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RESEARCH

Impact of suspected adverse drug reactions on mortality and length of hospital stay in the hospitalised patients: a meta-analysis

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Abstract

Purpose To estimate the risk of mortality and length of stay in hospitalised patients who have experienced suspected adverse drug reactions (ADRs) as compared to patients who did not experience suspected ADRs.

Methods A systematic literature search was conducted on databases for observational and randomised controlled studies conducted in any inpatient setting that reported deaths and/or length of hospital stay in patients who had suspected ADRs and did not have suspected ADRs during hospitalisation. PRISMA guidelines were strictly followed during the review. The methodological quality of included studies was assessed using a tool designed by Smyth et al. for the studies of adverse drug reactions. The meta-analytic summary of all-cause mortality was estimated using odds ratio—OR (95% CI) and length of stay using mean difference—MD (95% CI). Both outcomes were pooled using a random effect model (DerSimonian and Laird method). Subgroup and meta-regression were performed based on study variables: study design, age group, study ward, study region, types of suspected ADRs (ADR_{Ad}—suspected ADRs that lead to hospitalisation and ADR_{In}—suspected ADRs that occur following hospitalisation), study duration, sample size and study period. The statistical analysis was conducted through the 'Review manager software version 5.4.1 and JASP (Version 0.14.1)'.

Results After screening 475 relevant articles, 55 studies were included in this meta-analysis. Patients having suspected ADRs had reported significantly higher odds of all-cause mortality [OR: 1.50 (95% CI: 1.21–1.86; $I^2 = 100\%$) than those patients who did not have suspected ADRs during hospitalisation. Study wards, types of suspected ADRs and sample size were observed as significant predictors of all-cause mortality ($p < 0.05$). Patients having suspected ADRs had reported significantly higher mean difference in hospital stay [MD: 3.98 (95% CI: 2.91, 5.05; $I^2 = 99\%$) than those patients who did not have suspected ADRs during hospitalisation. Types of suspected ADRs and study periods were observed as significant predictors of length of stay ($p < 0.05$).

Conclusion Suspected ADRs significantly increase the risk of mortality and length of stay in hospitalised patients.
Systematic review registration.
CRD42020176320.

Keywords Adverse drug event · Mortality · Length of stay · Meta-analysis

Introduction

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. It can be any symptom, abnormal laboratory finding or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product [1]. A suspected adverse drug reaction (ADR) is defined as a noxious and unintended response to a medicine [1]. In contrast to an adverse event, a causal relationship between a medicinal product and an

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occurrence is suspected in the case of ADR. This definition includes overdose, off-label use, abuse, misuse, occupational exposure to a medicinal product and medication error [1, 2]. ADRs are an important cause of hospital admission as well as could prolong hospitalisation. The prevalence of suspected ADRs in hospitalised patients could vary from 0.2 to 58% [3–7]. An earlier meta-analysis has estimated that suspected ADRs are the six leading causes of death in the USA in hospitalised patients [8]. The prevalence of mortality among patients due to suspected ADRs in hospitalised patients could vary from 0.0 to 5.2% [9, 10]. The drugs were suspected in 0.0 to 18.2% of inpatient deaths [11].

All-cause mortality refers to the number of people who died from any cause in a given period. It is used to compare additional deaths compared with the baseline. It could provide a measure of the excess mortality, directly and indirectly, attributable to drug-related harm to patients who had suspected ADRs during their hospital stay compared with those who did not have suspected ADRs. Length of stay is an indicator of the use of medical services. Increased hospital stay has been associated with economic burden, risks of complications and mortality [12, 13]. The ADRs may be life threatening and often lead to emergency department visits, hospital admission and prolongation of hospital stay. All earlier meta-analyses on suspected ADRs had focused on the prevalence estimation due to ADR-related mortality in hospitalised patients [3, 7–11] or ADR leading to hospital admission [6, 7, 14] to highlight associated mortality and hospital admission burden. However, no data are available on all-cause mortality due to suspected ADRs and length of stay among the inpatients. In this meta-analysis, we want to estimate the risk of mortality and length of hospital stay in hospitalised patients who have experienced suspected ADRs as compared to patients who do not experience suspected ADRs.

Methods

PRISMA guidelines were strictly adhered to during the systematic review and the study protocol was registered on PROSPERO (CRD42020176320).

Information sources and search strategy

Two investigators (TKP and PBP) independently searched PubMed, Google Scholar, LILACS, SCOPUS, Cochrane Database of Systematic Reviews and a bibliography of relevant articles, systematic reviews and meta-analyses. The keywords used for PubMed and Google Scholar search were (adverse drug event OR adverse drug effect OR adverse drug reaction OR drug related problem OR medication error) AND (inpatient OR hospital*) AND (fatal* OR death OR lethal OR mortality). There were no time and language restrictions. The last search was carried out on 6 May 2021.

Working definition

Suspected ADR: A noxious and unintended response to a medicine. This definition extends beyond suspected reactions at appropriate use of medicine and includes harm from an overdose, off-label use, abuse, misuse, occupational exposure to a medicinal product and medication error [1].

ADR_{Ad}: Patient should be admitted to the hospital because of suspected ADR.

ADR_{In}: Patient develops suspected ADRs following hospitalisation.

Population, intervention, comparator, outcome and study design (PICOS) criteria for the systematic review are presented in Table 1.

Study participants

The study population comprised patients of any age group in the inpatient setting. The study population did not comprise patients who received treatment in ambulatory care or emergency care setting without requiring hospitalisation. The emergency care studies which provided data of patients on subsequent hospitalisation were included.

Study arm (ADR arm)

- Patients who had at least one suspected ADR in the inpatient setting

Control arm (non-ADR arm)

- Patients who did not have suspected ADR in the inpatient setting

Exposure

The exposure included administration of drugs to the patients regardless of dose, setting (inpatient or outpatient), administrator (health care professional, caregiver or patient) or use (appropriate or inappropriate) and subsequent occurrence of adverse drug events.

Study selection criteria

We included all observational (cross-sectional, case–control and cohort designs) and randomised controlled studies conducted in the inpatient setting on any study wards. Studies should have reported all-cause deaths and/or length of hospital stay in study arms (suspected ADR and non-suspected

Table 1 Population, intervention, comparator, outcome and study design (PICOS) criteria for the systematic review

Criteria	Inclusion criteria	Exclusion criteria
Study population	• Patients of any age group in the inpatient setting	• Patients receiving treatment in ambulatory care or emergency care setting without requiring hospitalisation
Intervention	• Patients who had at least one suspected ADR in the inpatient setting	• Studies not differentiating adverse event due to non-drug-related interventions (e.g. low oxygen saturation after tracheostomy, infection in the surgical wound) or complications of surgical or medical procedures with suspected ADRs • Studies having voluntary or spontaneous reporting methods to detect suspected ADRs
Comparator	• Patients who did not have suspected ADR in the inpatient setting	–
Outcome	• All-cause mortality as OR (95% CI) • Length of hospital stay as MD (95% CI)	–
Study design	• Cross-sectional • Case–control • Cohort • Randomised controlled studies	• Review articles • Systematic reviews • Meta-analysis • Case-reports • Commentary articles

ADR, adverse drug reaction; *OR*, odds ratio; *MD*, mean difference; *CI*, confidence interval

ADR arms) or should have provided sufficient data to compute them. We excluded studies not differentiating suspected ADRs from adverse events due to non-drug-related interventions or complications of surgical or medical procedures (e.g. low oxygen saturation after tracheostomy, infection in the surgical wound). Studies also excluded if solely depended on voluntary or spontaneous reporting methods to detect suspected ADRs, outpatient or ambulatory care settings, focused on specific drugs (e.g. antiepileptic drugs) or clinical conditions (e.g. renal failure) or events (e.g. anaphylactic reaction) and duplicate studies.

Primary outcome

- All-cause mortality: meta-analytic summary of all-cause mortality between suspected ADR and the non-suspected ADR groups was the primary outcome

Secondary outcome

- Length of stay: meta-analytic summary of the mean length of hospital stay between suspected ADR and the non-suspected ADR group was the secondary outcome.

Study screening

Initially, two investigators independently screened the title and abstract as per a predefined questionnaire. In the next stage, retrieving full texts were assessed as per the selection criteria and availability of outcome data. Any disagreements in study selection were resolved through discussion and consensus.

Data extraction

The following data were extracted in the predefined Excel sheet: first author, publication year, geographical location, study design, study period, study duration, study ward, age group, data collection methods, suspected ADR definition used, types of suspected ADR studied, personnel who identified suspected ADR, causality, severity and preventability assessment, baseline data of population in study arms (age, gender, number of drugs received), total number of inpatients in a study ward, number of patients in suspected ADR and non-suspected ADR arm, total number of deaths in suspected ADR and non-suspected ADR arm, length of hospital stay in suspected ADR and non-suspected ADR arm patients. All extracted variables were cross-checked to ensure the quality of data extraction.

Risk of bias assessment of included studies

The risk of bias was assessed using the tool designed by Smyth et al. for the studies of adverse drug reactions [15]. The assessment was based on a description of the study design, methods for identifying suspected ADRs and methods for determining causality, preventability and severity [15]. The publication bias was assessed through visual inspection of the funnel plot and Egger's regression test.

Data synthesis

The meta-analytic summary of all-cause mortality was estimated using odds ratio—OR (95% CI) and length of stay using

mean difference—MD (95% CI). High heterogeneity was anticipated, and a random effect model (DerSimonian and Laird method) was preferred over a fixed effect for the meta-analysis.

A forest plot was generated to display OR (95% CIs) and MD (95% CI) for each study. An I^2 test was used to evaluate heterogeneity. An I^2 value of 25%, 50% and 75% was considered low, medium and high heterogeneity, respectively. The sensitivity analysis of the primary and secondary outcomes was performed using a low risk of bias studies.

Subgroup analysis

The subgroup analysis of both outcome parameters (mortality and length of stay) was performed to explore the possible sources of heterogeneity. The following study variables were used: study design, age group, study ward, study region, types of suspected ADRs based on their setting of occurrence (ADR_{Ad}—suspected ADRs that lead to hospitalisation and ADR_{In}—suspected ADRs that occur following hospitalisation), study duration, sample size and study period.

Meta-regression

Initially, the influence of all study variables on mortality and length of stay was assessed through univariable meta-regression. The subgroup with a minimum of 4 studies was selected as a moderator [16]. Subsequently, the study variables showing a significance level of $p < 0.10$ were further explored through multivariable regression using the random effect model [17].

Statistical package

Review Manager software (RevMan version 5.4.1) was used for meta-analysis and subgroup analysis. JASP (Version 0.14.1) was used for univariable and multivariable meta-regression analysis.

Result

Literature search

A total of 55 full-text articles were included from 21,919 retrieved references from the literature of databases and other sources [18–72]. A PRISMA flow chart of included studies is presented in Fig. 1. The study designs of excluded full-text studies were cross-sectional (215), case–control (2), cohort (3) and randomised controlled trial (1).

Study characteristics

The general characteristics of included studies are presented in Table 2. The included studies had used cross-sectional (prospective—31, retrospective—17, prospective and retrospective—1), case–control (5) and cohort (1) study designs. Studies were conducted in the internal medicine ward (13), whole hospital (13), emergency department (8), intensive care unit—ICU (6), multispecialty wards (6), geriatric ward (2), paediatric ward and ICU (2), paediatric ward (2), internal medicine and ICU (1), medical and surgical wards and ICU (1) and surgical ward (1). The emergency department studies admitted patients through emergency units [25, 54, 57–59] or had admission inemergency wards [62, 68, 72]. A total of 21 studiesfocused on ADR_{Ad} and 19 studies on ADR_{In}. Ten studiesincluded both ADR_{Ad} and ADR_{In}, while 5 studies did notspecify the type of suspected ADRs. Studies used different data collectionmethods to detect suspected ADRs: medicalrecord review (28), interview and medical record review (19), ADE triggertool–based medical record review (2), ADE trigger tool–based medical recordreview through computerised record system (1), medical record review withvoluntary reporting by health care professionals (1) and medical record reviewthrough computerised record system (1). A total of 15 studies used WHO or asimilar definition, 7 studies Edwards and Aronson definition, 3 studies ICD-9 Ecodes and 2 studies Aronson and Ferner definition to identify suspected ADRs.Claret et al. only focused on medication errors [25].In the case of Darchy et al., data of iatrogenic disease due to drug exposurewere considered a suspected ADR, while data ofiatrogenic disease due to medical and surgical procedures were excluded [28]. In the case of ICD-9 and ICD-10 code–based studies, only data on suspected ADRs[19, 21, 48, 60, 71] were considered. Thedetailed general characteristics of included studies are presented in Supplementary Table 1.

Risk of bias assessment in individual studies

All studies clearly described the study design. One study did not specify the suspected ADR identification method [63], while three studies did not describe data collection methods [45, 50, 63]. Seven studies did not specify individuals who identified suspected ADRs [19, 21, 35, 45, 48, 60, 71]. A total of 39 studies specified the methods of causality, 24 preventability and 38 severity assessment of suspected ADRs [Supplementary Table 2]. The risk of bias summary is described in Supplementary Fig. 1.

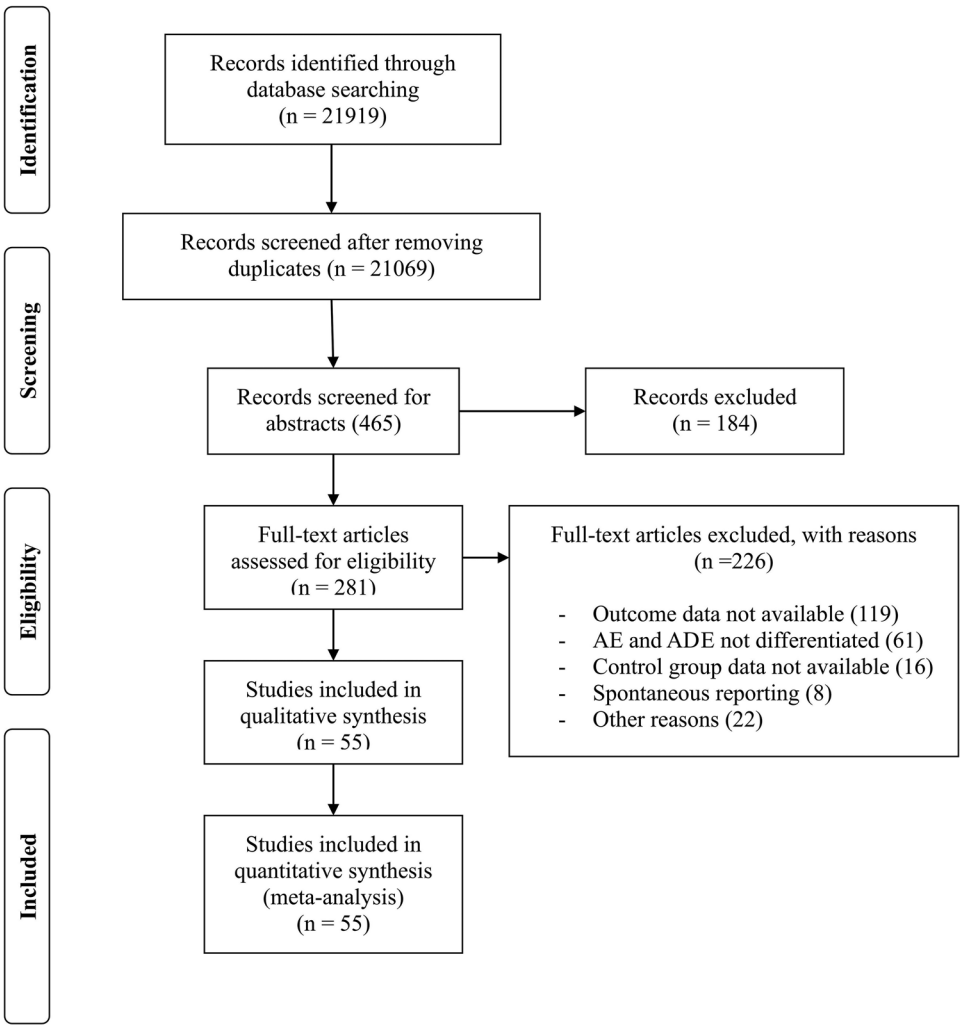

Fig. 1 PRISMA flow diagram showing the study selection process

All-cause mortality

A total of 31 studies (1,577,946 all-cause deaths; 38,377,918 patients) contributed to all-cause mortality outcome. The suspected ADR arm reported 35,644 all-cause deaths (5.50%) out of 648,289 inpatients, while the non-suspected ADR arm reported 1,542,302 all-cause deaths (4.09%) out of 37,729,629 inpatients. As shown in Fig. 2, patients having suspected ADR had reported significantly higher odds of mortality [OR: 1.50 (95% CI: 1.21–1.86; $I^2 = 100\%$) than those patients who did not have suspected ADR during hospitalisation. On sensitivity analysis, the OR of all-cause mortality varied from 1.25 to 1.61 with a low risk of bias studies [Supplementary table 3].

Length of hospital stay

A total of 40 studies (8,282,929 patients) contributed to the length of hospital stay outcome. As shown in Fig. 3, patients having suspected ADR had reported significantly higher mean difference in hospital stay [MD: 3.98 (95% CI: 2.91–5.05; $I^2 = 99\%$) than those patients who did not have suspected ADR during hospitalisation. On sensitivity analysis, MD in the length of hospital stay varied from 3.06 to 3.98 with a low risk of bias studies [Supplementary table 3].

Subgroup analysis of all-cause mortality and length of hospital stay based on the study characteristics

Study design: Retrospective studies showed a trend of higher odds of all-cause mortality and mean length of stay than prospective (Tables 3 and 4). Prospective studies showed low heterogeneity (7%).

Age groups: Age groups showed different trends for all-cause mortality and hospital stay. 'Adults and elderly' studies showed a trend of higher odds of all-cause mortality (Table 3), while 'paediatric' and 'elderly' age group studies showed a trend of higher mean length of stay (Table 4). 'All

Table 2 General characteristic of the included all studies

Study	Study design	Study characteristics							Study groups (Number of patients)		Outcomes			
		Age group	**Study ward**	**Study location**	**Study duration in month**	**Study period**	**Types of suspected ADRs**	**Sample size**	**Patients with suspected ADR**	**Patients without suspected ADR**	**All-cause mortality (No. of deaths/total patients)**		**Hospital Stay Mean (SD)**	
											Patients with suspected ADR	**Patients without suspected ADR**	**Patients with suspected ADR**	**Patients without suspected ADR**
Alexopoulou et al. [18]	P	Adults and elderly	IM	Greece	6	Jan to June 2005	ADR_{Ad}	548	70	478	–	–	5.4 (1.7)	6.5 (3.3)
Amann et al. [19]	R	All age	WH	Germany	12	2006	ADR_{Ad}	16,230,407	149,605	16,080,802	1.4	2.4	–	–
Angamo et al. [20]	P	Adults and elderly	IM	Ethiopia	15	May 2015 to August 2016	ADR_{Ad}	1001	103	898	14.6	11.2	–	–
Bond and Raehl, [21]	R	NS	WH	USA	12	1998	NS	12,261,737	141,398	12,120,339	7.6	6.4	6.7 (8.2)	6.1 (5.9)
Bravar et al. [22]	R	Adults and elderly	MW	Slovenia	NS	NS	ADR_{Ad}	520	30	490	0.0	3.9	–	–
Camargo et al. [23]	P	Adults and elderly	IM	Brazil	6	May to Oct 2001	$ADR_{Ad,}$ ADR_{In}	335	143	192	–	–	18.6 (12.4)	11.2 (7.9)
Chan et al. [24]	P	Elderly	IM	Australia	2	Aug to Sept 1998	ADR_{Ad}	313	73	240	–	–	10.0 (11.6)	9.0 (11.0)
Claret et al. [25]	R	Adults and elderly	ED	France	0.75	Jan 2012	ADR_{In}	608	154	454	10.4	8.6	12.0 (12.0)	10.0 (11.0)
Classen et al. [26]	Case–control	NS	WH	USA	36	Jan 1990 to Dec 1993	NS	21,777	1580	20,197	3.5	1.0	–	–
Damen et al. [27]	R	All age	WH	Netherland	36	2008, 2011–2012	ADR_{In}	8071	204	7867	67.2	49.5	–	–
Darchy et al. [28]	R	Adults and elderly	ICU	France	12	Jan to Dec 1994	ADR_{Ad}	596	41	555	14.6	16.8	4.3 (2.9)	6.0 (7.5)
Davies et al. [29]	P	NS	MW	UK	0.5	April to May 2005	ADR_{In}	125	25	100	12.0	5.0	15.2 (8.6)	7.7 (6.8)
Davies et al. [30]	P	Adults and elderly	MW	UK	6	June to Dec 2005	ADR_{In}	3322	545	2777	10.6	4.5	22.5 (17.1)	8.7 (5.9)

Table 2 (continued)

Study	Study design	Study characteristics							Study groups (Number of patients)		Outcomes			
		Age group	**Study ward**	**Study location**	**Study duration in month**	**Study period**	**Types of suspected ADRs**	**Sample size**	**Patients with suspected ADR**	**Patients without suspected ADR**	**All-cause mortality (No. of deaths/total patients)**		**Hospital Stay Mean (SD)**	
											Patients with suspected ADR	**Patients without suspected ADR**	**Patients with suspected ADR**	**Patients without suspected ADR**
de Boer et al. [31]	P	Adults and elderly	SW	Netherland	4	Mar to Jun 2009	ADR_{In}	567	130	437	–	–	10.1 (5.2)	6.0 (4.5)
de Las Salas et al. [2006]	P	Paediatric	PW	Colombia	6	June to Dec 2013	ADR_{In}	772	147	625	–	–	7.1 (5.2)	5.3 (2.6)
Dequito et al. [33]	P	Adults and elderly	MW	Netherland	5	April 2006 to May 2008	ADR_{In}	603	349	254	–	–	16.4 (13.0)	6.1 (5.3)
Dormann et al. [34]	Cohort	Adults and elderly	IM	Germany	18	NS	ADR_{Ad}	844	181	663	–	–	16.7 (13.4)	9.2 (9.9)
Esteban Jiménez et al. [35]	P	Adults and elderly	IM	Spain	12	2014	$ADR_{Ad,}$ ADR_{In}	253	54	199	7.4	8.5	14.0 (9.3)	11.0 (12.8)
Fattinger et al. [36]	P	Adults and elderly	IM	Switzerland	24	Jan 1996 to Dec 1998	$ADR_{Ad,}$ ADR_{In}	3624	431	3193	–	–	14.3 (11.7)	10.7 (8.9)
Giordani et al. [37]	R	Adults and elderly	WH	Brazil	7	Jan to July 2008	ADR_{In}	240	35	205	14.3	4.9	–	–
Grenouillet-Delacre et al. [38]	P	Adults and elderly	ICU	France	6	May to Oct 2003	ADR_{Ad}	405	111	294	18.9	17.3	6.4 (8.0)	5.6 (9.0)
Haffner et al. [39]	P	Paediatric	PW, PICU	Germany	4	Feb to May 2001	$ADR_{Ad,}$ ADR_{In}	703	84	619	–	–	14.3 (27.3)	6.3 (9.5)
Haukland et al. [40]	Case–control	Adults and elderly	WH	Norway	12	Jan to Dec 2013	NS	2052	103	1949	73.8	15.2	–	–
Hofer-Dueckelmann et al. [41]	P	Adults and elderly	MW	Austria	6	May to Aug 2007 and Jan 2008 to April 2008	ADR_{Ad}	3190	242	2948	3.7	4.3	9.6 (6.3)	7.0 (6.5)

Table 2 (continued)

Study	Study design	Study characteristics							Study groups (Number of patients)		Outcomes			
		Age group	**Study ward**	**Study location**	**Study duration in month**	**Study period**	**Types of suspected ADRs**	**Sample size**	**Patients with suspected ADR**	**Patients without suspected ADR**	**All-cause mortality (No. of deaths/total patients)**		**Hospital Stay Mean (SD)**	
											Patients with suspected ADR	**Patients without suspected ADR**	**Patients with suspected ADR**	**Patients without suspected ADR**
Hu et al. [42]	R	Elderly	WH	China	36	Jan 2015 to Dec 2017	ADR_{In}	1800	234	1566	–	–	15.2 (12.3)	9.4 (8.1)
Ji et al. [43]	R	Paediatric	PW	China	24	Jan 2013 to Dec 2015	ADR_{In}	1746	221	1525	–	–	10.2 (8.0)	7.5 (4.7)
Jolivot et al. [44]	R	Adults and elderly	ICU	France	12	Feb 2013 to Feb 2014	ADR_{Ad}	743	173	570	18.5	16.3	4.6 (4.5)	4.4 (3.7)
Kojima et al. [45]	R	Elderly	GW	Japan	4	April 2013 to March 2015	ADR_{In}	1155	178	977	–	–	29.2 (23.3)	25.1 (19.8)
Liao et al. [46]	Case–control	Elderly	WH	Taiwan	72	Jan 2006 to Dec 2012	ADR_{In}	2393	539	1854	14.8	9.1	30.8 (30.2)	16.9 (14.7)
Mehta et al. [47]	P	Adults and elderly	IM	South Africa	2.5	Sept to Nov 2005	ADR_{Ad}, ADR_{In}	665	93	572	12.9	11.9	10.5 (7.2)	6.4 (3.7)
Miguel et al. [48]	R	All age	WH	Portugal	120	2000 to 2009	ADR_{Ad}, ADR_{In}	9,271,122	116,720	9,154,402	9.1	4.4	–	–
Mjörndal et al. [49]	P	Adults and elderly	IM, ICU	Sweden	9	Sept 1997 to Oct 1998	ADR_{Ad}	669	82	587	–	–	6.2 (7.2)	5.1 (12.5)
Moore et al. [50]	P	Adults and elderly	IM	France	6	May to Oct 1993	ADR_{Ad}, ADR_{In}	329	31	298	12.9	2.0	–	–
Mouton et al. [51]	P	Adults and elderly	IM	South Africa	1	2013	ADR_{Ad}	1904	162	1742	23.5	20.8	7.0 (4.5)	7.4 (5.2)
Mouton et al. [52]	P-R	Paediatric	PW, PICU	South Africa	2	April to July 2015	NS	1106	120	986	1.7	1.1	8.4 (6.8)	2.2 (3.4)
Nazer et al. [53]	P	Adults and elderly	ICU	Jordan	5	Aug to Dec 2010	ADR_{Ad}	249	57	192	28.1	31.3	6.2 (9.8)	6.2 (8.0)

Table 2 (continued)

Study	Study design	Study characteristics							Study groups (Number of patients)		Outcomes			
		Age group	**Study ward**	**Study location**	**Study duration in month**	**Study period**	**Types of suspected ADRs**	**Sample size**	**Patients with suspected ADR**	**Patients without suspected ADR**	**All-cause mortality (No. of deaths/total patients)**		**Hospital Stay Mean (SD)**	
											Patients with suspected ADR	**Patients without suspected ADR**	**Patients with suspected ADR**	**Patients without suspected ADR**
Olivier et al. [54]	P	Elderly	ED	France	1	1st week of Aug, Oct, Nov, 2002 and Feb 2003	ADR_{Ad}	789	66	723	–	–	7.4 (9.8)	8.5 (11.2)
Park et al. [55]	R	All age	ICU	South Korea	4	Nov 2008 to Feb 2009	ADR_{In}	149	48	101	–	–	18.7 (14.4)	13.3 (10.4)
Passarelli et al. [56]	P	Elderly	IM	Brazil	21	Sept 2002 to May 2004	$ADR_{Ad,}$ ADR_{In}	186	115	71	–	–	20.0 (14.2)	10.4 (5.6)
Pedrós et al. [57]	P	Adults and elderly	ED	Spain	4	1st 10 days of July 2009 to June 2010	ADR_{Ad}	4403	186	4217	–	–	8.0 (9.4)	9.1 (42.3)
Pedrós et al. [58]	P	Elderly	ED	Spain	54	Jan 2008 to Dec 2014	ADR_{Ad}	60,263	1976	58,287	10.2	9.0	–	–
Phillips et al. [59]	P	Adults and elderly	ED	Australia	2	May to July 2009	ADR_{Ad}	370	59	311	–	–	6.0 (6.1)	5.0 (6.0)
Riaz and Brown [60]	R	Elderly	WH	USA	12	2014	NS	3,832,322	203,432	3,628,890	4.4	5.4	NS	NS
Rozenfeld et al. [61]	R	Adults and elderly	MW	Brazil	4	Jan, Apr, July, Oct 2007	ADR_{In}	128	20	108	–	–	35.2 (28.0)	10.7 (15.3)
Rydberg et al. [62]	P	Adults and elderly	ED	Sweden	6	Sept 2008 to Sept 2009	ADR_{Ad}	706	284	422	–	–	3.0 (1.5)	2.3 (0.7)

Table 2 (continued)

Study	Study design	Study characteristics							Study groups (Number of patients)		Outcomes			
		Age group	**Study ward**	**Study location**	**Study duration in month**	**Study period**	**Types of suspected ADRs**	**Sample size**	**Patients with suspected ADR**	**Patients without suspected ADR**	**All-cause mortality (No. of deaths/total patients)**		**Hospital Stay Mean (SD)**	
											Patients with suspected ADR	**Patients without suspected ADR**	**Patients with suspected ADR**	**Patients without suspected ADR**
Sánchez Muñoz-Torrero et al. [63]	P	Adults and elderly	IM	Spain	2.5	Sept 2009 to Nov 2009	$ADR_{Ad,}$ ADR_{In}	405	126	279	–	–	18.0 (17.0)	9.6 (5.8)
Suh et al. [64]	Case–control	All age	WH	USA	5	Aug to Dec 1998	ADR_{In}	1469	131	1338	–	–	10.6 (0.9)	6.8 (0.9)
Takahashi et al. [65]	P	Adults and elderly	IM, SW and ICU	Japan	6	Jan to June 2004	ADR_{In}	2508	546	1962	15.2	6.6	–	–
Tangiisuran et al. [66]	P	Elderly	GW	UK	6	Jan to March 2007 and 2008	ADR_{In}	560	74	486	12.2	17.7	16.8 (12.3)	12.7 (8.9)
Toscano Guzmán et al. [67]	R	Elderly	IM	Spain	3	March–June 2017	$ADR_{Ad,}$ ADR_{In}	720	178	542	–	–	17.8 (9.5)	20.8 (10.7)
Tirifiro et al. [68]	P	All age	ED	Italy	0.8	2000	ADR_{Ad}	18,854	629	18,225	0.2	0.2	–	–
van der Hooft et al. [69]	R	All age	WH	Netherland	12	2001	ADR_{Ad}	668,714	12,249	656,465	6.0	5.6	–	–
Vargas et al. [70]	P	Adults and elderly	ICU	Spain	10	March to Dec 1996	ADR_{In}	420	85	335	–	–	6.6 (7.1)	4.2 (5.0)
Vitorino et al. [71]	Case–control	NS	WH	Portugal	36	2013 to 2015	ADR_{In}	34,426	17,213	17,213	9.6	4.5	22.6 (29.0)	6.4 (10.3)
Zed et al. [72]	P	All age	ED	Canada	3	March to Jun 2006	ADR_{Ad}	233	45	188	0.0	7.4	–	–

ADR adverse drug reaction, ADR_{Ad} suspected ADRs that leads to hospitalisation, ADR_{In} suspected ADRs that occurs following hospitalisation, *P* prospective, *R* retrospective, *UK* United Kingdom, *USA* United States of America, *NS* not stated, *ND* not done, *PICU* paediatric intensive care unit, *PW* paediatric ward, *ICU* intensive care unit, *IM* internal medicine, *WH* whole hospital, *MW* multispecialty wards, *ED* emergency department, *GW* geriatric ward, *SW* surgical ward

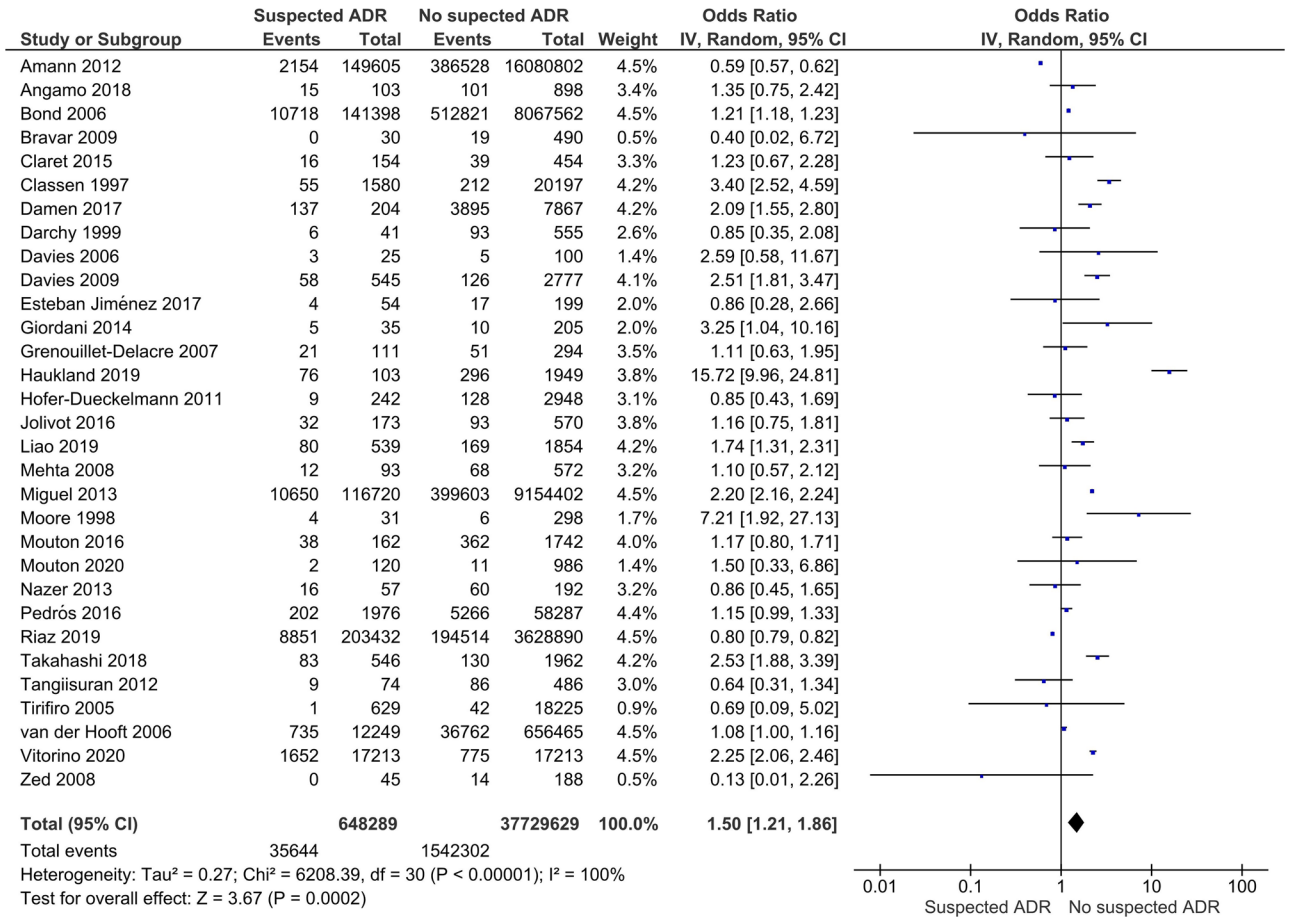

Fig. 2 Meta-analytic summary of the odds ratio of all-cause mortality through a random effect model

age' studies ($n=2$) also showed low heterogeneity ($I^2=0\%$) for a hospital stay. Both 'all age' studies used a retrospective study design.

Study wards: Whole hospital and multispecialty studies showed a trend of higher odds of all-cause mortality and mean length of hospital stay than intensive care unit and emergency department studies. Emergency department studies showed low heterogeneity for all-cause mortality ($I^2=0\%$; $n=4$) and length of stay ($I^2=44\%$; $n=5$). Their common characteristics were prospective design, study region and shorter duration.

Study regions: South American and Asian studies showed a trend of higher odds of all-cause mortality and mean length of stay than other region studies.

Types of suspected ADRs: Studies focusing on ADR_{In} showed a trend of higher odds of all-cause mortality [OR: 2.01 (95% CI: 1.68–2.42); $I^2=58\%$, $n=9$ vs. OR: 0.96 (95% CI: 0.72–1.27); $I^2=95\%$, $n=13$] and mean length of stay [MD: 7.13 (95% CI: 3.90–10.37); $I^2=99\%$, $n=16$ vs. OR: 0.58 (95% CI: −0.21 to 1.38); $I^2=91\%$, $n=14$] than studies focusing on $ADRA_d$ (Tables 3 and 4). Both groups showed high heterogeneity and differed in study characteristics.

Study duration: Longer duration (≥ 12 months) studies showed a trend of higher odds of all-cause mortality and mean length of stay than shorter duration (< 12 months) studies.

Sample size: Large sample size (≥ 1000) studies showed a trend of higher odds of all-cause mortality and mean length of stay than small sample size (< 1000) studies.

Study period: The study period showed different trends for all-cause mortality and hospital stay. Studies conducted 'before 2000' showed a trend of higher odds of all-cause mortality (Table 3), while studies conducted 'after 2010' showed a trend of longer length of stay (Table 4).

Meta-regression

The univariable analysis showed that all-cause mortality was higher in 'Medical and surgical wards, ICU' studies (regression coefficient: 1.37), ADR_{In} (regression coefficient: 0.89),

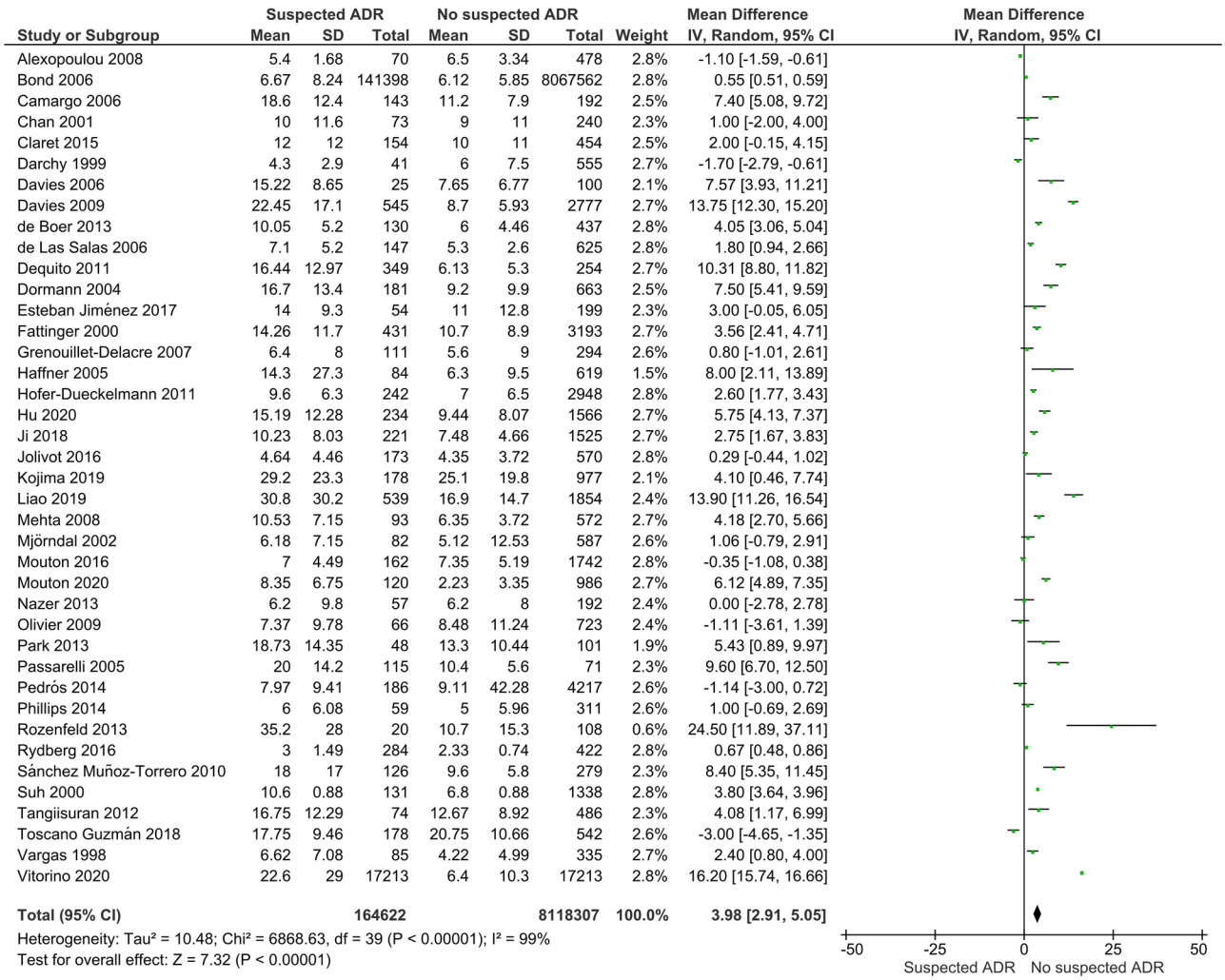

Fig. 3 Meta-analytic summary of the mean difference of length of stay through a random effect model

'ADR_{Ad} and ADR_{In}' studies (regression coefficient: 0.81) and large sample size studies (regression coefficient: 0.63). Study wards, types of suspected ADRs and sample size were further explored through a multivariable regression model. All three study characteristics were observed as significant predictors of all-cause mortality ($p < 0.05$) (Table 3).

The univariable analysis showed that length of stay was higher in 'multispecialty wards' (regression coefficient: 6.17), whole Hospital studies (regression coefficient: 4.39), ADR_{In} (regression coefficient: 6.28) and 'ADR_{Ad} and ADR_{In}' studies (regression coefficient: 4.29) and studies conducted between 2000 and 2010 (regression coefficient: 2.85). Study wards, types of suspected ADRs and study periods were further explored through a multivariable regression model. As shown in Table 4, types of suspected ADRs and study periods were observed as significant predictors of length of stay ($p < 0.05$).

Discussion

The findings of our meta-analysis suggest that suspected ADRs are significantly associated with the risk of mortality and length of stay in hospitalised patients. This is the first meta-analysis that reported odds of all-cause mortality and extra days of the length of hospital stay associated with suspected ADRs. All earlier meta-analyses had estimated the prevalence of suspected ADR-related mortality among inpatients [2, 6–11, 14]. None of them compared the odds of mortality and length of hospital stay between patients with suspected ADRs with those who did not develop suspected ADRs.

This meta-analysis presents two main findings. First, the odds of mortality in patients who had suspected ADRs is one and half times higher than those patients who did not have suspected ADRs during their hospitalisation. Second, patients who had suspected ADRs are 4 days likely to stay

Table 3 Subgroup, univariable and multivariable predictor analysis of the all-cause mortality data ($n=31$)

Variable	No	Subgroup analysis		Univariable			Multivariable		
		OR (95% CI)	I^2	Regression coefficient (95% CI)	SE	*p*-value	Regression coefficient (95% CI)	SE	*p*-value
Study design									
Prospective	15	1.32 [0.99, 1.74]	75	1	–	–	–	–	–
Retrospective	15	1.67 [1.25, 2.24]	100	0.31 (−0.16, 0.78);	0.24	0.195	NA	NA	NA
Prospective-retrospective	1	1.50 [0.33, 6.86]	–	0.30 (−3.13, 3.74)	1.75	0.862	NA	NA	NA
Age group									
Paediatric	1	1.50 [0.33, 6.86]	–	1	–	–	–	–	–
Adults and elderly	16	1.66 [1.08, 2.54]	89	−0.10 (−3.92, 3.72)	1.95	0.958	NA	NA	NA
Elderly	4	1.06 [0.74, 1.51]	94	−0.42 (−4.32, 3.48)	1.99	0.832	NA	NA	NA
All age	6	1.09 [0.52, 2.31]	100	−0.28 (−4.15, 3.59)	1.97	0.887	NA	NA	NA
Not specified	4	2.11 [1.26, 3.52]	100	0.71 (−3.23, 4.65)	2.01	0.724	NA	NA	NA
Study wards									
Internal medicine	5	1.35 [0.88, 2.06]	46	1	–	–	1	–	–
Multispecialty wards	4	1.54 [0.70, 3.42]	67	0.40 (−0.66, 1.45)	0.54	0.463	−0.08 (−0.94, 0.78)	0.44	0.857
Whole hospital	11	1.86 [1.35, 2.56]	100	0.46 (−0.27, 1.20)	0.37	0.214	−0.29 (−0.94, 0.36)	0.33	0.388
Intensive care units	4	1.05 [0.78, 1.40]	0	−0.15 (−1.03, 0.72)	0.45	0.731	1.06 (0.15, 1.96)	0.46	0.022
Emergency department	4	1.14 [0.99, 1.32]	0	−0.23 (−1.16, 0.71)	0.48	0.637	0.02 (−0.68, 0.73)	0.36	0.952
Paediatric ward and PICU	1	1.50 [0.33, 6.86]	–	0.34 (−3.31, 3.82)	1.77	0.847	−0.09 (−3.49, 3.31)	1.74	0.958
Medical and surgical wards, ICU	1	2.53 [1.88, 3.39]	–	1.37 (−0.04, 2.78)	0.72	0.057	0.13 (−1.09, 1.34)	0.62	0.837
Geriatric ward	1	0.64 [0.31, 1.34]	–	−0.52 (−1.82, 0.78)	0.66	0.434	−0.58 (−1.69, 0.52)	0.56	0.300
Study region									
Africa	4	1.20 [0.91, 1.60]	0	1	–	–	–	–	–
Asia	3	1.69 [1.05, 2.71]	79	0.46 (−0.65, 1.58)	0.57	0.415	NA	NA	NA
Europe	19	1.52 [1.04, 2.22]	99	0.14 (−0.72, 1.01)	0.44	0.747	NA	NA	NA
North America	4	1.35 [0.95, 1.92]	100	0.08 (−0.97, 1.13)	0.54	0.877	NA	NA	NA
South America	1	3.25 [1.04, 10.16]	–	2.03 (−2.75, 6.82)	2.44	0.405	NA	NA	NA
Types of ADRs									
ADR_{Ad}	13	0.96 [0.72, 1.27]	95	1	–	–	1	–	–
ADR_{In}	9	2.01 [1.68, 2.42]	58	0.89 (0.50, 1.28)	0.20	<0.01	1.27 (0.76, 1.78)	0.26	<0.01
ADR_{Ad} and ADR_{In}	4	1.82 [0.98, 3.40]	70	0.81 (0.27, 1.34)	0.27	0.003	1.26 (0.61, 1.90)	0.33	<0.01
Not specified	5	2.19 [1.57, 3.06]	100	0.36 (−0.11, 0.82)	0.24	0.131	0.46 (−0.09, 1.01)	0.28	0.100
Study duration									
Short (< 12 months)	15	1.41 [1.03, 1.94]	69	1	–	–	–	–	–
Long (≥ 12 months)	15	1.58 [1.20, 2.10]	100	0.23 (−0.25, 0.71)	0.25	0.346	NA	NA	NA
Not specified	1	0.40 [0.02, 6.72]	–	−0.83 (−4.35, 2.69)	1.79	0.644	NA	NA	NA
Sample size									
Small (< 1000)	13	1.15 [0.86, 1.53]	35	1	–	–	1	–	–
Large (≥ 1000)	18	1.67 [1.29, 2.17]	100	0.63 (0.13, 1.14)	0.26	0.014	1.18 (0.41, 1.95)	0.39	0.003
Study period									
Before 2000	4	2.05 [0.94, 4.46]	94	1	–	–	–	–	–
Between 2000 and 2010	14	1.23 [0.76, 1.99]	100	−0.53 (−1.87, 0.81)	0.68	0.437	NA	NA	NA
After 2010	8	1.76 [0.98, 3.18]	99	−0.33 (−1.78, 1.12)	0.74	0.658	NA	NA	NA
Overlapping/not specified period	5	1.46 [1.07, 2.00]	100	−0.34 (−1.89, 1.20)	0.79	0.664	NA	NA	NA

OR, odds ratio; *CI*, confidence interval; *SE*, standard error

Table 4 Subgroup, univariable and multivariable predictor analysis of the hospital stay ($n=40$)

Variable	No	Subgroup analysis		Univariable			Multivariable		
		MD (95% CI)	I^2	Regression coefficient (95% CI)	SE	*p*-value	Regression coefficient (95% CI)	SE	*p*-value
Study design									
Prospective	26	3.64 [2.46, 4.82]	97	1	–	–	–	–	–
Retrospective	13	4.62 [2.25, 6.99]	100	1.40 (−2.05, 4.85)	1.76	0.428	NA	NA	NA
Prospective-retrospective	1	6.12 [4.89, 7.35]	–	−0.42 (−7.41, 6.56)	3.56	0.906	NA	NA	NA
Age group									
Paediatric	4	4.00 [1.66, 6.34]	91	1	–	–	–	–	–
Adults and elderly	23	3.21 [2.01, 4.41]	97	−0.94 (−7.52, 5.64)	3.36	0.780	NA	NA	NA
Elderly	8	4.26 [0.20, 8.32]	96	−0.23 (−7.67, 7.21)	3.79	0.952	NA	NA	NA
All age	2	3.80 [3.64, 3.96]	0	0.06 (−10.50, 10.63)	5.39	0.991	NA	NA	NA
Not specified	3	8.11 [−4.39, 20.61]	100	3.62 (−5.59, 12.84)	4.70	0.441	NA	NA	NA
Study wards									
Internal medicine	11	3.49 [1.43, 5.55]	96	1	–	–	1	–	–
Paediatric ward	2	2.22 [1.29, 3.14]	45	−1.28 (−7.62, 5.07)	3.24	0.693	−5.06 (−13.60, 3.48)	4.36	0.245
Multispecialty wards	5	10.32 [4.50, 16.14]	98	6.17 (1.39, 10.95)	2.44	0.011	2.92 (−4.52, 10.37)	3.80	0.442
Whole hospital	5	7.94 [4.15, 11.74]	100	4.39 (−0.10, 8.88)	2.29	0.055	2.17 (−4.59, 8.93)	3.45	0.529
Intensive care units	6	0.67 [−0.75, 2.10]	80	−2.50 (−6.79, 1.80)	2.19	0.255	−1.42 (−7.11, 4.27)	2.90	0.625
Emergency department	5	0.45 [−0.42, 1.32]	44	−3.25 (−7.78, 1.27)	2.31	0.158	−2.71 (−8.72, 3.30)	3.06	0.377
Paediatric ward and PICU	2	6.20 [5.00, 7.40]	0	3.33 (−3.54, 10.19)	3.50	0.342	3.99 (−4.50, 12.48)	4.33	0.357
Internal medicine, ICU	1	1.06 [−0.79, 2.91]	–	−2.49 (−11.23, 6.25)	4.46	0.577	2.48 (−7.22, 12.19)	4.95	0.616
Geriatric ward	2	4.09 [1.81, 6.36]	0	0.54 (−6.18, 7.26)	3.43	0.875	−3.27 (−12.11, 5.56)	4.51	0.468
Surgical ward	1	4.05 [3.06, 5.04]	–	0.50 (−8.10, 9.10)	4.39	0.909	−4.19 (−14.88, 6.486)	5.45	0.441
Study region									
Africa	4	4.27 [0.37, 8.18]	97	1	–	–	–	–	–
Asia	6	5.31 [1.89, 8.73]	93	1.04 (−4.11, 6.19)	2.63	0.693	NA	NA	NA
Australia	2	1.00 [−0.47, 2.47]	0	−3.27 (−10.18, 3.64)	3.52	0.353	NA	NA	NA
Europe	23	3.79 [1.13, 6.46]	100	−0.53 (−4.78, 3.73)	2.17	0.808	NA	NA	NA
North America	2	2.17 [−1.01, 5.36]	100	−2.10 (−8.79, 4.60)	3.42	0.539	NA	NA	NA
South America	3	9.42 [1.48, 17.35]	95	3.61 (−2.95, 10.16)	3.34	0.281	NA	NA	NA
Types of ADRs									
ADR_{Ad}	14	0.58 [−0.21, 1.38]	91	1	–	–	1	–	–
ADR_{In}	16	7.13 [3.90, 10.37]	99	6.28 (2.97, 9.58)	1.69	<0.001	6.08 (1.29, 10.86)	2.44	0.013
ADR_{Ad} and ADR_{In}	8	4.91 [2.09, 7.74]	93	4.29 (0.27, 8.32)	2.05	0.036	3.37 (−1.88, 8.62)	2.68	0.208
Not specified	2	3.36 [−2.12, 8.85]	99	2.64 (−4.00, 9.27)	3.38	0.436	0.78 (−7.79, 9.36)	4.38	0.858
Study duration									
Short (<12 months)	28	3.26 [2.22, 4.31]	98	1	–	–	–	–	–
Long (≥12 months)	12	5.44 [0.99, 9.89]	100	1.89 (−1.31, 5.09)	1.63	0247	NA	NA	NA
Sample size									
Small (<1000)	27	3.02 [2.01, 4.03]	95	1	–	–	–	–	–
Large (≥1000)	13	5.48 [3.18, 7.77]	100	2.17 (−0.49, 4.84)	1.36	0.109	NA	NA	NA
Study period									
Before 2000	7	1.55 [−0.21, 3.32]	100	1	–	–	1	–	–
Between 2000 and 2010	21	4.35 [2.88, 5.81]	97	2.85 (−0.18, 5.89)	1.55	0.065	3.59 (−1.11, 8.29)	2.40	0.135
After 2010	9	4.07 [−1.88, 10.03]	100	2.19 (−1.20, 5.59)	1.73	0.206	1.76 (−2.79, 6.32)	2.32	0.447
Overlapping/not specified period	3	7.15 [−0.89, 15.20]	98	9.08 (3.43, 14.73)	2.88	0.002	8.01 (0.71, 15.32)	3.73	0.032

MD mean difference, *CI* confidence interval, *SE* standard error

more in the hospital than those patients who did not have suspected ADRs during their hospital stay.. This suggests prevention of ADRs will significantly reduce the burden on the patient and hospital. A sizable proportion of inpatients develops suspected ADRs during their hospitalisation. Earlier meta-analyses suggest one out of five to seven patients had ADRs during their hospitalisation [4, 5]. Almost half of suspected ADRs among inpatients are preventable [73, 74].

Study wards, types of suspected ADRs and sample size could accurately predict higher odds of all-cause mortality in patients having suspected ADRs. An earlier meta-analysis observed study wards were a significant predictor of the percentage of drug-related deaths out of the total inpatient mortality [11]. Panagioti et al. observed medical care settings (general hospitals, primary and advanced hospital specialities) as a significant predictor of the prevalence of preventable patient harm in medical care [17]. However, Martins et al. in an earlier meta-analysis did not find any study characteristics as a significant predictor of the percentage of suspected ADRs among adults [75]. The predictor of heterogeneity among meta-analysis of suspected ADR studies could be varied depending upon the variability in the study population (all age vs adults), the denominator (all inpatients vs inpatient deaths) and types of suspected ADRs (all suspected ADRs vs preventable adverse events). The preventive strategies should focus on all these factors to identify the priority areas.

One of the important findings of this meta-analysis is the difference in the impact of types of suspected ADRs based on their origin in outpatient (ADR_{Ad}) or inpatient settings (ADR_{In}) on all-cause mortality and length of hospital stay. The patients who experienced ADR_{In} had two times higher odds of all-cause mortality and 7 days higher length of hospital stay than those patients who did not experience ADR_{In}. All-cause of mortality and length of stay do not differ between patients who were admitted due to ADRs and other disease conditions. This could be because of circumstances involved in the occurrence of ADRs based on the setting and the need for different preventive strategies for ADR_{Ad} and ADR_{In}.

Sample size rather than study design (prospective or retrospective) is an important factor in assessing suspected ADR-related all-cause mortality. Large (≥ 1000) sample size studies had shown significantly higher odds of mortality than the small sample size (< 1000) studies. Small sample studies do not yield precise or reliable effect size estimates [76, 77]. Our findings suggest suspected ADR-related all-cause mortality data should be cautiously interpreted from the small sample size studies. We did not observe the impact of study design (prospective or retrospective) on all all-cause mortality and length of hospital stay. Seven out of fifteen retrospective and one out of fifteen prospective studies had large sample sizes.

Though the trend of all-cause mortality has reduced in studies conducted in the twenty-first century over the twentieth century, the pattern of a rising trend in hospital stay in the last two decades should be of concern. Patients experiencing a suspected ADR during hospitalisation stay 4 days longer in the hospital. This is important because the extra length of stay contributes to the economic burden on the patients [78]. Higher hospital stay enhances the risk of opportunistic infections, worse treatment outcomes and the economic burden on the patients. Higher stay decreases the bed turnover rate, which can reduce the profit margin and enhance the social costs [79, 80]. Suspected ADRs are a significant burden to patients and healthcare systems.

The study admission wards are the important predictors of suspected ADR-related mortality. Patients admitted to the whole hospital and 'medical and surgical wards and ICU' experienced higher odds of mortality in the suspected ADR arm. Patients experiencing suspected ADRs had more than 5 days of additional hospital stay in studies conducted in the whole hospital, multispeciality wards, paediatric wards and PICU. There is a critical need to understand the nature of suspected ADRs and their unique complexities in different admission wards to provide safe patient care. An earlier meta-analysis has shown that pharmacist-led interventions, a brief educational session and a technology intervention could significantly reduce the risk of acquiring serious ADRs [81–83]. Such interventions should be validated in different admission wards and settings to devise the best ADR preventive strategies to reduce the mortality and length of hospital stay. Patients admitted to ICUs are considered most at risk of errors and adverse outcomes [84]. ICUs and emergency department studies did not show high mortality and longer lengths of stay due to suspected ADRs. This could be because four out of six ICU and seven out of eight emergency department studies focused on ADR_{Ad}.

This meta-analysis has several limitations. The definition of suspected ADRs varied among the included studies. Studies that followed the WHO definition could have excluded medication errors and unintentional drug overdoses related to ADRs. Edwards and Aaronson Edwards and Aaronson's ADR definition includes ADRs at therapeutic doses and medication errors. This definition also covers reactions related to excipients. ICD-9 E code–based studies could have included ADRs at therapeutic doses, accidental overdoses and poisoning. Few studies also included non-compliance as a suspected ADR. We could not assess the impact of a computerised medical record system as a data collection tool due to the few numbers of included studies. Twelve out of thirty-one included studies in all-cause mortality outcome assessment did not specify the causality assessment methods between suspected ADRs and suspected drugs. However, we did not observe its impact on sensitivity analysis after excluding these studies on sensitivity analysis. All-cause mortality and

length of hospital stay varied among included studies. Meta-regression and subgroup analyses could only partially explain the variability in the estimation of the length of stay. There is a possibility that other relevant factors could also account for the unexplained heterogeneity. Both outcomes could have been affected by the underlying condition for admission, its severity and co-morbidity. The findings of subgroup analysis and meta-regression require cautious interpretation due to the small number of studies on each characteristic.

Conclusion

Patients having suspected ADRs in the hospital setting are at increased risk of all-cause mortality and longer hospital stay than those who did not experience suspected ADRs. Study wards, types of suspected ADRs and sample size are heterogeneity modifiers in the case of all-cause mortality, while types of suspected ADRs and admission wards are heterogeneity modifiers in the case of length of hospital stay.

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Author contribution TKP contributed to all aspects of this manuscript, including conception and design; acquisition, analysis, interpretation of data and drafting of the manuscript. PBP contributed to the design, acquisition, analysis and interpretation of data. HLB contributed to the analysis, interpretation of data and drafting of the manuscript. PD, VB and SK contributed to the interpretation of data and drafting of the manuscript.

Data availability The study data are included in the main text/supplementary data file; further inquiries can be directed to the corresponding author.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

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