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Somatic symptom and related disorder in a large cohort of people with epilepsy: a cohort study

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of Interest

None of the authors has any conflict of interest to disclose in relation to this work.

Statement of Ethics

This study was approved by the Ethics Committee of the West China Hospital (Nos. 2020-1303).

Consent to participate

Written informed consent was obtained from all participants in this study.

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Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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Abstract:

Objective: To characterize somatic symptoms and related disorders (SSD) in epilepsy.

Methods: Adults with epilepsy under active follow-up at a tertiary epilepsy centre were consecutively enrolled. The diagnosis of SSD was performed by an experienced psychologist based on the structured clinical interview for DSM-5. Detailed social/demographic data, epilepsy features, psychiatric features, life quality, disability and economic burden were collected and compared between people with SSD and those without. Bodily distress syndrome checklist (BDS-checklist), Somatic Symptom Disorder–B Criteria Scale (SSD-12), Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder 7-item scale (GAD-7) were used to evaluate SSD individuals' somatic symptoms, symptom-related psychological distress, depressive and anxious symptom, respectively. Quality of life and disability was assessed by Quality of Life in Epilepsy Inventory 31 (QOLIE-31) and WHO Disability Assessment Schedule V.2.0 (WHO DAS 2.0). A risk prediction nomogram was generated using least absolute shrinkage and selection operator (LASSO) analysis and validated.

Results: One-hundred-and-fifty of 631 participants (24%) were diagnosed with SSD. In people with SSD, the top 3 most common somatic symptoms were memory impairment, headache and dizziness (85%, 80% and 78%, respectively), and multiple systems are involved in most (82%) people with SSD. Compared with people without SSD, those with SSD had lower QOLIE-31 total scores, higher WHO DAS 2.0 scores and disease economic burdens. LASSO analysis suggested that a history of severe traumatic brain injury, hippocampal sclerosis, low seizure worry and medication effects scores of

QOLIE-31, multiple systems that somatic symptoms affected, and a high GAD-7 score were risk factors of SSD. The nomogram was validated for good accuracy in the training and testing cohorts.

Significance: SSD is likely to be common comorbidity in epilepsy and harm epilepsy prognosis. Our risk prediction nomogram was successfully developed but needs further validation in larger cohorts.

Keywords: Somatoform disorder, mental health, comorbidity, seizure

Key bullet points:

1. The prevalence of SSD in people with epilepsy was near a quarter, comparable to that of depression and anxiety disorders.

2. Multiple organ systems affect most people with epilepsy comorbid SSD.

3. SSD harmed epilepsy prognosis (poor seizure control, poor QOL, higher disability severity and higher health care costs).

4. Psychological variables have the most significant impact on SSD than other demographic and epilepsy-related variables.

Introduction

Epilepsy is one of the most common neurological disorders, affecting around 65 million people worldwide. Mental disorders are common in people with epilepsy[1, 2]. Previous studies focused on anxiety and depression and suggested poor quality of life [3-6], increased health care use [7-9], more severe seizure-related disability [10, 11] and poor seizure control [12]. Somatoform disorders have hardly been assessed in epilepsy. The reason may be its ambiguity and low practicability of criteria according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, DSM-4) and International Classification of Diseases (tenth edition, ICD-10)[13, 14].

In 2013, the concept of somatoform disorders was redefined in DSM-5 and replaced by somatic symptom and related disorders (SSD), which was expressed as "the presence of one or more somatic symptoms that it is associated with excessive worries, that thoughts and energies are spent dealing with them, causing a loss of opportunities in personal and social lives". The individual must present at least one problematic physical symptom (A criterion). Along with the physical symptom(s), individuals must also have at least one cognitive, affective or behavioral sign (B criteria) to fulfil the diagnostic criteria. The symptoms must persist for at least six months (C criterion)[15]. In ICD-11, somatoform disorders is replaced by bodily distress disorder (BDD), which is characterized by the presence of physical symptoms and excessive attention directed toward the symptoms for more than 3 months[16]. It is in large parts similar to SSD.

The prevalence of SSD has been reported as high as 56%[17] and is associated with low quality of life[18] and higher healthcare use[19]. There is little knowledge of SSD in epilepsy, including its prevalence,

clinical characteristics and risk factors. We screened for SSD in people with epilepsy and collected social/demographic, epilepsy-related, psychiatric status variables, quality of life (QOL), disability and disease economic burden data. A risk prediction model for SSD was then developed and validated.

Methods

Participants

Individuals included in this study were drawn from a longitudinal follow-up cohort of an epilepsy center at the West China Hospital since 2006. This cohort includes all people diagnosed with epilepsy according to ILAE Criteria at any time and routinely followed up. We consecutively enrolled all adults attending our center between 10 Jul 2020 and 10 May 2021 in this study.

Inclusion criteria (1) people aged 18 years or older; (2) people with a diagnosis of epilepsy for at least one year; (3) Being able to read standard Chinese as terminated by the Wide Range Achievement Test (age corrected); (4) Agreed to undergo a structural interview by a physician and to complete questionnaires.

Exclusion criteria (1) People who have lost their self-assessment ability or refuse to participate; (2) people who had a working vagal nerve stimulator in situ as it may cause autonomic dysfunction, which could be difficult to distinguish from somatic symptoms; (3) people who have been confirmed to have dementia or clinically significant psychiatric diagnosis.

Those attending between 10 Jul 2020 and 10 Mar 2021 were recruited as a training cohort, which was then used to develop a risk prediction model for SSD. Participants attending between 11 Mar 2021 and 10 May 2021 were recruited as a testing cohort.

The Ethics Committee of the West China Hospital approved the study (Nos. 2020-1303). All participants provided written informed consent.

Standard protocol

Every participant underwent a structured interview using the Structured Clinical Interview for DSM-5 to establish the diagnosis of SSD. The diagnostic criteria were as follows: A. One or more somatic symptoms that are distressing and/or result in significant disruption of daily life; B. Excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns as manifested by at least one of the following: 1) Disproportionate and persistent thoughts about the seriousness of one's symptoms; 2) Persistently high level of anxiety about health or symptoms; 3) Excessive time and energy devoted to these symptoms or health concerns. C. Although any one symptom may not be continuously present, the state of being symptomatic is persistent (typically > 6 months). The condition is considered to be mild when only one of the psychobehavioral aspect is fulfilled; moderate, when two or more of these aspects are fulfilled; and severe, when two or more of the psychobehavioral aspects are fulfilled, plus when there are multiple somatic complaints (or one very severe somatic symptom)[15].The diagnosis was verified by experienced psychologist (ZD) .

After the interview, the participants were treated by epileptologist JL or DZ at their clinic. Epilepsy features were collected from electronic medical records and evaluated in accordance with ILAE standards. To excluded possible false positives, we attended to differentiate SSD from the seizure and adverse effects of anti-seizure medications (ASMs). This was done by evaluating the chronology of the onset of

somatic symptoms and the appearance on withdrawal and re-challenge ASMs by the two epileptologists (JL and DZ).

Participants were also asked to complete an internet-based questionnaire after the routine clinical consultation either at home or in the outpatient department. Social/demographic data, psychiatric data, life quality, disability and economic burden were collected from the participants. Answers to all self-report questionnaires were reviewed via a telephone call within 1 week after the questionnaires being submitted to ensure data reliability (SS). Participants with key information missing or invalid call responses were eliminated.

Collected variables

Social/demographic, epileptic, psychiatric, life quality, disability and economic burden variables were collected and listed in Box 1.

Demographic data were collected from internet-based self-compiled questionnaire. Epileptic variables were collected from electronic medical records and by expert assessments. Epilepsy type, etiology of epilepsy and presence of drug-refractory epilepsy (DRE) were evaluated by two epileptologists according to ILAE criteria [20-22]. Chalfont-National Hospital Seizure Severity Scale (NHS3) was used to assess seizure severity. Frequent seizures were defined as seizure frequencies higher than once a month.

Assessment scales

Chalfont-National Hospital Seizure Severity Scale (NHS3): The scale contains 7 seizure related factors generating a score from 1 to 27, and higher scores mean more severe seizures[23].

The Bodily Distress Syndrome Checklist (BDS-checklist): This self-report questionnaire consists of 25 items on somatic symptoms of four systems: cardiopulmonary (CP), gastrointestinal (GI), musculoskeletal (MS) and general symptoms (GS) system[24] (eBox 1). People were asked, 'During the past four weeks, have you been bothered by' each of 25 listed symptoms on a 5-point Likert scale from 0 (`not at all´) to 4 (`a lot´), with a total score of 0-100 points. Having ≥4 symptoms from one system, the system is considered to be affected. Having ≥4 symptoms from any of above four systems, the across system is considered to be affected[24]. It was used to assess the most common somatic symptoms and affected systems in people with epilepsy and SSD.

Somatic Symptom Disorder–B Criteria Scale (SSD-12): It is also a self-report questionnaire and consists of 12 items measured the three psychological sub-criteria of SSD (cognitive, affective and behavioral aspects associated with bothersome somatic symptoms, eBox 1) in the past 4 weeks [25]. Each item is scored from 0 (never) to 4 (very often) points, with a total score of 0-48 points. Previous study in China have shown that a total score of 16 is the optimal cutoff point for the diagnosis of SSD with sensitivity of 76% and specificity of 80%[26]. The higher is the total score, the more severe are the symptom-related psychological distress.

Generalized Anxiety Disorder scale (GAD-7): This scale consists of 7 items related to generalized anxiety and assesses the degree of distress caused by anxious symptoms in the past 2 weeks. Each item is scored from 0 (not at all) to 3 (every day) points, with a total score of 0-21 points. The higher is the total score, the more severe are the anxious symptoms. Previous studies showed that the cutoff scores

ranged from >5 to >10 among different countries in epilepsy[27-29]. In our previous study, 7 points was verified as the optimal cut-off score, with a sensitivity of 94% and specificity of 91.4%[30]. Thus, GAD-7 total score ≥ 7 was used to screen people with anxiety in our study.

Health Questionnaire (PHQ-9): This questionnaire consists of 9 depression screening items and assesses the degree of distress caused by depressive symptoms in people in the previous two weeks. Each item is scored from 0 (not at all) to 3 (every day) points, with a total score of 0-27 points. The higher the total score, the more severe are the depressive symptoms. Previous studies have shown that a total score of 10 points is the optimal threshold for screening depression in epilepsy, with specificity ranging from 80.0%-94.1% and sensitivity ranging from 78.0%-92.0%[31-33]. In our study, score ≥ 10 was used to screen people with depressive symptom.

Quality of Life in Epilepsy Inventory 31 (QOLIE-31): The scale has 31 items in 7 subscales: emotional well-being, social functioning, energy /fatigue, cognitive functioning, seizure anxiety, medication effects, and overall quality of life[34]. Each item is scored using the percentile system, and each item has a corresponding score for different options. When scoring, the subscale score is first calculated; the subscale score is equal to the sum of the scores of all the items in the subscale divided by the number of items in the subscale. The total scale score is then calculated; the total scale score, ranging from 0 to 100 points, is equal to the sum of the scores of each subscale from the previous step multiplied by the weight of that subscale. The higher is the total score, the better is QOL.

WHO Disability Assessment Schedule V.2.0 (WHO DAS 2.0): It is used to measure individual's difficulty in daily life over the past 30 days. It contains 36 items, belonging to 6 domains: "Understanding and communicating", "Getting around", "Self-care", "Getting along with people", "Life activities"

(household and school/work), and "Participation in society". Each item is scored from 1 (non) to 5 (extreme or cannot do) points. Higher scores indicate higher disability.

Social Support Rating Scale Social Support Rating Scale (SSRS): This self-report scale measures people's social support. It has 10 items in 3 subscales: objective support, subjective support, and supports utilisation. The total score of the scale is the sum of each item, and the higher the score, the better the social support[35].

Statistical analysis

Using Kolmogorov–Smirnov test, all continuous variables were non-normally distributed. We used Mann-Whitney U tests for continuous variables and Chi-square statistics for categorical variables. In the training cohort, LASSO analysis, a popular method for variable selection and shrinkage in the Cox proportional hazards model with high dimensional predictors [36], was used to identify risk factors of SSD. Stepwise linear regression was performed from LASSO selected features using 1000 times bootstrap calculation to form a risk nomogram. The predictive accuracy of the nomogram was measured by area under the curve (AUC) of the receiver operating characteristic curve (ROC), the calibration curve and decision curve analysis (DCA) in training and testing cohorts. As nomogram might be suitable for academic use, the result of stepwise linear regression of LASSO analysis were used to develop a singular SSD Risk Score Tool to screen SSD for non-academic centers. Each risk factor was assigned a score based on its beta coefficient. ROC curve was used to determine the optimal cut-off score for detecting people with SSD. Analyses was performed in R software (version 3.6.2, R Project for Statistical Computing, http://www.r-project.org). Two tails $P < 0.05$ was considered statistically significant.

Results

Eight-hundred-and-sixty-eight people were assessed for eligibility. Six-hundred-and forty-nine completed the structured interview and internet-based questionnaire. Eighteen individuals were excluded for providing inaccurate/inconsistent phone answers on the questionnaire. At final, 631 participants (343 male, 288 female) were included, with a median age of 26.0 (20.0 -34.0) years. The number of people excluded from the analysis can be seen in the study flow chart (eFigure 1). There were no significant differences in demographic and clinic features between training (n=524) and testing cohorts (n=107) (P>0.05, table 1, condensed). The complete list is available in Supplementary eTable 1.

Prevalence

One hundred ninety-eight participants fulfilled the DSM-5 SSD criteria in a structured interview. Of them, 81 had somatic symptoms attributed to ASMs' adverse events leading to optimization of drug regimen. Re-interview for SSD and re-report SSD-12 scores were arranged 4 Weeks after ASMs optimization to determine whether psychological treatment was needed. As a result, the somatic symptoms of 48 people resolved, and they did not meet the criteria for SSD in a re-interview. The SSD-12 scale score was also significantly lower. They were excluded from the SSD group. Somatic symptoms persisted in the other 33 people, and they continued to meet the SSD. ASMs at first structural interview, main somatic symptoms, ASMs optimization, the result of re-interview for SSD and SSD-12 scores 4 Weeks after ASMs optimization of those 48 participants are shown in supplementary eTable2. Eventually, 150 people were confirmed to have comorbid SSD (24%).

Location, the intensity of somatic symptoms

BDS checklist results showed that the top 3 most common symptoms were memory impairment (85%), headache (80%) and dizziness (78%) (Figure 1A). GS system was the most frequently affected system. Compared with people without SSD, somatic symptoms of those with involved multi-systems are more frequent (82% vs 28%, P <0.001). The distribution of individuals reporting positive BDS-checklist systems can be seen in Figure 1B.

Associated psycho-behavioural features

Compared with people without SSD, people with SSD showed significantly higher SSD-12 total score and all subscale scores (Figure 1C), showing higher psychological burden. Their excessive symptom-related thoughts, feelings, and behaviours were far more frequent than people without SSD (Figure 1D-E).

In our cohort, 23 people (15%) had moderate SSD, and 127 (85%) had severe SSD.

People with SSD showed significantly higher GAD-7 score, higher PHQ-9 score (Figure 2A). Of the 631 participants, 150 (24%) had been diagnosed as SSD by structured interview, 156 (25%) had depressive symptoms (PHQ-9 score≥10), and 230 (21%) had anxious symptoms (GAD-7 score ≥7). The overlap of these three syndromes is shown in Figure 2B. Each syndrome appeared together with the other syndromes more frequently than alone: 77% of people with SSD had comorbid depressive symptoms, anxious symptoms or both; 93% of people with depressive symptoms had comorbid anxious symptoms, SSD or both. Among them, 11% (9/82) were moderate SSD, and 89% (73/82) were severe SSD. 77% of the people with anxiety symptoms had comorbid depressive symptoms, SSD or both. Among them, 13% (15/114) were moderate SSD, and 87% (99/114) were severe SSD. Thirty-four (23%) of people with SSD had neither depression nor anxiety measured using PHQ-9 and GAD-7 questionnaires.

Clinical characteristics

Compared with participants without SSD, those with SSD were more likely to live in the countryside, with low family monthly income (under 4000 RMB) and low educational background (high school or lower) (Figure 2C).

People with SSD had significantly more focal epilepsy than those without, with a higher percentage of hippocampal sclerosis (HS) etiology and lower SSRS total score than people without (Figure 2D).

Illness consequences of SSD

People with SSD had frequent seizures (more than once a month) and DRE, showing significantly higher NHS3 total scores (Figure 2E).

People with SSD also showed lower QOLIE-31 total score and all subscale scores, higher WHO DAS 2.0 total scores, and higher economic burden (Figure 2F). The complete list of comparasion of SSD characteristics between epilepsy people with SSD and those without SSD can be seen in eTable 3.

Risk markers from LASSO analysis

History of severe traumatic brain injury, hippocampal sclerosis, low seizure worry and medication effects scores of QOLIE-31, multiple systems that somatic symptoms affected, and high GAD-7 score were six risk markers of SSD in epilepsy people after stepwise linear regression of LASSO selected features using 1000 times bootstrap calculation (Figure 3A, 3B). The final predictive nomogram, consisting by these six risk markers, for predicting SSD was developed (Figure 3C) and validated to have good accuracy by AUC of ROC, the calibration curve and DCA in training and testing cohorts (Figure 4). After assigning a score for each risk factor based on their beta coefficients (eTable 4), a singular SSD Risk Score Tool, suitable for use in non-academic centers, was developed and shown in supplementary

materials (eTable 5). According to ROC curve of SSD Risk Score Tool (eFigure 2), AUC was 0.898 (95% CI = 0.869–0.928). The best cut-off score was ≥12 points, with a sensitivity of 88.9%, and a specificity of 78.1% (eTable 6).

Discussion

We found that the prevalence of SSD in people with epilepsy was near a quarter and comparable to depression[1,2] and anxiety [2]. These three psychiatric disorders overlapped; about one-quarter of people with SSD had neither depression nor anxiety. This highlights the need to screen SSD in people with epilepsy. People with SSD experienced frequent seizures and DRE with significantly higher NHS3 total scores than those without. They had lower QOLIE-31 total score, higher WHO DAS 2.0 total score and health care costs, consistent with previous SSD studies in primary care [37,38]. SSD affected epilepsy prognosis also underlines the importance of early identification and stratification of people suffering from SSD.

An accurate, individualized and convenient predictive tool, such as a nomogram, is helpful in clinical practice. To develop a better prediction model, 64 high-dimensional candidate variables (far more than other risk factor studies of psychiatric comorbidity in epilepsy) were on our list of risk factors of SSD in the training stage. Accordingly, the Lasso regression analysis, a method for high dimensional variables selection proven to improve the predictive accuracy and avoid over fitting[39], and a stepwise linear regression using 1000 times bootstrap calculation was utilized to select the most important predictors. Our predictive nomogram satisfied diagnostic accuracy and discriminative ability by many statistical

methods (ROC, DCA, and calibration curve) in training and testing cohorts. We also used this result to develop a singular SSD Risk Score Tool. It might be applicable in non-academic centers.

In our model, no demographic features were retained in the final risk prediction model. The reason for this lack of association may be the small contribution of demographic features to the risk of SSD compared with that of epileptic and psychiatric variables.

We found some evidence of the association of severe traumatic brain injury or HS and the presence of SSD. The reason for this association may be the neuroanatomical change[40]. A study summarizing nine MRI studies assessing the neuroanatomical correlates of SSD found that SSD was characterized by structural brain alterations mostly allocated in prefrontal, somatosensory and limbic regions known to be involved in emotion and stress regulation as well as pain processing[41]. The exact association between severe traumatic brain injury or HS and SSD require further work.

In our model, psychological variables (seizure worry, medication effects and level of anxiety) impact SSD more significantly than other demographic and epilepsy-related variables. These factors bear a resemblance to illness worry. There are many reports of the correlation between SSD and higher levels of illness worry in the general populations and medical outpatients [42-44]. Similar links between psychological variables and depression have been reported in people with epilepsy [45]. These findings implied psychological variables as treatment targets in managing SSD in epilepsy.

Recently, according to a global survey of the Psychology Task Force of the Medical Therapies Commission of ILAE, when identified with mental disorders in epilepsy people, most healthcare providers will refer individuals to a psychiatrist (>55%) and psychologists (>41%) [46]. For the management of somatoform disorders, a stepped-care approach according to the severity levels of the

symptoms and psychological distress was recommended [47]. Our finding of risk markers suggested specific medical care and psychotherapy; perhaps Cognitive Behavioral Therapy (CBT), in combination with personalized management and treatment of comorbid anxiety and depression, would be suitable for managing SSD in people with epilepsy.

Diagnosing SSD without considering an underlying medical disorder may cause overdiagnosis[48, 49]. In people with epilepsy, ASMs such as valproate, oxcarbazepine, levetiracetam, topiramate and zonisamide may cause somatic adverse events that result in early treatment discontinuation in up to a quarter[50]. In terms of somatic symptoms, there is no difference between the adverse effect of ASM and SSD. In the study, people were symptom-free four weeks after ASM withdrawal or reduction and didn't require further treatment. For a good response to the alteration of ASM, these people were excluded from SSD to avoid overdiagnosis. Somatic symptoms in these people should, however, be followed up in the long term to prevent overlooking an SSD diagnosis. We didn't use the suggestion of a diagnosis of depression or anxiety disorders arising from the interviews as a final diagnosis. Thus, the actual clinical overlap among depression, anxiety disorder, and SSD remains uncertain. Prospective longitudinal studies are needed to validate our findings.

Conclusion

We provide insights into the prevalence, clinical characteristics and risk factors of SSD in people with epilepsy. SSD seems prevalent and comorbid with epilepsy. We present an accurate and convenient predictive nomogram for the early identification of SSD in people with epilepsy.

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Author Contributions

JML: Provided critical intellectual input to the study's conceptualisation, obtaining funding, design, analysis and drafting of the manuscript.

DZ: Provided critical intellectual input to the study's conceptualisation, obtaining funding, design, and analysis, reviewed the manuscript and is the guarantor of the study.

SS: Undertook data collection, carried out the main analysis and reviewed the manuscript.

ZD: Undertook data collection and provided input to the reviewed manuscript.

JWS: Provided critical intellectual input to the study's design, analysis and reviewing of the manuscript.

All reviewed and approved the submitted manuscript.

Conflict of Interests

None of the authors has any conflict of interest to disclose in relation to this work.

Ethical Publication Statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Box 1. Variable included in our study

Social/demographic	Epileptic	Psychiatric and life quality, disability and economic burden
Age	Age of seizure onset (y)	Presence of SSD
Sex	Course of the disease (y)	Severity of somatic symptoms
Race	Asphyxia at birth	No. of positive BDS-checklist systems
Residence	History biomarkers	Symptom-related psychological distress
City	Febrile convulsion	SSD-12 total score
Countryside	Severe traumatic brain injury	SSD-12 cognitive aspects
Live status	Encephalitis	SSD-12 affective aspects
Relationship	Craniotomy	SSD-12 behavioral aspects
Occupation	Family history	GAD-7 score
Individual salary	EEG	PHQ-9 score
Family monthly income	MRI image	SSRS total score
Under 4000RMB	Epilepsy type	Life quality of epilepsy
More than 4000RMB	Temporal lobe epilepsy	QOLIE-31 total score
Educational background	Epilepsy etiology	Seizure worry
High school or lower	Structure etiology	Overall quality of life
Above high school	Infectious etiology	Emotional well-being
Medical insurance	Genetic etiology	Energy/fatigue
BMI	Hippocampal sclerosis	Cognitive
Physical training in winter	Traumatic brain injury	Medication effects

Physical training in summer	Immune etiology	Social function
Current smoking	Cerebral tumor	Disability
Current drinking	Cerebrovascular disease	WHO DAS 2.0 score
	Perinatal causes	Disease economic burden (y)
	Unknown etiology	
	ASMs	
	Anti-seizure effects of ASMs	
	NHS3 total score	
	Frequent seizure	
	Drug-refractory epilepsy	
	Internal of last seizure to investigate (d)	
	Longest seizure-free interval (m)	

BMI, body mass index; EEG, electroencephalogram; MRI, Magnetic Resonance Imaging; ASMs, anti-seizure medications; NHS3, Chalfont-National Hospital Seizure Severity Scale; SSD, somatic symptom and related disorders; BDS-checklist, The Bodily Distress Syndrome Checklist; SSD-12, Somatic Symptom Disorder–B Criteria Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; PHQ-9, Patient Health Questionnaire; SSRS, Social support rating scale; QOLIE-31, the Quality of Life in Epilepsy 31 Patient Inventory; WHO DAS 2.0, WHO Disability Assessment Schedule V.2.0.

Table 1 Demographics and clinical characteristics of people in training and testing cohort

Variables	Training cohort (n=524)	Testing cohort(n=107)	P-value
Age	25.00 (20.00-34.00)	26.00 (21.00-34.00)	0.777
Sex			0.082
Male	293 (55.92%)	50 (46.73%)	
Female	231 (44.08%)	57 (53.27%)	
Residence			0.175
City	266 (50.76%)	62 (57.94%)	
Countryside	258 (49.24%)	45 (42.06%)	
Age of seizure onset (y)	17.97 (11.48-25.48)	17.59 (10.23-24.45)	0.513
Course of the disease (y)	6.24 (3.08-12.97)	6.42 (2.98-13.15)	0.702
Epilepsy type			0.138
Focal epilepsy	420 (80.15%)	89 (83.18%)	
Generalized epilepsy	66 (12.60%)	7 (6.54%)	
Unknown	38 (7.25%)	11 (10.28%)	
ASMs			0.611
Monotherapy	265 (50.57%)	57 (53.27%)	
Polytherapy	259 (49.43%)	50 (46.73%)	
NHS3 total score	9.00 (1.00-13.00)	1.00 (1.00-12.00)	0.088
Frequent seizure (more than once a month)			0.84
No	372 (70.99%)	77 (71.96%)	
Yes	152 (29.01%)	30 (28.04%)	

Drug Refractory Epilepsy			0.485
No	337 (64.31%)	65 (60.75%)	
Yes	187 (35.69%)	42 (39.25%)	
Number of affected systems (according BDS-checklist)			0.167
0	258 (49.24%)	42 (39.25%)	
1	56 (10.69%)	18 (16.82%)	
2	87 (16.60%)	15 (14.02%)	
3	52 (9.92%)	15 (14.02%)	
4	37 (7.06%)	11 (10.28%)	
5	34 (6.49%)	6 (5.61%)	
SSD			0.72
Absence	398 (75.95%)	83 (77.57%)	
Presence	126 (24.05%)	24 (22.43%)	
GAD-7 score	4.00 (0.00-9.00)	3.00 (0.50-7.00)	0.109
PHQ-9 score	5.00 (1.00-10.00)	5.00 (2.00-8.00)	0.349
QOLIE-31 total score	60.23 (47.75-73.90)	63.12 (51.06-71.34)	0.476
WHO DAS 2.0 score	57.00 (44.00-83.00)	57.00 (43.00-83.00)	0.945
Disease economic burden (y)	28700.00 (11230.00-60140.25)	32100.00 (11898.25-71618.58)	0.892

ASMs, anti-seizure medications; NHS3, Chalfont-National Hospital Seizure Severity Scale; BDS-checklist, The Bodily Distress Syndrome Checklist; SSD, somatic symptom and related disorders; GAD-7, Generalized Anxiety Disorder 7-item scale; PHQ-9, Patient Health Questionnaire; QOLIE-31, the Quality of Life in Epilepsy 31 Patient Inventory; WHO DAS 2.0, WHO Disability Assessment Schedule V.2.0.

Figures and figure legends

Figure 1. Comparison of SSD characteristics between epilepsy people without SSD and those with SSD. (**A)** Higher frequency of 25 somatic symptoms according to BDS-checklist in epilepsy people with SSD; **(B)** Distribution of the number of affected systems in epilepsy people with SSD; **(C)** Higher SSD-12 total score (23.00 (20.00-28.00) & 6.00 (1.00-12.00), P <0.001) and all subscale scores (cognitive aspects: 6.00 (5.00-8.00) & 2.00 (0.00-4.00), P <0.001; affective aspects: 9.00 (7.00-10.00) & 2.00 (0.00-4.00), P <0.001; behavioral aspects: 8.00 (7.00-11.00) & 2.00 (0.00-4.00), P <0.001) in epilepsy people with SSD than those without; **(D)** Radar map of individuals having experienced on 12 items of SSD-12 showed higher frequency in epilepsy people with SSD than those without; **(E)** Radar map of individuals having experienced "often" and "very often" on 12 items of SSD-12 is more frequent in epilepsy people with SSD than those without.

BDS-checklist =bodily distress syndrome checklist; SSD =Somatic symptom and related disorders; CP =cardiopulmonary; GI =gastrointestinal; MS =musculoskeletal; GS =general symptoms; BWE =breathlessness without exertion; FLBM =Frequent loose bowel movements; PMFOPTA =pain moving from one place to another. Cog =cognitive aspects; Aff =Affective aspects; Beh =Behavioral aspects. *, ** and *** represent p<0.05, 0.01, 0.001, respectively.

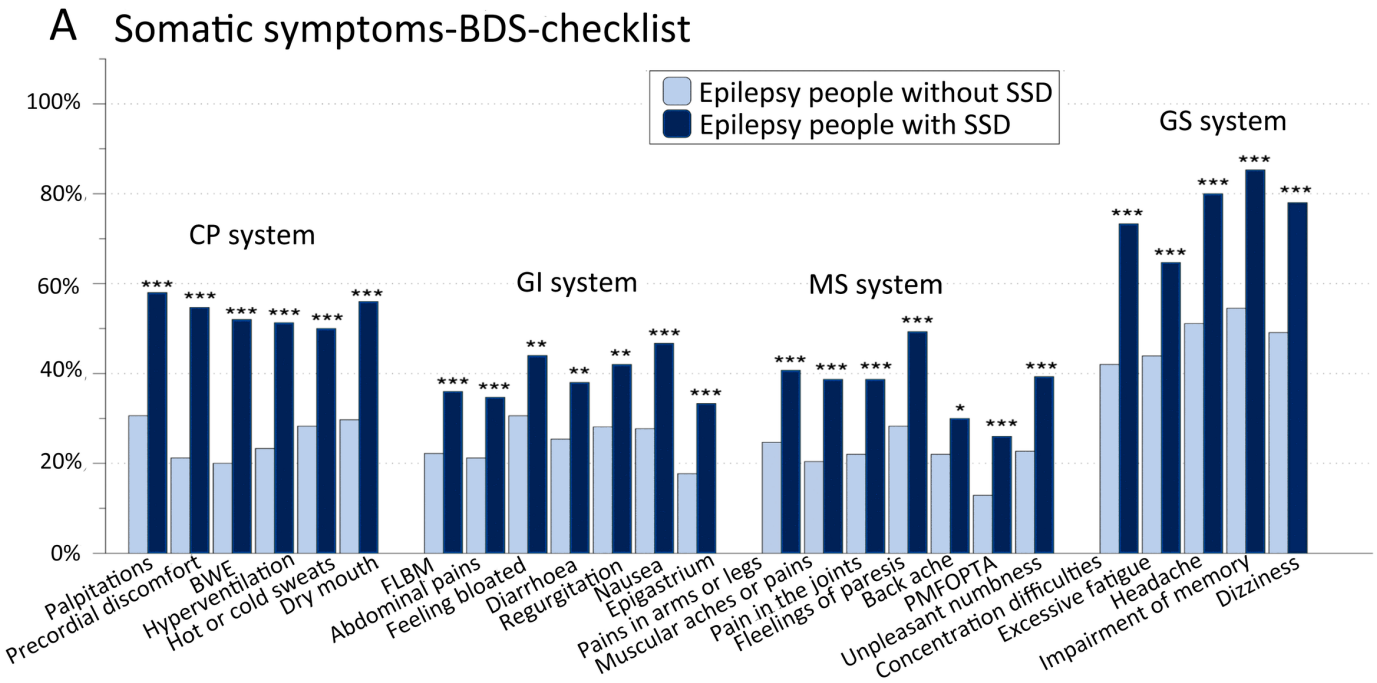
Figure 2. Comparison of psychosis comorbidity, epileptic related illness consequence and life quality. (**A)** Epilepsy people with SSD have higher GAD-7 (10.00 (7.00-14.00) & 2.00 (0.00-6.00), P <0.001) and PHQ-9 (10.00 (7.00-16.75) & 4.00 (1.00-8.00), P <0.001) than those without; (**B)** Venn diagram shows high overlap of SSD, depression and anxiety in epilepsy people. More poor economic condition (Live in the countryside: 60% & 44%, P<0.001, low family monthly income: under 4000 RMB, 52% & 38%, P =0.002 and low educational background: high school or lower, 69% & 58%, P =0.02) **(C)**, higher focal epilepsy (87% & 79%, P =0.01) and HS (9% & 4%, P =0.015) occurrence and poor social support (34.50 (31.00-41.00) & 37.00 (32.00-43.00), P =0.041) **(D)** and more severe severity (frequent seizures: more than once a month, 39% & 26%, P =0.002, DRE: 49% & 32%, P <0.001 and NHS3 total scores: 11.00 (1.00-15.00) & 1.00 (1.00-12.00), P<0.001) **(E)** can be seen in epilepsy people with SSD than those without. (**F)** Significant Lower life quality (QOLIE-31 Total score: 47.70 (39.83-55.44) & 65.57 (53.84-75.79), P <0.001), higher disability (WHO DAS 2.0 total scores: 77.50 (62.50-99.00) & 52.00 (41.00-73.00), P <0.001) and economic burden (48265.00 (21710.00-80900.00) & 24630.00 (9932.50-55325.00), P <0.001) can be seen in people with SSD than non-SSD people with epilepsy.

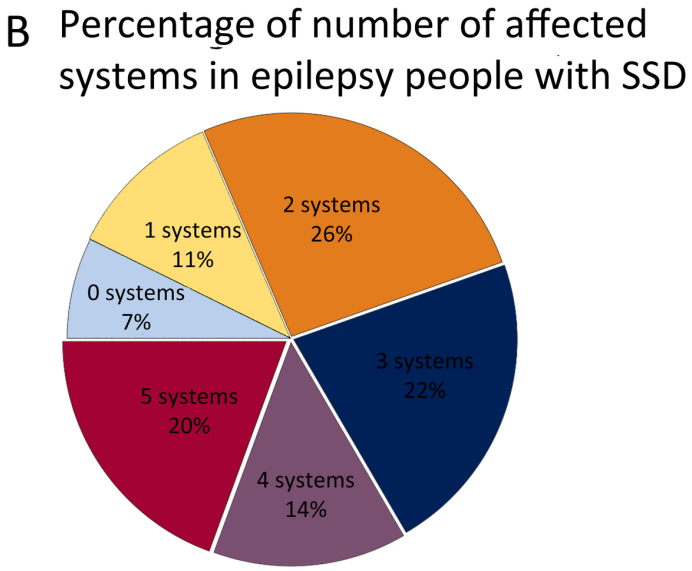
GAD-7 =7-item Generalized Anxiety Disorder scale; PHQ-9 =9-item Patient Health Questionnaire; SSD =Somatic symptom and related disorders; LEB =low educational background; HS =hippocampal sclerosis; SSRS =Social support rating scale; NHS3 =Chalfont-National Hospital Seizure Severity Scale; QOLIE-31=the Quality of Life in Epilepsy 31 Patient Inventory; WHO DAS 2.0 =WHO Disability Assessment Schedule V.2.0. *, ** and *** represent $p<0.05$, 0.01, 0.001, respectively.

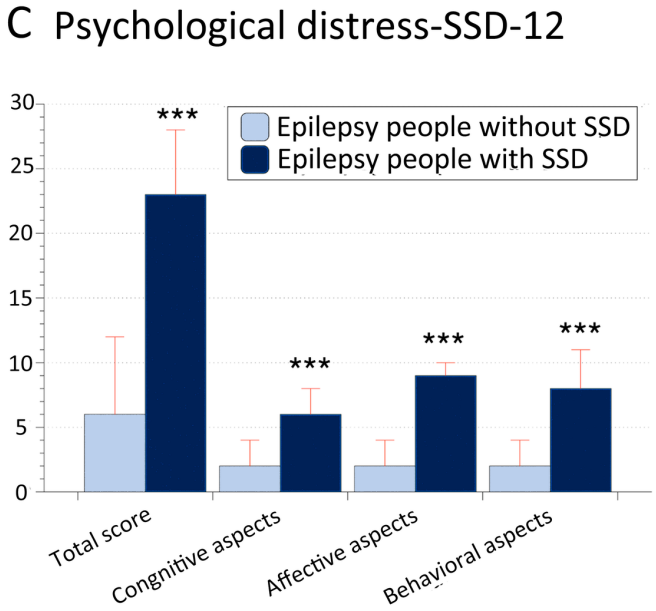
Figure 3. Risk factors selection for SSD prediction models using the least absolute shrinkage and selection operator (LASSO) regression and nomogram for predicting SSD. **(A)** The LASSO model identified the optimal penalization coefficient lambda (λ) using 10-fold cross-validation. And the vertical black dashed line represents the lowest mean-square error corresponding to log(λ) is -3.757. **(B)** LASSO coefficient profiles of all the 64 features. The vertical black dashed line (log(λ) is -3.757) represents the optimal model resulting in nine nonzero features. **(C)** Six features were retained in the final predictive model after a stepwise linear regression of LASSO-selected features using 1000 times bootstrap calculation. Locate the individual's position on the scale associated with each risk factor. The top axis displays prognostic points. Connect the position on each risk factor axis with the "Points" axis to determine the number of points for the corresponding risk factor position. Add up the points for all of the risk factors, then find the appropriate position on the "Total points" axis and connect it with the associated work on the "Predicted probability of SSD" (bottom) axis to determine the individual's risk. QOLIE-31 =the Quality of Life in Epilepsy 31 Patient Inventory; BDS-checklist =bodily distress syndrome checklist; GAD-7 =7-item Generalized Anxiety Disorder scale; SSD =Somatic symptom and related disorders.

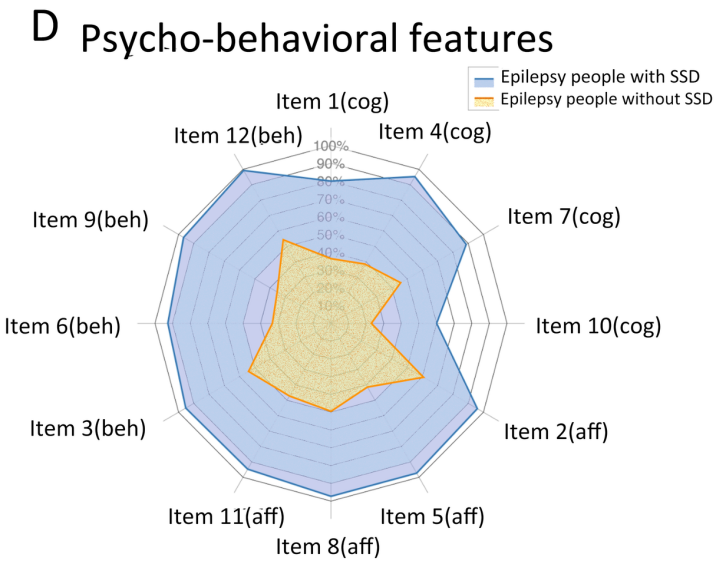
Figure 4. The nomogram's receiver operating characteristic (ROC), calibration curve and decision curve analysis (DCA) for predicting SSD in the training and testing cohorts. The area under the curve (AUC) under the ROC curve of the predictive nomogram was 0.925 (95% CI 0.90–0.95) in the training cohort **(A)** and 0.924 (95% CI 0.87–0.98) in the testing cohort **(B)**, showing a favorable predictive efficacy. The calibration curve for our nomograms showed good agreement between predictions and actual observations in the training **(C)** and the testing cohort **(D)**. DCA curve showed a great overall net benefit in training **(E)** and testing cohort **(F)**. These results indicated that the predictive nomogram displayed good accuracy.

The calibration curve of the training cohort and the nomogram-predicted outcomes for SSD were plotted on the x-axis, while the actual observed effect was on the y-axis. The 45° line represented the best prediction; the solid dark line represented the performance of the nomograms. DCA was employed to evaluate the clinical utility of our model. The x-axis of the decision curve was the threshold of the predicted probability using the models to classify people with SSD. The y-axis shows the clinical decision net benefit for people based on the classification result in this threshold. The decision curves of the treat-all scheme (solid blue line) and the treat-none scheme (horizontal solid black line) were used as references.

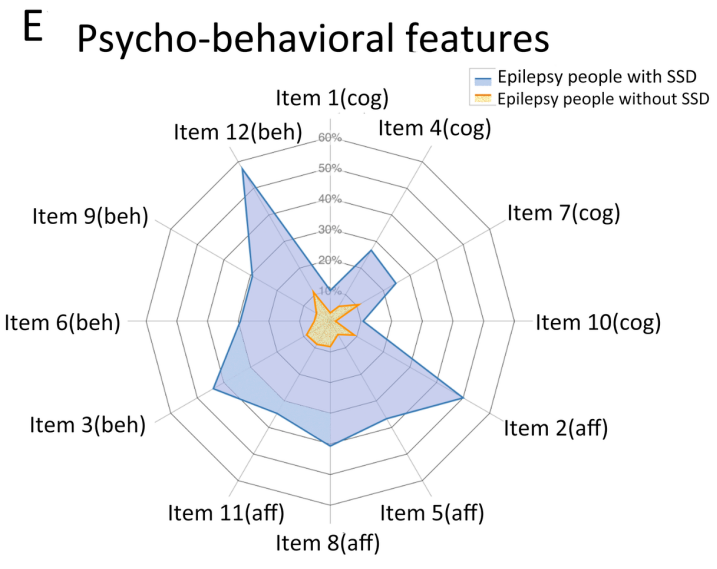








Having experienced on 12 items of SSD-12



Experiencing “often” and “very often” on 12 items of SSD-12

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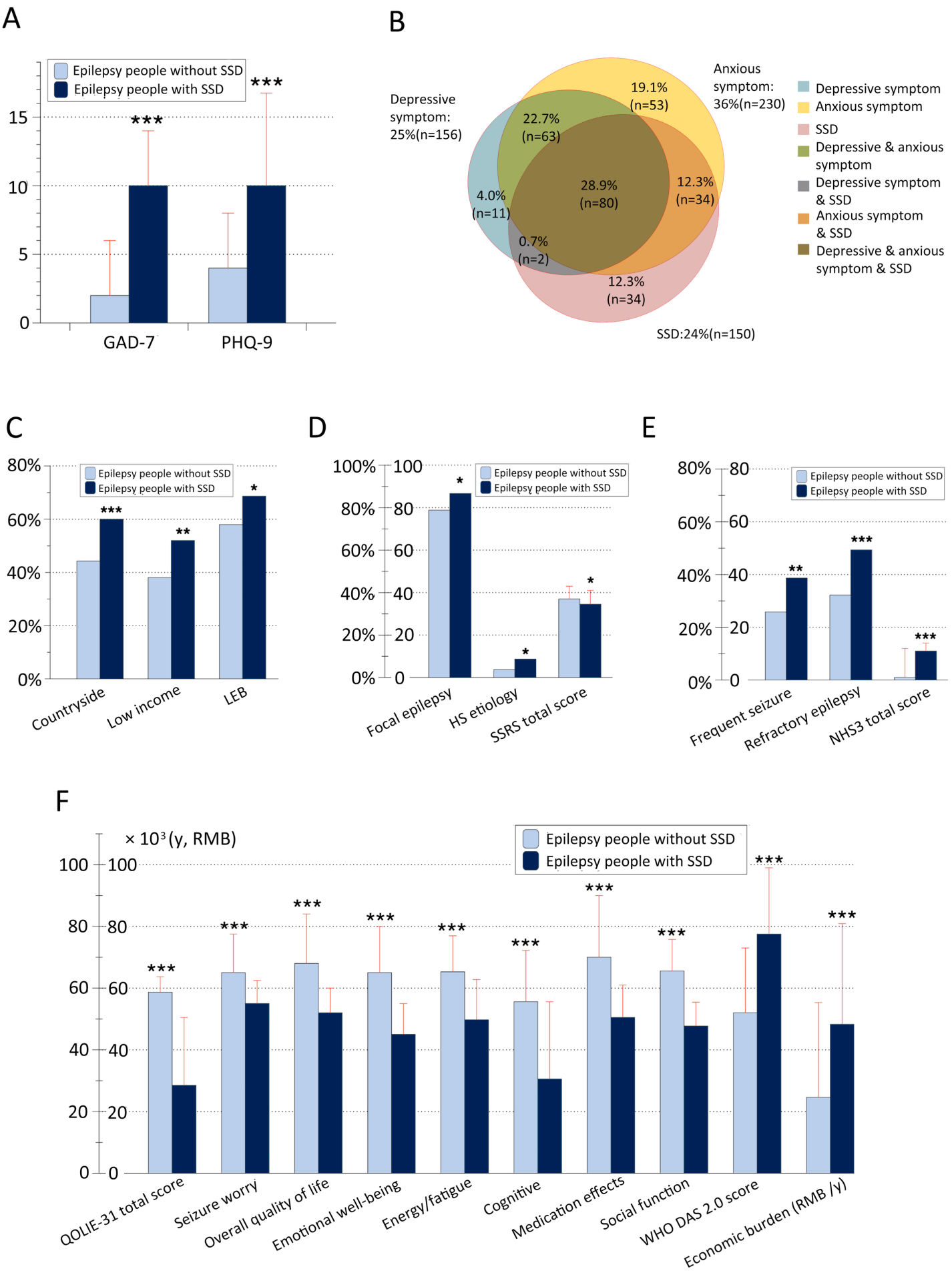

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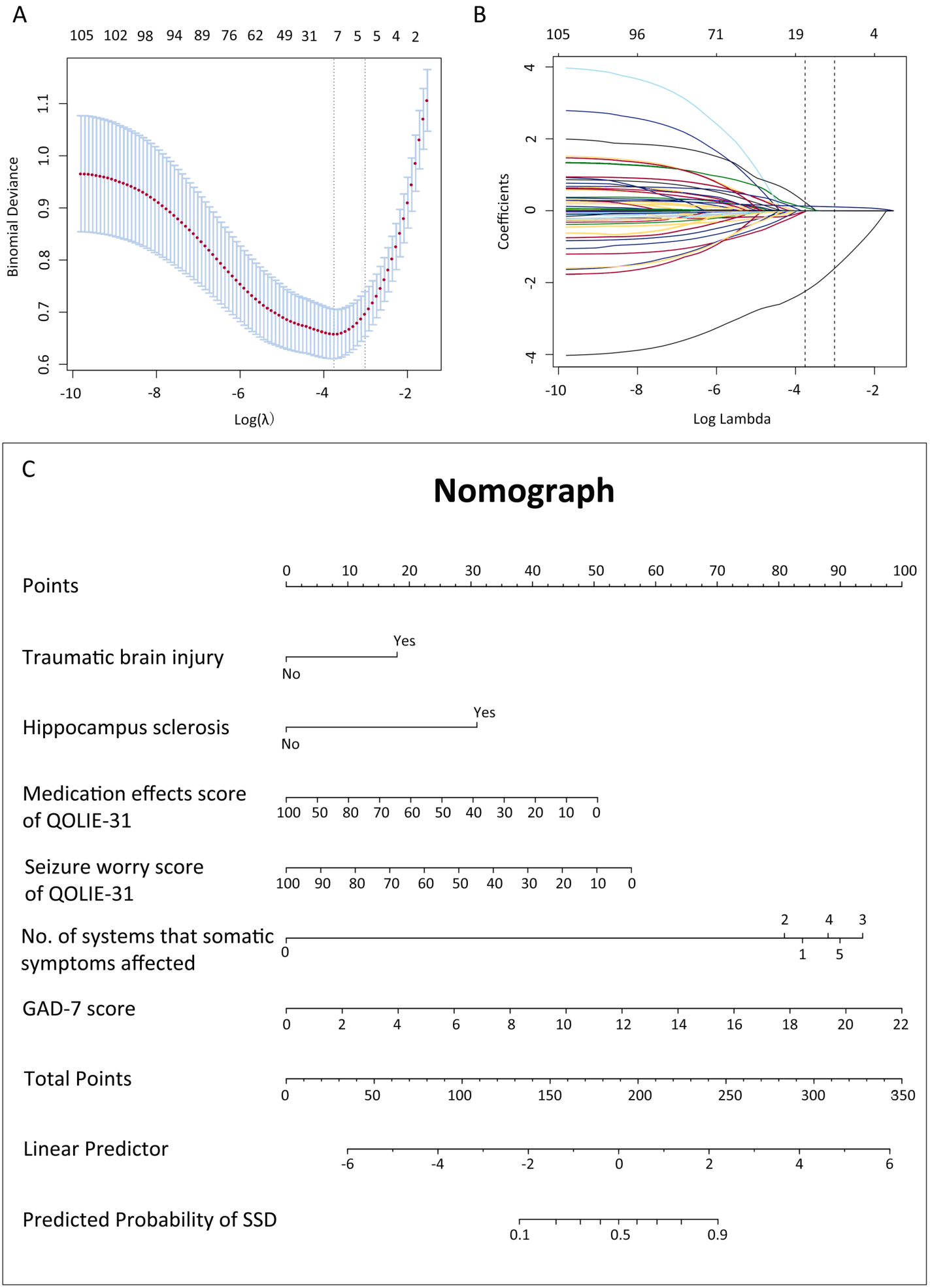

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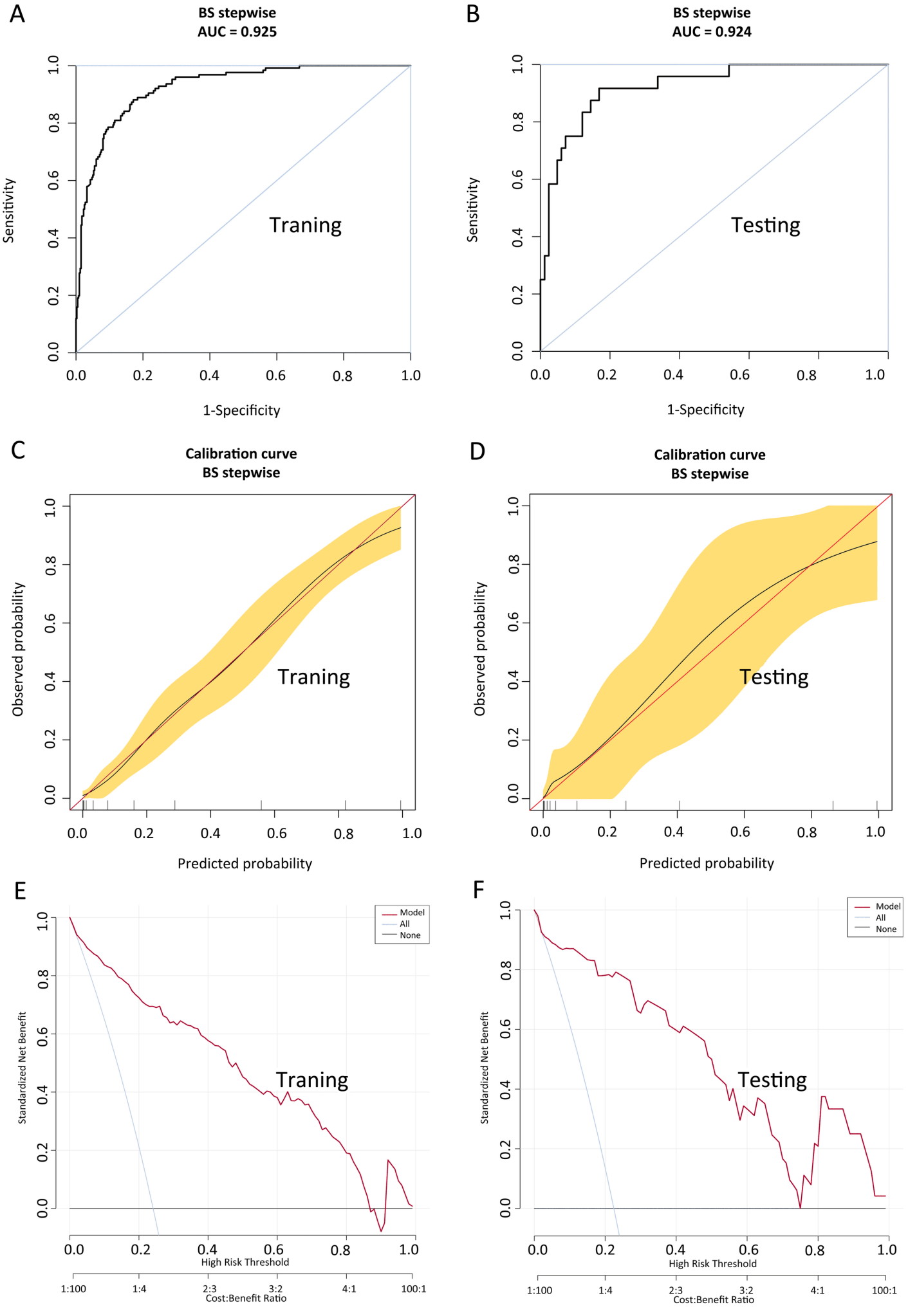

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