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Original article

DESCRIPTIVE AND ANALYTICAL STUDY OF CUTANOUS ADVERSE DRUG REACTIONS (CADRs): A HOSPITAL BASED OBSERVATIONAL STUDY IN SOUTHERN ODISHA

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ABSTRACT –

Background- Skin being largest organ in body is frequently affected by drug reactions accounting for 2% in OPD , 10% in IPD admissions and 2-7% have serious, fatal consequences.

Thus spontaneous reporting is very essential .

objectives -

1.To analyze the clinical characteristics and to identify the Culprit drugs **,**responsible for CADRs,

2.Assess the severity, know the outcome of CADRs

3. Associate the degree of severity with different risk factors..

Methods - It was a prospective observational study was done both in the OPD and IPD of Skin and VD department of MKCG hospital , Berhampur, Odisha from September 2022 to March 2023. 82 cases of CADR of either sex of any age were included in this study. Data were collected in suspected ADRs reporting form version 1.3 , PvPI .The Causality,severity assessment was done by valid scale and data were analyzed by descriptive statistics in numbers and percentages . The severe form of CADRs associated with risk factors were analyzed by Chi –square test. P value < 0.05 was considered as statistically significant.

Results –CADRs had female preponderance 58.5%) and the most commonly affected age group was the elderly population (42.6 %) in this study. Fixed drug eruption (FDE) was most

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common (29.2%) type and the commonly involved culprit drugs suspected were anti-microbials (52.4%). Major CADRs belonged to probable (54%) category in Causality assessment and were of Mild (40.2 %) variety in Severity assessment . The risk factors found to be significantly associated were extreme age (> 60 years), H/O previous skin allergy , multi-medications (>2 drugs) with p=0.019* , p=0.001† , p= 0.02* respectively.

Conclusions - FDE are identified as major type of cutaneous adverse drug reactions. Major Group of drugs responsible for this were found to be Antimicrobials. The severe CADRs were mostly associated with extreme age , previous allergic history and multi -medications which should be taken with caution to avoid CADRs.

Keywords: CADR, SJS,TEN, FDE, PvPI

INTRODUCTION-

CADRs are unwanted effects of drugs manifested through skin and adnexae (hair, nail, glands). Skin is also the highest affected organs (45%) to manifest ADR. Around 1-3% adults, 2.5% of children manifested adverse skin reactions [1,2]. Estimated 2% OPD, 10 % IPD patients manifested these reactions and mostly self resolving. But 2-6.7% patients developed life threatening skin reactions [3,4] . These severe cutaneous adverse reactions (SCARs), have a global frequency of 0.4–1.2 cases per million per year but the incidence varies according to population and drugs character [5]·Many new molecules discovered every year and there is changing trends in use of drugs made skin reactions to change continuously[6] .

There are 30-35 types of skin reactions have been presented by patients. These are maculopapular drug eruptions, fixed drug eruption, erythematic multiforme (EM) of less severe variety , and dangerous life threatening skin reactions are erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) spectrum, acute generalized exanthematous pustulosis (AGEP) and serum sickness (SS) [7-10]. The systemic drugs especially antibiotics, anti-convulsants, anti-neoplastic drugs, NSAIDS and allopurinol are mainly reported for causing CADRs [11].These skin reaction develop gradually and produce feature similar to disease which cause diagnosis more confusing [12].

Though CADRs are common but reports in pharmacovigilance network showed many lacunae regarding incidence, severity, morbidity, mortality and its impact on health of our population. [13-14]

Thus, for determination of cause of reactions, early diagnosis, knowing clinical characteristics of CADR, chronology of reactions, elimination of differential diagnosis, spontaneous reporting is required. ADR reporting may influence the recommendations for drug use through regulatory authorities and save the precious lives of the patients.

On this context, our study aimed to describe clinical characteristics, culprit drugs, assessment of severity and causality by using valid scales, treatment outcome and association of severity grades with risk factors among CADR cases.

MATERIALS AND METHODS: -

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It is a prospective, observational study done in OPD and IPD of Skin and VD department, MKCG Medical College, Berhampur, Odisha from September, 2022 to March, 2023. 82 CADR cases of all age groups and genders were included from both OPD and IPD. Diagnosis done by dermatologist and it was purely clinical .The patients were explained about nature of study and informed consent was obtained from the patient/ attendant / guardian. This study was approved by IEC of the institution (Vide Approval No.1163).

Inclusion criteria –

Drug used 3 weeks prior to development of adverse drug reactions were included.

Exclusion criteria -

a)Patients unable to recall or produce medications consumed in last 3 weeks (prevent recall bias),

b) Cases involving overlapping symptoms,

c) Clinical manifestations differ from drug reactions,

d) Patients taking alternative medicines i.e. AYUSH

e) Reactions caused due to drug abuse or medication error.

Data Collection:

The data were collected in a suspected ADR reporting form version 1.3 by PvPI . The patient details like age, sex, onset of and duration of CADRs were recorded. The suspected drug and type of CADRs were also mentioned. The treatment given for CADRs and their outcome in terms of cured or death were recorded in a separate case record form. The details of drugs suspected to produce ADR like name, dose, route of administration, number of drugs taken simultaneously were taken. History of self medication of OTC medicine / herbal remedies, H/O previous allergy and family history of similar drug reaction were noted. The clinical features of CADRs like morphology of reactions, features of desquamation, systemic features, mucosal involvement, severity, and causality assessment were noted.

Causality assessment of CADRs were reported as definite, probable, possible and unlikely according to WHO-UMC causality assessment scale [15].The severity of CADRs were assessed by modified Hartwig′s and Siegel severity assessment scale[16] .

The association of severity of CADR with risk factors like age, history of allergy and multi-medications (≥ 2 drugs) was done.

The data were tabulated and shown as graphical pictures .

STATISTICAL ANALYSIS -

Statistical analysis was done by using Graph-pad Prism version 5 in a personal computer. The data of clinical subtype of CADRs, skin and systemic feature, outcome of treated patients, culprit

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drugs, and severity of CADRs and causality assessment result were done by descriptive analysis and expressed in terms of numbers and percentages.

The grade of severity of CADRs were associated with risk factors like extreme age , history of previous skin allergy and multi-medications (≥ 2) by using chi-square test and Odd's ratio . P-value < 0.05 was considered statistically significant.

RESULTS –

Total 82 patients were diagnosed of CADRs , which were treated by dermatologist.

Table 1 -Demographic , clinical and drug details among CADR Cases-

Demographic parameters	**Observed values**
Female	48 (58.5%)
Male	34 (41.5%)
Mean age(year)	49.2 yr
Age (yr)	
<20	22 (26.8%)
20-40	9 (10.9%)
40-60	15 (18.29%)
>60	35 (42.6%)
Previous History of CADR	31 (37.8%)
Latent period of CADR	Weeks
i. Exanthematous reaction	1 - 2
ii. Lichenoid reaction	8 -12
IPD admission	31(37.8%)
Death	1(1.21%)
≥ 2 medication	76 (92.6 %)

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Oral route	71(86.5%)

Table 1 –Demographic feature like age , sex distribution , clinical and drug details collected among CADR Cases (n=82) , Data were analyzed by descriptive statistics as number , percentages and Study had female preponderance and mostly involved the older age group i.e > 60 yrs with a mean age belonging mostly to middle age group .

Almost a third of patients had previous H/O allergic skin reactions. Latent period required to develop cutaneous adverse reactions (CADRs) was longest in lichenoid reactions while being shortest in exanthematous reaction . More than 2/3rd cases had oral routé of drug administration eek of development .

Table 2 -Severity Assessment by Modified Hartwig's and Siegel scale (n=82)

Types of CADR	Number	Percentage(%)
Mild	**21**	**40.2**
Moderate	**14**	**28.04**
Severe	**47**	**31.7**
Total	**82**	**100**

Above table depicts Majority of cases found to be in level -1 (mild) followed by level- 3 severity (severe) in Modified Hartwig's and Siegel Severity assessment scale.

Figure 1 –Causality assessment of CADR s by WHO-UMC scale (n=82)

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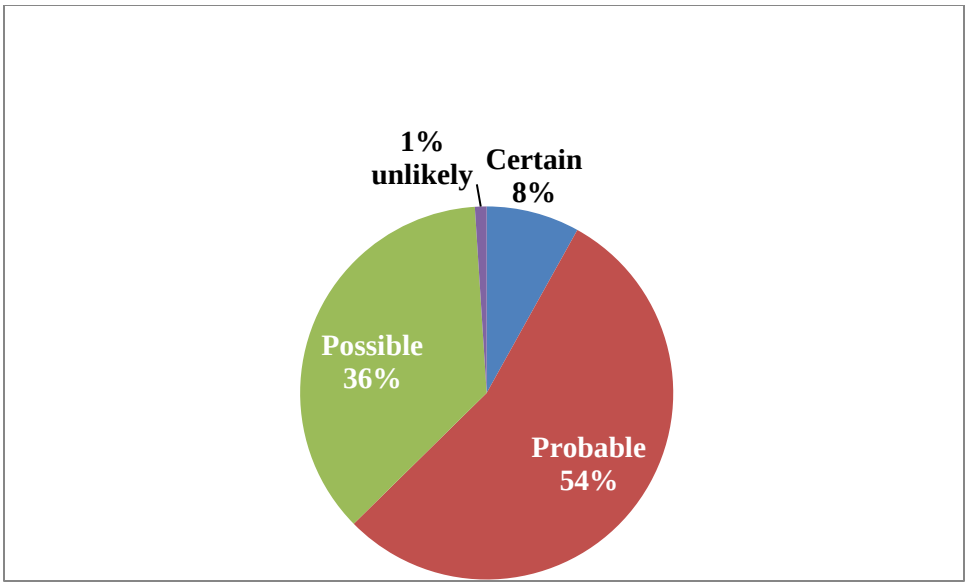

Data were expressed in percentages , According WHO–UMC scale of Causality assessment, majority of cases were probable followed by possible and certain in CADR cases .

Figure 2- Distribution of various types/pattern of CADRs

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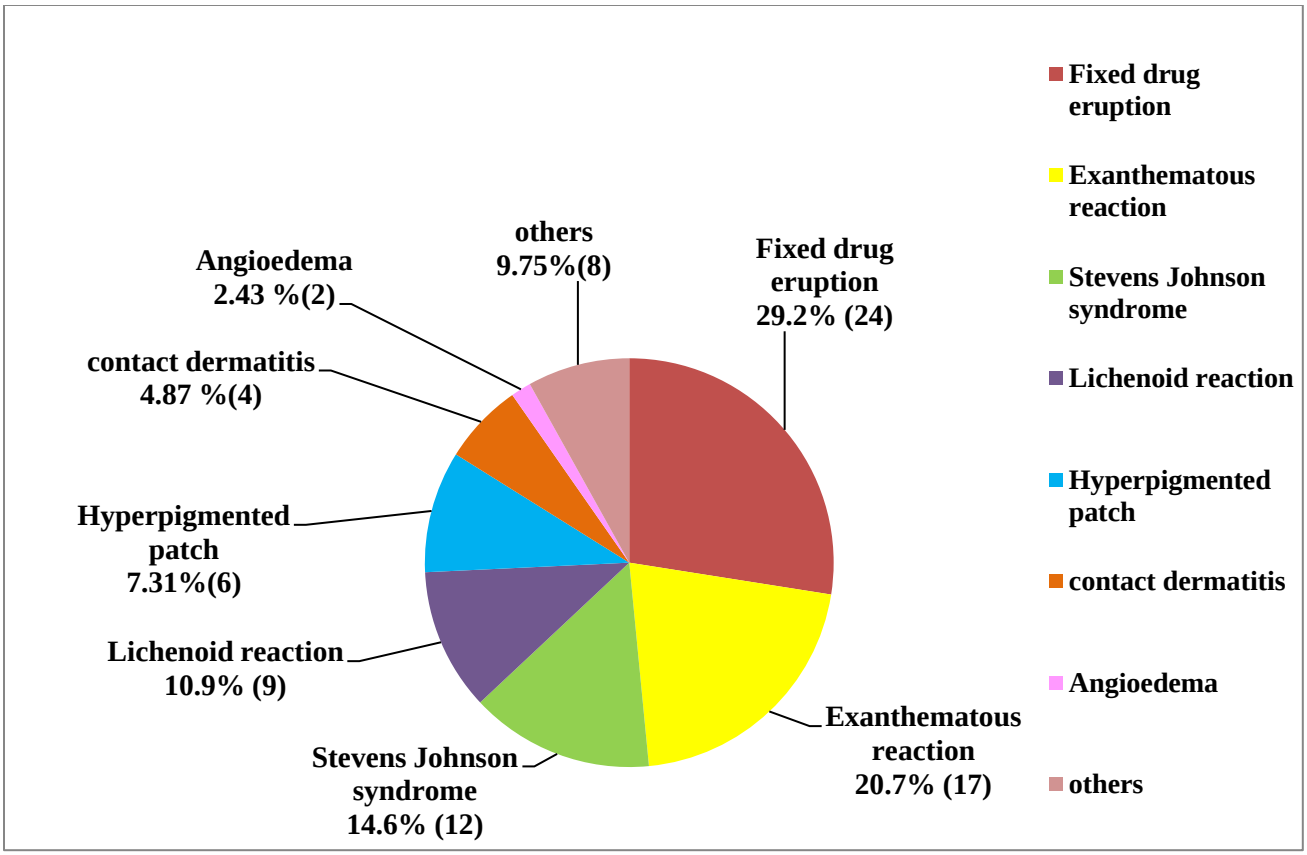

Data were expressed in number and percentage (n=82) . The figure depicts the most common type of CADRs found in this study were fixed drug eruptions (FDE) followed by exanthematous eruption , Stevens Johnson syndrome (SJS) and lichenoid reactions .

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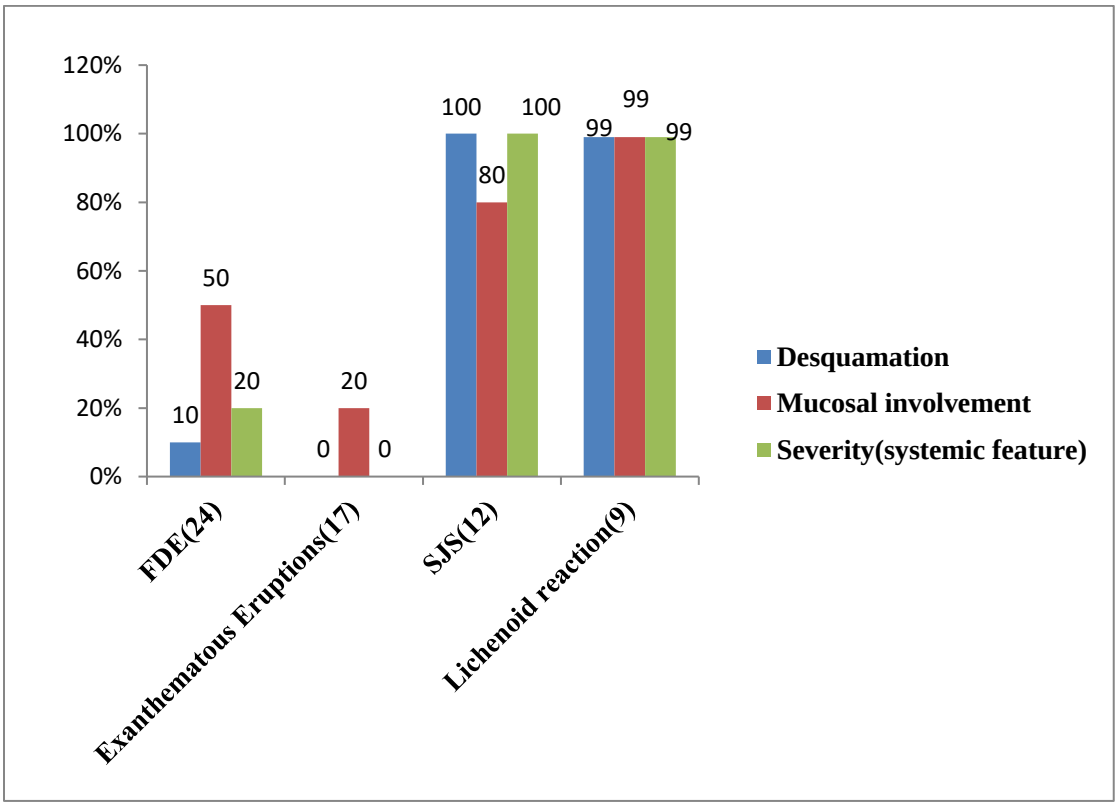
Figure -3 Cutaneous and systemic features of common CADRs



Data expressed in percentages (n=52), On detailed observation of cutaneous and systemic features of all CADRs, the highest rate of desquamation, systemic features with symptoms like fever, vomiting, diarrhea, constipation and oliguria (> 2 weeks duration) were observed in SJS but highest mucosal involvement was found in lichenoid reaction and all these features were lowest in Exanthematous reactions

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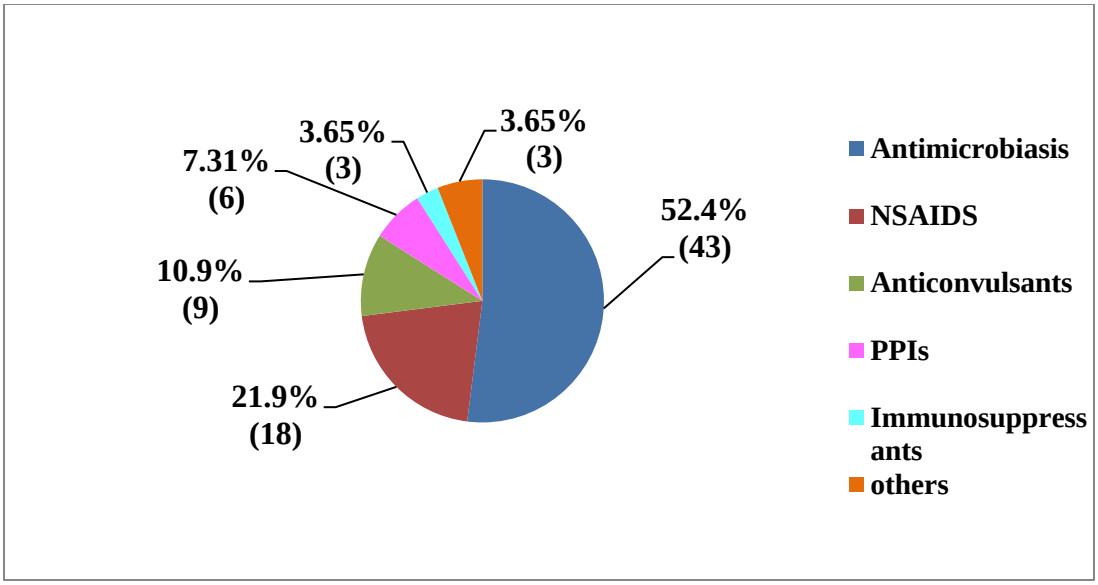
Figure 4-Distribution of Suspected Culprit drugs of CADRs (n=82)



Data expressed in number and percentage, The figure depicts Suspicious Culprit drugs responsible for CADRs were maximum with antimicrobials use followed by NSAIDs, anticonvulsants , Proton pump inhibitors (PPIs) , immune-suppressants and others.

Table 3- Distribution of different suspected drug class and sub class among CADR case

Drug subtypes		**Frequency of CADR (number, percentages)**
Antimicrobial agents (n=43)	Anti-TB	12 (27.9%)
	Floroquinolone	9 (20.9%)
	Metronidazole	7(16.2%)
	Tinidazole	5(11.6%)
	B- lactam	6(13.9%)
	Tetracycline	4(11.6%)

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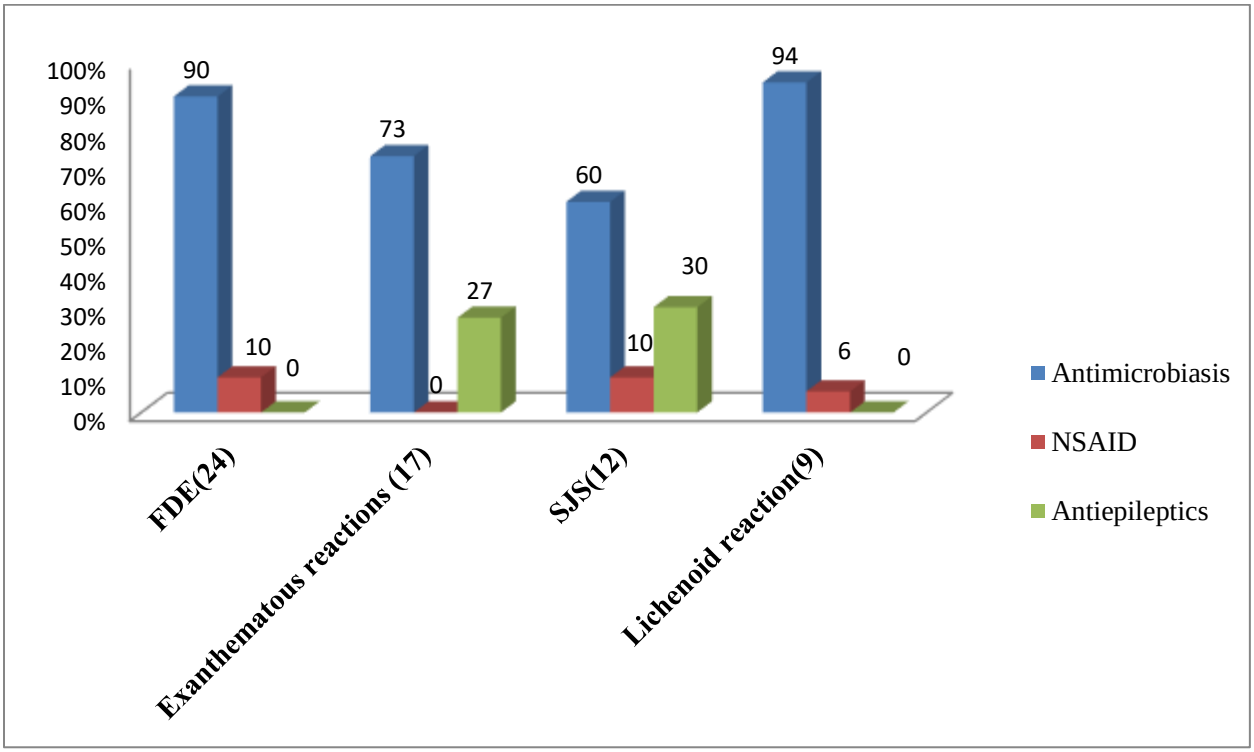
NSAIDs(n=18)	Paracetamol	9(50.0%)
	Ibuprofen	5(27.7%)
	Diclofenac	2(11.1%)
	Others	2(11.!%)

Descriptive data expressed in frequency and percentages, Among Antimicrobial agents (n=43), Anti –tubercular drugs were the major subtype and among NSAIDs(18), Paracetamol was the most common drug responsible for CADRs

Figure 5- Suspected Culprit drugs for common types of CADR (n=52)



Data expressed in percentages**,** On detailed study of drugs used in commonly found CADRs, Antimicrobials were largest consumed drugs responsible for FDE ,Exanthematous reactions , SJS , Lichenoid reactions . Anti-epileptics were 2nd largest consumed drugs causing SJS , exanthematous drug reactions . NSAIDs the 3rd most common suspicious culprit drug type , responsible for all the above mentioned CADRs except exanthematous drug reactions .

Figure -6 Treatment outcome of CADRs (n=82)

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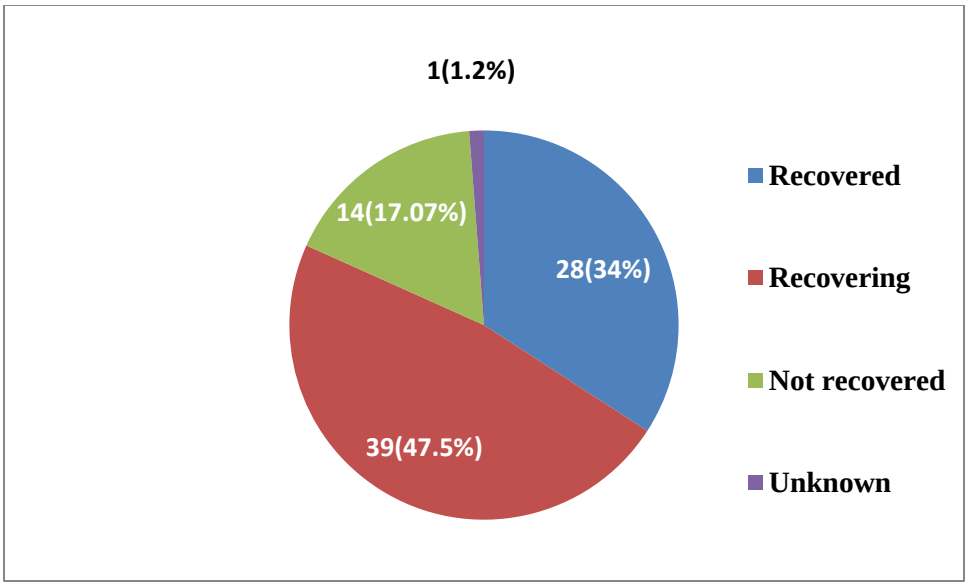

Data expressed in number and percentages**,** The treatment outcome of CADRs showed highest patients in recovering stage followed by recovered then unrecovered

Table -4 -Associations of various risk categories with severe variety of CADRs

Risk category		**Severity (Mild and severe)**				
		Mild	**Severe**	**Confidence interval (CI)**	**Odds ratio (5.938)**	**P-Value**
Extreme age	<20 year	10(55.5%)	4(17.3%)	1.42-24.66	5.938	**0.019***
	>60 year	8 (44.4%)	19(82.6%)			
	Present	4(15.3%)	20(55.5%)	0.041-0.5	0.145	**0.001†**

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H/O Allergy						
	Absent	22(84.6%)	16(44.4%)			
Multi medications (≥2)	Present	12 (80%)	38(97.4%)	0.009-1.109	0.105	**0.02***
	Absent	3 (20%)	1 (2.56%)			

Data were analysed by Chi –Square test and odds ratio. * , ǂ, indicates p value <0.05 and

< 0.001respectively and statistically significant association with risk factors, The above table depicts Analysis of severity with risk factors showed that extreme age (>60 years) H/O allergy and multi-medications (≥ 2 drugs) had statistically significant risk association with severe variety of CADRs compared with mild form.

Morphology of Skin reactions:-

Figure -7 ,TEN (Toxic epidermal necrolysis)

Mucosal (eye ,lips) and cutaneous blistering bullae with peeling off epidermis shown by arrow of TEN

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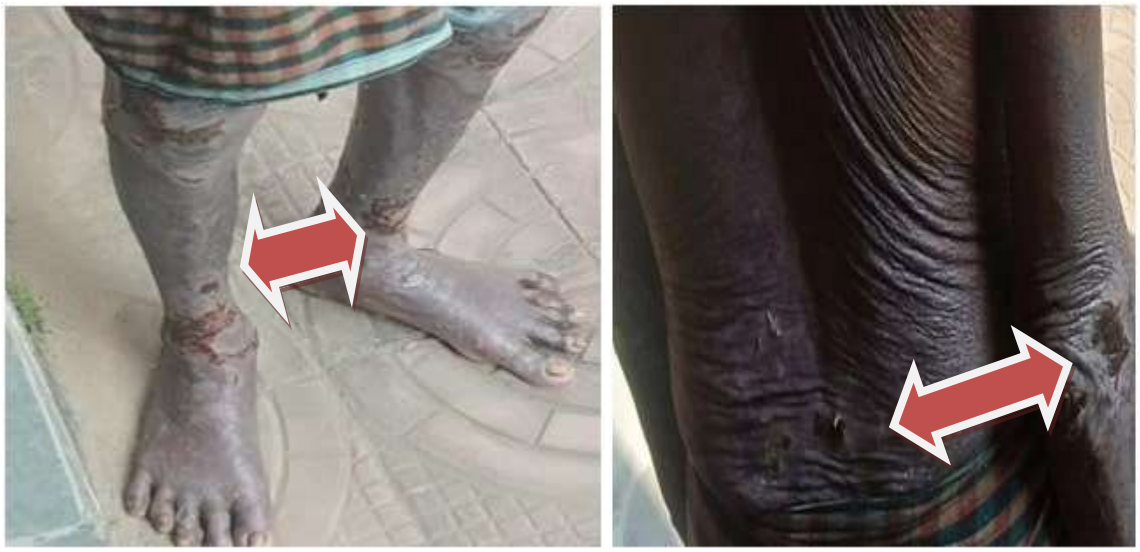
Figure 8- Lichenoid reactions



Symmetric scale like lesions distributed over whole body with desquamation shown by arrow

Figure -9 - Fixed drug eruption (FDE)

Erythematous patches distributed over shoulder, trunk, upper and lower arm which heal as hyperpigmented patches shown by arrow

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DISCUSSION:

In 7 month prospective study of CADRs , 82 CADRs patients attended OPD and IPD of dermatology department and females were in major chunk. According to some studies reported that CADR were more common in women, probably they were more conscious of the skin reactions for cosmetic purposes [Padukan Thappa etal] [13], Kacalak et tal [18], but did not according to Patel and Marfatia's etal[19], Rajendran et al [20], and Jha et al. [21], where male preponderance observed.

Age dominance of >60 yrs was not similar in other studies as different geographical locations had different genotype and hence risk for drug reactions differ according to report from Rajendran et al [20], Sharma et al. [22] .

Latent period required to develop cutaneous adverse reactions was longest (2-3 months) in lichenoid reactions which was corroborated with the result of Maul et al. [25]

In WHO-UMC causality assessment scale maximum suspected drugs were under probable category which was similar to other study. [14]

In severity assessment by modified Hartwig and Siegel Scale, major cases belongs to mild (level-1) severity of CADR, while in other studies like Padmavathi et al.[14] reported moderate severity (level-2) in highest number.

FDE was the major CADR found in our present study which was similar with Padukan Thapa et al [13] and S P, K M, S A et al. [14] It was unlike other studies where drug induced utricarial rash was more common [Sharma et al [22], Al-Raiee et al. [23], and Chatterjee et al [24].]

Antimicrobials were major culprit drugs in this study and similar to other previous research results[13,14] but not according to Al-Raiee et al. [23] Tank B [26] and Baijayanti Rath etal [27] where NSAIDs were major culprit drugs found. Among antimicrobials , antitubercular drugs were major groups found in our study whereas Jhaj R etal [28] reported Beta-lactams were major culprits.

Treatment outcome of CADR were in recovering phase in majority during discharge in our study , while in other study[Rajalakshmi Rukmangathen et al] [29] ,mostly were in recovered stage. This may be due to anticipation of delay recovery, the patients were discharged with treatment advice in this study and followed up till complete recovery.

Extreme age, H/O allergy, and multi -medications (>2 drugs) were found to be significant risk factors associated with severe grade of CADR in this study while in S P, K M, S A et al[14] reported . H/O allergy , polypharmacy as risk factors similar to our result but the other risk factor was age ,sex not as per our study.

Strength of this study:

It was a good study which describe various parameters of CADRs like subtype , culprit drugs of CADR can alert pharmacist ,physician and general population about the same to take precautions to avoid them .

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It assessed the severity and causality of CADR by valid and widely accepted scales. Risk factor association with severe form of CADR was done and also gathered information regarding various treatment options and their outcomes which may favor health care system to provide better healthcare and impart knowledge about prevention and management of CADRs.

Limitation(S):

Our study did not focus on mechanism of CADR. Histo-pathological examination was not done to know the pathological changes. Sophisticated laboratory tests like cardiac enzyme abnormality, TNF-α, IL-6 were not done. Some important information regarding sociodemographic characteristics like educational status, socio-economic status, awareness about ADR and genetic makeup of the patients were not taken into consideration.

CONCLUSION(S):

In this study among diagnosed cases of CADR attended OPD and IPD of skin & VD department, maximum cases were FDE and antimicrobials was found to be major culprit drugs. Causality grade was probable and severity grade was mild in general. More than 60 years of age and H/o previous allergy, multimedications were significant risk factors associated with severity grading of CADR. With increasing marketing of drugs its paramount important that prescribing physicians should understand the various type of CADR, possible drugs that might be responsible for the adverse reactions before hand and make sufficient arrangements of rescue medications to prevent any life threatening event. So it is important to recognize and report the CADR to NCC, PVPi for the betterment of the patients and formulation of guideline for use of such drugs. In all health facilities, survey projects should be carried out on monthly basis and data base should be maintained for providing safety information among treating physicians regularly.

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DECLARATION

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self funded.

Conflict Of interest –

No Conflict of Interest

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