**How should we define a ‘good’ outcome from encephalitis? A systematic review of the range of outcome measures used in the long-term follow up of encephalitis patients**

**Abstract**

**Introduction**

Encephalitis is typically caused by infection or autoimmunity. Most survivors suffer complex neurological and psychiatric sequelae. Standardised outcome measures are needed for accurate interpretation of observational studies and clinical trials. Step one in this process is understanding the strengths and weaknesses of those in use.

**Methods**

We performed a systematic literature review searching six databases. One reviewer screened titles, abstracts and two reviewers determined if shortlisted full-text articles met inclusion criteria. Key data were extracted from these papers and presented as a narrative summary.

**Results**

37 outcome measures were used in 3,133 patients across the 35 included papers of which only one was developed for encephalitis. The outcome measures used in most patients were Glasgow outcome score (GOS) used in 1,436 (46%), Barthel index used in 1,173 (37%), Euro-QoL-5D 1,107 (35%), and modified Rankin Score used in 1,034 (33%).

**Conclusion**

Most of the 37 measures assessed a single category of sequelae using 5-8 point scales and were not validated for use in encephalitis. Research is needed to develop a composite outcome measure for use in clinical practice and a core outcomes set for use in clinical trials. For now, the Liverpool Outcome Score, offers a good choice for clinicians.

**Running title: Outcome measures in encephalitis**

**Key Words: Encephalitis, systematic review, outcome**

**Introduction**

Encephalitis is inflammation of the brain parenchyma that usually presents as an encephalopathy and has an incidence of up to 12.6 per 100,000/year.1 There are a broad range of potential infective and autoimmune aetiologies reflecting demography, geography, and co-morbidities. 2

Regardless of aetiology, the majority of survivors suffer long-term sequelae of some form. Around two thirds of patients fail to make a full recovery even over two years after a diagnosis, often reflecting impairments in concentration, behaviour, speech, memory, and seizures, which together can result in significant inter-personal and professional disability 3. The combination of both neurological and psychiatric symptoms may explain why so many patients are unable to return to work following encephalitis.4 Conversely, although these neurocognitive sequelae are significant, they are potentially missed early in many, as opposed to those occurring in other more common conditions that effect the brain, such as stroke. Because many patients with encephalitis don't have major obvious physical disability, they are often discharged from hospital, with little in the way of plans for rehabilitation 5. This lack of early identification risks patients not receiving sufficient early support for their recovery from the brain injury and the appropriate onward referrals for longer-term care not being made 5,6.

Parents of children with encephalitis have changing priorities at different phases of the recovery 7. Their priorities after the acute illness focus on the pain their child is experiencing and re-learning of everyday tasks, such as eating, talking and walking 7. Later in the child’s recovery, parents consider school achievement, participation in social activities and wellbeing the most important outcomes 7. This mirrors the findings in adult patients following encephalitis, in which the initial challenges they face are symptoms that effect their everyday functioning 4. However, in addition to physical and mental health sequelae, persistent challenges relate to changes to employment status and inter-personal relationships 4. This was also identified in a narrative assessment of patient outcomes, which identified that it is not only the patients that are affected by the ongoing effects after encephalitis, but close family and friends who are often also caregivers 5.

The Core Outcomes Measures Effectiveness Trials (COMET) Initiative was established to address similar concerns, in particular ensuring results of studies can be directly compared; it has been successfully applied to other inflammatory diseases, such as rheumatoid arthritis and other neurological disorders, such as Amyotrophic Lateral Sclerosis.8,9 However, there is currently no core outcome set for encephalitis using the COMET approach.10 The heterogeneity in outcome measures used in studies of encephalitis has meant that using meta-analyses to draw conclusions regarding outcomes in these patients is challenging; which is particularly important for clinical trials of repurposed existing and novel therapies to reduce cerebral oedema.11 Additionally, clinicians have a difficult choice when considering an outcome measure to use for immediate recovery, prognostication or follow up. Moreover, the importance of integrating patient and family reported outcome measures is increasingly recognised and has resulted in substantive improvements in outcome measures in brain injury due to trauma 12. We hypothesise that due to both the complex neurological, psychiatric, cognitive, and physical outcomes and the ‘hidden’ (i.e. largely non-physical) nature of these encephalitis sequelae, some of the important outcomes for patients and their relatives are not captured in measures which have been applied routinely.

The first step in the process for developing a dedicated outcome score for patients with encephalitis is to evaluate those existing measures which have been applied in clinical observational studies and trials. This review aims to outline the range of outcome measures that have been used to assess long-term morbidity in patients following encephalitis and see how they compare with features patients consider important.

**Methods**

We searched the Cochrane Library, Web of Science, the National Institute of Healthcare Excellence (NICE) Healthcare Databases Advanced Search (HDAS), Embase, PubMed, MEDLINE and CINAHL from 1990-current (Appendix 1). A single reviewer screened the titles and abstracts (HVDT) and two Reviewers (HVDT and BDM) examined the screened full-text articles to determine if they met the inclusion criteria. A single reviewer (HVDT) then extracted relevant data from the included reports (Appendix 2).

The inclusion criteria were (1) human subjects, (2) the diagnosis of encephalitis meeting one of the following criteria: aetiology identified with clinical correlation, clinical diagnosis meets consensus statement of the international encephalitis consortium 13, or the case definition for autoimmune encephalitis 14, or the International paediatric multiple sclerosis study group criteria for the diagnosis of acute disseminated encephalomyelitis (ADEM) 15 (3) a defined outcome measure was used to follow the patient up, (4) minimum follow up time of 6 months, (5) full text available in English after reasonable efforts to translate. Studies were included if they were case series including more than 10 patients, case-control studies, cohort studies, and controlled trials.

**Results**

In total 4,074 abstracts were identified, of which 1,746 were duplicates, therefore 2,328 abstracts were screened. 235 met the inclusion criteria, of these 72 were not available in English. 163 articles were reviewed in full and 35 met the inclusion criteria, of which two were protocols (Figure 1).

In total there were 37 outcome measures used in the 35 included studies which assessed, in total, 3,133 patients (Appendix 2). Of these outcome measures 22 were used in only one paper each, whilst 15 of the outcome measures were used in multiple papers. These outcome measures broadly fall into five categories: physical, cognitive, mood, quality of life, and functional outcomes.

The majority of patients were assessed using a 5 to 8 point scale in which patients are rated as either having minimal disability to death. Of the 35 included studies, 18 used the modified Rankin scale (mRS) and six used the Glasgow outcome score (GOS). Of the 3,133 patients, the GOS was used in 1436 (46%) and the mRS in 1034 (33%). 14 studies used either the mRS or GOS as its single outcome measure to assess the long-term outcome of 607 (19%) patients with encephalitis. Whilst the majority of studies assessed patients for physical disability, only 10 assessed cognitive function. A wide range of measures to assess cognitive function were included within the studies, from simple bedside tests usually used to assess patients for dementia, to complex neuropsychological batteries that would be carried out by clinical psychologists. Seven studies assessed mood as part of their outcomes, most often testing for depression, but two assessed for anxiety and one general wellbeing. Quality of life was quantified in six of the studies, with one focusing on paediatric quality of life. There were two measures of functional outcome used: the Barthel Index and the Liverpool outcome score (LOS). The LOS was the only outcome measure identified which was developed for use in encephalitis, and was used in 370 (12%) patients across six studies. Almost all studies had a limited minimum follow-up of 1 year.

**Discussion**

Of the 35 studies identified, there were 37 outcome measures used, which assessed five broad domains. The most assessed category was physical outcomes, in which all of the measures used were developed for other neurological conditions, such as stroke 16, traumatic brain injury 17 or multiple sclerosis 18 and most were neither developed nor validated for use in encephalitis. The only outcome measure used within the identified studies that has been developed for use in patients with encephalitis was the LOS, which was not used for 88% of patients within included studies. The LOS also includes elements from multiple categories identified within this study, assessing components of physical, cognitive and psychological recovery.19

Whilst the outcome measures identified may determine the short-term physical and mental sequelae of encephalitis appropriately, none addresses the long-term effects of encephalitis, especially on patients’ inter-personal relationships, which patients have reported is critically important to their long-term recovery. 4 Development and validation of an outcome measure that includes the effect of encephalitis on family and wider societal impacts is required. This is critical to both direct clinicians as to what rehabilitation support an individual patient may require and also to direct regional and supra-regional service development and associated quality improvement projects.

 As the reliability and validity of an outcome measure can only be determined in relation to a particular population 20, if these outcome measures are going to be used in future studies of encephalitis, they should be validated in these patients.

The three included protocols had a wider range of outcome measures, spanning more of the five outcome domains with many overlapping outcome assessment methods across the protocols 21–23. This suggests the studies will have a more detailed understanding of the sequelae of encephalitis. To solidify this progression, the development of a core outcomes set may be useful 24. However, these protocols are for randomised controlled trials and include outcomes measures which would require a long time to administer. In clinical practice and studies with more patient-clinician time constraints, a single composite outcome score may be more useful, which should encompass aspects of all the five outcome domains, as well as identifying the effect of illness and recovery on patients’ relationships.

**Conclusion**

There is a wide variation in the outcome measures used in the assessment of patients following encephalitis, with multiple named assessment tools for a single given problem. Despite the complexity and breadth of sequelae following encephalitis, the majority of patients had outcome measures reported on a 5 or 8 point scale, which would fail to identify effects on mood, cognition or quality of life. Except for the LOS, none of these outcome measures have been developed for assessing outcomes from encephalitis. Encouragingly, recently published protocols are increasing the range of outcome measures used, but there is still significant variation in the choice of these measures. Therefore, research into the sequelae of encephalitis needs to focus on validating the outcome measures in use and determining a core-outcomes set of measures across domains. Throughout this process, identifying outcomes that are important to patients and carers of those who have lived experience of encephalitis is essential.

For clinicians, the choice of measures that could be used to prognosticate and quantify recovery is vast. Whilst there is no perfect option that encompasses all relevant categories of potentially impaired function, the LOS offers a broad assessment of common sequelae, is easy to administer, and importantly, is validated for use in the encephalitis population.

Key Practice Implications

* Sequelae following encephalitis are complex and can affect many aspects of a patient’s life including physical capabilities, cognition, mood, quality of life and maintaining relationships.
* For clinicians wanting to use an outcome measure to quantify recovery and direct rehabilitation during immediate and long-term follow-up, the Liverpool Outcome Score offers a good option.
* However, clinicians and researchers need to consider the effect of encephalitis on patients’ personal and professional relationships, as this is currently not included on any of the outcome measures in the identified studies; although is often critical for patients.
* Work should be undertaken to incorporate and validate patient and clinician reported outcome measures into a composite outcome score of utility in both clinical practice and treatment trials.

Legends

Figure 1 Prisma flow chart outlining the selection process for included articles. 4,074 abstracts were found once duplicates were removed 2,328 abstracts were screened for relevance. 235 abstracts were deemed relevant, of these 72 were abstracts were not available as full text articles in English leaving 163 articles that were reviewed in full. 35 studies met the inclusion criteria, of which two were protocols.

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**Appendix 1**

"long-term outcome\*" OR "long-term prognos\*" OR "long-term sequelae\*" OR "long-term effect\*" OR "long-term deficit\*" OR "long-term problem\*" OR "long-term symptom\*" OR "long-term impairment\*" OR "long-term defect\*" OR "persisting defect\*" OR "persisting deficit\*" OR "persisting problem\*" OR "persisting impairment\*" OR "persisting symptom\*" OR "persisting effect\*" OR "persisting outcome\*" OR "persisting sequelae\*" OR "permanent sequelae\*" OR "permanent outcome\*" OR "permanent effect\*" OR "permanent symptom\*" OR "permanent impairment\*" OR "permanent problem\*" OR "permanent defect\*" OR "permanent deficit\*" OR "lasting deficit\*" OR "lasting defect\*" OR "lasting problem\*" OR "lasting impairment\*" OR "lasting symptom\*" OR "lasting outcome\*" OR "lasting sequelae\*" OR "ongoing sequelae\*" OR "ongoing prognos\*" OR "ongoing outcome\*" OR "ongoing symptom\*" OR "ongoing impairment\*" OR "ongoing problem\*" OR "ongoing defect\*" OR "ongoing deficit\*" OR "ongoing effect\*" OR "lasting effect\*" OR "outcome score\*" OR "outcome measure\*" OR “long-term follow-up” Or “ongoing follow up”

AND

encephalit\* OR "brain infect\*" OR "parenchyma\* infect\*" OR "brain inflammat\*" OR "parenchyma\* inflammat\*" or panencephalit\* or meningoencephalit\*

**Appendix 2**

*Table 1. Table to summarise included* papers

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Title  | Journal | First Author | Year  | Minimum follow up time  | Follow up | Number of patients | Physical Outcome Measure | Cognitive Outcome Measure | Emotional Outcome Measure | Quality of Life Outcome Measure |
| Analysis of electroencephalogram characteristics of anti-NMDA receptor encephalitis patients in China | Clinical neurophysiology | Zhang, Y | 2017 | 6 Months | Minimum 6 months, range 6-54 months  | 62 | mRS |  |  |  |
| Anti-NMDA receptor encephalitis: Case series and long term outcomes  | Southeast Asian Journal of Tropical Medicine and Public Health | Chanvanichtrakool, M | 2017 | 2.3 Years | Range 2.3 - 5.6 years | 13 | mRS |  |  |  |
| Association of Progressive Cerebellar Atrophy with Long-term Outcome in Patients With Anti-N-Methyl-d-Aspartate Receptor Encephalitis. | JAMA neurology | Iizuka, T | 2016 | 10 Months | Median 68 months (10-179 months) | 15 | mRS |  |  |  |
| Can we differentiate between herpes simplex encephalitis and Japanese encephalitis? | Journal of the Neurological Sciences | Kalita, J | 2016 | 1 Year | 1 year  | 137 | mRS | MMSE |  |  |
| Cerebrospinal fluid markers of neuronal and glial cell damage to monitor disease activity and predict long-term outcome in patients with autoimmune encephalitis | European Journal of Neurology | Constantinescu, R | 2016 | 9 Months | 12 +/- 3 months  | 25 | mRS |  |  |  |
| Characteristics of Seizure and Antiepileptic Drug Utilization in Outpatients with Autoimmune Encephalitis. | Frontiers in neurology | Huang, Q | 2018 | 14 Months | 14-62 months | 75 | mRS |  |  |  |
| Clinical characteristics and outcome of clinically diagnosed viral encephalitis in southwest China | Neurological Sciences | Zhao, L | 2015 | 6 Months | 6-53 months | 1107 | Glascow Outcome Score |  |  | EuroQoL-5D |
| Clinical Characteristics and Prognosis of Severe Anti-N-methyl-D-aspartate Receptor Encephalitis Patients. | Neurocritical Care | Zhang, Y | 2018 | 6 Months | 6-64 months  | 111 | mRS |  |  |  |
| Clinical outcome and life quality of patients after monophasic encephalitis | Infectious Diseases in Clinical Practice | Hahn, K | 2010 | 6 Months | 6-93 months | 72 | Adapted mRS |  | Beck Depression Inventory | Lancashire QoL profile |
| Clinical outcome of children presenting with a severe manifestation of acute disseminated encephalomyelitis | Neuropediatrics | Rostasy, K | 2009 | 19 Months | 19 months - 10 years 5 months | 12 | EDSS | KOPKIJ, HAWIK-III or HAWIVA-III, Visuospatial battery, K-ABC or KiTAP |  |  |
| Depressive symptoms following herpes simplex encephalitis - an underestimated phenomenon? | General Hospital Psychiatry | Fazekas, C | 2006 | 1 Year | 1-11 years | 26 | Rankin scale,  |  | WHO-5 Wellbeing index | SF-12 |
| Dexamethasone in Herpes Simplex Virus Encephalitis Trial | International Clinical Trials Registry Platform | Stahl, J | 2017 | 6 Month | 6 months and 18 months | Protocol | mRS, GOS | Verbal memory score (WMS-IV), WMS-IV, WAIS-IV, trail making tests part A&B, Test of Premorbid Functioning (TOPF), percieved deficits questionnaire | Beck Depression Index and Beck Anxiety Inventory | Euro-QoL-5D-5L, SF-36 |
| Does dexamethasone improve outcomes in adults with HSV encephalitis? | International Clinical Trials Registry Platform | Davies, K | 2016 | 26 Weeks | 26 and 78 weeks | Protocol | GOS-E, mRS,  | WMS-IV auditory memory index, WMS-IV, WAIS-IV, language module in neuropsychological assessment battery, trail making test parts A+B, percieved deficits questionnaire, ACE-III | Beck Depression Index and Beck Anxiety Inventory | Euro-QoL-5D-5L, SF-36, |
| Encephalitis due to Mycobacterium tuberculosis in France. | Medecine et maladies infectieuses | Honnorat, E | 2013 | 3 Years | 3 years  | 20 | GOS |  |  |  |
| Etiological associations and outcome predictors of acute electroencephalography in childhood encephalitis. | Clinical neurophysiology | Mohammad, SS | 2016 | 2 Years | 2.0–15.8 years | 119 |  |  |  |  |
| Factors related to long term motor, behavioural and scholastic outcome in children with acute disseminated encephalomyelitis | Neurorehabilitation and Neural Repair | Iype, M | 2018 | 1 Year | 1-10 years | 102 | mRS, EDSS |  |  |  |
| Factors underlying the development of chronic temporal lobe epilepsy in autoimmune encephalitis | Journal of the Neurological Sciences | Casciato, S | 2019 | 12 Months | 12-60 months | 33 | mRS | MMSE, MOCA, ACE | hamilton depression rating scale |  |
| Features and prognostic value of quantitative electroencephalogram changes in critically ill and non-critically ill anti-NMDAR encephalitis patients: A pilot study | Frontiers in Neurology | Jiang, N | 2018 | 12 Months | 12 months  | 26 | mRS |  |  |  |
| Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. | Journal of neurology, neurosurgery, and psychiatry | McGrath, N | 1997 | 6 Months | 6months-11years | 42 | GOS |  |  |  |
| Immunoglobulin in the teatment of encephalitis (IgNiTE): protocol for a multicentre randomised controlled trial | BMJ open | Iro, MA | 2016 | 6 Months | 6 and 12 months | Protocol | GOS-e Peds, Gross motor function classification system,  | ABAS-II, Bayley Scales for Infant Development (BSID-III)/Wechsler preschool and Primary Scale of Intelligence III (WPPSI-III)/ Wechsler Intelligence Scale for Children IV (WISC-IV) | Strength and difficulties questionnaire (SDQ) |  |
| Infectious and Autoantibody-Associated Encephalitis: Clinical Features and Long-term Outcome. | Pediatrics | Pillai, SC | 2015 | 1.1 Years | 1.1-14.4 years range | 164 |  |  |  |  |
| Isolated seizures are a common early feature of paraneoplastic anti-GABA(B) receptor encephalitis | Journal of Neurology | Maureille, A | 2019 | 12 Months | 12 and 24 months | 22 | mRS |  |  |  |
| Long-Term Cognitive Outcomes in Patients with Autoimmune Encephalitis. | The Canadian journal of neurological sciences. | Hébert, J | 2018 | 13 Months | 13-182 months | 21 |  | MOCA |  |  |
| Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. | Clinical Infectious Diseases | Mailles, A | 2012 | 27 Months | 27-40months | 253 | GOS | Informant questionnaire on cognitive decline in the elderly |  |  |
| Long-term outcome of severe herpes simplex encephalitis: a population-based observational study. | Critical Care | Jouan, Y | 2015 | 1 Year | 1 year  | 14 | GOS |  |  |  |
| Long-term outcomes and risk factors associated with acute encephalitis in children | Journal of the Pediatric Infectious Diseases Society | Rao, S | 2017 | 1 Year | Minimum 1 year, Median 1.3 years | 49 |  |  |  | Pediatric Quality of Life Inventory (PedsQL) |
| Long-term prognosis of pediatric patients with relapsing acute disseminated encephalomyelitis | Journal of Child Neurology | Mar, S | 2010 | 2 Years | 2-23.1 years | 33 | EDSS |  |  |  |
| Outcome of children with japanese encephalitis and predictors of outcome in southwestern China | Transactions of the Royal Society of Tropical Medicine and Hygiene | Ma, J | 2013 | 6 Months | Minimum 6 months | 87 |  |  |  |  |
| Outcomes of West Nile encephalitis patients after 1 year of West Nile encephalitis outbreak in Kerala, India: A follow-up study | Journal of Medical Virology | Balakrishnan, A | 2016 | 12 Months | 12 months | 40 |  | MMSE |  |  |
| Predictors of outcome in HSV encephalitis | Neurology | Singh, TD | 2016 | 41.4 Months | 41.4-116.3 months | 45 | mRS |  |  |  |
| Risk factors for mortality in patients with anti-NMDA receptor encephalitis. | Acta neurologica Scandinavica | Chi, X | 2017 | 7 Months | 7-57 months | 96 | mRS |  | Zung depression scale, (ZDS) and Zung anxiety scale (ZAS) |  |
| Seizure outcomes in patients with anti-NMDAR encephalitis: A follow-up study | Epilepsia | Liu, X | 2017 | 6 Months | 6-60 months | 109 | National Hospital Seizure Severity Scale, mRS |  |  |  |
| Status epilepticus as a risk factor for postencephalitic parenchyma loss evaluated by ventricle brain ratio measurement on MR imaging | American Journal of Neuroradiology | Herrmann, EK | 2006 | 6 Months | 6–84 months (median, 35 months; lower quartile, 12.3; upper quar- tile, 57; mean, 36.9; SD, 23.9). | 40 | mRS adapted for encephalitis |  |  |  |
| Status epilepticus associated with acute encephalitis: long-term follow-up of functional and cognitive outcomes in 72 patients | European Journal of Neurology | Chen, W | 2018 | 12 Months | 12 months | 72 | mRS, ADL | Telephone Interview for Cognitive Status (TICS-M) |  |  |
| Tocilizumab in Autoimmune Encephalitis Refractory to Rituximab: An Institutional Cohort Study. | Neurotherapeutics | Lee, WJ | 2016 | 9 Months  | 21.1 +/- 9.2 months (minimum 9 months) | 91 | mRS |  |  |  |

**ABAS** – Adaptive Behaviour Assessment System**, ACE-III** - addenbrookes cognitive assessment, **ADL** – Activities of Daily Living**, BAI** – Beck Anxiety Inventory, **BDI** – Beck Depression Inventory, **BSID** - Bayley Scales for Infant Development, **EQ-5D** - European 5-deimentional health scale, **EDSS** - Expanded Disability Status Scale**, GMFCS** - Gross motor function classification system, **GOS** – Glasgow Outcome Scale, **GOS-E** - Glasgow Outcome Scale Extended, **HAWIK** - Hamburg Wechsler Intelligence Tests for Children, **HDRS** - Hamilton Depression Rating Scale, **HOWIVA** - Hannover–Wechsler Intelligence Scale for Preschool Children, **IQCODE** - Informant questionnaire on cognitive decline in the elderly, , **K-ABC** - Kaufman Assessment Battery for Children, **KiTAP** - Test of Attentional Performance for Children, **KOPKIJ** - kognitive probleme bei Kindren und Jegendlichen, **LOS** - Liverpool outcome score, **MMSE** – Mini Mental State Examination, **MOCA** – Montreal Cognitive Assessment, **mRS** – Modified Ranking Scale, **NAB** – Neuropsychological Assessment Battery **NHS3** - National Hospital Seizure Severity Scale, **PedsQL** - Pediatric Quality of Life Inventory, **SDQ** - strength and difficulties questionnaire, **SF-12/36** – Short Form 12/36, **TICS-M**  - Telephone Interview for Cognitive Status, **TOPF** – Test of Premorbid functioning, **WAIS** - Wechsler Adult Intelligence Scale, **WISC-IV** - Wechsler Intelligence Scale for Children,  **WMS** - Wechsler Memory Scale, **WPPSI-III** - Wechsler preschool and Primary Scale of Intelligence III, **ZAS** – Zung Anxiety Scale, **ZDS** – Zung Depression Scale.