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Review Paper

A SYSTEMATIC REVIEW OF RISK FACTORS OF ADVERSE DRUG REACTIONS IN HOSPITALIZED PATIENTS

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ABSTRACT

Adverse drug reactions (ADRs) pose both financial and health encumbrances for patients. Although prevalence and risk factors associated with ADRs have been published in many studies, most of them lack the statistical evidence for predictors. The aim of this study was to review the published literature to determine the risk factors in the adult and elderly population for ADRs. An electronic search of articles published in English language in databases such as Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, Scopus, and Google Scholar was conducted in between January 2001 and April 2018. The search terms used were: "ADRs," "drug-related problems," "risk factors," "general adult population," "elderly patients," and "hospital admission." For inclusion in the review, studies had to include an explicit definition of what was considered an ADR and/or an explicit assessment of causality, as well as a clear description of the method used for ADR identification. Polypharmacy was the major risk factor of ADR followed by comorbidities and length of hospital stay.

Keywords: Adverse drug reactions, Risk factors, Elderly patients, Adult patients, Logistic regression.

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INTRODUCTION

Patient safety is one of the most essential elements of modern-day health-care systems [1]. With the mounting reliance on medication therapy as the primary intervention for most illnesses, medications may also cause either non-preventable adverse effects or potentially preventable medications errors [1,2]. Adverse drug reactions (ADRs) are common causes of mortality and morbidity worldwide, and its occurrence in real-world medical practice cannot always be predicted by pre-marketing data given that a limited number of selected patients are enrolled in clinical trials for specific indications and monitored for a limited period of time [3]. Various studies in general adult populations have quantified that 5%–7% of all hospitalizations are due to ADRs, with over half of these arbitrated to be preventable, and that 3%–6% of ADRs are fatal or have serious health consequences [4-6]. Health-care costs attributable to ADRs have been estimated to be 5%–9% of total inpatient costs per annum [7]. Older people experience greater morbidity with a corresponding increase in medication utilization, resulting in a higher risk of ADRs. The relative physiological change that occurs with aging affects the pharmacokinetics and pharmacodynamics of medications, which may increase the potential for drug toxicity and ADRs [8]. Various definitions are being identified by researchers for ADR, for instance, the US FDA definition described it as "any adverse event for which there is a reasonable possibility that the drug caused the adverse event, 'reasonable possibility' suggesting a causal relationship between the drug and the adverse event"[9], the World Health Organization (WHO) defines it as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man" [10], and as per Edwards and Aronson definition, "ADR is an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"[11].

There are various factors that predispose patients to ADRs such as polypharmacy, age, intercurrent diseases, comorbidity, gender, history of ADRs, and length of hospital stays [12]. Although few authors have explored the relationship between the risk factors and ADRs [13-15], there exists a controversial corroboration due to differences in definitions, study settings, study designs, study population, statistical methods, race, and ethinicity [16]. Few studies explored that female gender is the major predictor of adverse reactions [17-20], while other findings documented that patients with age above 65 years had more than 50% of hospitalizations due to ADRs [5,21].

Even though a large number of studies have identified and assessed ADRs, little has been focused on the associated risk factors with appropriate statistical analysis in adult and elderly population. This review was conducted with the aim to determine potential significant risk factors of ADRs during hospitalization in the adult and elderly population.

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. An electronic search of articles published in English language in databases such as Cochrane database of systematic reviews, MEDLINE, EMBASE, Scopus, and Google Scholar in between January 2001 and April 2018 was conducted. Medical subject heading terminology and other keywords were used for studies published in different databases. The search terms used were: "Adverse reactions," "ADRs," "adverse effects," "drug-related problems," "risk factors," "predictive factors," "general adult population," "elderly patients," and "hospital admission." The auxiliary search terms used included: "Drug adverse effects," "drug therapy," "geriatric," "hospitalization," and "emergency admissions." All the titles and abstracts of identified studies were examined critically for potential relevance. The reference lists of all eligible full-text articles were hand searched and reviewed to locate other relevant original studies. Two reviewers undertook searches independently and assessed and discussed study findings, and the final consensus was reached to ensure the search strategy was accurate and reproducible.

All studies that were peer-reviewed, highly citation, available in English language, and full-text articles were included. Those studies that

reported ADRs either prospectively or retrospectively in hospitalized adult and elderly patients were included, irrespective of hospital department or specialty. For inclusion in the review, studies had to include an explicit definition of what was considered an ADR and/or an explicit assessment of causality, as well as a clear description of the method used for ADR identification. In particular, studies also had to explore factors associated with an increased risk of an ADR statistically through logistic regression (univariate and multivariate).

Studies that looked at ADR-related hospital readmissions were excluded from the review. Those studies with only abstracts were excluded if the full-text article could not be found, as it restricts meaningful evaluation and quality appraisal provided in abstracts. Studies and/or clinical trials that reported adverse reactions in special population such as pediatric and pregnant women and lactating mothers were excluded. Those studies that reported ADRs associated with off-labeled drug usage were also excluded from the study.

All the titles and abstracts that fulfilled inclusion criteria were assessed critically for relevance of title, year of publication, first author, country of origin, study sample size, study population, study design, and subject age groups. Data were extracted including explicit ADR definition, identification method, risk factors, statistical method and prevalence, and causality assessment using a custom-designed data extraction form. In those studies, where the prevalence was not directly reported, it was calculated by dividing the number of patients identified with an ADR of all included patients. Extracted data were entered into Microsoft Excel 365 for descriptive data analysis. Overall mean±standard deviation of ADR prevalence was calculated at 95% confidence intervals (CIs).

ADR ASSOCIATED RISK FACTORS - ADULT POPULATION

The risk factors were categorized as patient-related and medication-related risk factors. Univariate analysis identified very few significant medication-related risk factors such as polypharmacy [1,15,22,23], non-adherence [1], anti-tuberculosis drugs [23], and ART drugs [23]. Whereas results of multivariate analysis concluded that polypharmacy [1,15,22,23] was the highly influential independent predictor of ADR. Patient-related risk factors such as comorbidities, female gender, body mass index, h/o ADR, length of hospital stay, impaired renal function, number of diagnoses, and dependent living situation were significant [1,15,22,23]. Among these, comorbidity was evidenced as independent predictor in four studies, followed by h/o ADR and length of hospital stay.

ADR-ASSOCIATED RISK FACTORS - ELDERLY POPULATION

In this assessment of the effect of predictors in the development of ADRs, under univariate analysis, patient-related determinants were age, female gender, comorbidities, length of hospital stay, renal failure, liver disease, dementia, IHD, heart failure, depression, hyperlipidemia, and increased serum concentration and the medication-related predictors were polypharmacy, number of doses, narrow therapeutic drugs, anticholinergic drugs, antiarrhythmics, and antihyperglycemic drugs, and inappropriate prescription was significant [25-30]. While in the multivariate analysis, age ≥85 years [27], female gender [26], and length of hospital stay [29] were patient-related independent predictors and polypharmacy was the only one medication-related independent predictor identified in four studies, in which polypharmacy with ≥8 drugs was observed as the highly influential predictor in two studies [28,29] and ≥5 drugs was evidenced in a single study [26].

To the best of our knowledge, this is the first kind of systematic review that appraised univariate and multivariate logistic regression in the identification of significant risk factors for ADRs. This search found only 11 studies that met the inclusion criteria, and nearly half of the studies were done in adult population. Studies showed explaining the variations in prevalence rates and risk factors of ADRs.

An overall up to 13.7% of patients admitted to hospital experience an ADR during their hospitalization, while previously conducted systematic review [31] projected that up to 4% of all adult patients admitted to hospital experience an ADR either leading to or during their hospital admission. However, a meta-analysis conducted by Oscanoal *et al.* [32]., in the year 2017, reported that the prevalence of ADR among elderly patients that led to hospital admissions accurately to be 8.7% (95% CI, 7.6%–9.8%).

In our review, three unambiguous definitions were being utilized in the studies for ADR identification which might explain the differences in ADR prevalence rate reported. Previous literatures [33] have sufficiently elaborated on the contribution of different fundamental criteria adopted in various setting in the identification of ADR between reported studies with respect to prevalence. Although one study used USFDA definition, there was no significant change in prevalence rate reported owing to the slenderest difference compared to the WHO definition.

RISK FACTORS OF ADRs

In our review, overall 80 risk factors were studied among the total population of 20,974, wherein 30 significant risk factors were recognized as potential and 18 as independent predictors of ADRs based on univariate and multivariate logistic regression analysis (Table 1).

Polypharmacy

Polypharmacy was the most consistent and highly acknowledged predictor witnessed in almost all the literature to quantify the risk associated with ADR [1,15,24,26-29,34]. In continuation, few studies quoted that polypharmacy is chosen when a patient presents with multiple comorbidities in order to augment the initial therapy and advanced age of patients who may require drugs with varied mechanisms of action [35]. However, polypharmacy intensifies the possibility of ADRs due to drug- drug interactions from 2% to 5% [36-40] and may heighten it up to 9% with each additional prescribed drug thereafter [27]. And also, it can increase the risk of multiple ADRs than single ADR [41]. It is important for the prescribers to ponder on this risk factor, take imperative steps to reduce the risk through usage of combinational drugs, or discontinuation of unnecessary drugs through reevaluating the disease condition of the patients specifically in older adults. Reducing the number of drugs in the prescription is the simplest way of reducing the ADRs [42]. Furthermore, the total number of drugs along with the individual drug's risk could be incorporated into an electronic algorithm and determining the benefit-to-risk ratio of individual drug therapy is essential to minimize polypharmacy.

Comorbidities

Comorbidity was the second most frequently reported significant risk factor for ADR in the adult and elderly patients [1,22,23,25,26,28,30]. However, three studies particularized through the application of multivariate logistic regression to identify it as an independent predictor of ADR but then only in adult patients [1,22,23]. Two authors expressed renal dysfunction and limited sample size as the possible cause of refuting comorbidity as a significant risk factor. Patients with polymorbidity may have altered pharmacodynamic and pharmacokinetic mechanisms due to drug-disease interaction predisposing them to ADRs and other explanations that require further research in this area.

Length of hospital stay

ADRs are considered as serious health hazard in hospitalized patients. From the findings of the review, significant association was built up between the length of hospital stay and ADRs [24,29]. Findings clarified that the length of stay is the proxy measure of comorbidity and chronic illness with an increased number of prescribed drugs at higher doses, reflecting an increased risk of ADR. The probability of adverse reactions increases 6% for every additional day of hospitalization [43], and every 2.2 hospital bed day of patient was due to ADRs [26]. Length of hospital stays ≥12 days was 2.3 times of the risk for ADR [33], and it has more importance than patient characteristics in the explanation of ADR [44]. To back up this, literature witnessed that about 5% of all hospital

Table 1: Significant predictors of ADRs in univariate and multivariate logistic regression model

Identified risk factors associated with ADRs	Univariate analysis p<0.05	Multivariate analysis p<0.05
Patient-related factors		
Female gender	Yes	Yes
Comorbidity	Yes	No
Length of hospital stay	Yes	Yes
H/o allergy to the drugs	Yes	No
Renal failure	Yes	Yes
Liver disease	Yes	No
Age	Yes	Yes
Dementia	Yes	Yes
Heart failure	Yes	Yes
Hyperlipidemia	Yes	Yes
High WBC count on admission	Yes	No
Non-adherence to the medication regimen	Yes	Yes
H/o ADR	Yes	Yes
BMI	Yes	Yes
Ischemic heart disease	Yes	Yes
Depression	Yes	Yes
Medication-related factors		
Inappropriate prescription/STOPP medication	Yes	Yes
Drug changes in the preceding 3 months	Yes	Yes
Anticholinergics	Yes	Yes
Antiarrhythmics	Yes	No
Polypharmacy	Yes	Yes
Number of doses	Yes	No
Drugs of NTI	Yes	No
Anti-hypertensives	Yes	Yes
ACE inhibitors	Yes	No
Beta-blockers	Yes	No
Diuretics	Yes	No
Antidiabetic agents	Yes	Yes
Anti-TB drugs	Yes	No
ART drugs	Yes	No

ART: Antiretroviral therapy, WBC: White blood cell, ACE: Angiotensin-converting enzyme, TB: Tuberculosis

admissions were due to ADR with an average length of hospital stay of 1.8-8.5 days per patient per ADR. [45-48].

Age

Older age was reported as an independent predictor of ADR, evidenced only in one study [27], while other studies reported that age was not an independent predictor of ADR. This mismatch may be due to dissimilarities in matching criteria and demonstration of the significance of age as a risk factor only in univariate analysis. However, the incidence of ADRs was significantly higher in the elderly patients compared to other age groups [22,34,49,50], owing to increased age, deteriorating organ function, reduced hepatic and renal clearance, polymorbidity, polypharmacy, usage of over the counter drugs, and alternative medicine [34,51,52].

Renal impairment

It is widely accepted that renal impairment has a direct effect on a number of ADRs, and it was recognized first time in the year 1966 by the Smith *et al.* [53]. However, our review findings identified that it was an independent predictor of ADR in both adult patients and elderly patients [1,23,27,30]. The patients with renal impairment display altered drug clearance results that may ensue either drug toxicity or subtherapeutic effect. Hence, it is pretty much important for early estimation of creatinine clearance to identify the renal function, before prescription of such drugs having higher risk ADRs, particularly in elderly patients.

History of ADR

This review highlighted that history of ADR as a significant predictor in adult population which may be because of their active immunity compared to elderly patients. Two studies stated that patients with previously experienced ADRs were having 17.46 times odds of ADR in tuberculosis and 28.94 times odds in HIV/AIDs positive [22,23]. Prescriber's attention toward medication and ADR history taking may reduce the recurrence of ADR in such vulnerable population.

Gender

Female gender was identified to be an independent predictor of ADR in the two articles [22,26], while one study revealed significance only through univariate logistic regression analysis [15]. However, further detailed research is required for a definite relationship. Few explanations behind the predisposition of women for ADR were attributed to them having lower lean body mass, reduction in hepatic clearance, differences in activity of cytochrome P450 (CYP) enzymes, and metabolization of drugs at different rates compared with men [54]. Moreover, females are known to use oral contraceptives, hormonal supplements adding on to increased number of drugs, especially in their reproductive years, and vitamin and mineral supplements during pre and postmenopausal periods that may predispose them for ADRs [55]. However, few studies recommended that it was not a significant risk factor of ADR through their observations [35,56].

Strengths and limitations

Strength of the present review was strict inclusion criteria mandating assessment of risk factor with fitting statistical method and usage explicit definitions of ADR. The number of studies selected was low, as many studies did not mention true sample sizes had to be excluded. Many studies failed to give the appropriate explanation for their insignificance of risk factors. However, our quality assessment of each study was subjected to affirm the independent predictors of ADRs.

CONCLUSION

Review of literature found eleven papers that detailed the following measurable risk factors polypharmacy, comorbidities, length of stay, age, renal impairment, history of ADR, and gender linked with ADRs. Multiple drug regimen is the most frequently documented independent medication-related risk factor of ADR. Renal impairment had non-discrimination in both adult and elderly patients with respect to their risk. Gender is an independent predictor of ADR evidenced in a negligible amount of studies; further, more research is required to find its definite relationship with ADR. Aging increases the risk of ADR in association with multiple diseases and number of drugs. There is a great significance for reevaluation of pharmacotherapy in the elderly patients to reduce the risk of drug-related issues. Researchers and health-care professionals should consider all the factors of drug-related issues for the rationale of treatment.

AUTHOR'S CONTRIBUTION

Manoj Kumar Mudigubba: Conceptualized the article, compiled full literature search, and drafted the manuscript. Mamatha Krishna Murthy: Developed the standards of manuscript. Ann Mary Swaroop: Reviewed and edited the manuscript. Nayantara M: Compiled literature search and evaluated. Saurabh Dahiya: Supervisor of the research work, provided guidance in the preparation of a standard paper.

CONFLICTS OF INTEREST

Authors declared no conflict of interest.

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