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Depressive Symptoms and Quality of Life in Adults with Epilepsy: A Moderation Analysis

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Abstract

Objective: This study aimed to investigate the association between depressive symptoms and quality of life (QoL) in adults with epilepsy and to examine whether this relationship differs across clinically relevant subgroups, particularly age at epilepsy onset and antiseizure medication regimen.

Methods: This cross-sectional study included 135 adult patients with epilepsy attending a tertiary outpatient clinic in Türkiye. QoL was assessed using the Quality of Life in Epilepsy Inventory-31 (QOLIE-31), and depressive symptoms were measured with the Neurological Disorders Depression Inventory for Epilepsy. Correlation analyses, multivariate linear regression analyses, and moderation analyses with interaction terms were performed.

Results: The mean QOLIE-31 total score was 59.74±15.24. Depressive symptoms were strongly and inversely correlated with QoL ($r=-0.607$; $p<0.001$) and emerged as the strongest independent predictor in multivariate analysis ($B=-2.57$; $p<0.001$), even after adjusting for clinical variables. Moderation analyses demonstrated that the negative association between depressive symptoms and QoL was significantly stronger in patients with epilepsy onset ≤18 years and in those receiving polytherapy.

Conclusion: Depressive symptoms are a key determinant of QoL in adults with epilepsy, with differential effects across clinical subgroups. These findings highlight the importance of routine depression screening and suggest that patients with early-onset epilepsy and higher treatment burden may require more targeted psychosocial interventions beyond seizure control.

Keywords: Epilepsy, depression, quality of life, antiseizure medications, psychiatric comorbidity

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent and unprovoked seizures, affecting more than 50 million individuals worldwide.[1] Achieving seizure control remains the primary goal of epilepsy treatment. However, it is increasingly recognized that seizure control alone does not fully capture the overall disease burden. Many patients continue to experience impairments in physical, psychological, and social functioning despite adequate seizure management. Therefore, quality of life (QoL) has emerged as a key outcome measure in epilepsy care.[2,3] QoL in epilepsy is a multidimensional construct shaped by the interaction of clinical, psychological, and social factors. Traditional clinical indicators such as seizure frequency, seizure type, disease duration, and antiseizure medication (ASM) burden have been consistently associated with reduced QoL.[4] Nevertheless, accumulating evidence suggests that psychiatric comorbidities—particularly depressive symptoms—may have a stronger and more persistent impact on QoL than seizure-related variables.[5,6] Depression is more prevalent in people with epilepsy compared to the general population and is associated with increased functional impairment, poorer treatment adherence, and greater healthcare utilization.[7] Numerous studies have demonstrated a strong inverse relationship between depressive symptoms and QoL in individuals with epilepsy, often identifying depression as one of the most important independent predictors of patient-reported outcomes.[6-8] Despite this, depression remains underrecognized and undertreated in clinical practice. This may be due to symptom overlap between epilepsy-related cognitive complaints and depressive features, as well as the prioritization of seizure control over psychosocial assessment in routine care.[9] As a result, depressive symptoms may be overlooked, leading to substantial impairment in QoL even among patients with relatively well-controlled seizures. Although the association between depression and QoL in epilepsy is well established, most previous studies have assumed a homogeneous effect across patient populations. This approach may overlook clinically meaningful heterogeneity, particularly in subgroups characterized by early disease onset or increased treatment burden. Evidence examining such effect modification remains limited, and its implications for clinical decision-making are not yet well defined. Early-onset

epilepsy may interfere with psychosocial development, education, and coping mechanisms, while polytherapy is often associated with increased treatment complexity and cumulative side-effect burden. These factors may amplify the negative impact of depressive symptoms on QoL.[10] Epilepsy also represents a significant public health concern in Türkiye, with prevalence rates comparable to global estimates. Despite advances in antiseizure treatment, many patients continue to experience substantial psychosocial burden, including stigma, limited access to mental health services, and underrecognition of psychiatric comorbidities such as depression. These contextual factors may influence not only the detection of depressive symptoms but also their impact on QoL. Therefore, investigating the relationship between depression and QoL in the national population with epilepsy is essential for developing context-specific, patient-centered care strategies.

Therefore, this study aimed to investigate the association between depressive symptoms and QoL in adults with epilepsy and to determine whether this relationship varies across clinically relevant subgroups. Specifically, we examined the moderating roles of age at epilepsy onset and ASM regimen. By identifying subgroups in which the burden of depressive symptoms is disproportionately high, this study seeks to contribute to more targeted, individualized approaches to epilepsy care.

METHODS

Study Design and Participants

This was a single-center, cross-sectional, observational study conducted at a tertiary epilepsy outpatient clinic in Türkiye. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The cross-sectional design was chosen to explore associations between depressive symptoms and QoL, as well as potential effect modifiers, without inferring causality. A total of 135 adult patients with epilepsy were included. Eligible participants were aged 18 years or older, had a confirmed diagnosis of epilepsy, and had been receiving ASM for at least one year. All participants were required to be literate and to provide written informed consent.

Exclusion criteria included a history of cerebrovascular disease, a craniotomy within the past year, severe systemic illness affecting QoL, and significant cognitive impairment that would interfere with questionnaire completion. Patients with severe psychiatric disorders were also excluded; however, prior history of depression and psychotropic medication use was not systematically recorded.

Clinical Variables

Demographic and clinical data were collected through face-to-face interviews and medical record review. The variables included: age, sex, education level, marital status, employment status, age at epilepsy onset, disease duration, seizure type, seizure frequency, and ASM regimen. Seizures were classified according to the International League Against Epilepsy classification system as focal or generalized seizures.[11] Age at epilepsy onset was categorized as ≤18 years or >18 years. Seizure frequency in the previous year was categorized as seizure-free, 1-9 seizures, 10-20 seizures, and ≥21 seizures/year. These categories were based on commonly used groupings in clinical practice and prior QoL studies. Epilepsy duration was categorized as <5 years, 5-10 years, and >10 years, consistent with clinically meaningful groupings commonly used in previous epilepsy QoL studies.[3,4] The ASM treatment regimen was classified as monotherapy or polytherapy. Although specific medication-level analysis was not performed, different ASMs may have variable effects on mood and depressive symptoms.

MAIN POINTS

- Depressive symptoms are the most significant independent determinant of quality of life in people with epilepsy.
- The negative impact of depression on quality of life is more pronounced in patients with early-onset epilepsy and those receiving polytherapy.
- Routine depression screening may contribute to improved quality of life beyond seizure control, particularly in clinically vulnerable subgroups.

Instruments

QoL was assessed using the Turkish version of the Quality of Life in Epilepsy Inventory-31 (QOLIE-31), a validated epilepsy-specific instrument. The QOLIE-31 consists of seven subscales: seizure worry, overall QoL, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning. Scores range from 0 to 100, with higher scores indicating better QoL.[12] Depressive symptoms were evaluated using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), a validated screening tool consisting of six items, each scored on a 4-point Likert scale. A total score above 15 was considered indicative of clinically significant depressive symptoms. To enhance diagnostic accuracy, patients with elevated NDDI-E scores were further evaluated by a psychiatrist experienced in epilepsy.[13]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (Version 20.0) and Jamovi (version 2.5.3). A significance level of $p<0.05$ was adopted. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Normality of the distribution was assessed prior to analysis. Group comparisons were conducted using independent samples t-tests or one-way analysis of variance for normally distributed data, and appropriate non-parametric tests when assumptions were not met. Post-hoc comparisons were performed using Tukey, Games-Howell, or Bonferroni corrections, as appropriate. For analyses involving multiple comparisons, the Bonferroni correction was applied, and statistical significance was set at $p<0.005$.

Correlation analyses (Pearson or Spearman) were used to examine associations between QOLIE-31 scores and NDDI-E scores. Multivariate linear regression analysis was conducted to identify independent predictors of QoL. Moderation analyses were performed using interaction terms to evaluate whether the relationship between depressive symptoms and QoL was modified by age at epilepsy onset and ASM treatment regimen. Given the exploratory nature of these analyses, the findings were interpreted cautiously. A post-hoc power analysis indicated that the sample size provided >80% statistical power to detect moderate effect sizes in regression analyses. Due to the low rate of missing data, analyses were conducted using a complete-case approach.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee (approval no: 2625/128, date: 08.06.2023). Written informed consent has been obtained from the patients to publish this paper.

RESULTS

Demographic and Clinical Characteristics

The mean age of the 135 patients included in the analysis was 33.0±13.48 years (range: 18-68). Overall, 61.5% of the patients were male (n=83), and 38.5% were female (n=52). Their demographic characteristics, including education level, employment status, and marital status, are presented in Table 1. Analysis of clinical characteristics showed that 58.5% of patients had generalized epilepsy and 41.5% had focal epilepsy. The age at onset of epilepsy was ≤18 years in approximately half of the patients (49.6%). Regarding seizure frequency in the last year, 38.5% of the patients had no seizures, 43.7% had 1-9 seizures, 6.7% had 10-20 seizures, and 11.1% had ≥21 seizures. Regarding ASM treatment, the majority of patients received monotherapy (90.4%), whereas 9.6% received polytherapy. Epilepsy duration <5 years was 39.3%, that of 5-10 years was 31.1%, and that >10 years was 29.6%.

Table 1. Sociodemographic characteristics and clinical characteristics of the study population (n=135)

	Category	n (%)
Sex	**Male**	83 (61.5%)
	Female	52 (38.5%)
Marital status	**Single**	56 (41.5%)
	Married	79 (58.5%)
Seizure type	Focal	56 (41.5%)
	Generalized	79 (58.5%)
Age at onset	≤18 years	67 (49.6%)
	>18 years	68 (50.4%)
ASM regimen	Monotherapy	122 (90.4%)
	Polytherapy	13 (9.6%)
Number of seizure attacks in the previous year	Seizure-free	52 (38.5%)
	1-9 episodes/year	59 (43.7%)
	10-20 episodes/year	9 (6.7%)
	≥ 21 episodes	15 (11.1%)
Epilepsy duration	<5 years	53 (39.3%)
	5-10 years	42 (31.1%)
	>10 years	40 (29.6%)
	Mean ± SD	Range
Age (years)	33.0±13.48	18-68

Clinical variables were extracted from medical records. ASM: Antiseizure medication SD: Standard deviation

QOLIE-31 Descriptive Results

The total QOLIE-31 score was 59.74±15.24, indicating an overall decreased QoL. Among the sub-dimensions, the highest mean score was observed in the social functioning domain (67.57), and the lowest in the energy/fatigue domain (45.74). The internal consistency of the total and subscale QOLIE-31 scores was high (Cronbach's alpha =0.82), indicating that the scale was reliable in the study population (Table 2).

The Relationship Between Depressive Symptoms and Quality of Life

A strong, statistically negative correlation was found between NDDI-E scores and the total QOLIE-31 score (r=-0.607; p<0.001) (Figure 1). Similarly, the seizure anxiety, general QoL, emotional well-being, energy/fatigue, cognitive functioning, and social functioning subscales all showed significant inverse correlations with NDDI-E scores (all p<0.005). The relationship between the medication effects subscale and depressive symptoms was weaker than that observed for other domains (Figure 2).

Table 2. Descriptive statistics of QOLIE-31 total score and subscales

Domain	Mean ± SD	Cronbach's α
SW	62.09±30.51	0.85
OQoL	59.57±16.14	0.86
EWB	53.63±18.29	0.85
E/F	45.74±21.19	0.85
COG	62.74±19.74	0.85
MED	59.11±25.54	0.87
SOC	67.57±21.12	0.84
Overall score	59.74±15.24	0.82

Higher scores indicate better quality of life. COG: Cognitive, E/F: Energy/fatigue, EWB: Emotional well-being, MED: Medication effects, OQoL: Overall quality of life, SOC: Social function, SW: Seizure worry, QOLIE-31: Quality of Life in Epilepsy Inventory-31

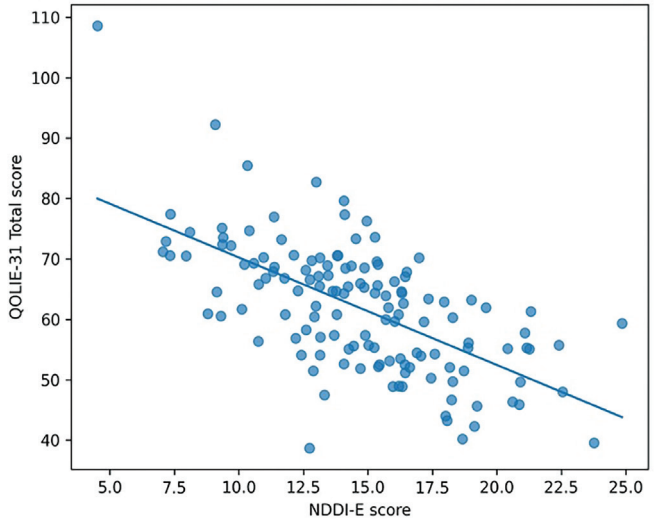

Figure 1. Association between depressive symptoms and overall quality of life. Each dot represents an individual patient. The solid line represents the fitted linear regression, indicating an inverse relationship between NDDI-E scores and QOLIE-31 total scores
QOLIE-31: Quality of Life in Epilepsy Inventory-31, NDDI-E: Neurological Disorders Depression Inventory for Epilepsy

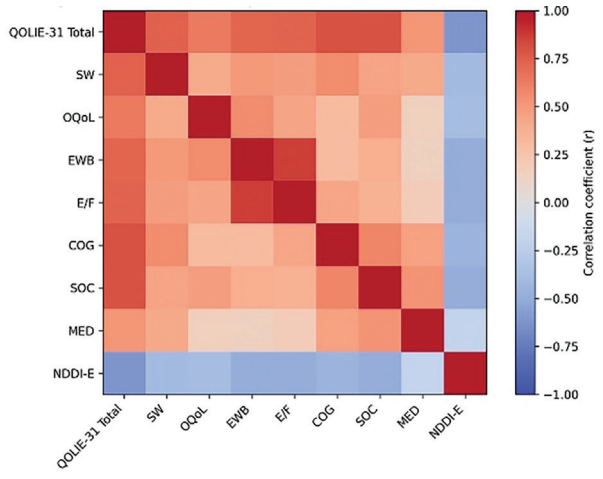

Figure 2. Correlation heatmap between QOLIE-31 domains and NDDI-E. Colors represent Pearson correlation coefficients, with warmer tones indicating positive correlations and cooler tones indicating negative correlations. Higher NDDI-E scores were consistently associated with lower QOLIE-31 total and subdomain scores
QOLIE-31: Quality of Life in Epilepsy Inventory-31, NDDI-E: Neurological Disorders Depression Inventory for Epilepsy, SW: Seizure worry, OQoL: Overall quality of life, EWB: Emotional well-being, E/F: Energy/fatigue, COG: Cognitive function, SOC: Social function, MED: Medication effects

Clinical and Demographic Factors Affecting Quality of Life

The total and subscale QOLIE-31 scores differed significantly across various clinical and demographic variables (Table 3). Male patients had significantly lower scores on total QoL and most subscales than female patients (all p<0.01). Generalized epilepsy was associated with lower total QOLIE-31 scores (p=0.008). QoL decreased gradually with increasing seizure frequency. Seizure-free patients had the highest total QOLIE-31 scores (67.32±14.38), while patients with ≥21 seizures per year showed the lowest scores (53.30±14.28; p<0.001) (Figure 3). Similarly, QoL was significantly lower in patients with an epilepsy duration >10 years compared with those with a duration <5 years (p=0.002).

Table 3. Comparison of QOLIE-31 total scores according to key variables

Variable	Group	Mean ± SD	p-value	ES
Sex	Male	55.61±13.86	<0.001	0.118
	Female	66.35±15.13		
Seizure type	Focal	63.28±15.02	0.008	0.052
	Generalized	57.02±14.91		
Antiseizure medication	Monotherapy	59.95±14.88	0.624	0.002
	Polytherapy	57.76±18.89		
Seizure frequency (last year)	Seizure-free	67.32±14.38	<0.001	0.116
	1-9 seizures	59.41±13.77		
	10-20 seizures	55.02±14.61		
	≥21 seizures	53.30±14.28		
Epilepsy duration	<5 years	63.91±14.83	0.002	0.090
	5-10 years	60.24±14.67		
	>10 years	54.86±15.21		

Group comparisons were performed using appropriate parametric tests. SD: Standard deviation, ES: Effect size, QOLIE-31: Quality of Life in Epilepsy Inventory-31

Multivariate Analyses

In multivariate linear regression analyses, NDDI-E score was found to be the strongest independent predictor of total QOLIE-31 score (unstandardized B=-2.57; p<0.001). This relationship remained significant after adjustment for seizure frequency, seizure type, epilepsy duration, age, and gender. The effect of depressive symptoms on QoL was more pronounced than that of traditional epilepsy-related clinical variables (Table 4).

Moderation Analyses

Age at epilepsy onset appeared to modify the association between depressive symptoms and QoL. Although age at onset alone was not associated with QoL (p=0.653), the interaction term between NDDI-E and age at onset was statistically significant (B=1.19; p=0.033). This finding suggests that the association between depressive symptoms and QoL may differ according to age at epilepsy onset, with a more pronounced negative association observed among patients whose epilepsy began at age ≤18 years.

Similarly, the interaction between depressive symptoms and the ASM treatment regimen was statistically significant (B=-4.30; p=0.001), whereas the ASM regimen alone was not associated with QoL (p=0.904). This result suggests that the ASM regimen may

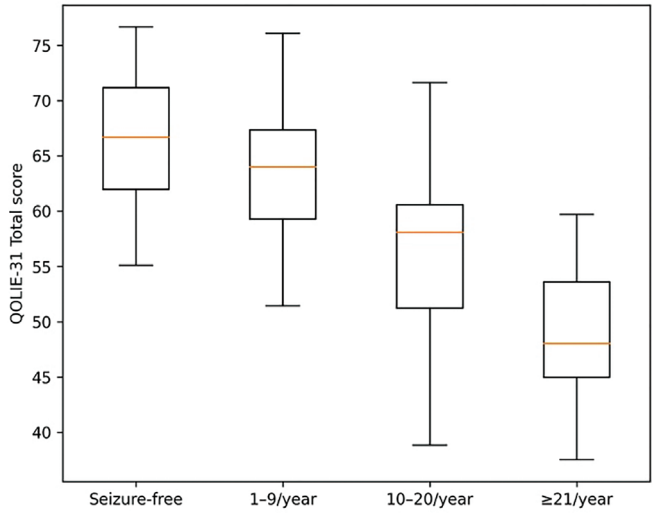

Figure 3. Distribution of QOLIE-31 total scores according to seizure frequency. Patients with higher seizure frequency exhibited progressively lower QOLIE-31 total scores
QOLIE-31: Quality of Life in Epilepsy Inventory-31

Table 4. Multivariable linear regression analysis for QOLIE-31 total score

Variable	Standardized β	95% CI for β	p-value
NDDI-E score	-0.57	-0.70 to -0.44	<0.001
Seizure frequency	-0.21	-0.35 to -0.07	0.004
Seizure type (generalized)	-0.18	-0.33 to -0.03	0.018
Epilepsy duration (years)	-0.15	-0.27 to -0.03	0.011
Sex (male)	-0.14	-0.26 to -0.02	0.021
Age (years)	-0.09	-0.22 to 0.04	0.172

Standardized regression coefficients (β) are reported. Negative β values indicate lower QOLIE-31 total scores. NDDI-E: Neurological Disorders Depression Inventory for Epilepsy, QOLIE-31: Quality of Life in Epilepsy Inventory-31, CI: Confidence interval

play in the relationship between depressive symptoms and QoL. However, given the relatively small number of patients receiving polytherapy, this finding should be interpreted with caution and considered exploratory (Table 5).

DISCUSSION

This study examined the relationship between depressive symptoms and QoL in adults with epilepsy and explored whether this association differs across clinically relevant subgroups. The findings demonstrate that QoL is substantially reduced in this population and that depressive symptoms are strongly and consistently associated with poorer QoL outcomes. Notably, depressive symptoms emerged as the strongest independent predictor of QoL, even after adjusting for key clinical variables such as seizure frequency and disease duration. These results are consistent with a growing body of literature indicating that psychiatric comorbidities, particularly depression, may play a more central role in determining patient-reported outcomes than traditional epilepsy-related clinical factors. While seizure control remains a primary therapeutic goal, the present findings support the view that psychosocial dimensions are critical determinants of overall disease burden.[14-16] At the subdomain level, depressive symptoms were associated with impairments across multiple dimensions of QoL, particularly emotional well-being, energy/fatigue, and cognitive and social functioning. In contrast, the relatively weaker association observed in the medication effects domain suggests that reduced QoL cannot be explained solely by pharmacological burden. Instead, these findings highlight the broader psychosocial impact of depressive symptoms in epilepsy.[17-20] A key contribution of this study is the demonstration that the relationship between depressive symptoms and QoL is not uniform across all patients. Moderation analyses indicated that this association was more pronounced in individuals with early-onset epilepsy and in those receiving polytherapy. Although these findings should be interpreted cautiously, particularly given the relatively small number of patients in the polytherapy subgroup, they nevertheless point toward the presence of clinically meaningful heterogeneity rather than a uniform effect. Given that only 13 patients were receiving polytherapy, the observed moderation effect should be considered exploratory and hypothesis-generating. Therefore, the robustness and generalizability of this finding are limited and require confirmation in larger independent cohorts. Early-onset epilepsy may be associated with long-standing disruptions in psychosocial development, educational attainment, and the formation of adaptive coping strategies. Epilepsy that begins during critical developmental periods can interfere with identity formation, peer relationships, and academic progression, potentially leading to cumulative psychosocial disadvantage over time. These long-term effects may render individuals more vulnerable to the detrimental impact of depressive symptoms in adulthood. These interpretations are consistent with previous literature.[21,22] Similarly, the moderating effect observed for the ASM regimen suggests that polytherapy may represent more than a simple increase in medication count. Rather, it may reflect greater disease severity, increased treatment complexity, and a higher cumulative burden of adverse effects. The interaction between depressive symptoms and polytherapy indicates that biological burden and psychological vulnerability may act synergistically, leading to a disproportionate reduction in QoL.[23-26] From a clinical perspective, these findings support a shift toward a more individualized and stratified approach to epilepsy care. Instead of conceptualizing depression as a uniform comorbidity, it may be more appropriate to consider it as a differential risk factor with varying impact across patient subgroups. In particular, individuals with early-onset epilepsy and those receiving polytherapy may represent high-risk populations in whom depressive symptoms have a disproportionately large effect on QoL. These findings support targeted psychosocial assessment and intervention strategies.[27-30] An important methodological strength of this study is that depressive symptoms were not assessed solely through a self-reported screening instrument. Instead, NDDI-E findings were supported by clinical evaluation conducted by a psychiatrist experienced in epilepsy. This approach reduces the likelihood of misclassification and enhances the clinical validity of the observed associations.

Table 5. Moderation analysis: interaction effects on QOLIE-31 total score

Interaction term	β	p-value
NDDI-E × age at onset (≤18 years)	1.19	0.033
NDDI-E × ASM regimen	-4.30	0.001

Significant interaction terms indicate moderation effects. Unstandardized regression coefficients (B) are reported. ASM: Antiseizure medication, NDDI-E: Neurological Disorders Depression Inventory for Epilepsy, QOLIE-31: Quality of Life in Epilepsy Inventory-31

Study Limitations

Nevertheless, several limitations should be acknowledged. First, due to the cross-sectional design, causal relationships cannot be established. Second, the relatively small number of patients in the polytherapy subgroup may limit the robustness of moderation analyses. Third, the absence of a healthy control group restricts direct comparisons with the general population. Additionally, variables such as anxiety, sleep disturbances, and social support were not systematically evaluated. Despite these limitations, the study provides clinically meaningful insights by integrating multivariate and moderation analyses within a real-world clinical sample.

CONCLUSION

The current study shows that depressive symptoms are strongly associated with reduced QoL in adults with epilepsy, irrespective of important clinical variables such as seizure frequency and duration of the disease. Importantly, this relationship appears to differ across clinically relevant subgroups, with a more robust association observed in patients with early-onset epilepsy and in patients receiving polytherapy. The findings underscore the need for regular screening for depression as part of the management of people with epilepsy. Rather than a one-size-fits-all approach, clinicians may prioritize psychosocial assessment for patients with greater clinical vulnerability. Due to the cross-sectional design, results should be interpreted as associative rather than causal. Further longitudinal studies are needed to better understand the directionality of this relationship and to evaluate the effectiveness of targeted psychosocial interventions. The current study advocates a more comprehensive, individualized approach to epilepsy management that extends beyond seizure control to include mental health as a fundamental component of patient care.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee (approval no: 2625/128, date: 08.06.2023).

Informed Consent: Written informed consent has been obtained from the patients to publish this paper.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.S.Ş., S.P., Concept: Z.S.Ş., Design: Z.S.Ş., S.P., H.B., Data Collection or Processing: Z.S.Ş., S.P., Analysis or Interpretation: Z.S.Ş., H.B., Literature Search: Z.S.Ş., S.P., H.B., Writing: Z.S.Ş.

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

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