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Costs of Adverse Drug Events in German Hospitals—A Microcosting Study

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A B S T R A C T

Objective: In Germany, only limited data are available to quantify the attributable resource utilization associated with adverse drug events (ADEs). The aim of this study was twofold: first, to calculate the direct treatment costs associated with ADEs leading to hospitalization and, second, to derive the excess costs and extra hospital days attributable to ADEs of inpatient treatments in selected German hospitals. **Methods:** This was a retrospective and medical record–based study performed from the hospitals' perspective based on administrative accounting data from three hospitals (49,462 patients) in Germany. Total treatment costs ("analysis 1") and excess costs (i.e., incremental resource utilization) between patients suffering from an ADE and those without ADEs were calculated by means of a propensity score–based matching algorithm ("analysis 2"). **Results:** Mean treatment costs ("analysis 1") of ADEs leading to hospitalization (n = 564) were €1,978 ± 2,036 (range €191–18,147; median €1,446; €843–2,480 [Q1–Q3]). In analysis 2, the mean costs of inpatients suffering from an ADE (n = 1,891) as a concomitant disease or complication (€5,113 ± 10,059; range €179–246,288; median €2,701; €1,636–5,111 [Q1–Q3]) were significantly higher (€970; $P < 0.0001$) than those of non-ADE inpatients (€4,143 ± 6,968; range €154–148,479; median €2,387; €1,432–4,701 [Q1–Q3]). Mean inpatient length of stay of ADE patients (12.7 ± 17.2 days) and non-ADE patients (9.8 ± 11.6 days) differed by 2.9 days ($P < 0.0001$). A nationwide extrapolation resulted in annual total treatment costs of €1.058 billion. **Conclusions:** This is one of the first administrative data–based analyses calculating the economic consequences of ADEs in Germany. Further efforts are necessary to improve pharmacotherapy and relieve health care payers of preventable treatment costs.

Keywords: adverse drug events, cost accounting, diagnosis related groups, hospitalization.

Introduction

Drug therapies are associated with a risk of patients suffering from adverse drug events (ADEs), which may result in moderate to fatal treatment outcomes. ADEs occur frequently in both ambulatory and inpatient settings and often lead to hospitalization; these events occur more often in the elderly [1–3]. *ADEs* are defined as an injury resulting from medical interventions related to drugs either caused by medication errors or occurring despite proper drug usage [4–6]. Hence, ADEs may result from medication errors at any stage in the medication process (e.g., dispensing or administration) or from adverse drug reactions (ADRs) [7]. In Germany, recent studies indicate that no significant improvements in drug safety have been realized in recent years, resulting in many iatrogenic risks of drug therapy and insufficient patient safety [8–11]. Besides frequently preventable losses in quality of life and life expectancy, ADEs are associated with considerable costs for both payers and health care providers [12,13]. A review of selected international studies regarding the economic consequences of ADEs reported additional mean costs in the range of €934 to €5783 per case [14]. Stark et al. [15] reported costs of €816 million for ADEs resulting from outpatient treatment based on a 1-year-period probability pathway model. Despite the widespread agreement that ADEs are expensive, limited studies have been conducted from the hospital perspective. In this context, Bates et al. [16] estimated the ADE-induced annual overall costs to be $8000 per hospital bed. Costs were mostly assessed from the payers' perspective on the basis of the calculation of reimbursement tariffs. This particularly neglects the growing economic importance of treating ADE patients in hospitals under severe cost constraints. No conclusions can be drawn from prior studies, whether treatment patterns can be performed cost-covering. The objectives of our study were twofold: first, the treatment costs of ADE-induced hospitalizations were calculated ("analysis 1") and, second, the excess costs (i.e., the additional resource consumption; "analysis 2") of inpatients suffering from an ADE as a concomitant disease or complication were compared with those of a respective control group (non-ADE patients) by using a propensity score matching approach. Both objectives were performed from the hospitals' perspective. A microcosting approach based on resource consumption data from three selected German hospitals was applied. To the best of our knowledge, this is one of the first studies based on administrative data to calculate the economic consequences attributable to ADEs.

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Methods

Data description

Data for this retrospective analysis were collected from January 1, 2008, to December 31, 2008, in three public utility service hospitals including a total capacity of 1,208 beds (hospital A: 260, hospital B: 490, and hospital C: 458) in Berlin, Germany. The study base population consisted of 49,462 patients (hospital A: 10,776 [21.8%], hospital B: 17,851 [36.1%], and hospital C: 20,835 [42.1%]) who were hospitalized during this period (excluding inpatient deliveries). Computerized medical records were stored in the hospital information systems and compiled for the analyses.

Clinical, demographic, and economic data were analyzed to describe the patient sample and calculate the treatment costs. The *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German modification* (ICD-10-GM), is used for coding inpatients in German hospitals. The main reason for admission would be given as the primary diagnosis. Data collected from all patients included primary and secondary diagnoses (i.e., concomitant diseases and complications), age, sex, length of stay (LOS), and performed surgeries. Statistical data for the nationwide extrapolation were retrieved from the Federal Statistical Office in Germany [17].

Identification of ADEs

For the identification of ADEs, an algorithm (published elsewhere [6,18]) developed by two of the authors was applied. Suitable ICD codes grouped into the following categories (labeled A–C) were considered: "caused by a drug" (A.1), "caused by a drug or other substance" (A.2), "poisoning by drug" (B.1), "poisoning by or harmful use of a drug or other substance" (B.2), and "ADE very likely" (C). It is acknowledged, however, that concerning the two categories A.2 and B.2, other substances or measures may have caused the adverse event (e.g., "mental and behavioural disorders due to use of opioids" [ICD F11], "mental and behavioural disorders due to multiple drug use and use of other psychoactive substances" [F19], or "abuse of non-dependence-producing substances" [F55]). The recording of an ADE requires the identification of a drug as the cause of the symptom or the disease. This identification may be difficult, but it is imperative when using the specific codes of the ICD-10-GM (categories A.1, A.2, B.1, and B.2). A bias due to the inclusion of other causes (e.g., self-poisoning and suicide attempts) in categories "A.2" and "B.2" is acknowledged but must be accepted given the variety of different causes covered by a single ICD-10 code. In total, this selection included 360 ICD codes that were applied to our data set. Patients with relevant ICD codes in their primary diagnoses were selected in a first step ("analysis 1"). In these cases, a causal relationship between ambulatorily sustained ADEs and hospitalization can certainly be assumed, as the primary diagnosis was recorded to be the reason for hospitalization. Secondary diagnoses are concomitant diseases at the time of admission or complications that developed during hospitalization. We assumed that ICDs indicating an ADE as secondary diagnosis developed during hospitalization ("analysis 2"). This approach is in line with the German coding standards ("Deutsche Kodierrichtlinen") [19]. ADE detection was performed in both analyses in the total population described above.

Cost determination and calculation

Direct medical costs were calculated from the perspective of the treating hospitals. The data set is part of the mandatory annual report to the Institute for the Hospital Remuneration System (InEK) in order to calculate the diagnosis related groups reimbursement tariffs in Germany (§21 KHEntgG). Cost application to the cost unit "treatment case" is based on actual costing, whereby only costs and services covered by diagnosis related group reimbursement principles are considered [19]. Our analyses are based on a bottom-up approach ("microcosting") to estimate the true economic costs, whereby all services rendered are collected in-depth and monetary values are assigned [20,21]. Microcosting systems specify every resource consumed in health care service provision and assign its unit costs. This enables both high transparency and accuracy for cost assessment. For the retrieved ADE treatment cases, the relevant costs were determined and total costs were calculated for each cost unit (i.e., patient). The treatment costs per patient were assessed by summing all single cost components that contributed to the inpatient treatment. The relevant cost types for this study were retrospectively derived from the hospitals' in-house cost-unit accounting based on routine data ("InEK-Matrix") [22]. For the calculation of treatment costs, the following cost categories were covered: personnel (i.e., clinicians, nursing staff, and medical technicians) and nonpersonnel costs (i.e., pharmaceuticals, implants, grafts, and medical expenditure not otherwise specified) and personnel and material costs for medical and nonmedical infrastructure. Responsible cost centers were general ward, intensive care units, operating room, anesthesia, cardiac and endoscopic diagnostics and therapies, radiology, laboratory tests, and diagnostic and therapeutic areas not otherwise specified. For ADEs causing hospitalization, the total (annual) costs and LOS were assigned to these events. Hence, the term "cost" is defined as total hospital costs.

Statistical analyses

The excess costs of inpatients suffering from ADEs compared with non-ADE patients were calculated as the difference between cases and control subjects for each patient ("analysis 2"). Hence, we matched cases and control subjects in a stepwise manner by using a propensity score matched-pair approach called "greedy 5→1 matching algorithm" [23]. This method matches cases and control subjects on known attributes to create a control group that mimics the case group. Cases were those patients exhibiting an ADE in secondary diagnoses. Control subjects were selected by creating a comparison group by calculating a propensity score (performed via multivariate logistic regression) controlling for the patients' individual patient clinical complexity level, which reflects the severity of comorbidity, the major diagnostic category, sex, and the patients' age at the time of admission [24]. Each case was matched to one control subject. Patients suffering from multiple ADEs were considered only once in the economic analysis. Statistical analyses were performed by using SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, NC). All metric and normally distributed variables were reported as mean ± SD, range, and median; nonnormally distributed data and cost data were reported as mean ± SD, range, and median (including first quartile [Q1]–third quartile [Q3]). Categorical variables were presented as frequency and percentage. *P* values of less than 0.05 were considered to be statistically significant (Mann-Whitney *U* test).

Results

Patient demographics

In our total population (n = 49,462), 51.6% of the patients were women (n = 25,543) and 48.4% of the patients were men (n = 23,919). The mean age was 56.6 ± 23.6 years (range 0–106 years, median 63 years). The mean inpatient LOS was 6.8 ± 8.7 days (range 0–273 days; median 4 days; 2–9 days [Q1–Q3]). In total, the cumulative hospitalization time was 335,961 days, with no significant difference between women and men. The 10 most common primary diagnoses (24.9%; 12,339 patients) are displayed in Table 1.

Table 1 – Description of most frequent primary diagnoses (base population).

Rank	ICD code (three digits)	Description	n (%)
1	G47	Sleep disorders	1,998 (4.04)
2	I70	Atherosclerosis	1,660 (3.36)
3	I50	Heart failure	1,535 (3.10)
4	C34	Malignant neoplasm of bronchus and lung	1,491 (3.01)
5	I20	Angina pectoris	1,415 (2.86)
6	F10	Mental and behavioral disorders due to use of alcohol	923 (1.87)
7	I48	Atrial fibrillation and flutter	843 (1.70)
8	K80	Cholelithiasis	839 (1.70)
9	C50	Malignant neoplasm of breast	828 (1.67)
10	I21	Acute myocardial infarction	807 (1.63)
11	NA	Others	37,123 (75.06)

ICD, *International Classification of Diseases*; NA, not applicable/available.

Treatment costs of ADE-induced hospitalizations (ADEs causing admissions)

Application of the ADE detection algorithm to this population identified 564 patients (1.14%) who had been hospitalized on account of an ADE classified by one of the ICD codes selected above (Table 2).

The mean age of these patients ("analysis 1") was 47.4 ± 23.2 years (range 0–96 years; median 43.5 years). Female sex was predominant (n = 297, 52.7%). The mean inpatient LOS was 6.2 ± 6.9 days (range 0–59 days; median 4 days; 1–9 days [Q1–Q3]). Most frequent single diagnoses were "enterocolitis due to *Clostridium difficile*" (A04.7; n = 78), "mental and behavioural disorders due to multiple drug use and use of other psychoactive substances: withdrawal state" (F19.3; n = 44), and "mental and behavioural disorders due to use of opioids: dependence syndrome" (F11.2; n = 34). Table 3 provides an overview of the most frequent ADEs including the costs per ICD group (three-character categories).

Total hospitalizations summed to 3,502 days. The mean total treatment costs were calculated to be €1,978 ± €2,036 (range €191–18,147; median €1,446; €843–2,480 [Q1–Q3]) per case. Most expensive treatment cases were "complications following infusion, transfusion, and therapeutic injection" (€3,527 ± €3,789; range €317–13,060; median €2,602; €655–5,035 [Q1–Q3]), "toxic liver disease" (€3,101 ± €3,334; range €211–18,147; median €2,832; €1,270–3,407 [Q1–Q3]), "other bacterial intestinal infections" (€3,083 ± €2,725; range €475–15,443; median €2,316; €1,531–3,532 [Q1–Q3]), and "poisoning by hormones and their synthetic substitutes and antagonists, not elsewhere classified" (mean €2,607 ± €737; range €1,669–3,597; median €2,711; €1,847–3,110 [Q1–Q3]). In the study period, total costs in the respective hospitals for patients admitted as the result of an ADE were €1.12 million.

Treatment costs attributable to inpatient ADEs (occurring during hospitalization)

In total, 2049 ADEs coded in secondary diagnoses occurred. Some 1748 patients (92.3%) suffered from one ADE, 137 patients (7.2%) from two ADEs, and 9 patients (0.5%) from three ADEs.

More than three fourth of all ADEs were classified as "caused by a drug or other substance" (55.4%) and "caused by a drug" (22.5%). In contrast to ambulatorily acquired ADEs (26.4%), the categories "poisoning by drug" and "poisoning by a harmful use of a drug or other substance" accounted for only 6.3% of the ADEs (Table 2). In addition, Table 4 provides an overview of the most frequent ADEs per ICD group (three-character categories).

Calculating the excess costs (i.e., the additional resource use) of inpatient treatment attributable to an ADE ("analysis 2") resulted in 1891 treatment cases (3.8% of the hospitalizations) that occurred in the hospital during the study period. In this subsample, 1095 patients were females (57.9%) and 796 were males (42.1%).

Cases were matched to the respective control subjects according to the approach described in the Methods section. The results are displayed in Table 5.

Patients who were identified as suffering from an ADE were associated with significantly higher average treatment costs of €970 (median €314) per patient (€5,113 ± 10,059; range €179–246,288; median €2,701; €1,636–5,111 [Q1–Q3]) than people in the control group (€4,143 ± 6,968; range €154–148,479; median €2,387; €1,432–4,701 [Q1–Q3]) and required an extended hospital stay of 2.9 (median 1.0 day) extra days ($P < 0.0001$). Table 6 provides a summary of the differences in LOS and the excess costs between cases and control subjects. Annual total treatment costs in ADE patients (€9.67 million) exceeded those in non-ADE patients (€7.83 million) by €1.84 million.

Extrapolation of our results to the national level resulted in a substantial economic burden for German hospitals. For patients with an ADE as primary diagnosis ("analysis 1"), total costs amount to approximately €457 million (=16.5 million patients × 0.014 × €1978). For patients with an ADE as a concomitant disease or complication ("analysis 2"), excess costs equal approximately €601 million (=16.3 million patients × 0.038 × €970) and ADEs may sum to a total of 1.8 million extra days of hospitalization (=16.3 million patients × 0.038 × 2.9 days). Considering these figures, one might estimate that ADEs cause total direct costs of €1.058 billion per year.

Table 2 – Classification and frequency of ADEs.

Level	Description	n (%)	
		ADEs leading to hospitalization (i.e., ADEs coded as primary diagnosis)	ADEs acquired during inpatient treatment (i.e., ADEs coded as secondary diagnosis)
A1	Caused by a drug	52 (9.2)	461 (22.5)
A2	Caused by a drug or other substance	222 (39.4)	1136 (55.4)
B1	Poisoning by drug	133 (23.6)	94 (4.6)
B2	Poisoning by or harmful use of a drug or other substance	16 (2.8)	35 (1.7)
C	ADE very likely	141 (25.0)	323 (15.8)
—	Total	564 (100.0)	2049 (100.0)

ADEs, adverse drug events.

Table 3 – Classification of ADEs leading to hospitalization (primary diagnoses).

Rank	ICD code (three digits)	Description	n (%)	Costs (€), mean ± SD	Range (€)	Median costs (€) (Q1–Q3)
1	A04	Other bacterial intestinal infections	78 (13.8)	3,083 ± 2,725	475–15,443	2,316 (1,531–3,532)
2	F19	Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	72 (12.8)	1,708 ± 852	208–4,352	1,667 (1,172–2,321)
3	F11	Mental and behavioral disorders due to use of opioids	64 (11.4)	1,387 ± 861	208–3,881	1,344 (708–1,820)
4	T42	Poisoning by antiepileptic, sedative-hypnotic, and antiparkinsonism drugs	44 (7.8)	1,280 ± 788	232–4,128	1,011 (797–1,655)
5	F13	Mental and behavioral disorders due to use of sedatives or hypnotics	31 (5.5)	2,164 ± 1,131	280–4,223	2,068 (1,234–3,178)
6	K71	Toxic liver disease	29 (5.1)	3,101 ± 3,334	211–18,147	2,832 (1,270–3,407)
7	T43	Poisoning by psychotropic drugs, not elsewhere classified	26 (4.6)	1,536 ± 1,472	409–7,580	1,010 (697–1,916)
8	T78	Adverse effects, not elsewhere classified	24 (4.3)	1,131 ± 1,337	223–5,317	662 (384–1,224)
9	T40	Poisoning by narcotics and psychodysleptics (hallucinogens)	20 (3.6)	2,235 ± 3,585	320–16,262	914 (512–2,138)
10	D69	Purpura and other hemorrhagic conditions	19 (3.4)	2,040 ± 1,926	615–7,511	1,392 (970–2,478)
11	D70	Agranulocytosis	17 (3.0)	1,436 ± 763	191–3,336	1,240 (1,126–1,432)
12	D61	Other aplastic anemias	16 (2.8)	1,548 ± 1,412	500–5,265	880 (651–1,599)
13	T88	Other complications of surgical and medical care, not elsewhere classified	15 (2.7)	1,992 ± 3,883	271–15,884	983 (532–1,772)
14	T50	Poisoning by diuretics and other unspecified drugs, medicaments, and biological substances	15 (2.7)	1,079 ± 819	334–3,320	744 (472–1,501)
15	T39	Poisoning by nonopioid analgesics, antipyretics, and antirheumatics	14 (2.5)	1,645 ± 2,413	358–9,951	1,023 (828–1,441)
16	T80	Complications following infusion, transfusion, and therapeutic injection	11 (2.0)	3,527 ± 3,789	317–13,060	2,602 (655–5,035)
17	K52	Other noninfective gastroenteritis and colitis	10 (1.8)	2,349 ± 1,717	577–6,674	2,163 (1,035–2,595)
18	T45	Poisoning by primarily systemic and hematological agents, not elsewhere classified	9 (1.6)	2,100 (1,381)	388–3,964	1,418 (1,090–3,303)
19	T46	Poisoning by agents primarily affecting the cardiovascular system	8 (1.4)	2,541 ± 2,010	958–6,831	1,796 (1,142–3,331)
20	I95	Hypotension	7 (1.2)	1,507 ± 732	411–2,528	1,374 (1,183–2,383)
21	T38	Poisoning by hormones and their synthetic substitutes and antagonists, not elsewhere classified	6 (1.1)	2,607 ± 737	1,669–3,597	2,711 (1,847–3,110)
22	—	Others	29 (4.9)	1,854 ± 1,516	304–6,949	1,373 (645–2,497)
		Total	564 (100.0)	1,978 ± 2,036	191–18,147	1,446 (843–2,480)

ADEs, adverse drug events; ICD, *International Classification of Diseases*.

Discussion

In our study, we identified a substantial number of ADEs (n = 564) that were highly likely to have resulted in hospitalizations with costs of €1,978 ± €2,036 (range €191–18,147; median €1,446; €843–2,480 [Q1–Q3]) per patient ("analysis 1"). In the second part, the mean excess treatment costs of ADE patients equal €970 (median €314) and the respective control subjects (n = 1,891) were calculated ("analysis 2"). Total annual nationwide costs were estimated to be €1.058 billion. Considerable similarities in the economic consequences of ADEs, but also a number of differences (particularly when focusing on epidemiology), exist between this and previous studies. Ambulatory ADEs often lead to hospitalization and occur in 1.4% to 15.4% of the hospitalized patients [18,25,26]. The admission rate frequency that we identified in our sample (1.14%) was lower than the 2% to 15% attributable to ADEs reported elsewhere [5,27,28]. The difference may result from the young patient sample (mean age 47.4 years) or the possibility that the detection algorithm missed ADEs included in other studies. Regarding ADEs occurring after hospitalization, our result (3.8%) is in line with that of Senst et al. [28], who reported an ADE rate of 4.2% in a four-hospital health care network in the United States. Considering LOS in ADEs causing admission to hospital, our results (median 4 days) are comparable to those presented in the literature. Jha et al. [25] reported a median stay of 5 days for ADE patients who were hospitalized. Various research groups calculated an (average) LOS increase of between 0.77 and 2.2 days attributable to ADE patients, which is comparable to the extra days in our study [16,28–31]. Preventability of ADEs is estimated to vary between 30% and 40% according to various studies, and half of the preventable ADEs require hospital admission [5,25,32–34]. This could reveal a significant savings potential for the hospitals. ADE cases in categories "A.2" to "B.2" are classified as type A reactions and recover after a reduction in drug dosage. Although many events are predictable, however, they are not always preventable [35]. To date, no satisfactory approach has been developed on this issue [36,37]. When a reviewer classifies an event as definitely or probably preventable, it remains ambiguous whether there is a 90% or a 10% chance that the event could have actually been prevented if care had been optimal [38]. But the transfer of these probability elements into economic studies has not been considered yet.

Table 4 – Description of ADEs acquired during hospitalization (ADEs coded as secondary diagnoses).

Rank	ICD code (three digits)	Description	n (%)
1	T88	Other complications of surgical and medical care, not elsewhere classified	583 (28.5)
2	D61	Other aplastic anemias	196 (9.6)
3	F13	Mental and behavioral disorders due to use of sedatives or hypnotics	157 (7.7)
4	D69	Purpura and other hemorrhagic conditions	142 (6.9)
5	E03	Other hypothyroidism	97 (4.7)
5	T78	Adverse effects, not elsewhere classified	97 (4.7)
7	A04	Other bacterial intestinal infections	94 (4.6)
8	D70	Agranulocytosis	87 (4.3)
9	M81	Osteoporosis without pathological fracture	84 (4.1)
10	K71	Toxic liver disease	79 (3.9)
11	F11	Mental and behavioral disorders due to use of opioids	49 (2.4)
12	F19	Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	48 (2.3)
13	T45	Poisoning by primarily systemic and hematological agents, not elsewhere classified	39 (1.9)
14	T80	Complications following infusion, transfusion, and therapeutic injection	38 (1.9)
15	L27	Dermatitis due to substances taken internally	22 (1.1)
16	T46	Poisoning by agents primarily affecting the cardiovascular system	20 (1.0)
17	—	Others	217 (10.6)
		Total	2,049 (100.0)

ADEs, adverse drug events; ICD, *International Classification of Diseases*.

Accurate costs associated with ADEs are rarely known, and earlier studies determined these costs through a wide variety of methodological approaches and definitions. So far, economic data on ADEs provide a heterogeneous landscape and prior results are scarcely comparable because of the different national health care settings and their specifics (e.g., patient mix, institutional processes, and different methods for prescribing and dispensing drugs), the patients' individual context, and different methods

Table 5 – Matching results.

Variable	Identifier	Cases (n = 1,891)	Controls (n = 1,891)
Sex, n (%)	Female	796 (42.09)	794 (41.99)
	Male	1095 (57.91)	1097 (58.01)
Age (y)	Mean ± SD	64.72 ± 17.26	64.33 ± 19.95
PCCL, n (%)	0 (no complication or comorbidity)	454 (24.01)	456 (24.11)
	1 (minor complication or comorbidity)	22 (1.16)	22 (1.16)
	2 (moderate complication or comorbidity)	229 (12.11)	228 (12.06)
	3 (severe complication or comorbidity)	411 (21.73)	431 (22.79)
	4 (catastrophic complication or comorbidity)	775 (40.98)	754 (39.87)
MDC, n (%)	1 (Diseases & Disorders of the Nervous System)	93 (4.92)	93 (4.92)
	3 (Diseases & Disorders of the Ear, Nose, Mouth, & Throat)	7 (0.37)	6 (0.32)
	4 (Diseases & Disorders of the Respiratory System)	438 (23.16)	439 (23.22)
	5 (Diseases & Disorders of the Circulatory System)	366 (19.35)	366 (19.35)
	6 (Diseases & Disorders of the Digestive System)	257 (13.59)	257 (13.59)
	7 (Diseases & Disorders of the Hepatobiliary System & Pancreas)	145 (7.67)	145 (7.67)
	8 (Diseases & Disorders of the Musculoskeletal System & Connective Tissue)	188 (9.94)	189 (9.99)
	9 (Diseases & Disorders of the Skin, Subcutaneous Tissue, & Breast)	53 (2.80)	53 (2.80)
	10 (Endocrine, Nutritional, & Metabolic Diseases & Disorders)	56 (2.96)	56 (2.96)
	11 (Diseases & Disorders of the Kidney & Urinary Tract)	58 (3.07)	38 (2.01)
	12 (Diseases & Disorders of the Male Reproductive System)	1 (0.05)	1 (0.05)
	13 (Diseases & Disorders of the Female Reproductive System)	27 (1.43)	27 (1.43)
	14 (Pregnancy, Childbirth, & the Puerperium)	2 (0.11)	2 (0.11)
	15 (Newborns & Other Neonates)	4 (0.21)	4 (0.21)
	16 (Diseases & Disorders of Blood, Blood-Forming Organs, Immunological Disorders)	24 (1.27)	24 (1.27)
	17 (Neoplastic Disorders [Hematological & Solid Neoplasms])	35 (1.85)	55 (2.91)
	18B (Infectious & Parasitic Diseases, Systemic or Unspecified Sites)	36 (1.90)	36 (1.90)
	19 (Mental Diseases & Disorders)	8 (0.42)	8 (0.42)
	20 (Alcohol/Drug Use & Alcohol/Drug-Induced Organic Mental Disorders)	68 (3.60)	68 (3.60)
	21B (Injuries, Poisonings, & Toxic Effects of Drugs)	17 (0.90)	16 (0.85)
	23 (Factors Influencing Health Status & Other Contacts with Health Services)	8 (0.42)	8 (0.42)

MDC, major diagnostic category; PCCL, patient clinical complexity level.

Table 6 – Length of stay and excess costs.

	Cases (n = 1,891)	Control subjects (n = 1,891)	Difference
Length of stay (d)			
Mean ± SD	12.7 ± 17.2	9.8 ± 11.6	2.9
Median (Q1–Q3)	8.0 (4.0–15.0)	7.0 (3.0–13.0)	1.0
Range	0–273	0–161	—
Costs (€)			
Mean ± SD	5,113 ± 10,059	4,143 ± 6,968	970
Median (Q1–Q3)	2,701 (1,636–5,111)	2,387 (1,432–4,701)	314
Range	179–246,288	154–148,479	—

used to achieve medication adherence. In the United States, Bates et al. [32] calculated the costs of preventable inpatient events to be $2 billion. Dartnell et al. [39] reported the annual costs to be approximately $3 million (Australian academic hospital). Bates et al. [16] estimated the excess costs associated with an ADE to be $3244 and overall costs to a hospital to be $5.6 million per year (US 700-bed teaching hospital). Jha et al. [25] mention annual costs of $6.3 million for all admissions resulting from ADEs, and $1.2 million for preventable ADEs that led to admission to a large academic US hospital. But the authors note that the events revealed were very expensive. Senst et al. [28] calculated an average increase in costs of $2162 for a patient suffering from an ADE that occurred after hospitalization (annual extrapolated costs of $1.7 million) and $6685 per case for ADEs causing admission to hospital (annual projected sum equaled $4.9 million). Field et al. [40] calculated the costs associated with ADEs among older adults in an ambulatory setting for 6 weeks before and 6 weeks after the ADE occurred, resulting in a cost increase of $1310. Considering the accountability of costs with respect to their origin, it is known that by covering ADRs leading to hospitalization, even ADR-associated risks in outpatient treatment are incorporated [41].

Limitations

Our study, however, faces several limitations. First, the nationwide extrapolation of our economic estimates should be kept in perspective as the preselection of three hospitals in a single geographic region may not be representative of all German hospitals (failure to account for clinical heterogeneity by pooling all data) because differences may exist in costs, medical treatment patterns, and hospital care levels. The large proportion of mental and behavioral disorders (approximately a quarter of all ADE-induced hospitalizations) and the lower patients' average age (47.4 years) seem to result from this selection, as it differs from those reported in international studies (e.g., 6% mental disorders and 5% injury/poisoning) with mostly elderly patients suffering from ADEs [27]. Quite apart from that, our study is unique on account of its more comprehensive cost survey approach. Second, we refrained from considering categories "D" (i.e., "ADE likely") and "E" (i.e., "ADE possible") in ADE detection, which pertain to ADEs but are associated with considerable uncertainty [18]. Third, the analysis of administrative data is limited on account of several restrictions (e.g., hospital-specific differences in coding practices) [42]. As data were collected for accounting purposes, overall data quality is extraordinary, but the course of disease is not adequately displayed for subsequent use [24,43]. No comprehensive data sources are available in Germany, covering the whole drug treatment process in all stages. Other possible databases are the database of ADR-induced hospitalizations to departments of internal medicine provided by the Federal Institute for Drugs and Medical Devices (BfArM) or the population-based German Pharmacoepidemiological Research Database (GePaRD-BIPS) covering Statutory Health Insurance and prescription information [44,45]. These, however, do not contain detailed information on inpatient resource consumption during hospitalization.

Fourth, various studies reported a limited number of drugs to be the most frequent cause of ADE-related hospital admissions. In a systematic review and data synthesis, Howard et al. [46] found that preventable drug-related hospital admissions were caused by antiplatelets (16.0%), diuretics (15.9%), nonsteroidal anti-inflammatory drugs (11.0%), and anticoagulants (8.3%). In Germany, Schneeweiss et al. [45] found that most ADRs were on account of cardiovascular drugs, antithrombotics, analgesics, and antirheumatics. In another German study, Dormann et al. [47] reported central nervous system, cardiovascular, and anti-infective agents to be the most common causative drugs of ADEs resulting in (re-)hospitalization. In this study, similar drugs were supposed to be the cause of hospitalization. There was, however, a strong emphasis on antibiotics (about 14%), antipsychotic/sedatives (>25%), and opiates (>11%), which was affected by the selection of the three hospitals. In addition, the ICD-10–based identification of drug-induced events is not comprehensive in scope, as consistent secondary codes (e.g., Y40–59.9) are required for more precise ADE detection [48,49]. Hence, it cannot be assumed that these already existed at the time of admission or occurred during the hospital stay. A subsequent separation between existing ADEs and those that developed while hospitalized is impossible.

Fifth, we did not adjust for pre-ADE hospitalization (because this was unfeasible from our data), which is known to be an important confounder [16,29]. Beyond that, we did not have any data on prehospital drug utilization, preventability, and severity of ADEs. This impedes the determination of delayed effects and end-of-treatment effects. Last, the calculation of excess costs is impaired by the small sample size and the patient characteristics included in the propensity score calculation (i.e., major diagnostic category and patient clinical complexity level) [50]. The cases were matched with control subjects on severity, comorbidity, and patient sociodemographics to estimate excess costs and LOS attributable to ADEs. A reflection of disease patterns by the inclusion of diagnosis related group would improve the quality of matching considerably.

Managerial implications

Our results highlight the considerable costs associated with both inpatient and outpatient ADEs. Hence, this study supports health policy decision-makers in supporting the allocation of research grants, estimating the impact of ADEs on the German health care systems, analyzing the provision of health care patterns that encompass the risk of ADEs, and forecasting future demand for ADE-related health care provision when translated to a nationwide patient population. The hospital management could use our methodological approach to identify the relevant cost drivers, to detect the magnitude of ADEs in their institution, to analyze the provision of health care against the background of ADEs, to redesign medical service processes, to decide on the implementation

of evidence-based medicine treatment patterns, and to evaluate the effectiveness and prioritization of prevention strategies (e.g., clinical decision support systems) [51,52]. Particularly if patients suffer from multiple ADEs, or the ADE is not the primary diagnosis in coding processes, this may impose serious problems. Hence, the preventability of these events is difficult to quantify. In this context, actual results show that structured pharmaceutical supervision provides more effective results in drug therapy [53]. Pharmacists are enabled to offer an enhanced counseling interview ("medicines-use-reviews") with patients to optimize the individual therapy in order to simplify drug regimens and reduce ADEs [54,55]. Currently, however, only weak evidence exists on whether this pharmacist-led approach influences adherence or contributes to a reduction in ADEs or medication-related hospitalizations [56,57].

The capability for detecting and preventing potential ADEs by the use of electronic patient records, computerized physician order entry, and clinical decision support systems was identified in previous studies, resulting in high ADR preventability when using adequate decision support systems [58–61]. Studies from other health care settings revealed high returns on investment and a significant lowering of both inpatient LOS and total costs [62,63]. In a cutting-edge evaluation study, Wu et al. [64] calculated the cost-effectiveness of a combined electronic medication order entry and medication administration record system from a Canadian hospital perspective. The analysis resulted in costs of $12,700 per ADE avoided. This value appears to be high compared with the direct costs of empirical studies. But it should be noted that specific hospitals or rather departments (internal medicine) were considered, and long-term consequences in particular are costly. Hug et al. [30] reported that the majority (>80%) of preventable ADEs (i.e., ADEs that were due to an error or preventable by any means available) would be avoided by powerful computerized physician order entry–related decision support. In addition, these authors present a comprehensive compilation of the most important ADE prevention strategies as a result of their research. The top five strategies were drug-laboratory checks, renal function checks, drug-dose suggestion, drug-age checks, and drug-specific guidelines [30]. Maviglia et al. [65] conducted a cost-benefit analysis of the impact of bar-code systems on ADEs in US academic hospitals. Potential ADE rates decreased by 63%, and breakeven for return on investment was reached after 1 year of bringing the system into service. Although the benefits of electronic prescribing and personal health records are well established in inpatient hospital settings, its contribution to patient safety in outpatient care remains ambiguous [61,66]. Notwithstanding, these technical solutions are suitable only to a limited extent, particularly if they are not integrated into the decision-making process [67].

Conclusions

We have presented a practical and inexpensive approach to assess ADE-associated resource consumption and estimate the frequency of ADEs. To the best of our knowledge, no published study has ever utilized these administrative data to calculate the economic burden of ADEs. The matching approach allowed us to derive cost and hospitalization estimates based on case and control groups that share similar characteristics in disease patterns, patient characteristics, and medical severity. Prevention of ADEs by improving medication safety in inpatient and outpatient care is mandatory from both an economic and a medical point of view. In conclusion, the substantial costs (almost a billion euros) associated with these events justify additional investments in efforts to detect and prevent ADEs. Nevertheless, a methodologically accurate attribution of hospital costs to ADEs is challenging. The analysis of administrative data can essentially contribute to the acquisition of pharmacovigilance knowledge, as small efforts in data collection and high integrity allow new insights.

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