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Clinical Outcome Assessments in Encephalitis

A Systematic Review

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Abstract

Background and Objectives

Most patients with encephalitis experience persisting neurocognitive and neuropsychiatric sequelae in the years following this acute illness. Reported outcomes are often based on generic clinical outcome assessments that rarely capture the patient perspective. This may result in an underestimation of disease-specific sequelae. Disease-specific clinical outcome assessments can improve clinical relevance of reported outcomes and increase the power of research and trials. There are no patient-reported outcome measures (PROMs) developed or validated specifically for patients with encephalitis. The primary objective of this systematic literature review was to identify PROMs that have been developed for or validated in patients with encephalitis.

Methods

We performed a systematic review of the literature published from inception until May 2023 in 3 large international databases (MEDLINE, EMBASE and Cochrane libraries). Eligible studies should have developed or validated a PROM in patients with encephalitis or encephalopathy. Methodologic quality was evaluated using the Consensus-based Standards for the selection of health status Measurement Instruments study design checklist for PROMs.

Results

We identified no disease-specific PROMs developed or validated for patients with encephalitis. We identified one study on the development and validation of a disease-specific PROM for hepatic encephalopathy, although this disease course is substantially different to that of patients with encephalitis. The methodologic quality of the included study was generally rated as "doubtful." We identified 30 PROMs that have been *applied* in 46 studies on encephalitis or encephalopathy, although not validated in these populations. The most commonly applied PROMs for measuring Health-Related Quality of Life were the *Medical Outcomes Study Short Form-36* and the *Sickness Impact Profile*. Emotional well-being was often assessed with the *Beck Depression Inventory (BDI-II)*. Sporadically, PROMs were applied to address other aspects of outcome including daily functioning and sleep quality.

Discussion

This systematic review confirms a critical gap in clinical outcome assessments in patients with encephalitis, failing to identify a validated measuring tool for detecting neurocognitive, functional, and health status. It is therefore essential to develop and/or validate disease-specific PROMs for the population with encephalitis to capture relevant information for patient management and clinical trials about the effects of disease that are at risk of being overlooked.

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Glossary

CASE = Clinical Assessment Scale for Autoimmune Encephalitis; **COSMIN** = Consensus-based Standards for the selection of health status Measurement Instruments; **EQ-5D** = EuroQol-5D; **GOS** = Glasgow Outcome Score; **HRQoL** = Health-Related Quality of Life; **LOS** = Liverpool Outcome Score; **mHE** = minimal hepatic encephalopathy; **mRS** = modified Rankin scale; **NIHSS** = NIH Stroke Scale; **PROMs** = patient-reported outcome measures; **SF36** = Short Form-36.

Introduction

Encephalitis is a collective term for inflammation of the brain, caused by infectious agents or autoimmunity. The inflammation can affect preferred locations in the brain or have a more diffuse impact, depending on the etiology. As a result, a range of symptoms may persist after diagnosis and treatment. The most important being seizures, deficits in memory, concentration, and speech, and emotional and behavioral changes.[1-3] The often-reported high chances of good prognosis are often based on generic, aspecific clinical outcome assessments. Approximately two-thirds of patients with encephalitis will not fully recover within 2 years of diagnosis, when assessed with detailed cognitive assessments.[4-6] Even this may be an underestimation because patient-reported outcomes (i.e., quality of life) do not always correlate to objective cognitive outcomes.[7,8]

A recent systematic literature review on clinical outcome assessment tools applied in encephalitis[4] describes well-known scales including the modified Rankin scale (mRS), the Glasgow outcome score (GOS), and the Barthel index, all originally developed in patients with other neurologic diseases. The most often applied mRS was originally developed for stroke patients.[e1] The mRS is a clinician-reported outcome assessment, which categorizes patients from zero—no symptoms—to 6—death, with different levels of disability. Although easily applicable and relevant for stroke patients, it does not capture the range of potential sequelae of encephalitis (or other types of brain injury). More recently, disease-specific clinical outcome assessments have been developed for patients with encephalitis including the Liverpool Outcome Score (LOS), which is a combination tool scored by clinician reports and patient reports. Another disease-specific clinician-reported outcome assessment for encephalitis is the Clinical Assessment Scale for Autoimmune Encephalitis (CASE).[9] This tool captures the potential sequelae of encephalitis with more detail than the mRS, especially in the acute phase.[10] Although it has good discriminative ability in the acute phase/severely affected patients, the applicability for long-term and more subtle sequelae is limited.

To capture all important outcomes for patients with encephalitis over the disease course, the World Health Organization's "International Classification of Functioning, Disability and Health (ICF)" framework can be used. The ICF was made for measuring health and disability. The classification includes the domains *anatomic, physiologic or psychological structure* and *function*—in medicine, also defined as *symptoms*. It comprises the ability to perform *activities*, such as walking and personal care and the ability to *participate* in society—e.g., independent transportation, the ability to work, economic self-sufficiency, and social integration. To assess anatomic structure and physiologic function in patients with encephalitis, the standard physical examination and ancillary tests may be used. The mRS or Barthel index focus on the activity level. Assessments for participation level, well-being, and/or quality of life are often measured with patient-reported outcome measures (PROMs).[e2,e3] PROMs are outcome assessment tools used to express self-reported outcomes on a numeric scale. A study dedicated to compare the effects of stroke on physical and cognitive health using the mRS and the PROM NeuroQoL demonstrated that the mRS captured approximately half of the variance in self-reported functioning.[11] Self-reported sequelae of brain injury may also persist after objectively measured (cognitive) deficits have improved.[8]

To ensure precision and accuracy, a high-quality PROM must demonstrate objectivity, reliability, and validity. A rigorous item selection process with attention to responsiveness to change over time are key aspects of the methodologic design for PROM development and validation. It is also important to differentiate between a "generic" PROM, targeting a construct in any population, and a 'disease-specific' PROM, targeting 1 or multiple constructs in a specific population of patients.[3]

Objective

There are no PROMs developed for or validated specifically for patients with encephalitis.[12] The primary objective of this systematic literature review was to identify PROMs that have been developed for or validated in the population of patients with encephalitis. We do not aim to evaluate the outcomes of the population over time but specifically the tools used to assess the outcome.

A secondary objective was to appraise which PROMs from the neurology field are applied to this population; however, they have not been validated for this use.

Methods

Search Strategy

We performed a systematic search of the literature published from inception until May 2023. The search strategy was proposed by the systematic review team and refined by a librarian. Three variants were created and applied for the MEDLINE (OvidSP), EMBASE, and Cochrane libraries. All searches included MeSH terms and free text terms for (1) scales and tools, questionnaires, and Patient-Reported

Table 1 Search Strategy and Terms

Concept	Search terms per database (including MESH terms)	Years of coverage (for all 4 concepts)	Records identified (for all 4 concepts)
1. Encephalitis & encephalopathy	**Embase**: ('encephalitis'/exp OR (encephali* OR (encephalomyeli* NOT myalgic-encephalomyelitis) OR meningoencephalit* OR panencephalit* OR rhombencephalit*):ab,ti,kw OR encephalopath*:ti,kw) NOT 'chronic fatigue syndrome'/de **Medline**: (exp Encephalomyelitis/OR (encephali* OR (encephalomyeli* NOT myalgic-encephalomyelitis) OR meningoencephalit* OR panencephalit* OR rhombencephalit*).ab,ti,kf. OR (encephalopath*).ti,kf) NOT Fatigue Syndrome, Chronic/ **Cochrane**: ((encephali* OR (encephalomyeli* NOT myalgic NEXT encephalomyelitis) OR meningoencephalit* OR panencephalit* OR rhombencephalit*):ab,ti,kw OR encephalopath*:ti,kw)	**Embase**: 1971–2023 **Medline**: 1946–2023 **Cochrane Central Register of Controlled Trials**: 1992–2023	**Embase**: 5,889 **Medline**: 3,026 **Cochrane Central Register of Controlled Trials**: 524
2. Patient-reported outcome measures	**Embase**: 'patient-reported outcome'/de OR 'health survey'/de OR 'questionnaire'/exp OR 'self report'/de OR 'outcome assessment'/de OR (patient-reported-outcome* OR PROM OR PROMs OR health-survey* OR questionnaire* OR self-report* OR ((outcome*) NEAR/3 (Measure* OR assessment* OR score* OR Tool* OR Scale*))):ab,ti,kw) **Medline**: (Patient Reported Outcome Measures/OR Patient Outcome Assessment/OR exp "Surveys and Questionnaires"/OR Outcome Assessment, Health Care/OR (patient-reported-outcome* OR PROM OR PROMs OR health-survey* OR questionnaire* OR self-report* OR ((outcome*) ADJ3 (Measure* OR assessment* OR score* OR Tool* OR Scale*))).ab,ti,kf.) **Cochrane**: ((patient NEXT reported NEXT outcome* OR PROM OR PROMs OR health NEXT survey* OR questionnaire* OR self NEXT report* OR ((outcome*) NEAR/3 (Measure* OR assessment* OR score* OR Tool* OR Scale*))):ab,ti,kw)		
3. Population able to self-report (older children and adults)	**Embase**: NOT ('infant'/exp NOT ('adult'/exp OR 'juvenile'/de OR 'adolescent'/exp OR 'child'/de OR 'abandoned child'/de OR 'adopted child'/de OR 'boy'/de OR 'brain damaged child'/de OR 'child of impaired parents'/de OR 'foster child'/de OR 'gifted child'/de OR 'girl'/de OR 'handicapped child'/de OR 'hospitalized child'/de OR 'institutionalized child'/de OR 'orphaned child'/de OR 'preschool child'/de OR 'school child'/de OR 'single parent child'/de OR 'toddler'/de OR 'unwanted child'/de)) NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) **Medline**: NOT (exp Infant/NOT (exp Adult/OR exp Child/OR Adolescent/)) NOT (exp animals/NOT humans/)		
4. Article type	**Embase**: NOT [conference abstract]/lim **Medline**: NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt **Cochrane**: NOT "conference abstract":pt		

Outcome Measures and (2) terms for encephalitis or encephalopathy (Table 1). We included PROMs developed or validated in patients with an encephalopathy as well to increase the possibility to identify relevant clinical outcome assessments for the targeted population. We also screened for potentially relevant papers that did not appear in the primary search in reference lists of included full-text articles.

Screening

Titles and abstracts of articles retrieved were screened by 3 authors (J.B., M.R.M., and S.H.O.) based on the following inclusion and exclusion criteria. Full texts were all independently evaluated by 2 authors (J.B. and S.H.O.). Any disagreement was discussed, if necessary together with a third author (M.J.T.).

Inclusion and Exclusion Criteria

Inclusion criteria:

- Articles on the topic of a Patient-Reported Outcome Measure
- Addressing the population with encephalitis or encephalopathy
- Patients of all ages who can self-report
- Original development or validation papers of the Patient-Reported Outcome Measure

Exclusion criteria:

- Questionnaires targeting other aspects of encephalitis or encephalopathy than outcome (i.e., diagnostic tools, epidemiology; therefore not a PROM)
- Articles purely on physician-reported or caregiver-reported outcome measures (*not self-reported*)
- Articles reporting patient-reported outcomes; however, not the development and validation process of the outcome measure
- Patients with diseases of the peripheral nervous system
- No English full text available

The same inclusion and exclusion criteria were applied for the secondary objective, except we included articles reporting but not validating PROMs (an exclusion criterion for the primary objective).

Data Extraction and Quality Assessment

First, the methodologic quality of the included study was assessed using the Consensus-based Standards for the selection of health status Measurement Instruments (COSMIN) study design checklist for PROMs. The checklist is used to assess the study design and adequate consideration of content validity, structural validity, internal consistency, cross-cultural validity, reliability and measurement error, criterion validity, hypothesis testing for construct validity, and responsiveness in articles reporting on the development or validation of PROMs.[13,14] Each measurement property consists of multiple items regarding the methodologic standards for the property. All items were independently scored by 2 researchers (S.H.O., J.B.) using a 4-point rating scale based on the COSMIN Risk of Bias checklist (i.e., *very good, adequate, doubtful,* or *inadequate*).[15] The 2 researchers discussed the deviating scores and came to a consensus. An overall score per measurement property was based on the lowest score for any of the items.

As a second step, the quality of the measurement properties are rated using the updated criteria for good measurement properties (i.e., *sufficient*, *insufficient*, or *indeterminate*).[14] This was also independently scored by 2 researchers (S.H.O., J.B.) and discussed afterward. Finally, we evaluated the availability of normative data and the applicability in cognitively impaired patients.

Data Availability

Any data not published within this article are available at the Erasmus University Medical Center and will be shared on reasonable request from any qualified investigator.

Results

Search and Screening Results

The search strategy yielded 9,439 articles, originating from 1958 to May 2023, of which 7,865 remained after manually removing duplicates. After screening the titles and abstracts based on the inclusion and exclusion criteria, 84 papers remained. Nineteen potentially relevant article from the reference list of these articles were additionally added to the articles for full-text screening.

In the full-text screening of 103 articles, 102 articles were excluded for reasons, as shown in the Figure. Many articles could be classified in more than 1 category (i.e., "not targeting the outcome" and "not patient reported"), which was the explanation for all discrepancies in the individual full-text screening of the 2 authors.

We found only 1 study meeting the inclusion criteria detailing the development and formal validation of a Patient-Reported Outcome Measure; however, this was in patients with hepatic encephalopathy.[16] We identified no study that developed or validated a PROM for encephalitis patients. Several studies reported patient-reported outcomes in patients with encephalitis, although the applied tools were not specifically developed for or validated in the targeted population. These studies were included to address our secondary objective to evaluate applied PROMs.

Primary Results: Development and Validation of a PROM

Characteristics of the Population and Measuring Instrument

The aim of the included multicenter study was to develop and validate a health-related quality of life (HRQoL) instrument that measures the functional and health status of patients with minimal hepatic encephalopathy (mHE).[16]

For item selection for the primary questionnaire, a total of 10 patients with mHE from the Zhingshan Hospital in Shanghai, China (5 men, 5 women, mean age 51.2 years) created a list of items that were important to them. In addition, the authors performed a PubMed search for papers on HRQoL instruments for patients with mHE. Finally, 7 specialists of chronic liver disease and 4 epidemiologists were involved to provide expert review.

The primary questionnaire consisted of 75 items. The authors conducted the questionnaire in 178 patients with mHE; but in the final analysis, 10 of the 178 were excluded because of incompleteness or inability to fulfill the questionnaire. 168 patients remained from 5 Chinese hospitals, 69.6% male, with a mean age of 53 years. 64 patients were interviewed for the item reduction phase; 35 items were identified as important by more than 50% of the respondents. By retesting the 35 items in 26 patients, 30 items remained within 5 domains: physical functioning, psychological well-being, symptoms/side effects, social functioning, and general health.

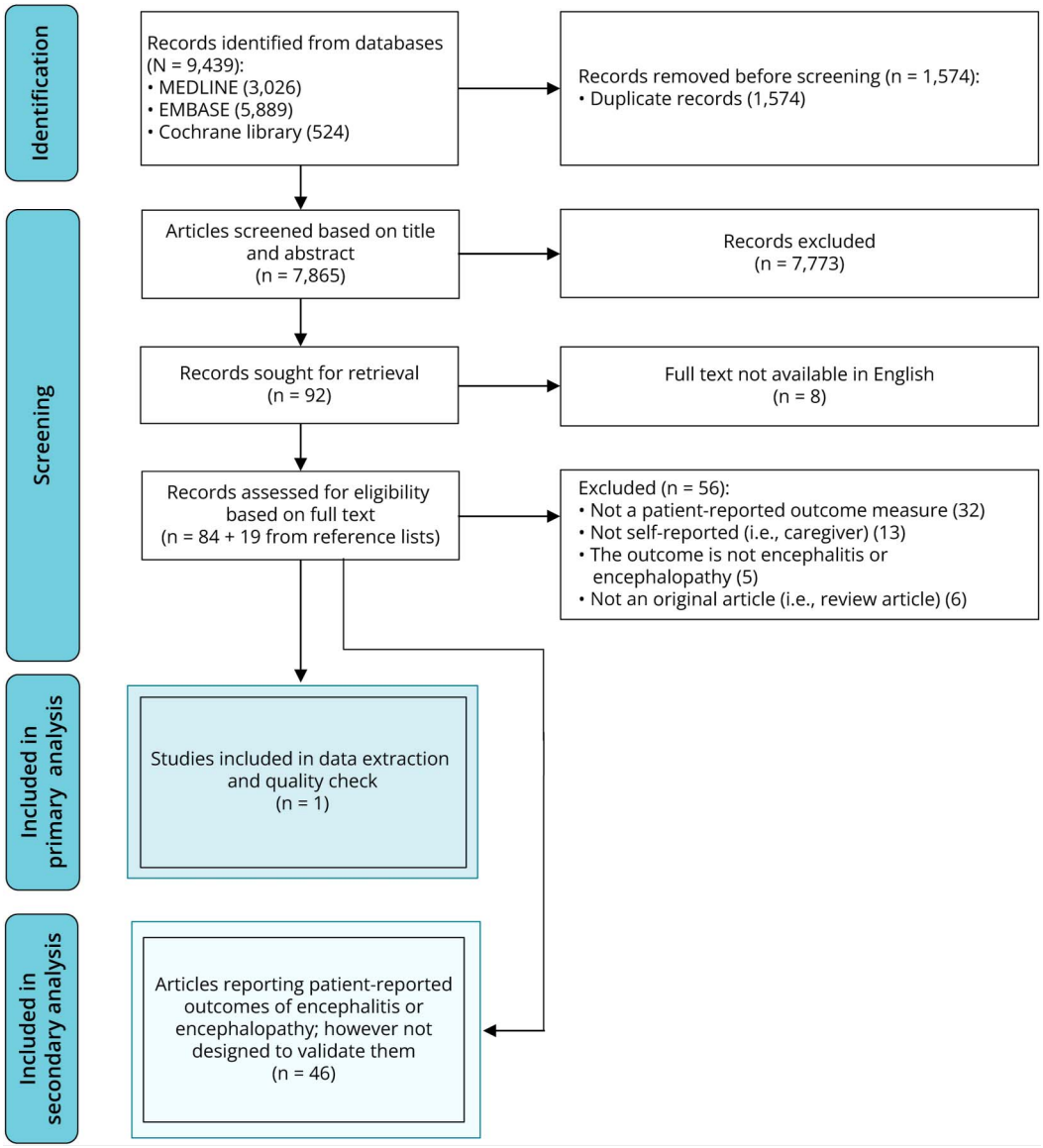
Normative Data and Applicability in Cognitively Impaired Patient

The authors compared the outcomes of patients with mHE on the developed measurement tool with those of 20 age-matched, sex-matched, and educational level-matched healthy volunteers. Normative data are therefore available for this (limited) control group. In all domains, the healthy controls had a better quality of life than the patient group, which supported the discriminant validity of the measurement tool, as an element of construct validity. Patients with mHE, per definition, have cognitive impairments, and therefore, we can assume applicability in patients with (mild) cognitive impairment, although the extent of this was not formally assessed.

Quality of the Included Study

The methodologic quality assessment of the included study per measurement property is summarized in Table 2. See Table 3 for the definitions of the measurement properties that were scored. The general recommendations of the study design was overall rated adequate or very good, but the context of use was not clearly described whereby we had to score this

Figure Flowchart of the Systematic Screening Process, Performed by 2 Independent Researchers and Discussed With a Third if Necessary



as doubtful. The content validity was scored doubtful because it was not clearly described whether interviewers were trained and whether the professionals were asked whether each item was relevant. The structural validity was scored adequate because the number of patients (i.e., 168) was at least 5 times the number of items (i.e., 30).

The internal consistency was scored as very good. The test-retest reliability was scored as inadequate because it was performed in less than 30 patients. The hypothesis testing for construct validity was rated doubtful because there was no hypothesis formulated. No assessment could be made because of missing data for the following measurement properties: measurement error (not described), cross-cultural validity and criterion validity (not tested), and responsiveness (cross-sectional study design).

The quality of the assessed measurement properties is summarized in Table 4.The internal consistency was scored as sufficient because of the Cronbach alpha ≥0.70. The reliability as well was scored sufficient because the intraclass correlation coefficient was ≥0.70. Hypothesis testing for construct validity was scored indeterminate because no hypothesis was defined. The structural validity, cross-cultural validity, measurement error, criterion validity, and responsiveness could again not be scored because of missing data.

Secondary Results: Applied PROMs

The secondary analysis was conducted on included articles (N = 46) *reporting* but not validating PROMs (N = 30) in patients with encephalitis and encephalopathy. Table 5 summarizes a brief overview of the PROMs and the population they were applied in.

Table 2 Methodologic Quality Assessment of the Included Study per Measurement Property

	General recommendations	Content validity	Structural validity	Internal consistency	Cross-cultural validity	Reliability	Measurement error	Criterion validity	Hypothesis testing for construct validity	Responsiveness
Zhou 2009	3	3	2	1	-	4	-	-	3	-

1 = very good; 2 = adequate; 3 = doubtful; 4 = inadequate; - = could not be scored.

Health-Related Quality of Life

Most of the studies reporting on patient-reported HRQoL after encephalitis or encephalopathy apply the *Medical Outcomes Study Short Form-36 (SF36)*.[17-28] The SF36 is a generic—as opposed to disease-specific—PROM on HRQoL. It is suggested to target the full range of health status and well-being[17]; specifically, it addresses 4 "physical health" domains ("physical functioning," "physical role limitation," "bodily pain," and "general health") and 4 "mental health" domains ("mental health," "emotional role limitation," "vitality," and "social functioning").

A common applied HRQoL assessment tool in hepatic encephalopathy is the *Sickness Impact Profile*.[29-37] This tool is also applied for measuring sleep and social activity in the same population. Several studies also mentioned the application of the *Euro-QoL-5D (EQ-5D)* in evaluating general health outcome after viral encephalitis and hepatic encephalopathy.[38,39]

Other generic patient-reported tools addressing HRQoL or the impact of illness in patients with encephalitis and encephalopathy are sporadically described in articles: *Quality of Life after Brain Injury–Overall Scale* in 3 anti-NMDAR encephalitis patients,[40] the *Nottingham Health Profile* in patients with hepatic encephalopathy,[27] and the *Lancashire Quality of Life Profile* and *Brief Illness Perception Questionnaire* in patients with any form (infectious or inflammatory) of acute encephalitis.[3,41] Two studies have applied, however not formally validated, PROMIS (Patient-Reported Outcome Measurement Information System) tools for measuring HRQoL[42] and the impact of illness[43] in patients with hepatic encephalopathy and anti-NMDAR encephalitis, respectively. PROMIS assessment tools are composed—often with a specific disease, population, or construct in mind—of items from a large item bank, using Item Response Theory. The tools can be administered online, and the results are automatically compared with a diverse reference population including patients with various diseases.

In children, HRQoL—after anti-NMDAR encephalitis, acute disseminated Encephalomyelitis, and other inflammatory CNS diseases—was measured almost exclusively with the *Pediatric Quality of Life Inventory*.[7,44-46] This tool consists of 2 surveys; one self-reported survey and one caregiver-reported survey. It addresses the subdomains "physical," "emotional," "social," and "school." In all papers the tools and outcomes are only described and not validated.

The *Neuro-QOL* is a HRQoL measure more specifically designed for neurologic diseases and was used for measuring the quality of life of patients after cryptococcal meningoencephalitis.[47] This scale is validated in several, mostly chronic, neurologic conditions with varied sequelae, among others epilepsy, Huntington disease, and MS.[e4-e6]

Disease-specific Quality of Life outcome assessments have more often been applied in hepatic encephalopathy, one of the most

Table 3 Definitions of the Scored Measurement Properties

Measurement property	Definition
General recommendations for study design	The study requires a clear research aim and a clear description of the PROM and the study population. The quality should be determined in the target population in which the PROM will be used
Content validity	Whether the PROM items are relevant, comprehensive, and comprehensible in terms of the construct of interest and study population, by asking patients and professionals. This is a subjective judgment of the reviewers
Structural validity	The degree to which the scores of a PROM are an adequate reflection of the dimensionality of the construct to be measured, usually assesses by factor analysis
Internal consistency	The degree of interrelatedness among the items, assessed by Cronbach alpha
Reliability	The extent to which the measurement yields consistent reproducible estimates of what is assumed to be an underlying true score
Hypothesis testing for construct validity	As no 'gold standards' exist for PROMs, the commonly used way to investigate the validity is to test hypothesis about expected relationships with other outcome measurements. The authors used the SF-36

Table 4 Quality of the Assessed Measurement Properties of the Included Study

	Structural validity	Internal consistency	Cross-cultural validity	Reliability	Measurement error	Criterion validity	Hypothesis testing for construct validity	Responsiveness
Zhou 2009	-	+	-	+	-	-	?	-

+ = sufficient; ? = indeterminate; - = could not be scored.

common being the *Chronic Liver Disease Questionnaire*.[26,28,48-50] As the name implies, this tool was originally developed for liver disease and therefore not specifically for hepatic *encephalopathy*.

Functioning and Community Integration

In addition to PROMs targeting quality of life, Patient-Reported Outcome Measures were applied to assess daily functioning and participation or integration in the community. The long-term outcome of patients with a tick-borne encephalitis was assessed through a telephone interview, with the *Encephalitis Support Group Questionnaire* 2000. This questionnaire, as the name suggests, was developed by The Encephalitis Society but never officially published or validated as a Patient-Reported Outcome Measure.[12]

The *European Brain Injury Questionnaire* is another applied clinical outcome assessment of cognitive, emotional, and social functioning after brain injury. It was already developed in 1997 in brain-injured patients—consisting for the larger part of patients with cerebrovascular events (63%) or traumatic brain injury (29%).[8] It was applied by Yeshokumar et al.[51] in patients after an acute encephalitis. Albeit not formally validating the tool in this population, the authors did inquire respondents how well the questions reflected their experiences. The response was positive in 59%, 'a little' in 34%, and 'not at all' in 3% (with 5% missing data).

The (re)integration in the community of 3 post–anti-NMDAR encephalitis patients was assessed with the *BIRCO39*.[40] In addition to measuring physical, emotional, and social functioning, this questionnaire focuses on self-organization and employment. The *Environmental Status Scale* is an alternative scale that was applied for these targets (i.e., working life, living conditions, and financial situation), originally developed for MS.[3]

Emotional Well-being and Mood

The *Beck Depression Inventory (BDI) II* is the most frequently applied PROM for emotional well-being or mood status after encephalitis or encephalopathy.[3,18,47,52-54] In addition, the *Hospital Anxiety and Depression Scale (HADS)*, the *Self-Rating Depression Scale (SDS)*, and the *WHO-5 Well-Being Index* have been incorporated in literature on the emotional effects of anti-NMDAR encephalitis,[5,40,55] herpes simplex encephalitis,[56] and hepatic encephalopathy.[24] The HADS aims to screen for the core symptoms of anxiety and depression in patients presenting to nonpsychiatric hospital departments, without including the physical symptoms that may be influenced by somatic comorbidities.[57] The WHO-5 Well-Being Index is a screening tool for depressive symptoms in the general population, and the SDS targets the severity of depressive symptoms.

In an article on the feasibility of a large-scale international web-based inventory of mental health outcomes after encephalitis, items were adapted from the *Maudsley three item VAS (M3VAS)* and the *Psychiatric Diagnostic Screening Questionnaire (PDSQ)*.[41] The M3VAS consists of Visual Analog Scale (VAS) on 3 core depressive symptoms: mood, anhedonia, and suicidality. The PDSQ is a tool to screen for the most prevalent mental health disorders, i.e., mood disorders, anxiety disorders, psychotic disorders, somatoform disorders, and substance use.

Finally, the *Beck Anxiety Inventory (BAI)*[47,53] and the *Zung Self-Rating Anxiety Scale (SAS)*[18,55] have been applied for specifically appraising anxiety. These tools were both developed to address the presence and severity of anxiety symptoms in the general population and in psychiatric populations; the BAI explicitly targets symptoms of anxiety that may not be affected by comorbid depressive symptoms.[e7]

Sleep and Fatigue

Diaz-Arias et al.[52] have emphasized the relevance of fatigue and sleep after autoimmune encephalitis, as measured with the *Modified Fatigue Impact Scale and* the *Pittsburgh Sleep Questionnaire Inventory (PSQI)*, respectively. They denote that fatigue symptoms after encephalitis are not completely accounted for by problems related to sleep or mood. The PSQI has been applied in autoimmune (anti-LGI1) encephalitis more often[58] and has been used in hepatic encephalopathy.[21,24] Sleep quality after autoimmune limbic encephalitis, infectious encephalitis, and hepatic encephalopathy has also been evaluated with the *Epworth Sleepiness Score*[21,24,54,59] and *Insomnia Severity Index*, and after tick-borne encephalitis with the *Functional Outcome of Sleep Questionnaire*.[12,54] The *Fatigue Severity Scale (FSS)* was applied in patients with (post)infectious encephalitis and encephalopathy.[18,54]

Discussion

We systematically reviewed the literature on PROMs developed or validated for patients with encephalitis or encephalopathy. PROMs are imperative to evaluate the patient perspective on

Table 5 Characteristics of the Patient-Reported Outcome Measures (PROMs) From the Secondary Analysis

Domain	PROM	Applied in population with encephalitis	Total number of patients	Applied in population with encephalopathy	Total number of patients
HRQoL	SF-36	All-cause encephalitis[23]	61	Hepatic encephalopathy[17,19-22,24-28] Lyme encephalopathy[18]	1,219 37
	SIP	—	—	Hepatic encephalopathy[29-37]	787
	Euro-QOL-5D	Viral encephalitis[38]	1,107	Hepatic encephalopathy[39]	38
	QOLIBRI-OS	Anti-NMDAR encephalitis[40]	3	—	—
	NHP	—	—	Hepatic encephalopathy[27]	554
	LQoLP	All-cause encephalitis[3]	72	—	—
	BIPQ	All-cause encephalitis[3,41]	517	—	—
	PROMIS HRQoL	—	—	Hepatic encephalopathy[42]	83
	PROMIS Impact of Illness	Anti-NMDAR encephalitis[43]	61	—	—
	PedsQL	Anti-NMDAR encephalitis,[7] ADEM,[44] all-cause encephalitis[45,46]	141	—	—
	Neuro-QOL	Cryptococcal meningoencephalitis[47]	46	—	—
	CLDQ	—	—	Hepatic encephalopathy[26,28,48-50]	521
Functioning and community integration	ESGQ	Tick-borne encephalitis[12]	96	—	—
	EBIQ	All-cause encephalitis[51]	266	—	—
	BIRCO39	Anti-NMDAR encephalitis[40]	3	—	—
	ESS[1]	All-cause encephalitis[3]	72	—	—
Emotional well-being and mood	BDI II	All-cause encephalitis,[3,54] cryptococcal meningoencephalitis,[47] autoimmune encephalitis,[52] anti-NMDAR encephalitis[53]	716	—	—
	HADS	Anti-NMDAR encephalitis[5,40]	10	Hepatic encephalopathy[24]	15
	SDS	Anti-NMDAR encephalitis[55]	16	—	—
	WHO-5 Well-Being index	Herpes simplex encephalitis[56]	26	Hepatic encephalopathy[24]	15
	M3VAS	All-cause encephalitis[41]	445	—	—
	PDSQ	All-cause encephalitis[41]	445	—	—
	BAI	Cryptococcal meningoencephalitis,[47] anti-NMDAR encephalitis[53]	49	—	—
	SAS	Anti-NMDAR encephalitis[55]	16	Lyme encephalopathy[18]	37
Sleep and fatigue	MFIS	Autoimmune encephalitis[52]	407	—	—
	PSQI	Autoimmune encephalitis,[52] anti-LGI1 encephalitis[58]	452	Hepatic encephalopathy[21,24]	65
	ESS[2]	All-cause encephalitis[54], autoimmune limbic encephalitis[59]	200	Hepatic encephalopathy[21,24]	65
	ISI	All-cause encephalitis[54]	188	—	—
	FOSQ	Tick-borne encephalitis[12]	96	—	—
	FSS	All-cause encephalitis[54]	188	Lyme encephalopathy[18]	37

Abbreviation: ADEM = acute disseminated encephalomyelitis; BDI = Beck Depression Inventory; BIPQ = Brief Illness Perception Questionnaire; CLDQ = Chronic Liver Disease Questionnaire; EBIQ = European Brain Injury Questionnaire; ESGQ = Encephalitis Support Group Questionnaire 2000; ESS = Epworth Sleepiness Score; FOSQ = Functional Outcome of Sleep Questionnaire; FSS = Fatigue Severity Scale; HADS = Hospital Anxiety and Depression Scale; ISI = Insomnia Severity Index; LQoLP = Lancashire Quality of Life Profile; M3VAS = Maudsley three-item VAS; MFIS = Modified Fatigue Impact Scale; NHP = Nottingham Health Profile; PDSQ = Psychiatric Diagnostic Screening Questionnaire; PedsQL = Pediatric Quality of Life Inventory; QOLIBRI-OS = Quality of Life after Brain Injury–Overall Scale; SDS = Self-Rating Depression Scale; SIP = Sickness Impact Profile.
1 = Environmental Status Scale; 2 = Epworth Sleepiness Score.

how a disease affects their life, for example, in terms of physical and emotional well-being, daily functioning, and quality of life. They use items to measure outcomes most important to patients, ensuring clinical relevance in standard care and clinical trials. In addition, a dedicated clinical outcome assessment providing detailed insight into the potential disease-specific sequelae can increase the power of future research. For patients with encephalitis, often aspecific clinician-scored scales are presently used, such as the well-known mRS, which do not fully comprehend the cognitive, behavioral, and emotional symptoms that are often endured by this population. Without carefully assessing clinical outcomes, detail and accuracy are compromised and important relevant changes in outcome may go undetected. This problem was illuminated in a study of patients with stroke, comparing results of a generic clinician-reported outcome assessment with a PROM.[11] The mRS captured approximately half of the variance in self-reported functioning. Whereas the correlation between static measurements with the mRS and PROM was reasonable, the correlation between a *change* in patient-reported scores and a change on the mRS score was weak. As far as change in mRS could be explained by self-reported change, this was mostly by items targeting mobility. The authors conclude that PROMs could complement the limitations in content validity and sensitivity of the mRS. It is to be expected that the gap between aspecific scales and self-reported assessments is even larger in patients with encephalitis because the amount of cognitive, behavioral, and emotional symptoms is larger.

Another study comparing neurologic sequelae measured with the NIH Stroke Scale (NIHSS) and the generic Quality of Life PROM EuroQol-5D reports the similar finding that variance in EQ-5D scores is largely explained by motor deficits, with the contrary conclusion that the EQ-5D is *less sensitive* to nonmotor deficits that are captured with the NIHSS (i.e., aphasia and neglect), potentially leading to an overestimation of quality of life.[60] These studies elicit important limitations to take into account when implementing PROMs in the clinical practice and research field of Neurology. Although presumably complementing the 'ceiling effect' of scales such as the mRS, there can be a 'floor effect' of patient-reported outcomes in neurologic patients; it is not possible to administer them to severely cognitively impaired or comatose patients. Furthermore, neurologic patients may not always have the ability to express their symptoms due to specific neurologic deficits including language or disease insight.[3] Clinicians and researchers should also be aware that the measured outcomes also reflect coping strategies of patients in addition to the (pathophysiologic) severity of the effects of the disease. A final consideration on the use of PROMs is that restrictions in activities and participation in society are a comparison with the norm and therefore by definition culturally dependent, making cultural sensitivity an important aspect to consider in validation studies.[e8,e9]

The objective of this systematic review was to identify PROMs developed or validated specifically for patients with encephalitis. At present, the generic mRS is often applied for outcome assessment in encephalitis. In addition, the disease-specific CASE and LOS have been developed for encephalitis. Like the mRS, these scales are clinician scored, which is why they were excluded from this review. Although relevant for the population, the CASE and LOS also predominantly target symptoms of encephalitis in and around the acute phase of the disease, as opposed to long-term outcomes.

After screening nearly 8000 articles, we identified no disease-specific PROMs developed or validated for patients with encephalitis. We identified one study on the development and validation of a disease-specific PROM for hepatic encephalopathy, although this disease course is substantially different to that of patients with encephalitis. The authors developed and validated a PROM to measure the functional and health status of patients with hepatic encephalopathy. While there were some limitations to the methodologic design of the study, as identified by the COSMIN checklist, this PROM was designed to measure quality of life in patients with hepatic encephalopathy. The developed clinical outcome assessment consisted of 5 domains, i.e., physical functioning, psychological well-being, symptoms and side effects, social functioning, and general health. The study did not provide detailed information about what these domains comprise, but it lacked face validity for the application in the population with encephalitis. Important long-term sequelae in this population include seizures, deficits in memory, concentration and speech, and behavioral changes. This PROM covered some of these items; however, it necessitated a more detailed cognitive functioning domain. In addition, this clinical outcome assessment is developed for a population with a chronic disease, whereas for the population with encephalitis, the condition is initially an acute illness, subsequently developing into a chronic phase with long-lasting disability. Furthermore, the clinical outcome assessment was only validated in a Chinese population and might not be applicable in other global regions with a different race, ethnicity, and culture. Another limitation of this study was the small sample size; therefore, the results overall should be interpreted with caution. Finally, the cross-sectional design made it impossible to evaluate longitudinal responsiveness.

For the secondary objective of this study, we identified articles reporting the results of 30 outcome assessments that were not specifically validated for patients with encephalitis or encephalopathy. Most of the articles reported on HRQOL using the SF36. This tool was never formally validated in the population with encephalitis, and therefore, we advise caution in interpreting these findings in this population. The SF36 is validated for many chronic diseases; however, encephalitis is an acute illness. The Neuro-QOL was used for measuring the quality of life of patients after cryptococcal meningoencephalitis.[47] The sample size was not large enough to formally assess the internal consistency, test-retest reliability, or validity in the population and the authors suggest a larger

study is needed to validate the tool in the population with (meningo)encephalitis. There are numerous other clinical outcome assessment tools used in these studies, such as the well-known SF36, BDI-II, and FSS; however, these are not specifically developed nor validated in patients with encephalitis. The results of this systematic review confirmed that there are currently no PROMs available for use in clinical practice or upcoming trials that were developed and validated in patients with encephalitis.

In our systematic review, we did not identify any PROMs developed or validated in the population with encephalitis. We did identify 1 PROM developed and validated in patients with hepatic *encephalopathy*. Our search was limited to English publications and might therefore not have captured relevant articles published in other languages. Furthermore, the search strategy was developed for our primary objective to identify landmark validation studies of PROMs for encephalitis. Therefore, it is possible that articles were missed for the results of our secondary objective, which aimed to investigate applied PROMs.

The secondary results of this study clearly demonstrate the heterogeneity in applied patient-reported outcome assessments. This makes it impossible to reliably compare outcomes across studies. An established set of validated assessment tools for encephalitis is essential for future research. Future outcome assessment should not be solely dependent on self-reported outcomes. A combination of objective, clinician-reported outcome assessments and patient-reported outcome assessments would provide the most complete and reliable evaluation of the scope of outcomes of encephalitis. Particularly in the acute-to-subacute phase of the disease, a 'floor effect' of self-reported outcome assessments, due to, for example, inability to complete questionnaires or attempt activities of daily living, would be overcome by combining results with clinical outcome assessments such as the mRS, CASE, and LOS. PROMs are the key to adding important missing information on long-term outcome.

Many of the previously applied tools are well-established, including the availability of normative reference data and data of other (neurologic) patient groups, allowing comparison. However, none have been validated for the population with encephalitis. For future research, it would be relevant to validate these well-established (generic) PROMs for encephalitis. Validated generic outcome assessments could then be combined with disease-specific items into an established set of clinical outcome assessments of encephalitis.

This systematic review confirms a critical gap in the field, failing to identify a validated measuring tool for neurocognitive, functional, and health status for patients with encephalitis that are at risk of being overlooked. A valid and sensitive outcome measure has the potential to improve the quality of care and the power of future research. It is therefore essential to develop and/or validate disease-specific PROMs for the population with encephalitis to capture the full burden of disease.

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Appendix *(continued)*

Name	Location	Contribution
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