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REVIEW

Categorization and association analysis of risk factors for adverse drug events

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Abstract
Purpose Adverse drug events (ADE) are among the leading causes of morbidity and hospitalization. This review analyzes risk factors for ADE, particularly their categorizations and association patterns, the prevalence, severity, and preventability of ADE, and method characteristics of reviewed studies.
Methods Literature search was conducted via PubMed, Science Direct, CINAHL, and MEDLINE. A review was conducted of research articles that reported original data about specific risk factors for ADE since 2000. Data analyses were performed using Excel and R.
Results We summarized 211 risk factors for ADE, and grouped them into five main categories: patient-, disease-, medication-, health service-, and genetics-related. Among them, medication- and disease-related risk factors were most frequently studied. We further classified risk factors within each main category into subtypes. Among them, polypharmacy, age, gender, central nervous system agents, comorbidity, service utilization, inappropriate use/change use of drugs, cardiovascular agents, and anti-infectives were most studied subtypes. An association analysis of risk factors uncovered many interesting patterns. The median prevalence, preventability, and severity rate of reported ADE was 19.5% (0.29%~86.2%), 36.2% (2.63%~91%), and 16% (0.01%~47.4%), respectively.
Conclusions This review introduced new categories and subtypes of risk factors for ADE. The broad and in-depth coverage of risk factors and their association patterns elucidate the complexity of risk factor analysis. Managing risk factors for ADE is crucial for improving patient safety, particularly for the elderly, comorbid, and polypharmacy patients. Some under-explored risk factors such as genetics, mental health and wellness, education, lifestyle, and physical environment invite future research.

Keywords Adverse drug events · Risk factor · Categorization · Association analysis

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Introduction

Adverse drug events (ADE) can cause mild to severe harm and even death to patients [1–4]. Preventable ADE are among the leading cause of death in the USA [5]. Risk factors are defined as conditions or measurements associated with the probability of disease or death not necessarily recognized by the patient [6–8]. For instance, the most commonly prescribed drugs for type 2 diabetes are potentially associated with an increased risk of acute pancreatitis occurrence [9]. ADE mainly consist of adverse drug effects and adverse drug reactions, among others [10]. The latter two are related but differ in that adverse drug effects are usually detected by laboratory tests or by clinical investigations, and adverse drug reactions are detected by their clinical manifestations (symptoms and/or signs) [10]. Adverse drug effects may account for up to 140,000 deaths annually in USA [11, 12], which cost more than 3000 dollars per patient on average in community hospitals and increase the length of stay by 3.1 days an average [13]. Adverse drug reactions occur frequently in the post-discharge period [14], which cost about 136 billion USD, and cause 1 out of 5 injuries or death per year to hospitalized patients,

according to the FDA. The cost of drug-related morbidity and mortality exceeded 177.4 billion dollars in 2000 [15]. There were 47,055 drug overdose deaths in the USA in 2014 [16]. Many adverse drug reactions could potentially have been prevented or ameliorated with simple strategies [14]. Therefore, this review study investigates risk factors for ADE, including adverse drug effects and adverse drug reactions.

There are a handful of review articles on risk factors for ADE; however, their coverage of risk factors is very limited. For instance, Alomar [17] provided a categorization scheme of risk factors for adverse drug reactions, which did not consider those for adverse drug effects. In addition, the scheme consists of four main categories: patient-related, drug-related, disease-related, and social factors [17, 18], but ignores health service-related risk factors. Boeker et al. [19] focused on adverse drug effects in surgical and non-surgical inpatients but excluded children and incidents registered in the emergency department and outpatient clinical settings. Al Hamid et al. [20] studied 9 risk factors for ADE (e.g., old age, depression, and immobilization) in adult patients. Resende and Santos-Neto [21] summarized 9 risk factors for adverse drug reactions to antituberculosis drugs (e.g., age, gender, treatment regimen, HIV co-infection, and genetic factors). Due to their limited scopes, previous reviews covered a much smaller number of original research studies than the current investigation. More importantly, these review studies did not attempt to categorize risk factors; even when they provide such a categorization, it is very general, and does not offer a systematic understanding of risk factors. Furthermore, none of the previous studies has examined the association patterns among different risk factors for ADE (when two or more risk factors co-exist), and the latter can be instrumental for illuminating the complex interactions among risk factors.

To address the above limitations, this review aims to provide a broad and in-depth understanding of risk factors for ADE, by covering more and recent related studies, categorizing risk factors, analyzing their association patterns, summarizing the prevalence, severity, and preventability of ADE, and identifying method characteristics of related original research studies.

Methods

This review includes studies that contain original research results pertaining to specific risk factors for ADE. It excludes articles that do not provide details about specific risk factors, and that are not related to ADE, written in languages other than English, or published before 2000.

We conducted literature search in multiple databases, including PubMed, Science Direct, CINAHL, and MEDLINE, during July to September 2016. The search queries were a combination of risk factor and any of the variant expressions of ADE such as drug related side effects, adverse drug effects, medicine-related problems, drug therapy problems, ADE, adverse drug event, adverse drug reaction, and ADR.

Figure 1 illustrates detailed steps of our article selection process. The search queries were used to match against the titles and abstracts of publications. The matched search results were further expanded by including matched articles from their lists of references using the snowballing method. The expanded set of 661 articles went through an initial screening process based on our review of their abstracts and subsequently browsing of full texts. Among them, 247 titles deemed pertinent to our study were selected for detailed full-text review. The review led to the removal of studies that did not report data about specific risk factors for ADE. Finally, the remaining 106 articles were selected for our investigation of risk factors for ADE.

In addition to risk factors, we also extracted the prevalence, preventability, and severity rates of ADE as authors reported in their studies, if any. These rates are defined as the percentage of patients who experienced ADE, preventable ADE, and severe ADE, respectively, which indicate the significance of studying their risk factors. In view that the method design of previous studies can inform future research, we identified six key aspects of research methods used by the selected studies, including data collection location (e.g., country), setting (e.g., hospital), participants (e.g., population type), duration of the study, sample size, and research type (e.g., case-control study).

The authors selected articles based on the inclusion and exclusion criteria and prepared instructions for data extraction from those articles. Two reviewers carried out the extraction task independently. One reviewer completed all the selected articles, and the other processed a randomly selected subset of 40 articles. An analysis of inter-rater reliability of extracted risk factors from the overlapped articles yielded a kappa statistic of 0.74. The two reviewers discussed inconsistent results via two face-to-face meetings, and a third reviewer adjudicated the results. Based on the feedbacks from the discussion and

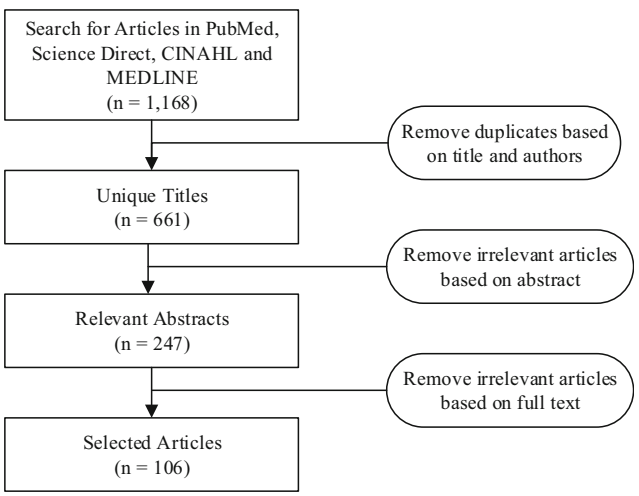

Fig. 1 Article selection process

adjudication, the first reviewer reviewed her extraction results for the remaining 66 articles and revised them as appropriate.

Starting with the collection of verified risk factors, the first and the third reviewers categorized the risk factors independently in two steps. The first step involved grouping risk factors into main categories, and the second step involved further grouping risk factors within each main category into subtypes. The grouping results were discussed via face-to-face meetings to resolve any differences. The second step started after the reviewers had reached a consensus on the main categories. The subcategorization of some main types was conducted via mapping by drawing on corresponding medical resources, including ICD, a drug taxonomy, and an integrated database of human genes [22]. For several risk factors that involved mapping ambiguities, we consulted a fourth reviewer who held a medical degree for further validation. The subtypes of remaining main categories were determined based on consensus.

The association patterns among different risk factors were extracted using association analysis. Association analysis is a technique for discovering strong and interesting relationships between items (e.g., risk factors) that are hidden in a dataset (e.g., research studies) [23]. The uncovered relationships or patterns can be represented in form of association rule, $RF_L \rightarrow RF_R$, where both RF_L and RF_R belong to a set of risk factors for ADE. The strength of an association rule can be measured by support and confidence, and its interestingness by lift [24]. Support is computed as the ratio of research studies that investigated a particular set of risk factors (RF_L and RF_R), and confidence as the ratio of research studies that investigated RF_L simultaneously investigated RF_R. Lift is defined as a ratio of the confidence of an association rule to the support of RF_R. A rule is generally considered interesting if lift > 1, which indicates that RF_L are useful for predicting RF_R. In addition, we selected subtype of risk factors as the unit of association analysis to seek a middle ground for the level of detail of association rules.

Results

Based on our analysis of the selected articles, we summarized to a total of 211 specific risk factors, introduced a two-level classification scheme of the risk factors, and discovered association patterns of risk factors.

Categorization of risk factors

We grouped those factors into five main categories—patient-related (e.g., age, gender), disease-related (e.g., history and comorbidity), medication-related (e.g., polypharmacy), health service-related (e.g., #prescribing physicians), and genetics risk factors (e.g., MHC class I), as shown in Table 1. Among them, medication- and disease-related risk factors dominate the previous studies. We further divided each of the main categories of risk factors into its subtypes.

For the patient-related risk factors, we grouped them into nine subtypes, including age, gender, weight, ethnic group, ADE history, socioeconomic status, lifestyle, functional status, and treatment compliance. Age and gender are most frequently studied subtypes, among others. It is shown from Table 1 that most studies focus on the elderly and a few on the young population. Among the studies of gender, some focused on females [29, 31, 35, 39, 40, 42, 43, 47, 55–61], some others on males [34, 36, 62], and yet a few others on gender in general [26, 33, 54]. Lifecycle is another highly reported risk factors subcategory such as alcohol abuse [29, 43, 70, 71], history of alcohol consumption [43], higher alcohol consumption [72], and smoking status [33, 73].

The categorization of the disease-related risk factors followed ICD, which consisted of the following subtypes: comorbidity, genitourinary system disorders, nervous system diseases, circulatory system diseases, musculoskeletal system and connective tissue diseases, digestive system disorders, mental and behavioral disorders, lower respiratory diseases, oncology disorders, certain infectious and parasitic diseases, immunodeficiency and blood diseases, disease complexity and medical history, and health condition. Among them, comorbidity is most frequently reported. In other words, patients with a high number of medical conditions are subject to higher risks of ADE. In addition, genitourinary system disorders, circulatory system diseases, and immunodeficiency and blood diseases contained a relatively higher number of risk factors than the rest of the disease-related subcategories. We can infer that patient with the above disease conditions are highly susceptible to ADE.

For the medication-related risk factors, we grouped them based on drug classes into subtypes as the following: polypharmacy, cardiovascular agents, central nervous system agents, anti-infectives, antineoplastic agents, psychotherapeutic agents, metabolic agents, gastrointestinal drugs, inappropriate use or change of drugs, intravenous use of drugs, and miscellaneous agents. Among them, polypharmacy receives the highest rate of reporting. In addition, the results show that central nervous system agents and cardiovascular agents are more likely to lead to ADE compared with drugs used to treat other medical conditions. Interestingly, inappropriate use or change of drugs is another common category of medication-related risk factors, which is potentially preventable.

We grouped health service-related risk factors into two subtypes: service utilization and service provision. The results also reveal that postoperative days after hospital discharge [54] and cost associated with getting access to medical services/medicines [78] are significant risk factors for ADE.

The genetic risk factors were grouped based on their gene families with reference to an integrated database of human genes [22]. These gene families include MHC class I, ABC transporter, cytochrome P450, VKOR, concentrative

Table 1 Categorization of risk factors for ADE

Category	Subtype	Specific factors
Patient-related risk factors	Age	Age [25–33]
		Age ≥ 65 years [34–39]
		Age ≥ 80 [40, 41]
		Elderly patients aged 50 to 60 years [42]
		Old age [43]
		Older age [44]
		Age 11 to 18 years [45]
		Increasing age [46–48]
		Advancing age [49]
		Age on admission [50]
		Geriatric status [51]
		≥ 34 years of age [52]
		≤ 8 years old [53]
	Gender	Gender [26, 33, 54]
		Female [29, 31, 35, 39, 40, 42, 43, 47, 55–61]
		Male [34, 36, 62]
	Weight	HIV-infected women with low body weight [63]
		Baseline body weight ≥ 40 kg [64]
	Ethnic group	Ethnicity [33]
		All race minorities with the exception of Asians [39]
		Patients from South [39]
		Patient from the French-speaking part of Switzerland [62]
		New resident [65]
	ADE history	Family history of ADR caused by NSAID [66]
		History of ADE [67]
		History of drug eruption [68]
	Socioeconomic status	Socioeconomic status [69]
		Patients with lower median household incomes [39]
		Poor nutritional status [43]
	Lifestyle	Alcohol abuse [29, 43, 70, 71]
		History of alcohol consumption [43]
		Higher alcohol consumption [72]
		Smoking status [33, 73]
	Functional status	Number of mobility limitations [74]
		Dependency in at least 1 activities of daily living [75]
		History of falls [75]
	Treatment compliance	Compliance to the therapy by the patients [69]
Disease-related risk factors	Comorbidity	Comorbidity [26, 29]
		Number of diseases suffered [58, 69]
		Number of diagnoses [76]
		Having ≥ 6 chronic medical conditions [77, 78]
		Cardiovascular comorbidity [37]
		Multiple underlying medical conditions, especially cerebrovascular diseases [79]
		≥ 3 chronic diseases [39]
		Charlson comorbidity index [40]
		Comorbidity odds ratio = 6.54 [80]
		High number of disease-related symptoms [81]
	Genitourinary system disorders	Renal dysfunction [36, 82]
		Impaired renal function [41]
		Overt renal failure [83]
		Concealed renal failure [83]
		Renal impairment [84]
		Increased concentration of serum creatinine [85]
		Creatinine clearance < 50 ml/min [86]
		Acetylator status [43]
	Nervous system diseases	Non-vascular neurological disorders [87]
		Central and peripheral nervous system disorders [88]
		Extrapyramidal reactions [88]
	Circulatory system diseases	Cardiac dysrhythmias [34]
		Cardiac failure [62]
		Coronary artery disease [25]
		Arrhythmias [62]
		Left ventricular ejection fraction 45–54% [60]
		Cerebrovascular diseases [62]

Table 1 (continued)

Category	Subtype	Specific factors
		Ischemic heart disease [89]
		Heart failure [89]
	Musculoskeletal system and connective tissue diseases	Diagnosis of gout [62]
		Rheumatoid arthritis [90]
		Connective tissue disease [68]
	Digestive system disorders	Regional enteritis [34]
		Ulcerative colitis [34]
		Diverticulitis [34]
		A previous episode of UGIB [32]
		Pre-existing liver disease [43]
		History of hepatitis [43]
	Mental and behavioral disorders	History of depression [67]
		Depression [89, 91]
		Past psychiatric history [92]
	Lower respiratory diseases	Chronic obstructive pulmonary disease [34]
		Radiological extension of lung fields on chest X-ray [43]
	Oncology disorders	Oncological disease [55]
		Cancer [90]
		Multiple myeloma [90]
		Performance status [36]
		Massive ascites [36]
	Certain infectious and parasitic diseases	Certain infectious and parasitic diseases [93]
		Infection [36, 84]
	Immunodeficiency and blood diseases	HIV co-infection [63, 68, 70]
		HIV positivity [94]
		Immunosuppression [68]
		Low erythrocyte levels [61]
		Low thrombocyte levels [61]
		Raised temperature [61]
	Disease complexity	Advanced disease [43]
		Patient's disease complexity [95]
	Medical history and health condition	Medical history [84]
		Patients with prior outpatient visits, ER visits, and hospitalizations [39]
		self-rated health [77]
Medication-related risk factors	Polypharmacy	Polypharmacy [28, 35, 85, 88, 93, 95–101]
		Number of medications [25, 26, 29, 45, 47, 48, 50, 56, 58, 62, 67, 69, 74, 76, 77, 93, 102]
		Current medications [40]
		Number of drugs prescribed [27, 31, 87, 93, 103–105]
		Number. of scheduled medications [40, 65]
		Number of contraindicated medications [77]
		Receiving drugs > 5 [38]
		Receiving drugs > 8 [39]
		Cardiovascular co-medication [99]
		Number of drugs being taken before admission [106]
		Number of authorized medicines [50]
		Use of more than four drugs during stay [83]
		Number of off-label medicines [102, 107]
		Number of off-label and/or unlicensed medicines [50]
		Number of over the counter (OTC) drugs [56]
		Number of contraindicated medications [77]
		Drug interactions [99]
		Concomitant intake of other hepatotoxic drugs [43]
		Noncomitant use of sedating drugs [51]
		children with multiple prescriptions [108]
	Cardiovascular agents	Vascular surgery [37]
		Cardiovascular agents [85]
		Calcium channel blockers [29]
		The use of drugs acting on the blood [27]
		Recent anticoagulant [109]
		Antithrombotic agents [106]
		History of ACE inhibitor-induced cough and other medical conditions [33]
		History of ACE inhibitors [33]

Table 1 (continued)

Category	Subtype	Specific factors
		Diuretics [29, 85]
	Central nervous system agents	Analgesics [85]
		A high acetaminophen concentration [110]
		An acetaminophen concentration above the "possible toxicity" treatment line [110]
		General anesthesia [50]
		Children who underwent general anesthesia [48]
		Nonsteroidal anti-inflammatory drugs and digoxin [29]
		Opioids [65]
		Prior opioid use [34]
		Central nervous system drugs [27]
		Use of anticonvulsants [111]
		Combined use of phenytoin and carbamazepine [112]
		Carbamazepine [113]
		Phenytoin [113]
		Lamotrigine [113]
	Anti-infectives	Antibacterial for systemic use [106]
		Antibiotics [27]
		Daily dose of 16 mg/kg of TMP/SMX [52]
		Anti-infective drugs [65]
		Protease inhibitor-based regimen [86]
		Non-nucleoside reverse transcriptase inhibitors-based regimen [86]
		Regimen containing atazanavir [86]
		Nevirapine [114]
		Zidovudine [114]
		Stavudine [114]
	Antineoplastic agents	Oncological treatment [48]
		Antineoplastic agents [90]
		A high cumulative cisplatin dose in combination with particular tumor types [115]
	Psychotherapeutic agents	Psychoactive medications [65]
		Antipsychotic [109]
		Typical antipsychotics [88]
		Oxycodone [90]
	Metabolic agents	Anti-diabetic agents [85]
		Long-term bisphosphonate treatment [90]
	Gastrointestinal drugs	Gastrointestinal drugs [27]
		Drugs for acid-related disorders [106]
	Inappropriate use or change of drugs	Inappropriate medication use [74]
		Use of inappropriate drugs [116]
		Unlabeled use of the drug [117]
		Inappropriate prescribing [69]
		Newly prescribed drugs [27]
		Self-medication [106]
		Starting new high-risk drugs [38]
		Cessation of drugs on hospital admission [27]
		Intentional ingestion of drug [110]
		The length of drug use [103]
		Number of doses used [58]
		General negative medication beliefs [81]
	Intravenous use of drugs	Rapid intravenous injection [117]
		Intravenous bisphosphonate administration [90]
		Intravenous n-acetylcysteine administration [110]
	Miscellaneous agents	Patients who underwent coronary computed tomography angiography [42]
		Previous patient history of allergic reactions to cephalosporins or penicillins [117]
		Application of drugs to skin wounds or to skin with impaired barrier function [118]
		Dental procedures and prostheses [90]
		Influenza vaccine [84]
		At least $3144 in annual drug spend [39]
Health service-related risk factors	Service utilization	Length of stay in hospital [25, 58, 76, 87, 104, 109]
		A long hospital stay [110]

Table 1 (continued)

Category	Subtype	Specific factors
		Primary care physician visit count [77]
		Specialist visit count [77]
		Greater than 1 physician prescriber [119]
		At least 1 surgical subspecialist [77]
		Number of prescribing physicians [77]
		Higher utilization of healthcare services [78]
	Service provision	Poor coordination of care [78]
		Admission by any service other than infectious diseases service [86]
		Admission to a medical ward [47]
		Cost-related barriers to medical services/medicines [78]
		Postoperative days after hospital discharge [54]
Genetic risk factors	MHC class I	HLA-B*1502 [120], HLA-B*1511 [121, 122], HLA-B*5701[123], HLA-B*5801 allele [82], HLA-A*31:01 [124, 125]
	ABC transporter	ABCC2 haplotype (IVS3-49C > T and I1324I polymorphisms) [126], ABCC2 polymorphisms (GG genotype at the g.–1774delG locus) [127], ABCC1, ABCB1, ABCB4 [128]
	Cytochrome P450	CYP2D6 alleles [54], CYP2D6*10 allele [129], CYP2C9*3 variant [130, 131], CYP4F2 [131]
	Concentrative nucleoside transporter	rs7853758 within SLC28A3, SLC28A1 [128]
	Glycosyltransferase 29 family	rs10937275 in ST6GAL1 on chromosome 3 [123]
	VKOR	VKORC1 [131]
	ETS transcription factor	G allele of rs2724635 in ETV6 [132]
	Peptidase M13	rs989692 in MME [132]
	Serine hydrolase enzyme	FAAH SNPs (rs4141964, rs3766246, rs324420, rs2295632, kgp12517369) [133]

nucleoside transporter, glycosyltransferase 29 family, ETS transcription factor, peptidase M13, and serine hydrolase enzyme. Among them, the first three gene families were most frequently studied.

There was a total of 45 subtypes of risk factors. Figure 2 shows the distribution of article account over various subtypes of risk factors that were reported in three or more research studies. The figure shows that the top-10 most frequently reported subtypes of risk factors for ADE are polypharmacy, age, gender, comorbidity, inappropriate use or change use of drugs, central nervous system agents, cardiovascular agents, service utilization, anti-infectives, and lifestyle.

Association patterns of risk factors

Prior to the association analysis, we need to first answer the question of whether more than one subtype of risk factors has been investigated by a significant percentage of previous studies. To this end, we summarized article count for varying number of subtypes of risk factors for ADE. The results show that 73 articles (~69%) reported two or more subtypes of risk factors. Among them, 26 studies examined two and 20 studies examined three subtypes of risk factors, respectively; eight studies investigated four and five subtypes, separately; and the rest of the studies examined six or more types of risk factors, including one that considered 11 subtypes. The results provide base for performing association analysis.

Association analysis typically requires setting the minimum thresholds for support, confidence, and lift, which were set to 0.03, 0.5, and 1, respectively. The setting of threshold for minimum support considered the above-mentioned statistics of article count and the large number of risk factors (we did not exclude studies that examined only one subtype of risk factors for sake of ecological validity of our analysis results). The thresholds for confidence and lift were set based on commonsense. The analysis yielded a total of 40 association rules, and the top-21 rules are listed in Table 2 ranked in a descending order of lift. Take the first rule as an example for illustration. Among the research studies that investigated both polypharmacy and central nervous system agents as risk factors for ADE, half of them also considered the risk factor of cardiovascular agents. Additionally, compared with a randomly selected research study, investigating polypharmacy and central nervous system agents as risk factors for ADE in a research study boosted its chance of considering cardiovascular agents as a risk factor by 8 folds (lift = 8). We did not consider genetic factors in the association analysis mainly due to its small number of studies in relation to the large number of subtypes.

Severity, prevalence, and preventability of ADE

Among the reviewed studies, 67% reported the prevalence rate of ADE. The median prevalence rate was 19.5% (0.29%~86.2%). Highest prevalence rates of ADE were

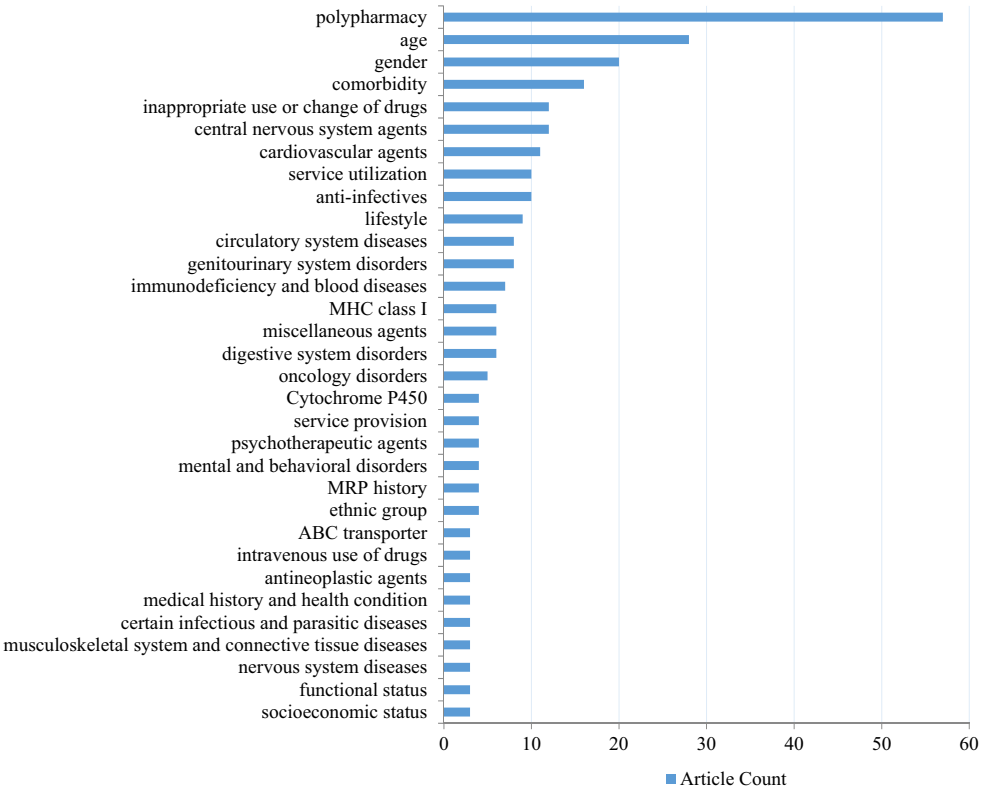

Fig. 2 The distribution of article count (≥3) over various subtypes of risk factors for ADE

reported for MDR-TB patients (72.4%) [64], HIV-infected patients ≥18 years (86%) [86], and patients with HIV infection who completed IFN-based treatment (86.2%) [92]. In contrast, lowest prevalence rates were found in patients

Table 2 Top-21 association rules on risk factors for ADE

Association rules	Lift	Confidence
Polypharmacy, central nervous system agents → cardiovascular agents	8	0.5
Polypharmacy, cardiovascular agents → central nervous system agents	7.2	0.75
Age, comorbidity → gender, polypharmacy	6.98	0.8
Age, comorbidity, polypharmacy → gender	4.8	1
Age, lifestyle → gender	4.8	1
Cardiovascular agents → central nervous system agents	4.8	0.5
Gender, comorbidity → age, polypharmacy	4.27	0.8
Age, comorbidity → gender	3.84	0.8
Polypharmacy, service utilization → comorbidity	3.66	0.57
Ethnic group → gender	3.6	0.75
Digestive system disorders → age	3.43	1
Gender, lifestyle →age	3.43	1
Age, gender, polypharmacy → comorbidity	3.2	0.5
Service utilization → comorbidity	3.2	0.5
Circulatory system diseases → gender	2.88	0.6
Gender, comorbidity, polypharmacy →age	2.74	0.8
Gender, comorbidity → age	2.74	0.8
Comorbidity, polypharmacy → gender	2.67	0.56
Gender, polypharmacy → age	2.49	0.73
Cardiovascular agents → age	2.29	0.67
Polypharmacy, central nervous system agents →age	2.29	0.67

who had an indication for the scan and use of the contrast medium Ultravist-370 or Isovue-370 (0.31%) [42], patients from psychiatry department (0.69%) [88], and hospitalized patients (0.29~0.36%) [68, 95].

There were 19% of the selected studies that reported the preventability rate of ADE. The median preventability rate was 36.2% (2.63%~91%). Relatively high preventability rates of ADE were reported for hospitalized patients aged over 80 years old (63%) [104], adult patients visiting the tertiary care hospital (81.57%) [47], and children admitted to a medical ward (less than18 years) (81.7%) [93]. In contrast, HIV/AIDs patients who had been taking anti-retroviral treatment had very low preventability rate (2.63%) [114].

Among the selected studies, 29% reported the severity rate. The median severity rate was 16% (0.01%~47.4%). The highest severity rates were reported for ADE such as adverse events induced by ceftriaxone (30%) [117], cutaneous drug reactions (34%) [68], and ADE to first-line antituberculous agents (28%) [70], and the number of off-level medication associated ADR (41.3%) [107].

Characteristics of methods

About 94% of the reviewed studies used clinical trial data, and the remaining 6% studies drew data from databases such as Eclipsys Sunrise (EPSI), IPC, FDA Online Label Repository, Swedish national database of spontaneously reported ADRs, and Pittsburgh Medical Center–Presbyterian Hospital (UPMC-P) ADE. The elderly population accounted for one-fifth (19%) of the selected studies on risk factors for ADE. About 10% of selected studies used adults and children as the patient population. About 86% studies reported sample size and the median sample size was 595 (14~2,578,336). A diverse set of research types was employed by the selected studies, including 28% prospective study, 19% retrospective study, and 17% case-control study. The research studies conducted in hospital settings lasted between 4 weeks and 8 years, and the studies that used data from databases selected from 10 to 44 years' worth of data.

The location where the selected studies were conducted spread across 33 countries, spanning six continents. They include North America (e.g., USA [30, 33, 39, 51, 54, 65, 67, 73, 74, 77, 78, 86, 107, 108, 132, 133] and Canada [26, 78, 128]), Europe (e.g., UK [38, 40, 45, 48, 50, 78, 104, 123], Germany [31, 45, 60, 61, 78, 99, 118], the Netherlands [27, 37, 57, 78, 81], Sweden [41, 90, 129, 131], France [59, 68, 106, 109], Italy [29, 63, 75, 83, 91, 97], Finland [25, 49], Norway [96], Ireland [32], Turkey [43], Portugal [35], Czech Republic [55], Spain [28, 92], Slovak Republic [89], and Switzerland [62]), Asia (e.g., China [42, 45, 66, 121], South Korea [53, 126, 127, 131], India [47, 56, 58, 69, 70, 76, 88, 102, 112, 114, 119, 134], Iran [87, 117], Thailand [79, 94], Taiwan [52, 82, 85, 95, 113], Vietnam [120], Japan [36, 84, 124, 125, 129], Pakistan [64], Hong Kong [45, 93], and Malaysia [45, 110]), Australia (e.g., Australia [45, 46, 78] and New Zealand [78]), South America (e.g., Brazil [72, 80, 100, 103, 111, 116] and Mexico [115]), and Africa (e.g., Ethiopia [44, 72]).

Discussion

The coverage of risk factors in this review is much broader and more in-depth than previous studies to better reflect the landscape of risk factors. Among the five main categories, health service-related risk factors are novel. Examples include poor coordination of care and length of hospital stay, which are potentially preventable and have practical implications for improving patient safety.

Genetic factors are identified as a separate category in this review. It has been long posited in pharmacogenetics that specific generic factors contribute to pharmacology [135]. However, only until recent years have many genetic discoveries been made owing to the drastic reduction in the cost of sequencing technologies. Genome-wide association studies [136] have fueled the search for genetic basis of disease susceptibility. The distinct characteristics and analysis methods of genetics factors separate them apart from other types of risk factors for ADE.

The two-level scheme provides an unprecedentedly fine-grained categorization of risk factors for ADE. Among the subtypes of risk factors, some have been under explored such as treatment compliance, concentrative nucleoside transporter, glycosyltransferase 29 family, VKOR, ETS transcription factor, peptidase M13, serine hydrolase enzyme, weight, lower respiratory diseases, disease complexity, metabolic agents, and gastrointestinal drugs. The results of this study show that the elderly population has been the focus of ADE study possibly due to their high vulnerability to ADE [137]. Additionally, patient with certain disease conditions such as genitourinary system disorders, circulatory system diseases and immunodeficiency, and blood diseases are highly susceptible to ADE. There are also potential gender differences in susceptibility to ADE [138–140]. For instance, females can be at a higher risk for ADE than their male counterparts possibly due to gender-associated differences in drug exposure. Furthermore, polypharmacy being the most frequently reported risk factor suggests that drug-drug interaction is a major risk for ADE. Interestingly, this review found that inappropriate use or change of drugs is another common subtype of medication-related risk factors, which is potentially preventable. The association analysis of risk factors contribute towards a fuller understanding of the complexity and interactions of risk factors by uncovering a number of interesting co-occurrence patterns of risk factors.

- Cardiovascular agents and central nervous system agents commonly appear in the same research studies. The chance of simultaneous investigation of the two types of risk factors is even higher when polypharmacy is considered.

- Age, gender, polypharmacy, and comorbidity are common and interacting themes across previous studies of risk factors for ADE. In addition, age is likely incorporated into the investigation of risk factors related to digestive system disorders, lifestyle, cardiovascular agents, and central nervous system agents; gender is likely considered in studies of ethnic group and circulatory system diseases as risk factors; and comorbidity is considered in studies of service utilization factors.
- Polypharmacy is studied not only along with other common risk factors (e.g., age) but also along with other infrequently studied risk factors such as socioeconomic status and psychotherapeutic agents.
- Some of the association rules achieved the perfect confidence score (i.e., 1) and extremely high lift values (> 30). For instance, studies examining digestive system disorders, or age, and lifestyle as risk factors, also considered gender with no exception. Polypharmacy was always included while studying gender and comorbidity or socioeconomic status as risk factors. If we lower the minimum threshold for support to 0.02, we would be able to identify another 63 association rules that have the perfect confidence score (= 1). For instance, gender and digestive system disorders were always examined along with lower respiratory diseases as risk factors; and gender and cardiovascular agents were always considered along with age and lifestyle as risk factors.

This study reveals contradicting findings about risk factors. Take the three most frequently studied risk factors (see Fig. 2) as examples. Despite that polypharmacy is a frequently reported risk factor, it was not found to be a risk factor for elderly patients admitted to the Emergency Department [41]. Age was reported as a risk factor for adult patients in some studies [30, 32], but not in others [119]. The majority of studies reported female [29, 31, 35, 39, 40, 42, 43, 47, 55–61], but some studies found male [34, 36, 62] as a risk factor. Therefore, the interpretations of the findings should be made with respect to specific patient population or conditions.

The results of this study reveal several issues related to risk factors for ADE that have been under studied.

- Genetic factors. Genetic risk factors of ADE hold a great promise for personalized or precision medicine. As the technologies for genome sequencing and for performing large-scale analysis of gene expressions become more cost-effective, they will enable the discovery of pharmacogenomic markers and molecular pathways of ADE.
- Mental health and wellness. It can be an important subtype of patient-related risk factors because there is a close connection between our mental and physical health, and our body responds to the way we think, feel, and act. Depression has been reported as a risk factor for ADE in several studies [67, 89, 91]. Other mental health-related problems such as stress and anxiety may cause high blood pressure, back pain, and chest pain, which are potential risk factors.
- Education level. The education level of patients can have potential impacts on their awareness of ADE and adherence to medication interventions. However, education below high school as a risk factor has only been considered in one study [56]. General negative medication beliefs, reported as risk factor by one study [81], can be attributed to the lack of education.
- Lifestyle. In addition to smoking and alcohol, patient's lifestyle encompasses many other aspects such as unhealthy diet, lack of physical exercise, and lack of sleep, which may have a profound impact on patient's health. One study shows that a large proportion of coronary patients do not achieve the lifestyle for cardiovascular disease prevention [141]. Physical exercise boosts metabolism and may help to reduce ADE. A challenging question is how to determine an appropriate type of lifestyle to avoid the harm of ADE.
- Prevention. Avoiding risk factors could fundamentally mitigate ADE. Prevention may target different stages of medication administration, including prescription, dispensing, administration, and monitoring. Our findings show that inappropriate use or change of medications is a common subtype of risk factors and is preventable. In addition, computerized physician order entry with clinical decision support systems, ward-based clinical pharmacists, and improved communications among physicians, nurses, and pharmacists may prevent potential medication errors [142]. Clinicians should also consider the benefit of periodic systematic drug regimen reviews in an effort to reduce the occurrence ADE in older people [143].
- Physical environment. The physical environment where patients reside such as climate, weather condition, and humidity could be associated with ADE. One primary way to draw such insights is by comparing patients across different countries and/or regions.

The list of specific risk factors for ADE included in this review is by no means complete. Their inclusion is limited by the coverage of selected databases of publications and the access to the full articles. For example, we reviewed only 15 studies on genetic risk factors. In addition, risk factors can vary with specific medication or disease condition. Furthermore, the review studies on risk factors typically did not differentiate specific ADE but only reported the percentage of ADE ([18, 19]). Differences also existed in the definition of severity of ADE across different studies.

Conclusion

ADE is subject to risk factors, and some are preventable. Risk factors can be categorized into five main categories, including

patient, disease, medication, health service, and genetics. Among them, medication-related risk factors have been studied most frequently. Moreover, the most studied subtypes of risk factors include polypharmacy, age, gender, central nervous system agents, comorbidity, service utilization, inappropriate use/change use of drugs, cardiovascular agents, and anti-infectives. Among the subtypes, age, gender, polypharmacy, and comorbidity frequently appear in the same studies of risk factors for ADE. Each of the above subtypes is also frequently investigated along with various other types of risk factors. Cardiovascular agents and central nervous system agents are routinely considered in the same research studies of risk factors. Based on the two-level classification scheme of risk factors for ADE, this study suggests research issues related to risk factors that call for more future research. The findings of this study can be used to guide future studies in improving patient safety in care management by minimizing and preventing the harm of ADE.

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Authors' contributions LZ: data annotation and categorization; idea conceiving and study design; analysis and interpretation of the data; and preparation, review, revisions, and approval of the manuscript. AR: collection, management, annotation, analysis, and interpretation of the data; and preparation, revisions, and approval of the manuscript.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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