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Analysis of risk factors for adverse drug events in critically ill patients*

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Abstract

Objectives—An evaluation of risk factors for adverse drug events in critically ill patients has not been previously studied. The purpose of this original study was to determine risk factors for adverse drug events in critically ill adult patients.

Design—This retrospective case-control study includes patients who were admitted to the intensive care unit during a 7.5-yr period.

Setting—Academic medical center with 647 beds that contains approximately 120 intensive care unit beds.

Patients—Patients in the case group experienced an adverse drug event as documented in the hospital's database. The control group comprised the next two patients admitted to the same intensive care unit by the same admitting service.

Interventions—None.

Measurements and Main Results—Twenty-nine suspected risk factors identified from the literature were evaluated, including patient characteristics, drug characteristics, and laboratory values using a multiple logistic regression. A sample of 1101 cases and controls (54% male), with a mean age of 59.4 ± 17.5 yrs, were identified. In 367 cases, there was a total of 499 documented adverse drug events. Patients with kidney injury, thrombocytopenia, and those admitted emergently were 16-times, 3-times, and 2-times more likely to have an adverse drug event, respectively. Patients who were administered intravenous medications had a 3% higher risk of having an adverse drug event for each drug dispensed. Overall, the case group received more drugs per intensive care unit day and more drugs per intensive care unit stay.

Conclusions—Several patient and drug-related characteristics contribute to the risk of adverse drug events in critically ill patients. Diligent monitoring of factors that can influence the pharmacokinetic properties for existing drug therapies is necessary. Drug regimens should be evaluated daily for minimization. Based on previous studies, pharmacists as part of the interdisciplinary team could help to manage these risks.

*See also p. 998.

The authors have not disclosed any potential conflicts of interest.

Keywords

adverse drug event reporting system; critical care; intensive care unit; medication error; risk factor; safety

Adverse drug events (ADEs) can be life-threatening, particularly in the critically ill population (1). Life-threatening events associated with ADEs occur in 26% of intensive care unit (ICU) patients as compared to 11% in non-ICU patients ($p < .001$) (2). Patient factors, environmental factors, and drug classes related to ADEs are different in the ICU compared to general care units (1). The rate of preventable and potential ADEs in a medical ICU is reported to be 19 events per 1000 patient days, compared to 10 events per 1000 patient days reported for general care units (2). Critically ill patients are vulnerable to ADEs because of changing organ function leading to alterations in the pharmacokinetics of drugs, complex drug regimens, and fast-paced decision-making (1). Also, the severity, length of stay, and costs associated with ADEs are greater in the ICU compared to general care units (1, 2).

Many ADE studies completed in critical care patients have focused on detection. Evaluating prevention of ADEs by institutions, professional organizations, and government is more challenging, in large part because of the burden of labor and cost of prospective ADE surveillance. The mounting public concern about patient safety gives additional motivation to shift attention toward prevention, especially with the increase in reported serious ADEs. Successful ADE prevention methods include: pharmacist participation in ICU patient care rounds, which has shown to reduce preventable ADEs by 66% (3); diligent monitoring of abnormal laboratory values presaging ADEs referred to as drug-related hazardous conditions could preclude occurrences of injury, thereby improving patient safety (4); and the use of technology to prevent ADEs (5–7). Identifying patient risk factors for ADEs is the next logical approach for prevention of patient injury.

Potential risk factors for medication errors in the ICU have been summarized, whereas risk factors for ADEs are less well-known and not limited to the ICU (8–12). Accordingly, to address this paucity, the primary objective of this study was to identify potential risk factors for patients having ADEs while in the ICU.

MATERIALS AND METHODS

Study Design

This was a retrospective case-control stuy conducted at a large tertiary academic medical center. The University of Pittsburgh Medical Center-Presbyterian is a 647-bed academic medical center that contains approximately 120 ICU beds caring for those undergoing adult solid organ transplantation, cardiac surgery, general surgery, medicine, neurotrauma, neurovascular, general trauma, and coronary care patients.

Description of University of Pittsburgh Medical Center-Presbyterian ADE Database

ADEs were identified using the University of Pittsburgh Medical Center-Presbyterian ADE database that has been in existence since 1994 to aid in satisfying regulatory requirements and for quality-improvement initiatives previously described (13). Adverse events involving blood products and nutritional products, if reported, were also included in this database. The ADEs in this database come from several sources: voluntary reporting by healthcare professionals, identification by targeted quality-improvement initiatives, retrospective chart review using administrative data (International Classification of Disease codes), and pharmacist review of antidotal medication use or potentially drug-related electrolyte or laboratory abnormalities. The ADE surveillance system at our institution extends beyond

spontaneous reporting to include administrative data and trigger methods because different surveillance methods detect different types of ADEs (6, 14–16). Suspected ADEs are reviewed by the institution's interdisciplinary ADE review team consisting of approximately ten members, including physicians, pharmacists, nurses, and risk management representatives who further review all reported ADEs to validate causality and severity.

The review team uses the following definitions for ADEs, severity, and causality. An ADE is defined as an injury resulting from drug treatment. ADE severity has been classified using a modified version of the National Cancer Institute Toxicity Criteria. "Severity I" events required minor interventions (e.g., discontinuation of suspected medication or additional patient monitoring). "Severity II" ADEs required a moderate intervention (e.g., initiation of antidotal therapy). "Severity III" events required immediate life-sustaining treatment or transfer to an acute care unit (e.g., use of vasopressors, cardiac monitoring, or respiratory support) (17). Causality is assessed using the Jones algorithm (18), which determines if the event is highly probably related, probably related, possibly related, or remotely related to the suspect drug.

Patient Population

Patients were included in the case group if they were older than 18 yrs, admitted to a University of Pittsburgh Medical Center-Presbyterian ICU from July 1998 to January 2006, and had a documented ADE in the University of Pittsburgh Medical Center-Presbyterian ADE database. For the purposes of this evaluation, only patients with a likelihood of ADEs ranked as possible or greater were included in the case group, which is similar to previous studies using objective assessment tools (19–22). Patients in the control group were older than age 18 yrs, admitted to a University of Pittsburgh Medical Center-Presbyterian ICU from July 1998 to January 2006, and were not in the ADE University of Pittsburgh Medical Center-Presbyterian database. Additionally, the control group selection included the next two patients admitted to the same ICU and same admitting service as the patient with an ADE, matching patients based on admitting date, type of ICU, and admitting service. The case-to-control group ratio for the sample was 1:2. Patients in the control group were excluded if they had an E-code for a drug, medicinal substance, or biological substance causing adverse effects in a therapeutic class (E930–E949). An E-code is a supplemental International Classification of Disease revision nine code for external causes of injury that have been used to identify ADEs (6, 23). This study was approved by the University of Pittsburgh Institutional Review Board.

Risk Factor Selection

A comprehensive list of suspected risk factors that has not been thoroughly validated regarding their predictive inference was identified from the literature (8–11, 24). Patient risk factors evaluated were severity of illness, history of drug allergy, impaired renal and liver function, age, comorbidities, abnormal laboratory values (platelet count, albumin), history of substance abuse, gender, and smoking status (24). Patient-specific risk factors associated with their hospitalization such as ICU length of stay, previous hospital admissions, and previous ICU admissions were included. Drug-related risk variables evaluated were the route of administration, number of concomitant drugs (maximum drugs per day, maximum drugs per ICU stay), narrow therapeutic index drugs, drugs with enzyme inhibition/induction properties, and drugs that alter protein binding (10).

Data Collection

Patients were identified using the clinical, administrative, pharmacy, and financial data repository (Medical Archival Repository System [MARS], Pittsburgh, PA). Patient demographic and characteristics collected were age, gender, type of patient insurance,

patient's drug allergies, and admitting service. Electronic hospital admission and discharge summaries were obtained from MARS. These data were reviewed for all cases and controls to identify drug allergies (in addition to allergy information available in MARS), smoking history, alcohol use, and medical history (in addition to International Classification of Disease revision nine codes from MARS).

The Charlson comorbidity index and Simplified Acute Physiology Score II (SAPS II) severity of illness scores were calculated for the cases and controls. The Eclipsys/EMTEK ICU clinical information system (Chicago, IL) was used to obtain data for the calculation of SAPS II. All ICU flow sheet records are computerized in the Eclipsys/EMTEK and include vital signs, inspired fraction of oxygen, the Glasgow Coma Scale score, and urine output.

Laboratory values were collected for patients from MARS. Patients were considered to have acute kidney injury if it was documented in the electronic hospital admission or discharge summary or had a two-fold increase in creatinine (25). Hepatic injury was determined by chart review or a patient having a bilirubin of >3 mg/dL and an albumin of <2.8 g/dL (26). Albumin was interpreted as low if the value was <3.5 g/dL. The platelet count was considered low if it was <100,000/mm^3.

Patient hospitalization information obtained included ICU length of stay, hospital length of stay, number of admissions to the hospital in the year previous to the date of the first ADE, and number of admissions to an ICU in the year previous to the first ADE in the ICU.

Patient information and details about their medication regimen during the hospital stay were obtained from MARS. The medication regimens were assessed for route of administration, narrow therapeutic index classification, high protein binding (defined as >70%), CYP P450 enzyme inducers, and enzyme inhibitors. Drugs were categorized by drug class according to the American Hospital Formulary System classification. Drugs were categorized according to high-risk medications as per the Institute for Safe Medication Practices list. In addition, the charge data were used to determine the maximum number of drugs per day and number of drugs per ICU stay.

Statistical Analysis

Potential patient-related and drug-related risk factors predicting ADEs were assessed using univariate logistic regression analyses. Risk factors significant at α level of 0.01 were then entered into a standard multiple logistic regression analysis together to select the smallest subset of risk factors that predict an ADE. The risk factors used in the multiple logistic regression analysis included type of admission, SAPS II score, acute kidney injury, low albumin, and low platelet count. If there was high dependency between risk factors, then they were not used in the multiple logistic analysis. For example, total intravenous medications and oral medications could not be included with total number of drugs during the ICU stay. A sample of 350 subjects in the case group and 700 subjects in the control group provided 0.80 power to detect a difference of 5.6% in proportions between cases and controls, which is significant for α of 0.01 and for a two-tailed test. Furthermore, this also detected an odds ratio as small as 1.65, which is significant when we set α at 0.01 and power at 0.80, correlations among predictors to 0.5, and probability of an event as 9.5% for a two-sided test based on a conservative estimation of published data (27). In addition, a receiver-operator characteristics curve analysis was conducted to determine the area under the curve and the sensitivity/specificity of the multiple logistic regression model in predicting an ADE.

RESULTS

A sample of 1,101 cases and controls (54% male) with a mean age of 59.4 ± 17.5 yrs was identified. The patients represented surgical (41%), medical (26%), cardiology (12%), transplant (8%), and other (13%) patients according to admitting service. Type of admission varied among groups, with more cases being admitted emergently/urgently (57% vs. 45%; $p < .001$). The mortality rate between groups was 24% and 14% for cases and controls, respectively ($p < .001$).

In 367 cases there were a total of 499 documented ADEs, with 27% of patients experiencing more than one ADE (range, 1–8). The most common drug classes related to these ADEs were analgesics/anxiolytics/sedatives (23%), antimicrobials (20.2%), and anticoagulants (14.2%). The most common drugs associated with ADEs were heparin (9.2%), morphine (7.0%), fentanyl (5.6%), piperacillins (3.8%), and phenytoin (3.6%). Frequent reactions by system included neurologic (23.4%), hematologic (21%), allergic reactions (13%), respiratory (8.2%), cardiovascular (8.0%), and renal (5.6%). The severity of these reactions were 10.2%, 55.7%, and 34.1%, for National Cancer Institute toxicity criteria severity category I (minor intervention), severity category II (moderate intervention), and severity category III (life-sustaining intervention), respectively.

The results of the univarate analyses for patient-related risk factors are provided in Table 1 and the drug-related risk factors are shown in Table 2. Overall, drugs with the potential for pharmacokinetic drug interactions (enzyme-inducing and enzyme-inhibiting drugs), drugs with narrow therapeutic indices, and high-risk medications were more common in the case group. In general, the case group received more drugs per ICU day and more drugs per ICU stay. The case group received more anti-infectives, autonomic drugs, cardiovascular, central nervous system, and gastrointestinal drugs.

Six of the risk factors included in the multiple logistic regression analysis had significantly greater likelihood of occurring in the case group, as shown in Table 3. The model explains 53% of the variance, which is significant at the 0.001 level. The overall correct classification (area under the curve) is 88% (99% confidence interval, 0.84–0.91). In addition, the sensitivity and the specificity of the model are both 80%. In other words, the probability of predicting a patient with an ADE and also of predicting a patient without an ADE correctly is 80%. Patients with kidney injury were approximately sixteen-times more likely to have an ADE. Patients with thrombocytopenia were approximately three-times more likely to have an ADE. Patients admitted emergently were twice as likely to have an ADE. The drug-related risk factor, administration of intravenous medications, was identified as a risk factor with a 1.03-times or 3% greater likelihood of having an ADE for each additional drug administered. To put this in perspective, the case group had an average of seven more drugs (24 vs. 17) administered intravenously during their ICU stay. This would translate into a 23% greater likelihood of having an ADE. A higher SAPS II score and lower albumin were variables less likely associated with having an ADE.

DISCUSSION

This is the first study to exclusively evaluate the critically ill population for risk factors for ADEs. Approximately one-half of the potential patient-related ADE risk factors were significant and all of the drug-related risk factors were significant in the univariate analysis. Based on the multiple variable analysis, identifying critically ill patients who are at risk for ADEs include those who are admitted emergently, have acute kidney injury, have thrombocytopenia, and receive a substantial number of medications administered

intravenously. These medication regimens are influenced by pharmacokinetic alterations that occur in critically ill patients, which can further increase the risk for ADEs.

The risk factors evaluated in this study can be categorized according to the opportunity for an intervention during in-patient care to potentially prevent an ADE, also known as modifiable risk factors or no potential for intervention described as fixed (nonmodifiable) risk factors. Many of the risk factors evaluated would be considered modifiable, including all the drug-related risk factors and length of stay. Risk factors such as number of drug allergies, hepatic injury, acute kidney injury, low albumin, and low platelet count may be more challenging to intervene on but could still be considered modifiable with the assistance of an advanced computer monitoring system that assists with the detection of drug-related hazardous conditions, allowing for the prevention of ADEs (4). The fixed risk factors would be age, gender, severity of illness, type of insurance, and substance abuse. The majority of the risk factors determined significant by the univariate analyses are considered modifiable and present an opportunity for preventing ADEs in the ICU. It is difficult to determine which is more important for ADE surveillance tracking the drug-related risk factors or the patient-related risk factors. Drug-related risk factors could be easier to modify but patient-related risk factors have greater odds ratios. Ideally, an institution would track both to optimize ADE prevention; however, if this is not feasible because of a lack of computerized monitoring systems to assist with the patient-related factors, then the drug-related risk factors may be an easier target. The following discussion emphasizes the modifiable risk factors.

Evan et al (11) performed a large retrospective analysis of risk factors for hospitalized patients. During the 10-yr study, 4,376 ADEs were identified in 4,140 patients, with gender, age weight, creatinine clearance, number of comorbidities, and drug dosage found to be important ADE risk factors. This study did not examine organ dysfunction as a potential risk factor, nor were critically ill patients analyzed as a subset for these risk factors. Advanced age has been described as a potential risk factor differentiating ambulatory and hospital patients (23). However, in our critically ill population, age and gender were not significant risk factors. We were unable to assess weight because of the lack of documented information in the chart. Although drug dosage was not assessed, we did assess many other drug-related risk factors that were significant. In our critically ill population, the number of patients with acute kidney injury was significantly greater in patients having an ADE, but Charlson comorbidity index was not. Other studies have indicated that liver failure is a risk factor for ADEs, but this was not apparent in our study (28). These findings indicate that the same risk factors that apply to a non-ICU population may not similarly apply to critically ill patients (11, 28).

Drug classes evaluated in our study demonstrated that anti-infectives, autonomic, cardiovascular, electrolyte, gastrointestinal, and drugs affecting the central nervous system were more commonly administered in the patients having an ADE. Patients having an ADE received more high-risk medications than the control group. The drug classes identified continue to demonstrate that targeting high-risk medications for ADE prevention is appropriate.

A prospective study investigated patient risk factors for ADEs in hospitalized patients, evaluating 113 ADEs from a 6-month study period (8). The authors concluded that sicker patients who are in the hospital longer are more apt to have an ADE. There were only eight risk factors analyzed in this previous evaluation and the question remains if these risk factors are applicable to the critically ill population. In our analysis, the critically ill patients in both the case and control groups had high SAPS II scores, so there was not much variability to allow for comparison. In fact, patients without an ADE had a higher SAPS II

score, although the Charlson comorbidity index was similar between groups. Also, patients without an ADE had a lower mortality, shorter ICU length of stay, and received less medication. A higher mortality and longer ICU length of stay for critically ill patients having an ADE have been demonstrated previously (2). Patients with an ADE in our study had a longer length of stay before ICU admission, presenting another potential risk factor that could be associated with the increased number of medications administered.

Critically ill patients experience many physiologic changes that can influence drug metabolism and excretion. Organ dysfunction, in particular renal insufficiency, can lead to the potential for ADEs. In our study, acute kidney injury was a significant risk factor. This emphasizes the need for constant monitoring of drug clearance throughout a patient's ICU stay. Computer-based decision support often assists with the initial dosing based on glomerular filtration rate, but more advanced alerting systems are needed for continuous monitoring. The pharmacist can be an asset to the patient care team, with a primary role in monitoring the patient's pharmacokinetic and pharmacodynamic responses. Surprisingly, low albumin was not a risk factor for ADE occurrence because patients with ADEs received more protein-bound drugs. Patients having an ADE did receive more CYP P450 enzyme-inhibiting and enzyme-inducing drugs potentially contributing to alterations in the pharmacokinetic properties of the patient's drug regimen.

Intravenous therapy is considered a high-risk activity because of the potential for errors and resulting harm (11, 29, 30). Previously, intravenous administration has been shown to be a risk for ADEs in hospitalized patients (11). Our study confirms that the intravenous route of administration is a risk factor for ADEs in the ICU. ADEs related to intravenous medications in academic centers is costly, resulting in an additional $6,647 in costs and a 4.8-day longer stay (31). Intravenous administration of medications should be minimized when possible by encouraging switches from intravenous to oral routes or initiating oral therapy when possible. Other preventive measures include the use of advanced infusion pumps, standardization of infusion concentrations and rates, development of intravenous administration policies, and promoting best practices.

In general, drug regimens complicated by the high number of medications consistently appear to be a risk for ADEs (9, 11, 28, 30, 32, 33) and, from the results of our study, this remains true for the ICU environment. Diligent monitoring of medication regimens in the ICU is essential in an effort to discontinue medications when no longer necessary, such as drugs with prophylactic indications. Pharmacist participation in patient care rounds can be helpful with this monitoring (3). Clinical decision support to monitor for drug–drug interactions can be useful as well. Patients with longer ICU stays should have their medication regimens evaluated frequently for opportunities to discontinue medications when appropriate.

The combination of ADE detection methods used in our study did not capture all ADEs that could be identified with a comprehensive chart review (6). Different ADE detection methods are more or less likely to find different types of ADEs; spontaneous reporting systems contain more serious ADEs than chart review, chart review misses ADEs related to administration errors that are more likely caught by spontaneous reporting if severe and direct observation is more likely to detect administration related ADEs. The use of spontaneous reporting may explain why 90% of the ADEs in our study were category II and III. A comprehensive chart review can detect the most ADEs; however, because of the time constraints and substantial resources associated with this approach, most surveillance systems use targeted chart reviews provoked by triggers, as our institution does. In fact, the Institute for Healthcare Improvement recommends the targeted chart review using triggers as a part of an institution's surveillance systems (34).

Limitations

It is possible that patients in the control group may have had an ADE. We intended to minimize this possibility by using a selection approach of the next two patients who met the matching criteria after admission of a case patient and by excluding patients with an E-code. The E-code is assigned by the patient reimbursement department to double-check for the occurrence of an ADE. The best design to avert this limitation is to proceed with a prospective study. We chose to match controls on admission date, admission service, and type of ICU in sequential enrollment rather than matching with random selection, because in the 7.5-yr study we wanted to assure that patient care was as similar as possible and felt that relatively close admission times were important. Matching did not occur based on gender, age, and severity of illness because these were risk factors of interest in the analysis. The multiple variable analyses did control for severity of illness.

The retrospective study design was selected to obtain data over a long period of time (7.5 yrs) because it is an efficient way of tracking presaging factors to verified outcomes. Although a prospective study offers the opportunity to obtain all ADEs occurring within the environment, it is a resource-intensive approach to obtain an adequate sample size. For example, the study by Bates et al (8) occurred during a 6-month period and yielded a sample of 113 ADEs in 2019 admissions, which is a statistically inadequate sample for our analysis. Data collection in our study was optimized using a combination of electronic chart review of medical notes and administrative data such as International Classification of Disease revision nine codes. Also, a prospective study could provide a better understanding of the higher SAPS II score and the low albumin appearing mildly protective in our study.

Additional limitations include the drug administration analysis that was completed for the entire ICU stay and did not reflect before or after the ADE because this could not be calculated for the controls. In addition, the oral and intravenous drug administration analysis was based on drug charges, therefore necessitating the assumption that a charge equaled administration to the patient. The definition for an ADE included the likelihood ranking of possibly or higher is a common approach used in other ADE assessment studies (19–22); however, this approach is likely to overestimate the true ADE rate because it includes borderline events. Although the type of ICU and admitting service related to the ADE were previously identified, these could not be evaluated as risk factors because they were also used for the selection of the control group. Type of ICU and service have been identified previously as risk factors for ADEs (2, 11).

CONCLUSION

There are several patient-related and drug-related factors contributing to the risk for ADEs in critically ill patients. Drug regimens complicated by the number of medications should be monitored closely. The addition or removal of medications that can alter the pharmacokinetic properties of concomitantly administered drugs should be evaluated because this increases the potential for ADEs. Changing organ function of critically ill patients should be examined frequently to determine the impact on drug dosing. These findings provide additional support for a clinical pharmacist as part of a patient care team in the ICU to promote safe medication use.

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Table 1

Univariate logistic regression analysis of potential patient related risk factors in predicting adverse drug events

Patient-Related Risk Factors	Case	Control	*p*	Odds Ratio (99% Confidence Interval)
Age (yr)	58.86 ± 16.69	59.68 ± 17.92	.47	0.99 (0.99–1.0)
Gender (male)	53%	55%	.58	0.93 (.67–1.30)
Race (white)	81%	81%	.79	0.96 (0.63–1.45)
Type of insurance				
Medicare/Medicaid	52%	45%	.033	1.31 (0.95–1.83)
Type of admission				
Emergent/urgent	57%	45%	<.001	1.66 (1.19–2.31)
Scheduled	14%	19%	.08	0.74 (0.47–1.16)
Unscheduled through emergency department	28%	37%	.01	0.68 (0.48–0.98)
Charlson comorbidity index	2.17 ± 1.96	2.14 ± 2.19	.85	1.00 (0.93–1.09)
Simplified Acute Physiology Score II (on admission)	34.49 ± 19.7	39.96 ± 17.90	<.001	0.98 (0.98–0.99)
Smoker	24%	25%	.89	1.03 (0.59–1.79)
Substance abuse (including alcohol)	14%	12%	.48	1.16 (0.66–1.95)
History of drug allergy	37%	32%	.09	1.25 (0.89–1.78)
Number of drug allergies	0.88 ± 1.05	0.97 ± 1.56	.66	0.96 (0.74–1.24)
Hepatic injury	2.7%	3.5%	.47	0.76 (0.29–2.02)
Acute kidney injury	55%	11%	<.001	9.6 (6.4–14.4)
Low albumin (<3.5)	0.5%	18%	<.001	0.03 (0.004–0.16)
Low platelet count (<100)	45%	19%	<.001	3.40 (2.37–4.89)
Hospital length of stay before ICU admission (d)	5.1 ± 13.2	2.9 ± 7.8	.003	1.28 (1.03–1.59)
ICU length of stay (d)	14.16 ± 19.61	4.87 ± 7.96	<.001	2.64 (2.00–3.48)
Hospital length of stay (d)	29.87 ± 33.95	15.64 ± 21.59	<.001	1.93 (1.60–2.31)
Number of admissions to the hospital in the year before the date of the first adverse drug event	0.97 ± 2.01	0.85 ± 2.03	.36	1.30 (0.95–1.11)
Number of admissions to an ICU in the year previous to the date of the first adverse drug event	0.25 ± 0.67	0.20 ± 0.78	.32	1.10 (0.88–1.35)

ICU, intensive care unit.

Table 2

Univariate logistic regression analysis of drug-related potential risk factors in predicting adverse drug events

Drug-Related Risk Factors	Case	Control	*p*	Odds Ratio (99% Confidence Interval)
Number of narrow therapeutic index drugs received	2.31 ± 1.31	1.78 ± 1.20	<.001	1.40 (1.23–1.61)
Number of protein-bound drugs received (>70%)	2.04 ± 1.28	1.70 ± 1.34	<.001	1.21 (1.07–1.37)
Number of enzyme-inducing drugs received	1.46 ± 1.22	1.00 ± 1.08	<.001	1.43 (1.24–1.65)
Number of enzyme-inhibiting drugs received	1.75 ± 1.58	1.05 ± 1.27	<.001	1.41 (1.25–1.6)
Number of high-risk medications drugs received	10.16 ± 5.07	7.95 ± 4.99	<.001	1.09 (1.05–1.13)
Number of drugs administered by intravenous route	23.9 ± 13.39	16.75 ± 11.13	<.001	1.05 (1.03–1.06)
Number of drugs administered by oral route	9.28 ± 6.63	6.59 ± 6.22	<.001	1.07 (1.04–1.09)
Maximum number of drugs received during 1 day in the intensive care unit	17.00 ± 7.44	15.91 ± 8.02	.03	1.02 (1.00–1.04)
Maximum number of drugs received during the intensive care unit admission	34.31 ± 18.17	24.91 ± 16.26	<.001	1.03 (1.02–1.04)
Most commonly administered drug classes				
Anti-infectives	4.68 ± 4.05	2.78 ± 2.92	<.001	1.17 (1.11–1.24)
Blood formation, coagulation, and thrombosis	1.67 ± 1.37	1.67 ± 1.43	.92	1.00 (0.89–1.13)
Autonomic	2.90 ± 2.55	2.49 ± 2.36	.01	1.07 (1.00–1.15)
Cardiovascular	3.67 ± 2.61	3.00 ± 2.52	<.001	1.11 (1.04–1.18)
Central nervous system	7.16 ± 3.31	5.59 ± 3.52	<.001	1.14 (1.08–1.19)
Electrolytes caloric/water balance	2.32 ± 1.88	1.44 ± 1.58	<.001	1.34 (1.21–1.48)
Gastrointestinal	2.90 ± 2.15	2.07 ± 1.82	<.001	1.23 (1.13–1.34)

Table 3

Multiple logistic regression analysis in predicting adverse drug events[a]

Variable	β Coefficient	Odds Ratio (99% Confidence Interval)	*p*
Simplified Acute Physiology Score II	−0.05	0.95 (0.93–0.97)	<.001
Acute kidney injury	2.79	16.20 (8.13–32.28)	<.001
Albumin <3.5 g/dL	−4.75	0.01 (0.001–0.06)	<.001
Platelet count <100,000 mm^3	1.07	2.93 (1.56–5.48)	<.001
Type of admission: emergent	0.71	2.04 (1.04–4.00)	.006
Type of admission: unscheduled through emergency department	0.58	1.77 (0.85–3.71)	.04
Number of intravenous drugs	0.03	1.03 (1.00–1.06)	.003
Number of oral drugs	−0.04	0.96 (0.71–1.30)	.74

[a]The Negelkerke R^2 for the model = 0.529.