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Letter to the Editor

Prevalence and risk factors associated with fatal adverse drug reactions among patients admitted at a Spanish teaching hospital

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To the Editor,

The toxicity of pharmacological treatments remains a major clinical challenge with important health implications. Best estimates from the medical and scientific literature suggest that 0.12%–0.22% of hospital admissions result in death due to an adverse drug reaction (ADR) corresponding to 100,800–197,000 deaths annually in the European Union [1]. A review of European observational studies reported the highest percentage of fatal ADRs was 0.49% of all admissions in studies where an ADR was the reason for hospital admission or visit to the emergency department and 0.52% of all admitted patients in studies reporting the percentage of patients who experienced an ADR during hospitalization [2]. Because of the importance of the subject, we conducted a study involving a large sample of patients during admission to a Spanish university hospital to determine the prevalence of deaths by fatal ADR and some of the risk factors associated with such deaths.

This is a single-center, retrospective observational study including inpatients admitted to a teaching hospital between January 1, 2009, and October 31, 2010. A total of 34,590 hospital admissions of adult patients of both sexes were included, covering a period of 22 consecutive months according to data provided by the hospital clinical documentation service. The data included the length of stay (days), age, sex, and hospital-ward at discharge. This information was transferred to a bespoke database. To this database were added 1388 deceased registered in the same period at the hospital whose analysis was previously reported by our research group [3] including the patients who died by an ADR and the assessment probability method.

A descriptive analysis was carried out for the nominal covariates building a frequency table, and the mean and standard deviation were calculated for the numeric variables. The differences between global mortality and ADR mortality of inpatients were calculated with the chi-square test for sex and ward at discharge; and for age and length-of-stay, a comparison means test using Welch's approach was used. The independent effects of the different covariates were studied by multivariate analysis with Poisson regression used to calculate the Incidence Rate Ratio (IRR) and confidence intervals (CI 95%) for each. Data were weighted by the reverse of the probability of global death by the ADR-related death (hospital-acquired or not), and non-weighted. We finally estimate the predictive potential for the different variables calculating the value of the area under curve of Receiver Operating Characteristic (AUC ROC). The STATA 14.0 program was used for statistical analysis. $P < .05$ was considered significant. This study was authorized by the Clinical Research Ethics Committee of Hospital Universitario San Cecilio, Granada (Spain).

Of the total of 34,590 admissions, we recorded 1388 discharges by death (4.01%; 95% CI, 3.81–4.22%), with the rest ($n = 33,202$) being discharged due to improvement or cure. Deceased inpatients were older (75 ± 13 vs. 55 ± 7.5 years; $p = .001$), and had longer length-of-stay (9 ± 10 vs. 7.4 ± 9 days; $p = .001$) than patients discharged alive. Besides, men had a significant higher mortality than women (5.28% vs. 3.07%; $p = .01$). Respect to hospital-ward at discharge, the mortality was significantly lower ($p = .001$) in Internal Medicine and Surgery specialties (6.25% and 1% respectively) than in Intensive Care Unit and Oncology (35.2% and 16.2% respectively).

The total number of suspected ADR-related deaths was 256 (0.74%; 95% CI, 0.65–0.83%), which was significantly associated with age (≥ 70 years), length-of-stay, discharge from Oncology and Intensive Care services, but not sex although males suffered a larger percentage of fatal ADRs than women, the difference was not significant (0.93% vs. 0.60%; $p > .1$).

The total number of hospital-acquired ADR-related deaths was 161 (0.47%; 95% CI, 0.40–0.54%), which was significantly associated with age (≥ 70 years), length-of-stay, and Intensive Care, but not with Oncology ($p > .1$). A larger percentage of males suffered a hospital-acquired fatal ADR than women but the difference was not significant (0.59% vs. 0.38%; $p > .1$). These 161 cases constituted 62.9% of the total number of ADR-related deaths.

The results of multivariate analysis showed that age (≥ 70 years), length-of-stay, and discharge from Intensive Care were independent predictors of ADR-related death. Women had around half the risk of suffering a fatal ADR as men (Table 1). The AUC ROC value found for the covariates of age (≥ 70 years), length-of-stay (days), and discharge from Intensive Care Unit was 0.82.

Our results show drug-related mortality of 0.74% of inpatients admitted to a teaching hospital; this prevalence is higher than previously reported in a review of European observational studies [2] probably

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Table 1
Results of multivariate analysis for the hospital total deaths recorded; deaths by a fatal ADR; and deaths by a fatal ADR hospital-acquired. Data show weighted and non-weighted values (Incidence Rate Ratio and CI 95%).

	Total deaths (n = 1388)	ADR-related deaths (n = 256)		Hospital acquired ADR-related deaths (n = 161)	
		Non-weighted values	Weighted values	Non-weighted values	Weighted values
Age (Years above 70)	1.06 (1.05–1.06)*	1.07(1.06–1.08)*	1.1(1.07–1.13)*	1.07(1.06–1.09)*	1.09(1.06–1.13)*
Sex (Female)	0.85 (0.76–0.95)*	0.88(0.69–1.13)	0.64(0.44–0.93)*	0.85(0.62–1.16)	0.55(0.34–0.88)*
Sex (Male)	1	1	1	1	1
Length-of-stay (Days)	1 (1–1.01)	1.01(1–1.02)	1.02(1.02–1.03)*	1.02(1.01–1.03)*	1.03(1.02–1.03)*
Intensive Care discharge	1.4 (1.15–1.71)*	1.8(1.05–3.09)*	1.51(0.73–3.11)	2.24(0.97–5.15)	2.97(1.04–8.5)**
Internal Medicine specialties discharge	0.22 (0.19–0.26)*	0.3(0.19–0.48)*	0.17(0.08–0.36)*	0.49(0.24–0.98)*	0.46(0.17–1.25)
Surgery specialties discharge	0.07 (0.06–0.09)*	0.15(0.09–0.24)*	0.05(0.03–0.09)*	0.28(0.14–0.58)*	0.15(0.07–0.32)*
Oncology discharge	1	1	1	1	1

* $p < .01$.
** $p < .001$.

because differences in methodology and underreporting (almost one-third of the 32 studies included in the review did not report fatal ADRs). On the other hand, the hospital-acquired ADR-related mortality that we found was similar to previously reported in the aforementioned review [2] probably because of similarities in methodology to use of intensive chart review in most of the studies as in our case and the prescribing of drugs in a more controlled hospital environment that make easier to assess drug causality.

In our study, ADR-related mortality was associated with sex (males being more at risk), age (≥ 70 years), length-of-stay (days), and the requirement for Intensive Care Unit corroborating previous studies [4–6]. These variables significantly increased the risk of death of inpatients by ADR whether community- or hospital-acquired. Patients from Intensive Care had almost three times the risk of death by a fatal ADR caused by their critical state and the reduced response to drug-induced injury [6]. Furthermore, it is well known that aging modifies the response to drugs due to progressive impairment of physiological functions and this fact increases the probability of suffering serious or fatal ADRs. It has also been reported that the length of stay is a risk factor for death and ADRs in inpatients [4]. Several authors have reported that females are more at risk of an ADR because of greater drugs consumption and differences in pharmacological response to some drugs compared to males; these include cardiovascular, opiates, and psychotropic drugs [5]. However, in our data, women had almost half the risk of death due to a fatal ADR than males. We think this may be because women's hospital mortality was significantly smaller than that of men, and because males suffer more serious ADR and ADR-related deaths than women as previously reported [7]. Anyway, we consider that the role of sex in the pathogenesis of fatal ADRs is a topic that requires further studies.

Despite the fact that the study was retrospective and single-centered, we think that the results obtained might be useful for developing a good tool for predicting ADR-related deaths according to the AUC ROC obtained. We conclude that the results obtained to make a contribution to the study of drug-related death in inpatients.

Declaration of Competing Interests

None.

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Author declaration

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We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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