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FACTORS CAUSING BREAKTHROUGH SEIZURES IN KNOWN EPILEPTIC PATIENTS TAKING PRESCRIBED ANTI-EPILEPTIC DRUGS REGULARLY

Original Article (ID: 454)

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ABSTRACT

Background: Epilepsy is a chronic neurological disorder marked by recurrent unprovoked seizures and remains a major cause of neurological morbidity worldwide. Although anti-epileptic drugs control seizures in many patients, breakthrough seizures may still occur despite regular medication intake. These episodes increase the risk of injury, emergency visits, psychological distress, and reduced quality of life. Identifying preventable triggers is therefore essential for improving seizure control and guiding more comprehensive epilepsy care and counselling in routine practice settings.

Objective: To determine the common factors associated with breakthrough seizures among known epileptic patients taking prescribed anti-epileptic drugs regularly.

Methods: This descriptive cross-sectional study was conducted in the Department of Neurology, CMH, Peshawar, from June 2024 to December 2024. A total of 150 known epileptic patients aged 18–65 years who presented with breakthrough seizures despite regular anti-epileptic drug use were included through non-probability convenience sampling. Patients with new-onset seizures, acute symptomatic seizures, poor medication adherence, pregnancy, or significant uncontrolled comorbidities were excluded. Data were collected using a structured questionnaire, medical record review, clinical examination, and relevant investigations. Demographic characteristics, duration of epilepsy, seizure type, anti-epileptic drug regimen, precipitating factors, laboratory findings, EEG, and neuroimaging findings were recorded. Data were analyzed using SPSS version 25, with frequencies, percentages, mean, standard deviation, and chi-square test where applicable.

Results: The mean age was 34.7 ± 12.5 years. Among 150 patients, 90 were male and 60 were female. Generalized tonic-clonic seizures were reported in 90 patients, focal seizures in 45, and absence seizures in 15. Polytherapy was used by 85 patients, while 65 were on monotherapy. Sleep deprivation was identified in 45 patients, infection or fever in 37, psychological stress in 30, drug interaction in 30, missed medication in 20, and metabolic disturbance in 12. Abnormal EEG findings were observed in 22 patients, elevated white blood cell count in 15, liver enzyme elevation in 12, hyponatremia in 8, hypokalemia in 5, and minor nonspecific CT/MRI changes in 7 patients.

Conclusion: Breakthrough seizures among patients taking anti-epileptic drugs regularly were associated with multiple modifiable factors. Routine assessment of sleep, infection, stress, metabolic status, and medication interactions may improve seizure control and support more holistic epilepsy management.

Keywords: Anticonvulsants; Drug Interactions; Epilepsy; Fever; Medication Adherence; Psychological Stress; Sleep Deprivation.

INTRODUCTION

Epilepsy is a common chronic neurological disorder characterized by a persistent tendency to develop recurrent, unprovoked seizures due to abnormal and excessive electrical activity within the brain. It affects people of all ages and remains a major public health concern, with an estimated 50 million individuals living with epilepsy worldwide (1-3). Beyond the clinical burden of seizures, epilepsy can significantly affect education, employment, social participation, psychological well-being, and overall quality of life. Although seizure type, frequency, severity, and underlying cause may vary widely among patients, long-term seizure control remains the central goal of epilepsy management. Anti-epileptic drugs (AEDs) are the mainstay of treatment and are effective in achieving seizure control in a large proportion of patients. The World Health Organization has reported that nearly 70% of people with epilepsy may live seizure-free with appropriate diagnosis, regular treatment, and adequate follow-up (4). However, a considerable number of patients continue to experience seizures despite taking prescribed AEDs regularly. These episodes, commonly referred to as breakthrough seizures, are clinically important because they may lead to emergency visits, hospital admission, injury, loss of confidence, driving and occupational restrictions, psychological distress, and reduced quality of life (5-7). For clinicians, breakthrough seizures raise an important question: why do seizures occur in patients who appear to be compliant with treatment?

Medication non-adherence is often considered the most common cause of seizure recurrence, but this explanation may not be sufficient in patients who report regular AED use. Breakthrough seizures in such patients may reflect a more complex interaction of patient-related, disease-related, environmental, metabolic, and pharmacological factors. Possible contributors include subtherapeutic drug levels, altered drug absorption, drug resistance, inappropriate dosage, interactions with other medications, intercurrent illness, fever, electrolyte imbalance, sleep deprivation, psychological stress, and hormonal changes such as menstruation (8-11). These factors may lower the seizure threshold or reduce the effectiveness of AEDs, allowing seizures to occur even when medication is being taken as advised. Several precipitating factors are potentially modifiable, which makes their identification clinically valuable. Sleep deprivation and psychological stress are frequently reported by patients before seizure recurrence, while infections and fever may increase neuronal excitability and worsen seizure control. Metabolic disturbances, particularly abnormalities of glucose, sodium, calcium, or renal and hepatic function, may also contribute to seizure precipitation or alter AED metabolism. Similarly, concomitant use of certain medications may interfere with AED levels and reduce therapeutic protection. In patients with chronic epilepsy, anxiety, depression, and emotional stress may further complicate disease control and should be considered as part of comprehensive epilepsy care (11-14).

In emergency and hospital settings, patients presenting with breakthrough seizures provide an important opportunity to identify immediate and preventable triggers. This is particularly relevant in resource-limited healthcare environments, where regular therapeutic drug monitoring, specialist follow-up, and patient counseling may not always be easily accessible. Identifying the common factors associated with breakthrough seizures among patients who are already taking AEDs regularly may help clinicians improve counseling, adjust treatment when required, manage comorbid conditions, and prevent avoidable seizure-related complications. The present study was therefore designed to determine the factors causing breakthrough seizures in known epileptic patients who were taking prescribed anti-epileptic drugs regularly. The study aimed to assess the frequency of common precipitating factors, including environmental, psychological, metabolic, infectious, and drug-related contributors, so that preventable causes may be recognized early and incorporated into more effective epilepsy management strategies.

METHODS

This descriptive cross-sectional study was conducted in the Department of Neurology, Combined Military Hospital (CMH), Peshawar, from June 2024 to December 2024. The study was designed to identify factors associated with breakthrough seizures among known patients with epilepsy who had been taking prescribed anti-epileptic drugs (AEDs) regularly. CMH, Peshawar is a tertiary care hospital that receives patients from both urban and rural areas and caters to individuals from diverse socioeconomic backgrounds, thereby providing an appropriate clinical setting for evaluating seizure-related presentations in a mixed patient population. The study population comprised patients with a previously established diagnosis of epilepsy who presented with breakthrough seizures during the study period despite regular use of prescribed AEDs. For the purpose of the study, a breakthrough seizure was considered as the occurrence of a seizure in a known epileptic patient already receiving AED therapy, without an obvious new acute neurological cause. Patients of either sex were included if they had a documented history of epilepsy, had been prescribed AEDs by a physician, and reported regular intake of medication according to the advised dosage and schedule. Patients were excluded if they had new-onset seizures, acute symptomatic seizures secondary to recent neurological events such as stroke, head injury, central nervous system infection, or intracranial space-occupying lesion, poor medication adherence, pregnancy, or significant uncontrolled systemic comorbidities that could independently provoke seizures. A total of 150 eligible patients were enrolled through non-probability convenience sampling during the six-month study period.

Data were collected using a structured questionnaire and review of patients' medical records. The questionnaire included demographic information such as age, sex, residence, and relevant socioeconomic details, along with clinical variables including duration of epilepsy, previous seizure history, seizure type, seizure frequency, and history of recent breakthrough seizure episodes. Seizures were categorized clinically as generalized tonic-clonic, focal, absence, or other seizure types based on history, available medical records, and neurologist

assessment. Details of AED therapy were recorded, including the type of AED, monotherapy or polytherapy, prescribed dose, dosing schedule, duration of treatment, and any recent change in medication. Medication adherence was assessed through patient or caregiver self-report regarding regular intake of AEDs as prescribed. Potential precipitating factors for breakthrough seizures were assessed through direct patient or caregiver interview and clinical evaluation. These included sleep deprivation, psychological stress, fever or infection, recent systemic illness, metabolic disturbances, possible drug interactions, recent medication changes, alcohol or substance use, and, where applicable, menstrual-related seizure clustering. Clinical examination was performed by a neurologist, and relevant investigations were reviewed or performed when clinically indicated. Laboratory evaluation included complete blood count, serum electrolytes, blood glucose, liver function tests, and renal function tests to identify possible infectious, metabolic, or drug-related contributors. Electroencephalography was reviewed where available or advised according to clinical need. Neuroimaging, including computed tomography or magnetic resonance imaging, was performed only when indicated by clinical presentation, such as focal neurological deficits, change in seizure pattern, prolonged postictal state, suspected structural lesion, or concern for an acute intracranial event.

Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS), version 25. Continuous variables such as age and duration of epilepsy were summarized as mean and standard deviation, while categorical variables including sex, seizure type, AED regimen, and precipitating factors were presented as frequencies and percentages. Associations between categorical variables were assessed using the chi-square test, while Fisher's exact test was considered where expected cell counts were small. A p-value of less than 0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Review Board of CMH, Peshawar, before initiation of the study. Written informed consent was obtained from all participants or from legal guardians where applicable. Participation was voluntary, and patients were informed about the purpose of the study, confidentiality of information, and their right to withdraw at any stage without any effect on their clinical care. Patient anonymity was maintained by using coded data, and all collected information was used only for research purposes. Certain limitations were recognized. Medication adherence and lifestyle-related triggers were mainly assessed through patient or caregiver self-report, which could have introduced recall bias or reporting bias. As the study was conducted at a single tertiary care center, the findings may not be fully generalizable to all epileptic patients in other healthcare settings. In addition, routine therapeutic drug monitoring of AED levels was not available for all patients, which may have limited the ability to identify subtherapeutic drug levels as a contributor to breakthrough seizures.

RESULTS

A total of 150 known epileptic patients who were taking prescribed anti-epileptic drugs and presented with breakthrough seizures were included in the study. The mean age of the participants was 34.7 ± 12.5 years, with an age range of 18 to 65 years. Among the study participants, 90 were male and 60 were female, representing 60.0% and 40.0% of the cohort, respectively. The highest proportion of patients belonged to the 26–35 years age group, comprising 44 patients (29.3%), followed by 38 patients (25.3%) in the 18–25 years age group, 31 patients (20.7%) in the 36–45 years age group, 22 patients (14.7%) in the 46–55 years age group, and 15 patients (10.0%) in the 56–65 years age group. The duration of epilepsy varied among the participants. Thirty patients (20.0%) had epilepsy for less than one year, while 60 patients (40.0%) had epilepsy for one to five years. Another 60 patients (40.0%) had a history of epilepsy for more than five years. Regarding seizure type, generalized tonic-clonic seizures were the most frequently reported seizure pattern and were observed in 90 patients (60.0%). Focal seizures were reported in 45 patients (30.0%), while absence seizures were documented in 15 patients (10.0%).

With respect to anti-epileptic drug regimens, 65 patients (43.3%) were receiving monotherapy, whereas 85 patients (56.7%) were receiving polytherapy. Sodium valproate was the most commonly used anti-epileptic drug and was recorded in 68 patients (45.3%). Levetiracetam was used by 45 patients (30.0%), carbamazepine by 38 patients (25.3%), phenytoin by 22 patients (14.7%), and lamotrigine by 12 patients (8.0%). As some patients were receiving more than one anti-epileptic drug, individual drug frequencies exceeded the total number of patients receiving monotherapy. Among the reported precipitating factors for breakthrough seizures, sleep deprivation was the most frequent factor and was identified in 45 patients (30.0%). Infection or fever was reported in 37 patients (24.7%), followed by psychological stress in 30 patients (20.0%) and possible drug interaction in 30 patients (20.0%). Missed medication was reported in 20 patients (13.3%), while metabolic disturbance was documented in 12 patients (8.0%). The total frequency of precipitating factors exceeded the number of patients, indicating that some patients had more than one reported trigger.

Laboratory and diagnostic findings showed that elevated white blood cell count was present in 15 patients (10.0%). Hyponatremia was identified in 8 patients (5.3%), while hypokalemia was found in 5 patients (3.3%). Mild elevation of liver enzymes was observed in 12 patients (8.0%). Electroencephalography showed abnormal findings in 22 patients (14.7%). Neuroimaging with computed tomography or magnetic resonance imaging showed minor nonspecific changes in 7 patients (5.3%). Statistical analysis showed significant associations between selected clinical and laboratory variables. Sleep deprivation was significantly associated with seizure type on chi-square testing ($p = 0.021$). Infection was significantly associated with raised white blood cell count ($p = 0.003$). Metabolic disturbance was significantly associated with electrolyte abnormality ($p < 0.001$). A significant association was also observed between possible drug interaction and liver function abnormality ($p = 0.047$).

Table 1. Demographic Characteristics of the Study Population

Variable	Frequency (n)	Percentage (%)
Total patients	150	100.0
Gender		
Male	90	60.0
Female	60	40.0
Age group		
18–25 years	38	25.3
26–35 years	44	29.3
36–45 years	31	20.7
46–55 years	22	14.7
56–65 years	15	10.0
Mean age ± SD	34.7 ± 12.5 years	Range: 18–65 years

Table 2. Clinical and Epilepsy-Related Characteristics of Patients

Variable	Frequency (n)	Percentage (%)
Duration of epilepsy		
Less than 1 year	30	20.0
1–5 years	60	40.0
More than 5 years	60	40.0
Type of seizure		
Generalized tonic-clonic seizures	90	60.0
Focal seizures	45	30.0
Absence seizures	15	10.0
Anti-epileptic drug regimen		
Monotherapy	65	43.3
Polytherapy	85	56.7

Table 3. Anti-Epileptic Drugs Used and Precipitating Factors for Breakthrough Seizures

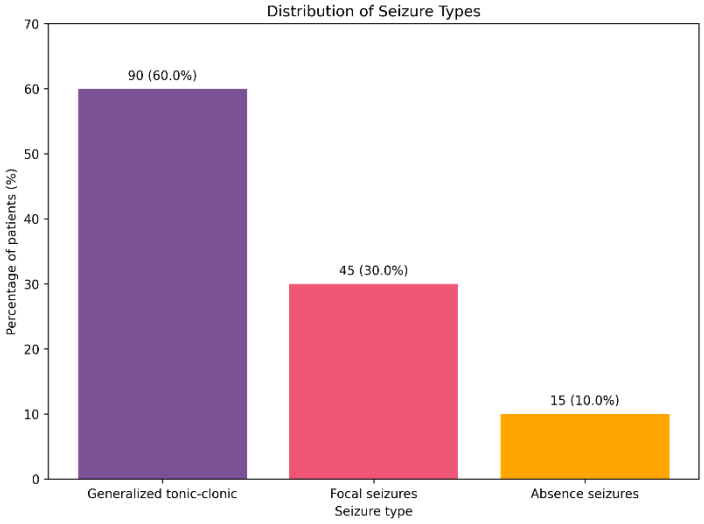
Variable	Frequency (n)	Percentage (%)
Anti-epileptic drugs used		
Sodium valproate	68	45.3
Levetiracetam	45	30.0
Carbamazepine	38	25.3
Phenytoin	22	14.7
Lamotrigine	12	8.0
Precipitating factors		
Sleep deprivation	45	30.0

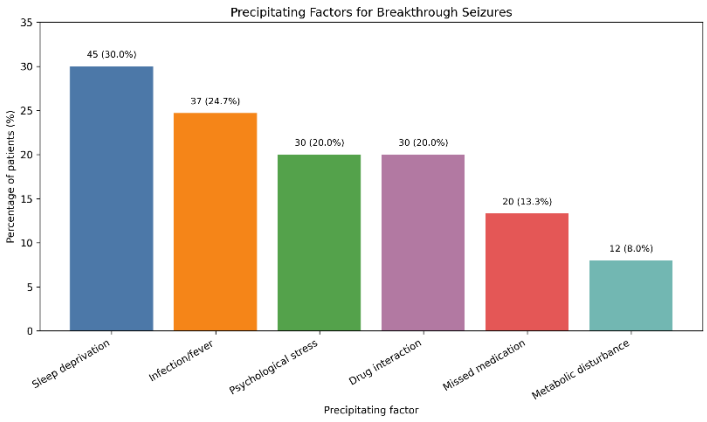
Infection / fever	37	24.7
Psychological stress	30	20.0
Drug interaction	30	20.0
Missed medication	20	13.3
Metabolic disturbance	12	8.0

Table 4. Laboratory, Diagnostic Findings, and Statistical Associations

Variable / Investigation	**Abnormal Finding**	**Frequency (n)**	**Percentage (%)**
White blood cell count	Elevated	15	10.0
Serum sodium	Low	8	5.3
Serum potassium	Low	5	3.3
ALT/AST	Mild elevation	12	8.0
EEG	Abnormal findings	22	14.7
CT/MRI brain	Minor nonspecific changes	7	5.3

Association Tested	**Statistical Test**	**p-value**	**Interpretation**
Sleep deprivation and seizure type	Chi-square test	0.021	Significant
Infection and raised WBC count	Chi-square test	0.003	Significant
Metabolic disturbance and electrolyte abnormality	Chi-square test	<0.001	Highly significant
Drug interaction and liver function abnormality	Chi-square test	0.047	Significant





DISCUSSION

The present study evaluated the factors associated with breakthrough seizures among known epileptic patients who were taking prescribed anti-epileptic drugs regularly. The findings showed that breakthrough seizures were not explained by medication use alone, but appeared to result from a combination of lifestyle-related, infectious, psychological, metabolic, and drug-related factors. Sleep deprivation was the most frequently reported precipitating factor, followed by infection or fever, psychological stress, possible drug interaction, missed medication, and metabolic disturbance. These findings supported the clinical understanding that seizure control depends not only on anti-epileptic drug therapy, but also on the identification and control of factors that may lower the seizure threshold (14,15). Sleep deprivation was reported in 30.0% of patients and emerged as the most common factor associated with breakthrough

seizures. This finding was consistent with previous literature suggesting that insufficient sleep can increase cortical excitability, disturb normal neuronal regulation, and reduce the threshold for seizure occurrence. In patients with epilepsy, irregular sleep patterns may also interfere with medication timing, daytime functioning, and overall seizure stability. The significant association observed between sleep deprivation and seizure type further indicated that sleep disturbance may have an important relationship with seizure presentation. These findings emphasized the need to include sleep hygiene counseling as a routine part of epilepsy management, particularly in patients who continue to experience seizures despite regular drug intake (15,16).

Infection or fever was identified in 24.7% of patients, making it the second most frequently reported precipitating factor. This finding was clinically relevant because infections may provoke seizures through fever, systemic inflammation, metabolic stress, dehydration, reduced oral intake, and altered absorption or metabolism of anti-epileptic drugs. The significant association between infection and raised white blood cell count supported the presence of an inflammatory or infectious process in a proportion of patients. These results were in agreement with earlier studies that described acute systemic illness as an important contributor to seizure recurrence in patients with established epilepsy. Early recognition and timely treatment of infections may therefore help reduce preventable seizure episodes in this population (16). Psychological stress was reported in 20.0% of patients and represented another important modifiable factor. Chronic stress, anxiety, emotional distress, and poor coping mechanisms may contribute to seizure recurrence through neuroendocrine activation, sleep disruption, autonomic instability, and reduced overall resilience. Although stress is often difficult to measure objectively, its frequent reporting among patients with breakthrough seizures highlighted the importance of addressing mental health as part of epilepsy care. The findings were consistent with previous evidence indicating that emotional well-being and psychosocial support have a meaningful role in long-term seizure control. Incorporation of stress management, counseling, family education, and screening for anxiety or depression may therefore improve patient-centered outcomes (15, 17).

Drug interaction was reported in 20.0% of patients, while mild liver enzyme elevation was observed in 8.0%. A significant association between possible drug interaction and liver function abnormality suggested that pharmacological factors might have contributed to breakthrough seizures in some patients. This was particularly relevant because more than half of the patients were receiving polytherapy. Anti-epileptic drugs may interact with antibiotics, antituberculous drugs, psychotropic medications, hormonal therapies, and other commonly prescribed medicines. Some interactions may reduce serum AED concentrations, while others may increase toxicity or affect hepatic metabolism. These findings supported the importance of regular medication review, careful prescribing, and patient education regarding over-the-counter medicines and newly added drugs (17,18). Metabolic disturbance was documented in 8.0% of patients, while hyponatremia and hypokalemia were identified in 5.3% and 3.3% of patients, respectively. The significant association between metabolic disturbance and electrolyte abnormality indicated that biochemical derangements were relevant in a subset of patients presenting with breakthrough seizures. Although metabolic abnormalities were less common than sleep deprivation or infection, they carried important clinical implications because many are identifiable through basic laboratory testing and are potentially reversible. Screening for serum electrolytes, blood glucose, renal function, and hepatic function may therefore be useful, especially in patients with recurrent episodes, altered sensorium, systemic illness, or recent medication changes (18,19).

The finding that 13.3% of patients reported missed medication required cautious interpretation. Since the study focused on patients taking AEDs regularly and excluded poor medication adherence, this result most likely reflected occasional missed or delayed doses rather than persistent non-adherence. Even isolated missed doses may be clinically meaningful in patients with low seizure threshold, short drug half-life, polytherapy, or irregular routines. However, reliance on self-reported adherence may have underestimated the true frequency of non-adherence. Future studies should incorporate objective adherence measures, such as pill counts, prescription refill records, caregiver verification, or therapeutic drug monitoring, where feasible (20). The findings of this study reinforced the broader view that epilepsy management should extend beyond prescribing anti-epileptic drugs. Lifestyle modification, infection prevention and early treatment, psychological support, metabolic screening, medication reconciliation, and patient counseling may all contribute to improved seizure control. The results also highlighted the practical value of evaluating breakthrough seizures systematically rather than assuming treatment failure or drug resistance alone. In clinical practice, identifying modifiable triggers may help reduce emergency visits, hospital admissions, seizure-related injuries, and psychosocial burden.

A key strength of this study was that it focused specifically on known epileptic patients who were already taking prescribed anti-epileptic drugs, allowing assessment of factors beyond routine medication use. The study also included clinical evaluation, laboratory testing, EEG findings, and neuroimaging where indicated, which provided a broader assessment of possible contributors. In addition, the sample included patients from a tertiary care hospital serving both urban and rural populations, which added clinical relevance to the findings. However, some limitations were present. The cross-sectional design restricted the ability to establish a temporal or causal relationship between precipitating factors and breakthrough seizures. Medication adherence, sleep deprivation, stress, and some lifestyle-related triggers were assessed mainly through patient or caregiver self-report, which may have introduced recall bias and reporting bias. The study was conducted at a single center, which may limit the generalizability of the findings to other regions and healthcare settings. Therapeutic drug monitoring was not routinely performed, so subtherapeutic AED levels could not be confirmed in all patients. In addition, some precipitating factors may have overlapped, as a single patient could have more than one trigger, such as infection with sleep deprivation or stress with missed medication.

Future research should include multicenter prospective studies with larger sample sizes and standardized definitions of breakthrough seizures and precipitating factors. Objective measures of adherence, therapeutic drug monitoring, validated stress and sleep assessment tools, and detailed evaluation of drug interactions should be incorporated to strengthen the evidence. Longitudinal follow-up would also help determine whether correction of modifiable factors leads to measurable reduction in seizure recurrence. Such improvements may support the development of structured clinical protocols for evaluating and preventing breakthrough seizures in patients with epilepsy. Overall, the study suggested that sleep deprivation, infection or fever, psychological stress, drug interaction, and metabolic abnormalities were important contributors to breakthrough seizures among known epileptic patients receiving anti-epileptic drugs. These findings supported a comprehensive and multidisciplinary approach to epilepsy care, in which medication optimization is combined with lifestyle counseling, early management of systemic illness, psychological support, and regular clinical review.

CONCLUSION

This study concluded that breakthrough seizures in known epileptic patients taking prescribed anti-epileptic drugs regularly were associated with multiple modifiable factors rather than medication use alone. Sleep disturbance, infections, psychological stress, drug-related issues, and metabolic abnormalities emerged as important contributors that may lower seizure threshold and compromise seizure control. The findings highlight the need for a comprehensive approach to epilepsy management, including patient counseling, sleep hygiene, timely treatment of infections, medication review, metabolic assessment, and psychological support. Early recognition and correction of these factors may help reduce seizure recurrence, prevent avoidable hospital visits, and improve the overall quality of life of patients with epilepsy.

AUTHOR CONTRIBUTION

Author	Contribution
Dr Shah Nawaz Khan	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Dr Abid Sharif	Methodology, Investigation, Data Curation, Writing - Review & Editing
Dr Maryam Hussain	Investigation, Data Curation, Formal Analysis, Software
Dr Muhammad Yasin	Software, Validation, Writing - Original Draft
Dr Khayam	Formal Analysis, Writing - Review & Editing

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