Archives of Epilepsy

Original Article

Obstructive Sleep Apnea and Epilepsy: Study from a Tertiary Care Centre in Southern India

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Cite this article as: Naaz S, Rao CS, T SP. Obstructive sleep apnea and epilepsy: study from a tertiary care centre in southern India. *Arch Epilepsy*. 2025;31(2):65-70.

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Received: 28.10.2024 **Accepted:** 07.01.2025 **Epub:** 07.05.2025 **Publication Date:** 14.05.2025

DOI: 10.4274/ArchEpilepsy.2025.24159

Abstract

Objective: Obstructive sleep apnea (OSA) is a sleep-related disorder resulting in hypoxemia and epilepsy itself causes central and obstructive apnea. Studies looking at this relation are limited. Hence, we aimed to examine the incidence of OSA in patients with epilepsy. To estimate the prevalence of OSA in patients with epilepsy. To study seizure characteristics among patients with comorbid OSA.

Methods: Patients above 18 years, and diagnosed with seizures/epilepsy attending our neurology epilepsy clinic for the past 1 year were included in our study. Patients with metabolic causes, psychogenic seizures, and symptomatic or provoked seizures were excluded. Retrospective analysis was done. Patients were screened for OSA using the Berlin questionnaire. Those with high scores underwent complete clinical evaluation, evaluation using the Epworth Sleepiness Scale, and diagnostic polysomnography with a portable ResMed USA device. Univariate binary logistic regression analysis was used to obtain the results.

Results: Out of 195 epileptic patients screened, 63 patients scored high on the Berlin questionnaire. Of them, 4 had severe OSA, 6 had moderate OSA, and 11 had mild OSA based on polysomnography. Prevalence of OSA is 33.3%. Age and body mass index were strongly associated with OSA syndrome, (p values 0.001 and 0.0003). There is no association between seizure type and the occurrence of OSA (p value=0.5).

Conclusion: Even though we found no direct relationship, we observed that treating underlying OSA reduced the frequency of seizures, resulting in the patient's overall well-being.

Keywords: Epilepsy, seizure, OSA, Berlin questionnaire

INTRODUCTION

The relationship between epilepsy and sleep has long been known, but our understanding of its practical application is incomplete. Sleep fragmentation due to obstructive sleep apnea (OSA) causes metabolic dysregulation with sympathetic overactivity, leading to alterations in glucose metabolism, orexin, and ghrelin levels.[1] On the other hand, epilepsy itself can exacerbate OSA. William Gowers in the 19th century first highlighted the effects of sleep on seizures. In his study, he observed that seizures occurred only at night in 21% of patients, only during the day in 42%, and in the remaining 37% they occurred either during the day or at night.[2] This led to the concept of 'pure sleep epilepsy', which is used for epilepsy seen exclusively during sleep. A variety of syndromic and non-syndromic epilepsies can manifest as pure sleep epilepsy but are usually associated with focal epilepsies.[3] Pure sleep epilepsies often respond well to antiepileptic drugs. polysomnographic abnormalities include increased wakefulness after sleep onset time, increased rapid eye movement (REM) latency, and increased slow-wave sleep, with reduced REM sleep compared to controls.[4]

Sleep deprivation increases the rate of kindling, and REM sleep deprivation accelerates the kindling of the amygdala. Hence, sleep fragmentation may increase seizure frequency by interfering with seizure inhibitory mechanisms, potentially aggravating the kindling process, and accelerating the progression of the epileptic focus, as derived from studies by Shouse on animals.

Patients with neurologic disorders seem to have a greater prevalence of sleep disturbance than normal subjects. A study done by Miller et al.[5] showed that the majority of patients with epilepsy had complaints regarding sleep. A polysomnographic investigation by Malow et al.[6] showed that nearly one-third of patients with medically refractory epilepsy had a respiratory disturbance index of more than 56. Therapeutic intervention for epilepsy may also increase the risk of sleep apnea. Some of the anticonvulsant medications have weight gain as a side effect and may alter respiratory regulation. Valproate, vigabatrin, and gabapentin are well known to accelerate obesity, which increases the likelihood of sleep apnea. Benzodiazepines and barbiturates may cause carbon dioxide and oxygen desaturation and increase upper

airway musculature relaxation.[7] The changes in the regulation of breathing may be more sensitive to these inhibitory medications and exacerbate underlying sleep-related breathing disturbance during certain stages of sleep. Vagus nerve stimulation has also been reported to increase airway disturbance potentially during sleep in some patients.[8]

There is a need to address the possibility that the seizure focus may cause apnea. Snoring and apnea that occur as a part of seizures may be ictal or postictal phenomena. Repetitive nightly seizures can be mistaken for sleep apnea.[9] Seizures cause nocturnal choking, as seen in insular epilepsy[10]. This is one reason that adequate electroencephalographic monitoring should be included in the overnight polysomnogram. Studies looking at this bidirectional influence are limited. Hence, we aimed to examine the incidence of OSA in patients presenting with epilepsy in a tertiary care hospital.

Aim: To study the correlation between OSA and epilepsy.

Objectives: 1. To estimate the prevalence of OSA in patients with epilepsy.

2. To study seizure characteristics among patients with comorbid OSA.

Inclusion Criteria

Patients above 18 years and diagnosed with epilepsy/seizure based on 2017 International League Against Epilepsy criteria, electroencephalogram (EEG) and brain imaging [magnetic resonance imaging (MRI) was considered].

Exclusion Criteria

Patients with hypothyroidism, obesity, hepatic dysfunction, renal dysfunction, purely psychogenic seizures, uncertain diagnosis (for instance patients with a differential diagnosis of seizure vs. syncope), symptomatic or provoked seizures (seizure occurring as a symptom or manifestation of a known cerebral insult) were excluded.

METHODS

This is a retrospective single-center study done over 1 year. In this study, patients with epilepsy were screened for OSA syndrome (OSAS) by direct interview using the Berlin questionnaire. Those with high scores on the questionnaire underwent diagnostic polysomnography (PSG). Each patient underwent a complete clinical evaluation, including an appropriate medical history and clinical examination, an EEG, an MRI brain, the Epworth Sleepiness Scale, and a portable home-based PSG (ResMed USA device). The PSG was scored according to American Academy of Sleep Medicine (AASM) guidelines. Informed consent was obtained. The study was started after getting clearance from the Project and Budget Approval Committee and the Nizam's Institute of Medical Sciences Institutional Ethics Committee (decision no: ECINIMS/2236/2018, date: 02.11.2018). We included patients above the age of 18 years. Information regarding the patient's demographic profile, including age, sex, body mass index (BMI), associated comorbidities, epilepsy characteristics, and seizure frequency, was noted. PSG was done with a portable home-based device (ResMed USA). It was classified according to AASM guidelines as mild, moderate, and severe OSA. Apnea, hypopnea interval, and oxygen desaturation index were noted. The overnight PSG is the standard diagnostic test for OSA. It involves simultaneous recordings of multiple physiologic signals during sleep, including the EEG, electrooculogram, electromyogram, oronasal airflow, and oxyhemoglobin saturation. Collectively, these recordings allow identification and classification of sleep-related apneas and hypopneas. Since we used a portable device, nasal cannula, sensor placed around the chest for chest expansion, and a pulse oximeter. An apnea is defined as the complete halt of airflow for at least 10 seconds. Apneas are again classified as obstructive, central, or mixed based on whether effort to breathe is present during the event. AASM guidelines define hypopneas as a reduction of 30% or more in nasal flow with >3% desaturation of arterial oxygen, measured by pulse oximetry, or EEG arousal. Identification and avoidance of factors that might trigger or exacerbate seizures is important in patients with epilepsy. The most frequent factors are sleep disturbance, alcohol ingestion, drugs, stress, and photosensitivity.

MAIN POINTS

- In our study, we found no direct association between epilepsy and the occurrence of obstructive sleep apnea (OSA) (p value 0.5).
- However, treating underlying OSA reduced the frequency of seizures, resulting in the patient's overall well-being.

Statistical Analysis

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, and frequency and proportion for categorical variables. Data were also represented using bar diagrams. All the outcome scores were categorized into poor and good outcomes based on standard cut-off values. Univariate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. The unadjusted odds ratio along with the 95% confidence interval (CI) is presented. Variables with statistical significance in univariate analysis were used to conduct multivariate regression analysis. The adjusted odds ratios along with their 95% CI are presented. The p value <0.05 was considered statistically significant. IBM Statistical Package for the Social Sciences (SPSS) version 22 was used for statistical analysis. IBM Corp., released in 2013. IBM SPSS statistics for Windows, version 22.0. Armonk, NY: IBM Corp.

RESULTS

A total of 195 epileptic patients were screened, out of which 63 patients scored high on the Berlin questionnaire (Table 1) and were included in the analysis. Demographic details are listed in Table 2. There were 41 males and 22 females, with a female-male ratio of 1.86. The mean age was 40.63 years with a standard deviation of 17.58. The eldest patient was aged 73 years, while the youngest patient was aged 20 years. Among the participants, most were in the age group of 20 to 40 years, i.e., 36 members, whereas 4 members were below 20 years of age and the rest of the participants were above 40 years. The BMI of the participants ranged between 18.9 and 40.8 kg/m^2, and the mean BMI of the participants was 29.5 kg/m^2 with a standard deviation of 3.25. Among 63 epileptic patients, 33 patients had generalised epilepsy and 30 patients had

focal epilepsy (Figure 1). Out of which, 11 had a frontal focus, and 19 had a temporal focus. Almost all patients had snoring (Figure 2). After analyzing all 63 patients who underwent PSG, 4 had severe OSAS, 6 had moderate OSAS, and 11 had mild OSAS (Figure 3). A total of 21 patients had OSAS, which accounts for 33.3% of the study group. The types of epilepsy among patients with OSA are depicted in Table 3. No association was seen between epilepsy and OSAS, (p value 0.5) (Table 3). When we study the association between various demographic characteristics of epileptic patients some characteristics were significantly associated with the occurrence of OSA. Age was significantly associated with OSAS with a p value of 0.001 (Table 4).

Table 1. Subjects response to Berlin questionnaire

Item	Number of patients
Do you snore?	
Yes	63
No	0
Your snoring is:	
Slightly louder than breathing	58
As loud as talking	5
Louder than talking	0
Very loud-can be heard in adjacent rooms	0
How often do you snore?	
Nearly every day	1
3-4 times a week	9
1-2 times a week	29
1-2 times a month	22
Never or nearly never	8
Has your snoring ever bothered other people?	
Yes	0
No	63
Has anyone noticed that you quit breathing during your sleep?	
Nearly every day	0
3-4 times a week	0
1-2 times a week	0
1-2 times a month	0
Never or nearly never	63

Table 2. Descriptive analysis for baseline characteristics in the study population (n=63)

Baseline characteristics	Number of patients
Gender	
Male	41
Female	22
Age range	
<20 years	4
20-40 years	36
>40 years	23
Median age	35
Mean	40.63±17.58
Body mass index	
Mean	29.5±3.25
Median	29.3
Range	18.9 to 40.8
Co-morbid medical conditions	
Hypertension	18
Diabetes	9
Types of epilepsy	
Generalized	33
Focal	30
Seizure frequency	
Per month	22
Per year	41
Disease duration	3.19±2.49

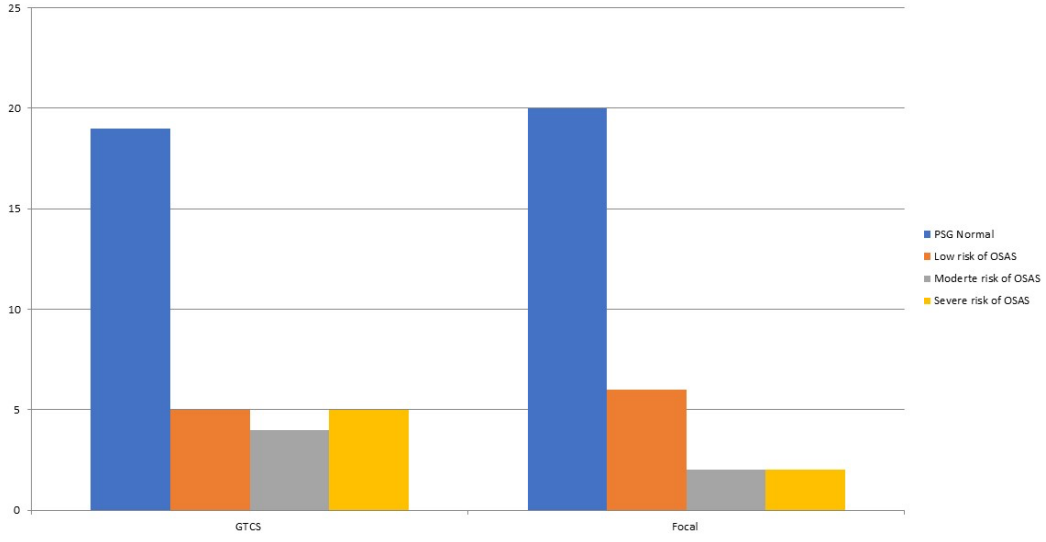

Figure 1. Distribution of OSAS among patients with epilepsy
OSAS: Obstructive sleep apnea syndrome, PSG: Polysomnography, GTCS: Generalised tonic-clonic seizures

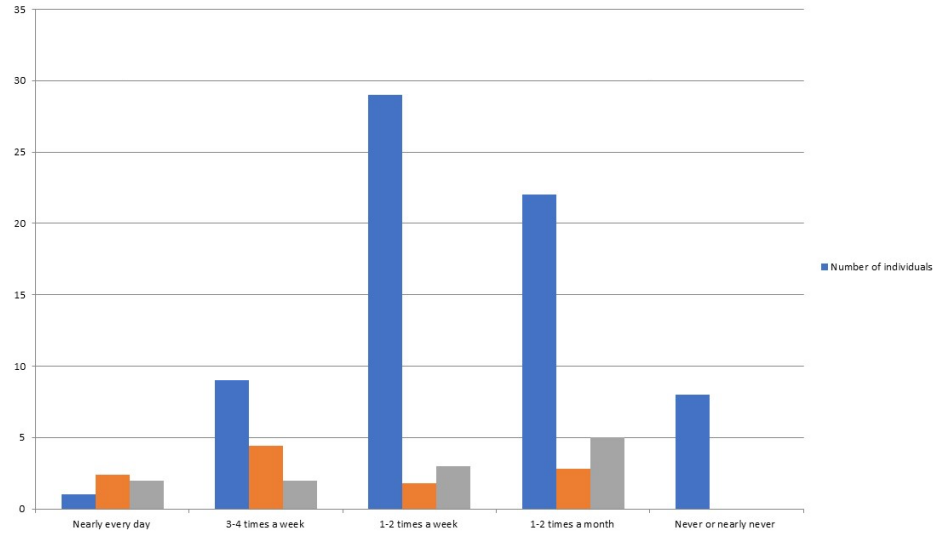

Figure 2. Frequency of snoring among the study population

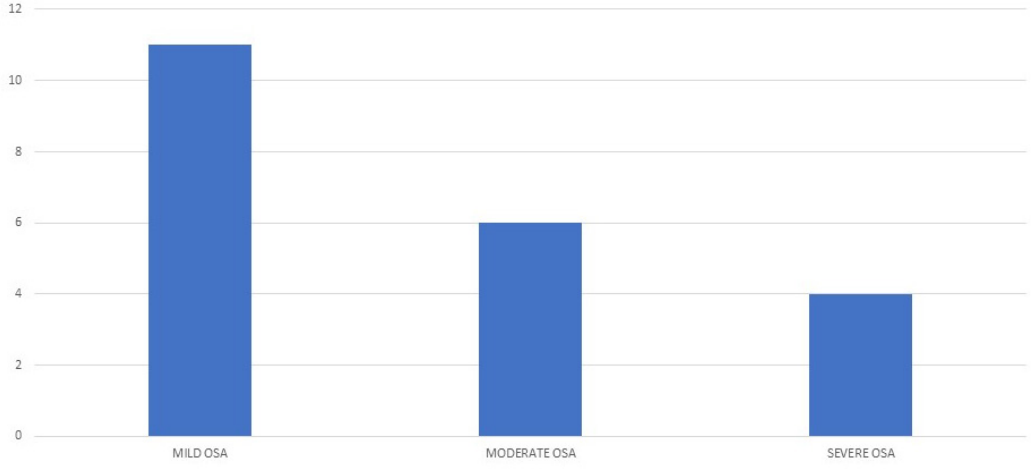

Figure 3. Polysomnography findings in the study group
OSA: Obstructive sleep apnea

BMI was also significantly associated with OSAS with a p value of 0.0003 (Table 5). Multiple regression analysis showed that age and BMI are strongly associated with OSAS. The presence of co-morbidities, such as hypertension (HTN) and diabetes mellitus (DM), was also significantly associated with OSAS.

DISCUSSION

The prevalence of epilepsy in developing countries is 14 per 1000 subjects.[11] Seizures are typically encountered during sleep in certain syndromes, for example, nocturnal frontal lobe epilepsy. However, in recent years, considerable attention has been given to studying the relationship between sleep and epilepsy.[2,12] Among these, OSAS is a common condition occurring in about 2% of adult women and 4% of adult men in the general population.[3]

OSAS causes significant sleep deprivation and fragmentation, leading to impaired sleep continuity; hence, increased daytime sleepiness and impaired cognitive functions.[13] Such alterations could have a considerable negative influence on seizure activity in patients with epilepsy. The frequency of OSAS among patients with epilepsy and the relationship between the severity of epilepsy and the severity of OSAS are still not clear. Hence, we aim to study the frequency of OSAS among patients with epilepsy.

The mean age was 40.63 years with a standard deviation of 17.58. Our patients with epilepsy had a higher age at presentation compared to the general population. Female preponderance was noted. The participants' BMI ranged between 18.9 and 40.8 kg/m^2, and the mean BMI was 29.5 kg/m^2 with a standard deviation of 3.25. Among 63 epileptic patients, 33 patients had generalised epilepsy, and the remaining 30 patients had focal epilepsy. Among focal epilepsy patients, the majority had a temporal focus, followed by a frontal focus. Almost all patients experienced snoring. Among the 63 patients who underwent PSG, 4 had severe OSAS, 6 had moderate OSAS, and 11 had mild OSAS. The majority of mild OSA patients had focal epilepsy (54.5%) and the majority of the patients with moderate and severe OSA had generalized epilepsy (66.6% and 71.4%, respectively). We included only patients >18 years old, which may have led to the limited number of patients

Table 3. Association between epilepsy subtypes and OSA risk

Characteristics	Patients with normal PSG	Low risk of OSAS	Moderate risk of OSAS	High risk of OSAS	p value
Type of epilepsy					
GTCS	19	5	4	5	0.5
Focal	20	6	2	2	

The chi-square value has 3 degrees of freedom.
The chi-square value is 1.93.
P value 0.5.
OSAS: Obstructive sleep apnea syndrome, PSG: Polysomnography, GTCS: Generalised tonic-clonic seizures

Table 4. Association between age and OSA risk

Characteristics	Patients with normal PSG	Low risk of OSAS	Moderate risk of OSAS	High risk of OSAS	p value
Age					
<20 years	4	0	0	0	0.001
20-40 years	27	2	6	1	
>40 years	8	9	3	6	

The chi-square value has 6 degrees of freedom.
Chi-square value is 21.75.
The p value is 0.001.
OSA: Obstructive sleep apnea, OSAS: OSA syndrome, PSG: Polysomnography

Table 5. Association between BMI and OSA risk

Characteristics	Patients with normal PSG	Low risk of OSAS	Moderate risk of OSAS	High risk of OSAS	p value
BMI					
<25	2	1	0	0	0.0003
25-30	28	1	5	0	
>30	9	7	1	7	

The chi-square has a value of 24.41.
P value 0.0003.
OSA: Obstructive sleep apnea, OSAS: OSA syndrome, BMI: Body mass index, PSG: Polysomnography

below the age of 20 (6%). Most of the patients were 20-40 years old, with a median age of 35 years.

Our epilepsy patients with OSA had higher age and increased BMI, which are common risk factors for OSA in the general population. These people also experienced associated comorbidities like DM and HTN. This has been reported in other studies by Malow et al.[4] In our study, the frequency of OSAS among patients with epilepsy was assessed using a simple methodology, the Berlin questionnaire, which is a valid tool used to screen OSAS in a source-limited setting like ours. The prevalence of OSAS was 33.3% in our study. A study conducted by Al-Abri et al.[14] in Oman showed the frequency of OSAS in a similar population to 9%. However, Indian studies similar to our study are not yet available to date. Indian studies done on the general population showed a prevalence of 6.2% according to Singh et al.[15] Our study showed a significant increase in the prevalence of OSAS in epilepsy patients; further studies are needed to either confirm or refute our results. Until now, there are no well-conducted randomized studies. Our study is the first of its kind from India. Other factors contributing to increased prevalence were increased age, and BMI. The chi-square test showed a significant association between age and the presence of OSAS with a p value of 0.001. A study by Deng et al.[16] showed a similar association, wherein multiple linear regression showed that increasing age was associated with OSA exacerbation. BMI was also significantly associated with the occurrence of OSAS with a p value of 0.0003. Deng et al.[16] showed a similar association where they stated that BMI was independently associated with an increased risk of OSAS.

Our study did not show any association between the type of epilepsy and the occurrence of OSAS, similar to the findings reported by Al-Abri et al.[14] In our study, the frequency of OSAS was greater in patients with epilepsy than in the general population. Thirty-three percent of patients had a BMI in the obese or overweight range. Similarly, other studies reported obesity and overweight in 30% to 50% of patients with epilepsy. One culprit could be the type of antiepileptic drug (AED) the patient is taking, especially sodium valproate. However, we did not study the effect of antiepileptic drugs on body weight and OSA. Snoring was present in all participants. Almost all patients reported daytime sleepiness with no significant association with either the type or severity of epilepsy, nor with the number of AEDs.

Other comorbidities like HTN and DM were also significantly associated with OSAS in our study. Manni et al.[17] found that the major risk factors for OSAS in epilepsy patients were the same as those typically found in the general population. He also found evidence that OSAS coexists in epilepsy in 10% of unselected adult epilepsy patients, 20% of children with epilepsy, and up to

30% of drug-resistant epilepsy patients. The major limitation in this study was the small sample size. A larger sample size may give a better understanding of the real association between epilepsy and OSAS. During our study period, we observed that treating underlying OSAS in epileptic patients reduced the frequency of seizures and associated co-morbidities of the patients. For example, a 72-year-old male, known epileptic for 3 years on levetiracetam 1 gm/day, lacosamide 400 mg/day, and clobazam 20 mg/day, presented with multiple episodes of generalised tonic-clonic seizures. On average, he had two episodes per month. He was compliant with AEDs; he was also taking regular medication for HTN. He satisfied the inclusion criteria for our study and gave consent. He complained of snoring and daytime sleepiness. He had a BMI of 33.1; overnight PSG showed the presence of OSA with an apnea hypopnea index of 21. He was advised to undergo weight reduction and to seek a pulmonologist consultation. He had used nighttime CPAP for 6 months. After this, his frequency of seizures reduced to approximately one every two months. We observed a similar situation in three more patients. This study highlights the importance of screening for OSAS and other associated co-morbidities in all patients with epilepsy, as an effective treatment of these will benefit epileptic patients in reducing seizure frequency.

Study Limitations

1. Small sample size.

2. Limited study period.

3. Our study is done at a tertiary center, correspondingly there is every chance of selection bias.

4. We did not study the effects of AEDs on the occurrence of OSAS in epileptic patients.

5. In particular, our study is limited by the fact that in diagnosing OSAS, we used a portable device that doesn't allow EEG recording. Thus, nocturnal seizures occurring during the monitored night and the consequences of these on breathing patterns might have been undiagnosed.

CONCLUSION

The prevalence of OSAS is 33.3% in our study. Age and BMI were the demographic characteristics that were strongly associated with the presence of OSAS. HTN and DM were also significantly associated with the presence of OSAS. There is no direct association between epilepsy and the occurrence of OSAS (p value 0.5). Even though we found no direct relationship in our study, we observed that treating underlying OSAS and other comorbidities in epileptic patients reduced the frequency of seizures and improved overall well-being.

Ethics

Ethics Committee Approval: The study was started after getting clearance from the Project and Budget Approval Committee and the Nizam's Institute of Medical Sciences Institutional Ethics Committee (decision no: ECINIMS/2236/2018, date: 02.11.2018).

Informed Consent: Informed consent was obtained.

Footnotes

Author Contributions: Surgical and Medical Practices: S.P.T., S.N., C.S.R., Concept: S.N., C.S.R., Design: S.P.T., S.N., C.S.R., Data Collection or Processing: S.P.T., S.N., C.S.R., Analysis or Interpretation: S.P.T., S.N., Literature Search: S.P.T., C.S.R., Writing: S.P.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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