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TO STUDY THE CUTANEOUS ADVERSE DRUG REACTIONS PATTERNS WITH CONSIDERATION OF SEVERITY ASSESSMENT CARRIED OUT IN THE DEPARTMENT OF SKIN & VENEREAL DISEASES AT TERTIARY CARE TEACHING HOSPITAL

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Abstract

The goal of prescription drugs is to lessen pain while a patient is unwell. Adverse medicine Reactions (ADRs) can occur occasionally as a result of the unexpected pharmacological nature of the medicine, the patient's particular physiological condition, and/or other reasons. A small number of ADRs are extremely significant and can result in fatal consequences if they are not treated appropriately and quickly. In addition, a high rate of bothersome adverse drug reactions (ADRs) may cause patients to doubt the efficacy of the prescribed medication, which could result in medication nonadherence.

Few cutaneous ADRs are really severe, despite the fact that they are fairly common; this results in notable comorbidities. The first step in managing the condition and preventing a more serious reaction is early diagnosis of the illness and the medicine causing it, together with prompt withdrawal of the medication. As a result, it's critical to have good reporting and monitoring practices for cutaneous ADRs, as well as sufficient analysis and interpretation of the full pattern of occurrence.

Studying the patterns of cutaneous adverse medication responses in tertiary care hospitals while determining their causation and degree of severity is the goal.

The goal is to identify, evaluate, and report the drug classes and cutaneous adverse drug reactions that cause them.

Supplies and Procedures: Over the course of five months, a prospective study involving both in- and out-patients from the Department of Skin and Venereal Diseases was conducted. 35 patients in all were enrolled based on the selection criteria. The chi-square test was utilized to examine potential differences in the distribution of the category variables.

Result: Of the 35 patients who were recruited in the trial, 12 experienced maculopapular drug rash, with phenytoin being the most often cited cause. Nimesulide was the most often reported reason of fixed medication reaction in the nine research subjects. NSAIDS was the most frequent cause of erythema multiforme in 4 of the individuals. Steven Johnson syndrome and toxic epidermal necrosis each have three patients.

One case of methotrexate-induced idiosyncratic drug toxicity, one case of phenytoin-induced drug response with eosinophilia and systemic symptoms, one case of metronidazole-produced drug induced urticaria, and one case of bullous drug reaction were reported.

In conclusion, patients received counseling and an ADR alert card for emergency situations following the diagnosis and treatment of the cutaneous medication eruption.

Key words: Cutaneous, Naranjo, Hartwig, Adverse medication effects.

1. Introduction

The World Health Organisation (WHO) defines an ADR as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

ADRs causes alterations in functions of various organ systems such as respiratory system, vascular system, nervous system, musculoskeletal system, urinary system, skin and appendages, biliary system and gastrointestinal system.2 In our hospital settings we have observed some notably harmful and detrimental cutaneous reactions. The main motive of this study was to ascertain the specific site, type of cutaneous ADR, causative drug and drug class along with any risk factors. Cutaneous ADR caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompasses all adverse events related to drug eruption, regardless of the etiology.

gardless of the etiology. The most common cutaneous manifestations are maculopapular rash, morbilliform drug eruption, Fixed Drug Eruption (FDE), Erythema Multiforme (EM), Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Drug Hypersensitivity syndrome (DHS), lichenoid drug eruption, photoallergic drug eruption, urticarial, and drug induced vasculitis.2

The most predominating drug classes responsible for causing cutaneous conditions are antibiotics, antimicrobials, NSAIDS, sulfa drugs, biopharmaceuticals, chemotherapy agents, anticonvulsants and psychotrophic drugs. On the contrary, there are certain drugs which are less likely to cause cutaneous drug eruptions including digoxin, aluminum hydroxide, multivitamins, acetaminophen, bisacodyl, aspirin, thiamine, prednisone, atropine, codeine, hydrochlorothiazide, morphine, insulin, warfarin, and spironolactone.

Cutaneous ADRs are frequent and affects 2-3% of all hospitalized patients. It is found that approximately 2% of cutaneous ADRs are severe whereas most of the other drug eruptions are mild and self-limiting. The incidence of cutaneous ADRs in developed countries range from 1-3% among the in-patients, whereas in developing countries such as India, some studies show that it is 2-5% of the in-patients. This difference is observed due to varying prescribing habits and level of health care. However, the assimilation of offending drug enables early withdrawal and improved outcomes. Furthermore, it is established from most studies that the symptoms of reactions alleviate after the offending drug has been discontinued.3.

2. Materials and Methods

Before initiating the study, publications describing cutaneous ADRs in Indian population were thoroughly searched using electronic databases such as Google Scholar, PubMed, Micromedex, Medscape, and Medline. The bibliographies of relevant articles were also taken into account and the considerable points from suitable articles were discussed with guide and clinical guide.

Furthermore, a systematic procedure of performing the study was devised and an appropriate title for the study was framed. The sample size was calculated with the assistance of statistician and thereafter the

first stone of our study was laid by initiating data collection process.

The data collection for this prospective observational study was carried out with intensive monitoring for a period of 6 months in Dermatology Department. First, written informed consent of the subjects were taken via Informed Consent Form (ICF).

Patients with the presence of clinical features suggestive of cutaneous ADRs pertaining to allopathic medications were clinically observed and included in our study. In contrast to this, the patients on nonallopathic medications such as homeopathic, ayurvedic and herbal were excluded from the study

Patient's demographics (age, gender, body weight), history of present illness (duration, causative drug, type of reaction, constitutional symptoms), general physical examination, cutaneous examination and relevant lab reports were analysed. On the basis of patient's medication history, clinical presentation and lab data; the diagnosis regarding cutaneous ADR was carried out. The photographs of clinical features suggesting drug related cutaneous reactions were also captured. Biopsy was performed when required. Suspected ADR was monitored on the basis of regular follow ups carried out by the clinicians and the relevant data of clinical features obtained by each follow up was documented by the researchers.

Causality of the ADR was measured with the help of Naranjo's Algorithm and severity of ADR was measured by Hartwig and Siegel scale (Fig. 1 & Table 1). An ADR alert card was issued to the patient to notify other clinicians about the suspected drug and to refrain them from prescribing it (Fig. 2). Patient Education Leaflet was also provided to patient for better understanding of cutaneous ADR and their prevention. Finally, statistical tests such as Chi-square test and p-value were applied and results were drawn.

Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			

Naranjo Algorithm - ADR Probability Scale

Score	Interpretation of Scores
Total Score ≥9	**Definite.** The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	**Probable.** The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible.** The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful.** The reaction was likely related to factors other than a drug.

Fig. 1: Naranjo probability

Table 1: Hartwig & Siegel scale

Severity Level	Description
1.	An ADR occurred but no change in treatment with suspected drug.
2.	The ADR required treatment with suspected drug withheld, discontinued/changed. No antidote/other treatment required. No increased length of hospital stay.
3.	ADR required treatment with suspected drug withheld, discontinued/changed and required an antidote or other treatment. No increased length of hospital stay.
4.	Any level 3 ADR which increased length of stay at least by 1 day/the ADR was reason for administration
5.	Any level 4 ADR which required intensive medical care
6.	ADR caused permanent harm to the patient
7a	ADR was indirectly linked to death of the patient
7b	ADR was directly linked to death of the patient
Mild	Level 1 and 2
Moderate	Level 3 and 4
Severe	Level 5, 6 and 7

Fig. 2: Adverse drug reaction alert card

3. Results

All together 35 patients suggestive of cutaneous drug reaction were included in our study. An elaborated analysis of all the findings are given below. Patient demographics

Amidst 35 patients, 19 (54%) were males and 16 (46%) were female.

In our study, the age of the patients ranged from 14 years to 70 years, additionally, the mean age of male and female patients was 35.26 ± 15.13 years and 35.26 ± 15.13 years respectively. [Table 2]

Table 2: Age

Gender	Number of patients	Percentage
Male	19	54%
Female	16	46%
Total	35	100%
Gender	Mean	STDEV
Male	35.26	15.13
Female	35.26	15.13

The maximum number of cutaneous ADRs were observed in the age group of 21-30 years (N=11) followed by the age group of 31-40 years (N=8), 11-20 years (N=5), 41-50 years (N=5), 51-60 years (N=4) respectively. In contrast to this, the least number of cutaneous ADRs were found in senior age group of 61- 70 years (N=2).

Diagnosis of Cutaneous ADRs

During the course of cutaneous examination of outpatients and in-patients in the skin OPD various manifestations of cutaneous ADR were detected.

The paramount reaction that highlighted amidst all types of cutaneous ADRs was maculopapular rash (Fig. 3). Total 12 patients have developed maculopapular rash. [Table 3]

Table 3: Diagnosis

Diagnosis	Total	%
Dress	1	2.86%
Fixed drug reaction	9	25.71%
Erythema multiforme	4	11.43%
Maculopapular rash	12	34.29%
Methotrexate induced reaction	1	2.86%
Idiopathic drug toxicity	1	2.86%
Steven jhonson's syndrome	3	8.57%
Toxic epidermal necrolysis	3	8.57%
Urticaria	1	2.86%
Total	**35**	**100.00%**

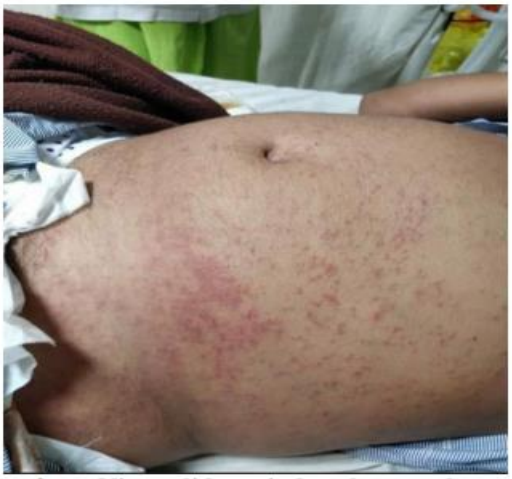

Fig 3: Nimesulide induced erythematous maculopapular rash on trunk and limbs

The second most common cutaneous ADR identified was FDE (Fig. 4), affecting total 9 patients. Chronologically, other reactions accounted were EM with total 4 patients, SJS and TEN (Fig. 5a, b) each were seen in total 3 patients.

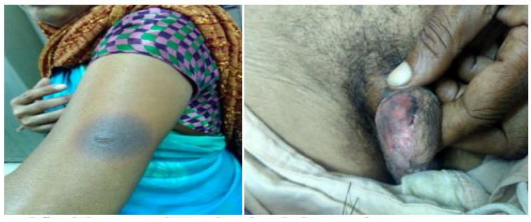

Fig 4: Ofloxacin induced fixed drug eruption on hand and glans penis

Furthermore, other cutaneous ADRs identified were DRESS, bullous drug eruption, idiosyncratic drug reaction and drug induced urticaria.

Causative Drugs for Cutaneous ADRs

Among the various drugs attributed for the causation of cutaneous ADR in the study population, phenytoin and nimesulide were noted to be the most involved drug for causing cutaneous ADR each with 8 cases. Furthermore, occurrence of reaction from olfoxacin, carbamazepine, co-trimoxazole, cefpodoxine, furazolidone and tramadol each were witnessed in 2 patients. (Table 4)

Table 4: Causative Drug

Most common causative drug	Total	%
Carbamazepine	2	5.71%
Cefpodoxime	2	5.71%
Combination	3	8.57%
Co-trimoxazole	2	5.71%
Furazolidone	2	5.71%
Methotrexate	1	2.86%
Metronidazole	1	2.86%
Nimesulide	8	22.86%
Ofloxacin	2	5.71%
Amoxicillin	1	2.86%
Phenytoin	8	22.86%
Tramadol	2	5.71%
Unknown	1	2.86%
Total	**35**	**100.00%**

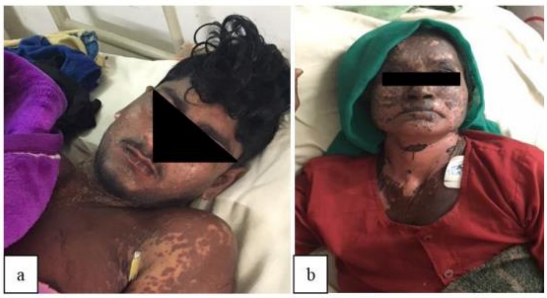

Fig 5a: Carbamazepine-induced Steven Johnson syndrome and toxic epidermal necrolysis]; (b): Ofloxacininduced toxic epidermal necrolysis]

Other drugs liable for causality of cutaneous ADRs includes metronidazole, methotrexate and amoxicillin each reporting single case. Idiosyncratic drug toxicity was seen in 1 patient. Tablet containing combination of cetrizine, acetaminophen and phenylephrine was consumed by 1 patient having cutaneous ADR. Moreover, 1 patient was on medications such as roxithromycin, levocetrizine and combined tablet of dextromethorphan, phenylephrine, cpm etc.

Cutaneous Examination: The patients enrolled in the study were examined thoroughly to determine the pattern of cutaneous reaction including site specific involvement. The table below is composite, selfexplanatory and numerically depicts the incidence of site of reaction in the subject. The cutaneous examination of patients who ingested causative drugs showed reaction on various body parts as show in [Table 5 & 6).

Table 5: Site of reaction

Drug	Cutaneous Involvement								
	Head, neck Face	Scalp	Trunk	Back	Palms Soles	Oral	Genitals	Limb	Eyes
Carbamazepine	2	0	2	2	1	2	1	2	2
Amoxicillin	0	0	0	0	1	0	0	0	0
Cefpodoxime	0	0	2	1	2	0	0	0	0
Combination drugs	2	1	2	1	2	2	1	1	1
Co-trimoxazole	0	0	0	0	2	2	2	0	0
Furazolidone	1	0	0	0	0	1	2	0	0
Methotrexate	0	1	1	0	0	1	1	0	0
Metronidazole	0	0	1	0	0	0	0	0	0
Nimesulide	4	1	2	3	1	6	4	0	1
Ofloxacin	1	0	1	0	0	1	2	1	1
Phenytoin	6	1	3	3	1	3	1	5	1
Idiopathic drug	0	0	1	0	0	1	0	0	0
Tramadol	0	0	2	1	2	0	0	1	0

Table 6: Cutaneous reaction caused by different drugs

Drug	Type of reaction	Number of patients
Phenytoin	Maculopapular rash	5
	Steven johnson syndrome	1
	Dress	1
	Bullous drug eruption	1
Carbamazepine	Maculopapular rash	1
	Toxic epidermal necrolysis	1
Nimesulide	Maculopapular rash	2
	Fixed drug eruption	5
	Erythema multiforme	1
Tramadol	Maculopapular rash	2
Ofloxacin	Toxic epidermal necrolysis	1
	Fixed drug eruption	1
Cefpodoxime	Maculopapular rash	2
Co-trimoxazole	Fixed drug eruption	2
Furazolidone	Fixed drug eruption	1
	Steven johnson syndrome	1
Amoxicillin	Erythema multiforme	1
Metronidazole	Urticaria	1
Methotrexate	Methotrexate induced reaction	1
Combination drugs	Steven johnson syndrome	1
	Toxic epidermal necrolysis	1
	Erythema multiforme	1
Idiopathic drug	Erythema multiforme	1

While examining the patients with various cutaneous ADRs, anticonvulsants were found as the most common class cumulating 10 cases out of 35. This class demonstrated higher significance when compared to other classes ($p = 0.0001$, $x2 = 33.90$). NSAIDs subordinated with the report of 8 cases. Therefore, it is important to know that similar drugs can cause different reactions. For instance, in the

present study anticonvulsants have caused maculopapular rash, SJS, TEN, bullous drug eruption and DRESS (Fig. 6). Similarly, NSAIDs were reported in maculopapular rash, fixed drug eruption and EM.

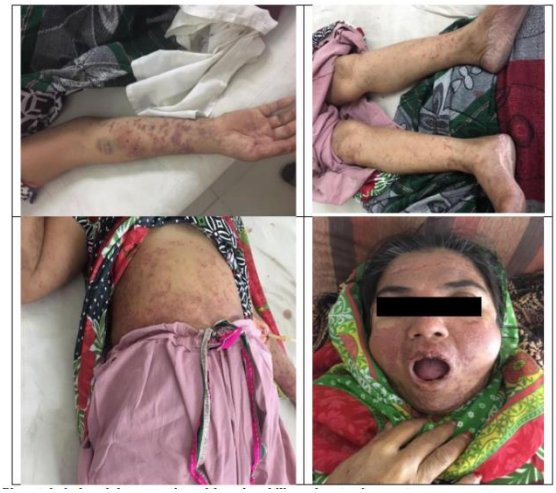

Fig 6: Phenytoin induced drug reaction with eosinophilia and systemic symptoms

Other drug classes involved for causing cutaneous ADRs were fluoroquinolones, antibiotics, cephalosporins, analgesics, antimetabolites, antimicrobials and opioid analgesics as shown in the [Table 7).

Table 7: Most common drug class

Drug class	Total	%
Anticonvulsants	10	29%
Nsaids	8	23%
Flouroquinolones	2	6%
Penicillins	1	3%
Nitroimidazoles	1	3%
Cephalosporins	2	6%
Sulfonamides	2	6%
Antimetabolites	1	3%
Nitrofurantoins	2	6%
Opioid analgesics	2	6%
Unknown	1	3%
Combinations	3	9%
Total	35	100%

Causality and Severity Assessment:

As per Naranjo's severity scale criteria, 93% of cutaneous ADRs were found to be probable and the rest (6%) were found to be possible

Assessment done as per Hartwig scale showed that 83% of cutaneous ADRs were categorised as moderate and 17% constituted severe category.

4. Discussion

Gender Ratio:

Out of 35 patients in our study, 19 were males and 16 were females. Therefore, male to female ratio established was 1.17:1 which is suggestive of slight predominance of male population. In contrast to this, we have come across two academic work done by Abanti Saha et al4 and Padukadan et al which have shown that male to female ratio was found to be 0.96:1 and 0.87:1 respectively.

Age: In our study, age of patients was ranging from 14 years to 70 years. Furthermore, it is seen that 68.57% of subjects were having the age less than 40 years. This result is quite consistent with the result obtained in another study carried out by Tejas K Patel et al5 in which the majority of population (70%) was having age less than 40 years.

A slight deviating from the present study, we have encountered a study conducted by Raksha Marfatia et al6 in which majority of patients belonged to the age group of 41-50 years. In a nutshell, we may conclude that most of the patients who developed cutaneous ADRs were young and adult population rather than geriatrics.

Types of Cutaneous ADRs: The most common clinical pattern of drug reaction in the current study was found to be maculopapular rash which is similar to the study conducted by Tejas K Patel et al5 which also highlighted maculopapular rash as the most common cutaneous ADR with total incidence of 32.32%. Other than this, research study conducted by Mahmood Farschian et al7 pinpointed acute urticaria as the most common cutaneous ADR with total incidence of 52.9%.

Common Causative Drugs: One of the different outcomes we have obtained in our exploration compared to other relevant findings was the identification of phenytoin and nimesulide as the most commonly involved drugs causing cutaneous ADRs. The highest frequency of cutaneous ADRs we have obtained is with phenytoin and nimesulide. On the other hand, the investigation conducted by Hotchandani S C et al8 , Rohini Sharma et al, 9 Tejas K Patel et al5 and Mahmood Farshchian et al7 has shown antimicrobials to be the most common causative agents.

In contrast, the few other studies conducted by authors Raksha Marfatia et al, 7 Surjit Nayak et al3 and Abanti Saha et al4 depicts that the maximum number of cutaneous ADRs were due to causative drugs cotrimoxazole, carbamazepine and sulfonamides respectively.

Causality Assessment: Results drawn as per Naranjo's severity scale criteria demonstrates that 93% of cutaneous ADRs were evaluated as being probable and 6% constituted the possible category. The results of present study is contradictory to the study performed by Rohini Sharma et al, 9 in which Naranjo ADR probability scale indicated probable association of 77.3%, highly probable association of 12.6%, and 1% possible association with the implicated drugs. Reasons behind lesser score on Naranjo probability scale in our study:

1. The suspected drugs were not re-administered.
2. Lack of relevant lab data.
3. There was no objective evidence available.

Severity Assessment: Assessment done as per Hartwig scale in our present study showed that 83% of cutaneous ADRs were assigned as moderate and 17% were placed in severe category. The lesser percentage of severe reactions in our study is attributed to the proper management of cutaneous ADRs.

Distinguished Feature of the Present Study: One of the distinguished outcome we have obtained in our appraisal is the description of the different sites involved in specific cutaneous ADR. We did a separate analysis for the involvement of the different sites in case of each drug related cutaneous ADRs. Cutaneous ADRs were observed on scalp, face, trunk, back, palms, soles, oral, genitals, head,
neck, limbs and eyes depending on the pattern of cutaneous reactions seen.

5. Conclusion

The investigation conducted at the Department of Dermatology has led us to a number of conclusions. After analyzing the gender ratio data, it can be inferred that male patients have exhibited a higher tendency to cause cutaneous adverse drug reactions (ADRs) than female patients.

A variety of reactions have been seen throughout the clinical spectrum of cutaneous ADRs that have been reported to the Department of Dermatology. Of all the cutaneous ADRs, maculopapular rash was found to be the most prevalent.

FDE was the second most frequent cutaneous ADR.Additional responses that were reported included urticaria, bullous drug eruption, TEN, SJS, EM, and DRESS. A few responses have also caused patients' hospital stays to be longer. However, no recorded deaths from cutaneous ADRs were made.The medications phenytoin and nimesulide were the most frequently implicated in cutaneous ADRs.

Other medications that appeared to contribute to the trend of cutaneous adverse drug reactions (ADRs) were furazolidone,

methotrexate, carbamazepine, co-trimoxazole, tramadol, cefpodoxine, and metronidazole. Anticonvulsants were shown to be the most often implicated drug class among those that cause cutaneous ADRs, followed by NSAIDS. Additional drug classes that were involved included opioid analgesics, cephalosporins, analgesics, antimetabolites, antibiotics, and fluoroquinolones.Based on the Naranjo scale, the majority of cutaneous ADRs were classified as probable, and a small number were classified as perhaps caused. In addition, the Hartwig scale evaluation results, which showed that most reactions were fairly severe and a small number were classified as severe, were used to determine the reaction's intensity.

Limitations

Short duration of the study was one of the limitations as few of the results of our study were not consistent with those observed in studies conducted for longer duration.

As we opted for just an observational study not an interventional, we have not carried out a rechallenge of a drug causing cutaneous ADR and this might have affected the causality assessment.

In some of the cases we could not obtain all the details regarding medication history (brand name, manufacturer, batch number and expiry date) and this has influenced documentation in our data collection procedure. This is due to the fact that several patients came from a rural background and did not have supportive data for the treatment they had already received

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