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REVIEW

Hospitalizations due to preventable adverse reactions—a systematic review

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Abstract
Purpose The study aimed to measure the percentage of preventable adverse drug reactions that lead to the hospitalization ($PADR_{Ad}$) and to explore the heterogeneity in its estimation through subgroup analysis of study characteristics.
Methods Two investigators independently searched in electronic databases and related bibliography for prospective studies involving $PADR_{Ad}$. We excluded studies investigating medication errors and spontaneous and retrospective reporting. The primary outcome was $PADR_{Ad}$ percentage. To explore the heterogeneity, we performed subgroup analysis based on study region, wards, age groups, adverse drug reaction (ADR) definitions, preventability assessment, ADR identification methods, study duration and sample size. We explored fatal $PADR_{Ad}$ and causative drugs as a secondary outcome. We used the generic inverse variance method with random effect model to compute meta-analytic summary.
Results Of the 68 full-text articles assessed, we included 22 studies. The mean $PADR_{Ad}$ percentage was 45.11 % (95 % CI = 33.06–57.15; I^2 = 99 %). Studies including elderly (63.31 %) and all age groups (49.03 %) showed higher percentages than paediatric population (16.40 %). Studies examining all hospital populations showed higher percentages than specific wards. We observed high percentages in studies using Edwards and Aronson as an ADR definition and Hallas et al. as a preventability assessment tool. After age group adjustment, ADR detection methods did not show significant difference. The fatal $PADR_{Ad}$ percentage was 1.58 % (95 % CI = −0.60 to 3.76; I^2 = 47 %). Paediatric and elderly studies showed a different causative drug pattern.
Conclusion Variation in $PADR_{Ad}$ across the studies can be explained by difference in study populations and data collection methods. Extrapolation of preventable reactions should be carried out considering all these factors with caution.

Keywords Adverse drug reaction · Hospital · Preventable · Fatal reaction · Systematic review

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Introduction

Drug-related problems are important public health problems. They include adverse drug reactions (ADRs), inappropriate drug selection, drug use without indications, non-compliance, drug interactions and use of subtherapeutic and supratherapeutic dosage [1]. ADRs are an important cause of hospital admissions [2, 3]. They account for almost two thirds of all drug-related hospital admissions and emergency

department visits [4, 5]. Beijer et al. estimated 4.9 % (range = 0.2–41.3 %) of hospital admissions were due to ADRs. The authors observed about 30 % ADRs as preventable [6]. Leendertse et al. observed low weighted mean prevalence (0.46 %) for drug-related hospitalization. The authors observed variations in prevalence based on study setting, population and data collection methods. So, many characteristics of the study can influence the ADR prevalence [7].

In an earlier systematic review, Hakkarainen et al. observed 52 and 45 % of ADRs were preventable among outpatients and inpatients, respectively [8]. ADRs resulting in hospital admission (ADR_{Ad}) generally represent more severe reactions than ADRs occurring during hospitalization (ADR_{In}) and are one of the leading causes of death in the population [4, 9, 10]. Preventable ADRs cause unnecessary loss of health, quality of life and money [6]. Earlier systematic reviews of preventable ADRs considered both prospective and retrospective studies and did not investigate the heterogeneity for the various study characteristics like population, data collection methods, etc. [6, 8]. So, we conducted this updated systematic review to measure the percentage of preventable ADR_{Ad} ($PADR_{Ad}$) among the prospective studies and to explore the heterogeneity in its estimation based on study characteristics.

Materials and methods

Search strategy

Two investigators independently searched in electronic databases (PubMed, Google Scholar and Cochrane Database of Systematic Reviews). PubMed searches only journals, while Google Scholar searches all internet resources [11]. PubMed database searches abstract, while Google Scholar searches the full text to retrieve the articles. So, we choose different search terms for PubMed and Google Scholar. We used synonyms and truncation in PubMed search only. The key terms of PubMed search were 'adverse drug reaction' OR 'adverse drug event' OR 'adverse reaction' OR 'adverse event' OR 'drug related problem' OR 'drug induced problem' AND ('avoid*' OR 'prevent*') AND hospital*. The key terms of Google Scholar search were 'Adverse drug reaction' AND 'Preventable' AND 'Hospitalization'. We also searched the bibliographies of relevant articles. We only searched English language articles. We searched the studies published between January 2000 and June 2015 for review (last search on 18 June 2015).

We assessed title, abstract and if necessary full-text articles from retrieving references according to selection criteria. Any disagreement between the two investigators was discussed and resolved by consensus or by a third investigator.

Selection criteria

We included all prospective studies related to ADRs that provide sufficient data to calculate $PADR_{Ad}$. All studies should have identified ADR_{Ad} through WHO or "Edwards and Aronson" [12] or other similar definitions and specified preventability assessment tools. We excluded studies of retrospective or spontaneous reporting design; those did not differentiate ADRs from adverse drug events or medication errors; considered all augmented reactions as preventable without applying specified measurement tools; and focused on particular reactions or specific drug exposure only. Detailed selection criteria are in Supplementary file 1.

Data extraction

We extracted the following information from each study in Excel sheet: study year, its duration, number of the study centre, level of care provided by a hospital, study specific departments, region, country, demographic data, ADR definition used, total number of patients studied, number of patients with ADR_{Ad}, number of preventable ADR_{Ad}, fatal reactions, causative drugs, causality, preventability and severity. Two investigators cross checked the accuracy of data entry. We assessed the methodological quality of the included studies as per Smyth et al. considering study design, methods for identifying ADRs, causality, preventability and severity assessment [13].

Primary outcome assessment

The primary outcome was to assess the percentage of $PADR_{Ad}$. We used an Excel sheet to estimate $PADR_{Ad}$ percentage and its standard error (SE). Based on an expectation of high heterogeneity from earlier ADR-related studies, we used generic inverse variance method with random effect model to calculate mean $PADR_{Ad}$ percentage and its 95 % confidence interval [14]. There is no ideal approach in the presence of high heterogeneity. We selected random effect model which incorporates heterogeneity in overall analysis of effects and gives a more conservative estimate with wider confidence intervals. We assessed the heterogeneity for the percentage of $PADR_{Ad}$ using I^2 test—25 % as low, 50 % moderate and 75 % as high [15]. We observed high heterogeneity for the percentage of $PADR_{Ad}$ (I^2 = 99 %).

Subgroup analysis of primary outcome assessment

To explore the heterogeneity, we did the subgroup analysis of primary outcome based on the study characteristics like study population (region, wards, age groups), data collection methods (ADR definition, preventability assessment tools, ADR identification method), study duration (≤3, 4–11 and

≥12 months) and sample size (<1000 and ≥1000 patients). Study region was based on continents. Study ward includes admission wards. Age group includes paediatric, elderly and all age groups. We considered Karch and Lasagna definition similar to WHO definition [16]. The ADR identification method includes a medical record review or combined approach (interview plus medical record review). Detailed study characteristics for subgroup analysis are in Supplementary file 2.

Based on the results of subgroup analysis, we again explored the percentage of $PADR_{Ad}$ in 'all age group studies' for the different study characteristics.

Secondary outcome assessments

Prevalence of $PADR_{Ad}$ and fatal ADR_{Ad} We used number of patients with $PADR_{Ad}$ as numerator and total number of hospitalized patients as denominator to calculate prevalence from each study. We used an Excel sheet to estimate the $PADR_{Ad}$ prevalence, percentage of fatal ADR_{Ad}, preventable fatal ADR_{Ad} and their SE through Excel sheet. We used generic inverse variance method with random effect model to compute meta-analytic summary and its 95 % confidence interval. We assessed the heterogeneity using I^2 test.

Suspected drugs We extracted the causative drugs of PADRAd and summarized using absolute numbers of cases and percentage. We labelled the causative drugs as per anatomical therapeutic chemical classification system [17]. We also presented the data of causative drugs from paediatric and elderly studies separately.

The meta-analysis was performed through 'Review manager software version 5.0'.

Results

Literature search

As shown in Fig. 1, we evaluated a total of 68 full-text articles as per selection criteria and included 22 studies.

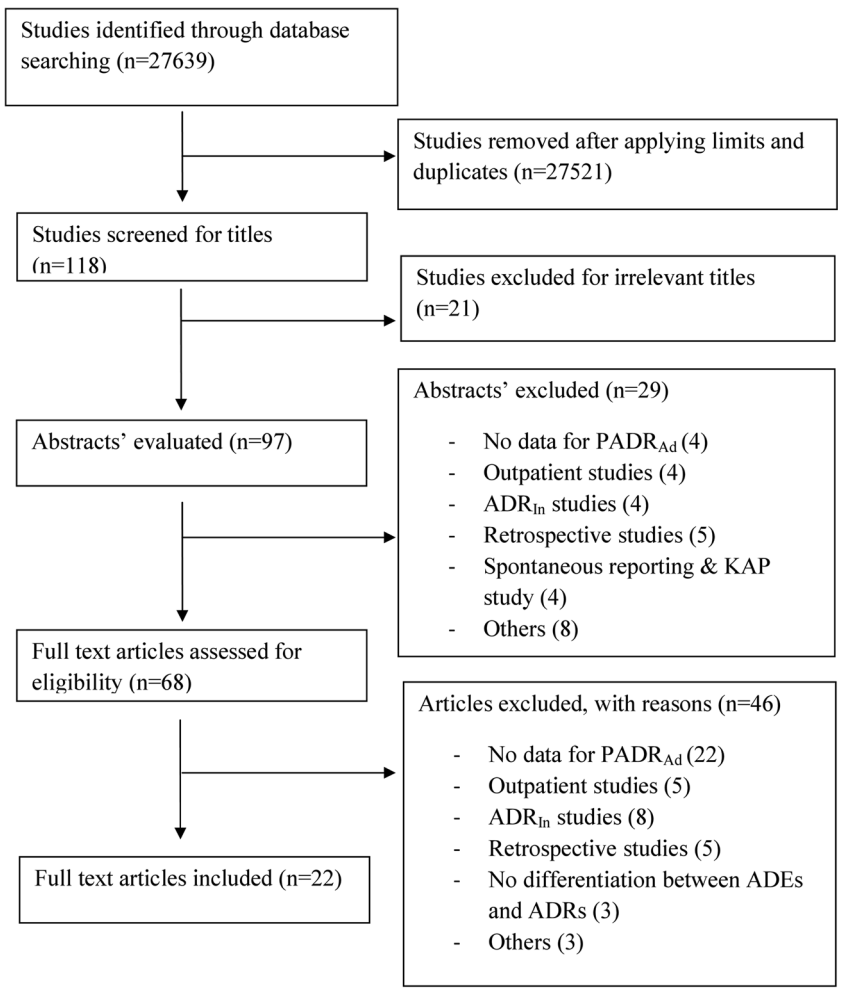

Fig. 1 Data extraction and study selection process. Abbreviations are as follows: *ADRs* adverse drug reactions; *ADEs* adverse drug events; ADR_{In} ADRs occurring during hospitalization; $PADR_{Ad}$ preventable ADRs resulting in hospital admission

Characteristics and methodological quality of the included studies

Table 1 shows the characteristics of all included studies [18–39]. Two studies included both ADR_{Ad} and ADR_{In} data [24, 25]. Chan et al. studied adverse drug event. Easton et al. and Al-Arifi et al. analysed all drug-related problems. We only included ADR_{Ad} data of these studies. Two studies included ADR_{Ad} and ADRs concurrently present during admission [23, 24]. We only extracted ADR_{Ad} data. Fourteen studies identified ADRs using WHO definition. Doshi et al. communicated use of WHO definition on contact of our previous systematic review [25]. One study used Karch and Lasagna ADR definition [20]. Six studies used Edwards and Aronson ADR definition. The studies detected ADRs using interview (one study), medical record review (nine studies) and combined approach (ten studies). Two studies did not state the methods used to detect ADRs [25, 31]. Total 21 studies used the causality assessment. The preventability assessment tools used were Schumock and Thornton (eight studies), Hallas et al. (nine studies), French ADR preventability scale (two studies), Nelson and Talbert (one study), Nebeker et al. (one study) and Livio et al. (one study). Detailed study characteristics of included studies according to age are presented in Supplementary file 3.

Prevalence of $PADR_{Ad}$

Among the 15 studies [18–20, 24, 26–28, 31, 32, 34–39], 3948 out of 95,278 patients were admitted due to $PADR_{Ad}$. The number of patients hospitalized due to $PADR_{Ad}$ varied from 2 to 1852 in the included studies. The $PADR_{Ad}$ prevalence varied from 0.10 to 6.41 %. The mean $PADR_{Ad}$ prevalence was 2.45 % (95 % CI = 1.77–3.12 %; I^2 = 99 %) (Supplementary Fig. 1).

Percentage of $PADR_{Ad}$

In 22 included studies, a total 4797 ADR_{Ad} observed in 4462 patients and 1886 were reported as preventable. The $PADR_{Ad}$ percentage varied from 4.26 to 83.33 %. The mean percentage of $PADR_{Ad}$ was 45.11 % (95 % CI = 33.06–57.15; I^2 = 99 %) (Fig. 2).

Subgroup analysis of the percentage of $PADR_{Ad}$ based on the study characteristics

Based on the findings of subgroup analysis of study characteristics, we identified age group as a most important heterogeneity modifier. As shown in Fig. 3, age group showed important influence on $PADR_{Ad}$ percentage ranging from 16.40 (paediatric population) to 63.31 (elderly population). So, we further compared the study characteristics by adjusting the age groups.

Age groups

As shown in Table 2, paediatric age group studies showed a low $PADR_{Ad}$ percentage (16.40 %) and high heterogeneity (I^2 = 87 %). Two paediatric studies used Hallas et al. preventability tool and Edwards and Aronson definition. By combining these studies, we observed relatively high percentage and reduction in the heterogeneity [24.67 % (95 % CI = 15.38–34.14), I^2 = 37 %]. Other two paediatric studies used Schumock and Thornton algorithm and WHO definition. By combining these studies, we observed relatively low percentage and reduction in the heterogeneity [5.76 % (95 % CI = 0.10–11.43), I^2 = 0 %] (Supplementary Fig. 2).

Elderly studies showed a high $PADR_{Ad}$ percentage (63.31 %) and heterogeneity (I^2 = 91 %). Both elderly studies used Hallas et al. preventability tool. We could not explore it further due to the presence of only two studies in elderly group.

All age group studies showed high $PADR_{Ad}$ percentage (49.03 %) and heterogeneity (I^2 = 96 %). As shown in Table 2, we explored all age group studies for each study characteristics and described its finding along with each characteristic description.

Study wards

Whole hospital studies (61.65 %) showed a high $PADR_{Ad}$ percentage followed by emergency department studies (42.45 %) and internal medicine (40.24 %). Like age group, paediatric ward studies (12.46 %) showed a low $PADR_{Ad}$ percentage.

Adjustment for age groups

All age group studies showed similar patterns in percentage of $PADR_{Ad}$. Internal medicine studies showed low heterogeneity (I^2 = 0 %). Their other similar characteristics were WHO definition, all age groups and no study of less than 3 months duration. We also observed a reduction in heterogeneity in emergency studies (I^2 = 42 %). Their other similar characteristic was WHO definition (Fig. 4).

Study regions

European (44.37 %) and Asian studies (45.38 %) showed comparable percentages of $PADR_{Ad}$. Asian studies showed low heterogeneity (I^2 = 0 %). Their other common characteristic was WHO definition. However, Australian studies showed lower prevalence (29.34 %) and high heterogeneity (I^2 = 94 %). Both Australian studies used the WHO definition.

Adjustment for age groups

Table 1 General characteristic of the included studies on ADRs

Study	Study region	Study duration (months)	Study ward	Study population	ADR identification method	ADR def. used	Preventability	Total study sample	% of $PADR_{Ad}$
Ahern et al. [18]	Europe	1	ED	NS	MRR	WHO	Hallas et al.	856	57.33
Alexopoulou et al. [19].	Europe	6	IM	15–100	I, MRR	WHO	Hallas et al.	548	40.54
Al-Arifi et al. [20]	Asia	1	ED	<12 to >65	I, MRR	Karch and Lasagna	Nelson and Talbert	300	52.94
Chan et al. [21]	Australia	2	ED	≥75	I	WHO	Hallas et al.	240	48.84
Davies et al. [22]	Europe	12	WH	NS	MRR	Edwards and Aronson	Hallas et al.	403	57.14
Dormann et al. [23]	Europe	13	IM	17–97	MRR	WHO	Schumok and Thronton	915	44.44
Dormann et al. [24]	Europe	18	IM	18–97	MRR	WHO	Schumok and Thronton	844	50.00
Doshi et al. [25]	Asia	18	IM	NS	NS	WHO	Schumok and Thronton	6601	42.22
Easton et al. [26]	Australia	5.5	PD	≤17	MRR	WHO	Schumok and Thronton	2933	10.34
Fransceschi et al. [27]	Europe	14	GD	≥65	I, MRR	Edwards and Aronson	Hallas et al.	1756	76.47
Gallagher et al. [28]	Europe	0.5	ED	Paediatrics	I, MRR	Edwards and Aronson	Hallas et al.	822	33.33
Gallagher et al. [29]	Europe	12	PD	Paediatrics	I, MRR	Edwards and Aronson	Hallas et al.	6821	22.09
Grenouillet et al. [30]	Europe	6	MICU	>15	I, MRR	Edwards and Aronson	Nebeker et al., Cullen et al.	405	47.73
Hopf et al. [31]	Europe	0.5	WH	>16	NS	WHO	Hallas et al.	1101	83.33
Bénard-Laribière et al. [32]	Europe	7	IM	≤15 to ≥75	MRR	WHO	French preventability scale	2692	48.45
Olivier et al. [33]	Europe	4	ED	>15	MRR	WHO	French preventability scale	671	34.09
Pirmohamed et al. [34]	Europe	6	WH	>16	I, MRR	Edwards and Aronson	Hallas et al.	18,820	71.84
Posthumus et al. [35]	Europe	5	PD	0–18	I, MRR	WHO	Schumok and Thronton	683	4.26
Rottenkolber et al. [36]	Europe	6	IM	NS	MRR	WHO	Schumok and Thronton	57,000	18.06
Rivkin et al. [37]	North America	6	MICU and IM	NS	MRR	WHO	Schumok and Thronton	281	85.71
Ruiz et al. [38]	Europe	21	WH	≤50 to >80	I, MRR	WHO	Schumok and Thronton	1802	34.57
Wasserfallen et al. [39]	Europe	6	ED	16–93	I, MRR	WHO	Livio et al.	4840	31.88

$PADR_{Ad}$ preventable ADR leads to hospitalization, *NS* not stated, *MICU* medical intensive care unit, *ED* emergency department, *WH* whole hospital, *PD* paediatric department, *GD* geriatric department, *IM* internal medicine, *I* interview, *MRR* medical record review, *WHO* World Health Organization

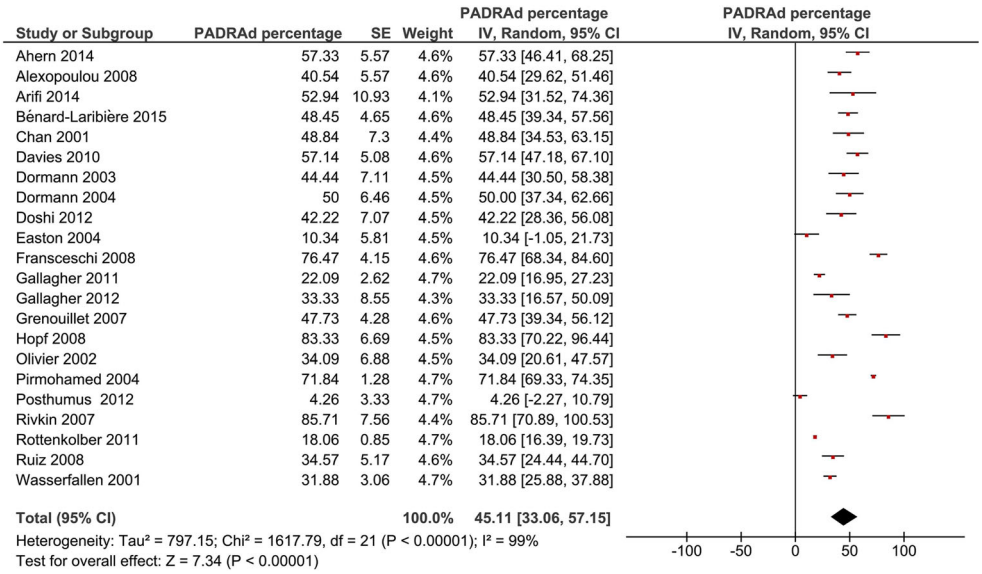

Fig. 2 Meta-analytic summary of percentage of $PADR_{Ad}$. Abbreviation is as follows: *$PADR_{Ad}$* preventable ADRs resulting in hospital admission

There is no effect of adjustment of age group in European studies on $PADR_{Ad}$ (Supplementary Fig. 3).

ADR definition

We observed a slightly high $PADR_{Ad}$ percentage in studies using Edwards and Aronson (51.66 %) than WHO (42.32 %) definition. This trend continues in all age group studies (60.13 vs. 46.13 %; $I^2 \geq 86$ %) (Supplementary Fig. 4).

Preventability assessment tools

Hallas et al. (54.65 %) showed a high $PADR_{Ad}$ percentage followed by French preventability scale (42.17 %) and Schumock and Thornton algorithm (35.25 %).

Adjustment for age groups

We observed a high percentage in Hallas et al. (65.21 %) group. All three studies of Hallas et al. group were of the European continent. Two of them belonged to whole hospital setup and two used WHO definition. Both Schumock and

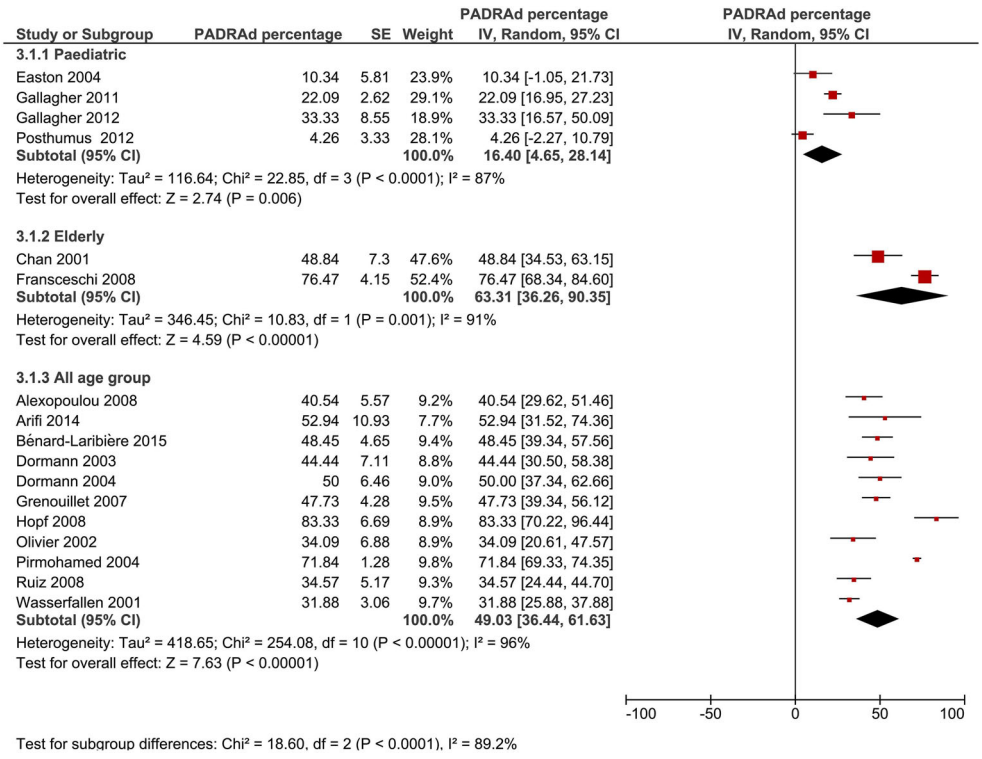

Fig. 3 Meta-analytic summary of percentage of $PADR_{Ad}$ according to age. Abbreviation is as follows: *$PADR_{Ad}$* preventable ADRs resulting in hospital admission

Table 2 Subgroup analysis of $PADR_{Ad}$ percentage

	All studies Mean (95 % CI)	I^2		All age group studies Mean (95 % CI)	I^2	No.
Age groups						
Paediatrics	16.40 (4.65, 28.14)	87	4	–	–	–
Elderly	63.31 (36.26, 90.35)	91	2	–	–	–
All age group	49.03 (36.44, 61.63)	96	11	49.03 (36.44, 61.63)	96	11
Study wards						
Internal medicine	40.24 (24.60, 55.88)	95	6	46.02 (40.41, 51.63)	0	4
Emergency	42.45 (32.14, 52.75)	76	6	35.63 (26.42, 44.84)	42	3
Paediatric	12.46 (−0.14, 25.06)	89	3	–	–	–
Whole hospital	61.65 (43.61, 79.68)	95	4	63.16 (38.33, 88.00)	96	3
Study region						
Europe	44.37 (30.58, 58.16)	99	17	48.71 (35.46, 61.96)	96	10
Asia	45.38 (33.75, 57.02)	0	2	52.94 (31.52, 74.36)	–	1
Australia	29.34 (−8.39, 67.06)	94	2	–	–	–
ADR definition						
WHO	42.32 (32.12, 52.52)	96	16	46.13 (36.26, 56.00)	86	9
Edwards and Aronson	51.66 (30.70, 72.61)	98	6	60.13 (36.51, 83.75)	97	2
Preventability assessment methods						
Schumock and Thornton	35.25 (21.80,48.71)	96	8	42.28 (32.75, 51.81)	46	3
Hallas et al.	54.65 (38.22, 71.09)	98	9	65.21 (44.52, 85.90)	94	3
French preventability scale	42.17 (28.20, 56.13)	67	2	42.17 (28.20, 56.13)	67	2
ADR identification method						
Interview			1			
MRR	44.77 (28.70, 60.85)	97	9	45.11 (38.52, 51.70)	18	4
Combined approach (interview and MRR)	41.50 (23.22, 59.78)	99	10	46.56 (27.67, 65.45)	98	6
Study duration						
<3 months	55.66 (39.44, 71.89)	84	5	69.36 (39.68, 99.05)	82	2
4–11 months	39.15 (19.63, 58.68)	99	10	45.99 (28.13, 63.85)	98	6
≥12 months	46.68 (29.41, 63.94)	96	7	42.28 (32.75, 51.81)	46	3
Sample size						
<1000	46.11 (32.57, 59.66)	94	12	44.69 (39.79, 49.59)	0	6
>1000	45.21 (23.93, 66.48)	99	10	53.85 (32.81, 74.90)	98	5

$PADR_{Ad}$ preventable ADR leads to hospitalization, *CI* confidence interval, *MRR* medical record review

Thornton algorithm (42.28 %) and French preventability scale (42.17 %) showed comparable percentage. We also observed moderate heterogeneity in Schumock and Thornton algorithm group. Their other similar characteristics were European continent, WHO definition and study duration >12 months. Similar characteristics of French preventability scale studies were European continent, WHO definition, medical record review and study duration 4–11 months (Fig. 5).

ADR identification method

We observed comparable $PADR_{Ad}$ percentage between studies using medical record review and combined approach (interview plus medical record review). We observed similar trend in percentage in all age group studies.

However, we observed significant reduction in heterogeneity in studies using medical record review (I^2 = 18 %). Their similar characteristics were European continent and WHO definition (Supplementary Fig. 5).

Findings of study duration and sample size along with their inference are presented in a Supplementary file 4.

Fatal reactions

Ten out of 21 included studies mentioned the number of fatal reactions [21–23, 30–32, 34, 36, 37, 39], 4 out of 21 studies mentioned zero fatal reactions [25, 28, 29, 33] and 4 out of 8 studies mentioned data about preventable fatal reactions [21, 22, 31, 37]. The meta-analytic summary percentage of fatal reactions was 2.69 % [(95 %

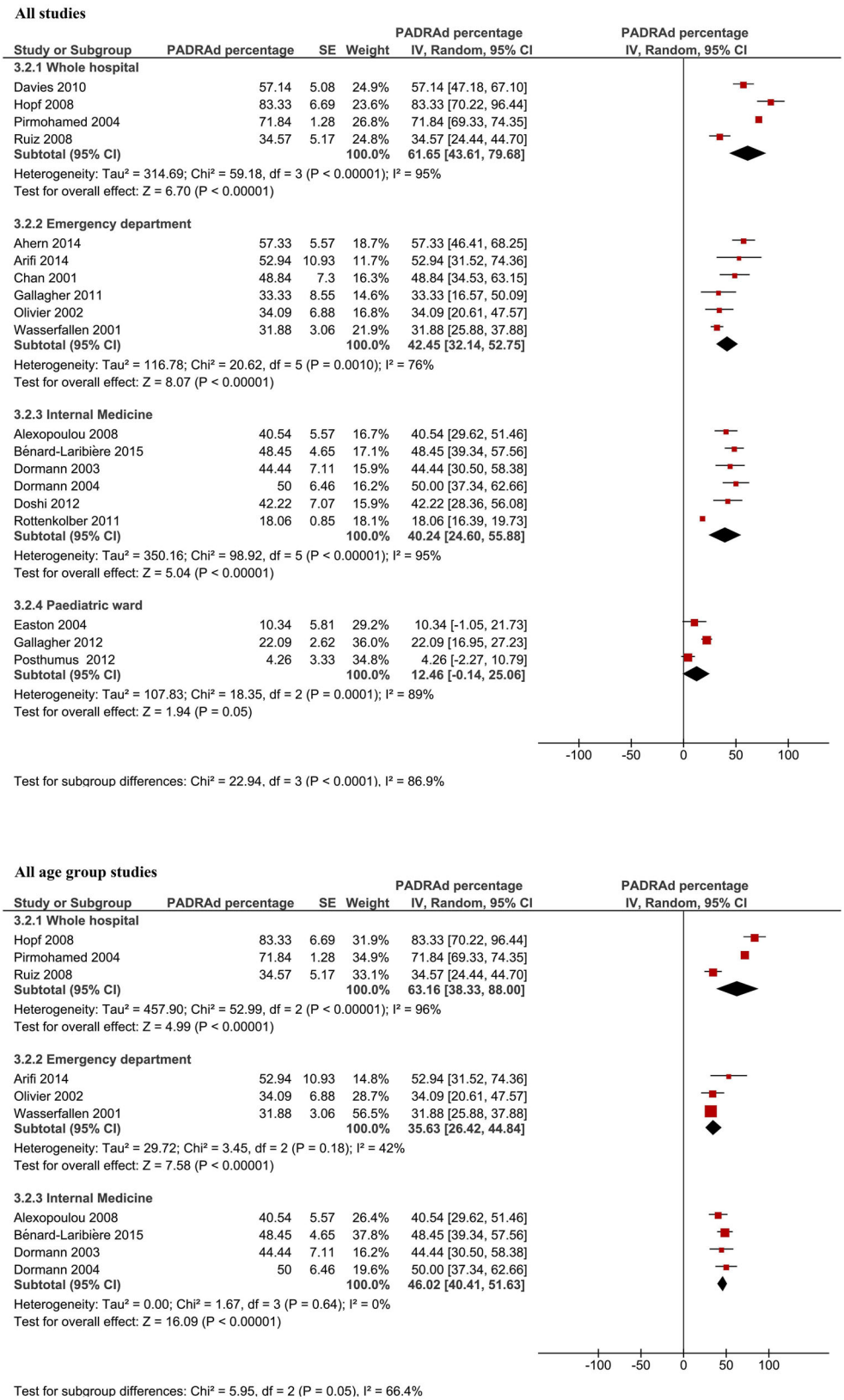

Fig. 4 Meta-analytic summary of subgroup analysis of percentage of $PADR_{Ad}$ according to study wards. Abbreviation is as follows: *$PADR_{Ad}$* preventable ADRs resulting in hospital admission

CI = 1.32–4.06 %), I^2 = 82 %]. The percentage of preventable fatal reactions was 1.58 % (95 % CI = –0.60 to 3.76) with moderate heterogeneity (I^2 = 47 %) (Supplementary Fig. 6).

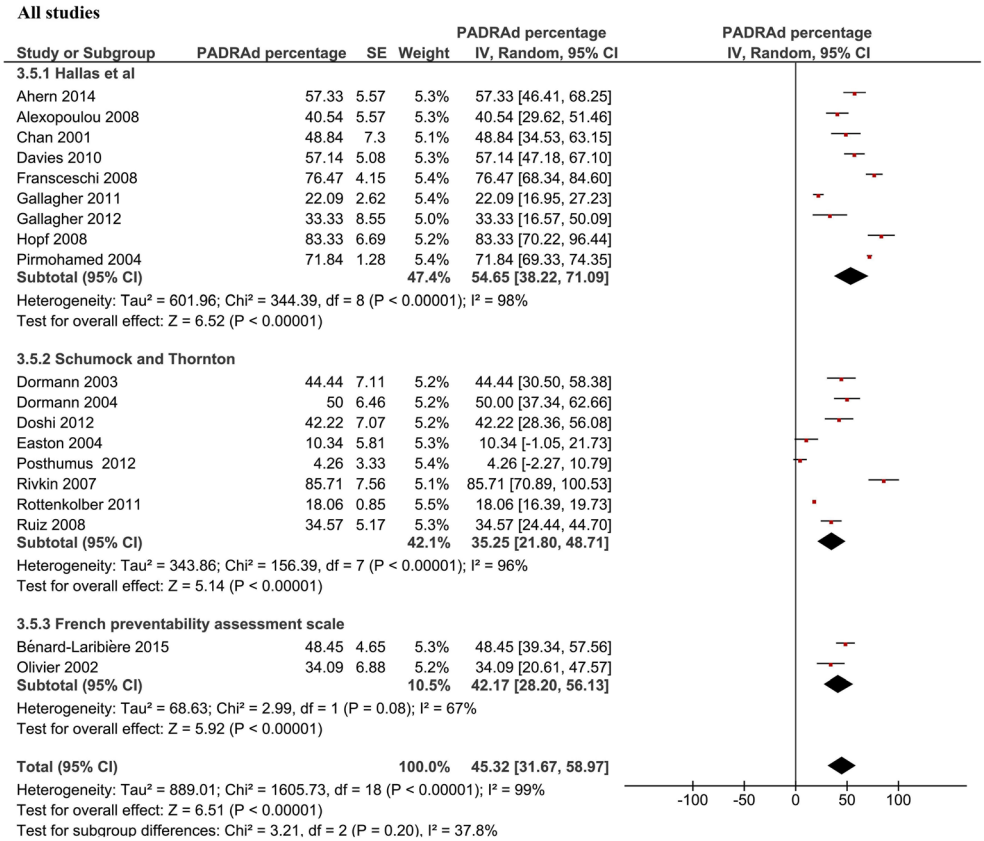

Fig. 5 Meta-analytic summary of subgroup analysis of percentage of $PADR_{Ad}$ according to preventability assessment tools. Abbreviation is as follows: *$PADR_{Ad}$* preventable ADRs resulting in hospital admission

Suspected drugs

Nine studies mentioned the drugs causing $PADR_{Ad}$ [27, 29–31, 33, 35, 37–39]. We observed cardiovascular drugs in one fourth of cases. Other major incriminated groups were musculoskeletal (16.13 %) and nervous system (16.89 %). Commonly implicated drugs were non-steroidal anti-inflammatory drugs (NSAIDs) (16.13 %), antithrombotics (12.14 %), cardiac glycosides (9.87 %) and diuretics (7.97 %). Paediatric and elderly studies showed a different

causative drug pattern. Nervous system (25 %) and alimentary tract and metabolism (25 %) were major causative class in paediatric studies, while musculoskeletal (44.87 %) and cardiovascular systems (28.21 %) were major class in elderly [Table 3].

Discussion

In the present study, we analysed the $PADR_{Ad}$ percentage based on prospective ADR-related studies of the last one and half decade. We observed $PADR_{Ad}$ as an important cause of morbidity and mortality. We observed a wide range of preventability (4.26–83.33 %) among the included studies. This variation can be explained by study population and data collection methods.

We observed higher (45.11 %) $PADR_{Ad}$ percentage than Beijer et al. (28.1 %) and Goettler et al. (31 %) [6, 40]. Both systematic reviews included retrospective studies, did not specify the preventability assessment tools in included studies and were based on studies mainly conducted before 2000. Their primary objective was not the preventable ADR_{Ad}. We observed low $PADR_{Ad}$ percentage than Hakkarainen et al. (52 %) [8]. One possible reason could be exclusion of paediatric population in earlier systematic review. As compared to Hakkarainen et al., we restricted our search to last one and half decade and did not include retrospective studies [8]. We also observed low $PADR_{Ad}$ percentage than Winterstein et al. (59 %) [41]. The earlier systematic review included all undesirable events related to drug therapy to assess preventability and was based on studies conducted before 2000. We observed high $PADR_{Ad}$ prevalence than Hakkarainen et al. (2.0 %) [8] and lower than Howard et al. (3.7 %) and Winterstein et al. (4.3 %) [41, 42]. This difference in prevalence can be explained by the difference in study methodology. None of these studies explored the heterogeneity in $PADR_{Ad}$ percentage estimation through subgroup analysis of study characteristics.

We observed lower percentage of $PADR_{Ad}$ in paediatric age groups. Even after adjusting for ADR definition and preventability assessment methods, this percentage remains low as compared to elderly and all age group studies. The earlier systematic review suggested a wide range of preventable ADRs (7–98 %) in paediatric population [13]. This could be due to the inclusion of all setting studies (community as well as inpatient) and all drug-related problems in assessing preventability by Smyth et al. [13]. Earlier systematic reviews on ADR_{Ad} observed low prevalence of ADRs in paediatric age

Table 3 Suspected drugs associated with $PADR_{Ad}$

Suspected drugs (ATC code)	All studies No. (%) (n = 502)	Paediatric studies No. (%) (n = 96)	Elderly studies No. (%) (n = 78)
Cardiovascular system drugs (C)	148 (28.08)	6 (6.25)	22 (28.21)
Cardiac glycosides (C01A)	52 (9.87)	–	13 (16.67)
Diuretics (C03)	42 (7.97)	–	–
Antihypertensive agents (C02)	25 (4.74)	–	7 (8.97)
Musculoskeletal system (M)	85 (16.13)	7 (7.29)	35 (44.87)
NSAIDs (MO1A)	85 (16.13)	7 (7.29)	35 (44.87)
Nervous system drugs (N)	89 (16.89)	24 (25.00)	3 (3.85)
Analgesics (N02)	30 (5.69)	9 (9.38)	–
Psycholeptic (N05)	22 (4.17)	9 (9.38)	–
Antiepileptic drugs (N03)	8 (1.52)	6 (6.25)	–
Blood and blood-forming organs (B)	64 (12.14)	–	16 (20.51)
Antithrombotic drugs (B01)	64 (12.14)	–	16 (20.51)
Alimentary tract and metabolism (A)	44 (8.35)	24 (25.00)	2 (2.56)
Drugs used in diabetes (A01)	29 (5.50)	9 (9.38)	2 (2.56)
Antinauseants (A04)	7 (1.33)	7 (7.29)	–
Anti-infective agents (J)	35 (6.64)	11 (11.46)	–
Antineoplastic and immunomodulating agents (L)	20 (3.80)	10 (10.42)	–
Hormonal preparations (H)	17 (3.23)	8 (8.33)	–
Corticosteroids (H02)	15 (2.85)	7 (7.29)	–
Total	502 (95.26)	90 (93.75)	78 (100)

$PADR_{Ad}$ preventable ADR leads to hospitalization, *ATC* anatomical therapeutic chemical classification, *NSAIDs* non-steroidal anti-inflammatory drugs

group as compared to elderly and all age group studies [6, 7, 43]. Leendertse et al. explained low prevalence with the use of the few drugs in paediatric admission studies [7]. This could also be the possible reason for the low percentage of $PADR_{Ad}$. Another reason could be a different drug utilization pattern that leads to different classes of drugs causing $PADR_{Ad}$ in paediatrics. In our study, we observed less or no $PADR_{Ad}$ due to cardiovascular, antithrombotic and NSAIDs in paediatric than other age groups. Finding of elderly subgroup is in line with earlier systematic reviews [6, 41]. Beijer et al. observed high rate of $PADR_{Ad}$ in elderly than non-elderly population (87.9 vs. 24.0 %) [6]. Winterstein et al. observed high $PADR_{Ad}$ prevalence in age group >70 than ≤70 years (7.6 vs. 3.9 %) [41]. The elderly are more prone to develop ADRs related to use of inappropriate drugs and polypharmacy [44, 45], which could result into a high percentage of $PADR_{Ad}$.

With respect to study wards, we observed a high percentage of $PADR_{Ad}$ in studies including entire hospital populations instead of subpopulations. This suggests $PADR_{Ad}$ as an important cause of morbidity in the hospitalized patients. We also observed relatively low heterogeneity in all age group studies adjusting for specific subpopulations (internal medicine and emergency ward). High heterogeneity in whole hospital setting could be due to mixture of study populations.

Leendertse et al. observed smaller ADR_{Ad} prevalence in European studies than North American and Australian studies [7]. Miguel et al. observed lower ADR_{In} prevalence in Asian studies than European and American studies [46]. We also observed low rate of $PADR_{Ad}$ in Australian studies without age group adjustment. This reinforces the importance of other study characteristics in the ADR assessment. We did not observe any effect of age group adjustment alone on European studies in terms of percentage and heterogeneity. We could not further evaluate the impact of different geographical locations on $PADR_{Ad}$ percentage due to availability of only one Asian study in all age group setting.

We observed slightly high $PADR_{Ad}$ percentage with studies using 'Edwards and Aronson' than 'WHO definition' for the ADR detection. The 'Edwards and Aaronson' uses 'medicinal product' as a causative agent and considers ADRs only to those events which predict hazard from future administration and warrants prevention or specific treatment or alteration of the dosage regimen or product withdrawal. The WHO definition considers ADR also to the minor reactions which do not have any consequences [12]. However, impact of ADR definition needs to be interpreted cautiously due to the presence of high heterogeneity.

$PADR_{Ad}$ percentages and heterogeneity could also vary due to its assessment tool. We observed moderate to very high heterogeneity for the different methods. This was expected based on an earlier systematic review suggesting lack of valid and reliable method to assess preventability [47]. We observed higher $PADR_{Ad}$ percentage as well as heterogeneity with 'Hallas et al.' than other methods. Unlike other methods, 'Hallas et al.' is not based on a fixed set of questionnaires and allows the investigator to label all events as preventable which are inconsistent with present-day knowledge of good medical practice, was clearly unrealistic, taking the known circumstances into account or could have been avoided by an effort exceeding the obligatory demands [48]. The reason for high heterogeneity of 'Hallas et al.' tool could be due to a mixture of different ADR definition studies. French preventability assessment method is an algorithm and assigns scores based on knowledge about the drug and its possible role, patient-related risk factors and conditions of prescription. Olivier et al. observed poor agreement among experts due to difficulty in terms of a clear understanding of the items [49]. This could be the reason for the moderate to high heterogeneity despite of having many similar characteristics in this group. We observed moderate heterogeneity among studies using Schumock and Thornton algorithm. Unlike the other two methods, this algorithm is more explicit and defines the preventability based on the history of previous allergy reactions, inappropriate drug selection according to diagnosis and patient characteristics, toxic serum drug concentration, lack of the required therapeutic drug monitoring or other necessary laboratory tests, known ADR treatment, drug interactions, poor compliance and lack of preventive measures [50].

In a paediatric population, we observed the impact of data collection methods on percentage and heterogeneity. Studies using Hallas et al. preventability tool and Edwards and Aronson definition yield high $PADR_{Ad}$ percentage than those using Schumock and Thornton algorithm and WHO definition. Both paediatric subpopulations also showed reduction in heterogeneity. However, we should interpret cautiously due to the presence of a small number of studies for this comparison and should be considered as an exploratory finding for the future studies.

We observed no difference of ADR detection methods (combined approach or medical record review alone) on $PADR_{Ad}$ percentage after the age group adjustment. There is little possibility of over- or underestimation due to ADR detection methods. This suggests the medical record review is an important tool to detect ADRs [7, 51]. Finding of low heterogeneity among medical record review group could be due to the similar ADR definition and same geographical location giving relatively homogenous setting.

The literature suggests ADR as an important cause of death in hospitalized patients and in general populations [52, 53]. We observed 2.69 % of reactions as fatal. Our analysis does not include ADRs leading to death outside the hospital. There is a possible window of ADR severity. So, ADR_{Ad} in this study represents ADRs are those severe enough to cause admission but not severe enough to cause death outside the hospital. There is a possibility of underestimation in the measuring of fatal reaction prevalence and its percentage. One

population-based study of deceased subjects reported that one fourth of fatal ADRs are preventable [54]. One fatal ADR_{Ad}-based study in internal medicine reported one fifth of reactions as preventable [55]. We observed more than half of fatal ADR_{Ad} as preventable which suggests ADR as an important preventable cause of mortality in the hospitalized patients.

NSAIDs, antithrombotic drugs, cardiac glycosides and diuretics accounted for almost 50 % incriminated drugs in $PADR_{Ad}$ cases. Earlier systematic review of preventable drug-related hospital admissions observed antithrombotic, diuretics and NSAIDs accounting for 50 % of incriminated drugs [42]. This could be due to difference in drug utilization pattern over a time. All except one study providing data about suspected drugs in our study are published after 2005. The earlier systematic review was mainly based on studies published before 2005. Drug class that requires attention for $PADR_{Ad}$ in paediatrics are analgesics, psycholeptics, antidiabetic drugs, antinauseants, NSAIDs and corticosteroids. Interventions on NSAIDs, cardiac glycosides, antithrombotic and antihypertensive agents could reduce $PADR_{Ad}$ in elderly patients. However, findings on drugs classes have to be weighed against their potential benefits.

The strengths of this study are its selection criteria and thorough literature search for more recent studies. We only focused on ADRs that lead to the hospitalization and did not include the ADRs that concurrently present during the admission. We have analysed only prospective studies and excluded the spontaneous reporting and retrospective studies. We have included only ADR data excluding adverse drug events and/or drug-related problems. We did a subgroup analysis to identify the factors associated with the heterogeneity and the impact of various study characteristics like populations and data collection methods on proportion of $PADR_{Ad}$. We could find causative drugs for the preventable reactions and suggest their pattern as per the age groups.

This systematic review has several limitations also. We acknowledge that some may consider exclusion of literature published before the year 2000 as arbitrary. Our decision was based on most of the earlier systematic reviews on this subject which were before this period. We searched only freely accessed databases PubMed and Google Scholar and could not search EMBASE. This systematic review is based on observational studies which usually had inherent biases and differences in study design. So, we explored our primary outcome to understand and quantify heterogeneity sources across studies. We could only compare study characteristics by adjusting for the age groups only. We could not adjust the multiple characteristic of study population and data collection methods due to mixture of study characteristics in the included studies. So, we could not do an analysis of risk factors for the $PADR_{Ad}$ and answer whether it is old age or the type of department or certain drug classes which result in the highest risk for a preventable ADR. This could have led to over- or underestimation in percentage of $PADR_{Ad}$. Moreover, subgroup analysis requires cautious interpretation in terms of small sample for each study characteristics. All included studies had preventability as a secondary objective. Future studies need to focus on these areas to suggest remedial measures for reducing the burden of $PADR_{Ad}$.

Conclusion

$PADR_{Ad}$ is an important cause of morbidity and mortality in the hospitalized patients and burdens to the health care system. We identified age groups, study wards, ADR definition and preventability assessment tools as important heterogeneity modifiers. $PADR_{Ad}$ percentages are higher in all age groups and elderly than paediatric studies. $PADR_{Ad}$ percentages are higher in the whole hospital than specific ward setting. With respect to data collection methods, studies using 'Hallas et al.' preventability assessment tool and 'Edwards and Aronson' ADR definition are likely to give high $PADR_{Ad}$ percentages. Paediatric and elderly studies showed a different causative drug pattern of $PADR_{Ad}$.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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