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Predictors of quality of life and their interrelations in Korean people with epilepsy: A MEPSY study

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ABSTRACT

Purpose: People with epilepsy (PWE) are more likely to have impaired quality of life (QOL) than the general population. We studied predictors of QOL and their interrelations in Korean PWE.
Methods: Subjects who consecutively visited outpatient clinics in four tertiary hospitals and one secondary care hospital were enrolled. These subjects completed the Korean version of the Neurological Disorders Depression Inventory for Epilepsy (K-NDDI-E), the Generalized Anxiety Disorder-7 (GAD-7), the Quality of Life in Epilepsy-10 (QOLIE-10), and the Korean version of Liverpool Adverse Event Profile (K-LAEP). We evaluated the predictors of QOL by multiple regression analyses and verified the interrelations between the variables using a structural equation model.
Results: A total of 702 PWE were eligible for the study. The strongest predictor of the overall QOLIE-10 score was the K-LAEP score ($\beta = -0.375$, $p < 0.001$), followed by the K-NDDI-E score ($\beta = -0.316$, $p < 0.001$), seizure control ($\beta = -0.152$, $p < 0.001$), household income ($\beta = -0.375$, $p < 0.001$), and GAD-7 score ($\beta = -0.119$, $p = 0.005$). These variables explained 68.7% of the variance in the overall QOLIE-31 score. Depression and seizure control had a bidirectional relationship and exerted direct effects on QOL. These factors also exerted indirect effects on QOL by provoking adverse effects of AEDs. Anxiety did not have a direct effect on QOL; it had only indirect effect through the adverse effects of AEDs.
Conclusion: Depression, anxiety, seizure control, and adverse effects of AEDs have complex interrelations that determine the QOL of PWE.

1. Introduction

People with epilepsy (PWE) appear to have poorer quality of life (QOL) than the general population not only because of the seizures but also because of comorbid conditions such as medical, psychiatric, and psychosocial problems.[1] Moreover, when PWE take an antiepileptic drug (AED) for a period of time, that drug can elicit adverse effects that further impair their QOL.[2] For these reasons, the identification of predictors of reduced QOL in PWE is critical for improving the targeting and optimization of existing and emerging interventions and management strategies for epilepsy.[3]

Predictors of QOL in PWE have been thoroughly summarized in a systematic review from the UK.[3] This review included 93 QOL studies that were identified by Medline, Embase, and Cochrane Library searches up to July 2010. Increases in seizure frequency, seizure severity, levels of depression, levels of anxiety, and the

Abbreviations: PWE, people with epilepsy; QOL, quality of life; AED, antiepileptic drug; TLE, temporal lobe epilepsy; WCE, well-controlled epilepsy; PCE, poorly controlled epilepsy; UCE, uncontrolled epilepsy; PDD, prescribed daily dose; DDD, defined daily dose; K-NDDI-E, Korean version of the Neurological Disorders Depression Inventory for Epilepsy; GAD-7, Generalized Anxiety Disorder-7; K-LAEP, Korean version of Liverpool Adverse Event Profile; QOLIE-10, Quality of Life in Epilepsy-10; NFI, Normed Fit Index; CFI, Comparative Fit Index; GFI, Goodness of Fit Index; RMR, root mean-square residual; LSSS, Liverpool Seizure Severity Scale; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SCID, Structured Clinical Interview for DSM-IV axis I disorders.

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presence of comorbidities were strongly associated with reduced QOL. However, age, gender, marital status, type of seizure, age at diagnosis, and duration of epilepsy were found to be unlikely to be associated with QOL. The predictive values of educational and employment statuses, the number of AEDs and the adverse effects of AEDs for QOL were not determined.

Many studies have consistently reported that the strongest predictors of QOL in PWE are depression and anxiety among various other factors.[4–9] Depression and anxiety have been found to be better predictors that seizure control or the adverse effects of AEDs. However, some studies have reported that other variables have the greatest predictive values. An Italian, multicenter study of people with pharmacoresistant epilepsy reported that the adverse effects of AEDs were the strongest predictor, followed by depression symptoms, pharmacoresistance grade, age, and lack of a driving license.[10] A hospital-based, Chinese study of people with various seizure frequencies also reported the adverse effects of AEDs were the strongest predictor, followed by the number of AEDs, depression symptoms, and anxiety symptoms.[11] A hospital-based, Russian study found seizure frequency to be a stronger predictor of QOL than depression; indeed, seizure frequency was found to be the strongest predictor in that study.[12]

Therefore, the factor with the strongest influence on QOL in PWE has yet to be elucidated.

Depression and anxiety, the adverse effects of AEDs, and seizure control are related to each other. Regarding the relationship between seizure control and depression and anxiety, people with drug-refractory epilepsy have been reported to exhibit higher frequencies of depression and anxiety than those with well-controlled epilepsy.[13,14] Regarding the relationship between the adverse effects of AEDs and depression and/or anxiety, PWE, depression and anxiety, even those presenting with subsyndromic types, are more likely to experience adverse effects of AEDs than those without these disorders.[15] People with pharmacoresistant epilepsy also exhibit higher frequencies of adverse effects of AEDs when they also have depression symptoms.[10] Regarding the relationship between seizure control and the adverse effects of AEDs, seizure control is one of predictors of adverse effects of AEDs in PWE.[16,17] Taken together, these results suggest that complex interrelations between these variables and their contributions to QOL likely exist.

The interrelations between the predictors of QOL in PWE have not been well studied. In an Asian, hospital-based study, the interrelations between the variables in terms of their contributions to QOL were clarified in PWE.[4] Depression, anxiety, seizure control, the number of AEDs, and sleep disturbances had complex interrelations in their contributions to QOL as documented by a structural equation model. However, due to the relatively small sample size, only a limited number of variables could be examined in this study. For example, socioeconomic status, the adverse effects of AEDs, the underlying epilepsy syndrome, and the seizure focus were not considered as variables. Therefore, our aims were to perform a cross-sectional study to determine the predictors of QOL in a large sample of PWE and to clarify their interrelations.

2. Methods

2.1. Subjects

We invited subjects who consecutively visited the epilepsy clinics of secondary and tertiary care hospitals. The subjects were adults between the ages of 20–70 years with current diagnoses of epilepsy who had taken one or more AEDs for at the year prior to recruitment and were capable of providing informed consent and agreeing to the study protocol. Subjects with insufficient information in their medical records, with mental retardation or serious medical, neurological, or psychiatric disorders that prevented them from understanding the questionnaire and cooperating with the study, and those who declined to complete the questionnaires were excluded.

2.2. Study design

The multicenter trial of epilepsy and psychiatric diseases (MEPSY) is a multicenter, cross-sectional study assessing depression, anxiety, suicidality, the burden of the adverse effects of AEDs, and the quality of life of Korean PWE. The subjects were enrolled consecutively beginning in November 2012 at the outpatient epilepsy clinics of four tertiary and one secondary care hospitals in Daegu city, which located in the southern part of Korea. This study was performed as a part of the MEPSY study. The institutional review board of each center approved the study, and all subjects provided written informed consent before participating in the study. The subjects were diagnosed according to the ILAE classification of seizures and epileptic syndromes.[18,19] All patients were interviewed by trained epileptologists who also reviewed the subjects' medical charts to collect demographic, socioeconomic, and clinical information, which was entered into a computerized database. The socioeconomic variables included the following: having a job versus not having a job; earning at least one million Korean won (KRW) per month (equivalent to US$ 900 per month) versus earning less than one million KRW per month; having a driving license versus not having a driving license; and being married versus being divorced, bereaved, or unmarried. The clinical variables included the following: age at onset, disease duration, seizure type, etiology, epilepsy syndrome, seizure control, MRI abnormality, history of febrile convulsion, family history of epilepsy, duration of AED intake, AED therapy regimen, and AED load. We divided the etiologies into idiopathic/cryptogenic and symptomatic epilepsy. We divided the epileptic syndromes into four groups: temporal lobe epilepsy (TLE), extraTLE, generalized epilepsy, and unknown syndromes. extraTLE included epilepsy syndromes in which the epileptic attacks originated from the frontal, parietal, or occipital lobes. We also divided seizure control into three groups: well-controlled epilepsy (WCE), poorly controlled epilepsy (PCE), and uncontrolled epilepsy (UCE). WCE was defined by freedom from seizures over the preceding year. UCE was defined according to the criteria used to determine drug-refractory epilepsy (i.e., the failure of adequate trials of two AEDs, an average of more than one seizure per month for 18 months and no seizure-free periods longer than three months[20]). PCE was defined as an intermediate degree of seizure control that did not meet the criteria for WCE or UCE. The seizure control classification for each PWE was determined based on information about seizure frequency that was obtained from the medical records. The AED load of each individual patient was estimated as the sum of the prescribed daily dose (PDD)/defined daily dose (DDD) ratios for each AED included in the treatment regimen[21] where DDD corresponds to the assumed average maintenance daily dose of a drug that is used for its main indication.[22]

Eligible subjects completed several self-report questionnaires that included the Korean version of the Neurological Disorders Depression Inventory for Epilepsy (K-NDDI-E),[23] the Generalized Anxiety Disorder-7 (GAD-7),[24] the Korean version of the Liverpool Adverse Event Profile (K-LAEP),[17] and the Quality of Life in Epilepsy-10 (QOLIE-10).[25]

2.3. Questionnaires

2.3.1. The Korean version of the Neurological Disorders Depression Inventory for Epilepsy

The K-NDDI-E is a reliable and valid screening tool for the detection of major depression in Korean PWE.[23] This tool consists

of a brief, 6-item questionnaire. The items are rated on a four-point scale that ranges from 1 to 4. Total scores range from 6 to 24, and higher scores indicate more intense depression. The Cronbach's α coefficient is 0.898, and total scores of 12 or greater are suggestive of major depressive disorder.

2.3.2. Generalized Anxiety Disorder-7

The GAD-7 consists of a self-report questionnaire that allows for the rapid detection of GAD.[24] Subjects are asked about how much they have been bothered by anxiety-related problems over the previous two weeks via seven items that they rate on a four-point scale. Total GAD-7 score range from 0 and 21, and total scores of 10 or greater are considered to indicate the presence of GAD. We used a version of the GAD-7 that has been translated into a Korean language and is freely downloadable on the Patient Health Questionnaire website (www.phqscreeners.com).[26]

2.3.3. The Korean version of Liverpool Adverse Event Profile

The K-LAEP is an appropriate instrument for measuring common adverse effects of AEDs that have occurred in the preceding four weeks.[17] The K-LAEP consists of a 19-item questionnaire. Each item is evaluated on a four-point Likert scale on which 1 indicates that the item is never a problem; 2, rarely a problem; 3, sometimes a problem; and 4, always or often a problem. Total scores range from 19 to 76, and higher scores are indicative of greater burdens of the adverse effects. The Cronbach's α coefficient of this instrument is 0.9. In the present analysis, the 21-item version, which includes two additional items (thinking clearly and slurred speech), was used according to the QOL study by Baker et al.[27] Therefore, the AEP scores could range from a minimum of 21 to a maximum of 84. We considered the items that were given three or four points to be related to the adverse effects of AEDs.

2.3.4. 2.3.4 Quality of Life in Epilepsy-10

The Quality of Life in Epilepsy-10 (QOLIE-10) was derived from the QOLIE-31. The Korean version of the QOLIE-10 is a valid screening tool for measuring the QOL of Korean PWE.[25] The QOLIE-10 is comprised of seven components, five of which correspond to single item for each of five subscales (seizure worry, overall QOL, emotional well-being, energy/fatigue, and cognitive functioning), one component includes two items about the effects of medications (physical effects and mental effects), and the last component includes three items about social functioning (work, driving, and social limitations). The ten items of the QOLIE-10 were grouped into two factors: Epilepsy Effects/Role Functioning (i.e., driving, social, work, physical, mental, and memory effects) and Mental Health (i.e., overall quality of life, depression, and energy). The Cronbach's α was 0.843 for the Epilepsy Effects/Role Functioning subscale and 0.606 for the Mental Health subscale. The QOLIE-10 was significantly correlated with the source scales of the Korean version of the QOLIE-31.

2.4. Statistical analyses

Data from continuous variables are expressed as the mean ± the SD values, and those for categorical variables are expressed as frequencies. Not only demographic, socioeconomic, and clinical variables but also the questionnaire scores were included as independent variables to measure the predictors of the QOLIE-10 overall and subscale scores by multiple linear regression analyses with stepwise selection. The probabilities of entry and exit were 0.05 and 0.1, respectively. Collinearity was addressed by performing collinearity statistical analyses. Variables selected from the linear regression analyses were used to construct a structural equation model to test the interrelations between the variables and the QOLIE-10 overall score. Based on a review of previous studies,[4–17] we developed a hypothetical model that outlined the paths of depression, anxiety, seizure control, the adverse effects of AEDs, and socioeconomic burden to QOL. We hypothesized that all of these variables directly influenced QOL directly and that depression, anxiety, and seizure control influenced QOL indirectly through the mediation of the adverse events of AEDs. The hypothesized path model was tested with structural equation modeling. The model fit was evaluated using path analysis, which is a method that estimates the relative importances of the different paths of the independent variables onto the dependent variables. An acceptable model fit was defined by the presence of a nonsignificant chi-square (χ^2) value, a normed fit index (NFI) $\geq$0.9, a comparative fit index (CFI) $\geq$0.9, a goodness of fit index (GFI) $\geq$0.9, and a root mean square residual (RMR) $\leq$0.05. Structural equation modeling was used to estimate the total effect of each predictor to establish a linear model for the prediction of the overall QOLIE-10 score that accounted for these interrelations. With the exception of the structural equation model, all statistical analyses were conducted with SPSS (version 19.0, IBM Inc.). LISREL 8.8 for Windows (SSI Inc., Skokie, IL, USA) was used for the path and structural equation modeling components of the analysis. The level of statistical significance was set at 0.05.

3. Results

Initially, 861 PWE were enrolled in the study. Among these PWE, 159 were excluded due to refusal to complete the questionnaires (n = 34), inability to complete the questionnaires due to mental retardation (n = 49) or serious diseases (n = 50), young age (n = 5), and old age (n = 21). Therefore, 702 PWE (mean age: 41 years; 57.7% male) were included. The demographic and clinical characteristics and the results of the self-report questionnaires of the eligible subjects are listed in Table 1. Approximately 50% of the patients had a job and a driving license. Concurrent medical diseases were present in 147 patients (20.9%) and included diabetes and other endocrinologic disorders (n = 41), hypertension and other cardiovascular disorders (n = 37), cerebrovascular disease and other neurologic disorders (n = 24), hepatic and gastrointestinal disorders (n = 20), renal disorders (n = 8), and other diseases (n = 48). Partial onset of seizures and cryptogenic or symptomatic etiologies accounted for greater proportions than did generalized seizure and idiopathic etiology. Sixty-one percent of the patients had experienced one year of seizure freedom. MRI abnormalities were found in 281 patients (40%), and the etiologies of these abnormalities were hippocampal sclerosis (n = 79), vascular lesions (n = 54), traumatic injury (n = 48), congenital anomalies (n = 45), infection (n = 37), tumor (n = 8), and others (n = 34). The duration of AED intake was 13.9 ± 10.7 years (range: 1–54 years). Nearly 50% of the patients had received AED monotherapy. The AED load was 1.5 ± 1.2 (range 0.1–7.7). The K-NDDI-E, GAD-7, and K-LAEP scores were 9.7 ± 4.1 (range 6–24), 4.1 ± 4.9 (range 0–21), and 34.0 ± 12.4 (range 21–81), respectively. The QOLIE-10 overall score was 76.1 ± 18.2 (range 3–100).

The predictors of the overall QOLIE-10 score from the multiple linear regression analyses are documented in Table 2. The strongest predictor was the K-LAEP score (β = −0.375, $p < 0.001$), followed by the K-NDDI-E score (β = −0.316, $p < 0.001$), seizure control (β = −0.152, $p < 0.001$), the GAD-7 score (β = −0.119, p = 0.005), and household income (β = −0.101, $p < 0.001$). Stepwise regression produced a five-variable model that explained 68.7% of the variance in the overall QOLIE-10 score. According to the standardized β, the contribution of the K-LAEP score to the overall QOLIE-10 score was 1.19 times greater than that of the K-NDDI-E score, 2.47 times greater than that of seizure control, 3.15 times greater than that of the GAD-7 score, and 3.71 times greater than that of household income. The variance inflation

Table 1
Demographic and clinical characteristics and results from the self-report questionnaires of the eligible subjects ($n = 702$).

Characteristic	Mean ± SD (range) or number (%)
Age, years	41.0 ± 12.5 (20–70)
Gender, male	405 (57.7)
Education, years	12.2 ± 3.3 (0–20)
Job, yes	323 (46.0)
Household income, at least 1 million KRW/month	546 (77.8)
Driving license, yes	371 (52.8)
Married but no divorce or bereavement	358 (51.0)
Concurrent medical disease, yes	147 (20.9)
Age at onset, years	24.3 ± 14.5 (0–68)
Disease duration, years	16.7 ± 11.8 (1–57)
Seizure type, partial	558 (79.5)
Etiology, cryptogenic or symptomatic	488 (69.5)
Epilepsy syndrome	
Temporal lobe epilepsy	253 (36.0)
Extratemporal lobe epilepsy	281 (40.0)
Generalized epilepsy	137 (19.5)
Unknown	31 (4.4)
Seizure control	
Well-controlled epilepsy	429 (61.1)
Poorly controlled epilepsy	178 (25.4)
Uncontrolled epilepsy	95 (13.5)
MRI abnormality, abnormal	281 (40.0)
History of febrile convulsion	130 (18.5)
Family history of epilepsy	56 (8.0)
Duration of AEDs intake, years	13.9 ± 10.7 (1–54)
Number of AEDs	
Monotherapy	345 (49.2)
Duotherapy	206 (29.3)
Triple or more AEDs	151 (21.5)
AED load	1.5 ± 1.2 (0.1–7.7)
K-NDDI-E score	9.7 ± 4.1 (6–24)
GAD-7 score	4.1 ± 4.9 (0–21)
K-LAEP score	34.0 ± 12.4 (21–81)
QOLIE-10	
Epilepsy effect	83.6 ± 21.8 (0–100)
Mental health	57.1 ± 22.0 (0–100)
Role function	84.9 ± 19.8 (6.3–100)
Overall score	76.1 ± 18.2 (3–100)

KRW: Korean won, MRI: magnetic resonance imaging, AEDs: antiepileptic drugs, K-NDDI-E: Korean version of the Neurological Disorders Depression Inventory for Epilepsy, GAD-7: Generalized Anxiety Disorder-7, K-LAEP: Korean version of the Liverpool Adverse Event Profile, QOLIE-10: Quality of Life in Epilepsy-10.

factors (VIF) were less than 10 for all four variables, which suggests that they exerted independent effects without redundancy. Although the adverse effects of AEDs significantly determined QOL, the duration of AED intake, AED regimen, and AED load did not contribute to the QOL.

The predictors of the QOLIE-10 subscale scores according to the multiple linear regression analyses are shown in Table 3. The strongest predictors of the Epilepsy Effects and Role Functioning subscale scores were the K-LAEP score followed by the K-NDDI-E score. In contrast, the strongest predictors of the Mental Health subscale score were the K-NDDI-E score followed by the K-LAEP score. AED load was the third best predictor of the Epilepsy Effects subscale score, whereas seizure control was the third best predictor of the Mental Health and Role Functioning subscale score. The contribution of the K-LAEP score to the Epilepsy Effects subscale score was 2.89 times greater than that of the K-NDDI-E score. The contribution of the K-LAEP score to the Role Functioning subscale score was 1.17 times greater than that of the K-NDDI-E score. The contribution of the K-NDDI-E score to the Mental Health subscale score was 2.31 times greater than that of the K-LAEP score.

Table 2
Predictors of the overall QOLIE-10 score based on stepwise multiple linear regression analyses.

Variable	Standardized coefficient β	Significance	Collinearity (VIF)	Adjusted R^2
				0.687
K-LAEP score	−0.375	<0.001	2.411	
K-NDDI-E score	−0.316	<0.001	3.172	
Seizure control	−0.152	<0.001	1.164	
Household income	−0.101	<0.001	1.118	
GAD-7 score	−0.119	0.005	3.538	

QOLIE-10: Quality of Life in Epilepsy-10, K-LAEP: Korean version of the Liverpool Adverse Event Profile, K-NDDI-E: Korean version of the Neurological Disorders Depression Inventory for Epilepsy, GAD-7: Generalized Anxiety Disorder-7.

Table 3
Predictors of the QOLIE-10 subscale scores based on stepwise multiple linear regression analyses.

Subscale and variable	Standardized coefficient β	Significance	Collinearity (VIF)	Adjusted R^2
Epilepsy Effects				0.521
K-LAEP score	−0.544	<0.001	1.962	
K-NDDI-E score	−0.188	<0.001	1.971	
AED load	−0.109	<0.001	1.07	
Mental Health				0.505
K-NDDI-E score	−0.395	<0.001	3.143	
K-LAEP score	−0.171	<0.001	2.413	
Seizure control	−0.127	<0.001	1.103	
GAD-7 score	−0.155	0.004	3.563	
Age	−0.078	0.007	1.009	
Role Functioning				0.579
K-LAEP score	−0.304	<0.001	2.434	
K-NDDI-E score	−0.26	<0.001	3.175	
Seizure control	−0.176	<0.001	1.168	
Household income	−0.176	<0.001	1.2	
GAD-7 score	−0.121	0.015	3.566	
Gender	0.065	0.015	1.024	
Age	0.061	0.026	1.079	

QOLIE-10: Quality of Life in Epilepsy-10, K-LAEP: Korean version of the Liverpool Adverse Event Profile, K-NDDI-E: Korean version of the Neurological Disorders Depression Inventory for Epilepsy, AED: antiepileptic drug, GAD-7: Generalized Anxiety Disorder-7.

The complex interrelations between the variables and the overall QOLIE-10 score are illustrated in the structure equation model shown in Fig. 1. According to the predefined criteria, the final model provided an excellent fit to the data ($\chi^2 = 5.72$, $p = 0.84$; NFI = 1, CFI = 1, GFI = 0.99, and RMR = 0.011). All regression coefficients were statistically significant ($p < 0.01$). Bidirectional relationships were noted between the K-NDDI-E score and the GAD-7 score and between the K-NDDI-E score and seizure control. The K-NDDI-E score, seizure control, and household income were found to exert direct effects on the overall QOLIE-10 score. In contrast to the hypothesized path model, the GAD-7 score did not directly affect the overall QOLIE-10 score; rather, the GAD-7 score, K-NDDI-E score and seizure control exerted indirect effects on the overall QOLIE-10 score through the K-LAEP score. The GAD-7 score had the strongest effect on the K-LAEP score, followed by the K-NDDI-E score, and seizure control.

4. Discussion

We conducted a multicenter trial to investigate QOL in Korean PWE. Among 702 PWE, the strongest predictor of QOL was the adverse effects of AEDs, followed by depression, seizure control, anxiety, and household income. These variables exhibited complex interrelations in determining QOL. Depression and seizure control had a bidirectional relationship and exerted direct effects on QOL. The variables also exerted indirect effects on QOL by provoking adverse effects of AEDs. Anxiety did not have a direct effect on QOL but had only an indirect effect mediated through adverse effects of AEDs.

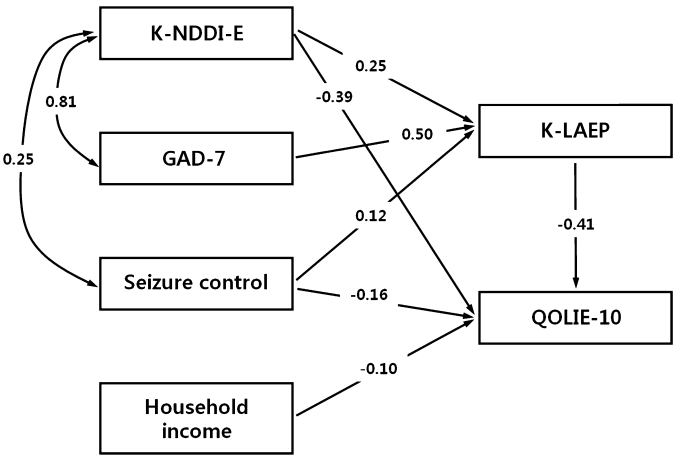

Fig. 1. Interrelations between the clinical variables and the overall Quality of Life in Epilepsy-10 (QOLIE-10) score defined by the structural equation model. Arrows indicate direct relationships of one variable on another. The numbers denote the standardized regression coefficients (beta weights) for each path. Negatively signed coefficients indicate that, when the predictor variable score increases by one standard deviation, the overall QOLIE-10 score decreases by the number of standard deviations indicated by the value of the coefficient. All regression coefficients were statistically significant ($p < 0.01$). K-NDDI-E: Neurological Disorders Depression Inventory for Epilepsy, GAD-7: Generalized Anxiety Disorder-7, K-LAEP: Korean version of Liverpool Adverse Event Profile.

Psychosocial functioning has not been well studied in large samples of PWE. According to a systemic review of 86 QOL studies up to July 2010, the majority of the studies were relatively small (median sample size: 113) cross-sectional studies of people drawn from a single medical center.[3] Because small sample sizes result in low statistical powers, it is critical to involve the participants in the study to the fullest extent possible. We searched the data published in Medline since July 2010 for investigations of the predictors of QOL that involved more than 500 PWE and found only two studies. The first study was a multicenter Italian study of 809 people with pharmacoresistant epilepsy that reported that the adverse effects of AEDs were the strongest predictor, followed by depression symptoms, pharmacoresistance grade, age, and lack of a driving license.[10] Although this study invited only people with drug-refractory epilepsy to participant, its results are similar to our own. The Italian study reported that the contribution of the adverse effects of AEDs to QOL was 1.13 times higher than that of depression symptoms, and this ratio is nearly identical to the ratio we found. However, unlike our study, seizure frequency was not a predictor of QOL in the Italian study. Because meaningful improvements in QOL have been reported only when complete seizure freedom is achieved,[28] it is difficult to anticipate significant improvement in the QOL of people with drug-refractory epilepsy regardless of whether they exhibit low or high seizure frequency. In our study, 61.1% of eligible subjects had WCE; thus, seizure frequency was a predictor of QOL. The Italian study did not include anxiety or household income among the variables that could potentially determine QOL, but we found that these variables were also predictors of QOL. The second study was a hospital-based, US study of 1931 PWE that reported that the two most clinically significant predictors of QOL were seizure severity and depression based on multivariate modeling.[7] In contrast to our study, seizure control was not a significant predictor. In this study, the Liverpool Seizure Severity Scale (LSSS) was used to measure seizure severity; this scale includes patients' perceptions of seizure control, the characteristics of the seizures, the after-effects of the seizures such as loss of consciousness, injury, incontinence, and postictal confusion.[29] Accordingly, the effect of seizure severity on QOL was likely to be stronger than that of seizure control in that study. We could not consider seizure severity as a variable that potentially determined QOL because no instrument that measured seizure severity has yet been developed or validated in Korea. In contrast to our study, the US study did not consider the adverse effects of AEDs or anxiety as variables that could potentially determine QOL. Because these two variables were found to be predictors in our study, a complete study utilizing both of these variables and the LSSS score should be conducted.

One strength of our study is the elucidation of interrelations among the predictors of QOL in a large sample of PWE. Bidirectional relationships were noted between depression and anxiety and between depression and seizure control. The coexistence of depression and anxiety has been well documented in PWE. Among 85 patients with depression or anxiety disorders as diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR), 21 (24.7%) had concurrent depression and anxiety disorders.[15] In a Korean, hospital-based study, 71 of 173 PWE (41%) who exhibited depression or anxiety had combined symptoms.[14] Based on these results, we suggest that depression and anxiety have a bidirectional relationship. A close relationship between depression and seizure control has also been reported. In a retrospective study from the UK, the predictors of pharmacoresistance were investigated in 780 patients with newly diagnosed epilepsy who were followed over a 20-year period.[30] Depression preceding the onset of the seizure disorder was associated with a greater than twofold increase in the risk of developing pharmacoresistant epilepsy. However, the opposite relationship has also been well documented. In a study conducted in two primary care practices in the UK, the frequencies of depression were 33% in patients with frequent seizures and 6% in patients with seizure freedom.[31] In a Korean survey, patients with uncontrolled epilepsy also exhibited higher rates of depression compared to those with poorly controlled or well-controlled epilepsy.[14] Together, these results may reflect the existence of a bidirectional relationship between depression and seizure control. We found that depression, seizure control, and household income exerted direct effects on QOL, which are intuitive results because depression and seizure control have been found to be major predictors of QOL in many studies.[3–12,27,28] Economic variables, including family income, have been evaluated in only a few studies; therefore, there is insufficient information to comment on their associations with QOL.[3] Only two recent studies included economic status as a variable. In a Chinese, hospital-based study, economic status was found to be the third best predictor of QOL followed by seizure severity and age.[32] However, this study did not consider depression or anxiety as variables; thus, it was unable to elucidate the effect of economic status on QOL in relation to these symptoms. In another hospital-based study from Korea, economic status was found to be the fourth best predictor of QOL and was followed by depression, the adverse effects of AEDs, and education level.[6] However, this study examined patients with well-controlled epilepsy; thus, this study could not examine the effect of economic status on QOL in relation to seizure control. Our study demonstrated that economic status was a predictor of QOL independent of depression and seizure control.

One of the interesting findings from the structure equation model clarifies the causal relationships between depression, anxiety, seizure control, and the adverse effects of AEDs. Regarding the relationships between the adverse effects of AEDs and depression or anxiety, two hospital-based studies of PWE with depression and/or anxiety found that these patients are more likely to exhibit adverse effects of AEDs than are those

without these disorders.[10,15] Regarding the relationship between seizure control and the adverse effects of AEDs, seizure control has been found to be one of the predictors that determine the adverse effects of AEDs in PWE.[16,17] However, the causal relationship between the variables was not deduced in those studies. We concluded that depression, anxiety, and seizure control exerted indirect effects on QOL that were mediated by the adverse effects of AEDs. In other words, although the adverse effects of AEDs were the strongest predictor of QOL, their effect on QOL was affected by these other variables. Anxiety did not directly influence QOL, but it had an indirect effect on QOL that was mediated by the increased effect of anxiety on the adverse effects of AEDs compared to the effects of depression and seizure control on the adverse effects of AEDs.

This study has some limitations. First, eligible subjects were enrolled at secondary and tertiary care hospitals; thus, the predictors of QOL in this population might be different from those in the community population of PWE. Second, we did not use a structured interview, such as the Structured Clinical Interview for DSM-IV Axis I disorders (SCID),[33] which is considered the gold standard for research on psychiatric problems. However, this interview requires a long time to complete and cannot be used in busy clinical settings. Therefore, we utilized the K-NDDI-E and the GAD-7 rather than the SCID. Third, our study was cross-sectional and therefore only allowed for the assessment of the association of the analyzed variables with QOL at a single point in time across the cohort of patients. A prospective study might allow for the examination of the variables that associated with changes in QOL over time and/or as the effects of specific interventions.

Epilepsy management has traditionally focused on seizure control with AEDs and adjunctive treatments that seeks to decrease seizure frequency and severity. However, our findings suggest that effective management might also depend on the early detection of comorbid psychiatric symptoms and the recognition of economic burdens. Unfortunately, most clinicians have limited time to communicate with patients and might fail to ask about these issues. In such situations, simple screening tools for the detection of depression and anxiety can be effective. The use of the K-NDDI-E to measure depression has been recommended,[23] and the GAD-7 has been recommended for the measurement of anxiety in busy clinical settings.[34] The rapid detection and appropriate management of psychiatric symptoms could directly improve QOL or reduce the perception of side effects associated with AEDs and subsequently ameliorate QOL. Epilepsy generates a substantial economic burden on individuals and society,[35] and increased health and societal expenditures could reduce this burden. A future prospective study is required to determine whether minimizing psychiatric symptoms and decreasing economic burden and seizure freedom can improve the QOL of PWE.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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