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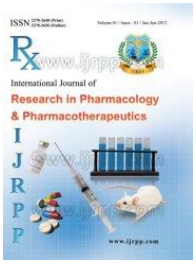

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Retrospective study of cutaneous adverse drug reactions reported at adverse drug reaction monitoring centre (AMC) at GMC/GGH, Guntur, Andhra - Pradesh, India

Dr. Vijaya Kumari Suryadevara. M.D[1*], Dr. Meena Kumari Amancharla. M.D[2], Mr. Pavan Kumar Kandula. Pharm D[3]

[1]*Associate Professor, Department of Pharmacology, Guntur Medical College, Guntur, Andhra-Pradesh, India.*
[2]*Professor, Department of Pharmacology, Guntur Medical College, Guntur, Andhra-Pradesh, India.*
[3]*Patient safety Pharmacovigilance Associate, Adverse Drug Monitoring Centre, Guntur Medical College/GGH, Guntur, Andhra-Pradesh, India.*

***Corresponding author: *Dr. Vijaya Kumari Suryadevara. M.D.**
Email: drsvkdrsvk@gmail.com

ABSTRACT

Background

One of the most common manifestation of adverse drug reactions is cutaneous adverse drug reaction, which includes skin and it's appendages, mucous membranes, occurring with a wide variation in morphological pattern.

Aim

To know the incidence, patterns and causality of Cutaneous Adverse Drug Reactions (CADRs), reported at ADR Monitoring Centre (AMC), Guntur Medical College/GGH.

Materials & Methods

After obtaining Institutional Ethics Committee approval, 840 CADRs reported to ADR Monitoring Centre (AMC), Guntur, over a period of 3 years were included in the study. For of each CADR - demographic details, suspected drug used, and concomitant medication details from their suspected Adverse Drug Reaction (sADR) reporting forms were taken. Causality assessment was done for each CADR with the help of WHO Causality assessment scale. Descriptive statistics were applied for the results analysis.

Results

Out of 840 CADRs, 567 (67.5%) occurred in females and 273 (32.5%) occurred in males. Age distribution ranged from 2 months to 75 years with a mean age of 37.09 $\pm$ 12.74 SD years. 28 (3%) CADRs were serious and required hospitalization, 812(97%) CADRs were not serious and most of them were medically treated and recovered. 647 (77%) CADRs were due to antiretroviral drugs, 109 (13%) were due to anticancer drugs, 84 (10%) were due to antibacterial agents, NSAIDs, antiepileptics and other drugs. Maculopapular rash (58.6%) was the most common CADR observed in the study and other CADRs were pruritus (15%), mouth ulcerations (10.7%) etc.

Conclusion

Most of the CADRs were due to antiretroviral drug combinations and anticancer drug combinations. To prevent and reduce the incidence of CADRs, development and implementation of various strategies is necessary.

Keywords: Cutaneous adverse drug reactions, Maculopapular rash, Causality assessment

INTRODUCTION

Nowadays adverse reactions to drugs are becoming more commonly and frequently occurring events during diagnosis process, therapy or prophylaxis of diseases. These Adverse Drug Reactions (ADRs) are one of the important causes of hospitalization, morbidity, even deaths of patients. Commonly used drugs like penicillins, sulfonamides, fluoroquinolones, anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDS) especially aspirin, angiotensin converting enzyme (ACE) inhibitors are frequently implicated in causing ADRs [1]. The common manifestation of ADRs is Cutaneous adverse drug reactions (CADRs) involving skin and it appendages, mucous membranes. Previous studies [2], [3] also showed that the cutaneous drug reactions are one of the most frequently encountered ADRs during drug therapy. According to some studies, the incidence of CADRs in developed countries is 1–3%, while the incidence in developing countries is little higher between 2 and 5% [4], [5]. CADRs are occurring in a varied and diverse pattern ranging from a trivial skin rash, pruritus, urticarial forms to severe thrombophlebitis, vasculitis, gangrene forms or even fatal forms like Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), exfoliative dermatitis which may cause even death. Thus the pattern of CADRs differs among various drugs. So better understanding the precise nature of CADRs and their suspected drugs is very useful in choosing safer drugs by clinicians and helps not only the patients and in large scale, reduce the burden on health care system. With this background, the present study was undertaken to know the incidence, patterns and causality of Cutaneous Adverse Drug Reactions (CADRs), reported at ADR Monitoring Centre (AMC), Guntur Medical College/GGH over a period of 3 years.

MATERIALS & METHODS

After obtaining permission from the Institutional Ethics Committee and permission from Indian pharmacopeia centre (IPC), Ghaziabad, the study was conducted at Adverse drug reaction Monitoring centre (AMC) in a tertiary care teaching hospital in Guntur, Andhra-Pradesh, India. From the AMC records, all the CADRs details that were reported over a period of 3 years was collected first. Among which 840 CADRs reported with complete details were only included in our study. For each CADR we collected the demographic details, CADR details about its onset, lasting duration of adverse reaction, seriousness of the reaction whether it is serious and required any hospitalization/ prolonged hospital stay or not serious which can be treated as outpatient case and data was analysed. The action taken after CADR occurrence i.e. whether the suspected drug was withdrawn from treatment or dose was reduced or dose was not changed was also analysed. The final outcome of the patient whether the patient was recovered or not continuing with the adverse reaction was also noted and analysed. The details about the suspected drug, and about concomitantly used drugs were taken and causality assessment done in accordance with WHO causality assessment scale which categorised CADRs as possible, probable and certain were recorded. From the records we noted that for any of these CADRs in our study no rechallenge test was done, may be due to ethical issues. Descriptive statistics, percentages and proportions were applied for the results and presented in figures and tables.

RESULTS

Out of 1468 ADRs reported over a period of 3 years at AMC, GMC/GGH, Guntur, 840 (57.22%) were CADRs. In this study, 567 (67.5%) CADRs patients were females and 273 (32.5%) patients were males [Fig. 1a]. The age of the youngest patient was

2 months and the oldest patient was 75 years. The mean age was 37.09 ± 12.74 SD. More number of CADRs 297 (35.36%) occurred in age group of 31yrs - 40yrs [Fig. 1b].

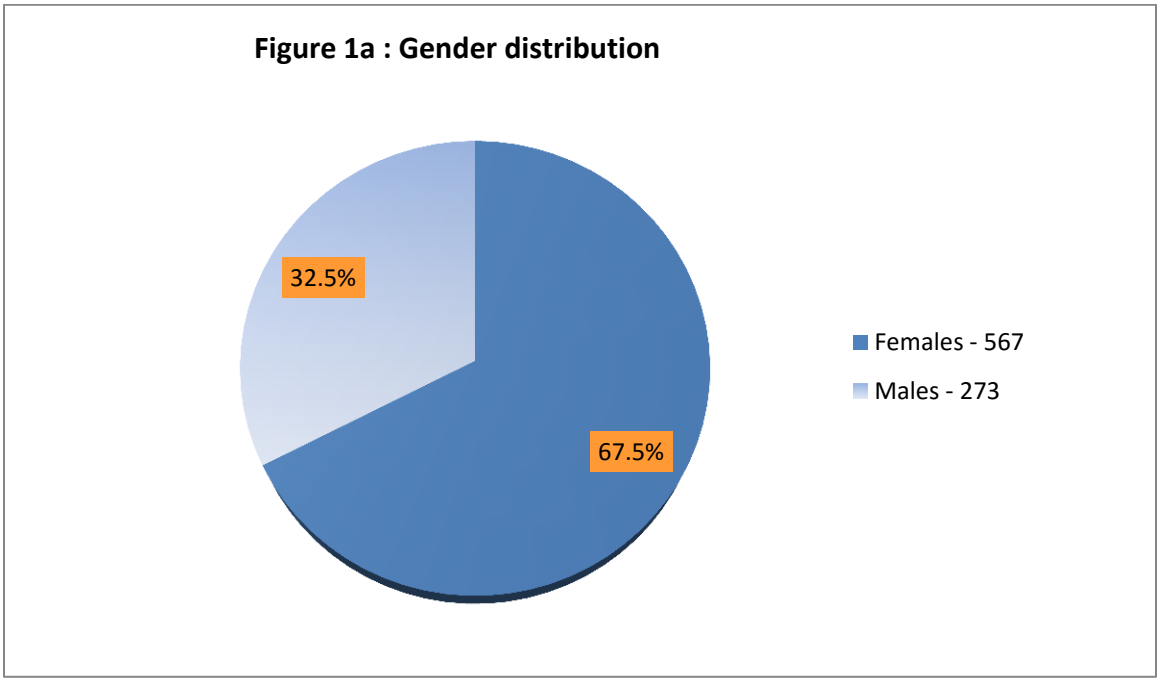
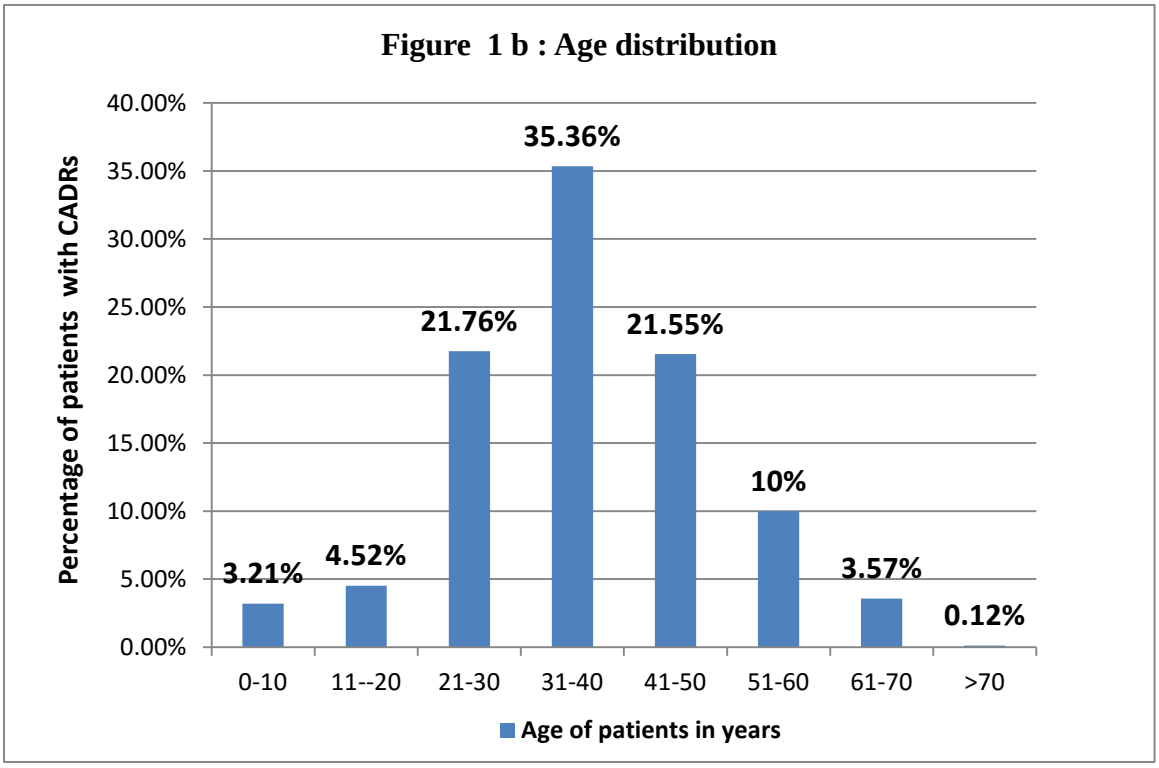


Figure 1 : Demographic profile of patients with CADRs (n=840) :



More commonly reported CADRs were maculopapular rash 492 (58.57%) and pruritus 125 (14.88%). Mouth ulceration/glossitis/mucositis patients were 90 (10.71%), hypersensitivity reactions - facial edema, lip swelling patients were 39 (4.64%) and fixed drug eruption patients reported were

14(1.67%). Serious type of CADRs like Stevens-Johnson syndrome patients were 10 (1.19%) Toxic Epidermal Necrolysis (TEN) patients were 3 (0.36%) and exfoliative dermatitis were 3 (0.36%) [Table 1].

Table 1: Types of CADRs

Type of ADR	No. of ADRs	% of ADRs
Maculopapular rash	492	58.57%
Pruritus	125	14.88%
Mouth ulceration, Glossitis, mucositis	90	10.71%
Hypersensitivity reactions - Facial edema, Lip swelling	39	4.64%
Urticaria	19	2.26%
Alopecia	18	2.14%
Stevens-Johnson Syndrome(10)	13	1.54%
TEN -Toxic Epidermal Necrolysis (3)		
Fixed drug eruption	14	1.67%
Skin Hyperpigmentation	13	1.54%
Xerostomia	3	0.36%
Exfoliative Dermatitis	3	0.36%
Hyperpigmentation of palms and Soles	2	0.24%
Erythematous rash	2	0.24%
Erythema multiforme	2	0.24%
Skin necrosis	1	0.12%
Candidiasis	1	0.12%
Hirsutism	1	0.12%
Ecchymosis	1	0.12%
Dermatitis - Lichinoid	1	0.12%

Antiretroviral fixed drug combination of Zidovudine + Lamivudine + Nevirapine caused more CADRs 348 (41.42%), and another combination of Tenofovir + Lamivudine + Efavirenz drugs caused 270 (32.14%) CADRs. On overall, the antiretroviral drugs caused 651 (77.5%) CADRs, antibacterial agents caused 75 (8.93%) CADRs, anticancer drugs caused 38 (4.52%) CADRs, antiepileptics caused 27 (3.21%) CADRs and NSAIDs caused 22 (2.62%) CADRs, other miscellaneous drugs caused 16 (1.9%) CADRs [Table 2].

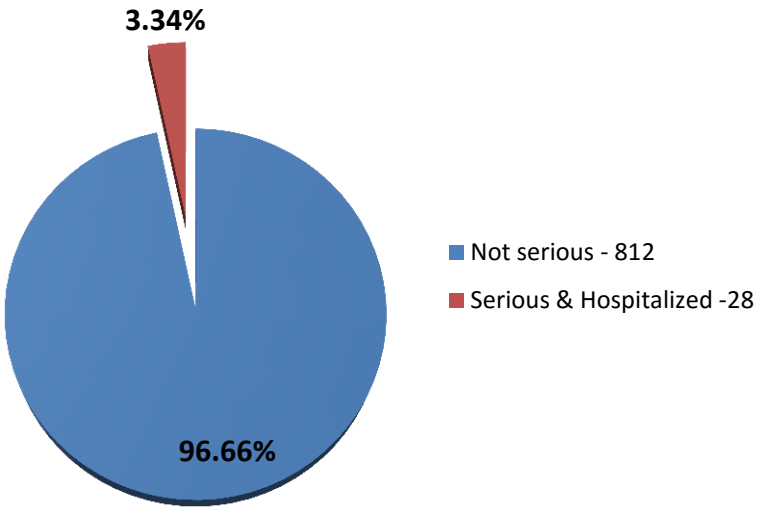
Table 2 : Suspected drugs responsible for CADRs:

Suspected drugs/combinations	No. of CADRs	% of CADRs (n=840)
Antiretroviral drugs	651	77.5%
zidovudine + lamivudine + nevirapine (348)		
tenofovir + lamivudine + efavirenz (270)		
zidovudine + lamivudine + efaverinz (22)		
tenofovir + lamivudine + lopinavir + ritonavir (7)		
tenofovir + lamivudine + atazanavir + ritonavir (4)		
Antibiotcs	75	8.93%
Penicillins (14) - amoxycillin (4), amoxy+clavulanic acid(6), piperacillin+tazobactum(2), cloxacillin(1) ampicillin+cloxa(1)		
Cephalosporins (24) - ceftriaxone(14), cefotaxime(5), cefuroxime(3),		

cefpodaxime(1), cefexime(1) **Fluoroquinolones (13) -** ciprofloxacin(5), norfloxacin(3), ofloxacin(3), levofloxacin(1), moxifloxacin(1) **Antitubercular&antileprrosy (7)** dapsone(1), rifampicin+dapsone(1) rifampicin+ pyrazinamide+ isoniazid +ethambutol(3), pyrazina+ ethamb(1), rifamp+ pyrazina+ ethamb(1) **Antimalarials (2) -** chloroquine(1), Arteether(1) **Others(15) -** cotrimoxazole(5), metronidazole(4) azithromycin(2), vancomycin(2), nitrofurantoin(2),		
Anticancer drugs adriamycin comb.(18),cyclophosphamide comb.(12) cisplatin comb.(11), 5FU com.(10), paclitaxel com.(4) others	38	4.52%
Antiepileptics Phenytoin(19), carbamazepine(6), sodium valproate(2)	27	3.21%
Antipsychotics Risperidone(1), chlorpromazine+ trihexyphenidyl(1)	2	0.24%
NSAIDs diclofenac(8), paracetamol(5), aceclofenac +paracetamol(3), aspirin(2), ibuprofen(2), nimusulide(1), aceclofenac(1),	22	2.62%
Steroids Dexamethasone(1), budesonide(1), clobetasol(1)	3	0.36%
Intravenous infusions whole blood(2), normal saline(1), amino acid infusion(1)	4	0.48%
Vaccines - DPT vaccine(1), pentavalent vaccine(1)	2	0.24%
Miscellaneous atorvastatin(2), ranitidine(2), GBHC lotion(1), atenolol(1), chlorphenaramine maleate(1), drotaverin(1), loperamide(1), salbutamol+ipratropium(1), temozolamide(1), glibeclamide+ metformin(1), trihexyphenidyl(1), acenocoumorol(1), cetrimide+chlorhexidine(1), iron sucrose(1)	16	1.9%

CADRs in 812 (96.66%) patients were not serious but 28 (3.34%) patients had serious reactions and were hospitalized [Fig. 2]

Figure 2 : Condition of patients with CADRs (n=840)



Medical treatment was given for 828 (98.57%) patients, non medical treatment was given for 8 (0.95%) patients and no treatment was given for 4 (0.48%) patients with mild alopecia [Table 3].

Table 3 : Type of treatment given to patients with CADRs:

Type of treatment given for ADRs	No. of ADRs
Medical treatment	828 (98.57%)
Non-medical treatment	8 (0.95%)
No treatment	4 (0.48%)

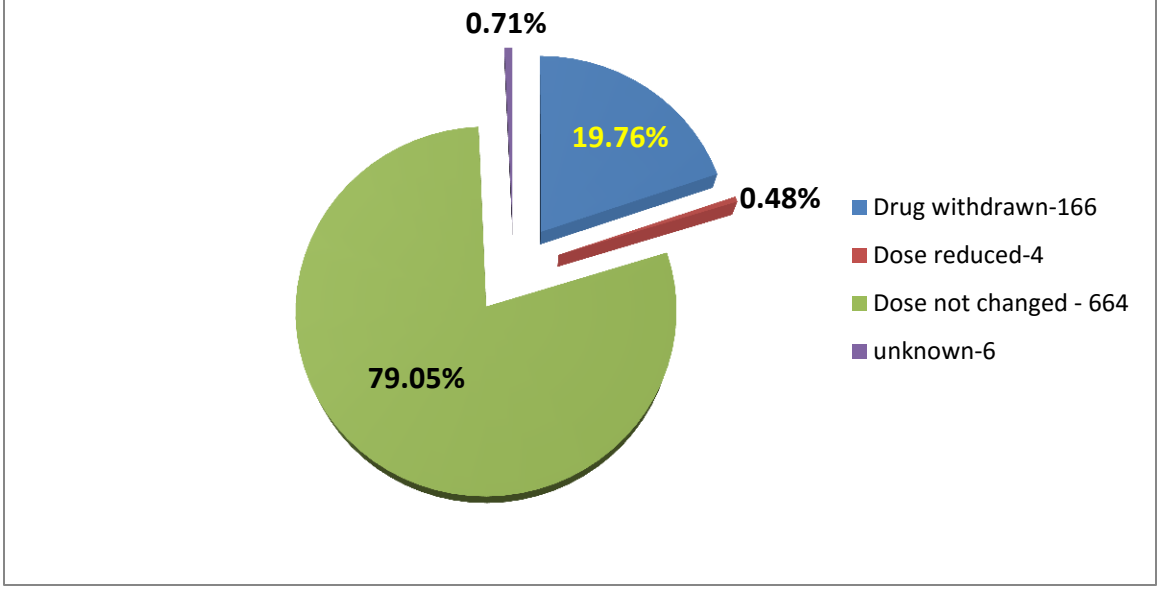
373 (44.29%) patients were recovered**.** Mean duration of CADRs was 19.85 ± 12.67SD days with a maximum of 51 days and a minimum of 1 day to recover from CADRs. [Table 4].

Table 4 : Status of the patients and Duration of CADRs :

Status of ADRs	No. of ADRs		Duration of CADRs (Days)	
Recovered	373	(44.29%)	Maximum	51
			Minimum	1
			Mean ± SD	19.85 ± 12.67
Not Recovered	8	(0.95%)		
Continuing	459	(54.76%)		

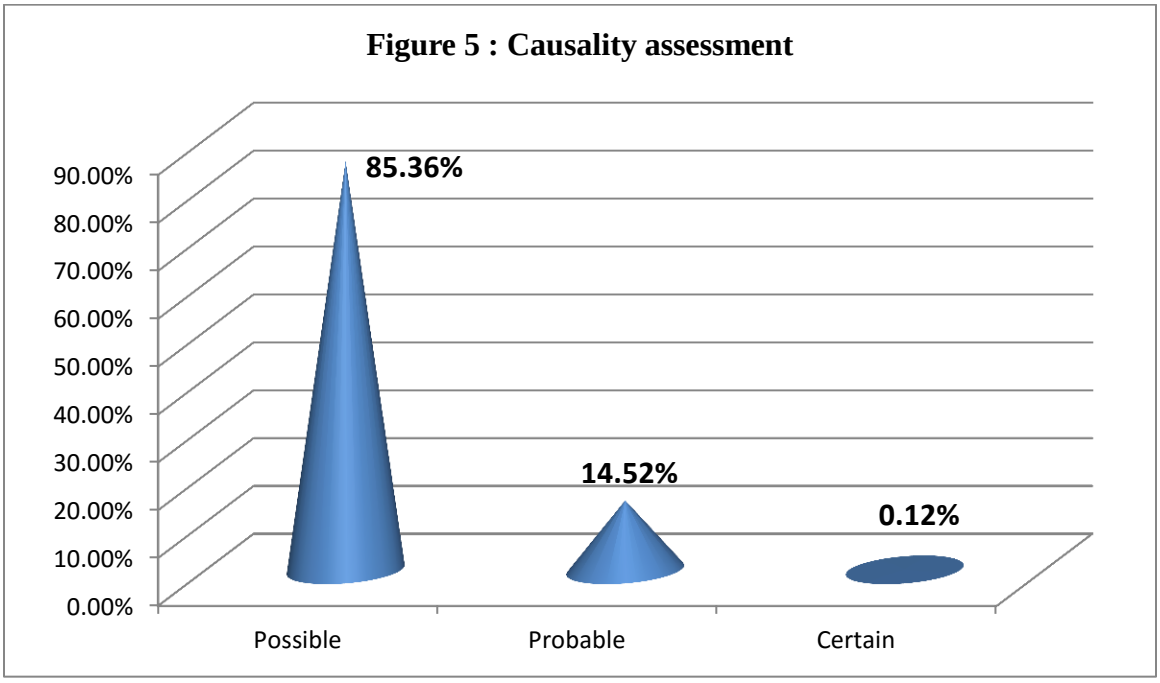
For CADRs patients the actions taken were as follows, in 166 (19.76%) patients the suspected drug was withdrawn, in 664 (79.05%) patients dose of suspected drug was not changed, but in 4 (0.48%) patients the suspected drug dose was reduced [Fig. 4].

Figure 4 : Action taken



Causality assessment (as per WHO scale) results showed "Possible" for 717(85.36%) CADRSs, "Probable" for 122 (14.52%) CADRs and "Certain" for 1(0.12%) CADR [Fig. 5].

Figure 5 : Causality assessment



DISCUSSION

Cutaneous adverse drug reactions are the most common manifestations of Adverse drug reactions [6]. Our present study included 840 CADRs out of 1468 ADRs reported at AMC. This occurrence of 57.22% of CADRs is similar with that of other studies on adverse drug reactions conducted by Arulmani R et. al [7]; another study conducted by Jose L Rao et. al [8]. On demographic data analysis there was a high incidence (67.5%) of CADRs in

females than in males (32.5%) and female to male CADRs incidence ratio is 2.07. A similar but a moderate high incidence of CADRs in females was reported by a study conducted by Babu LN et al [9] and a study by Qayoom S et al [10]. Age of the patients ranged from 2 months to 75 years, showing no age is exempted from CADRs [11]. The mean age of patients in the study was 37.09 ± 12.74 SD, which was similar to mean age of 33.8±17.19 years reported in a study by Saha A et al [12]. Majority of patients 660 (78.57%) were in between 21 years - 50 years of age. As the study was institution based, the differences in demographic data can be due to the difference in demography of the cases reporting to the AMC centre.

In our study, among the various cutaneous manifestations of adverse drug reactions, maculopapular rash 492 (58.57%) was the commonest reaction encountered and it is in concordance with the results of other previous studies [13, 14, 15]. After maculopapular rash, the other frequently observed CADRs in our study were generalized pruritus, mouth ulceration/glossitis, which were somewhat not similar with the results of other studies [16, 17] where fixed drug eruptions, urticaria were the most common. This could be due to difference in disease prevalence from place to place and difference in types of drugs used for their appropriate management. There was no significant difference in the incidence rate of urticaria, Alopecia, Stevens-Johnson Syndrome/TEN -Toxic Epidermal Necrolysis. We observed 1 out of 29 CADRs as serious reactions, which required hospitalization. A high incidence of TEN and SJS has been reported from other studies [13, 18, 19]. In our study also similar pattern of serious reactions which required hospitalization/prolongation of hospitalization and life-threatening was observed. Among the 28 (3.34%) serious CADRs 10 were Stevens - Johnson Syndrome (SJS) out of which, 4 were due to phenytoin, 2 were due to Zidovudine + Lamivudine + Nevirapine fixed drug combination while dapsone, nitrofurantoin, arteether, ofloxacin + ornidazole combination drugs caused 1 case each. Out of 3 Toxic Epidermal Necrolysis (TEN) cases 2 were due to carbamazepine and 1 case was due to diclofenac. These results correlates with many studies in which antimicrobials and anticonvulsants were the most common drugs causing such severe CADRs [10, 12, 13]. As mortality from CADRs results mostly due exfoliative dermatitis, SJS, TEN, they should be regarded as dermatological emergencies and should be treated with intensive/close monitoring. In our study all 28 patients with serious CADRs were recovered and no death was reported.

Cutaneous adverse drug reactions were found to be caused more commonly (88.7%) by prescribed drugs than over the counter drugs and due to frequent usage of drugs in combination or FDC [12]. Similarly in our study, 651 (77.5%) CADRs were due to antiretroviral fixed drug combinations, among which nevirapine , tenofovir were more frequent and among 38 (4.52%) CADRs caused by anticancer drug combinations, adriamycin, cyclophosphamide, cisplatin were more frequent. Among 75 (8.93%) CADRS caused by antibacterial agents, ceftriaxone, cefuroxime, cefotaxime, ciprofloxacin, amoxycillin were more frequent. Where as in 22 (2.62%) CADRs caused by NSAIDS, diclofenac, paracetamol, aceclofenac were more frequent. Among 27 (3.21%) CADRs caused by antiepileptics, phenytoin, carbamazepine were frequent.

In our study, in 166 (19.76%) patients with CADRs, the suspected drugs were withdrawn and in 664 (79.05%) patients the suspected drugs and even doses were not changed, which may be due to mild nature of the adverse reactions and/or due to usage of fixed/drug combinations. The results of causality assessment, which was done as per the WHO guidelines showed that in 717 (85.36%) CADRs the occurrence of adverse reactions were "possible" with their suspected drugs where as in 122 (14.52%) CADRs, the occurrence of adverse reactions were "probable" with their suspected drugs and in 1(0.12% CADRs presented as pruritus due to amino acids infusion, occurrence of adverse reaction was "certain".

In conclusion, as the number of fixed/drug combinations being used for various infective diseases/cancers is increasing every year, an in depth understanding of the possible adverse drug reactions should be the utmost importance for all the clinicians. At the same time, all the persons who are involved in healthcare delivery system should be trained adequately, to anticipate and prevent the ADRs incidence. According to the tertiary care hospitals/Institutions, development and implementation of various local standard strategies to recognize and respond actively to the ADRs, is a prime concern, for not only to reduce the morbidity,

mortality of the patients, but also to reduce burden on our health care system.

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Declarations

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Conflict of Interest: None declared
Ethical approval: The study was approved by Institutional Ethics Committee (GMC/IEC/113/2017)

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