J Korean Med Sci. 2023 Feb 27;38(8):e56
https://doi.org/10.3346/jkms.2023.38.e56
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Preventive & Social Medicine

Incidence and Economic Burden of Adverse Drug Reactions in Hospitalization: A Prospective Study in Korea

Bomi Seo [1,2,3*] **Min-Suk Yang** [4*] **So-Young Park** [5] **Bo Young Park** [1] **Jung-Hyun Kim** [6] **Woo-Jung Song** [1,2] **Hyouk-Soo Kwon** [1,2] **Yoon-Seok Chang** [7] **You Sook Cho** [1,2] **Sae-Hoon Kim** [7] **and Tae-Bum Kim** [1,2]

[1]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Pharmacovigilance Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3]Department of Pulmonary, Allergy and Critical Care Medicine, Seongnam Citizens Medical Center, Seongnam, Korea
[4]Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea
[5]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea
[6]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, Korea
[7]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Received: Aug 7, 2022
Accepted: Nov 30, 2022
Published online: Feb 9, 2023

Address for Correspondence:
Tae-Bum Kim, MD, PhD
Division of Allergy and Clinical Immunology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea.
Email: tbkim@amc.seoul.kr

Sae-Hoon Kim, MD, PhD
Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173-beon-gil, Bundang-gu, Seongnam 13620, Republic of Korea.
Email: shkrins@gmail.com

*Bomi Seo and Min-Suk Yang contributed equally to this work.

ORCID iDs
Bomi Seo
https://orcid.org/0000-0001-6250-8190
Min-Suk Yang
https://orcid.org/0000-0002-9861-0530

ABSTRACT

Background: Adverse drug reactions (ADRs) are escalating, and their socioeconomic burden is increasing. However, large-scale prospective studies investigating ADRs during hospitalization are rare in Korea. We prospectively investigated the incidence, characteristics, and economic burden of ADRs in hospitalized patients based on electronic medical records (EMRs).
Methods: Among patients admitted to three hospitals from October 2016 to October 2017, 5,000 patients were randomly selected and prospectively observed during hospitalization. Research nurses monitored and detected patients who had symptoms, signs, or laboratory findings suspicious for ADRs using an EMR-based detection protocol. Next, allergy and ADR specialists reviewed the medical records to determine the relationship between adverse reactions and drugs. Cases in which a causal relationship was certain, probable/likely, or possible were included in the ADR cases. Clinically meaningful ADR cases or those leading to prolonged hospitalization were defined as significant ADRs.
Results: ADRs occurred in 510 (10.2%) patients. The mean length of hospital stay was approximately 5 days longer in patients with ADRs. Opioids accounted for the highest percentage of total ADRs. Significant ADRs were observed in 148 (3.0%) patients. Antibiotics accounted for the highest percentage of significant ADRs. Drug hypersensitivity reactions (DHRs) occurred in 88 (1.8%) patients. Antibiotics accounted for the highest percentage of DHRs. The average medical expenses for one day of hospitalization per patient were highest in significant ADRs, followed by non-significant ADRs, and non-ADRs.
Conclusion: ADRs in hospitalized patients are an important clinical issue, resulting in a substantial socioeconomic burden. EMR-based strategy could be a useful tool for ADR monitoring and early detection.

Keywords: Drug-Related Side Effects and Adverse Reactions; Hospitalization; Electronic Health Records

So-Young Park
https://orcid.org/0000-0002-5224-3077
Bo Young Park
https://orcid.org/0000-0001-8962-0844
Jung-Hyun Kim
https://orcid.org/0000-0002-5498-5170
Woo-Jung Song
https://orcid.org/0000-0002-4630-9922
Hyouk-Soo Kwon
https://orcid.org/0000-0001-7695-997X
Yoon-Seok Chang
https://orcid.org/0000-0003-3157-0447
You Sook Cho
https://orcid.org/0000-0001-8767-2667
Sae-Hoon Kim
https://orcid.org/0000-0002-2572-5302
Tae-Bum Kim
https://orcid.org/0000-0001-5663-0640

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare (grant number: HI19C0481, HC20C0076) and Korea Institute of Drug Safety and Risk Management (2016OK1085), Republic of Korea.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim SH, Yang MS, Kim TB. Data curation: Seo B, Park BY, Kim SH, Yang MS. Formal analysis: Seo B, Park BY. Investigation: Seo B, Kim SH, Yang MS, Kim TB. Methodology: Seo B, Park SY, Kim SH, Yang MS, Kim TB. Validation: Kim JH, Song WJ, Kwon HS, Cho YS, Chang YS. Writing - original draft: Seo B, Kim SH. Writing - review & editing: Park SY, Kim JH, Song WJ, Kwon HS, Cho YS, Chang YS, Yang MS, Kim TB.

INTRODUCTION

Adverse drug reactions (ADRs) are a major healthcare challenge, both for individuals and the public sphere.[1,2] In general, ADRs account for 5–10% of all hospital admissions.[3-5] A meta-analysis has revealed that 15.1% of patients suffer from ADRs of all severities. According to a previous study, the overall incidence of serious ADRs is 6.7% and that of fatal ADRs is 0.32% in hospitalized patients.[6] The occurrence of ADRs in clinical practice may disturb adherence to treatment, worsening clinical outcomes. Serious ADRs may incur additional medical costs by requiring unexpected visits to clinics or emergency departments, lengthening hospital stay, and generating additional healthcare resource utilization. Moreover, ADRs are noted as one of the leading causes of death in the United States and Sweden.[6,7] Patients who have experienced an ADR present an increased risk of mortality when compared with those who have not had an ADR.[8]

In South Korea, the ADR spontaneous reporting and monitoring system was introduced in 1988 and was invigorated after the launch of the regional pharmacovigilance center in 2006. Currently, there are 28 regional pharmacovigilance centers nationwide, and spontaneous ADR reports have greatly increased each year.[9] However, the pharmacovigilance program based on spontaneous reporting presents several limitations in terms of evaluating the accurate incidence of ADRs in both inpatients and outpatients: 1) the lack of a control group and denominator data; 2) underreporting and biases by the reporter.[10] As these limitations are better controlled in inpatients than in outpatients, we conducted the present study through the active monitoring of inpatients to overcome the above-mentioned limitations, and to determine the accurate incidence of ADRs.

Numerous studies have reported the incidence of ADRs in hospitalized patients, including a landmark meta-analysis study reported by Lazarou et al.[6,8,11] Despite the large amount of data available regarding this topic, most of these studies were performed more than 20 years ago and in western countries, including the United States and European countries. Although a few recent observational studies have been performed in Italy, India, and China,[12-14] the incidence and burden of ADRs in hospitalized Korean patients remain unrecorded. Over the next several decades, awareness of ADRs has increased, and many new drugs have been introduced. Therefore, the incidence rate of ADR would be different from that in the past. In addition, new methods to better monitor ADRs, such as electronic medical records (EMRs), have been developed. Furthermore, clinical practice and prescription patterns of medical practitioners may differ from country to country, and differences in the medical practice environment may affect the incidence and characteristics of ADRs. In the present study, we investigated the incidence, clinical characteristics, risk factors, and economic burden of ADRs that occur in hospitalized patients using prospective observational strategies by monitoring the EMRs in three Korean hospitals.

METHODS

Study subjects and assessment of ADRs

We conducted a prospective observational study in one secondary and two tertiary hospitals between October 2016 and October 2017. The three hospitals were university affiliated teaching hospitals: Asan Medical Center (AMC), Seoul National University Bundang Hospital (SNUBH), and Seoul Metropolitan Government - Seoul National University (SMG-

SNU) Boramae Medical Center, with 2,700, 1,400, and 820 beds, respectively. Among the 99,449 patients who were admitted to three hospitals during the study period, we randomly selected 5,000 subjects, including 3,000 subjects from AMC, 1,000 subjects from SNUBH, and 1,000 subjects from SMG - SNU Boramae Medical Center. We prospectively observed the occurrence of ADRs during hospital stays. As a random sampling method, the total number of patients scheduled to be hospitalized on the day was divided by the number of patients to be recruited per day, and then subjects were selected from the patient list who were to be hospitalized on the day according to the calculated order by adding the generated values. For example, if 10 people are to be collected per day and 250 patients are to be admitted, every 25th (the 25th, 50th, 75th and so on.) patients on the list were enrolled. If the patient in that order does not agree to participate, the next number after that number was enrolled. For example, if the 25th patient refuses to enroll in this study, the 26th patient is recruited.

Medical records of 5,000 subjects were daily manually monitored by research nurses by utilizing EMRs from the date of admission to the date of discharge, to ascertain if any of the following signals were found; 1) the word "drug-related" was recorded on the doctor's or nurse's notes, 2) blood tests showed abnormal findings such as abnormal liver function tests, cytopenia, eosinophilia, and azotemia, 3) the description of abnormal skin lesions was recorded on the EMR. Abnormal liver function test, cytopenia, eosinophilia, and azotemia were defined as fulfillment of following criteria: 1) abnormal blood level exceeding upper (blood eosinophil count, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, alkaline phosphatase, and gamma-glutamyltransferase) or lower limit of normal value (white blood cells and platelets counts) set by each hospital and 2) change of blood level which is assessed to be related to drug during hospitalization. Next, allergy and ADR specialists reviewed the medical records to determine whether the signal was related to the use of specific drugs. The signal was designated as an ADR episode if the causal relationship was certain, probable/likely, or possible according to the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality categories.[15] The type of ADR was documented according to the World Health Organization Adverse Reaction Terminology (WHO-ART). Clinically meaningful ADRs that were potentially serious, fatal, or lead to a prolonged hospital stay, including abnormal liver function tests, cytopenia, hypotension, renal insufficiency, fever, hypoglycemia, anaphylaxis, and rhabdomyolysis, were defined as significant ADRs. Allergy and ADR specialists evaluated the ADRs with mucocutaneous symptoms, respiratory symptoms, hypotension, anaphylaxis, leukopenia, thrombocytopenia, and fever, and determined whether it was drug hypersensitivity reaction (DHR). When an individual subject experienced multiple ADRs during a single hospital stay, each ADR was regarded as an individual ADR case. If two or more drugs were presumed to be the causative agents in one ADR case, "a matter" was defined as one ADR in which one symptom was matched with one drug.

Evaluation of economic burden

Direct medical expenses and the number of hospitalization days were collected based on the total amount of medical expenses recorded in the medical fee bills incurred while the patients were admitted. The cost of medical care was divided by the number of patients, and the total cost of hospitalization per patient was calculated. Furthermore, the total cost of hospitalization per patient was divided by each patient's hospital days, and the daily cost of hospitalization per patient was calculated. The economic burden of medical cost was compared between patients without ADRs, patients with non-significant ADRs, and significant ADRs, adjusting for age, sex, and the Charlson comorbidity index (CCI).[16]

https://doi.org/10.3346/jkms.2023.38.e56

Statistical analysis

Continuous data are presented as mean ± standard deviation. The Student's *t*-test was used to analyze continuous variables (age, body mass index [BMI], hospitalization days), with the χ^2 test employed for categorical variables (sex, admission department, history of adverse drug events [ADEs], history of malignancy). Multiple regression analysis adjusted for age, sex, and CCI was used to determine the economic and clinical burden of ADRs during hospitalization. $P < 0.05$ was considered to indicate statistical significance. SPSS® version 25 for Windows® was used for statistical analysis (IBM Co., Armonk, NY, USA).

Ethics statement

This study was approved by the Institutional Review Boards of each hospital: Seoul Asan Medical Center (2016-1085), Seoul National University Bundang Hospital (B-1612/373-305), and SMG- SNU Boramae Medical Center (16-2016-134). Written informed consent was obtained from all participants.

RESULTS

Clinical characteristics of study subjects

During the study period, a total of 5,000 subjects were hospitalized 5,032 times. The mean age of the study subjects was 52.7 ± 18.4 years, and 52.9% were recorded as male. The breakdown by age shows that almost half (45.3%) were between 45 and 64 years, 4.9% were younger than 18 years, and 27.1% were older than 65 years. The mean BMI of the subjects was 24.0 ± 17.2 kg/m^2. The proportion of patients admitted to the medical department (57.9%) was greater than that admitted to the surgical department (42.1%). The percentage of patients with underlying malignancy was 37.6%. In total, 336 subjects (6.7%) presented a history of ADEs. The mean length of hospital stay of participating subjects was 7.0 ± 6.8 days (**Table 1**).

Incidence of ADRs

Among the 5,000 subjects and during 5,032 admission cases, 510 subjects (10.2%) experienced 547 ADR cases (10.8%). The incidence adjusted for hospital days was 15.6% per 1,000 patient-days. The total cases of significant ADRs were 157 and the incidence of significant ADRs was 3.1%. DHRs occurred in 1.8% (88 subjects) of hospitalized patients (**Table 2**).

Table 1. Demographics and clinical characteristics of study subjects

Variables	Values
No. of cases	5,000
Age, yr	52.7 ± 18.4
< 18	248 (4.9)
18–44	1,138 (22.6)
45–64	2,284 (45.3)
≥ 65	1,367 (27.1)
Male %	2,645 (52.9)
BMI, kg/m^2	24.0 ± 17.2
History of adverse drug events	336 (6.7)
Comorbidities	
Cancer	1,879 (37.6)
Admission department	
Medical	2,894 (57.9)
Surgical	2,106 (42.1)
Admission duration, days	7.0 ± 6.8

Values are presented as mean ± standard deviation or number (%).
BMI = body mass index.

https://doi.org/10.3346/jkms.2023.38.e56

Table 2. Incidence and prevalence of ADRs during hospitalization

Variables	Values
Total inpatients during the study period	99,449
Total patients enrolled in this study	5,000
Total admission cases enrolled in this study	5,032
Total patients with ADRs during admission	510
Total ADR cases	547
Total ADR matters[a]	756
Incidence[b] of ADR patients (%)	10.2
Incidence[b] of ADR cases (%)	10.8
Total days of hospitalization, days	34,988
Incidence adjusted for hospitalization days (rate per 1,000 patient-days) (95% CI)	15.6 (14.3–16.9)
Total patients with significant ADRs	148
Total cases of significant ADR	157
Incidence of patients with significant ADRs (%)	3.0
Incidence of significant ADR cases (%)	3.1
Total patients with drug hypersensitivity reaction	88
Total cases of drug hypersensitivity reaction	89
Incidence of patients with drug hypersensitivity reaction (%)	1.8
Incidence of drug hypersensitivity reaction cases (%)	1.8
Ratio patients with drug hypersensitivity reaction among ADR (%)	17.2
Ratio cases with drug hypersensitivity reaction among ADR (%)	16.3

Values are presented as number unless stated otherwise.
ADR = adverse drug reaction.
[a]Definition: one ADR in which one symptom was matched with one drug.
[b]ADR/Total number of registrations × 100.

Risk factors for ADRs

Of the 5,032 admission cases, 543 were cases with ADRs and 4489 were cases without ADRs. The risk factors for ADRs were female sex (54.7% vs. 46.4%, $P < 0.001$), a history of ADEs (10.9% vs. 6.4%, $P < 0.001$), and admission to the surgical department (65.7% vs. 57.4%, $P < 0.001$). Age, BMI, and the presence of cancer among comorbidities were not associated with a higher risk of ADRs. The mean length of hospital stay was significantly longer in ADR cases (12.0 days) than in non-ADR cases (6.5 days) (**Table 3** and **Supplementary Table 1**).

In patients 65 years and older, 135 were cases with ADRs and 1233 were cases without ADRs. The risk factors for ADRs in the elderly subgroup were age (74.0 ± 6.1 vs. 72.3 ± 5.6, $P = 0.001$),

Table 3. Comparison of clinical characteristics of ADR cases and non-ADR cases in the admission cases

Variables	Non-ADR cases (n = 4,489)	ADR cases (n = 543)	*P* value	Odds ratio (95% CI)
Age (yr)	52.6 ± 18.5	53.5 ± 17.2	0.242	
< 18	236 (5.2)	12 (2.2)		
18–44	1,000 (22.2)	138 (25.4)		
45–64	2,026 (45.0)	258 (47.4)		
≥ 65	1,233 (27.4)	134 (24.6)		
Male	2,406 (53.6)	246 (45.3)	< 0.001	0.72 (0.60–0.86)
BMI, kg/m^2	23.7 ± 4.0	23.3 ± 3.8	0.059	
History of ADEs	285 (6.4)	59 (10.9)	< 0.001	1.79 (1.34–2.42)
Comorbidities				
Cancer	1,761 (39.2)	255 (41.4)	0.320	1.10 (0.92–1.31)
Admission department			< 0.001	0.70 (0.58–0.85)
Medical	1,912 (42.6)	186 (34.3)		
Surgical	2,577 (57.4)	357 (65.7)		
Admission duration (days)	6.5 ± 6.0	12.0 ± 10.8	< 0.001	

Values are presented as mean ± standard deviation or number (%).
ADR = adverse drug reaction, CI = confidence interval, BMI = body mass index, ADE = adverse drug events.

https://doi.org/10.3346/jkms.2023.38.e56

female sex (53.3% vs. 41.6%, $P = 0.009$), BMI (23.4 ± 3.2 vs. 24.1 ± 3.4, $P = 0.010$), CCI (4.1 ± 1.1 vs. 3.8 ± 1.2, $P = 0.016$), and mean length of hospital stay (12.5 ± 10.6 vs. 7.0 ± 5.9, $P < 0.001$). A history of ADEs, the presence of cancer among comorbidity, admission department were not associated with a higher risk of ADRs in the elderly (**Supplementary Table 2**).

Causative drugs and clinical manifestations of ADRs

For all types of ADRs, the leading causal drugs classified by the Anatomical Therapeutic Chemical (ATC) Classification System code of ADRs were opioids, followed by antibiotics for systemic use, antineoplastic agents, drugs for acid-related disorders, anti-inflammatory and anti-rheumatic agents, other analgesics and antipyretics, anti-emetics and anti-nauseants, and radio-contrast dyes (**Fig. 1A**). The leading types of ADRs classified by the WHO-ART

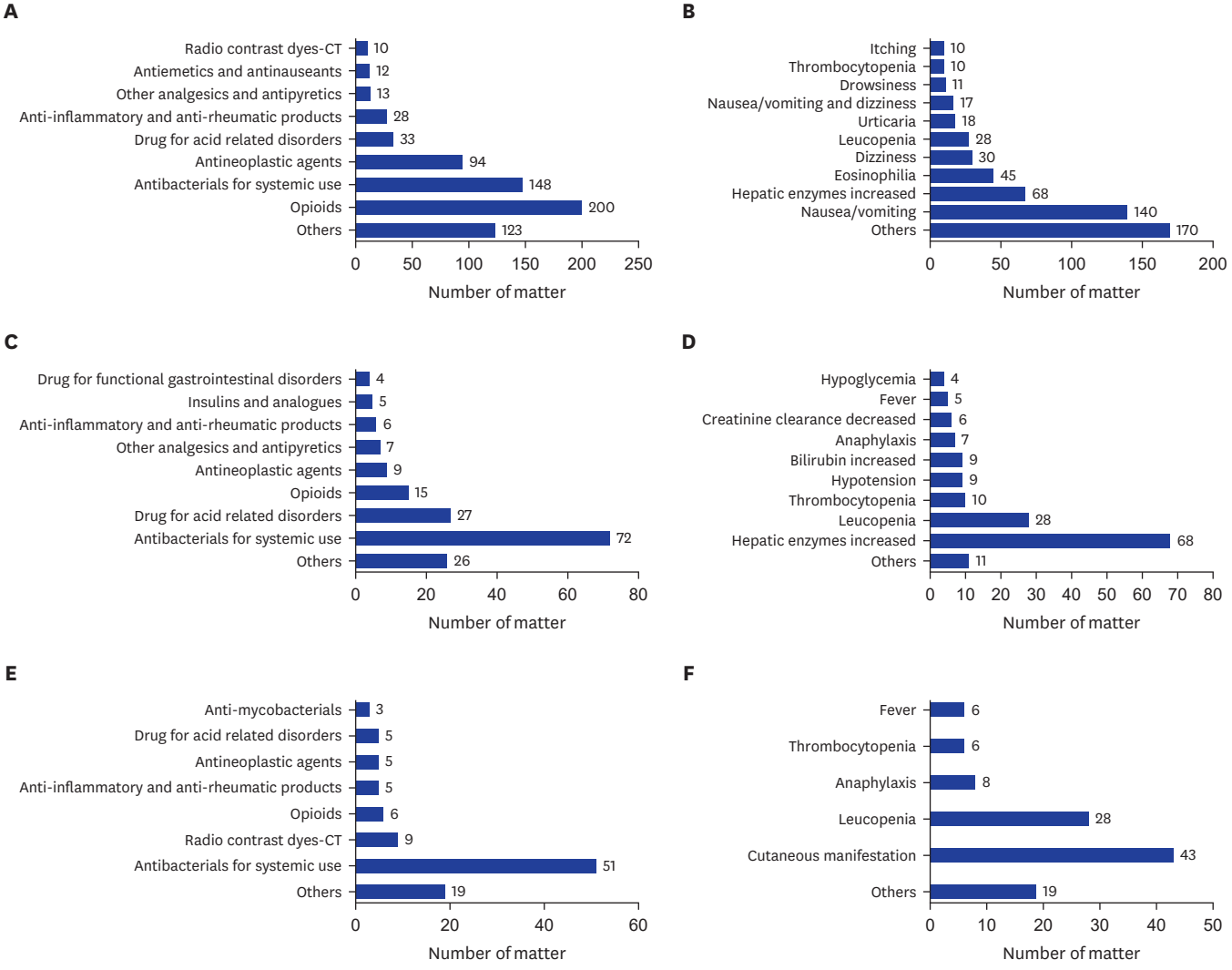

Fig. 1. Causative drugs classified by ATC code and clinical manifestations classified by WHO-ART SOC. (**A**) Causative drugs of adverse drug reactions. (**B**) Clinical manifestation of adverse drug reactions. (**C**) Causative drugs of significant adverse drug reactions. (**D**) Clinical manifestations of significant adverse drug reactions. (**E**) Causative drugs of drug hypersensitivity reactions. (**F**) Clinical manifestations of drug hypersensitivity reactions. Cutaneous manifestation means urticaria, angioedema, rash, flushing, itching.
CT = computed tomography, ATC code = Anatomical Therapeutic Chemical Classification System code, WHO-ART SOC = WHO Adverse Reactions Terminology System Organ Class.
Matters = ADRs in which one symptom was matched with one drug.

https://doi.org/10.3346/jkms.2023.38.e56

system organ class (SOC) were nausea/vomiting, followed by increased hepatic enzymes, eosinophilia, dizziness, leucopenia, urticaria, nausea/vomiting and dizziness, drowsiness, thrombocytopenia, and itching (**Fig. 1B**).

The leading causal drugs of significant ADRs were antibiotics for systemic use, followed by drugs for acid-related disorders, opioids, antineoplastic agents, other analgesics and antipyretics, anti-inflammatory and anti-rheumatic agents, insulins and analogues, and drugs for functional gastrointestinal disorders (**Fig. 1C**). The leading types of significant ADRs were increased hepatic enzymes, followed by leucopenia, thrombocytopenia, hypotension, increased bilirubin, anaphylaxis, decreased creatinine clearance, fever, and hypoglycemia (**Fig. 1D**). The leading causal drugs of DHRs were antibiotics for systemic use, followed by radiocontrast dye-CT, opioids, anti-inflammatory and anti-rheumatic agents, antineoplastic agents, drugs for acid-related disorders, and anti-mycobacteirals (**Fig. 1E**). The leading types of DHRs were cutaneous manifestation such as urticarial, angioedema, rash, flushing, itching, followed by leucopenia, anaphylaxis, thrombocytopenia, fever (**Fig. 1F**).

The common ADRs induced by major causative drugs in hospitalization are presented in **Supplementary Table 3**. The most common adverse reactions of each major causative drug are nausea and vomiting when administering opioids, increased eosinophil count when administering antibiotics for systemic use, nausea and vomiting when administering antineoplastic agents, increased hepatic enzymes of administering drug for acid-related disorders, and nausea and vomiting when administering anti-inflammatory and anti-rheumatic products.

Economic and clinical burden of ADR

The overall average medical cost of each hospitalization per patient was significantly higher in patients with ADRs than in those without ADRs ($9,360.2 ± 13,717.2 vs. $4,765.9 ± 6,178.3, $P < 0.001$). The overall average medical cost of each hospitalization per patient was significantly higher in patients with significant ADRs than in those with non-significant ADRs ($13,918.3 ± 20,846.1 vs. $7,738.3 ± 9,100.7, $P < 0.001$). The daily medical cost of each hospitalization was higher in patients with ADRs than in those without ADRs ($805.0 ± 670.5 vs. $760.3 ± 597.6) and higher in patients with significant ADRs than in those with non-significant ADRs ($867.7 ± 687.2 vs. 778.7 ± 655.1). However, there were no significant differences between them, adjusting for age, gender, and the CCI. The average length of stay in hospital was significantly longer in patients with ADRs than in those without ADRs (11.6 ± 10.6 vs. 6.5 ± 6.0, $P < 0.001$) and longer in patients with significant ADRs than in those with non-significant ADRs (15.3 ± 11.8 vs. 10.3 ± 10.0, $P < 0.001$) (**Table 4**).

Table 4. Economic and clinical burden of ADRs during hospitalization

Variables	Non-ADRs	ADRs	*P* value[a]	Non-Significant ADRs	Significant ADRs	*P* value[a]
Total medical expenses of each hospitalization per patient ($)	4,765.9 ± 6,178.3	9,360.2 ± 13,717.2	< 0.001	7,738.3 ± 9,100.7	13,918.3 ± 20,846.1	< 0.001
Daily medical expenses of each hospitalization per patient ($)	760.3 ± 597.6	805.0 ± 670.5	0.116	778.7 ± 655.1	867.7 ± 687.2	0.467
Hospitalization days	6.5 ± 6.0	11.6 ± 10.6	< 0.001	10.3 ± 10.0	15.3 ± 11.8	< 0.001

Values are presented as mean ± standard deviation. Average won-dollar exchange rate in study period: 1,143.
ADR = adverse drug reaction.
[a]Adjusted age, sex, Charlson comorbidity index using multiple regression analysis.

https://doi.org/10.3346/jkms.2023.38.e56

DISCUSSION

This study is the largest prospective observational study of ADRs conducted in hospitalized patients in Korea. There are numerous studies regarding the incidence of ADRs using spontaneous reporting systems in South Korea.[9] However, spontaneous reporting systems have an under-reporting problem that indicates a lower incidence than the real ADR incidence.[17] To identify the precise incidence of ADRs in hospitalized patients, we actively observed the number and type of ADRs that occur in hospitalized patients. Our data showed that ADRs occurred in 10.2% of hospitalized patients and 10.8% of hospital cases. This result is similar to other studies.[6,13,18-20] As prolonged hospitalization can be associated with the occurrence of ADRs during hospitalization,[21] the incidence rate was recalculated by adjusting the number of hospitalization days. The incidence of ADRs adjusted by hospitalization days was 15.6% (95% CI, 14.3–16.9%).

Significant ADRs occurred in 3.0% of hospital patients and 3.1% of hospital cases, similar to previous studies.[6,11] Most studies about ADRs occurring in inpatients were conducted in Western countries, and only a few studies were performed in Eastern countries.[5-8,11,21-31] The incidence and characteristics of ADRs may vary depending on the demographic characteristics of patients, including race, clinical practices, and prescription patterns of medical practitioners. Considering these aspects, our study reflects a relatively real ADR incidence of inpatients in Korea.

In our study, opioids were the most common cause of ADRs, followed by antibiotics for systemic use, and antineoplastic agents. Likewise, previous studies have indicated that opioids are the leading causal drugs of ADRs during hospitalization.[11,22] In other prospective studies performed since 2000, antibiotics were the most common causal drugs of ADRs.[27,32-35] The difference of causative drugs for each study can be explained by the high heterogeneity in the methods of classifying causative agents, prescription patterns of each country and each hospital, and characteristics of the patient group. Our study was conducted in large teaching hospitals; 37.6% of enrolled patients had cancer as a comorbidity and 42.1% of patients required pain management after surgery. Therefore, the use of antineoplastic agents and opioids was high, and the ADRs induced by these medications would be higher in our study than in other studies.

The leading types of ADRs were nausea/vomiting, hepatic enzyme increased, eosinophilia, dizziness, leucopenia, urticaria, nausea/vomiting and dizziness, drowsiness, thrombocytopenia, and itching. In the present study, the most common causal drugs were opioids, and hence, nausea and vomiting were the leading types of ADRs, as in other studies investigating opioid-related ADEs.[36] Unlike previous studies that mainly focused on ADR symptoms or organs affected by ADRs,[11,33,36,37] we included abnormalities in blood tests as criteria for detecting ADRs. Therefore, eosinophilia, increased hepatic enzyme, thrombocytopenia, and leucopenia were observed as leading types of ADRs.

Antibiotics for systemic use were the most common cause of significant ADRs, followed by drugs for acid-related disorders. The leading types of ADRs were increased hepatic enzyme, followed by leucopenia. These results are similar to those of previous studies showing that antibiotics are the most common cause of drug-induced liver disease.[38-41] In previous studies, elevated liver enzymes and leucopenia caused by proton pump inhibitor (PPI) and H2 receptor antagonist (H2RA) were uncommon.[42-46] On the other hand, it is noteworthy that drugs for

https://doi.org/10.3346/jkms.2023.38.e56

acid-related disorders such as PPI and H2RA are the second most common drugs of significant ADRs in this study. It is necessary to monitor the liver function test of patients taking PPI or H2RA, and to consider PPI or H2RA as the causative agent in case of elevated liver enzyme.

There are few studies on the prevalence of DHRs compared to ADRs.[47] The rate of DHRs among ADRs was 17.2%, which was similar to the results of previous studies (10–20%). However, the rate of DHRs among hospitalized patients was 1.8%, which was less than that reported in previous studies (about 10%).[47-49] Antibiotics for systemic use were the agents most often reported as culprit drugs, followed by radiocontrast dye-CT. Most studies report that antibiotics are the most common agents of DHRs. However, the second most common agent of DHRs differed from study to study.[47-51] As in other studies, cutaneous manifestations were the most common of DHRs.[47-51]

Previous studies have reported that female sex, elderly age, number of medications, length of hospital stay, and admission to the intensive care unit and medical unit were significantly associated with ADRs.[21,29-31,33,52,53] Our study showed female sex, length of hospital stay, history of ADEs, and admission to surgical department were significantly associated with ADRs. Unlike previous studies suggesting that age is associated with ADRs,[33,52] our study showed that there was no difference in age between ADRs and non-ADRs. This result was similar to that of a previous study in which age was not an independent risk factor for ADRs.[25] Considering age-related alterations in pharmacodynamics and pharmacokinetics, polypharmacy owing to comorbidities in older individuals was reported as a more important factor associated with ADRs than age.[54] Prolonged hospital stays may increase exposure to a higher number of drugs, which may be a risk factor for ADRs. Consistent with previous studies, female sex was one of the risk factors in our study owing to the administration of a greater number of drugs and presenting pharmacological reaction differences when compared with men.[31]

Our study suggests that the occurrence of ADRs during hospitalization causes a significant increase in hospitalization days and medical costs, which is consistent with other studies.[1,8,11,23,24,27,30,35,55,56] In particular, the increase in total medical costs according to the degree of ADR severity was similar to the results of a study reported in Taiwan.[30] As mentioned in other studies, the number of hospital days was one risk factor for ADRs; hence, the total medical expenses of each hospitalization per person were divided by the hospitalization days to identify whether the daily medical expenses differed in each group. The daily medical expenses of each hospitalization per patient were higher in patients with significant ADRs ($867.7 ± 687.2) when compared with those with non-significant ADRs ($778.7 ± 655.1), and in patients with ADRs ($805.0 ± 670.5) when compared with those without any ADRs ($760.3 ± 597.6); however, the difference was not statistically significant. This could be explained by the fact that medical expenses associated with ADRs increase mainly due to the prolongation of hospital stay caused by ADRs. Alternatively, exposure to various drugs during extended hospital stays might lead to an increase in the occurrence of ADRs, and the additional cost of managing these ADRs would be added to the increase in total medical expenses.

Our study has several limitations. First, this study was performed in one secondary and two tertiary care hospitals. Therefore, the results might not represent the entire population of hospitalized patients in Korea. However, we aimed to overcome this limitation by reflecting the differences in hospitals according to the individual number of beds and by selecting

three hospitals with different bed numbers available. Second, we detected ADRs based on EMRs using three criteria. ADRs may be omitted if symptoms are not recorded in the EMR. Consequently, it is possible that ADRs that did not meet the criteria were not reported, which could result in an underestimation of ADR incidence. Third, we could not confirm the total number of prescriptions, so the rate of ADR among total prescriptions was not shown. Fourth, in the analysis of economic burden, we compared only total medical expenses among groups according to the occurrence of ADRs. The additional cost or additional hospital stay owing to ADRs was not evaluated in this study.

Nonetheless, our study is the first large-sized prospective study about ADRs and DHRs in Korean inpatients and presents a more accurate incidence through active monitoring than spontaneous reporting. Compared with previous studies, this study provides extensive information on DHRs and ADRs during hospitalization for all inpatients, not for a specific age or a specific department. Also, this study reveals meaningful clinical information regarding common causative drugs and manifestations, risk factors, and the economic burden of ADRs and DHRs during hospital stay. Moreover, our study suggests a novel strategy to detect ADRs using EMRs of hospitalized patients. Further study is warranted to validate the effectiveness of our protocol to detect ADRs using EMRs in the future.

In conclusion, approximately 10% of hospitalized patients experience ADRs during their hospital stay in Korea. Opioids and antibiotics are the most common causative drugs. Hospitalization days, female sex, history of ADEs, and admission to the surgery department are important risk factors for ADRs in hospitalized patients. Medical costs and hospital stays increased significantly as the occurrence of ADRs increased. In order to reduce this socioeconomic burden, close monitoring and caution are required when caring for hospitalized patients receiving high-risk medications or presenting risk factors for ADRs.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Hospitalization days according to the number of ADRs during hospitalization

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Supplementary Table 2

Comparison of clinical characteristics of ADR cases and non-ADR cases in the elderly group (≥ 65 years old)

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Supplementary Table 3

Common adverse drug reactions induced by major causative drugs in hospitalization

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https://doi.org/10.3346/jkms.2023.38.e56

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