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RISK FACTORS ASSOCIATED WITH ADVERSE DRUG REACTIONS IN HOSPITALIZED PATIENTS

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ABSTRACT: Background: Understanding the association of risk factors to adverse drug reactions is very important to all healthcare professionals for the development of appropriate preventive strategies for better health care. **Objectives:** To identify and evaluate the risk factors associated with adverse drug reactions developed in the hospitalized patients of different departments. **Methods:** A prospective-retrospective study was conducted in a tertiary care hospital for a period of twenty two months, with a specific criterion. Multiple logistic regression analysis was used. Risk factors included provisional diagnoses, suspected drugs which were classified according to ICD-10 classification and therapeutic classification respectively and also subjects' age groups and gender were included. **Results:** A total of 204 cases' were identified with adverse drug reactions during the period of study for which 1:1 ratio of controls were taken. During the study 175 subjects developed single ADRs (adverse drug reactions) and 29 had multiple ADRs. Causality assessment and severity of reactions were evaluated by using standard scales. Greater association to ADR were shown in the age group of 61-70 years (OR 5.263 95 CI (29.693-0.935)) and males were more likely to experience ADRs. Polypharmacy was identified as major risk factor in the development of adverse drug reactions. **Conclusion:** In order to minimize the risk of ADRs, early detection and awareness of risk factors plays an important role. Healthcare team should pay more attention in vulnerable age groups and to reduce the irrational drug prescriptions for better patient healthcare.

INTRODUCTION: Adverse drug reactions are increasingly becoming a challenge to the health care professionals. Pharmacovigilance program was started a decade ago but still the understanding and awareness of adverse effect is in infancy in India. Reasons behind the associating and worsening of the adverse effects were predisposing factors which played a major role.

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The patient population faces economic adversities due to burden of adverse effects. As per World Health Organization definition, an Adverse Drug Reaction (ADR) is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for diagnosis, prophylaxis and therapy [1]. There is diversity in the effect of predisposing factors to the development of adverse drug reactions [2]. Kunnoor *et al.*, from his observations concluded that age group was the greater risk factor, age ≥ 60 years more likely developed higher rate of adverse drug reactions and gender has not shown the significant difference in ADR rates [3]. But from the observations of Stabile *et al.*, gender differences in relation to the onset of ADRs and effectiveness of drug was studied, where

the females (54.57%) developed higher rate of ADRs than males (45.43%) [4]. The impact of risk factors on adverse drug reactions may vary due to difference in ethnicity, study population, time duration of study, criteria etc. A failure of the drug action or wrong use of the drug is defined as medication error which leads to adverse drug event [5]. Usage of drugs in a proper manner helps in better curing of disease. The errors in the drug usage results in drug related injuries to patients [6].

Fattinger K *et al.,* concluded that out of 48% of the hospitalizations, one possible drug-related event was recorded and at least one clinically relevant adverse drug reaction was recorded in 11% of the hospitalizations. In these drug related problems majority were presented with clinical symptoms (8%) and very less were exhibited clinically relevant abnormal laboratory results (4%) [7]. Another definition which accounts causality assessment, defines ADR as an adverse drug event which is judged to be caused by the drug [8]. The importance of present study was to assess the risk factors behind the development and worsening of adverse drug reactions.

MATERIALS AND METHODS: This prospective-retrospective study was conducted at a tertiary care hospital in South India. Study period was defined based on the study design, three months of data retrospectively and nineteen months of data prospectively collected, assessed and evaluated. Cases were differentiated from controls with specific predefined criteria. Cases are the subjects' who had developed adverse drug reactions subsequent to prescribed drugs during hospitalization. These cases were identified during the regular ward rounds of various specified departments like General Medicine ward, Paediatrics ward, OBG ward, Dermatology ward, Psychiatry ward and Orthopaedic ward. Data was collected from the suspected case sheets. Subject and Care-taker were interviewed well about the previous medical and medication history, co-morbid conditions, life style and diet which also updated in patient case sheet for future reference. Retrospectively case data was collected from the reported documents which were stored in drug information center and control data from the medical record database of the hospital. Institutional Ethical Committee Clearance and No Objection Certificate from Medical Superintendent of the hospital were obtained prior to the initiation of the study (BMCH&RC/MS/2016-17/338). Controls were taken as 1:1 ratio. Severity of suspected adverse effects was evaluated as mild, moderate and severe by using the specific standard scale called Hartwig and Seigels scale, and causal relationship between the suspected drug and ADR was identified by using the Naranjo`s algorithm. For assessing the risk factors, in association of information obtained from subjects, various supportive recourses like Pharmacology textbooks, databases like Micromdex and Lexicomp were also used. Statistical software SPSS 20 version was used. Multiple logistic regression analysis was applied to evaluate the association of risk factors with the ADRs.

RESULTS: The criteria were fulfilled by 408 subjects, who were included in the study. Out of these subjects, 204 were included as cases and the rest were included as controls. By the distribution of cases as per gender, males (51.5%) developed more adverse drug reactions than females (48.5%) (**Table 1**). Development of greater association of the adverse drug reaction (OR 5.263 95CI (29.693-0.935) p-value 0.060 identified in the age group of 61-70 years (**Table 4**). But higher proportions (22.5%) of ADRs were identified in the age group of 41-50 years (**Table 1**).

TABLE 1: DISTRIBUTION OF ADVERSE EFFECTS ACCORDING TO PATIENT DEMOGRAPHIC CHARACTERISTICS AND ADR RECOVERY TIME IN 204 CASES

Gender	Percent (%)
Female	48.5
Male	51.5
Age Group	
0-1	1.5
1-10	6.9
11-20	3.4
21-30	17.2
31-40	14.2
41-50	22.5
51-60	11.8
61-70	19.6
71-80	2.0
81-90	1.0

The total recovery time found at an average of 88.8 days. The subjects' were exposed to various classes of drugs in their therapy, which included suspected drugs differentiated according to the therapeutic

class. Antibiotics (27.4%) were identified as the highest responsible for the development of adverse drug reactions (**Table 2**). Cephalosporins (30%) are majorly identified suspected drugs, followed by Fluroroquinolones (17%), Penicillamines (13.2%).

TABLE 2: DISTRIBUTION OF ADVERSE EFFECTS ACCORDING TO SUSPECTED DRUG THERAPEUTIC CLASSES

Therapeutic Class	Percent %
Adrenergic drugs	0.5
Ethanol dependency	0.5
Anthelmintics	0.5
Anti depressants	1.5
Anti epileptics	4.5
Anti fungal agents	0.5
Anti histamines	0.5
Anti manic Drugs	0.5
Anti rheumatic	0.5
Anti tubercular drugs	3.5
Anti- emetic	1.5
Anti-hypertensive	7.8
Anti- psychotics	3.0
Anti- reflux drugs	6.37
Anti-arrhythmic	0.5
Antibiotics	27.4
Bronchodilators	4.5
Bronchodilators + Antibiotic	0.5
Corticosteroids	3.0
GI Protective's	1.5
Glucocorticosteroids	3.0
Haemostatic's	0.5
Hypolipidaemics	1.0
Immunosupressants + Antimalarials	0.5
Insulin	3.5
Mood Disorder	0.5
Muscle Relaxants	0.5
Narcotics	0.5
Nsaids	7.8
Opioid analgesics	2.5
Oral hypoglycemics	3.0
Depigmenting agents	0.5
Sedatives	1.0
Thromboembolics	1.0
Thrombolytics	0.5
Urinary Antiseptic	0.5
Vitamins	0.5
Others	0.5

In our research findings Ceftriaxone (18.9%) is placed at first position as suspected drug of Cephalosporins class which caused higher number of ADRs, majorly it causes skin disorders, followed by redness, swelling and irritation of eyes, severe abdominal pain and headache. Thereafter follows Cefixime which induced facial edema, pedal edema, repeated vomiting which should be probably preventable. Among Fluroquinolones; Ofloxacin induced more adverse drug reactions. Chest pain, arthralgia, skin disorders, and diarrhoea were repeatedly developed ADRs due to fluroquinolones.

Non-steroidal anti-inflammatory drugs (7.8%) and anti-hypertensive drugs (7.8%) developed adverse drug reactions at similar proportions (**Table 2**). Predominantly anti-hypertensives induced adverse drug reactions which were identified in the age group of 61-80 years (50%) were moderately severe (35%) and majority was definitely preventable (55%). Calcium channel blockers (50%) inducing more ADRs followed by angiotensin receptor blockers (20%). NSAIDs induced ADRs which were majorly identified at the age group of 41-50 years, were moderately severe (60%), definitely preventable (45%) followed by probably preventable (30%). Adverse drug reactions affected the various organs of the body, which were classified according to the WHO-ART classification. Majority of ADRs were identified in the class skin and appendages (27.5%), followed by general disorder (20.6%) (**Table 3**).

Potential risk factors associated with ADRs were assessed using multiple logistic regression models, using ADR occurrence as the outcome. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each independent variable. Gender, age group, and provisional diagnoses as per ICD-10 classification were assessed. At the age group of 61-70 years subjects had 5.2 times higher risk of adverse drug reactions. With the statistical estimation of gender effect on the development of adverse drug reactions, it was estimated that there is no much identified differentiation. Males presented risk at the base line and females a bit more than males (OR 1.10 95 CI (1.628-0.784). Along with these we also included the associated diagnoses as per ICD-10 classification. The diseases of human immune deficiency virus to certain infectious and parasitic diseases (B00-B99), disorders of mental, behavioral and neuro-developmental and other specific developmental disorders (F01-F99), diseases of skin and subcutaneous tissue and other localized connective tissue disorders (L00-L99), diseases of upper respiratory infections and chronic lower respiratory diseases (J00-J99), have shown significant association in the development of ADRs (**Table 4**).

TABLE 3: IDENTIFIED ADRS IN THE STUDY CLASSIFIED ACCORDING TO WHOM ART CLASSIFICATION

System/Organ Class	Percentage (%)	ADRs
Skin and appendages	27.5	Steven Johnson syndrome, hyper pigmentation, urticaria, skin rashes
General disorder	20.6	Fever, swelling of limbs, edema,
Gastrointestinal system	15.7	Vomiting, constipation, diarrhea
Central and peripheral nervous system	9.3	Drowsiness, headache, tremors
Vision disorder	4.4	Blurred vision, lacrimation, conjunctivitis
Respiratory system disorder	3.9	Cough, breathlessness, asthma
Psychiatric disorder	3.4	Anxiety, depression
Metabolic and nutritional disorder	2.9	Hyperglycemia, hypoglycemia
Liver and Biliary system	2.5	Hepatitis
Cardiovascular system	1.5	Chest pain, hypertension hypotension
Endocrine disorder	1.5	Cushings syndrome
Platlet, bleeding and clotting disorder	1.0	Bleeding
Red blood cell disorder	0.5	Anemia
Urinary system disorder	0.5	Kidney damage

TABLE 4: RISK FACTORS OF ADVERSE DRUG REACTIONS IN THE STUDY POPULATION

a. Age	Group	p-value	Odds Ratio (95% Confidence Interval)
Below One Year	ADR	0.245	0.300 (2.286-0.039)
	Non-ADR		1.00
1-10 Year	ADR	0.838	0.833 (4.785-0.145)
	Non-ADR		1.00
11-20 Year	ADR	0.931	0.921 (5.885-0.144)
	Non-ADR		1.00
21-30 Year	ADR	0.105	4.167 (23.427-0.741)
	Non-ADR		1.00
31-40 Year	ADR	0.193	3.152 (17.758-0.560)
	Non-ADR		1.00
41-50 Year	ADR	0.073	4.792 (26.559-0.865)
	Non-ADR		1.00
51-60 Year	ADR	0.237	2.857 (16.299-0.501)
	Non-ADR		1.00
61-70 Year	ADR	0.060	5.263 (29.639-0.935)
	Non-ADR		1.00
71-80 Year	ADR	0.518	2.000 (16.362-0.244)
	Non-ADR		1.00
b. Gender	Female	0.620	1.10 (1.628-0.784)
	Male		1.00
c. ICD Classification			
A00.0-A99.9	ADR	.029	3.536 (10.951-1.142)
	Non-ADR		1.00
B00.0-B99.9	ADR	.000*	16.125(56.990-4.562)
	Non-ADR		1.00
D00.0-D99.9	ADR	0.355	0.474 (2.307-0.097)
	Non-ADR		1.00
E00.0-E99.9	ADR	0.116	3.000 (11.811-0.762)
	Non-ADR		1.00
F00.0-F99.9	ADR	0.001*	10.000 (39.064-2.560)
	Non-ADR		1.00
G00.0-G99.9	ADR	0.626	1.400 (5.414-0.362)
	Non-ADR		1.00
I00.0-I99.9	ADR	0.507	1.714 (8.421-0.349)
	Non-ADR		1.00
J00.0-J99.9	ADR	0.022	4.000 (13.048-1.226)
	Non-ADR		1.00
K00.0-K99.9	ADR	0.349	0.333 (3.327-0.033)
	Non-ADR		1.00
L00.0-L99.9	ADR	0.006*	6.000 (21.262-1.693)

	Non-ADR		1.00
M00.0-M99.9	ADR	0.643	1.500 (8.344-0.270)
	Non-ADR		1.00
N00.0-N99.9	ADR	0.346	1.833 (6.462-0.520)
	Non-ADR		1.00
O00.0-O99.9	ADR	0.210	3.000 (16.689-0.539)
	Non-ADR		1.00
Q00.0-Q99.9	ADR	0.998	1.372 (Not-Det-0.000)
	Non-ADR		

a. Reference category is : Non-ADR
b. Reference category is : Male
c. Reference category is : Non-ADR

Various other risk factors associated with ADRs were identified using frequencies, Polypharmacy (11.27%), age (9.8%), intercurrent diseases (8.3%), history of ADR to drug class (3.0%), concurrent interactive drugs (2.0%), gender (1.5%), multiple illness (1.5%) (**Table 5**). Out of 204 cases, 175 subjects developed single ADRs and 29 had developed multiple ADRs (59). We observed 52.50% of cases had undergone suspected drug withdraw and in 8.3% of cases suspected drugs were altered. While 40.2% of cases undergone de-challenge and improvement was identified in 3.9% of cases. 1.5% of cases showed re-occurrence of symptoms during re-challenge, while 98% of cases not undergone re-challenge and 0.5% were unknown. 33.3% of cases had given additional treatment.

TABLE 5: FREQUENCY OF OTHER RISK FACTORS OF ADRS IN THE STUDY POPULATION

Sl. no	Risk Factors	Percentage (%)
1	Age	9.8
2	Gender	1.5
3	Polypharmacy	11.27
4	Multiple illness	1.5
5	Intercurrent diseases	8.3
6	H/o ADR to the drug class	3.0
7	Concurrent interactive drugs	2.0
8	Others	2.5
9	Age + concurrent interactive drugs	0.5
10	Age + Polypharmacy	1.0

DISCUSSION: Adverse drug reactions are the salient cause of complications morbidity and mortality in patients of all ages [9-13]. Aim of this research was to find out association of risk factors in the development of adverse drug reactions and worsening the conditions. We considered the following predisposing factors, age, gender, polypharmacy, multiple illness, intercurrent disease, history of ADR to the drug class, concurrent interactive drugs. During the regular ward rounds of health care team, each patient's suspected case sheet was studied well, assessed and analyzed by using various reference sources and confirmed the adverse drug reaction.

Polypharmacy: It is the major risk factor in developing adverse drug reactions undoubtedly. Literature has been showing that polypharmacy is significantly associated with the occurrence of adverse drug reactions [7, 14-16]. It was confirmed in our study findings showing a relationship between the number of drugs prescribed and occurrence of ADRs. The patients with five to seven prescribed drugs during the hospital stay had highest risk of developing ADR.

In the elderly polypharmacy is an independent risk factor for adverse drug reactions and negative outcomes [17]. Prescribers should be cautious while prescribing the multiple drugs to older adults and during co morbidity, because of physiological alterations in the organ functions due to aging and disease which might lead to increased occurrence of adverse drug reactions [18]. Our research study points out that higher numbers of adverse effects due to polypharmacy were identified in the age group of 31 - 40 years subjects. Drug-drug interaction induced adverse effects were identified in the prescriptions with polypharmacy which were moderately serious. Adverse effects are one of the consequences of polypharmacy [19]. Some of the following adverse drug reactions were identified in our study because of polypharmacy, abdominal pain, blurred vision, breathlessness, chest pain, cushings syndrome, diarrhea, dizziness, drymouth, eyepain, hypoglycemia, loss of appetite, megaloblastic anemia, parkinsonism, pedal edema, Steven Johnson syndrome, toxic epidermal necrolysis, gastric irritation, vasculitis. NSAIDs

pose greater risk of developing peptic ulcer [20]. In our findings of polypharmacy prescriptions NSAIDs were major suspected drugs followed by antibiotics.

Age: Age is second major risk factor leading to ADRs which was identified in our study. All drugs may cause adverse drug reactions in all age groups but all age groups do not develop same adverse effects at same severity. Age is differentiated in to three classes as per our study requirement, paediatrics, adults and geriatrics. Paediatrics and geriatrics are the extreme age groups and more vulnerable to adverse drug reactions. Studies in these age groups regarding the drug absorption and metabolism are more variable and less predictable. It takes more efforts in the prevention of occurrence of adverse drug reactions in children [21]. In our study outcomes, greater association to adverse drug reactions was observed in the 61-70 years age group. It is due to multiple medical problems, enhanced drug consumption, polypharmacy, alterations in the functions of organs because of aging which affects pharmacokinetics and pharmacodynamics of the drug. Geriatrics is the major risk group to ADRs [22]. Another reported study has similar findings, higher incidence of ADRs in the elderly than the other age groups [23]. In the age group of 61-70 years; males (70%) developed higher ADRs than females (30%).

Antibiotics (22.5%) were the major suspected class of drugs identified at this age group which causes dermatological disorders, hepatic disorders severely followed by anti-hypertensive's causing moderate adverse effects. Higher numbers of adverse drug reactions were identified at the age group 41-50 years, where antibiotics (26%) were the major suspected class drugs to ADRs. At this age group higher number of adverse drug reactions belong to moderate level-3 (30%), level-4A (15.2%), level-4B (6.6%), and some severe adverse drug reactions like hepatitis, skin blisters and hair loss were the severe level-5. While if we see in the paediatrics, male subjects (57.7%) were higher numbers to the development of adverse drug reactions than females. Organs to metabolize the drugs are not completely developed in the children. There are several reasons which explain why paediatrics are more vulnerable, some of them are as follows; at the age of 8 weeks in neonates due to immature renal tubular function keep away the drugs like NSAIDs, amino-glycosides, ACE inhibitors, digoxin; due to physiologic hypoalbuminemia in neonates, caution is necessary to the drugs like NSAIDs; because of immature blood brain barrier at the age of less than 8 weeks enhanced risk of anaesthetic effects persists [24-26]. But in our study we found less incidence of adverse drug reactions in the paediatrics, and the older patients have been shown to have greater association with adverse drug reactions.

Gender: It plays an important role in the disease prevalence and outcomes. Literature has shown that females are more prone to develop adverse effects than males [27]. There is 1.5 to 1.7 folds increased risk of developing adverse drug reactions in women than men [28]. In our study findings, there was not much difference identified in gender association with ADR. But males developed little higher frequency of ADRs than females (51.5% and 48.5%) respectively. Analysis of hospitalized patients especially in geriatrics, males suffered with more chronic disorders than females; longer duration of therapy and OTC medication were more in males than compared to females.

Associated diagnoses: It was observed in our study that, the patients who were diagnosed with the following four ICD diagnoses were at higher risk of ADR and show greater association with ADR. Certain infections and parasitic diseases (B00-B99), mental, behavioral and neuro-developmental disorders (F01-F99), Diseases of the skin and subcutaneous tissue (L00-L99), Diseases of the respiratory system (J00-J99). From the observations of Rashed NA *et al*., patients with diseases of respiratory system (J00-J99) had higher ADRs followed by certain infections and parasitic diseases (B00-B99) [10]. The patients with less immune capacity to defend certain infections and prescribed higher antibiotics are more prone to develop the adverse drug effects. Especially the patients with suppressed immune system and metabolic disorders [29]. The health care professionals who prescribe the drugs for such severe conditions adds up, higher risk which in turn predisposes a patient to an ADR.

Drugs involved: Apart from these, suspected drugs are classified as per the therapeutic classification.

Antibiotics were the primary suspected therapeutic class which causes more adverse drug reactions. Cephalosporins, Fluroquinolones and Penicillamines were the most prescribed drugs to the hospitalized patients, either as a prophylactic medicine to the hospitalized infections or as a choice of treatment according to the diagnosis.

Previous studies have shown that Cephalosporins and Fluroquinolones were the most predominant drug classes related to ADRs respectively [30, 31].

Another study showed similar findings on Cephalosporins followed by Fluroquinolones were primarily accounted drug classes to develop ADRs [32]. Followed by antibiotics; NSAIDs and anti-hypertensive causes the adverse drug reactions at similar frequencies (7.8%). The analyses found in hospitalized patients that higher number of geriatrics who were admitted with known cases of hypertension and had a past medical history of anti-hypertensive drug usage on longer duration, was one of the major risk factor for the development of ADR to anti-hypertensive drugs.

CONCLUSION: This study was conducted in all age groups of inpatients with both genders in a South Indian hospital which showed that the following were the independent predictors of ADRs: multiple drug prescription, older age, certain infections and parasitic diseases, mental, behavioral and neuro-developmental disorders, diseases of the skin and subcutaneous tissue, diseases of the respiratory system. Gender has not shown much association to ADR, however proportion of ADRs were more in males than females. Our research findings conclude that in order to minimize the risk of ADRs, the health care team has to play a vital role in reducing the number of prescribed drugs as low as possible, should pay attention to the vulnerable age groups especially to geriatrics and immune compromised patients.

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CONFLICT OF INTEREST: Authors declare that there is no conflict of interest.

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