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Emerging Trends in Drug-Induced Seizures: A Pilot Study

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Abstract

Background: Seizures, indicative of uncontrolled and abnormal electrical activity in the brain, constitute a significant concern in emergency medicine.

Objectives: This pilot study, conducted in two toxicology centers in Yazd, Iran, aimed to enhance our understanding of drug-induced seizures (DIS).

Methods: This five-year cross-sectional study analyzed 205 cases in two toxicology centers in Yazd, Iran. The investigation focused on demographic distribution, causative agents, and clinical outcomes. Data entered into SPSS version 26 and analyzed. $p<0.05$ was assumed significant.

Results: Tramadol emerged as the predominant cause of DIS (74.15%), followed by benzodiazepine withdrawal (7.8%), organophosphorus toxins (3.41%), and methadone (3.41%). Tramadol ingestion was correlated with status epilepticus (Odds ratio (OR) = 4.166, 95% CI = 1.73-10.01), ICU admission (OR=3.394, CI = 1.623-7.1), and intubation (OR=0.057, CI = 0.012-0.272) $P<0.05$), but no significant correlation was observed between tramadol ingestion and overall outcome ($P>0.05$). A significant correlation was found between ICU admission and age ($P=0.04$). Additionally, a notable correlation was seen between drug categories with outcome, status epilepticus, ICU admission, and intubation ($P<0.05$). Among five deaths, 2 (40%) were related to tramadol, 2 (40%) to organophosphorus compounds, and 1 (20%) to methadone.

Conclusion: Drug-induced seizures present critical challenges in emergency settings. Moreover, the widespread use of tramadol and a recent trend in its abuse have contributed to drug-induced seizures. Organophosphorus toxins, though uncommon, led to severe complications and high mortality. Further research is essential to develop predictive models and refine clinical approaches in managing diverse drug-induced seizure scenarios.

Keywords: Benzodiazepine, Drug-Induced Seizures, Methadone, Tramadol

1. Background

A seizure is an abnormal activity in the brain that happens when there is uncontrolled and abnormal electrical activity. The effects of seizures are broad and diverse, such as loss or lower consciousness, behavior changes, and

memory or emotional disruptions (1). Seizures are among the most prevalent and harmful presentations of patients referred to the emergency ward, making them an important phenomenon to be considered by first-line caregivers. These events could be caused by hyperthermia, anoxia, electrolyte imbalance, and even severe brain damage resulting from drug toxicity (2, 3). Previous studies demonstrated that 6.1% of new-onset convulsions and 9% of status epilepticus are associated with drug intoxication; also, 10% of those with drug intoxication will suffer status epilepticus (3-5). Drug-related seizures, or so-called toxic seizures, are not only frequent but also require rapid, careful intervention to prevent critical complications and decrease their mortality and morbidity (6). Acute intoxication, drug overdose, recreational drug use, and withdrawal syndrome are the leading sources of toxic seizures. With the massive rise of recreational drug use and the evident rise in conventional drug abuse, toxic seizure has become a central issue in toxicology centers (7, 8). In a study by Thundiyil et al. (9) on 386 patients, the principal causes of toxic seizures were Bupropion (23%), diphenhydramine (8.3%), and tricyclic antidepressants (7.7%), whereas according to regional studies from Iran, tramadol, antidepressants, and recreational drugs in combination with alcohol along with opiates' withdrawal were the main reasons for drug-induced seizures (10, 11). In light of recent literature regarding toxic seizures, there is still controversy surrounding their causes and therapeutic management (12, 13). Moreover, an overview of the most frequent drugs causing toxic seizures enables physicians to have more concise clinical reasoning and more efficient medical management. The aim of this research was to extend current knowledge about the main reasons, demographic distribution, medications, and clinical outcomes of these patients referred to two clinical toxicology centers.

2. Objectives

This pilot study, conducted in two toxicology centers in Yazd, Iran, aimed to enhance our understanding of drug-induced seizures (DIS).

3. Methods

Study population and design

In this pilot study, all patients with the diagnosis of tonic-colonic drug-related seizures from March 2015 until March 2020 were included. Medical records were gathered from two toxicology centers located in Yazd, Iran. For case definition, the seizure must be the initial referring presentation. Moreover, a relationship between drug abuse or withdrawal and an ictal event should be confirmed based on clinical history. Patients with conditional disease, particularly epilepsy, consuming neurologic or anti-convulsant drugs, and possessing abnormal findings of a computed tomography scan were excluded. In addition, seizures related to non-drug-induced hypoglycemia and electrolyte imbalance, such as hypocalcemia or hyponatremia, which were not due to drug intoxication, and any other reasons that can cause seizures independently, such as trauma, were other exclusion criteria.

Data collection

After case definition, related medical records were provided by hospitals' archives. Demographic data, including age and sex, causative agent including the name of the drug and withdrawal, route of poisoning, intention, type of medication used for seizure control, and type of seizure, were collected. Furthermore, the outcome was measured by the admission rate of the intensive care unit (ICU), the rate of intubation, and mortality. Data correction and completion were done via phone calls with the patients, and their families did mortality case correction. Excel conducted data entry and then entered into SPSS version 26.

Definition

For reasons of exposure, an attempt to commit suicide was named suicidal, and overuse of a substance without the purpose of self-harm was considered drug abuse. Unintentional use of drugs was also defined as accidental. Medical records in which the reason for exposure was not mentioned were classified as non-defined. For age, the population was classified into three groups according to previous studies: less than 15 years as children, 15-40 years as young adolescents, and more than 40 years as elderly (14). Complication and poor prognosis were followed by four variables: status epilepticus (SE), ICU admission, intubation, and outcome. Outcome defines the final state of patients as alive or dead. The drug was a general term for causes of drug drug-induced seizure (DIS), including conventional and recreational drugs, toxins, and substances. Tramadol was also an independent variable, as it was the most prevalent ingested substance (12).

According to the Society of Critical Care Medicine of the US, admission to the ICU requires vast knowledge and wisdom about the present and future situation of the patient, and it relies on the physician's decision. Nevertheless, we can use some criteria to help in making this decision. Based on their criteria, these patients should be admitted to the ICU and cannot be admitted to the wards unless there are no criteria for ICU admission. Based on their criteria for diagnosis, the following conditions warrant admission to the intensive care unit (ICU) based on medical guidelines: 1. Cardiac System: A) Acute myocardial infarction with complications, B) Cardiogenic shock, C) Complex arrhythmias requiring close monitoring and intervention, D) Acute congestive heart failure with respiratory failure and requiring hemodynamic support, E) Hypertensive emergencies, F) Unstable angina, particularly with dysrhythmias, hemodynamic instability, or persistent chest pain, G) Post-cardiac arrest syndrome, H) Cardiac tamponade or constriction with hemodynamic instability, I) dissecting an aortic aneurysm, J) Complete heart block.

2. Pulmonary System: A) Acute respiratory failure requiring ventilatory support, B) Pulmonary emboli with hemodynamic instability, C) Patients in an intermediate care unit who are demonstrating respiratory deterioration, D) Need for nursing or respiratory care not available in lesser care areas such as the general floor or intermediate care unit, E) Massive hemoptysis (severe coughing up of blood), F) Respiratory failure with an imminent need for intubation.

3. Neurologic Disorders: A) Acute stroke with altered mental status, B) Coma: metabolic, toxic, or anoxic, C) Intracranial hemorrhage with potential for brain herniation, D) Acute subarachnoid hemorrhage, E) Meningitis with altered mental status or respiratory compromise, F) Central nervous system or neuromuscular disorders with deteriorating neurologic or pulmonary function, G) Status epilepticus (prolonged seizures), H) Brain-dead or potentially brain-dead patients who are being aggressively managed while determining organ donation status, I) Vasospasm (abnormal narrowing of blood vessels), J) Severely head-injured patients.

4. Drug Ingestion and Drug Overdose: A) Hemodynamically unstable patients, B) Drug ingestion with significantly altered mental status and inadequate airway protection, C) Seizure following drug ingestion.

5. Gastrointestinal Disorders: A) Life-threatening gastrointestinal bleeding including hypotension, angina (chest pain), continued bleeding, or with comorbid conditions, B) Fulminant hepatic failure (severe liver failure), C) Severe pancreatitis, D) Esophageal perforation with or without mediastinitis (inflammation of the tissues in the middle of the chest).

6. Endocrine: A) Diabetic ketoacidosis is complicated by hemodynamic instability, altered mental status, respiratory insufficiency, or severe acidosis, B) Thyroid

storm or myxedema coma with hemodynamic instability, C) Hyperosmolar state with coma and/or hemodynamic instability, D) Other endocrine problems such as adrenal crises with hemodynamic instability, E) Severe hypercalcemia with altered mental status, requiring hemodynamic monitoring, F) Hypo- or hypernatremia (low or high sodium levels) with seizures, altered mental status, G) Hypo- or hypermagnesemia (low or high magnesium levels) with hemodynamic compromise or dysrhythmias, H) Hypo- or hyperkalemia (low or high potassium levels) with dysrhythmias or muscular weakness, I) Hypophosphatemia (low phosphate levels) with muscular weakness.

7. Surgical: A) Postoperative patients requiring hemodynamic monitoring, ventilator support, or extensive nursing care.

8. Miscellaneous: A) Septic shock with hemodynamic instability, B) Hemodynamic monitoring, C) Clinical conditions requiring ICU-level nursing care, D) Environmental injuries (lightning strike, near drowning, hypo/hyperthermia), E) New or experimental therapies with potential for complications (15).

Intubation was mainly done due to a ventilation-perfusion mismatch, including hypoxia or hypercapnia, lower control of respiration due to loss or altered consciousness (GCS less than or equal to 8 is sometimes used as the cutoff point), or any obstructions in the respiratory tract due to trauma or apnea (16).

Status epilepticus was defined as an episode of seizures lasting more than 5 minutes or recurrent seizures without detectable recovery time (17).

Data analysis

Descriptive analysis of both demographic variables and prognostic indices was conducted using crosstabs. Dead cases were also analyzed separately. The correlation of demographics and drugs with prognostic indices, including SE, ICU admission, intubation, and outcome, was tested using the chi-2 test. For two-by-two tables of sex, habitat, and previous history of toxic seizure, a binominal test was performed, and therefore, a corrected chi-2 was reported. A binominal test was also conducted to find a probable correlation between tramadol and prognostic indices separately. Confidence intervals (CI) of 95% were reported along with the p-value. P-values less than 0.05 were considered significant.

Ethical issues

For this study, only previous medical records were required, and there was direct contact only in cases lacking information to fill those gaps. The ethics committee of Yazd Azad University approved this study. (IR.IAU.YAZD.REC.1401.021). The study design followed the Helsinki Declaration.

4.Results

During the five years of study, 205 cases of drug-induced seizures met the inclusion criteria.

The descriptive analysis and outcome report of the study population are shown in Table 1.

Table 1. Descriptive analysis of the study population

Variables	N (%)205 (100%)
Sex	
Male	138 (67.3%)
Female	67 (32.7%)
Age	
<15 years	6 (2.9%)
15-40 years	165 (80.5%)
>40 years	34 (16.6%)

Reason of exposure	
Accidental	21 (10.2%)
Suicide	152 (74.1%)
Abuse	17 (8.3%)
Others	15 (7.3%)
Previous history of toxic seizure	
Yes	8 (3.9%)
No	197 (96.1%)
Outcome	
Alive	200 (97.6%)
Dead	5(2.4%)
Admission	
Ward	167 (81.5%)
ICU	38 (18.5%)
Intubation	
Yes	12 (5.9%)
No	193 (94.1%)
An event of status epilepticus	
Yes	24 (11.7%)
No	181 (88.3%)
ICU: intensive care unit	

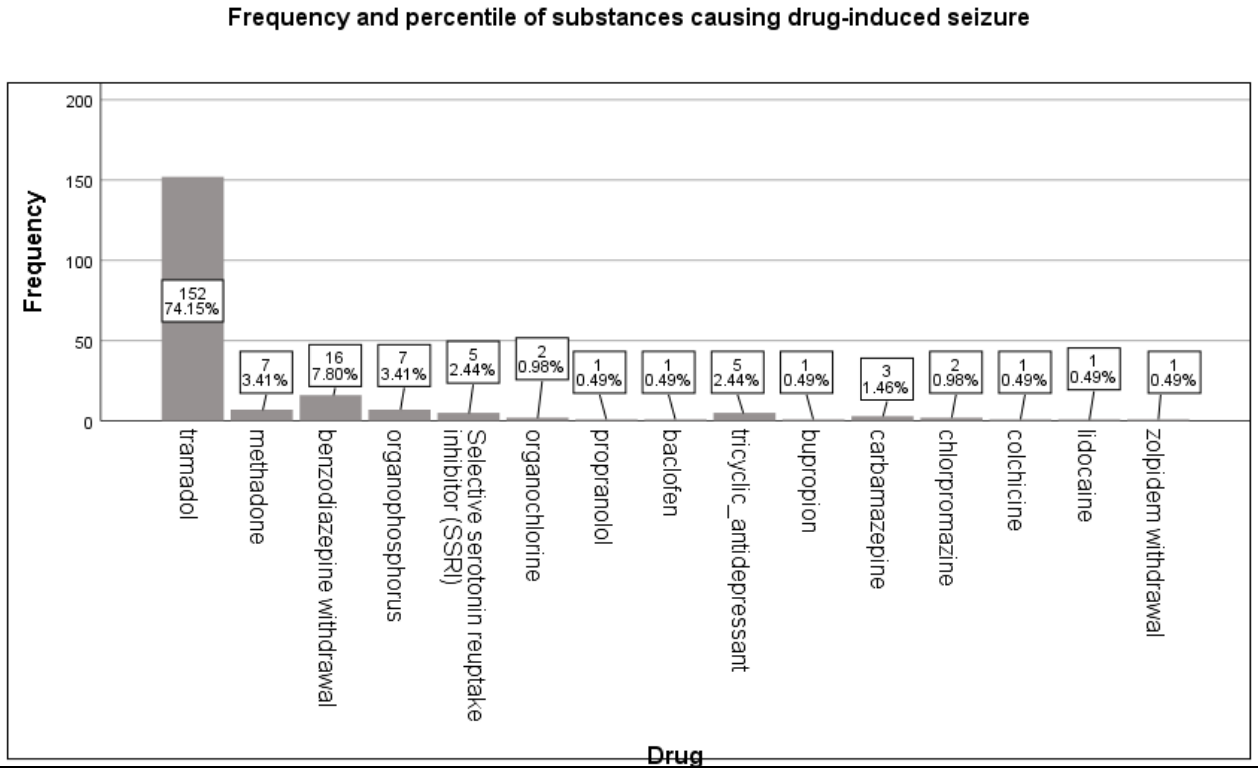

Figure 1: shows the frequency of substances causing drug-induced seizures.

As shown in Figure 1, the main reasons for drug-induced seizures were tramadol (74.15%), benzodiazepine withdrawal (7.8%), organophosphorus toxins (3.41%), and methadone (3.41%).

Table 2. Description of mortality cases of toxic seizures										
Case	Age	Sex	exposure	Previous toxic seizure	Route	Status epilepticus	outcome	intubation	admission	drug	Control drug
1	15-40 years	Male	Drug abuse	Negative	Oral	Positive	Dead	Positive	ICU	methadone	diazepam
2	>40 years	Female	Suicidal	Negative	Oral	Positive	Dead	Positive	ICU	organophosphorus	diazepam
3	15-40 years	Male	Suicidal	Negative	Oral	Positive	Dead	Negative	ward	tramadol	diazepam
4	>40 years	Female	Suicidal	Negative	Oral	Positive	Dead	Positive	ICU	organophosphorus	diazepam
5	15-40 years	Male	Suicidal	Negative	Oral	Positive	Dead	Negative	ICU	tramadol	diazepam

All patients had status epilepticus. Four cases (80%) intended to suicide. None of them had experienced previous events of drug-induced seizures.

Table 2 shows the correlation between prognostic variables and independent variables (probable risk factors).

Table 3. The correlation between prognostic variables and independent variables (probable risk factors) using chi-Square test or fisher-exact exam				
	Status epilepticus	**ICU admission**	**Intubation**	**Outcome**
Sex	0.761	0.725	0.317	1
Age	0.445	0.045	0.122	0.348
Reason of exposure	0.292	0.866	0.695	0.621
Previous history of toxic seizure	0.925	0.987	0.961	0.648
Drugs	<0.001	<0.001	<0.001	0.038
Cells with a p-value amount less than 0.05 were considered significant and therefore highlighted				

According to Table 3**,** regarding the probable correlation of independent variables with outcome and prognostic indices, significant correlations were seen between drug and status epilepticus (P- <0.001), ICU admission (P <0.001), intubation (P <0.001), and outcome (P

=0.038). Age was also significantly correlated with ICU admission (P =0.045).

Table 4 shows the correlation of tramadol ingestion with prognostic indices.

Table 4. Correlation of tramadol ingestion with prognostic indices

	Odds ratio	95% Confidence interval	p-value
Status epilepticus	4.166	1.73-10.01	0.002
Admission	3.394	1.623-7.1	0.002
Intubation	0.057	0.012-0.272	0.000
Outcome	4.5	0.73-27.71	0.212

Table 4 also demonstrated the correlation of tramadol ingestion as the most prevalent substance of this study (71%) with prognostic indices: tramadol ingestion was correlated with status epilepticus (Odds ratio (OR) = 4.166, 95% Confidence interval (CI) = 1.73-10.01), ICU admission (OR=3.394, CI = 1.623-7.1), and intubation (OR=0.057, CI = 0.012-0.272), but no significant correlation was observed between tramadol ingestion and overall outcome (P>0.05).

The comparison of drugs according to prognostic indices is demonstrated in Table 5.

Table 5. The comparison of drugs according to prognostic indices

Drug	SE (N=24)	% of drug	% of SE	ICU (N=38)	% of drug	% of ICU	Int (N=12)	% of drug	% of Int	Death (N=5)	% of drug	% of Death
Tramadol (N=152)	11	7.2	45.8	20	13.2	52.6	2	1.3	16.7	2	1.3	40
Methadone (N=7)	2	28.6	8.3	3	42.9	7.9	2	28.6	16.7	1	14.3	20
BDZ.W (N=16)	1	6.3	4.2	3	18.8	7.9	0	0	0	0	0	0
Org. Phos (N=7)	4	57.1	16.1	4	57.1	10.5	4	57.1	33.3	2	28.6	40
SSRI (N=5)	1	20	4.2	1	20	2.6	1	20	8.3	0	0	0
Org. Cl (N=2)	2	100	8.3	2	100	5.3	2	100	16.7	0	0	0
Colch (N=1)	1	100	4.2	1	100	2.6	1	100	8.3	0	0	0
Bupropion (N=1)	1	100	4.2	1	100	2.6	0	0	0	0	0	0
Carbmazp (N=3)	1	33.3	4.2	0	0	0	0	0	0	0	0	0
Chlorprmz (N=2)	0	0	0	2	100	5.3	0	0	0	0	0	0
Zolp. W (N=1)	0	0	0	1	100	2.6	0	0	0	0	0	0
Prop (N=1)	0	0	0	0	0	0	0	0	0	0	0	0
Baclofen (N=1)	0	0	0	0	0	0	0	0	0	0	0	0
TCA (N=5)	0	0	0	0	0	0	0	0	0	0	0	0
Lido (N=1)	0	0	0	0	0	0	0	0	0	0	0	0

SE: status epilepticus; ICU: intensive care unit admission; Int: intubation; BDZ.W: benzodiazepine withdrawal; Org.Phos: organophosphorus toxins; SSRI: selective serotonin reuptake inhibitor; Org.Cl: organochlorine toxins; TCA: tricyclic antidepressants; Carbmazp: carbamazepine; Chlorprmz: chlorpromazine; Colch: colchicine; Lido: lidocaine; Zolp.W: zolpidem withdrawal; Prop: propranolol

5. Discussion

Eighty percent of the study participants were between 15-40 years old, parallel to previous studies' findings (11, 18, 19). The

mortality rate and SE rate were higher for the elderly group (5.9% and 17.6%, respectively) in comparison with young adults (1.8%; 10.3%) and children (0%; 16.7%), while ICU admission and intubation rates were higher in children (50%; 16.7%).

All of the mortality cases had SE. Only one of the dead cases did not attempt suicide, and his DIS was a result of methadone abuse. Therefore, it is assumed that mortality is more likely to occur in suicidal attempts in comparison to drug abuse or accidental exposure. However, more studies are needed due to the insufficient number of cases in this group. Overall, suicidal intention (74.1%) was the most prevalent reason seen in the study. The previous history of seizures was an uncommon finding (3.9%) among the study population. Of them, 11.7% were SE, which was in accordance with previous studies (5%) (11-13). Tramadol and pesticides were the leading causes of SE in the current study.

In the current study, tramadol (74.15%) was the most prevalent substance. Behnoush et al. also achieved the same results (11) and reported that tramadol was the most common cause of drug-induced seizures. Hence, our study provided additional support for the new trend in tramadol abuse and its considerable complications, particularly seizures.

According to our findings, tramadol ingestion was significantly associated with SE (OR=4.166, %95CI=1.73-10.01) and ICU admission (OR=3.394, %95CI=1.623-7.1). Nakhaee et al. reported a seizure event rate of 38% in the subgroups of tramadol poisoning, 3% in therapeutic dosage cases, and 37% among tramadol abusers (20).

Boostani et al. conducted a 3-year study on tramadol-induced seizures involving 28 subjects with a history of tramadol use and seizures, predominantly males. They found that tramadol-induced neurotoxicity often led to generalized tonic-clonic seizures, occurring most frequently within 24 hours of tramadol intake. This neurotoxicity was common in individuals who also consumed alcohol, illicit drugs, antipsychotics, or antidepressants. (21). Rayan et al. examined tramadol overdose in 71 patients, noting seizures in 8 cases. Eight patients were admitted to the ICU, primarily due to co-ingestant toxicity or respiratory depression. They concluded that tramadol overdose carries a notable risk of seizures and respiratory depression, particularly in severe instances. (22).

Pesticides also played a crucial role in mortality cases. Organophosphorus toxin was the third prevalent cause of DIS in the current study. Seizure is not a common manifestation of Organophosphorus, but these seizures often have a critical malignant nature(23). Our results also parallel this theory: over half of this group had three poor prognostic indices of SE, ICU admission, and intubation. The mortality rate was also higher than most of the substances (28.6%), harboring 40% of death tolls. Also, all patients in this group reported having SE, ICU admission, and intubation. The widespread availability and usage of these pesticides in our country should be the reason for their higher-than-expected prevalence compared to the literature review (9, 12, 24). This explanation would also apply to the surprising lack of stimulants as a reason for DIS in this study. Likewise, methadone overdose was the second cause of DIS in our cases. The use of opiates, particularly methadone, has increased rapidly in recent years, which may also increase its critical complications as well as seizures.

A Few decades ago, TCA was also a leading cause of DIS since they were prescribed widely for depression, and therefore, they were much more available for drug abuse. However, recent advances in antidepressant drugs have declined TCA administration. In our findings, SSRI and TCA were DIS's fifth most common cause. Among the new antidepressants, Bupropion can also cause complicated DIS. In a study by Thundiyil et al.(9), Bupropion was the leading cause of DIS (23%), whereas only one patient in our study ingested Bupropion. This patient was a complicated case of SE who

needed ICU admission, as well. A similar clinical course was also taken for our only case of colchicine. It is implied that some drugs are not so common but may result in severe complications.

Limitations of the study:

A few potential shortfalls need to be considered. As the diagnosis of partial seizures was not reliable in an emergency setting, we have only included generalized tonic colonic seizures. Due to the retrospective nature of this study and the lack of some specific data in medical records, it was not plausible to include every confounding variable in the study. Since the study was conducted with a relatively small sample from a constrained region, the results may not apply to the general population. It would be better to present a predictive model of outcomes in drug-induced seizures using logistic regression. However, a lack of sufficient cases at each variable level and the absence of a normal distribution prevented the application of logistic regression. Finally, the dosage of an ingested substance and the use of multiple substances are correlated with outcome and dose-dependent responses, but this was not reported in medical records, and patients were not also aware of the exact amount of the ingested drug.

6. Conclusion

Drug-induced seizures are a critical manifestation of poisoning and are referred to the ER. Tramadol ingestion has been widely used, and a trend in its abuse has been demonstrated recently, causing drug-induced seizures. Consequent complications and mortality are not very common. However, due to the increasing rate of drug abuse and poor prognosis, in some cases, particularly organophosphorus toxins, they should be considered.

Although further research is essential to develop predictive models and refine clinical approaches in managing diverse drug-induced seizures, these findings contribute valuable insights into the emerging trends and clinical implications of drug-induced seizures despite limitations, such as a retrospective design and regional focus.

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Consent for publication: Not applicable.

Ethics approval and consent to participate: This study is based on a research project approved by Ethics Committee of Islamic Azad University of Shahrood with the code of ethics IR.IAU.NEYSHABUR.REC.1399.004. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable. Written informed consent was obtained from all participants or parent and/or legal guardian.

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