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SYSTEMS-LEVEL QUALITY IMPROVEMENT

Frequency and Impact of Adverse Events in Inpatients: A Nationwide Analysis of Episodes between 2000 and 2015

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Abstract

Despite being a potential cause of morbidity and economic costs, adverse events remain insufficiently studied. Therefore, we aimed to assess the frequency and impact of adverse events among inpatients. We analysed an administrative database containing a registration of all hospitalisations occurring in Portuguese public hospitals between 2000 and 2015. We identified all episodes with a registration of adverse events, and classified them into three categories, namely (1) misadventures of surgical and medical care, (2) complications of surgical or medical procedures, and (3) adverse drug events (including adverse drug reactions, poisoning events, and late effects). These episodes were compared over their length of stay, in-hospital mortality, and hospital costs with an equal number of hospitalisations matched for patients' and episodes' characteristics. Between 2000 and 2015, 5.8% ($n = 861{,}372$) of all Portuguese hospitalisations had a registration of at least one adverse event. Hospitalisations with registration of adverse events had a median length of stay of 8 days, median hospitalisation costs of 3060.7 Euro, and an in-hospital mortality of 6.7%. Hospitalisations with registration of misadventures of care, complications of procedures and adverse drug reactions had significantly higher lengths of stay and hospitalisation costs than their matched controls. In-hospital mortality was significantly higher for episodes of misadventures of care and complications of procedures, but lower for adverse drug events hospitalisations. Therefore, adverse events are common among inpatients, and have an important clinical and economic impact. Administrative databases may be useful in their epidemiological assessment.

Keywords Administrative data · Adverse drug events · Adverse events · Hospitalisation · ICD-9-CM

Introduction

Adverse events (AE) can be defined as undesirable and unintended incidents in care that may result in adverse outcomes or may require additional care efforts to prevent an adverse outcome [1, 2]. In hospitalised patients, AE have an important clinical and economic impact, resulting in higher morbidity and mortality, longer hospital stays, and increased costs – in a sample of over 1000 inpatients of the Greater London area, Vincent et al. found that AE resulted in an increase in the length of stay averaging 8.5 days [3]. The same authors estimated that additional bed days resulting from preventable AE could annually cost the National Health Service near 1 billion British Pounds [3]. A study performed in the Australian state of Victoria found not only that AE were associated with an increase of 10 days in the average length of stay, but also with a 7-fold increase of in-hospital mortality [4]. On the other hand, Goodman et al. estimated that AE may have caused over 187,000 deaths in 2006, associating with costs that can be as high as 958 billion US Dollars [5].

Adverse events remain insufficiently studied. Most studies have been conducted in specific populations/settings (e.g.: patients with a particular condition) [6, 7] or focused only on a specific type of AE (e.g.: adverse drug reactions) [8]. However, statewide or nationwide studies assessing the overall frequency and impact of AE remain rare. This may in part result from difficulties in assessing the frequency of AE, as there are different methods available, each one with both advantages and limitations. For example, spontaneous notifications systems are

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essential in a post-marketing safety context, but tend to underreport the incidence of AE and have a variable quality [9, 10]. On the other hand, studying AE by chart review provides expert-reviewed information but can be time-consuming, expensive, and difficult to implement in a nationwide scope [11]. Administrative data has also some flaws, such as being primarily used for billing purposes rather than for scientific ones. Nevertheless, analysis of such data might circumvent some time-, access- and cost-related limitations of other methods, allowing for studies with nationwide scope and covering long periods of time [9, 11].

Therefore, this study aims to estimate the frequency and impact of AE in all Portuguese public hospital admissions occurring within a 16-year period (from 2000 to 2015) in all Portuguese public hospitals. Additionally, by analysing an administrative database, this study aims to contribute to a critical assessment of the use of hospital administrative data as a tool for AE surveillance. This manuscript extends the authors' previous work [12], with an update of the inclusion criteria, as well as with new analyses over a larger and updated dataset, covering a wider period of time.

Methods

We conducted an observational retrospective study to assess the frequency of AE in Portuguese inpatients. We analysed an administrative database containing all hospitalisations occurring in Mainland Portuguese public hospitals, from 2000 to 2015. For each hospitalisation, the corresponding diagnoses and external causes of injuries and poisoning were coded based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

We analysed all hospitalisations with registration of AE. Adverse events were defined as undesirable and unintended incidents in care that may result in adverse outcomes or may require additional care efforts to prevent an adverse outcome [1, 2]. Adverse events were divided in three main categories – (1) misadventures of surgical and medical care, (2) complications of surgical or medical procedures, and (3) adverse drug events (ADE). Because of the complexity of ADE, this category was further subdivided in three groups, namely (3.1) poisoning, (3.2) adverse drug reactions, and (3.3) late effects. For these categories, the following definitions were used:

- *Misadventures of surgical and medical care*: Adverse events occurring during the delivery of care, and caused by medical or surgical care or providers.
- *Complications of surgical or medical procedures*: Abnormal reactions caused by surgical or medical procedures (and occurring during or after them), but without mention of misadventures at the time of procedure.
- *Adverse drug events*: Injuries resulting from the use of a drug, and including both harms caused by drugs (e.g.: adverse drug reactions and overdoses) and harms caused by their use (including dose reductions and discontinuations of drug therapy) [13, 14].
- *Poisoning:* Poisoning events include accidental drug overdoses, administration of wrong substances, inadvertent use of drugs, and accidents in the usage of drugs and biologicals in medical and surgical procedures [14].
- *Adverse drug reactions:* Events that are noxious and unintended, and which occur at doses normally used in humans for prophylaxis, diagnosis, therapy or modification of physiologic functions. This definition excludes intentional or deliberate overdose and drug abuse [13].
- *Late effects:* Conditions that appear after the acute phase of an earlier, causal condition has run its course [14].

We performed a comprehensive literature search to identify the ICD-9-CM codes most commonly used to define AE [15–19]. In order to find related codes not used in previous studies, this literature search was complemented by an additional search for ICD-9-CM codes particularly by including the conditions listed as consisting of AE by Portuguese experts in medical coding [20], as well as by searching for codes containing the keywords "due to drugs" or "drug induced" (and related terms) both in their description or in their explanation notes. This selection was subsequently revised, complemented and categorised by experts in medical coding and auditing. In the end, a total of 541 ICD-9-CM codes (encompassing 248 diagnosis codes and 293 external cause codes) were used to identify AE (Table 1).

We identified all hospitalisations with at least one associated diagnosis or external cause code of AE (except for the ICD-9-CM code 359.79, which only corresponds to an AE when accompanied by an external cause code). We calculated the frequencies of hospitalisations with registration of AE (and assessed their evolution over the studied period), obtaining both the overall frequencies as well as the frequencies for each category of AE. As some hospitalisations had a registration of two or more AE of different categories, the number of episodes with registration of at least one AE was lower than the sum of identified episodes with registration of AE of each category.

We compared episodes with registration of AE with a randomly selected sample of hospitalisations without such registration, on a ratio of 1:3. In particular, comparisons were performed over inpatients' gender, age and Charlson comorbidity index [21], type of hospital admission (planned versus unplanned), and type of episode (surgical versus medical episodes; this classification was based on whether a surgical procedure was or not performed). For each category of AE, variables with significant association in the univariable analyses ($p < 0.05$) were included in multivariable models aiming to identify demographic and clinical factors independently associated with each category of AE.

Table 1 Diagnosis and external cause ICD-9-CM codes selected for identification of adverse events of different categories

Adverse event category	Diagnosis codes		External cause codes		Total number of codes
	ICD-9-CM codes	Number of codes	ICD-9-CM codes	Number of codes	
Misadventures of surgical and medical care	998.2, 998.4, 998.7, 999.81, 999.82	5	E870-E876.9	58	61
Complications of surgical or medical procedures	996.0–996.7, 997.0–997.5, 997.7, 997.9, 998.0, 998.1, 998.3, 998.5, 998.6, 998.8, 999.9	22	E878.x, E879.x	10	32
Poisoning events	960–979.9	173	E850-E858.9	55	228
Adverse drug reactions	284.11, 284.12, 285.3, 288.03, 292.x, 333.72, 333.85, 339.3, 357.6, 359.24, 359.79, 528.01, 528.02, 655.5, 668.x, 692.3, 693.0, 693.8, 693.9, 760.72, 760.74, 763.5, 995.2, 995.4	46	E930-E949.9	171	217
Late effects	909.0, 909.5	2	E929.2	1	3

In order to evaluate the clinical and economic impact of AE, we compared episodes with and without registration of AE over their length of stay, hospitalisation costs (indirectly calculated using a classification system based on Diagnosis Related Groups [22]), and in-hospital mortality. Prior to these comparisons, we had performed a propensity score matching for each category of AE, so that hospitalisations of each category of AE were compared with an equal number of episodes matched for inpatients' gender, age, Major Diagnostic Category (a classification of the principal diagnosis into 26 mutually exclusive diagnosis areas), Charlson Comorbidity Index, type of hospital admission and type of episode.

Data are presented as absolute frequencies and percentages for categorical variables, and as means and standard deviations or medians and quartiles for continuous variables. Categorical variables were compared using the chi-square test, and continuous variables were analysed using the Mann-Whitney U test. The results of the multivariable analyses are expressed as odds ratio (OR) with 95% confidence intervals (95% CI). *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS, version 24.0 (Armonk, NY; IBM Corp).

Results

Between 2000 and 2015, there were 14,890,339 hospitalisations in Mainland Portugal, of which 5.8% (n = 861,372) had a registration of at least one AE. Overall, within the studied period, there were 564,727 episodes with registration of complications of surgical and medical procedures, followed by misadventures of surgical and medical care (n = 90,341) and ADE (n = 279,723). Among the latter, ADR comprised most episodes (78.9%; n = 220,700), followed by poisoning events (20.9%; n = 58,467), and late effects (0.2%; n = 556) (Table 2). 71,653 hospitalisations had registration of more than one AE of different categories. During the studied period, the proportion of hospitalisations with registration of AE increased 150% (from 3.2% in 2000 to 8.0% in 2015); in fact, except for poisoning events, all categories of AE increased their frequency (Fig. 1).

The absolute and relative frequencies of hospitalisations with each AE ICD-9-CM code are listed in Online Resource 1. Most poisoning events and late effects episodes had been solely assigned a diagnosis ICD-9-CM code (84.3% and 69.1%, respectively). On the other hand, most misadventures and adverse drug reactions episodes had only been assigned an external cause ICD-9-CM code (65.4% and 68.9%, respectively). Finally, most episodes of complications of surgical or medical procedures had been assigned both a diagnosis and an external cause code (70.2%) (Online Resource 2).

Most AE occurred in females (51.9% versus 48.1% in males) (Table 2); in fact, female gender independently associated with increased frequency of misadventures of care [OR = 1.13 (95%CI = 1.11–1.15; $p < 0.001$)], poisoning events [OR = 1.69 (95%CI = 1.65–1.72; $p < 0.001$)] and adverse drug reactions [OR = 1.03 (95%CI = 1.02–1.04; $p < 0.001$)] (Table 3). On the contrary, female gender associated with decreased frequency of complications of procedures and late effects. Inpatients' average age was significantly higher for AE hospitalisations than for those without such a registration (58.0 versus 47.2 years; $p < 0.001$). A similar trend was observed for Charlson comorbidity index (median: 1.1 versus 0.6; $p < 0.001$) (Table 2). In the multivariable analyses, higher inpatients' age and Charlson comorbidity index were associated with increased frequency of AE of all categories except late effects and poisoning events, respectively.

Most AE occurred in the context of urgent admissions (64.9% versus 35.1% for planned hospitalisations). In fact, urgent admissions were independently associated with higher frequency of poisoning events [OR = 7.20 (95%CI = 6.80–7.62)], adverse drug reactions [OR = 1.18 (95%CI = 1.16–1.19)] and misadventures of care [OR = 1.18 (95%CI = 1.16–1.20)]. While ADE episodes were mostly of medical type, most

Table 2 Characteristics of hospitalisations with and without registration of adverse events according to their category (Mainland Portugal; 2000–2015)

	Hospitalisations with registration of adverse events						Hospitalisations without registration of adverse events ($n = 2,584,175$)	p value[a]
	Misadventures of surgical and medical care ($n = 90,341$)	Complications of surgical or medical procedures ($n = 564,727$)	Poisoning events ($n = 58,467$)	Adverse drug reactions ($n = 220,700$)	Late effects ($n = 556$)	Total ($n = 861,372$)		
Gender – *n* (%)								
Male	38,788 (42.9)	290,857 (51.5)	18,803 (32.2)	102,249 (46.3)	283 (50.9)	414,204 (48.1)	1,150,263 (44.5)	<0.001
Female	51,551 (57.1)	273,865 (48.5)	39,664 (67.8)	118,450 (53.7)	273 (49.1)	447,161 (51.9)	1,433,876 (55.5)	
Patients' age – mean (SD)	52.8 (24.1)	59.0 (21.1)	46.4 (25.0)	61.7 (22.6)	49.8 (25.1)	58.0 (22.5)	47.2 (28.3)	<0.001
Charlson comorbidity index – median (IQR)	0.9 (1.7)	1.1 (1.7)	0.5 (1.2)	1.7 (2.0)	1.7 (2.2)	1.1 (1.8)	0.6 (1.4)	
Type of hospital admission – *n* (%)								
Planned	33,605 (37.2)	255,040 (45.2)	1358 (2.3)	39,525 (17.9)	189 (34.0)	302,274 (35.1)	802,393 (31.1)	<0.001
Urgent	56,732 (62.8)	309,661 (54.8)	57,108 (97.7)	181,172 (82.1)	367 (66.0)	559,071 (64.9)	1,781,659 (68.9)	
Type of episode – *n* (%)								
Surgical	48,373 (53.6)	355,451 (62.9)	1295 (2.2)	25,692 (11.6)	119 (21.4)	391,275 (45.4)	912,112 (35.3)	<0.001
Medical	41,946 (46.4)	209,232 (37.1)	57,136 (97.8)	194,974 (88.4)	437 (78.6)	469,984 (54.6)	1,671,415 (64.7)	

IQR interquartile range, *SD* standard deviation

[a] p value for the comparison between the total number of hospitalisations with registration of adverse events versus hospitalisations without registration of adverse events

hospitalisations with registration of misadventures or complications were of surgical type (53.6% and 62.9%, respectively); this pattern was observed even after adjustment for other variables, with medical episodes associating with increased frequency of poisoning events [OR = 13.12 (95%CI = 12.40–13.91)], adverse drug reactions [OR = 3.35 (95%CI = 3.30–3.41)] and late effects [OR = 1.59 (95%CI = 1.26–2.01)], but with decreased frequency of misadventures of care [OR = 0.44 (95%CI = 0.43–0.45)] and complications of procedures [OR = 0.32 (95%CI = 0.32–0.32)].

Episodes with registration of AE were significantly longer (median length of stay 8 versus 4 days; $p < 0.001$) and costlier (median hospitalisation costs 3060.7 versus 1759.6 Euro; $p < 0.001$) than those without such a registration. Additionally, AE hospitalisations also presented with significantly higher in-hospital mortality (6.7% versus 4.7%; $p < 0.001$). Hospitalisations with more than one AE of different categories had a median length of stay of 11 days, median hospitalisation costs of 4504.0 Euro, and an in-hospital mortality of 11.2%.

We performed a propensity score matching, comparing episodes of each AE category with an equal number of "non-AE" hospitalisations matched for inpatients' gender, age, Major Diagnostic Category, Charlson Comorbidity Index, type of hospital admission and type of episode. We found that episodes of every category presented with higher average lengths of stay and hospitalisation costs than their matched controls (the sums of hospitalisation days and costs in both compared groups are depicted in Fig. 2); median values, however, were not higher for episodes of poisoning events and late effects (Table 4). In-hospital mortality was found to be significantly higher for misadventures of care and complications of procedures than for their respective matched controls, but it was surprisingly lower for ADE hospitalisations of all categories (Table 4).

Discussion

In this study, we found that 5.8% of all hospitalisations occurring in Portuguese public hospitals between 2000 and 2015 had a registration of at least one AE. There are not many nationwide or statewide studies assessing all types of AE, and the existing ones have disparate methodologies, rendering difficult to compare our results. Nevertheless, we found a frequency of AE consistent with other studies – in particular, an administrative database-based Spanish study performed in inpatients of 12 hospitals between 2008 and 2010 found an AE prevalence of 6.8% [23]. A similar percentage – of 6.9% – was obtained in another study performed using an administrative database (covering the 45 largest hospitals of the Australian state of Victoria), although this percentage went up to 19.6% when only admissions lasting two or more days were considered [4].

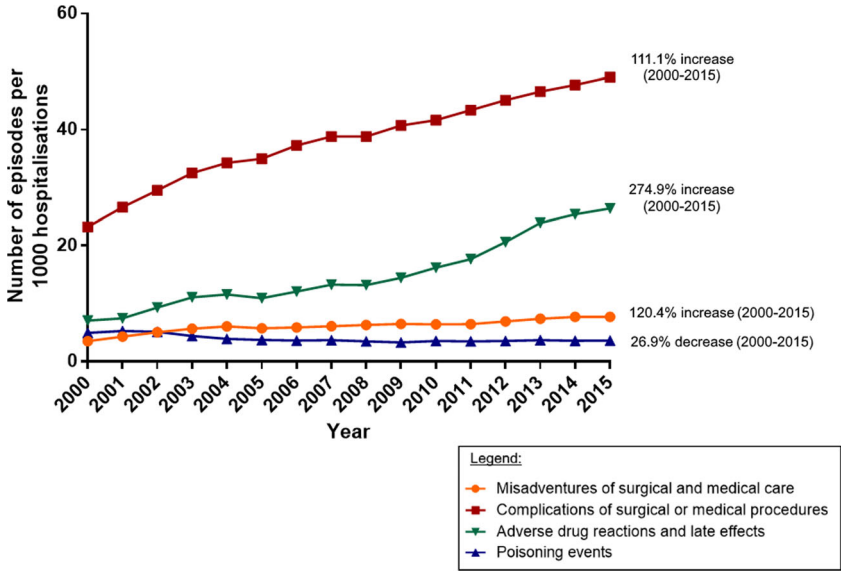

Fig. 1 Annual number of episodes with registration of adverse events of each category per 1000 hospitalisations (Mainland Portugal; 2000–2015)

During the studied period, we observed an 150% increase in the percentage of hospitalisations with registration of AE. While this trend might mirror a real increase in the frequency of AE, an improvement in the coding process should not be ruled out [24]. In fact, several ICD-9-CM codes used in this study to identify AE were created between 2000 and 2015. It is noteworthy to mention that, in the United States, studies performed in the 1980s and in the early 1990s found AE to occur in 2.9–3.7% of hospitalized patients [25, 26], while a more recent study obtained a frequency of 13.5% [27]. Despite the possibility of a real increase on the frequency of AE, this difference is more probably due to methodological differences between studies, including in their definitions of participants and of "adverse events" [5].

Overall, as described in previous studies [3–5, 23], hospitalisations with registration of AE were found to be associated with increased in-hospital mortality, length of stay and hospitalisation costs. Intriguingly, we observed a lower in-hospital mortality among ADE episodes. This association was only observed for medical episodes and for urgent admissions; in surgical hospitalisations and in planned admissions, in-hospital mortality was found to be higher for episodes with registration of ADE than for the remainder (data not shown). A possible explanation may involve very severe urgent admissions, in which early in-hospital mortality – prior to the occurrence of any ADE – is expected to be particularly frequent. On the other hand, surgical episodes requiring administration of more drugs – and, thus, more prone to the occurrence of ADE – might be themselves more severe and more often fatal. Unfortunately, we do not possess information regarding the cause of death and, therefore, we do not know the proportion of in-hospital deaths that were due to AE.

During the studied period, episodes with registration of AE amounted a total of 4.8 thousand million Euro in hospitalisation costs, as well as 12.6 million hospitalisation days; this compares to 3.1 thousand million Euro and 7.3 million days for their propensity score matched controls. This corresponds to an overall difference of 5.3 million days and 1.7 thousand million Euro. Complications of surgical or medical procedures were the category with highest impact on that difference, both in absolute and in relative terms; in fact, episodes with registration of complications were, in average, 91% longer and 59% more costlier than matched controls. Therefore, while we cannot rule out the occurrence of reverse causality, we may expect that the prevention of AE (roughly half of AE are preventable [3, 25, 26, 28]), would prompt substantial reductions of costs and hospitalisation days.

In this study, we aimed to study the clinical and economic burden of AE. While we adopted strategies aimed at controlling for possible confounders (such as propensity score matching), we cannot exclude the possibility of reverse causality. In fact, hospitalisations involving more severe situations might, on the one hand be themselves longer and more expensive, and on the other hand require additional and more complex procedures, thus being more prone to AE (in fact, patient comorbidities increase the risk for adverse events [29, 30]). Therefore, an important limitation of this study, concerns the absence of information on the severity of hospitalisations. Additional limitations result from lack of information on the preventability of the AE episodes, as well as from the impossibility to distinguish between AE present on admission and those occurring during hospital stay. The assessment of the impact of AE could also benefit from comparing the frequency of patient readmissions between episodes with and without registration of AE. However, that was not possible in our study, as the assessed data was anonymised, thus impairing an identification of individual patients.

Additional limitations resulting from the use of secondary administrative data should also be taken into account – as these databases are primarily used for hospital billing

Table 3 Results of the univariable (A) and multivariable (B) analyses aiming to identify demographic and clinical factors independently associated with adverse events of each category (Mainland Portugal; 2000–2015)

A. Results of the univariable analyses – OR (95%CI; *p* value)

	Misadventures of surgical and medical care (*n* = 90,341)	Complications of surgical or medical procedures (*n* = 564,727)	Poisoning events (*n* = 58,467)	Adverse drug reactions (*n* = 220,700)	Late effects (*n* = 556)	All adverse events (*n* = 861,372)
Female gender	1.07 (1.05–1.08; <0.001)	0.76 (0.75–0.76; <0.001)	1.70 (1.67–1.73; <0.001)	0.93 (0.92–0.94; <0.001)	0.70 (0.58–0.85; <0.001)	0.87 (0.86–0.87; <0.001)
Patients' age	1.01 (1.01–1.01; <0.001)	1.02 (1.02–1.02; <0.001)	0.99 (0.99–0.99; <0.001)	1.02 (1.02–1.02; <0.001)	1.00 (1.00–1.01; 0.056)	1.02 (1.02–1.02; <0.001)
Charlson comorbidity index	1.13 (1.12–1.13; <0.001)	1.18 (1.18–1.18; <0.001)	0.94 (0.94–0.95; <0.001)	1.43 (1.43–1.44; <0.001)	1.37 (1.30–1.45; <0.001)	1.22 (1.22–1.22; <0.001)
Type of hospital admission						
Planned[a]	1.0	1.0	1.0	1.0	1.0	1.0
Urgent	0.77 (0.75–0.78; <0.001)	0.55 (0.54–0.55; <0.001)	18.81 (17.81–19.87; <0.001)	2.07 (2.05–2.10; <0.001)	0.90 (0.73–1.10; 0.307)	0.83 (0.83–0.84; <0.001)
Type of episode						
Surgical[a]	1.0	1.0	1.0	1.0	1.0	1.0
Medical	0.48 (0.47–0.48; <0.001)	0.32 (0.32–0.32; <0.001)	24.04 (22.73–25.42; <0.001)	4.15 (4.09–4.21; <0.001)	1.98 (1.58–2.48; <0.001)	0.66 (0.65–0.66; <0.001)

B. Results of the multivariable analyses – OR (95%CI; *p* value)

	Misadventures of surgical and medical care (*n* = 90,341)	Complications of surgical or medical procedures (*n* = 564,727)	Poisoning events (*n* = 58,467)	Adverse drug reactions (*n* = 220,700)	Late effects (*n* = 556)	All adverse events (*n* = 861,372)
Female gender	1.13 (1.11–1.15; <0.001)	0.78 (0.78–0.79; <0.001)	1.69 (1.65–1.72; <0.001)	1.03 (1.02–1.04; <0.001)	0.76 (0.62–0.92; 0.006)	0.92 (0.92–0.93; <0.001)
Patients' age	1.00 (1.00–1.00; <0.001)	1.01 (1.01–1.02; <0.001)	1.00 (1.00–1.00; <0.001)	1.02 (1.02–1.02; <0.001)	–	1.01 (1.01–1.01; <0.001)
Charlson comorbidity index	1.13 (1.13–1.14; <0.001)	1.16 (1.15–1.16; <0.001)	0.88 (0.87–0.89; <0.001)	1.29 (1.28–1.29; <0.001)	1.34 (1.27–1.41; <0.001)	1.17 (1.17–1.17; <0.001)
Type of hospital admission						
Planned[a]	1.0	1.0	1.0	1.0	–	1.0
Urgent	1.18 (1.16–1.20; <0.001)	0.94 (0.93–0.94; <0.001)	7.20 (6.80–7.62; <0.001)	1.18 (1.16–1.19; <0.001)	–	1.07 (1.06–1.07; <0.001)
Type of episode						
Surgical[a]	1.0	1.0	1.0	1.0	1.0	1.0
Medical	0.44 (0.43–0.45; <0.001)	0.32 (0.32–0.32; <0.001)	13.12 (12.40–13.91; <0.001)	3.35 (3.30–3.41; <0.001)	1.59 (1.26–2.01; <0.001)	0.61 (0.61–0.62; <0.001)

CI confidence interval, *OR* odds ratio

[a] Reference category

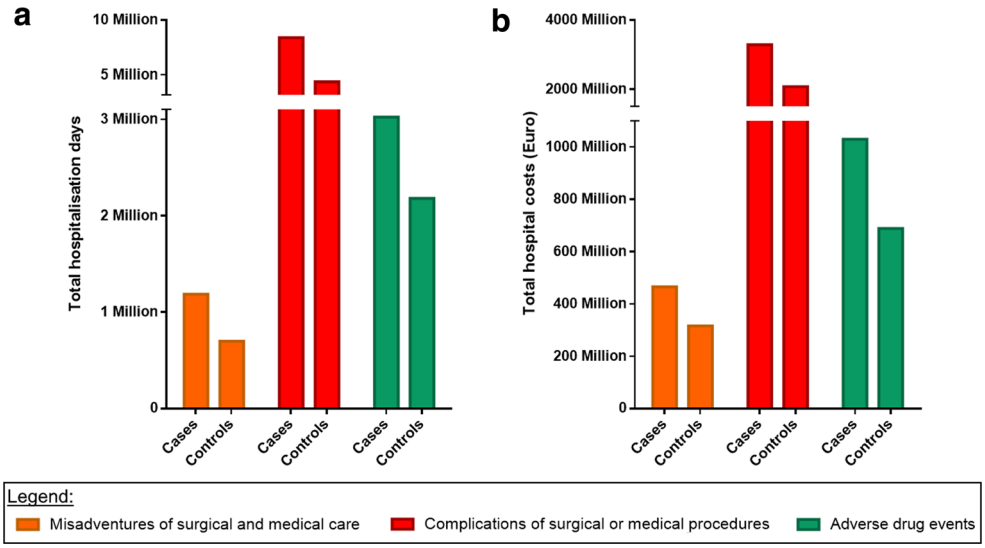

Fig. 2 Sums of total hospitalisation days (**a**) and costs (**b**) for hospitalisations with registration of AE of the different categories ("cases") versus an equal number of episodes without such a registry and matched for inpatients' gender, age, Major Diagnostic Category, Charlson Comorbidity Index, type of hospital admission and type of episode ("controls")

purposes, their accuracy and completeness (particularly the possibility of underreporting) might be called into question [11]. Nevertheless, a previous chart review study performed by our team found that AE diagnosis ICD-9-CM codes have a positive predictive value of 80.9% (ranging from 73.3% for adverse drug reactions to 86.8% for poisoning events), while AE external cause ICD-9-CM codes have a positive predictive value of 83.4% (ranging from 71.9% for misadventures of surgical and medical care to 90.8% for adverse drug reactions) (unpublished data). An approach that requires the presence of at least one diagnosis or an external cause ICD-9-CM code thus appears to maximise the quantity of AE identified in administrative databases.

Nevertheless, this study has also several strong points, as it assesses a period of 16 years within a nationwide scope. In fact, one of the advantages of using administrative databases in the study of AE concerns the possibility of efficiently assessing large populations over long periods of time [31, 32]. Additionally, in our analyses, we adopted different strategies aiming to control for potential confounders – in

Table 4 Comparison of the length of stay, in-hospital mortality and hospitalisation costs between episodes of each category of adverse events and an equal number of matched hospitalisations without registration of adverse events ("matched controls") (Mainland Portugal; 2000–2015)

	Length of stay – median (IQR)	In-hospital mortality – *n* (%)	Hospitalisation costs – median (IQR)
Misadventures of surgical and medical care (*n* = 84,856)	7 (13)	7143 (8.4)	3060.7 (5036.9)
Matched controls[a] (*n* = 84,856)	4 (7)[b]	3556 (4.2)[b]	2318.1 (2849.6)[b]
Complications of surgical or medical procedures (*n* = 490,874)	10 (17)	33,010 (6.7)	4197.7 (6669.2)
Matched controls[a] (*n* = 490,874)	6 (9)[b]	24,067 (4.9)[b]	2814.6 (3139.3)[b]
Poisoning events (*n* = 22,430)	6 (11)	1466 (6.5)	1683.8 (1822.6)
Matched controls[a] (*n* = 22,430)	6 (10)[c]	1751 (7.8)[b]	1796.7 (1615.6)[b]
Adverse drug reactions (*n* = 195,439)	8 (13)	15,928 (8.1)	2369.9 (2568.5)
Matched controls[a] (*n* = 195,439)	7 (9)[b]	19,372 (9.9)[b]	2120.0 (1463.4)[b]
Late effects (*n* = 513)	7 (13)	34 (6.6)	2194.5 (2093.8)
Matched controls[a] (*n* = 513)	7 (11)[d]	57 (11.1)[e]	2379.7 (2583.4)[b]

IQR interquartile range

[a] Cases and controls were matched for inpatients' gender, age, Major Diagnostic Category, Charlson Comorbidity Index, type of hospital admission and type of episode

[b] *p* value for the comparison <0.001

[c] *p* value for the comparison = 0.991

[d] *p* value for the comparison = 0.134

[e] *p* value for the comparison = 0.012

particular, we performed multivariable analyses for the identification of factors independently associated with each category of AE, and performed a propensity score matching prior to the assessment of the length of stay, in-hospital mortality and hospitalisation costs. Finally, we performed a comprehensive search validated by experts and auditors in medical coding to identify relevant AE ICD-9-CM codes – while it is impossible to guarantee its total completeness (particularly, taking into account variations in the ICD-9-CM codes between 2000 and 2015), our search was particularly exhaustive, capturing the frequency trends of AE.

In conclusion, we found that 5.8% of all Portuguese hospitalisations occurring between 2000 and 2015 had a registration of at least one AE. These episodes, whose frequency increased during the studied period, associate with higher length of stay, hospitalisation costs and, in the case of misadventures of care and complications of procedures, in-hospital mortality. Therefore, AE appear to have an important clinical and economic impact, whose assessment may be improved with methodological approaches using (among others) administrative databases.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study informed consent is not required, as data had previously been anonymised.

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