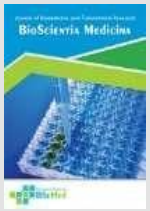
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Neuroinflammation and Sleep Dysfunction in Epilepsy: The Role of High Sensitivity C-Reactive Protein

Akmal Irsyadi Iswan[1], Restu Susanti[2]*, Lydia Susanti[2], Syarif Indra[2], Fanny Adhy Putri[2], Reno Bestari[2]

[1]Residency Program, Department of Neurology, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Department of Neurology, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
Epilepsy
High sensitivity C-reactive protein
Neuroinflammation
Pittsburgh sleep quality index
Sleep quality

***Corresponding author:**
Restu Susanti

E-mail address:
restususanti@yahoo.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i6.1313

A B S T R A C T

Background: Emerging evidence suggests a bidirectional relationship between systemic inflammation and both epilepsy and sleep dysfunction. High-sensitivity C-reactive protein (Hs-CRP), a sensitive marker of low-grade systemic inflammation, is elevated in response to pro-inflammatory cytokines. However, the specific link between Hs-CRP levels and subjective sleep quality within the epilepsy population required further investigation. This study aimed to investigate the relationship between serum Hs-CRP levels and sleep quality in patients diagnosed with epilepsy. **Methods:** A cross-sectional study was conducted involving 40 patients diagnosed with epilepsy attending the neurology clinic at Dr. M. Djamil General Hospital, Padang, Indonesia, between January and February 2025. Patients aged over 17 years diagnosed by a neurologist were included. Serum Hs-CRP levels were quantified using an enzyme-linked immunosorbent assay (ELISA). Sleep quality over the preceding month was assessed using the validated Indonesian version of the Pittsburgh Sleep Quality Index (PSQI). Mann-Whitney U test was employed to analyze the difference in median Hs-CRP levels between patients with good and poor sleep quality. Relationships between baseline characteristics and sleep quality were assessed using Chi-square/Fisher's exact tests for categorical variables and the Mann-Whitney U test for continuous variables. **Results:** Forty epilepsy patients (median age 25.5 years, range 17-50; 52.5% female) were enrolled. The median duration of epilepsy was 10 years (range 1-35). A majority of patients exhibited uncontrolled seizures (75%) and were receiving AED polytherapy (60%). Based on PSQI scores, 24 patients (60%) were classified as poor sleepers, while 16 (40%) were good sleepers. A significant difference was observed in median serum Hs-CRP levels between the two groups: patients with good sleep quality had significantly lower median Hs-CRP levels compared to those with poor sleep quality (1,271.50 ng/ml [range 58–5,837] vs. 2,771.50 ng/ml [range 509–27,187], p=0.027). Poor sleep quality was significantly associated with younger age (median 23 vs. 36 years, p=0.039) and AED polytherapy (75% vs. 25%, p=0.018). **Conclusion:** This study demonstrated a significant association between elevated serum Hs-CRP levels and poor subjective sleep quality in patients with epilepsy. Epilepsy patients experiencing poor sleep exhibited significantly higher levels of this inflammatory biomarker. These findings underscore the potential role of systemic inflammation in the complex interplay between epilepsy and sleep disturbances, suggesting Hs-CRP could serve as a potential biomarker linking these conditions.

1. Introduction

Epilepsy stands as one of the most prevalent chronic neurological disorders worldwide, imposing a substantial burden on individuals, healthcare systems, and society. The World Health Organization estimated in 2024 that approximately 50 million people worldwide live with epilepsy, with around 5 million new diagnoses occurring annually. The

condition is characterized by an enduring predisposition to generate epileptic seizures, unprovoked recurrent seizures, and the associated neurobiological, cognitive, psychological, and social consequences. Beyond the primary manifestation of seizures, epilepsy frequently leads to disability, diminished quality of life, and significant economic costs related to long-term treatment and management. A systematic analysis for the Global Burden of Disease Study highlighted the substantial global, regional, and national impact of epilepsy from 1990 to 2016, underscoring its continued public health significance. A critical and often underappreciated aspect of epilepsy management involves the intricate and bidirectional relationship between epilepsy and sleep. Sleep and epilepsy share complex physiological connections, influencing each other profoundly. On one hand, poor sleep quality, including sleep deprivation and fragmented sleep, is a well-recognized precipitant for seizures in susceptible individuals and can significantly impede efforts to achieve adequate seizure control. Conversely, the occurrence of epileptic seizures, particularly nocturnal seizures, along with underlying epileptiform activity, can severely disrupt normal sleep architecture, leading to reduced sleep efficiency, increased sleep fragmentation, and excessive daytime sleepiness. This reciprocal negative interaction creates a challenging cycle where poor sleep worsens seizure control, and seizures further degrade sleep quality, impacting overall well-being and daily functioning. Understanding and managing sleep problems is therefore becoming increasingly recognized as an integral component of comprehensive epilepsy care.[1-3]

In recent years, the role of inflammation, particularly neuroinflammation, has gained prominence in the pathophysiology of epilepsy. Recurrent seizures themselves are potent triggers of inflammatory cascades within the brain. Seizure activity can lead to neuronal stress and damage, potentially causing the release of damage-associated molecular patterns (DAMPs) such as High Mobility Group Box-1 (HMGB1). HMGB1, a nuclear protein released from damaged or stressed cells, acts as an alarmin, activating innate immune cells like microglia. Microglial activation, often via Toll-like receptors (TLRs), initiates downstream signaling pathways, notably involving the transcription factor Nuclear Factor kappa-B (NF-κB). NF-κB activation drives the production and release of various pro-inflammatory cytokines, including Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and Tumor Necrosis Factor-α (TNF-α). These cytokines contribute to a pro-inflammatory microenvironment within the brain, which can, in turn, lower the seizure threshold, increase neuronal hyperexcitability, and potentially contribute to epileptogenesis and the chronicity of epilepsy. This neuroinflammatory state represents a potential therapeutic target, and biomarkers reflecting this process are of significant interest. Concurrently, a substantial body of evidence implicates sleep disruption and poor sleep quality as potent modulators of systemic inflammation. Sleep plays a crucial homeostatic role in regulating the immune system. Consequently, disturbances such as sleep deprivation, sleep fragmentation, or circadian rhythm misalignment can lead to immune dysregulation and heightened inflammatory responses. Acute and chronic sleep loss have been shown to affect various immune parameters. For instance, sleep deprivation can acutely reduce the cytotoxic activity of natural killer (NK) cells, while chronic poor sleep may lead to reductions in NK cell numbers and activity, alterations in B lymphocyte function, increased expression of TLR-4, and changes in signaling pathways like STAT1. Furthermore, disrupted sleep promotes the upregulation of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, often mediated through pathways involving NF-κB, mirroring some of the inflammatory processes observed in epilepsy. This suggests a potential convergence point where both epilepsy and poor sleep contribute to a heightened systemic inflammatory state.[4-7]

C-Reactive Protein (CRP), an acute-phase reactant synthesized primarily by hepatocytes under the regulation of pro-inflammatory cytokines like IL-6,

serves as a well-established systemic marker of inflammation. High-sensitivity CRP (Hs-CRP) assays allow for the detection of very low levels of CRP within the normal range, providing a more sensitive measure of chronic, low-grade inflammation. Elevated levels of CRP/Hs-CRP have been reported in patients with epilepsy compared to healthy controls, as demonstrated in individual studies and corroborated by meta-analyses, suggesting an underlying systemic inflammatory component associated with the disorder. Similarly, numerous studies in the general population have linked poor subjective sleep quality, short sleep duration, and insomnia symptoms with elevated levels of CRP/Hs-CRP. A study found significant associations between poor sleep quality and increased CRP/Hs-CRP. Given that both epilepsy and poor sleep quality are independently associated with increased systemic inflammation, and recognizing the frequent co-occurrence of sleep problems in epilepsy, the interplay between these three factors – epilepsy, sleep quality, and inflammation (as marked by Hs-CRP) – warrants specific investigation. While the links between epilepsy and inflammation and between sleep quality and inflammation have been separately explored, research directly examining the relationship between sleep quality and inflammatory markers, specifically within an epilepsy cohort, has been limited. Understanding this relationship could provide valuable insights into the shared pathophysiology and potentially identify Hs-CRP as a useful biomarker reflecting the burden of sleep dysfunction in epilepsy.[8-10] Therefore, this study was designed to address this gap by investigating the specific association between serum Hs-CRP levels and subjective sleep quality, assessed using the Pittsburgh Sleep Quality Index (PSQI), in a cohort of patients diagnosed with epilepsy.

2. Methods

This investigation employed a cross-sectional study design. Patient recruitment and data collection were conducted over a two-month period, spanning from January 2025 to February 2025. The study was carried out at the outpatient Neurology Clinic of Dr. M. Djamil General Hospital, located in Padang, Indonesia. Dr. M. Djamil General Hospital functions as a tertiary referral center within the region, providing specialized medical care for a diverse patient population. The target population for this study consisted of all adult patients with a diagnosis of epilepsy who presented for routine follow-up appointments or consultations at the neurology clinic during the specified study period. Participants were recruited consecutively as they met the eligibility criteria. Prior to any study-related procedures, written informed consent was obtained from each individual, ensuring their voluntary participation.

To ensure the selection of a study group that was both relevant and relatively homogenous, specific inclusion and exclusion criteria were meticulously established. Patients were considered eligible for inclusion in the study if they met the following criteria; They were aged 17 years or older. This lower age limit was chosen to focus on adult epilepsy patients; They had a confirmed diagnosis of epilepsy. The diagnosis had to be established by a consultant neurologist affiliated with the study site, namely Dr. M. Djamil General Hospital Padang, ensuring that diagnoses were made by qualified professionals; They provided voluntary informed consent to participate in the study. This criterion emphasized the ethical principle of autonomy, ensuring that all participants willingly agreed to take part in the research. To minimize the influence of confounding factors that could independently affect inflammatory markers or sleep quality, patients were excluded from the study if they presented with any of the following conditions; Symptomatic epilepsy. This refers to epilepsy that arises due to an identifiable underlying structural or metabolic cause. Examples of such causes include a history of stroke, intracranial tumors, prior infections of the central nervous system (such as meningitis or encephalitis), or significant head trauma. These conditions can independently influence both inflammation and sleep patterns, potentially obscuring the relationship of interest; Evidence of an

acute infectious or inflammatory condition at the time of blood sampling. This was determined through a patient's clinical history (anamnesis). The absence of symptoms such as fever, cough, coryza (common cold symptoms), or dysuria (painful urination) was used to rule out acute conditions. Acute inflammation could significantly elevate Hs-CRP levels, potentially confounding the results; A documented history of chronic systemic inflammatory or autoimmune diseases. Examples of such conditions include rheumatoid arthritis, systemic lupus erythematosus, diagnosed malignancy, or diabetes mellitus. These diseases are characterized by chronic inflammation, which could affect baseline Hs-CRP levels and introduce variability into the data; Current use of medications with known anti-inflammatory properties. This specifically included the use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. These medications directly interfere with inflammatory processes and could therefore alter Hs-CRP levels; A pre-existing diagnosis of a primary sleep disorder. Examples of such disorders include obstructive sleep apnea, narcolepsy, or restless legs syndrome, when these diagnoses were established prior to the patient's enrollment in the study. Individuals with pre-existing sleep disorders have altered sleep patterns that could confound the assessment of sleep quality in relation to epilepsy; A documented history of significant liver disease or dysfunction.

Data were collected for each participant through a combination of structured interviews conducted by trained research personnel and a review of the patients' existing medical records. This comprehensive approach ensured that a wide range of relevant information was captured. The following specific information was gathered for each participant; Demographic Data: This included the patient's age (in years) and gender. Age and gender are fundamental demographic variables that can be important to characterize the study sample and explore potential associations; Clinical Epilepsy Characteristics: Several key characteristics related to the patient's epilepsy were recorded. Duration of diagnosed epilepsy, was measured as the number of years since the patient received their epilepsy diagnosis. Duration of epilepsy is a clinically relevant variable that may influence both sleep quality and inflammatory processes. Current anti-epileptic drug (AED) regimen was categorized as either monotherapy, indicating that the patient was receiving treatment with a single AED, or polytherapy, indicating that the patient was receiving treatment with two or more AEDs. The type of AED regimen can have implications for both seizure control and potential side effects, including effects on sleep. Patients were classified based on their seizure control. Seizure control was defined according to clinical practice guidelines. Patients were considered to have 'controlled' epilepsy if they reported being free of any clinical seizures for the preceding 12 months or longer. Patients who did not meet this criterion were classified as having 'uncontrolled' epilepsy. Seizure control is a critical clinical outcome in epilepsy management and can significantly impact a patient's quality of life, including their sleep; Sleep Quality Assessment: Subjective sleep quality over the month preceding data collection was evaluated using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a widely used self-rated (or interviewer-administered) questionnaire. It comprises 19 items designed to assess seven distinct components of sleep. These components are: subjective sleep quality, sleep latency (the time it takes to fall asleep), sleep duration, habitual sleep efficiency (the proportion of time spent asleep while in bed), sleep disturbances, use of sleep medication, and daytime dysfunction resulting from poor sleep. Each of these seven components is scored on a scale from 0 to 3, where higher scores indicate a greater degree of impairment. The scores from the seven components are then summed to yield a global PSQI score. This global score can range from 0 to 21. A higher global PSQI score indicates poorer overall sleep quality. In this study, the validated Indonesian language version of the PSQI was utilized. The Indonesian version has demonstrated good psychometric properties in the local context.

Specifically, it has shown high sensitivity (100%) and specificity (81%) for identifying poor sleepers when using a standard cutoff score. Based on their global PSQI scores, participants were categorized into one of two groups: 'Good Sleepers' and 'Poor Sleepers.' Participants with a global PSQI score of ≤ 5 were classified as 'Good Sleepers,' while those with a global PSQI score > 5 were classified as 'Poor Sleepers.' This cutoff score is commonly used to distinguish between individuals with good and poor sleep quality; Biomarker Measurement: To quantify systemic inflammation, serum levels of High Sensitivity C-Reactive Protein (Hs-CRP) were measured. Venous blood samples were collected from each participant. To ensure consistency and minimize potential variability, blood samples were collected under standardized conditions. When feasible, samples were collected in the morning after an overnight fast. The collected blood samples were processed according to established laboratory protocols. Serum was extracted from the blood and stored appropriately until analysis. Serum levels of Hs-CRP were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. The ELISA is a widely used and sensitive technique for measuring the concentration of specific proteins in biological samples. The procedure was carried out following the manufacturer's instructions to ensure accuracy and reliability of the results. The results of the Hs-CRP quantification were expressed in nanograms per milliliter (ng/ml), a standard unit for measuring protein concentrations in serum.

The collected data were entered into a computerized database to facilitate organization and analysis. Appropriate statistical software was used to perform the data analysis. Descriptive statistics were used to provide a summary of the baseline demographic and clinical characteristics of the study sample. This involved calculating measures of central tendency and dispersion for continuous variables and frequencies and percentages for categorical variables. For continuous variables that exhibited a non-normal distribution, the median and range (minimum-maximum values) were calculated. The reporting of median values in the results suggests that the data for variables such as age, duration of epilepsy, and Hs-CRP levels were not normally distributed. Categorical variables, such as gender, AED therapy regimen (monotherapy vs. polytherapy), seizure control status (controlled vs. uncontrolled), and sleep quality group (good sleepers vs. poor sleepers), were presented as frequencies and percentages. The primary analysis focused on comparing the median serum Hs-CRP levels between the two sleep quality groups (Good Sleepers and Poor Sleepers). Given the anticipated non-normal distribution of the Hs-CRP data, a non-parametric test was chosen for this comparison. Specifically, the Mann-Whitney U test was employed. Secondary analyses were conducted to explore the relationships between various baseline characteristics and sleep quality status (Good Sleepers vs. Poor Sleepers). To compare continuous variables (age and duration of epilepsy) between the two sleep quality groups, the Mann-Whitney U test was used. This allowed for the assessment of whether there were significant differences in the distribution of these continuous variables between individuals with good and poor sleep quality. To compare categorical variables (gender, AED therapy regimen, and seizure control status) between the sleep quality groups, either the Chi-square test or Fisher's exact test was applied. The Chi-square test is a statistical test used to examine associations between categorical variables. Fisher's exact test is used as an alternative to the Chi-square test when the expected cell counts in the contingency table are small (typically less than 5), as it provides a more accurate assessment of the association in such cases. For all statistical analyses, a p-value of less than 0.05 was used as the criterion for determining statistical significance. A p-value represents the probability of obtaining the observed results (or more extreme results) if there were truly no effect or association. A p-value less than 0.05 indicates that the observed results are unlikely to have occurred by chance, and thus, the results are considered statistically significant.

3. Results

Table 1 summarizes the baseline characteristics of the 40 individuals with epilepsy who participated in the research. Regarding age, the median age of the participants was 25.5 years, with ages ranging from 17 to 50 years. This indicates that the study population included a spectrum of young to middle-aged adults. In terms of gender, the distribution was nearly equal, with 19 participants being male (47.5%) and 21 participants being female (52.5%). This suggests that the study sample was relatively balanced in terms of gender representation. The median duration of epilepsy among the participants was 10 years, with a range from 1 to 35 years. This shows that the participants had varying lengths of time since their epilepsy diagnosis, including both relatively recent diagnoses and more long-standing cases. Regarding anti-epileptic drug (AED) treatment, a majority of the participants (24 individuals, 60%) were receiving polytherapy, meaning they were taking more than one AED. A smaller proportion (16 individuals, 40%) were on monotherapy, meaning they were taking only one AED. This suggests that a substantial portion of the study group required multiple medications to manage their epilepsy. Finally, concerning seizure control, the table reveals that most participants (30 individuals, 75%) had uncontrolled seizures, defined as experiencing seizures within the last 12 months. Only a minority (10 individuals, 25%) had controlled seizures. This indicates that a large proportion of the studied epilepsy patients experienced ongoing seizures.

Table 1. Baseline characteristics of epilepsy patients (N=40).

Characteristic	Category	Value	n (%)
Age (years)	Median (Range)	25.5 (17-50)	
Gender	Male		19 (47.5%)
	Female		21 (52.5%)
Duration (years)	Median (Range)	10 (1-35)	
Anti-epileptic drug	Monotherapy		16 (40.0%)
	Polytherapy		24 (60.0%)
Seizure control	Controlled		10 (25.0%)
	Not Controlled		30 (75.0%)

Table 2 presents a comparison of the baseline characteristics of the study participants, categorized into two groups based on their sleep quality: "Good Sleepers" and "Poor Sleepers." Regarding age, there's a notable difference between the two groups. The median age of the "Good Sleepers" was 36 years, with a range from 17 to 50 years. In contrast, the median age of the "Poor Sleepers" was 23 years, with a range from 18 to 41 years. The p-value of 0.039 indicates that this difference in age between the two groups is statistically significant. This suggests that younger epilepsy patients in this study were more likely to report poorer sleep quality. In terms of gender, the table shows the number and percentage of male and female participants in each sleep quality group. Among the "Good Sleepers," 6 were male (31.5%) and 10 were female (57.6%). Among the "Poor Sleepers," 13 were male (68.4%) and 11 were female (52.4%). The p-value of 0.301 indicates that there was no statistically significant difference in gender distribution between the two sleep quality groups. This suggests that gender was not a significant factor in determining sleep quality in this study. Concerning the duration of epilepsy, the median duration for "Good Sleepers" was 12 years, with a range from 1 to 35 years. For "Poor Sleepers," the median duration was 8 years, with a range from 1 to 27 years. The p-value of 0.091 suggests that there was no statistically significant difference in the duration of epilepsy between the two groups. This implies that the length of time a person had been diagnosed with epilepsy was not strongly associated with their sleep quality in this study.

Regarding anti-epileptic drug (AED) treatment, the table compares the use of monotherapy (one AED) versus polytherapy (multiple AEDs) in the two groups. Among "Good Sleepers," 10 were on monotherapy (62.5%), and 6 were on polytherapy (25.0%). Among "Poor Sleepers," 6 were on monotherapy (37.5%), and 18 were on polytherapy (75.0%). The p-value of 0.018 indicates a statistically significant difference in AED therapy type between the two groups. This highlights that patients receiving polytherapy were more likely to report poor sleep quality, while those on monotherapy were more likely to report good sleep quality. Finally, the table presents data on seizure control. Among "Good Sleepers," 7 had controlled seizures (70.0%), and 9 had uncontrolled seizures (30.0%). Among "Poor Sleepers," 3 had controlled seizures (30.0%), and 21 had uncontrolled seizures (70.0%). The p-value of 0.059 suggests a trend toward an association between seizure control and sleep quality, but this association did not reach the threshold for statistical significance. However, the data indicates that a higher percentage of patients with controlled seizures reported good sleep, and conversely, a higher percentage of patients with uncontrolled seizures reported poor sleep.

Table 2. Comparison of baseline characteristics by sleep quality group.

Characteristic	Sleep quality group	Good sleepers (n=16)	Poor sleepers (n=24)	p-value
Age (years)	Median (Range)	36 (17-50)	23 (18-41)	0.039*
Gender	Male, n (%)	6 (31.5%)	13 (68.4%)	0.301#
	Female, n (%)	10 (57.6%)	11 (52.4%)	
Duration (years)	Median (Range)	12 (1-35)	8 (1-27)	0.091*
Anti-epileptic drug	Monotherapy, n (%)	10 (62.5%)	6 (37.5%)	0.018#
	Polytherapy, n (%)	6 (25.0%)	18 (75.0%)	
Seizure control	Controlled, n (%)	7 (70.0%)	3 (30.0%)	0.059o
	Not Controlled, n (%)	9 (30.0%)	21 (70.0%)	

*Mann-Whitney U test; #Chi-square test; oFisher's exact test.

Table 3 presents the relationship between serum high-sensitivity C-reactive protein (Hs-CRP) levels and sleep quality in individuals with epilepsy. The participants are categorized into "Good Sleepers" and "Poor Sleepers." The key finding shown in the table is a comparison of the median serum Hs-CRP levels between these two groups. For the "Good Sleepers," the median Hs-CRP level was 1,271.50 ng/ml, with individual values ranging from 58 ng/ml to 5,837 ng/ml. In contrast, the "Poor Sleepers" had a significantly higher median Hs-CRP level of 2,771.50 ng/ml, with a range from 509 ng/ml to 27,187 ng/ml. The p-value associated with this comparison is 0.027. This p-value indicates that the difference in median serum Hs-CRP levels between the "Good Sleepers" and "Poor Sleepers" is statistically significant. In simpler terms, this result suggests that there is a real difference in Hs-CRP levels between the two groups and that this difference is unlikely to be due to chance.

Table 3. Relationship between serum Hs-CRP levels and sleep quality in epilepsy patients.

Variable	Sleep quality group	Good sleepers (n=16)	Poor sleepers (n=24)	p-value
Serum Hs-CRP (ng/ml)	Median (Min-Max)	1,271.50 (58 – 5,837)	2,771.50 (509 - 27,187)	0.027

*Mann-Whitney U test.

4. Discussion

The primary finding of this study reveals a statistically significant association between poorer subjective sleep quality and elevated serum Hs-CRP levels in patients with epilepsy. Specifically, patients who self-reported poor sleep quality, as indicated by their scores on the Pittsburgh Sleep Quality Index (PSQI), exhibited significantly higher levels of Hs-CRP, a marker of systemic inflammation, compared to those patients who reported good sleep quality. This finding is of considerable importance as it suggests a link between sleep disturbances and increased inflammation in individuals with epilepsy. To place this finding in context, it's important to consider previous research. Previous studies have independently established associations between epilepsy and increased CRP/Hs-CRP levels, suggesting a role for systemic inflammation in epilepsy, and also between poor sleep and increased CRP/Hs-CRP levels in the general population, indicating a link between sleep disruption and inflammation. However, this study bridges these separate observations by directly demonstrating this specific association within an epilepsy cohort. This novel finding suggests that the systemic inflammatory state, as reflected by Hs-CRP, may be particularly heightened in epilepsy patients who concurrently experience poor sleep. Several potential mechanisms could contribute to this heightened inflammatory state. It's plausible that there are additive inflammatory contributions stemming from both the underlying epilepsy and seizure activity itself, and from the physiological consequences of disturbed sleep. These combined factors could potentially act through shared pathways, such as the activation of Nuclear Factor kappa-B (NF-κB) and the subsequent release of pro-inflammatory cytokines. The observation of elevated Hs-CRP levels in poor sleepers with epilepsy might therefore signify a greater burden of underlying pathophysiological processes involving inflammation. This has important implications for understanding the complex interplay between epilepsy, sleep, and inflammation. It suggests that in epilepsy patients, poor sleep is not merely a symptom or a consequence of the condition, but it may also contribute to a state of heightened systemic inflammation, which could have further implications for their overall health and well-being.[11-13]

In addition to the primary finding linking Hs-CRP and sleep quality, this study also explored other factors that might be associated with sleep quality in epilepsy patients. Interestingly, the study revealed that younger age was significantly associated with poorer sleep quality in this specific sample of epilepsy patients. This finding warrants further examination as it appears to contrast with findings observed in the general population, where poor sleep quality is often observed to increase with advancing age. In the general population, age-related changes in sleep architecture, hormonal fluctuations, and increased prevalence of medical conditions can contribute to poorer sleep quality in older individuals. However, the present study's findings suggest a different pattern in epilepsy patients. Several potential explanations could account for this deviation. One possible explanation is the dominance of younger individuals within the study sample. The median age of the participants in this study was 25.5 years. The exclusion criteria employed in this study, which aimed to remove cases of symptomatic epilepsy often associated with conditions more prevalent in older age groups (such as stroke), likely contributed to this younger age distribution. It's possible that the unique characteristics of this younger epilepsy cohort influence the relationship between age and sleep quality. Another potential explanation lies in the potential overriding influence of epilepsy-specific factors. Factors such as seizures themselves, the effects of anti-epileptic drugs (AEDs), and the psychosocial challenges associated with epilepsy might exert a stronger influence on sleep quality in younger individuals, potentially masking or altering the typical age-related decline in sleep quality seen in the general population. Younger patients might be more susceptible to sleep disruption arising from lifestyle factors, such as irregular sleep schedules, social activities, or academic pressures,

and these factors could interact with their epilepsy to further disrupt sleep. Additionally, younger individuals may experience greater psychosocial stress related to their epilepsy diagnosis and its impact on their social development and independence, and this stress could contribute to sleep disturbances. It's also important to consider that younger patients with epilepsy may have different patterns of healthcare utilization and management compared to older patients. They might be more likely to be in the early stages of their epilepsy journey, potentially undergoing medication adjustments or experiencing more frequent seizures as their condition is being stabilized. These factors could contribute to poorer sleep quality in this age group. The finding that younger age is associated with poorer sleep quality in epilepsy patients highlights the need for further investigation into age-specific sleep patterns within this population. Understanding how sleep quality varies across different age groups in epilepsy could have important implications for clinical management and targeted interventions. Consistent with a number of previous reports, this study found that AED polytherapy was significantly associated with poorer sleep quality in epilepsy patients. Polytherapy, which involves the use of multiple anti-epileptic drugs, is often employed in cases of more severe or drug-resistant epilepsy, where monotherapy (the use of a single AED) is insufficient to achieve adequate seizure control. The association between polytherapy and poorer sleep quality can be explained by several factors. Firstly, the severity of the underlying epilepsy itself, which necessitates the use of multiple medications, might be inherently linked to worse sleep. Patients with more severe or difficult-to-treat epilepsy may experience more frequent or more severe seizures, and these seizures can directly disrupt sleep architecture and contribute to poor sleep quality. Secondly, the cumulative side-effect burden of multiple AEDs can play a significant role in sleep disturbances. AEDs, like many medications, can have a range of side effects, and these side effects can vary depending on the specific drug, the dosage, and individual patient factors. When multiple AEDs are used in combination, the likelihood and severity of side effects can increase. Some common AED side effects that can negatively impact sleep include sedation, insomnia, changes in sleep architecture, and increased frequency of nocturnal awakenings. Thirdly, potential drug interactions between different AEDs can also affect sleep-wake regulation. The complex pharmacokinetic and pharmacodynamic interactions between multiple AEDs can disrupt the delicate balance of neurotransmitters and other neurochemicals involved in regulating sleep. This disruption can lead to difficulties initiating or maintaining sleep, as well as alterations in the normal sleep stages. Finally, the complexity of managing multiple medications can indirectly contribute to sleep disturbances. Patients on polytherapy regimens may face challenges in adhering to their medication schedules, managing potential drug interactions, and dealing with the overall burden of their medication regimen. This can lead to increased stress and anxiety, which in turn can negatively affect sleep. The finding that AED polytherapy is associated with poorer sleep quality underscores the importance for clinicians to be mindful of the potential impact of polytherapy on sleep when managing epilepsy. Careful consideration should be given to minimizing the number of AEDs used whenever possible, while still ensuring adequate seizure control. When polytherapy is necessary, clinicians should proactively monitor patients for sleep disturbances and implement strategies to mitigate these effects.[14-17]

This study did not find a significant association between sleep quality and gender in the epilepsy patients studied. This result contrasts with some previous studies that have reported a higher risk of poor sleep in women with epilepsy. However, it's important to consider potential explanations for this discrepancy. One possible explanation is that the sample size in this study might have limited the statistical power to detect a gender difference if one truly exists. With a relatively small number of participants, the study might not have had sufficient

power to detect subtle differences in sleep quality between men and women with epilepsy. Another possibility is that other dominant factors, such as disease severity or the type of AED treatment, might have masked a gender effect in this particular cohort. Epilepsy is a heterogeneous condition, and various factors can influence sleep quality. It's possible that in this study population, the effects of these other factors were more prominent than any potential gender-related differences. It's also important to acknowledge that gender differences in sleep can be complex and influenced by a variety of biological, psychological, and social factors. Further research with larger sample sizes and more comprehensive assessments of these factors is needed to fully understand the role of gender in sleep quality in epilepsy. Similarly, this study did not find a significant association between sleep quality and the duration of epilepsy. This finding aligns with some previous research that has suggested that the duration of epilepsy is not a primary determinant of sleep quality in individuals with epilepsy. However, it's important to note that the relationship between epilepsy duration and sleep quality can be complex. While the duration of epilepsy might not be a direct predictor of sleep quality, it's possible that other factors related to the chronicity of epilepsy can influence sleep. For example, individuals with long-standing epilepsy may have experienced more cumulative effects of seizures and AED treatment, which could indirectly impact sleep. They may also have developed associated comorbidities, such as mood disorders or chronic pain, which can contribute to sleep disturbances. It's also important to consider that the impact of epilepsy duration on sleep quality might vary depending on individual factors, such as the type and severity of epilepsy, the effectiveness of treatment, and the presence of other medical or psychiatric conditions. Although the association between seizure control status and sleep quality did not reach statistical significance in this study, a clear trend was observed. The data indicated that a higher proportion of patients with uncontrolled seizures reported poor sleep quality, while conversely, a higher proportion of patients with controlled seizures reported good sleep quality. This observed trend is consistent with the well-established concept that seizure activity can disrupt sleep, and conversely, that poor sleep can lower seizure thresholds and increase the likelihood of seizures. Seizures, particularly nocturnal seizures or subclinical epileptiform activity during sleep, can directly interfere with normal sleep architecture. Seizures can cause arousals from sleep, sleep fragmentation, and a reduction in the amount of restorative sleep stages. This disruption of sleep can lead to daytime sleepiness, fatigue, and other sleep-related complaints. Conversely, poor sleep can also have a negative impact on seizure control. Sleep deprivation and sleep fragmentation can lower the seizure threshold, making individuals with epilepsy more susceptible to seizures. This creates a vicious cycle where seizures disrupt sleep, and poor sleep increases the risk of further seizures. The lack of statistical significance in this study, despite the observed trend, might be attributed to the limited sample size (N=40), and particularly the smaller number of patients with controlled seizures (n=10). With a larger sample size, it's possible that this trend would have reached statistical significance, providing stronger evidence for the relationship between seizure control and sleep quality. It's important to note that the relationship between seizure control and sleep quality is likely complex and bidirectional. While seizures can disrupt sleep, and poor sleep can increase seizure risk, other factors can also contribute to both poor seizure control and poor sleep quality. These factors might include the severity of epilepsy, the type of epilepsy syndrome, the effectiveness of AED treatment, and the presence of other medical or psychiatric comorbidities.[18-20]

5. Conclusion

This study provides evidence for a significant association between elevated serum Hs-CRP levels and poor subjective sleep quality in patients with epilepsy. The findings suggest that epilepsy patients experiencing poor sleep exhibit higher levels of

systemic inflammation, as indicated by increased Hs-CRP, compared to those with good sleep quality. Furthermore, the study identified younger age and AED polytherapy as factors associated with poorer sleep quality in this cohort. The association between polytherapy and poor sleep quality is consistent with previous research, potentially due to the severity of epilepsy requiring multiple medications and the cumulative side-effect burden of AEDs. However, the finding that younger age is associated with poorer sleep quality contrasts with observations in the general population, warranting further investigation to explore age-specific sleep patterns in epilepsy. While the study did not find a significant association between sleep quality and gender or epilepsy duration, a trend towards poorer sleep quality was observed in patients with uncontrolled seizures. This trend aligns with the understanding that seizures can disrupt sleep and poor sleep can increase seizure likelihood, although the limited sample size may have affected the statistical significance of this finding. In conclusion, this research highlights the complex interplay between epilepsy, sleep dysfunction, and systemic inflammation, suggesting that Hs-CRP could potentially serve as a biomarker linking these conditions. The findings underscore the importance of addressing sleep disturbances in epilepsy patients, particularly in younger individuals and those on polytherapy, to potentially mitigate the burden of inflammation and improve the overall management of the condition.

6. References

1. Granata T, Fusco L, Matricardi S, Tozzo A, Janigro D, Nabbout R. Inflammation in pediatric epilepsies: Update on clinical features and treatment options. Epilepsy Behav. 2022; 131(Pt B): 107959.
2. Abbasi H, Abbasi MM, Pasand M, Mohtadi M, Bakhshimoghaddam F, Eslamian G. Exploring the efficacy and safety of cannabidiol in individuals with epilepsy: an umbrella review of meta-analyses and systematic reviews. Inflammopharmacology. 2024; 32(5): 2987–3005.
3. Mu J, Cao C, Gong Y, Hu G. Relationship between inflammation/immunity and epilepsy: A multi-omics mendelian randomization study integrating GWAS, eQTL, and mQTL data. Epilepsy Behav. 2024; 161(110112): 110112.
4. Lai Q, Chen Y, Wang W, Lian Z, Liu T, Wen C. Identifying key prognostic indicators for relapse and chronic epilepsy in autoimmune encephalitis: Insights from a multicenter retrospective study. J Inflamm Res. 2024; 17: 11529–43.
5. Sharma A, Kondylis E, Srivatsa S, Sarmey N, Lachhwani D, Nedorezov L, et al. Refractory inflammatory hydrocephalus: A case report of a rare and complicated delayed sequelae following cerebral hemispherectomy surgery for epilepsy. Epilepsy Behav Rep. 2024; 27(100694): 100694.
6. Khoshkroodian B, Javid H, Pourbadie HG, Sayyah M. Toll-like receptor 1/2 postconditioning by the ligand Pam3cys tempers posttraumatic hyperexcitability, neuroinflammation, and microglial response: a potential candidate for posttraumatic epilepsy. Inflammation. 2024.
7. Wang W, Ma L, Liu M, Zhao Y, Ye W, Li X. Assessing the impact of circulating inflammatory cytokines and proteins as drivers and therapeutic targets in epilepsy: A Mendelian randomization study. Epilepsy Behav. 2024; 157(109868): 109868.
8. Mosini AC, Sanabria V, Nakamura TKE, Calió ML, Pompeu C, Silva CS, et al. Posttraumatic epilepsy: Integrating clinical, inflammatory, and genetic profiles in traumatic brain injury patients. Epilepsy Res. 2024; 205(107402): 107402.
9. Khatami SH, Alehossein P, Ehtiati S, Zarei T, Salmani F, Bagherzadeh S, et al. Therapeutic efficacy of intermittent ketogenesis in

modulating adenosine metabolism, immune response, and seizure severity in refractory temporal lobe epilepsy: a pilot human study. Inflammation. 2025.

10. Charpentier-Hélary M, de la Chapelle A, Linard M, André-Obadia N, Boulogne S, Catenoix H, et al. Dreaming in patients with epilepsy: a cross-sectional cohort study. J Sleep Res. 2025; e14464.
11. Emekli AS, Dörtkol ŞO, Savaş M, Öz F, İşcen P, Topaloğlu P, et al. Effects of immune modulatory treatment on language and psychiatric profile in patients with electrical status epilepticus in sleep (ESES). Epilepsy Behav. 2025; 163(110225): 110225.
12. Horvath CM, Drangova H, Stefela J, Schäfer C, Zubler F. Refuting a temporal correlation: Interictal epileptic discharges do not preferentially occur during respiratory events in patients with sleep-related breathing disorder and epilepsy. J Sleep Res. 2025; e70021.
13. Wang R, Teng S, Turanchik M, Zhen F, Peng Y. Tonic-clonic seizures induce hypersomnia and suppress REM sleep in mouse models of epilepsy. Sleep Adv. 2025.
14. Kamila G, Jauhari P, Kumar A, Singh S, Chakrabarty B, Gulati S, et al. Thalamic volumetric analysis in Developmental and/or Epileptic Encephalopathy with Spike Wave Activation in Sleep (D/EE-SWAS): a cross-sectional study. Seizure. 2025; 127: 94–100.
15. Amirhosseni H, Davoodvand S, Kheiri S, Jafari M, Masoudi R. The effect of an educative-supportive program based on the continuous care model on daily living activities and sleep quality in peoples with epilepsy. Epilepsy Behav. 2025; 166(110382): 110382.
16. Joshi C. Sleeping with the enemy: Drug-resistant epilepsy and sleep. Epilepsy Curr. 2025; 15357597251320139.
17. Nobili L, Cordani R, Arnaldi D, Mattioli P, Veneruso M, Ng M. Rapid eye movement sleep and epilepsy: exploring interactions and therapeutic prospects. J Sleep Res. 2025; 34(2): e14251.
18. Machado RA, Meylor J, Narayan SL, Norton NB. Characterization of a unique patient cohort with spike-wave activation in sleep without cognitive decline or increased seizure burden: Considerations for a more conservative treatment approach. Seizure. 2025; 127: 115–26.
19. Li K, Li H, Wang J, Chen X, Li L, Wang C, et al. Causal relationship between sleep traits and risk of Epilepsy: a Mendelian randomization study. Epilepsy Behav. 2025; 165(110310): 110310.
20. Sureshbabu S, Fellowship in Epilepsy, Fellowship in Sleep Medicine, India. Refractory focal epilepsy as a rare clinical presentation of systemic lupus erythematosus. J Clin Images Med Case Rep. 2024; 5(3).