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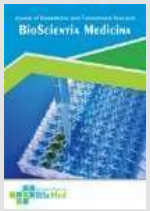

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Serum High Mobility Group Box 1 (HMGB1) Protein Levels and Cognitive Function in Epilepsy Patients: A Cross-Sectional Study

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A B S T R A C T

Background: Epilepsy is a neurological disease with a high incidence rate. Cognitive decline is one of the consequences of recurrent seizures. Neuroinflammation is closely related to the development of epilepsy and cognitive impairment. An increase in the expression and translocation of High Mobility Group Box 1 (HMGB1) from the nucleus to the extracellular space has been observed in epilepsy patients and experimental animal models. This study aimed to investigate the relationship between serum HMGB1 levels and cognitive function in epilepsy patients. **Methods:** This cross-sectional observational study involved 45 epilepsy patients. Cognitive function was assessed using the Indonesian version of the Montreal Cognitive Assessment (MoCA-Ina), and serum HMGB1 levels were measured using the ELISA technique. The relationship between cognitive function and HMGB1 levels was analyzed using the Kruskal-Wallis test, with a significance level set at $p < 0.05$. **Results:** The mean age of the participants was 28.5 years, with a higher proportion of females. The mean serum HMGB1 level was 22.6 ng/ml. No significant relationship was found between serum HMGB1 levels and cognitive function in epilepsy patients ($p = 0.188$). **Conclusion:** Serum HMGB1 protein levels were not associated with cognitive function in this sample of epilepsy patients.

1. Introduction

Epilepsy, a chronic neurological disorder characterized by recurrent seizures, presents a significant global health challenge. It affects approximately 50 million people worldwide, with an estimated global incidence of 50.4 per 100,000 individuals per year. The burden of epilepsy is disproportionately high in low and middle-income countries, where resources are limited, and access to care is often inadequate. These countries account for nearly 80% of the global epilepsy population. In Asia, with a population exceeding 4 billion, an estimated 23 million individuals live with epilepsy. The prevalence of epilepsy in Indonesia is reported to be 8.2 per 1,000 population, with an incidence rate of 50 per 100,000 population. The impact of epilepsy extends beyond the seizures themselves. Recurrent seizures can lead to a progressive decline in cognitive function, affecting various domains such as memory, attention, and executive function. This cognitive impairment can significantly impact an individual's quality of life, affecting their education, employment, and social interactions.[1-4]

The underlying mechanisms of epilepsy are complex and multifaceted, with neuroinflammation playing a central role in its development and progression. Neuroinflammation is a complex biological response involving the activation of glial cells, the release of inflammatory mediators, and changes in the blood-brain barrier (BBB) permeability.

In epilepsy, recurrent seizures can trigger and perpetuate neuroinflammation, creating a vicious cycle of neuronal damage and further seizures. High Mobility Group Box 1 (HMGB1) is a ubiquitous nuclear protein that has emerged as a key player in the pathogenesis of epilepsy. HMGB1 can be released from activated glial cells and neurons into the extracellular space, where it acts as an inflammatory mediator. In the context of epilepsy, HMGB1 has been shown to contribute to BBB disruption, promote neuronal hyperexcitability, and exacerbate seizure-induced brain injury.[5-7]

Several studies have investigated the role of HMGB1 in epilepsy. Animal models of epilepsy have demonstrated that HMGB1 levels are elevated in the brain and serum following seizures. Moreover, pharmacological inhibition or genetic deletion of HMGB1 has been shown to reduce seizure severity and protect against seizure-induced brain damage in these models. In human studies, elevated serum HMGB1 levels have been reported in patients with epilepsy, particularly those with drug-resistant epilepsy. However, the relationship between serum HMGB1 levels and cognitive function in epilepsy patients remains poorly understood. Some studies have suggested a negative correlation between HMGB1 levels and cognitive performance in epilepsy patients, while others have found no significant association.[8-10] This study aimed to investigate the relationship between serum HMGB1 levels and cognitive function in a cohort of epilepsy patients.

2. Methods

This study employed a cross-sectional observational design to investigate the relationship between serum High Mobility Group Box 1 (HMGB1) protein levels and cognitive function in epilepsy patients. This design is particularly suitable for exploring associations between variables and providing a snapshot of the relationship between HMGB1 levels and cognitive function at a specific point in time.

The study was conducted at the Neurology Outpatient Clinic of Dr. M. Djamil General Hospital Padang, a tertiary referral center in Padang, Indonesia. This setting provided access to a diverse population of epilepsy patients, ensuring the generalizability of the study findings. The study population consisted of adult patients diagnosed with epilepsy who visited the neurology outpatient clinic during the study period, which spanned from January 2024 to May 2024. This timeframe allowed for the recruitment of an adequate sample size to ensure the statistical power of the study.

The minimum required sample size was determined using a sample size formula, taking into account the estimated prevalence of cognitive impairment in epilepsy patients, the desired level of precision, and the estimated variability in HMGB1 levels. The calculated minimum sample size was 45 subjects, which was deemed sufficient to detect a clinically meaningful association between HMGB1 levels and cognitive function.

To ensure the homogeneity of the study sample and minimize the influence of confounding factors, specific inclusion and exclusion criteria were established. Inclusion criteria; Adult patients (18 years or older); Diagnosed with epilepsy; Willing to provide informed consent. Exclusion criteria; History of other neurological disorders (e.g., stroke, dementia); History of significant head trauma; Current use of medications known to affect cognitive function (e.g., antipsychotics, benzodiazepines); Presence of any medical condition that could interfere with cognitive assessment (e.g., severe hearing or visual impairment).

Data collection involved a combination of patient interviews, neuropsychological assessments, and laboratory investigations. Patients who met the inclusion criteria and did not have any exclusion criteria were approached and provided with information about the study. Those who expressed interest in participating were then screened for eligibility. Eligible patients were asked to provide written informed consent before proceeding with data

collection. A structured interview was conducted to collect demographic and clinical data, including age, gender, education level, duration of epilepsy, seizure frequency, current antiepileptic drug (AED) therapy, and history of epilepsy-related complications. Cognitive function was assessed using the Montreal Cognitive Assessment Indonesia (MoCA-Ina), a validated and widely used neuropsychological test for screening cognitive impairment. The MoCA-Ina assesses various cognitive domains, including attention, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The MoCA-Ina was administered by trained neuropsychologists in a quiet and well-lit room to minimize distractions. The test was conducted in accordance with standardized instructions to ensure consistency and reliability. A 2cc venous blood sample was collected from each participant by trained phlebotomists. The blood samples were processed and centrifuged to obtain serum, which was then stored at -80°C until analysis. Serum HMGB1 levels were measured using the enzyme-linked immunosorbent assay (ELISA) technique, a sensitive and specific method for quantifying protein levels in biological samples. The ELISA assay was performed in duplicate according to the manufacturer's instructions.

The collected data were entered into a database and analyzed using SPSS 25.0 statistical software. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. Univariate analysis was performed to describe the distribution of each variable, including measures of central tendency (mean, median) and dispersion (standard deviation, range). Bivariate analysis was conducted to assess the relationship between serum HMGB1 levels and cognitive function, as well as the association between HMGB1 levels and other factors influencing cognitive function. The relationship between serum HMGB1 levels and cognitive function was analyzed using the Kruskal-Wallis test, a non-parametric test used to compare the medians of two or more independent groups. The Kruskal-Wallis test was chosen because the distribution of HMGB1 levels was not normally distributed. The relationship between epilepsy control and HMGB1 levels was analyzed using the Anova test, a parametric test used to compare the means of two or more independent groups. The Anova test was chosen because the distribution of epilepsy control was normally distributed. A significance level of $p < 0.05$ was considered statistically significant for all analyses.

3. Results

Table 1 provides a detailed breakdown of the characteristics of the 45 participants enrolled in the study investigating the relationship between serum HMGB1 levels and cognitive function in epilepsy patients; Age: The average age of participants was 28.5 years, with a standard deviation of 8.2 years. This indicates a relatively young adult population with some variability in age. The age range spanned from 17 to 66 years, suggesting a diverse representation of age groups within the epilepsy patient population; Gender: There were more female participants (53.3%) than male participants (46.7%). This finding is consistent with other studies that have reported a slightly higher prevalence of epilepsy in women; Education Level: The majority of participants had completed high school (46.7%), followed by a bachelor's degree (24.4%). A small proportion had only completed primary or middle school (4.4% each). This distribution suggests a relatively high level of education among the participants, which is important to consider when interpreting cognitive function assessments; Duration of Epilepsy: More than half of the participants had been living with epilepsy for 6 years or more (57.8%). This indicates a substantial proportion of patients with chronic epilepsy, which can have implications for cognitive function; Antiepileptic Drug Therapy: A slightly higher proportion of participants were on polytherapy (53.3%) compared to monotherapy (46.7%). This finding reflects the challenges in managing epilepsy, with many patients requiring multiple medications to

achieve adequate seizure control; Seizure Frequency: The majority of participants experienced one or fewer seizures per month (62.2%). This suggests that most participants had relatively well-controlled epilepsy, although a significant proportion still experienced more frequent seizures; Type of Epilepsy: Generalized epilepsy was more common (60%) than focal epilepsy (40%) among the participants. This distribution is consistent with the overall prevalence of these epilepsy types in the general population; Seizure Control: A slightly higher proportion of participants had uncontrolled seizures (55.6%) compared to those with controlled seizures (44.4%). This finding highlights the ongoing challenges in achieving optimal seizure control for many epilepsy patients.

Table 1. Participants characteristics.

Characteristic	n (%)
Age (years)	
Mean (SD)	28.5 (8.2)
Range	17-66
Gender	
Female	24 (53.3)
Male	21 (46.7)
Education level	
Primary School	2 (4.4)
Middle School	2 (4.4)
High School	21 (46.7)
Vocational School	7 (15.6)
Bachelor's Degree	11 (24.4)
Master's Degree	2 (4.4)
Duration of epilepsy (years)	
< 6	19 (42.2)
≥ 6	26 (57.8)
Antiepileptic drug therapy	
Monotherapy	21 (46.7)
Polytherapy	24 (53.3)
Seizure frequency (per month)	
≤ 1	28 (62.2)
> 1	17 (37.8)
Type of epilepsy	
Generalized	27 (60.0)
Focal	18 (40.0)
Seizure control	
Controlled	20 (44.4)
Uncontrolled	25 (55.6)

Table 2 presents the distribution of cognitive function levels among the 45 epilepsy patients and their corresponding serum HMGB1 levels; Cognitive Function Distribution: 31.1% of the participants showed normal cognitive function. The largest group (35.5%) had mild cognitive impairment. 24.2% of the participants had moderate cognitive impairment. A small portion (8.9%) had severe cognitive impairment. This distribution highlights that cognitive impairment is prevalent among epilepsy patients, with varying degrees of severity; Serum HMGB1 Levels: The overall median HMGB1 level across all participants was 22.6 ng/ml. This provides a central tendency for HMGB1 levels in this specific epilepsy patient group. The mean

HMGB1 level was 27.12 ng/ml with a standard deviation of 28.91. The large standard deviation suggests a wide spread in the HMGB1 values, indicating individual variability in inflammatory response; Relationship between Cognitive Function and HMGB1 Levels: While the table doesn't directly show a statistically significant relationship (this would be indicated by a p-value from a statistical test), some trends can be observed. The group with severe cognitive impairment had the highest median HMGB1 level (27.8 ng/ml) and a notably higher mean HMGB1 (48.93 ng/ml) with a very large standard deviation (45.61). This could suggest a potential link between higher HMGB1 levels and more severe cognitive impairment, although further statistical analysis would be needed to confirm this. The median HMGB1 levels for the normal, mild, and moderate cognitive impairment groups were relatively similar, ranging from 21.46 to 22.6 ng/ml. This might indicate that HMGB1 may not be a strong discriminator of cognitive function within these less severe categories.

Table 2. Cognitive function and serum HMGB1 levels.

Cognitive function	**n (%)**	**Median HMGB1 (ng/ml)**	**Mean HMGB1 (ng/ml) (SD)**
Normal	14 (31.1)	21.92	30.21 (33.42)
Mild Cognitive Impairment	16 (35.5)	22.60	25.35 (15.67)
Moderate Cognitive Impairment	11 (24.2)	21.46	21.89 (10.21)
Severe Cognitive Impairment	4 (8.9)	27.80	48.93 (45.61)
Total	45 (100)	22.60	27.12 (28.91)

Table 3 presents the results of the statistical analysis examining the relationship between various factors and cognitive function in epilepsy patients; HMGB1 (p-value = 0.188): This indicates that there was no statistically significant relationship between serum HMGB1 levels and cognitive function in this study. Although some trends were observed in Table 2 (higher HMGB1 in the severe cognitive impairment group), this result suggests that those differences were not statistically significant; Age (p-value = 0.069): While not statistically significant at the $p<0.05$ level, this p-value is close to the threshold. This suggests a potential trend towards a relationship between age and cognitive function, where older age might be associated with poorer cognitive performance. Further investigation with a larger sample size might be needed to confirm this; Duration of Epilepsy (p-value = 0.069): Similar to age, this p-value indicates a possible trend. Longer duration of epilepsy might be linked to poorer cognitive function, potentially due to the cumulative effects of seizures and disease progression on the brain; Gender (p-value = 0.971), Education Level (p-value = 0.375), Antiepileptic Drug Therapy (p-value = 0.915), Seizure Frequency (p-value = 0.482), Type of Epilepsy (p-value = 0.713), Seizure Control (p-value = 0.637): These p-values all indicate that there was no statistically significant relationship between these variables and cognitive function in this study.

Table 3. The relationship among HMGB1, other variables, and cognitive function.

Variable	Cognitive function	p-value
HMGB1 (ng/ml)		0.188
Mean (SD)	27.12 (28.91)	
Median	22.60	
Age (years)		0.069
Mean (SD)	28.5 (8.2)	
Range	17-66	
Gender		0.971
Female	24 (53.3)	
Male	21 (46.7)	
Education level		0.375
Primary/Middle School	4 (8.8)	
High School	21 (46.7)	
Vocational School	7 (15.6)	
Bachelor's/Master's Degree	13 (28.9)	
Duration of epilepsy (years)		0.069
< 6	19 (42.2)	
≥ 6	26 (57.8)	
Antiepileptic drug therapy		0.915
Monotherapy	21 (46.7)	
Polytherapy	24 (53.3)	
Seizure frequency (per month)		0.482
≤ 1	28 (62.2)	
> 1	17 (37.8)	
Type of epilepsy		0.713
Generalized	27 (60.0)	
Focal	18 (40.0)	
Seizure control		0.637
Controlled	20 (44.4)	
Uncontrolled	25 (55.6)	

The p-values were derived from statistical tests (Kruskal-Wallis test for HMGB1 and cognitive function, and Kruskal-Wallis or Mann-Whitney U test for other variables, as appropriate).

Table 4 explores the relationship between various demographic and clinical characteristics of the epilepsy patients and their serum HMGB1 levels; Age (p-value = 0.284): This indicates no statistically significant relationship between age and HMGB1 levels. Although the median HMGB1 seems to slightly increase across age groups (from 22.25 to 23.11 ng/ml), this difference is not statistically significant. This suggests that age alone may not be a major determinant of HMGB1 levels in these patients; Gender (p-value = 0.524): No significant difference in HMGB1 levels between males and females; Education Level (p-value = 0.132): While not statistically significant, there's a trend towards higher HMGB1 levels in those with higher education (high school and above: 23.01 ng/ml vs. primary/middle school: 22.18 ng/ml). This might be related to other lifestyle or socioeconomic factors associated with education, but further investigation is needed; Duration of Epilepsy (p-value = 0.435): No significant difference in HMGB1 levels based on epilepsy duration; Antiepileptic Drug Therapy (p-value = 0.306): No significant difference in HMGB1 levels between those on monotherapy and polytherapy; Seizure Frequency (p-value = 0.815): No significant difference in HMGB1 levels based on seizure frequency; Type of Epilepsy (p-value = 0.571): No significant difference in HMGB1 levels between generalized and focal epilepsy; Seizure Control (p-value = 0.909): No significant difference in HMGB1 levels between those with controlled and uncontrolled seizures.

Table 4. Relationship between other variables and HMGB1.

Variable	HMGB1 (ng/ml)	p-value
Age (years)		0.284
18-30	22.25 (17.37-30.11)	
31-40	23.40 (17.72-115.17)	
41-66	23.11 (1.48-132.91)	
Gender		0.524
Female	22.47 (1.48-132.90)	
Male	22.60 (17.44-39.44)	
Education level		0.132
Primary/Middle School	22.18 (1.47-115.16)	
High School/Above	23.01 (17.71-132.91)	
Duration of epilepsy (years)		0.435
< 6	21.68 (17.72-115.17)	
≥ 6	22.61 (1.48-132.91)	
Antiepileptic drug therapy		0.306
Monotherapy	22.61 (1.48-132.91)	
Polytherapy	21.93 (17.37-67.76)	
Seizure frequency (per month)		0.815
≤ 1	22.38 (1.48-132.91)	
> 1	23.01 (17.37-115.17)	
Type of epilepsy		0.571
Generalized	22.60 (1.48-132.91)	
Focal	22.25 (17.37-115.17)	
Seizure control		0.909
Controlled	22.00 (17.72-132.91)	
Uncontrolled	22.54 (1.48-115.17)	

The p-values were derived from statistical tests (Kruskal-Wallis test for age, and Mann-Whitney U test for other variables).

4. Discussion

The mean age of 28.5 years in this study places the participants within the young adult demographic. This is consistent with the broader understanding of epilepsy, as the majority of cases are diagnosed in childhood or adolescence. However, it is crucial to recognize that epilepsy can manifest at any point in the lifespan, from infancy to old age. The age of onset can significantly influence the trajectory of the disease, its impact on the individual, and the specific challenges faced in managing it. When epilepsy begins in childhood, it can disrupt critical developmental milestones, affecting cognitive development, social interactions, and educational progress. Children with epilepsy may require special educational support and may face social stigma and discrimination. Managing epilepsy in children often involves a delicate balance between controlling seizures and minimizing the side effects of medications, which can impact growth and development. Epilepsy emerging during adolescence presents unique challenges, as this is a period of significant physical, emotional, and social changes. Adolescents with epilepsy may struggle with issues of identity, independence, and peer relationships. Seizures can disrupt school attendance, social activities, and driving privileges, impacting their sense of autonomy and social integration. While less common than childhood-onset epilepsy, epilepsy can also develop in adulthood, often triggered by head injuries, stroke, brain tumors, or infections. Adult-onset epilepsy can significantly disrupt established careers, family life, and social roles. Adults with epilepsy may face challenges related to employment, driving restrictions, and the stigma associated with the condition. Epilepsy in older adults is often associated with underlying medical conditions, such

as cerebrovascular disease, neurodegenerative disorders, and brain tumors. Managing epilepsy in older adults can be complex due to potential drug interactions with other medications, age-related changes in metabolism, and the presence of comorbidities. The observation of a slightly higher proportion of females in this study aligns with epidemiological data suggesting a slightly higher prevalence of epilepsy in women. Fluctuations in female hormones, particularly estrogen and progesterone, can influence seizure activity. Some women experience an increase in seizure frequency around the time of menstruation, ovulation, or during pregnancy. Hormonal changes during puberty, pregnancy, and menopause can also affect the effectiveness of antiepileptic drugs (AEDs). Some genetic mutations associated with epilepsy may be more prevalent or have a more pronounced effect in females. Further research is needed to fully understand the role of genetic factors in the gender differences observed in epilepsy. There may be subtle differences in brain structure and function between males and females that contribute to the susceptibility to epilepsy. For example, some studies have suggested that women may have a lower seizure threshold than men. For young women with epilepsy, family planning and reproductive health are important considerations. AEDs can interact with hormonal contraceptives, reducing their effectiveness. Some AEDs can also increase the risk of birth defects if taken during pregnancy. Women with epilepsy who are planning to become pregnant should discuss their medication options with their healthcare provider to ensure optimal seizure control and minimize risks to the developing fetus. Pregnancy can affect seizure frequency in women with epilepsy, with some women experiencing an increase in seizures and others a decrease. Close monitoring and medication adjustments may be necessary during pregnancy to ensure optimal seizure control and maternal and fetal well-being. Hormonal changes during menopause can also affect seizure control in women with epilepsy. Some women may experience an increase in seizure frequency during this time, while others may find that their seizures become easier to control. Regular follow-up with a healthcare provider is essential to manage epilepsy effectively during menopause. Catamenial epilepsy refers to a specific type of epilepsy in which seizures are linked to the menstrual cycle. Women with catamenial epilepsy may experience an increase in seizure frequency around the time of menstruation. Treatment options for catamenial epilepsy include hormonal therapies and adjustments to AED regimens. The observation that the most frequent education level among the participants was high school raises important questions about the complex interplay between epilepsy and educational attainment. While it is impossible to draw definitive conclusions about causality from this cross-sectional study, there is a growing body of evidence suggesting that epilepsy can significantly impact a person's educational trajectory. Seizures, especially those that occur during school hours, can disrupt learning and make it difficult for students with epilepsy to keep up with their peers. The unpredictable nature of seizures can create anxiety and fear, further hindering academic performance. Moreover, some antiepileptic drugs (AEDs) can cause side effects such as drowsiness, fatigue, and difficulty concentrating, which can further impair learning. Cognitive difficulties are common in people with epilepsy, affecting various domains such as memory, attention, and executive function. These difficulties can make it challenging for students with epilepsy to process information, retain knowledge, and complete academic tasks. The specific cognitive challenges faced by individuals with epilepsy can vary depending on the type of epilepsy, the location of seizure activity in the brain, and the medications used to manage the condition. The social stigma associated with epilepsy can also create barriers to education. Students with epilepsy may be subject to bullying, teasing, and social isolation, which can negatively impact their self-esteem and motivation to learn. Furthermore, some teachers and school administrators may have misconceptions about epilepsy, leading to

discriminatory practices or a lack of appropriate support for students with epilepsy. Studies have shown that individuals with epilepsy are more likely to have lower educational attainment compared to the general population. They may be less likely to complete high school or pursue higher education. This can have long-term consequences for employment opportunities, income potential, and overall quality of life. Students with epilepsy may qualify for IEPs, which are designed to provide individualized support and accommodations to meet their specific learning needs. IEPs may include modifications to assignments, extra time for tests, preferential seating, and access to assistive technology. Educating teachers and school staff about epilepsy is crucial to dispel myths and misconceptions and promote understanding and acceptance of students with epilepsy. Teachers should be trained to recognize seizure activity, administer first aid if needed, and provide appropriate support to students with epilepsy in the classroom. Students with epilepsy may benefit from social and emotional support to cope with the challenges of living with a chronic condition. School counselors, support groups, and peer mentoring programs can help students with epilepsy build self-esteem, develop coping strategies, and foster positive social relationships. The finding that over half of the participants had been living with epilepsy for 6 years or more underscores the chronic nature of this condition. Chronic diseases, such as epilepsy, require ongoing management to minimize symptoms, prevent complications, and optimize quality of life. People with epilepsy require regular follow-up with their healthcare provider to monitor seizure frequency, assess medication effectiveness, and adjust treatment plans as needed. Regular blood tests may be necessary to monitor for medication side effects and ensure therapeutic drug levels. AEDs are the cornerstone of epilepsy treatment, but they can have side effects and may require adjustments over time. People with epilepsy should work closely with their healthcare provider to find the most effective medication regimen with the fewest side effects. Certain lifestyle factors can influence seizure frequency, such as sleep deprivation, stress, and alcohol consumption. People with epilepsy may need to make modifications to their lifestyle to minimize these triggers and promote seizure control. Living with a chronic condition like epilepsy can take a toll on mental health. People with epilepsy may experience anxiety, depression, and social isolation. Access to mental health services and support groups can help individuals with epilepsy cope with these challenges and maintain a positive quality of life. Epilepsy can impact employment opportunities and social relationships. People with epilepsy may face discrimination in the workplace or may be unable to perform certain jobs due to seizure-related safety concerns. Social activities may also be limited due to fear of seizures or social stigma. Support groups and vocational rehabilitation services can help individuals with epilepsy navigate these challenges and achieve their personal and professional goals. The finding that a slightly higher proportion of participants in this study were on polytherapy (53.3%) compared to monotherapy (46.7%) underscores the often complex and individualized nature of epilepsy treatment. Antiepileptic drugs (AEDs) are the cornerstone of epilepsy management, aiming to suppress seizure activity and improve the quality of life for individuals with this neurological condition. However, the selection and implementation of AED therapy are not always straightforward and require careful consideration of various factors. Ideally, the goal is to achieve seizure freedom with a single AED, minimizing the risk of side effects and drug interactions. Monotherapy is generally preferred as the initial approach, starting with a low dose and gradually titrating upwards until seizure control is achieved or side effects become intolerable. When seizure control is not achieved with a single AED, a combination of two or more AEDs may be necessary. This approach, known as polytherapy, can be effective in controlling seizures but also carries an increased risk of side effects and drug interactions. Careful monitoring and dose adjustments are crucial when using polytherapy to ensure optimal efficacy and minimize adverse

events. Different AEDs have varying efficacy against different seizure types. For example, some AEDs are more effective for generalized seizures, while others are better suited for focal seizures. Specific epilepsy syndromes may respond better to certain AEDs. For example, childhood absence epilepsy often responds well to ethosuximide or valproic acid. Age, gender, comorbidities, and other individual factors can influence AED choice. For example, some AEDs are not recommended for use in women of childbearing age due to the risk of birth defects. AEDs can interact with other medications, including other AEDs, potentially altering their effectiveness or increasing the risk of side effects. A thorough medication review is essential before starting any new AED. All AEDs have potential side effects, ranging from mild to severe. Common side effects include drowsiness, dizziness, nausea, and cognitive impairment. The choice of AED should consider the individual's tolerance for specific side effects. The primary goal of AED therapy is to achieve the best possible seizure control with the fewest side effects. Effective AED therapy can significantly reduce the frequency and severity of seizures, improving overall quality of life. Uncontrolled seizures can lead to falls, burns, and other injuries. AEDs can help prevent these injuries by reducing seizure frequency. Seizures and some AEDs can impair cognitive function. Effective seizure control can help improve cognitive performance and reduce the impact of epilepsy on learning and memory. Uncontrolled seizures can lead to social isolation, anxiety, and depression. AED therapy can help improve social and emotional well-being by reducing seizure frequency and improving overall quality of life. The observation that over half of the participants in this study still had uncontrolled seizures despite AED therapy highlights the ongoing challenges in epilepsy management. Uncontrolled seizures can lead to injuries, including head trauma, fractures, and burns. They can also increase the risk of sudden unexpected death in epilepsy (SUDEP). Living with uncontrolled seizures can lead to anxiety, depression, and social isolation. The fear of having a seizure can restrict activities and limit social interactions. Seizures can impair cognitive function, affecting memory, attention, and executive function. This can have a significant impact on education, employment, and daily life. Uncontrolled seizures can disrupt education, limit employment opportunities, and strain social relationships. This can lead to financial hardship and social isolation. The reasons for uncontrolled seizures are complex and multifactorial. Some individuals with epilepsy develop medication resistance, meaning that their seizures do not respond adequately to AEDs. This can be due to various factors, including genetic variations, changes in drug metabolism, and the development of tolerance. Taking AEDs as prescribed is crucial for seizure control. Non-adherence can be due to various reasons, including forgetfulness, side effects, cost of medications, and lack of understanding about the importance of adherence. Certain medical conditions, such as sleep disorders, hormonal imbalances, and infections, can trigger seizures or worsen seizure control. Addressing these underlying conditions is essential for optimizing epilepsy management. Stress, anxiety, and depression can also contribute to uncontrolled seizures. Providing psychological support and coping strategies can help individuals with epilepsy manage these factors and improve seizure control. Effective epilepsy management requires a multidisciplinary approach, involving a team of healthcare professionals working together to address the complex needs of individuals with epilepsy. Neurologists specialize in the diagnosis and treatment of neurological conditions, including epilepsy. They play a central role in epilepsy management, prescribing AEDs, monitoring seizure control, and providing education and support to patients and their families. Nurses provide ongoing care and support to individuals with epilepsy, educating them about their condition, medication management, and lifestyle modifications. They also play a crucial role in monitoring for side effects and providing emotional support. Pharmacists provide expertise on AEDs, including drug interactions, side effects, and proper administration. They can also help

patients access affordable medications and provide education on medication adherence. Psychologists and counselors can provide support to individuals with epilepsy and their families, helping them cope with the emotional and social challenges of living with a chronic condition. Social workers can help individuals with epilepsy access resources and support services, such as vocational rehabilitation, disability benefits, and transportation assistance. By working together, this multidisciplinary team can provide comprehensive care and support to individuals with epilepsy, empowering them to achieve optimal seizure control and live full and productive lives.[11-14]

The core finding of this study—the lack of a statistically significant association between serum HMGB1 levels and cognitive function in epilepsy patients—presents a compelling puzzle. It challenges the initial hypothesis and prompts a closer examination of the role of HMGB1 in the complex landscape of epilepsy-related cognitive impairment. High Mobility Group Box 1 (HMGB1) is a ubiquitous protein that resides within the nucleus of cells, playing a critical role in DNA organization and gene expression. However, under conditions of cellular stress or injury, HMGB1 can be released into the extracellular space, where it takes on a new role as a potent inflammatory mediator. This dual nature of HMGB1 makes it a fascinating subject of study in various disease contexts, including epilepsy. HMGB1 is a key player in the neuroinflammatory cascade, promoting the activation of glial cells and the release of pro-inflammatory cytokines. Neuroinflammation is increasingly recognized as a critical contributor to epilepsy-related brain damage and cognitive dysfunction. HMGB1 can contribute to the breakdown of the blood-brain barrier, allowing inflammatory cells and molecules to infiltrate the brain, further exacerbating neuroinflammation and neuronal damage. Some studies suggest that HMGB1 may directly influence neuronal excitability and contribute to seizure generation. Given the multifaceted role of HMGB1 in epilepsy, it was hypothesized that higher serum HMGB1 levels would be associated with poorer cognitive function in epilepsy patients. However, this study did not find a statistically significant relationship between these two variables. This unexpected finding raises several questions and prompts further investigation. This study measured HMGB1 levels in peripheral blood. It is possible that HMGB1 levels in the brain, where it directly interacts with neurons and glial cells, may be more relevant to cognitive function. Future studies should explore the relationship between central HMGB1 levels (measured in cerebrospinal fluid or brain tissue) and cognitive performance in epilepsy. HMGB1 levels can fluctuate over time, particularly in relation to seizure activity. This study did not control for the timing of blood collection in relation to the most recent seizure. It is possible that measuring HMGB1 levels at different time points, such as immediately after a seizure or during a seizure-free period, may reveal a stronger association with cognitive function. HMGB1 may be a general marker of inflammation and disease severity in epilepsy, rather than a specific predictor of cognitive impairment. Higher HMGB1 levels may reflect a more active disease state, which could indirectly contribute to cognitive decline through various mechanisms, such as increased seizure frequency or greater neuronal damage. Cognitive impairment in epilepsy is a complex phenomenon with multiple contributing factors, including the underlying cause of epilepsy, seizure type and frequency, medication side effects, and psychosocial factors. HMGB1 may be just one piece of the puzzle, and its impact on cognitive function may be modulated by these other factors.[15-17]

While the primary focus of this study was on the relationship between HMGB1 and cognitive function in epilepsy patients, exploring the interplay with other variables provides valuable insights into the multifaceted nature of this condition. The observed trends, though not statistically significant, open up avenues for further investigation and highlight the need for a holistic approach to understanding and managing epilepsy. The near-significant p-values for

both age (p=0.069) and duration of epilepsy (p=0.069) hint at a potential cumulative effect on cognitive function. This observation aligns with the growing body of evidence suggesting that both aging and prolonged exposure to epilepsy-related challenges can contribute to cognitive decline. Aging is a natural process associated with gradual changes in brain structure and function. These changes can affect various cognitive domains, including memory, attention, and processing speed. In the context of epilepsy, aging may exacerbate these effects, particularly in individuals with long-standing epilepsy. Epilepsy is characterized by recurrent seizures, which can cause neuronal damage and disrupt brain networks. Over time, the cumulative effects of seizures and the underlying disease process can lead to progressive cognitive decline. The combination of aging and prolonged epilepsy may create a "double hit" on the brain, accelerating cognitive decline. This highlights the importance of early diagnosis and effective seizure control to minimize the long-term impact of epilepsy on cognitive function. The near-significant trend between education level and HMGB1 levels (p=0.132) presents an intriguing puzzle. The observation that higher education was potentially associated with higher HMGB1 levels was unexpected and warrants further exploration. Higher education levels are often associated with higher socioeconomic status, which can influence various lifestyle factors, such as diet, stress levels, and access to healthcare. These factors, in turn, could indirectly affect HMGB1 levels. The concept of cognitive reserve suggests that individuals with higher education levels may have greater resilience to cognitive decline. It is possible that higher HMGB1 levels in this group reflect a compensatory mechanism to counteract the potential negative effects of inflammation on the brain. Other unmeasured factors, such as genetic predisposition, specific epilepsy syndromes, or the presence of other comorbidities, could influence both education level and HMGB1 levels.[18-20]

5. Conclusion

This study investigated the relationship between serum HMGB1 levels and cognitive function in a cohort of 45 epilepsy patients. Contrary to the initial hypothesis, no statistically significant association was found between serum HMGB1 levels and cognitive function. This suggests that HMGB1, as measured in peripheral blood, may not be a primary driver of cognitive impairment in this population. However, trends were observed for age and duration of epilepsy, suggesting that the cumulative effects of these factors may contribute to cognitive decline. An unexpected trend was also observed between education level and HMGB1 levels, warranting further exploration.

6. References

1. Zhou H, Wang N, Xu L, Huang H, Yu C. The efficacy of gastrodin in combination with folate and vitamin B12 on patients with epilepsy after stroke and its effect on HMGB-1, IL-2 and IL-6 serum levels. Exp Ther Med. 2017; 14(5): 4801–6.
2. Paudel YN, Shaikh MF, Chakraborti A, Kumari Y, Aledo-Serrano Á, Aleksovska K, et al. HMGB1: a common biomarker and potential target for TBI, neuroinflammation, epilepsy, and cognitive dysfunction. Front Neurosci. 2018; 12: 628.
3. Shi Y, Zhang L, Teng J, Miao W. HMGB1 mediates microglia activation via the TLR4/NF-κB pathway in coriaria lactone induced epilepsy. Mol Med Rep. 2018.
4. Choi J, Choi SA, Kim SY, Kim H, Lim BC, Hwang H, et al. Association analysis of interleukin-1β, interleukin-6, and HMGB1 variants with postictal serum cytokine levels in children with febrile seizure and generalized epilepsy with febrile seizure plus. J Clin Neurol. 2019; 15(4): 555–63.
5. Han Y, Yang L, Liu X, Feng Y, Pang Z, Lin Y. HMGB1/CXCL12-mediated immunity and Th17 cells might underlie highly suspected

autoimmune epilepsy in elderly individuals. Neuropsychiatr Dis Treat. 2020; 16: 1285–93.
6. Huang Q, Liu J, Shi Z, Zhu X. Correlation of MMP-9 and HMGB1 expression with the cognitive function in patients with epilepsy and factors affecting the prognosis. Cell Mol Biol (Noisy-le-grand). 2020; 66(3): 39–47.
7. Wang S, Guan Y, Li T. The potential therapeutic role of the HMGB1-TLR pathway in epilepsy. Curr Drug Targets. 2021; 22(2): 171–82.
8. Dai S, Zheng Y, Wang Y, Chen Z. HMGB1, neuronal excitability and epilepsy. Acta Epileptologica. 2021; 3(1).
9. Zhang S, Chen F, Zhai F, Liang S. Role of HMGB1/TLR4 and IL-1β/IL-1R1 signaling pathways in epilepsy. Front Neurol. 2022; 13: 904225.
10. Chen Y, Chen X, Liang Y. Meta-analysis of HMGB1 levels in the cerebrospinal fluid and serum of patients with epilepsy. Neurol Sci. 2023; 44(7): 2329–37.
11. Dai S-J, Shao Y-Y, Zheng Y, Sun J-Y, Li Z-S, Shi J-Y, et al. Inflachromene attenuates seizure severity in mouse epilepsy models via inhibiting HMGB1 translocation. Acta Pharmacol Sin. 2023; 44(9): 1737–47.
12. Almostafa MM, Mohamed ME, Younis NS. Ameliorative effects of vanillin against pentylenetetrazole-induced epilepsy and associated memory loss in mice: The role of Nrf2/HO-1/NQO1 and HMGB1/RAGE/TLR4/NFκB pathways. Int Immunopharmacol. 2024; 129(111657): 111657.
13. Ngadimon IW, Seth EA, Shaikh MF. Exploring the neuroinflammatory pathway in epilepsy and cognitive impairment: Role of HMGB1 and translational challenges. Front Biosci (Landmark Ed). 2024; 29(6): 229.
14. Nugrahanto AP, Triono A, Iskandar K, Wijayanti VW, Herini ES. Increasing serum HMGB1 as a potential biomarker of treatment-resistant epilepsy in children: a case series and literature review. Neurosci Res Notes. 2024; 7(2).
15. Soytürk H, Önal C, Kılıç Ü, Türkoğlu ŞA, Ayaz E. The effect of the HMGB1/RAGE/TLR4/NF-κB signalling pathway in patients with idiopathic epilepsy and its relationship with toxoplasmosis. J Cell Mol Med. 2024; 28(14): e18542.
16. Luan G, Gao Q, Zhai F, Chen Y, Li T. Upregulation of HMGB1, toll-like receptor and RAGE in human Rasmussen's encephalitis. Epilepsy Res. 2016; 123: 36–49.
17. Kamaşak T, Dilber B, Yaman SÖ, Durgut BD, Kurt T, Çoban E, et al. HMGB-1, TLR4, IL-1R1, TNF-α, and IL-1β: novel epilepsy markers? Epileptic Disord. 2020; 22(2): 183–93.
18. Nass RD, Wagner M, Surges R, Holdenrieder S. Time courses of HMGB1 and other inflammatory markers after generalized convulsive seizures. Epilepsy Res. 2020; 162(106301): 106301.
19. Kaya MA, Erin N, Bozkurt O, Erkek N, Duman O, Haspolat S. Changes of HMGB-1 and sTLR4 levels in cerebrospinal fluid of patients with febrile seizures. Epilepsy Res. 2021; 169(106516): 106516.
20. Hautala MK, Mikkonen KH, Pokka TML, Rannikko SK, Koskela UV, Rantala HMJ, et al. Serum HMGB1 in febrile seizures. Epilepsy Res. 2024; 203(107381): 107381.