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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Psychosocial profiles and their predictors in epilepsy using patient-reported outcomes and machine learning

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Abstract

Objective: To apply unsupervised machine learning to patient-reported outcomes to identify clusters of epilepsy patients exhibiting unique psychosocial characteristics.

Methods: Consecutive outpatients seen at the Calgary Comprehensive Epilepsy Program outpatient clinics with complete patient-reported outcome measures on quality of life, health state valuation, depression, and epilepsy severity and disability were studied. Data were acquired at each patient's first clinic visit. We used k-means++ to segregate the population into three unique clusters. We then used multinomial regression to determine factors that were statistically associated with patient assignment to each cluster.

Results: We identified 462 consecutive patients with complete patient-reported outcome measure (PROM) data. Post hoc analysis of each cluster revealed one reporting elevated measures of psychosocial health on all five PROMs ("high psychosocial health" cluster), one with intermediate measures ("intermediate" cluster), and one with poor overall measures of psychosocial health ("poor psychosocial health" cluster). Failing to achieve at least 1 year of seizure freedom (relative risk [RR] = 4.34, 95% confidence interval [CI] = 2.13-9.09) predicted placement in the "intermediate" cluster relative to the "high" cluster. In addition, failing to achieve seizure freedom, social determinants of health, including the need for partially or completely subsidized income support (RR = 6.10, 95% CI = 2.79-13.31, $P < .001$) and inability to drive (RR = 4.03, 95% CI = 1.6-10.00, $P = .003$), and a history of a psychiatric disorder (RR = 3.16, 95% CI = 1.46-6.85, $P = .003$) were associated with the "poor" cluster relative to the "high" cluster.

Significance: Seizure-related factors appear to drive placement in the "intermediate" cluster, with social determinants driving placement in the "poor" cluster, suggesting a threshold effect. Precision intervention based on cluster assignment, with an initial emphasis on improving social support and careful titration of medications for those reporting the worst psychosocial health, could help optimize health for patients with epilepsy.

KEYWORDS
cohort studies, epilepsy/seizures, machine learning, patient-reported outcome measures, quality of life

1 | INTRODUCTION

Epilepsy is a major chronic health condition that affects between six and seven of 1000 people worldwide.[1] Although patients with epilepsy have an enduring predisposition to epileptic seizures, the disease is also defined by the biopsychosocial consequences of the illness.[2] These consequences contribute to epilepsy being the second most common neurological cause of years lived with disability in the world.[3] Both seizures and the biopsychosocial issues resulting from epilepsy have deleterious effects on self-perceived quality of life, health state valuation, and patient mental health.[4,5]

Patient-reported outcome measures (PROMs) are patients' direct appraisals of their own health status and quality of life.[6] A number of validated generic and epilepsy-specific PROMs exist that help the clinical team ascertain the patient's self-perceived quality of life (Quality of Life in Epilepsy Inventory-10 [QOLIE-10]),[7] health valuation (5-Level EuroQol-5 Dimension Quality of Life Assessment [EQ-5D-5L]),[8] epilepsy severity (Global Assessment of Severity of Epilepsy [GASE]),[9] and epilepsy disability (Global Assessment of Disability of Epilepsy [GAD]).[10] Additionally, screening questionnaires such as the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) have been readily deployed in clinics to detect comorbid conditions, such as depression,[11] that directly and independently detract from quality of life.[4,5]

As we strive toward precision medicine in epilepsy, machine learning allows us to parse patients into discrete clusters that may uniquely benefit from targeted interventions. Clustering algorithms are unsupervised machine learning techniques that assign data points to discrete groups with the aim of maximizing within-group similarity and between-group difference. It is our hypothesis that cluster-specific clinical characteristics at baseline may provide targets for tailored treatments that could confer disproportionately higher psychosocial benefit to members of that specific cluster. If confirmed, this means a clinician could provide precision intervention immediately during the patient's first visit to avoid undue delays in addressing psychosocial and quality of life issues. The objective of this study was to use multidimensional clustering methods to determine whether distinct groups of patients exist based on their PROM data and identify unique clinical and demographic factors associated with each cluster.

Key Points

- PROMs are critical for generating research and outcomes that are meaningful to patients
- Machine learning applied to PROMs can be used to segregate epilepsy patients into clusters with unique psychosocial traits
- Patients in the intermediate cluster are more likely to have frequent seizures compared to others
- Patients in the low psychosocial cluster are more likely to have socioeconomic instability compared to other clusters
- Cluster status should be evaluated for its ability to personalize interventions designed to improve psychosocial health in epilepsy

2 | MATERIALS AND METHODS

2.1 | Study population

The Calgary Comprehensive Epilepsy Programme (CEP) maintains a prospective local registry of systematically collected data on all adult (aged 16 years and older) outpatients at each clinical encounter. The CEP covers a local population of >1.3 million people but also regularly receives provincial and interprovincial referrals. All patients provide demographic, social, employment, basic health-related, and substance use, including cannabis, information at baseline and follow-up visits. Through direct questioning, the attending epileptologist additionally collects data pertaining to seizure and epilepsy characteristics, medical history, physical examination findings, diagnostic investigations, antiseizure medication (ASM) use including defined daily dose according to World Health Organization recommendations,[12] ASM response, ASM adverse effects, and surgical history. Epilepsy diagnosis is made through detailed patient history, physical examination, and review of antecedent imaging and ancillary testing such as prior routine and video-electroencephalographic telemetry results according to International League Against Epilepsy definitions.[2] The attending epileptologist makes or confirms all psychiatric diagnoses, including alcohol and drug dependence, according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria or through psychiatry consultation.[13]

Prospective data collection started in 2007, although additional variables have been added as the registry evolved.

PROMs included in this analysis were all routinely recorded by January 2019. The analyses that comprise this study include all baseline clinic visit data for consecutive patients with complete PROM data up to August 2019. Therefore, these data are cross-sectional from each patient's first clinic visit.

2.2 | Patient-reported outcome measures

The QOLIE-10[7] is a 10-item weighted score from 0 (no quality of life) to 100 (maximal quality of life) that evaluates self-perceived quality of life by asking about epilepsy-specific effects (physical and mental effects of epilepsy), mental health, and everyday functioning (driving, work, and epilepsy-specific worry and limitations). The EQ-5D-5L[8] is a measure of self-perceived health state valuation. It comprises a visual analogue scale (0-100 with "100" equating to the best health state imaginable) in which the patient is asked to rate their health on the day of the clinic visit. A time trade-off (TTO) value, calculated using weights specific to Canada (range of −0.148 to 0.949[8]), can also be derived using questions specific to mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression. The TTO represents the time a patient would trade in their current state to live in perfect health. For example, if the patient preferred to live 5 years in perfect health, rather than 10 years in their current state, then the TTO value would be 0.5. The NDDI-E[11] is a screening questionnaire for depression (scale range from 6 to 24; a score above 14 or 15 is considered a cut point for additional inquiries into major depression[14]). The GASE[9] and GAD[10] scales evaluate patient-reported epilepsy severity and disability, respectively, on a single-item 0-7 scale (higher numbers equate to more severe or disabling epilepsy).

2.3 | Demographic and clinical variables

We extracted factors known to influence quality of life in epilepsy (ASM adverse effects, clinician-diagnosed psychiatric illness as per DSM-5 criteria,[13] driving a noncommercial motor vehicle, and drug-resistance [measured as seizure-freedom over the past year])[4] from our registry. Based on clinical acumen, we also included current age, sex, marital status (married/common-law vs other), the need for social assistance for income support (determined through clinical interview and patient report), yearly seizure frequency, history of bilateral tonic-clonic seizures (binary yes or no), need for ASM polytherapy (defined as concurrent use of two or more ASMs), alcohol misuse (clinician diagnosed), and regular cannabis use as reported by the patient on standardized forms. Other clinical variables systematically recorded and explored where relevant included epilepsy risk factors, etiology, epilepsy[15] and seizure[16] classification (focal, generalized, or unknown), seizure triggers, and the epilepsy-specific comorbidity index.[17] We evaluated cigarette smoking and recreational drug use as binary outcomes defined by whether the patient regularly used (≥ once per week) each substance. This information was provided by both the physician and the patient questionnaires.

2.4 | Statistical analysis

Parametric (*t* test) and nonparametric statistics (Kruskal-Wallis test) were used where appropriate. We considered an alpha level of ≤0.05 to be significant for comparisons. Variables significant according to this criterion were included in all resultant multivariate models. Because of inherent challenges of incorporating ordinal data with constrained scales into clustering analyses dependent on Euclidean distances (eg, the GASE and GAD are 7-item scales), we first transformed data by scaling all PROMs between 0 and 1 using MinMaxScaler for scikit-learn in Python 3.6.3.[18]

We chose unsupervised machine learning methods because, unlike supervised methods, there are no a priori assumptions made about where the thresholds defining classes should lie. Rather, these algorithms use the data themselves to empirically establish thresholds within each PROM scale that reliably segregates patients into unique classes. Hence, K-means++ clustering was performed using QOLIE-10, EQ-5D-5L, NDDI-E, GASE, and GAD. This algorithm initially places k-number of multidimensional centroids (cluster centers; one centroid for each predetermined cluster number placed in five dimensions for this analysis) in positions that maximize between-centroid distance to improve performance.[19] It then calculates Euclidean distances between data points and centroids, assigning each data point to the cluster with the closest centroid. This is done iteratively until the within-cluster mean squared errors reach a nadir or when the centroids positions have stabilized.[20]

The k-means++ algorithm makes no a priori assumptions about the ideal number of patient clusters that exist in a population. Rather than making an arbitrary decision about the number of clusters that should exist, without any empirical foundation, we therefore first used the gap statistic[21] and elbow methods[22] to evaluate the optimal number of clusters. Both approaches plot the number of potential clusters along the x-axis, whereas the gap statistic (total within-cluster dispersion expected with a null distribution compared to the observed within-cluster dispersion) or total distortion (within-cluster sum of the squared estimate of the errors) is plotted on the y-axis in the gap statistic and elbow methods, respectively. The optimal cluster number

is that with the largest gap statistic (gap statistic method) or the maximal inflection point on a scree plot (elbow method).

Following this, we used nonparametric statistics to compare PROMs between clusters. We then performed multinomial logistic regression to determine the relative risk (RR) that a patient may exist in a cluster with worse PROMs according to their demographic and clinical characteristics. Although it is possible to relax the 10 variables per outcome rule in regression,[23] we still incorporated a Bonferroni correction for multiple comparisons to ease interpretation of the multivariate multinomial regression.

All analyses were completed using Stata version 13.0[24] and Python 3.6.3.[18]

2.5 | Ethics

Ethics approval for this study was obtained both through the University of Calgary's Conjoint Health Research Ethics Board and Alberta Health Services (REB17-0369_MOD4). Every patient (or guardians of patients) provided written informed consent. All CEP data are collected, managed, stored, and extracted using REDCap,[25] an electronic data capture tool hosted by the Clinical Research Unit at the University of Calgary.

3 | RESULTS

3.1 | Study population

Of 579 patients with epilepsy, 487 (84%) consented to research. Of these, 462 (95%) had complete PROM data. These patients had a median age of 38 years (interquartile range [IQR] = 25-56), and 235 (51%) were female (Table 1). These patients did not differ demographically from the 15% of patients not consenting to research. In total, 269 of the 462 patients (58%) were diagnosed with focal epilepsy, 143 (30%) with generalized epilepsy, and 57 (12%) with unknown onset epilepsy. Median QOLIE-10 score for the whole cohort was 54 (IQR = 21-83), EQ-5D-5L TTO was 0.87 (IQR = 0.72-0.94), GASE was 1 (IQR = 1-3), GAD was 2 (IQR = 1-4), and NDDI-E was 11 (IQR = 8-15).

TABLE 1 Distribution of clinical characteristics in 462 patients

Characteristic	Cohort value, n = 462
Age, median y (IQR)	38 (25-56)
Age at onset, median y (IQR)	19 (12-34)
Epilepsy duration, median y (IQR)	11 (5-23)
Female, n (%)	235 (51%)
Focal epilepsy, n (%)	239 (52%)
ASM polytherapy, n (%)	162 (35%)
ASM DDD (IQR)	1 (0.66-1.33)
Any reported ASM adverse effect, n (%)	157 (34%)
Yearly seizure frequency, n (IQR)	6 (0-33)
History of a bilateral tonic-clonic seizure, n (%)	287 (62%)
One-year seizure free at baseline, n (%)	107 (23%)
Postictal state, n (%)	189 (41%)
Epilepsy comorbidity index, median (IQR)	0 (0-0)
Psychiatric history, n (%)	130 (28%)
Married/common-law, n (%)	199 (43%)
Social services, n (%)	150 (32%)
Current driver, n (%)	185 (40%)
Cannabis user, n (%)	89 (19%)
Alcohol user, n (%)	21 (5%)
Cigarette user, n (%)	71 (15%)
QOLIE-10, median (IQR)	54 (21-83)
NDDI-E, median (IQR)	11 (8-15)
EQ-5D-5L time trade-off, median (IQR)	0.87 (0.72-0.94)
EQ-5D-5L visual analogue scale, median (IQR)	80 (68-90)
GASE, median (IQR)	1 (1-3)
GAD, median (IQR)	2 (1-4)

Note: Reported *P* values are for univariate comparisons.

Abbreviations: ASM, antiseizure medication; DDD, defined daily dose; EQ-5D-5L, 5-Level EuroQol-5 Dimension Quality of Life Assessment; GAD, Global Assessment of Disability of Epilepsy; GASE, Global Assessment of Severity of Epilepsy; IQR, interquartile range; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; QOLIE-10, Quality of Life in Epilepsy Inventory-10.

3.2 | Cluster analysis

The gap statistic and elbow methods both indicated three as an ideal cluster number (Figure S1). Between-group scores for each PROM were statistically significant at an alpha level of <0.001 (Table 2). The clusters appear to segregate into "high psychosocial health" (high measures of psychosocial health), "intermediate" (intermediate levels of psychosocial health), and "poor psychosocial health" (poor measures of psychosocial health) groups that are primarily driven by the QOLIE-10, GASE, GAD, and NDDI-E. The EQ-5D-5L TTO remained relatively invariant between the "high psychosocial health" and "intermediate" clusters, indicating high levels of current health state valuation irrespective of scores on other PROMs (Figure S2). Due to the challenges of visualizing five-dimensional data, we plotted the clusters in three dimensions using different permutations of PROMs and fixing QOLIE-10 on the x-axis (Figure 1A-D).

TABLE 2 Distribution of patient-reported outcome measures in 462 patients with epilepsy following k-means++ clustering using three groups

Characteristic	Cluster 1: "high psychosocial health"	Cluster 2: "intermediate"	Cluster 3: "poor psychosocial health"	*P*
n (%)	211 (46%)	153 (33%)	98 (21%)	n/a
QOLIE-10, median (IQR)	85 (68-94)	38 (23-52)	8 (3-16)	<.001
NDDI-E, median (IQR)	8 (6-10)	12 (10-15)	17 (14-19)	<.001
EQ-5D-5L time trade-off, median (IQR)	0.91 (0.87-0.94)	0.85 (0.75-0.91)	0.60 (0.45-0.74)	<.001
EQ-5D-5L visual analogue scale, median (IQR)	90 (80-95)	75 (68-85)	52 (40-71)	<.001
GASE, median (IQR)	1 (1-1)	2 (1-3)	4 (4-6)	<.001
GAD, median (IQR)	1 (1-1)	2 (2-3)	6 (5-6)	<.001

Note: Higher QOLIE-10 scores (range = 0-100) indicate better quality of life, higher NDDI-E scores (range = 6-24; cutoff of <14 triggers further evaluation for major depression disorder) are associated with depression, higher EQ-5D-5L scores (range = −0.148 to 0.949 for time trade-off and 0-100 for the visual analogue scale) indicate higher current health state valuation, and higher GASE (range = 0-7) and GAD (range = 0-7) indicate higher degrees of epilepsy-related severity and disability, respectively.

Abbreviations: EQ-5D-5L, 5-Level EuroQol-5 Dimension Quality of Life Assessment; GAD, Global Assessment of Disability of Epilepsy; GASE, Global Assessment of Severity of Epilepsy; IQR, interquartile range; n/a, not applicable; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; QOLIE-10, Quality of Life in Epilepsy Inventory-10.

3.3 | Multinomial regression

The three clusters were markedly different on several clinical characteristics (Table 3). Failure to achieve at least 1 year of seizure freedom at baseline clinic visit (RR = 4.34, 95% confidence interval [CI] = 2.13-9.09, $P < .001$) was statistically associated with placement in the "intermediate" cluster as compared to the "high psychosocial health" cluster following a Bonferroni correction requiring a *P* value of <.004. Trends were noted for yearly seizure frequency (RR = 1.004 for each one additional seizure per year, 95% CI = 1.001-1.008, $P = .007$) and a history of a psychiatric disorder (RR = 2.36, 95% CI = 1.24-4.49, $P = .009$) following multivariate multinomial regression (Table 4).

In contrast, the risk of existing in the "poor psychosocial health" cluster, as compared to the "high psychosocial health" cluster, was associated with a far more complex array of adverse clinical and psychosocial characteristics. Major predictors included failure to achieve at least 1 year of seizure freedom at baseline clinic visit (RR = 11.11, 95% CI = 2.70-50.00, $P = .001$), need for social services including complete income support (RR = 6.10, 95% CI = 2.79-13.31, $P < .001$), inability to hold a motor vehicle driver's license (RR = 4.17, 95% CI = 1.61-10.00, $P = .003$), and a history of a psychiatric disorder (RR = 3.16, 95% CI = 1.46-6.85, $P = .003$). However, trends were also noted for age (RR = 1.025 for each 1-year increment, 95% CI = 1.002-1.048, $P = .031$), female sex (RR = 2.54, 95% CI = 1.23-5.26, $P = .011$), yearly seizure frequency (RR = 1.004 for each one additional seizure per year, 95% CI = 1.001-1.008, $P = .011$), and self-reported ASM adverse effects (RR = 2.25, 95% CI = 1.07-4.70, $P = .031$). Additionally, there was a trend for an inverse association between epilepsy duration (RR = 0.96 for each 1-year increment, 95% CI = 0.94-0.99, $P = .013$) and placement in the "poor psychosocial health" cluster, as compared to the "high psychosocial health" cluster (Table 4).

Finally, need for social services (RR = 5.71, 95% CI = 2.81-11.58, $P < .001$) was statistically associated with being in the "poor psychosocial health" as compared to the "intermediate" cluster following Bonferroni correction (Table 4).

4 | DISCUSSION

Innovative approaches are required to improve psychosocial health in epilepsy. A critical prerequisite is accurate and relevant data. Patient-reported outcome measures convey patient perspectives on their own health status and quality of life at the point of care in an easily analyzable and interpretable fashion. Routine and systematic use of PROMs is associated with improved patient satisfaction and overall health in primary care, oncology, mental health, surgery, and rheumatology clinics.[26] We took the innovative step of applying machine learning to PROMs to help build a precision care pipeline. The goal is to identify specific subsets of patients who could benefit most from targeted interventions based on their distinct clinical characteristics. We leveraged unsupervised machine learning to identify three distinct clusters of patients exhibiting unique and potentially modifiable features that could influence psychosocial health. Post hoc analyses have highlighted clinical characteristics that can be used to design bespoke therapeutic interventions optimally suited for each patient cluster.

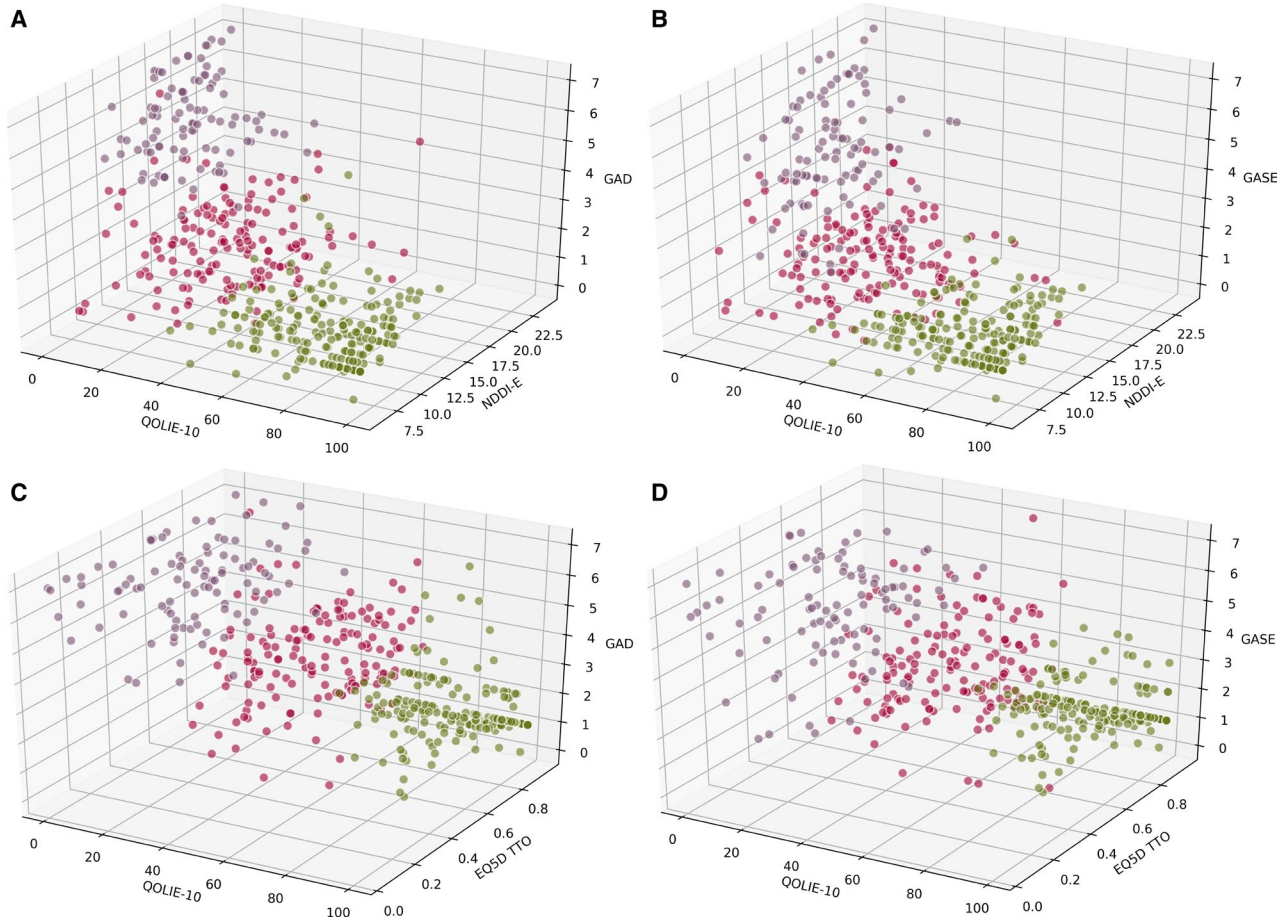

FIGURE 1 Clusters 1-3 mapped in three-dimensional space fixing Quality of Life in Epilepsy Inventory-10 (QOLIE-10) on the x-axis. Graphs are bounded by the following patient-reported outcome measures: A, QOLIE-10, Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), and Global Assessment of Disability of Epilepsy (GAD); B, QOLIE-10, NDDI-E, and Global Assessment of Severity of Epilepsy (GASE); C, QOLIE-10, 5-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-5L) time trade-off (TTO), and GAD; D, QOLIE-10, EQ-5D-5L TTO, and GASE. Green = "high psychosocial health" cluster; red = "intermediate psychosocial health" cluster; purple = "poor psychosocial health" cluster

High scores on quality of life and current health state valuation and low measures of self-perceived epilepsy severity, epilepsy disability, and depression mark the "high psychosocial health" cluster, a group comprising 46% of the entire population of epilepsy patients at their baseline visit. Interestingly, although the "intermediate" cluster exhibits low scores on quality of life (median = 38, IQR = 23-52) and NDDI-E scores verging on depression (median = 12, IQR = 10-15), the patients tend to rate the severity (median = 2, IQR = 1-3) and disability (median = 2, IQR = 2-3) of their epilepsy as relatively mild (Table 2). Likewise, current health state valuation (EQ-5D-5L TTO = 0.91 [IQR = 0.87-0.94] vs 0.85 [IQR = 0.75-0.91]) remains rather invariant to the significantly lower quality of life measure between the "intermediate" and "high psychosocial health" clusters. This can be expected, given that the EQ-5D-5L has been shown to have a high ceiling effect with low variability in effect sizes in epilepsy,[27] a phenomenon that is potentially related to the finding that meaningful changes in epilepsy states may not be as readily detected by the comparatively large "distances" between potential responses in the ordinal scales (ie, "no problems" vs "slight problems" vs "moderate problems") for each EQ-5D-5L dimension.[28] The "poor psychosocial health" group is characterized by low quality of life scores (median = 8, IQR = 3-16), low health state valuation (EQ-5D-5L TTO median = 0.60, IQR = 0.45-0.74), high depression scores (median = 17, IQR = 14-19), and high degrees of self-perceived epilepsy severity (GASE median = 4, IQR = 4-6) and disability (GAD median = 6, IQR = 5-6).

Future efforts will be required to determine whether targeted and sequential correction of modifiable factors can improve psychosocial health by shifting patients between clusters. To this end, we attempted to focus our efforts on evaluating potentially mutable factors to facilitate future precision intervention studies for psychosocial health. One approach would be for comprehensive epilepsy clinics to

TABLE 3 Distribution of clinical characteristics in 462 patients segregated into three clusters by a k-means++ algorithm

Characteristic	Cluster 1: "high psychosocial health"	Cluster 2: "intermediate"	Cluster 3: "poor psychosocial health"	*P*
Age at onset, y (IQR)	18 (10-32)	19 (12-34)	22 (12-39)	.157
Epilepsy duration, median y (IQR)	14 (6-28)	11 (4-19)	9 (5-21)	.020
Female, n (%)	99 (47%)	73 (48%)	63 (64%)	.012
Focal epilepsy, n (%)	106 (50%)	82 (54%)	51 (52%)	.813
ASM polytherapy, n (%)	57 (27%)	59 (39%)	46 (47%)	.001
ASM DDD (IQR)	1 (0.66-1.33)	1 (0.66-1.63)	1.33 (1-1.5)	.001
Any reported ASM adverse effect, n (%)	54 (26%)	60 (39%)	43 (44%)	.002
Yearly seizure frequency, n (IQR)	3 (0-23)	5 (0.5-28)	24 (1-62)	<.001
History of a bilateral tonic-clonic seizure, n (%)	131 (62%)	88 (58%)	68 (69%)	.168
One-year seizure-free at baseline, n (%)	84 (40%)	18 (12%)	5 (5%)	<.001
Postictal state, n (%)	76 (36%)	68 (44%)	45 (46%)	.142
Epilepsy comorbidity index, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	.352
Psychiatric history, n (%)	36 (17%)	47 (31%)	47 (48%)	<.001
Married/common-law, n (%)	96 (46%)	68 (44%)	35 (36%)	.285
Social services, n (%)	44 (21%)	44 (29%)	62 (63%)	<.001
Current driver, n (%)	122 (59%)	50 (33%)	12 (14%)	<.001
Cannabis user, n (%)	30 (14%)	30 (20%)	29 (30%)	.007
Alcohol user, n (%)	75 (36%)	52 (34%)	23 (23%)	.092
Cigarette user, n (%)	23 (11%)	24 (16%)	24 (24%)	.010

Note: Reported *P* values are for univariate comparisons.

Abbreviations: ASM, antiseizure medication; DDD, defined daily dose; IQR, interquartile range.

routinely collect these PROMs and then deploy the learned model in their electronic health records. The model will classify each patient, allowing the care team to employ tailored interventions that are ideally matched to the clinical characteristics of the patient's designated cluster.

Alternatively, a practical approach using clinical characteristics could form a more cost-effective and clinically feasible course of action. The major discriminating factor between the "poor psychosocial health" and "intermediate" clusters (RR = 5.17, 95% CI = 2.81-11.58, $P < .001$) and "poor psychosocial health" and "high psychosocial health" clusters (RR = 6.10, 95% CI = 2.79-13.30, $P < .001$) was a need for social services that included financial support. Hence, for patients requiring income assistance, the first step should be addressing the social burden of epilepsy, which may then improve patient outcomes with decreased need for medical intervention. Unsurprisingly, such interventions have been effective in small studies,[29] but it is this "poor psychosocial health" cluster that is predicted to derive the most benefit. Such interventions can involve early social work consultations with the goal of helping patients obtain gainful employment, secure living wages, and reliable transportation. Intensive yet careful treatment of seizures is also required. Aggressive ASM titration schedules may have to be tempered, because there was a trend toward an association between adverse effects and placement in the "poor psychosocial health" cluster ($P = .03$). However, efforts at establishing cause-effect are needed to test this inference. A concern is that the "poor psychosocial health" cluster may have more severe seizures requiring highly intensive medical management that may have led to higher rates of adverse effects. Despite this, it is compelling to note that the association of ASM adverse effects with existence in this cluster was independent of seizure frequency, bilateral tonic-clonic seizures, 1-year seizure freedom at baseline, and the defined daily ASM dose (Table 4). Finally, the trend toward an increased likelihood of female sex for existing in the "poor psychosocial health" cluster ($P = .01$) may be related in part to its association with ASM adverse effects[30] and a greater propensity for psychiatric comorbidity.[31] This emphasizes the need for sex-specific approaches to improving psychosocial health.

In the absence of these factors, the patient most likely exists in the "intermediate" cluster where more intensive and

TABLE 4 Factors associated with existence in specific clusters identified through k-means++ algorithm using multivariate multinomial logistic regression incorporating all listed variables determined to be significant in univariate comparisons

Characteristic	RR	95% CI	*P*
Risk of existing in the "intermediate" vs "high psychosocial health" cluster			
Age	1.0004	0.98-1.01	.961
Female sex	1.11	0.64-1.95	.695
Epilepsy duration	0.98	0.96-1.00	.067
Yearly seizure frequency	1.004	1.001-1.008	.007
1+ years seizure-free at baseline	0.23	0.11-0.47	<.001[a]
Defined daily ASM dose	1.40	0.93-2.12	.099
ASM polytherapy	1.43	0.74-2.73	.279
ASM adverse effects	1.75	0.98-3.12	.057
History of psychiatric disorder	2.36	1.24-4.49	.009
Currently able to drive	0.58	0.32-1.06	.075
Requires social assistance	1.03	0.53-2.02	.909
Self-reported cannabis use	1.01	0.49-2.07	.979
Self-reported cigarette use	1.59	0.71-3.54	.253
Risk of existing in the "poor psychosocial health" vs "high psychosocial health" cluster			
Age	1.02	1.002-1.048	.031
Female sex	2.54	1.23-5.26	.011
Epilepsy duration	0.96	0.94-0.99	.013
Yearly seizure frequency	1.004	1.001-1.008	.011
1+ years seizure-free at baseline	0.09	0.02-0.37	.001[a]
Defined daily ASM dose	1.44	0.85-2.45	.166
ASM polytherapy	1.71	0.75-3.90	.201
ASM adverse effects	2.25	1.07-4.70	.031
History of psychiatric disorder	3.16	1.46-6.85	.003[a]
Currently able to drive	0.24	0.10-0.62	.003[a]
Requires social assistance	6.10	2.79-13.3	<.001[a]
Self-reported cannabis use	1.03	0.41-2.57	.946
Self-reported cigarette use	2.18	0.79-6.00	.129
Risk of existing in the "poor psychosocial health" vs "intermediate" cluster			
Age	1.02	1.003-1.046	.020
Female sex	2.12	1.08-4.16	.027
Epilepsy duration	0.98	0.96-1.01	.281
Yearly seizure frequency	0.99	0.99-1.00	.964
1+ years seizure-free at baseline	0.43	0.10-1.69	.228
Defined daily ASM dose	1.02	0.64-1.64	.906
ASM polytherapy	1.11	0.52-2.38	.776
ASM adverse effects	1.26	0.63-2.51	.498
History of psychiatric disorder	1.34	0.68-2.62	.389
Currently able to drive	0.42	0.17-1.04	.061
Requires social assistance	5.71	2.81-11.58	<.001[a]
Self-reported cannabis use	1.06	0.45-2.46	.892
Self-reported cigarette use	1.34	0.53-3.33	.529

Note: Age is the risk for each 1-year increment; yearly seizure frequency is for each 1 additional per year.

Abbreviations: ASM, antiseizure medication; CI, 95% confidence interval; RR, risk ratio.

[a]Significant after a Bonferroni correction ($P < .004$).

aggressive efforts at reducing seizure frequency or establishing complete seizure freedom and addressing comorbid psychiatric disease are the priority. Such interventions appear to work on a population level,[32,33] but the "intermediate" cluster may especially enjoy disproportionate benefit, resulting in robust, cost-effective treatment protocols.

Interestingly, the epilepsy-specific comorbidity index[17] did not differ between groups, but this may be consequence of the median age of the cohort, which was only 38 years. These patients were largely healthy, and therefore eventual efforts should be made to explore clustering in older adults, who exhibit a larger quantity of more varied comorbidities, to determine whether this phenomenon is unique to young, healthy adults with epilepsy.

This study benefits from a large sample of consecutive patients with complete and systematically collected PROM data. The CEP has a large catchment area and regularly evaluates the entire spectrum of epilepsy, as appreciated by subjects' demographic and clinical characteristics (Table 3). The PROM data were complemented by robust and granular clinical data that permitted comprehensive evaluations of cluster characteristics. We have mitigated risks measurement and differential misclassification bias through our standardized data collection tools. Additionally, the k-means++ clustering algorithm is relatively easy to implement, ensuring this analysis can be replicated at other centers recording PROM data. The three clusters we identified are clinically intuitive, and the associations of seizure and psychiatric variables for existing in the "intermediate" cluster and seizure, psychiatric, and social variables for existing in the "poor psychosocial health" cluster are large and robust.

Despite these strengths, there are limitations to the analyses. Our patient population is derived from a tertiary care center, so caution must be taken when generalizing these results. Additionally, these clusters are derived from baseline data collected when patients are first seen in the CEP. This means that these data offer clinicians a chance to intervene early to improve quality of life issues that could become more intractable over time. However, it is still important to replicate this study on longitudinal data to determine whether the clusters remain stable over time. This will also help address heterogeneity in disease spectrum present at the baseline clinic visit. For instance, some patients have been referred following a first seizure or for routine follow-up, whereas others have drug-resistant epilepsy and are being evaluated due to the need for surgical intervention. Our data have demonstrated a statistically significant association between the presence of seizures over the prior year and trends toward greater duration of epilepsy and worse psychosocial health. These features should be further characterized in longitudinal data to permit a better understanding of how they relate to disease state, so that we can further refine prediction of psychosocial outcomes using baseline data in epilepsy. Although the study benefited from a large sample size, we did not explore potential associations between seizure onset anatomy or individual antiseizure drugs on cluster assignment due to the risk of multiple comparisons and limited data available at the baseline clinic visit. Finally, due to its observational nature, this study is not able to establish a cause-effect relationship between the presence of a specific clinical variable and patient assignment to a cluster.

We have begun to explore precision medicine approaches for psychosocial health needs in patients with epilepsy by applying machine learning to routinely collected PROMs. We identified three discrete patient clusters exhibiting unique psychosocial characteristics with modifiable clinical features amenable to future intervention trials. Based on these analyses, it appears seizure-related factors drive movement from the "high" to "intermediate" psychosocial cluster. After this, it appears as though a threshold is crossed whereby social determinants of health, such as the need for financial support and insecure transportation, and psychiatric disease drive movement into the "poor" psychosocial cluster. These analyses should be applied in other geographic locations to demonstrate external validity and with longitudinal data to determine whether transitions between groups can be modulated by targeted reversal of cluster risk factors. Across the globe, patients with epilepsy are at high risk of poor psychosocial health and stigma. Cost-effective interventions, informed by high-quality data and advanced analytics such as those employed in this study, are critically needed to improve overall personal well-being for patients affected by epilepsy.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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