patients. *ADEs* adverse drug events

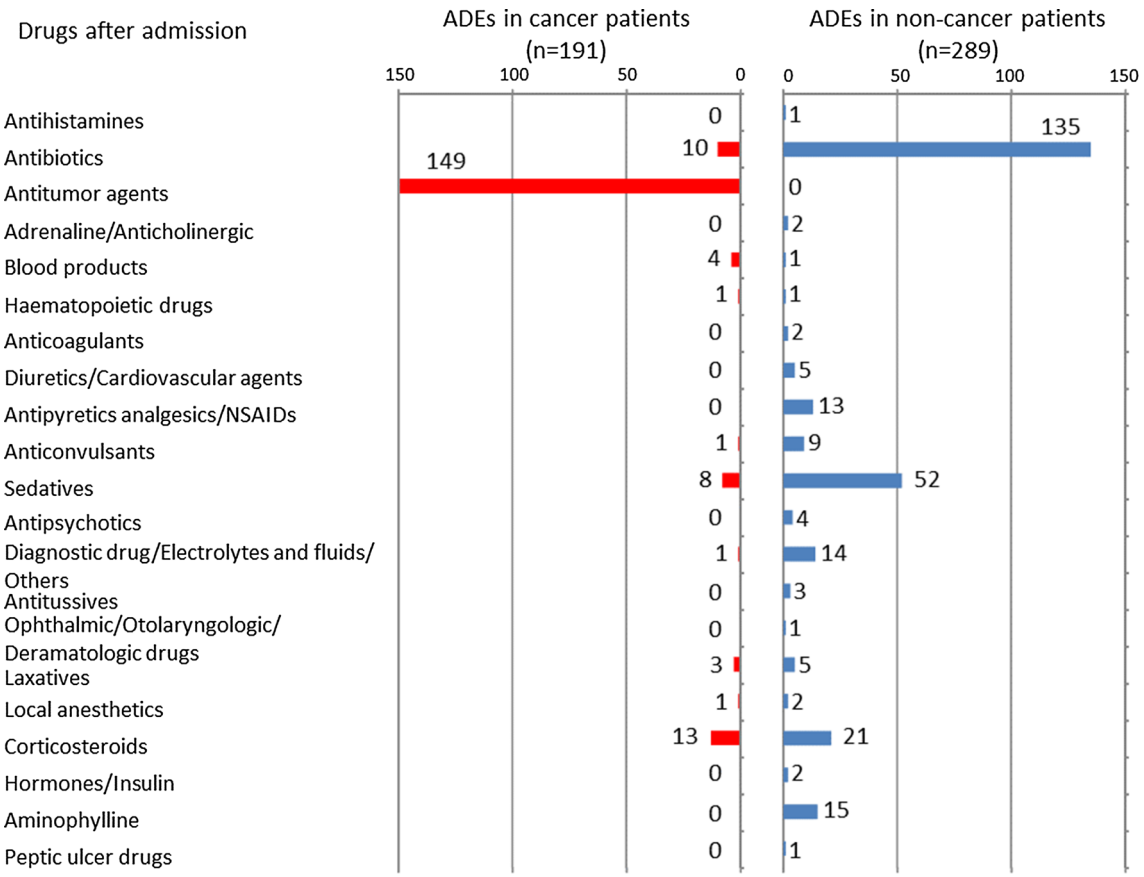

Fig. 2 Causative drugs of adverse drug events. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

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

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

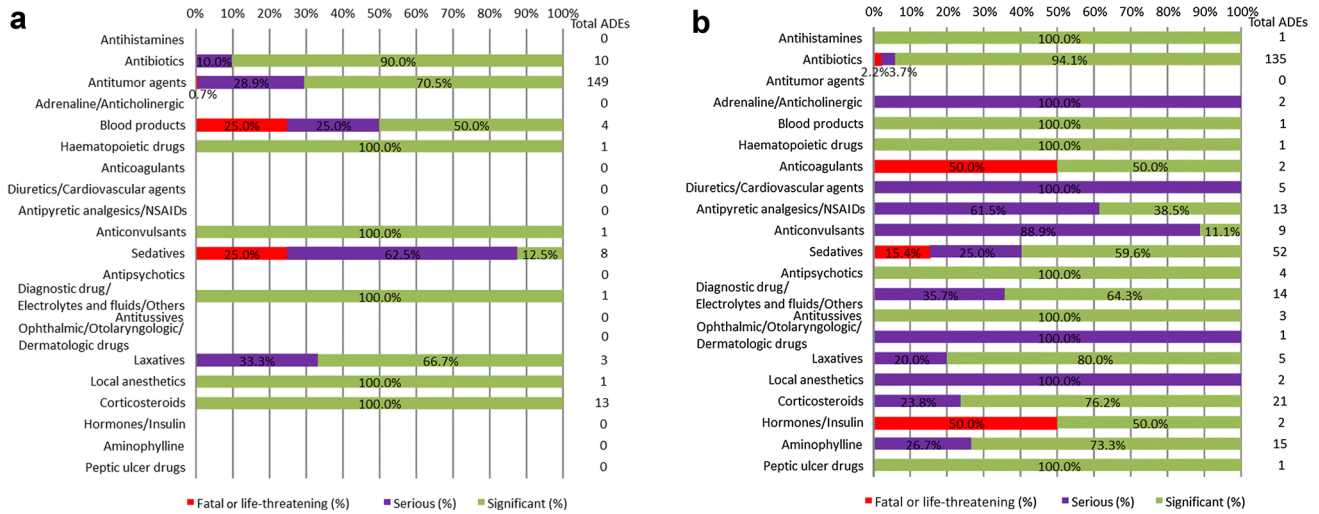

Fig. 3 Severity of adverse drug events in **a** cancer and **b** non-cancer patients. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

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

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

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

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

5 Conclusion

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

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Compliance with Ethical Standards

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

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

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

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