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Risk factors for adverse drug events in hospitalized patients: an overview of systematic reviews

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Abstract

Objectives: To perform an overview in order to identify risk factors related to the development of Adverse Drug Events (ADE) in hospitalized patients. **Methods:** A search for systematic reviews and meta-analyses was carried out in the Pubmed, Scopus, Lilacs and Scielo databases, until August 19, 2021. The search strategies contained the following MeSH descriptors: Drug-Related Side Effects and Adverse Reactions ; Inpatients; Hospitalization; Hospitals; Hospital; Logistics Models; Risk Factors; Drug Therapy; Risk Assessment; Pharmacy Service, Adverse Drug Events; Adverse Drug Reactions; Medication Errors; Risk; Systematic Review and Meta-Analysis. From this, publications in English, Portuguese or Spanish that exposed possible risk factors for ADE during hospitalization were included. Works were excluded when: characterized as narrative reviews, expert opinions, editorials, overview and reviews without a transparent search strategy; restricted to certain drug classes, patient groups or clinical features; reported only the assessment of Medication Errors (ME); they were duplicated; did not provide abstract and full text. Two independent authors performed the selection of studies, a third researcher was requested when there was disagreement. The studies that met the criteria for data extraction underwent a thematic analysis and, based on reading, the risk factors for ADE were raised. **Results:** Eleven studies met the inclusion criteria: ten systematic reviews and one meta-analysis. "Number of prescribed drugs" (OR: 1,21; CI 95%: 1,03-1,44; p: 0,024), "Advanced age" (OR: 2,12; CI 95%: 1,70-2,65; p: 0,000) and "Comorbidities" were the most cited risk factors, other characteristics described less frequently were "Hospital Length (HL)", "Allergies" and "Female sex". Furthermore, it has been observed that the use of certain medications can increase the patient's risk. **Conclusions:** The realization of overview made it possible to identify risk factors for ADE, which can help hospital teams to direct their care actions to patients at higher risk of developing such events.

Keywords: adverse drug events; adverse drug reactions; drug-related side effects and adverse reactions; risk factors; risk assessment; hospitalization.

Fatores de risco para eventos adversos a medicamentos em pacientes hospitalizados: uma overview de revisões sistemáticas

Resumo

Objetivos: Realizar uma *overview* com a finalidade de identificar os fatores de risco relacionados ao desenvolvimento de Eventos Adversos a Medicamentos (EAM) em pacientes hospitalizados. **Métodos:** Foi realizada uma pesquisa por revisões sistemáticas e meta-análises nas bases de dados Pubmed, Scopus, Lilacs e Scielo, até 19 de Agosto de 2021. As estratégias de buscas continham os seguintes descritores MeSH: *Drug-Related Side Effects and Adverse Reactions; Inpatients; Hospitalization; Hospitals; Hospital; Logistic Models; Risk Factors; Drug Therapy; Risk Assessment; Pharmacy Service, Adverse Drug Events; Adverse Drug Reactions; Medication Errors; Risk; Systematic Review e Meta-Analysis.* A partir disso, foram incluídas publicações em inglês, português ou espanhol que expuseram possíveis fatores de risco para EAM durante a hospitalização. Foram excluídos os trabalhos quando: caracterizados como revisões narrativas, opiniões de especialistas, editoriais, *overview* e revisões sem estratégia de busca transparente; restrito a certas classes de medicamentos, grupos de pacientes ou características clínicas; relataram apenas a avaliação de Erros de Medicação (EM); estavam duplicados; não forneceram resumo e texto completos. Dois autores independentes realizaram a seleção dos estudos, um terceiro pesquisador foi solicitado quando houve discordância. Os estudos que atenderam aos critérios para extração de dados passaram por uma análise temática e a partir da leitura, foram levantados os fatores de risco para EAM. **Resultados:** Onze estudos satisfizeram os critérios de inclusão: dez revisões sistemáticas e uma meta-análise. "Número de medicamentos prescritos" (OR: 1,21; IC 95%: 1,03-1,44; p: 0,024), "Idade avançada" (OR: 2,12; IC 95%: 1,70-2,65; p: 0,000) e "Comorbidades" foram os fatores de risco mais citados e associados a EAM, outras características descritas com menor frequência foram "Tempo de Internação (TI)", "Alergias" e "Sexo Feminino". Além disso, observou-se que o uso de determinados medicamentos pode aumentar o risco do paciente. **Conclusões:** A realização da overview possibilitou identificar fatores de risco para EAM, os quais podem ajudar as equipes hospitalares a direcionar suas ações de cuidado aos pacientes com maior risco de desenvolverem tais eventos.

Palavras-chave: eventos adversos a medicamentos; reações adversas a medicamentos; efeitos colaterais e reações adversas relacionados a medicamentos; fatores de risco; medição de risco; hospitalização.

Introduction

According to the Glossary of terms related to patient and medication safety,[1] Adverse Drug Events (ADEs) are defined as any harm that occurs during a patient's drug treatment and that results either from appropriate care or from inadequate or suboptimal care. Consequently, adverse events include adverse drug reactions and any harm derived from a medication error.

Adverse Drug Reactions (ADRs) are unintentional events, though harmful, attributed to the use of medications. ADRs are responsible for unscheduled hospitalizations, but also occur during the course of a significant percentage of these hospitalizations, representing a challenge for current medical care.[2] In contrast, Medication Errors (MEs) are preventable and affect prescription, transcription, dispensation, administration and monitoring practices, which can result in serious harms, disability and even death.[3]

In this sense, the literature points out that, in the United States of America (USA), nearly 3.7% of the hospitalized patients presented some adverse event; in addition to that, single preventable adverse events resulted in 7,000 deaths annually. It is observed that, even with the evolution in health care, these incidents represent a significant problem worldwide and continue to be a concern in the field of patient safety.[4,5] Furthermore, a recent Brazilian study that described the implementation of an active search service for ADEs in a teaching hospital reported that the ADE frequency was 7.23%; in addition to that, it was verified that, of the events identified, 24.14% involved transfusion reactions and that 53.85% of the related medications were of high surveillance[6].

Finally, considering that ADEs in hospitalized patients have important implications such as disability, death, prolonged hospital stay and increased costs,[7] the justification for conducting the overview comes from the need to propose a closer follow-up to the patients with a higher probability of developing these events, with the main purpose of preventing/mitigating the harms. Given the above, the objective of this article was to carry out an overview of systematic reviews in order to identify risk factors for ADEs in hospitalized patients.

Methods

The protocol of this study has been registered in Prospero with number CRD42020207132. A systematic search for publications was conducted up to August 19th, 2021, with no restriction regarding the start date, in order to expand the research strategy. The following databases were consulted: Scientific Electronic Library Online (SciELO), *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS), PubMed and Scopus. The search descriptors were defined using the controlled vocabulary from the National Library of Medicine (MeSH) and the Descriptors in Health Sciences (*Descritores em Ciências da Saúde*, DeCS). Consequently, the search strategy was as follows: ((Drug-Related Side Effects and Adverse Reactions AND Inpatients AND Hospitalization AND Logistic Models AND Risk Factors) OR (Drug-Related Side Effects and Adverse Reactions AND Hospitals AND Risk Factors) OR (Drug Therapy AND Risk Assessment AND Pharmacy Service, Hospital AND Hospitals) OR (Adverse Drug Events AND Adverse Drug Reactions AND Medication Errors AND Risk)) AND (Systematic Review OR Meta-Analysis).

The publications were compared to the inclusion criteria to determine their thematic relevance in meeting the objectives of the current study, namely: (I) to characterize possible risk factors for the development of ADEs; (II) being a systematic review or meta-analysis; (III) being written in English, Portuguese or Spanish; and (IV) assessing data related to hospitalized patients. The publications excluded were those that: (I) were characterized as narrative reviews, experts' opinions, editorials, overviews and reviews without a transparent search strategy; (II) restricted the analysis to certain medications classes; (III) limited the analysis to a specific patient group or clinical condition; (IV) only presented the appreciation of MEs as outcome; (V) were duplicates; and (VI) did not provide their abstracts or full texts for reading.

After the systematic search, a descriptive analysis of the articles was performed, divided into three stages: evaluation of the titles and of the abstracts and, finally, of the full texts. This screening process was in charge of two reviewers, according to the criteria defined. In case of disagreements, an assessment by a third reviewer was requested. The Rayyan web application (https://www.rayyan.ai/) was used for the selection stage.[8] To evaluate the titles, the eligibility criteria considered were the same as for inclusion; on the other hand, for the analysis of the abstracts and full texts, the exclusion criteria were used.

The critical assessment of the reports included was in charge of only one author, following the PRISMA recommendation. The 27 checklist items were evaluated regarding their occurrence in the systematic reviews. Some items – 14, 15, 16 and 21, 22, 23 – apply mainly to meta-analyses and, therefore, the maximum score of the studies could be 21 (systematic reviews) or 27 (meta-analyses) points.[9,10] The main purpose of this analysis was to evidence the PRISMA criteria met by each study, as well as the gaps in the quality of the reports.

The studies that met the criteria determined for data extraction were subjected to thematic analysis and, after intensive reading, the risk factors for ADEs listed in the research results were identified. The risk factors that were present in at least two systematic reviews were considered, as well as those that presented frequency/prevalence measures or statistically significant data.

The studies that met the inclusion criteria for data extraction were carefully examined regarding the following variables: language, year of publication, country where the study was conducted, population studied, objectives, search strategies, databases, number and types of studies reviewed, results obtained, method of analysis, main limitations, and conclusions.

Results

The search yielded 343 publications, of which 43 were excluded for being duplicates. Thus, 300 titles were evaluated in the first stage. Of these, 264 were rejected for not meeting the inclusion criteria. The 36 remaining studies were subjected to reading of their abstracts and, in this second stage, 17 were considered as potentially relevant systematic reviews for evaluation of their full texts. After the full-reading process, 11 publications met the criteria and were included in the overview. **Figure 01** details the selection process in each one of the three evaluation stages.

The characteristics of the reviews included are described in **Table 01**, and the critical evaluation of the publications included is presented in **Table 02**. All the reviews were published in English, between 2007 and 2019. The studies were mainly produced by European authors. The population under study in each review included hospitalized patients belonging to different age groups.

Regarding the databases consulted, the most frequent ones were Medical Literature Analysis and Retrieval System Online (Medline), Excerpta Médica dataBASE (Embase) and Scopus; in addition to that, the number of studies included in the reviews varied from four to 135. Only one of the 11 publications performed a meta-analysis;[11] in addition, the reviews included presented a series of limitations, whose exception becomes valid for the assessment of the risks of bias.

Nine of the publications included in this overview presented medication classes with a positive association for the development of adverse events. It was observed that 17 medication classes, in decreasing order regarding the number of systematic reviews in which they are included, are associated to ADEs: Cardiovascular (8), Antimicrobials (7), Medications for obstructive airway diseases (7), Anticoagulants/Antithrombolytics (6), Diuretics (6), Antidiabetics (5), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (5), Opiates (5), Antiepileptics (4), Corticosteroids (4), Chemotherapy (4), Diuretics (6); Antidepressants (3), Antipsychotics (3), CNS (Central Nervous System) Agents (3), Gastrointestinal (2), Intravenous Fluids (2), and Vitamins (2).[11–19] It is worth noting that the distribution of the medication classes used was based on the Anatomical Therapeutic Chemical (ATC) Classification System[20].

It is also emphasized that three publications associated the prescription of low- or high-risk medications to the development of ADEs[12,15,16]. One publication presented the medications found in the 28 studies included in its review as high-risk, with 73.6% prevalence for the ADE, ADR, ME and Drug-Related Problems (DRPs) outcomes.[15] It is important to define that DRPs are any undesirable event that involves or is suspected to involve drug therapy, interfering or potentially interfering with the desired goals for the patient.[21] In turn, another study, although having included high-risk medications as a factor for ADEs, with 88% prevalence, did not clearly define such medications[12]. In addition to that, the review that presented the low-risk medications did not specify which items were considered, although it did mention the related amount prescribed (≥1)[16]. Finally, two papers associated the use of narrow therapeutic index medications with the development of ADEs[15,18].

Eight systematic reviews and one meta-analysis established a positive relationship between the number of medications prescribed and the development of ADEs[11–16,18,22,23]. The number of medications described varied from 3 to ≥10; however, some publications did not describe the quantity, only mentioning the increase in the number of medications as a risk factor.

Five studies presented a logistic regression analysis to determine the significance of the "number of medications" variable[11,14,16]. Of these studies, the meta-analysis, based on a univariate analysis, considered that polymedication at admission significantly contributed to the occurrence of ADEs (OR: 1.21; 95% CI: 1.03-1.44; p: 0.024) and of preventable ADEs (OR: 1.85; 95% CI: 1.34-2.56; p: 0.000). In this same study, preventable ADEs were associated with more severe harms than non-preventable ADEs (54% vs. 32%, p<0.05)[11]. In another study, the "number of medications" risk factor was associated with ADRs and DRPs. For ADRs, the only statistically significant variable (bivariate and multivariate models) in all publications was the increase in the number of medications prescribed, sometimes associated with a number greater than five. Similarly, for DRPs, the studies inferred an increase in the number of medications prescribed, greater than or equal to five, as a risk factor for DRPs in both statistical models (univariate and multivariate).[16] In this sense, one review evaluated predictive risk models for ADEs and eight instruments considered the number of medications prescribed as a statistically significant variable[14]. The other studies used frequency measures, varying from 35.7% to 76.5%, to associate the number of medications prescribed with ADEs[12,13,15,18]. Finally, two publications using univariate and multivariate analysis, proved that the "number of medications prescribed" variable is associated with the development of ADRs[22,23].

Seven systematic reviews and one meta-analysis established a positive relationship between age and the development of ADEs[11–15,18,22,23]. The "age" variable varied from 53 to ≥84 years old; however, some publications did not describe the age group, only mentioning increases in age as a risk factor.

Five studies presented a logistic regression analysis to determine the significance of the "age" variable[11,14,15,22,23]. Of these studies, the meta-analysis, based on a univariate analysis, considered that age contributed significantly to the occurrence of ADEs and preventable ADEs. In this same study, the patients aged ≥77 years old experienced more ADEs (OR: 2.12; 95% CI: 1.70-2.65; p: 0.000) and of preventable ADEs (OR: 2.55; 95% CI: 1.69-3.84; p: 0.000) when compared to the other age groups[11]. Another study assessed age as a risk factor associated with the development of DRPs. It is relevant to note that the positive association had a prevalence of 36.8%, while the negative association had a prevalence of 18.4%. At the end, a multivariate analysis was performed, which verified that age was not an independent risk factor for DRPs[15]. In addition to that, in the review that assessed predictive risk models for ADEs, four instruments considered age as a statistically significant variable[14]. Finally, corroborating these data, a publication that performed a univariate analysis showed that age is a risk factor for ADRs[23]. Furthermore, one study recognized age as an independent predictor for ADRs, with application of univariate and multivariate logistic regression analyses[22].

Six systematic reviews established a positive relationship between comorbidities and the development of ADEs[12–15,22,23]. These studies presented the variable described as comorbidity; however, none of the publications offered a definition of the number or of the types. Two primary studies from one of these reviews also included the variable defined as the Charlson Comorbidity Index (CCI), which consists of twenty clinical conditions empirically selected based on the effect on the prognosis of patients hospitalized in a General Medicine service in the United States.[14]

In this sense, when specifying the comorbidities, alteration in liver function,[12–15] alteration in the renal function,[12–15,18,22,23] dementia,[13,14] hyperlipidemia,[13,14] heart failure[13,14] and depression[12,13] were positively associated with the occurrence of adverse events. It is noteworthy that three studies did not establish parameters to precisely define liver failure (LF);[12–14] on the other hand, one publication defined the change in liver function when associated with medications that cause liver damage.[15] As for the renal function, five reviews did not establish parameters that define it;[12,13,18,22,23] however, a primary study of a review defined kidney failure (KF) when the glomerular filtration rate is ≤60 ml/min,[14]

similarly to a primary study from another review that suggested creatinine clearance calculation to assess the renal function; this review pointed out the change in the respective function when associated with medications that cause damage to the kidneys.[15]

Three systematic reviews associated allergy history with the occurrence of ADEs[12,15,22]. Through univariate and multivariate logistic regression analysis, one of these studies showed that allergy is an independent predictor for ADRs[22]. In addition to that, although the other two publications have presented a positive relationship with ADEs, one of them had a 2.6% prevalence with a negative association with ADEs[15]. In this sense, four studies established a positive relationship between HT (Hospitalization Time) and ADEs,[12,14,15,22] highlighting that one of them performed univariate and multivariable logistic regression analysis,[22] but only a primary study of one of the aforementioned publications presented the number of days (≥12) that were considered a risk factor[14]. In conclusion, five publications associated female gender with the development of ADEs[13–15,18,22] and, although all of them made a positive association, one of the studies showed a 5.2% prevalence with a negative association with adverse events[15].

Figure 1. Overview studies selection flowchart

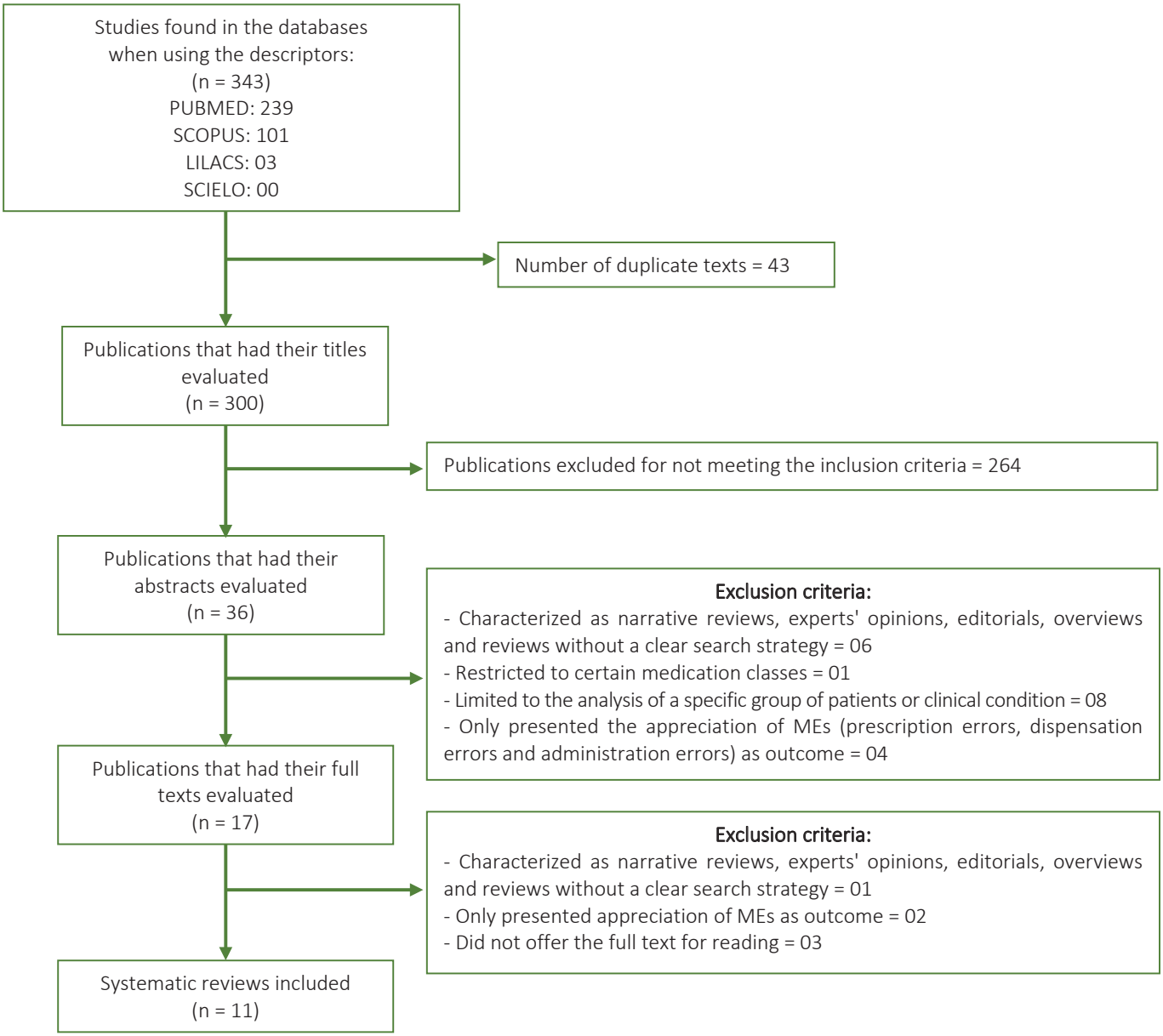

Table 01. Description of the systematic reviews included in the overview. (Continue)

Author/Year	Objectives	Population No. of studies included	Design of the studies	Outcomes	No. of studies/ outcomes	Results	Limitations
Alghamdi et al. (2019)[19]	To review empirical studies that examined the prevalence/ nature of MEs and preventable ADEs in pediatric and neonatal ICUs.	Children ≤18 years old 35	PS, RS e CS	MEs and preventable ADEs	15/MEs and preventable ADEs in a pediatric ICU 10/MEs and preventable ADEs in a neonatal ICU 4/MEs and preventable ADEs in pediatric and neonatal ICUs	The prescription and administration errors were the most common. However, the dosage error was more frequent. Anti-infective agents were commonly involved with MEs/preventable DAEs, both in the pediatric and in the neonatal ICU.	Limited ability to perform a meta-analysis, due to the heterogeneity of the studies included. There were only publications in English and, therefore, research terms in other languages may have been lost.
Alshakrah et al. (2019)[12]	To describe assessment tools used by hospital pharmacies to evaluate patients' priority and/or complexity.	All ages 19	Quali.S, Quanti.S, or mixed pharmaceutical assessment tools used in the hospital setting.	Not applicable	Not applicable	88% of the tools were designed to identify the patients at a higher risk of ADRs, ADEs or MEs and to guide proper pharmaceutical assistance. 59% of the tools were validated. The main risk factors were as follows: high-risk medication (88%), medication that requires monitoring (88%), polymedication (76.5%), use of total parenteral nutrition/ nasogastric tube (17.6%), high-cost medications and number of intravenous and unlicensed drugs (6%).	It only included studies in English and the bibliographic search was performed by only one author.
Falconer; Barras; Cottrell (2018)[14]	To assess the models developed to predict the risk of ADEs in hospitalized adult patients.	≥15 years old 11	Cohort PS and RS of predictive risk models developed with multivariate logistic regression and internal validation.	ADEs	11/ADEs	Ten studies described the development of a new model, whereas one revalidated and updated an existing score. The studies used different definitions for the outcome, although they were synonyms or closely related to ADEs. Four studies performed an external validation, five were internally validated, and two did not validate their models. No study assessed the impact of the risk scores on the patients' results.	Multivariate logistic regression analysis as inclusion criterion. The discussion focused on the predictive models for risk, instead of the risk factors for ADEs.
Mudigubba et al. (2018)[22]	To review the literature in order to determine the risk factors for ADRs in the adult and aged populations.	Adults (no specific age group) and Older adults (≥85 years old) 11	Studies with an explicit definition of ADR and/ or an explicit assessment of causality, as well as a clear description of the method used to identify ADRs.	ADR	4/ADRs in the adult population 6/ADRs in the aged population	Measurable risk factors for ADRs: polymedication, comorbidities, hospitalization time, age, kidney failure, ADR history, and gender. Polymedication was the independent risk factor for ADRs most frequently documented. Kidney impairment did not present any difference between adult and aged patients in relation to the risk. Gender is an independent predictor for ADRs, evidenced in a neglectable number of studies. Aging increases the risk of ADRs in association with several diseases and number of medications.	The number of studies selected was low, as many of them were excluded for not mentioning their sample sizes. Many studies failed to offer an adequate explanation for the non-significance of the risk factors.

Table 01. Description of the systematic reviews included in the overview. (Continue)

Author/Year	Objectives	Population No. of studies included	Design of the studies	Outcomes	No. of studies/ outcomes	Results	Limitations
Andrade et al. (2017)[16]	To identify the risk factors for ADRs in hospitalized pediatric patients.	<18 years old 7	Cohort PS	ADR	6/ADR	The only risk factor noticed in all the studies was the increase in the number of medications prescribed. Other factors: increase in the hospitalization time or in the number of low- or high-risk medications prescribed, use of general anesthesia, and cancer diagnosis. The cumulative incidence of ADRs was 16.4% (95% CI: 15.6-17-2). The main responsible for the identification of ADRs was the pharmacist, and the dominant category among the ADRs was that of gastrointestinal disorders. In addition to that, analgesics, antibacterial agents and corticosteroids were the medication classes commonly associated with ADRs.	It only assessed children. ADRs were the only outcome evaluated. Due to the discrepancies and heterogeneities, it was not possible to perform a meta-analysis.
Suggett; Marriott (2016)[15]	To determine the diverse evidence for measurable risk factors that predispose the patients to the need for a clinical pharmaceutical intervention in their treatment.	>16 years old 38	Primary studies and literature reviews.	Risk for ADRs with the need for pharmaceutical interventions	38/Risk factors for DRPs 28/Risk medications for DRPs	The ten risk factors most frequently associated with DRPs that could potentially lead to an in-hospital pharmaceutical intervention are as follows: prescription of certain medications or medications classes, polypharmacy, aged patients, female gender, impaired renal function, presence of multiple comorbidities, the patient's hospitalization time, history of allergy or sensitivity to medications, patient's compliance issues, and defficient liver function. The ten medication classes most associated with DRPs leading to an in-hospital pharmaceutical intervention are as follows: intravenous antimicrobials, thrombolytics/anticoagulants, cardiovascular agents, CNS agents, corticosteroids, diuretics, chemotherapy, insulin/hypoglycemic agents, opiates and anticonvulsants.	Exclusion of qualitative risk factors.
Boeker et al. (2015)[11]	To identify characteristics of the patients/ types of medications associated with ADEs, to suggest target areas to reduce the harms, and to implement targeted interventions.	≥18 years old 4	PS of multicenter randomized cohorts.	Preventable and non-preventable ADEs	4/Preventable and non-preventable ADEs	Patients aged ≥77 years old experienced more preventable and non-preventable ADEs when compared to those aged ≤52 years old. Polymedication at admission increased the risk of preventable and non-preventable ADEs. Preventable ADEs at admission were associated with more severe harms than non-preventable ADEs. The five main high-risk medications were antibiotics, sedatives, anticoagulants, diuretics and anti-hypertensives.	It removed HT from the analysis and selection of risk factors limited to studies with individual patients.

Table 01. Description of the systematic reviews included in the overview. (Continue)

Author/Year	Objectives	Population No. of studies included	Design of the studies	Outcomes	No. of studies/ outcomes	Results	Limitations
Saedder et al. (2015)[23]	To systematically review the diverse evidence about the relationship between the risk factors related to the patient and the development of severe ADRs.	Adults (no specific age group) and Older adults (≥65 years old) 26	OS and most of them are PS. A case-control study was included, and another included psychiatric patients.	ADR causing and/or during hospitalization	19/ADR causing hospitalization 5/ADR during hospitalization 2/ADR causing and during hospitalization	4% of the patients presented ADRs. The frequency of severe ADRs varied from 0.5% to 23.6% of the patients. In studies that exclusively investigated the aged population, the frequency of severe AR was 11.9%. The risk factors most frequently investigated were as follows: gender, age, comorbidities, number of medications, and impaired renal function.	The heterogeneity of the populations under study in relation to age, size and comorbidities precluded performance of a meta-analysis. Most of the studies were of a descriptive nature, with the consequent absence of a control group. Most of the studies included were cross-sectional and, as such, investigated the immediate relationship between exposure to medications and ADRs. It was not possible to adequately assess the influence of the independent variables, their confounding character, and the possible interactions between them. It did not formally assess the risk of bias.
Alhawassi et al. (2014)[13]	To review the literature in order to estimate the prevalence of ADRs in aged individuals on acute care and to identify factors associated with an increased risk of ADRs.	Older adults (≥65 years old) 14	OS, including large RSs of administrative data cohorts to smaller PSs in the clinical setting.	ADR	14/ADR causing and during hospitalization	The mean prevalence of ADRs in aged individuals in the studies included was 11.0% (95% CI: 5.1%-16.8%). The mean prevalence of ADRs causing hospitalizations was 10.0% (95% CI: 7.2%-12,8%), whereas the prevalence of ADRs during hospitalization was 11.5% (95% CI: 0%-27.7%). There was a significant variation in the overall prevalence of ADRs, from 5.8% to 46.3%. Female gender, increased comorbidity complexity, and increased number of medications were all significantly associated with an increased risk of ADRs.	The quality of the studies included presented a wide variation; no studies fully met the inclusion criteria, only three studies reported sample size calculations, and the heterogeneity of the studies included limited the ability to gather data and provide summary estimates of ADR prevalence across the population of the review.
Saedder et al. (2014)[17]	To conduct a bibliographic research study in order to define medications that cause severe MEs and to compile a list with those identified as high-risk.	Adults (no specific age group) 135	Of the 74 articles, 36 were reports of one or more cases and the others were ESs. The other 61 references were obtained from the NAPRC, the PIA homepage, and the DPSD.	Severe MEs	21/Fatal MEs 44/Non-fatal MEs	47% of all severe MEs were caused by seven medications or medication classes: methotrexate, warfarin, NSAIDs, digoxin, opioids, acetylsalicylic acid, and beta-blockers. 30 medications or medication classes caused 82% of all the MEs. The ten main medications involved in fatal events accounted for 73% of all the medications identified.	The number of fatal MEs constituted a large part of the total number of MEs, and the frequency of severe ME caused by some medications was very high when compared to the use frequency of these drugs. Another limitation was that the medications that have been on the market for many years will appear a greater number of times, despite the decline in clinical use when compared to newer drugs.

Table 01. Description of the systematic reviews included in the overview. (Conclusion)

Author/Year	Objectives	Population No. of studies included	Design of the studies	Outcomes	No. of studies/ outcomes	Results	Limitations
Krahenbuhl-Melcher et al. (2007)[18]	To conduct a bibliographic research study reporting the frequency of MEs and/ or ADRs in hospitalized patients.	It did not specify the age group 77	Frequency studies	MEs, ADRs and DAEs	35/MEs 46/ADRs or DAEs 4/MEs and DAEs	35 articles reported the ME frequencies and 46 articles reported the ADR or DAE frequencies in hospitalized patients. Four studies reported MEs and DAEs. The most important risk factors for MEs included lack of information about medications or about the patients to be treated, errors in medical records and/or nurses' documentation, and inadequate or decentralized pharmacy services. Important risk factors reported for ADRs and ADEs included polypharmacy, female gender, administration of medications with a narrow therapeutic range, renal elimination of drugs, age>65 years old, and administration of anticoagulants or diuretics.	-

NSAIDs = Non-Steroidal Anti-Inflammatory Drugs, DPSD = Danish Patient Safety Database, AE = Adverse Event, ADE = Adverse Drug Event, ES = Epidemiological Study, ME = Medication Error, OS = Observational Study, PS = Prospective Study, Quali.S = Qualitative Study, Quanti.S = Quantitative Study, RS = Retrospective Study, CS = Cross-sectional Study, CI = Confidence Interval, NAPRC = National Agency for Patients Rights and Complaints, PIA = The Patient Insurance Association, ADR = Adverse Drug Reaction, CNS = Central Nervous System, HT = Hospitalization Time, ICU = Intensive Care Unit.

Discussion

Using the PRISMA recommendation, as seen in **Table 02**, it was possible to note that the reviews presented adequate compliance with some criteria, such as description of the sources used and the data extraction processes, in addition to characterization of the studies selected and presentation of their own limitations. However, some reporting problems were found, given that not all reviews presented the eligibility criteria clearly, carried out study selection by paired review, or even made the research protocol available. These factors are worrisome, as they confer a strong risk of bias to the studies, with the possibility of producing errors and coming to wrong conclusions.

When considering the 17 medication classes associated with the risk of ADEs identified in this overview, it is verified that the precise description of the risk of each class, both alone and in combinations, is still incipient in the literature, as is the comparison between medications that belong to the same group. However, a recent study in UK hospitals showed, through multivariate analysis, that systemic antimicrobials (adjusted Odds Ratio: 1.44, 95% Confidence Interval: 1.08-1.92) and medications to treat epilepsy are independently associated with the occurrence of DRPs (adjusted Odds Ratio: 1.61, 95% Confidence Interval: 1.16-2.25), which corroborates the current overview.[24]

Regarding the number of medications, it is verified that polymedication increases the probability of ADRs, MEs, drug interactions, drug-disease interactions, falls, HT and mortality;[25–27] in addition to hindering adherence to the treatment, configuring an independent risk factor for ADEs.[15] Therefore, patients hospitalized on polymedication, more than any others, must be monitored and properly oriented regarding the use of their medications.[28]

When discussing the "age" variable in this overview, it was verified that the reviews included older-aged people, starting from 53 years old. However, some research studies indicate that advanced age alone does not represent an independent risk factor for ADEs, and that this probability is associated with other variables that characterize the general health status of the aged individual, such as presence of comorbidities, polymedication, use of potentially inappropriate medications (PIMs) and the quality of adherence to the treatment.[29–31] It is noteworthy that PIMs are those drugs that should be prevented or used with caution by the aged population, as the risks related to their use are greater than the benefits, especially in the face of other therapeutic alternatives available.[32]

Given the above, the presence of comorbidities tends to potentiate the risks for ADEs. Thus, older adults represent the most vulnerable group due to the numerous chronic diseases related to aging, such as dyslipidemia, hypertension, diabetes and depression, among other conditions that are less frequent among young people.[33] In turn, the simultaneous presentation of several diagnoses requires the concomitant use of multiple medications, which implies a strong association between these three variables (age, comorbidities and number of medications), as well as the difficulty of investigating the risks separately. In this sense, more studies are necessary to elucidate the actual contribution of each factor to the occurrence of ADEs.

Among the comorbidities, KF is strongly related to ADEs, due to the risk of drug-induced nephrotoxicity. This condition is developed when a person that presents a series of susceptibilities to renal dysfunction is exposed to a nephrotoxic drug or metabolite. This is a very common situation in older adults and in patients on polymedication due to the renal metabolism overload to

eliminate the drugs, in addition to the risk of drug interactions.[34] In addition to the risk factors related to the patient's characteristics, specific medication classes can contribute to the development of kidney injury, including antihypertensive agents that block the renin-angiotensin system, antimicrobials, chemotherapy drugs, analgesics, contrast solutions, immunosuppressants and herbal preparations or preparations containing heavy metals.[35] Another very frequent comorbidity in the research studies on ADEs is LF. Similarly to renal impairment, some studies show that liver dysfunction indicates an increased risk of ADEs when specific medications are used, including antimicrobials, anticonvulsants, statins, anticoagulants, proton pump inhibitors, inhalational anesthetics and NSAIDs, among others.[36]

With regard to HT, this overview was unable to find a direction on how to assess the relationship between hospitalization days and the risk of ADEs, due to the low number of studies that used this variable as a risk factor. It seems logical that the longer the hospitalization time in days, the higher the probability of having an ADE, and the diverse evidence verifies this positive association[37].

Another quite predictable risk factor concerns the patient's allergies. Similarly, few of the studies analyzed in this overview included this predictive variable. Despite that, allergies are unpredictable ADRs, and diagnosis of this reaction can result from a real event or from the patient's report. Some allergic reactions are severe and can trigger fatal anaphylaxis, while other individuals may have milder conditions, with self-limiting symptoms. Regardless of the allergy mechanism, knowledge of this characteristic of the patient almost always constitutes an absolute contraindication in hospital care.[38]

Table 02. Critical evaluation of the systematic reviews included in the overview.

No.	Item	Alghamdi et al. (2019)[19]	Alshakrah et al. (2019)[12]	Falconer; Barras; Cottrell (2018)[14]	Mudigubba et al. (2018)[22]	Andrade et al. (2017)[16]	Suggett; Marriott (2016)[15]	Boeker et al. (2015)[11]	Saedder et al. (2015)[23]	Alhawassi et al. (2014)[13]	Saedder et al. (2014)[17]	Krahenbuhl-Melcher et al. (2007)[18]	n
1	Title	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
2	Structured abstract	N	N	N	N	N	N	N	N	N	N	N	**0**
3	Reason	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
4	Objectives	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
5	Protocol and registration	N	N	Y	N	N	N	N	N	Y	N	N	**10**
6	Eligibility criteria	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	**10**
7	Information sources	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	**10**
8	Search	Y	Y	Y	N	Y	N	Y	N	Y	Y	N	**7**
9	Selection of the studies	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
10	Data collection process	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
11	Data list	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	**8**
12	Risk of bias in each study	N	Y	Y	N	Y	N	N	N	N	N	N	**3**
13	Summary measures	Y	N	N	Y	N	N	Y	N	Y	N	Y	**5**
14	Synthesis of the results	X	X	X	X	X	X	Y	X	X	X	X	**1**
15	Risk of bias across studies	X	X	X	X	X	X	N	X	X	X	X	**0**
16	Additional analyses	X	X	X	X	X	X	N	X	X	X	X	**0**
17	Selection of studies	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	**10**
18	Characteristics of the studies	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	**10**
19	Risk of bias in each study	N	N	N	N	N	N	N	N	N	N	N	**0**
20	Results of individual studies	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	**7**
21	Synthesis of the results	X	X	X	X	X	X	Y	X	X	X	X	**1**
22	Risk of bias across studies	X	X	X	X	X	X	N	X	X	X	X	**0**
23	Additional analyses	X	X	X	X	X	X	N	X	X	X	X	**0**
24	Summary of the evidence	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
25	Limitations	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	**10**
26	Conclusions	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
27	Funding	N	Y	N	N	N	Y	Y	N	N	Y	Y	**5**
T		**16/21**	**16/21**	**16/21**	**14/21**	**16/21**	**13/21**	**18/27**	**14/21**	**15/21**	**13/21**	**15/21**	

N = No, Y = Yes, T = Number of requirements met in relation to total requirements, X = PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) items not evaluated, n = Number of studies that obtained "yes " for each PRISMA item.

In turn, the association between female gender and ADEs is uncertain in the literature, and some studies show that this variable does not represent an independent risk factor[31,39]. In other words, it is not possible to state that the greater volume of evidence about ADEs in women is due to the gender's physiological characteristics, or whether specific women's issues are involved in these results, such as menstruation, pregnancy and menopause;[40] use of oral contraceptives;[41] better self-perception of health, which increases their complaints of discomfort, disease symptoms and adverse events[42] and, consequently, the number of visits to the health services;[43] in addition to a greater number of medications used by women as a result of all these situations.[13] Consequently, more studies are necessary to accurately elucidate the "gender and ADEs" relationship.

This overview presents some limitations. Only three publications focused on the ADE outcome itself; the others examined ADRs, MEs and the need for pharmaceutical interventions. Only one meta-analysis was included. Another potential limitation was the fact that some information was not available in the studies evaluated, which restricted content analysis. For example, one review included various pharmacotherapy risk score tools, although it did not discuss the variables selected by each instrument in depth. It is important to note that three articles were not evaluated for not having their full texts available.

Conclusion

The results of the current study indicate the following risk for the development of ADEs during hospitalization: number of medications prescribed, advanced age, comorbidities (in particular, LF and KF), allergy associated with medication use, female gender and HT. In addition, 17 medication classes can increase the patient's risk, the main ones being cardiovascular, antimicrobials, medications for obstructive airway diseases, anticoagulants/antithrombotics and diuretics. Finally, the risk factors for ADEs surveyed in this overview can help hospital teams direct their care actions to the patients at a higher risk of ADEs.

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Conflict of interest statement

The authors declare that there are no conflicts of interest in relation to this article.

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