Predictors of outcome in acute encephalitis

Kiran T. Thakur, MD
Melissa Motta, MD, MPH
Anthony O. Asemota, MBBS, MPH
Hannah L. Kirsch, BS
David R. Benavides, MD, PhD
Eric B. Schneider, PhD
Justin C. McArthur, MBBS, MPH, FAAN
Romergryko G. Geocadin, MD, FAAN
Arun Venkatesan, MD, PhD

Correspondence to Dr. Venkatesan: avenkat2@jhmi.edu

ABSTRACT

Objective: To investigate predictors of outcome in patients with all-cause encephalitis receiving care in the intensive care unit.

Methods: A retrospective analysis of encephalitis cases at The Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center was performed. Using multivariate logistic regression analysis, we examined mortality and predictors of good outcome (defined as modified Rankin Scale scores of 1–3) and poor outcome (scores 4 and 5) in those surviving to hospital discharge.

Results: In our cohort of 103 patients, the median age was 52 years (interquartile range 26), 52 patients (50.49%) were male, 28 patients (27.18%) had viral encephalitis, 19 (18.45%) developed status epilepticus (SE), 15 (14.56%) had cerebral edema, and 19 (18.45%) died. In our multivariate logistic regression analysis, death was associated with cerebral edema (odds ratio [OR] 18.06, 95% confidence interval [CI] 3.14–103.92), SE (OR 8.16, 95% CI 1.55–43.10), and thrombocytopenia (OR 6.28, 95% CI 1.41–28.03). Endotracheal intubation requirement with ventilator support was highly correlated with death (95%). In addition, in those patients who survived, viral, nonviral, and unknown causes of encephalitis were less likely to have a poor outcome at hospital discharge compared with an autoimmune etiology (viral encephalitis: OR 0.09, 95% CI 0.01–0.57; nonviral encephalitis: OR 0.02, 95% CI 0.01–0.31; unknown etiology: OR 0.18, 95% CI 0.04–0.91).

Conclusions: Our study suggests that predictors of death in patients with encephalitis comprise potentially reversible conditions including cerebral edema, SE, and thrombocytopenia. Further prospective studies are needed to determine whether aggressive management of these complications in patients with encephalitis improves outcome. *Neurology*® 2013;81:793–800

GLOSSARY

CI = confidence interval; **GCS** = Glasgow Coma Scale; **HSV** = herpes simplex virus; ***ICD-9*** = *International Classification of Diseases*, ninth revision; **ICP** = intracranial pressure; **ICU** = intensive care unit; **JHBMC** = Johns Hopkins Bayview Medical Center; **JHH** = The Johns Hopkins Hospital; **mRS** = modified Rankin Scale; **NCCU** = neurosciences critical care unit; **OR** = odds ratio; **RSE** = refractory status epilepticus; **SE** = status epilepticus; **WBC** = white blood cell.

Encephalitis is challenging to manage given the diversity of clinical and epidemiologic features. More than 100 infectious species have been identified as causative agents of meningoencephalitis, with a burgeoning of new infectious and autoimmune etiologies in the last decade. Despite advances in diagnosis, more than 50% of encephalitis cases remain cryptogenic, posing additional management challenges.[1–3]

Guidelines for management of encephalitis emphasize the role of targeted disease treatment with antimicrobial agents and anti-inflammatory treatment, as well as supportive care.[4,5] Little is known of the contribution of supportive measures, nor of the adverse consequences of medical and neurologic complications, in those with encephalitis. Many patients with encephalitis are critically ill and require care in intensive care units (ICUs) for prolonged periods of time, and we therefore focused on this population to investigate predictors of death and outcome at hospital

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From the Johns Hopkins Encephalitis Center, Department of Neurology (K.T.T., M.M., A.O.A., D.R.B., J.C.M., R.G.G., A.V.), and Departments of Anesthesiology/Critical Care Medicine, Neurosurgery, and Medicine (R.G.G.), The Johns Hopkins University School of Medicine; Departments of Neurology, Medicine, Pathology, and Epidemiology (J.C.M.), and Department of International Health, The Bloomberg School of Public Health (E.B.S.), The Johns Hopkins University, Baltimore, MD; New York University School of Medicine (H.L.K.), New York; and Department of Surgery (E.B.S.), The Johns Hopkins Hospital, Baltimore, MD.

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discharge in those who survived. To ensure broad applicability of our findings, we examined predictors of outcome in patients with encephalitis of all causes.

METHODS

Standard protocol approvals, registrations, and patient consents. The Johns Hopkins University Institutional Review Board approved this study.

Study design. We conducted a retrospective review of all patients with acute encephalitis presenting to The Johns Hopkins Hospital (JHH) and Johns Hopkins Bayview Medical Center (JHBMC), 2 medical centers in Baltimore, MD, between January 1997 and July 2011. We identified encephalitis cases within our database using *ICD-9* diagnosis codes corresponding to encephalitis. Diagnoses were confirmed by neurologists' review of patient charts including physicians' notes, laboratory results, neuroimaging studies, and other supporting data.

Definitions. Encephalitis was defined as a patient hospitalized with encephalopathy (defined by depressed or altered level of consciousness lasting 24 hours or more, lethargy, or personality change) with at least 2 of the following characteristics: fever, seizure, focal neurologic deficit, CSF pleocytosis (white blood cell [WBC] count >5 cells/mm^3), and EEG or neuroimaging findings consistent with encephalitis.[6] Active malignancy, HIV infection/AIDS, and use of chronic immunosuppressants defined immunocompromised state. Leukopenia was defined as WBC count <4,000/mm^3 and thrombocytopenia by platelet count <100,000/mm^3. Seizure activity was defined clinically or through EEG. Status epilepticus (SE) was defined as continuous seizure activity lasting longer than 5 minutes or recurrent seizures without regaining consciousness between seizures for more than 5 minutes.[7]

Inclusion/exclusion criteria. Patients were included in this study if they met the definition of encephalitis, with a length of stay in an ICU of at least 48 hours during their hospital stay, and were older than 16 years. A minimum length of stay in the ICU of 48 hours was determined in order to exclude those who had only transient critical care needs. We included patients admitted to the JHH and JHBMC neurosciences critical care unit (NCCU). Patients with hospital stays in the medical ICU, coronary care unit, and surgical ICU with acute encephalitis were also included and designated as being in "other" ICUs. Patients were excluded if they had a diagnosis of delirium or encephalopathy secondary to sepsis, toxins, or metabolic causes (hypoglycemia, electrolyte disturbances).

Clinical categories. Patients were categorized as having viral encephalitis, nonviral infectious (including bacterial and fungal) encephalitis, autoimmune encephalitis, or encephalitis of unknown etiology. Viral and nonviral infectious encephalitides were defined by serology, positive PCR, culture, or histopathology. Cases of presumed herpes simplex virus (HSV) encephalitis with acute presentation and brain MRI revealing hyperintensity and/or hemorrhage in the bilateral mesial temporal lobes were also included.[8] Autoimmune encephalitis was defined by the presence of antigen-specific antibodies in the serum and/or CSF or cases with histopathologic evidence of autoimmune encephalitis. Cases of acute disseminated encephalomyelitis were categorized as autoimmune etiology and defined by clinical features and imaging characteristic of acute disseminated encephalomyelitis or histology-proven cases.[9]

Clinicoradiographic parameters. Data collected included demographic information (age, sex, race), presence of comorbid conditions calculated by the Charlson comorbidity scale, and immunocompromised state.[10] Hospitalization data included outside hospital length of stay, total length of stay at JHH/JHBMC, ICU location (NCCU or other), and ICU length of stay. Clinical information gathered on admission to JHH/JHBMC included Glasgow Coma Scale (GCS) score as well as laboratory data including CSF profile (WBC count, red blood cell count, glucose, protein, culture/PCR data), and presence of leukopenia or thrombocytopenia. Medication administration of antimicrobial treatment, IV steroids, and treatment with hyperosmolar agents was recorded. The presence of seizure activity, SE, and pharmacologic burst suppression was examined. We identified patients who were intubated with ventilator support and those that had intracranial pressure (ICP) monitoring. Radiographic data based on noncontrast head CT and/or brain MRI were assessed for evidence of cerebral edema.

Clinical outcome. At discharge, all patients underwent a neurologic examination performed by a neurologist, and the outcome was graded according to the modified Rankin Scale (mRS). In those who survived, good outcome was defined as mRS scores 0 to 3 and poor outcome as mRS score 4 or 5.[11]

Statistical analysis. We calculated the mean, median, and SD on all continuous variables. Parametric and nonparametric tests were used to identify differences between groups in continuous outcomes, and χ^2 tests were used to compare categorical outcomes.

Univariate analysis examined clinical and demographic features to determine whether there was a statistically significant relationship with our outcomes of interest. We assessed all potential variables including etiology of encephalitis, host-related factors, clinical course, ICU care, and complications for their association with outcomes of interest. We performed multivariate logistic regression to examine the association between potential predictors and the likelihood of an unfavorable outcome. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to quantify the strength of these associations. Variables included in the multivariate logistic analysis were those found to be significant in our univariate analysis as well as those determined a priori based on clinical relevance. Our multivariable logistic model for mortality included age, sex, immunocompromised state, thrombocytopenia, Charlson comorbidity index, SE, and cerebral edema. Our final regression model for good and poor outcome in survivors included age, sex, etiology of encephalitis, intubation requirement with ventilator support, thrombocytopenia, Charlson comorbidity index, SE, and cerebral edema. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess all models for final model fit. There were no missing data fields in the variables analyzed. To determine the contribution of each variable to outcome prediction, we also performed marginal probability analysis. Coefficients from the logistic regression analysis were used in computing average marginal coefficients for each variable of interest.

Further subset analysis was performed on patients admitted directly to JHH/JHBMC or transferred from an outside hospital within 24 hours of presentation. This was done to restrict the analysis to those patients managed primarily at JHH/JHBMC. All statistical tests were 2-tailed, and p values <0.05 were considered statistically significant. All statistical analyses were performed using STATA version 11 software (StataCorp, College Station, TX).

RESULTS

Patient characteristics. From the encephalitis databases at JHH and JHBMC, 103 of a total of 487 patients with encephalitis met our inclusion criteria. The median age was 52 years (interquartile

range 26), 52 patients (50.49%) were male, 24 (23.30%) were 65 years and older, 70 (67.96%) Caucasian, 26 (25.24%) African American, and 31 (30.10%) immunocompromised (see table 1). Charlson comorbidity scores were used as a surrogate marker of degree of comorbidity.

The etiologies of encephalitis included 28 patients (27.18%) with viral encephalitis, 10 patients (9.71%) with bacterial or fungal encephalitis, 17 (16.50%) with autoimmune encephalitis, and 48 (46.60%) with encephalitis of unknown cause (see figure 1). The most common specific etiology of encephalitis was HSV, with 17 cases (16.50%) in our cohort.

Clinical course. The mean GCS score on admission was 10.14 (SD 4.33) with 39 patients (37.86%) having a GCS score <8. Mean total length of hospital stay was 26.17 days (SD 26.17) and mean ICU length of stay was 12.53 days (SD 15.05). Overall, 75 patients (72.82%) were cared for in the NCCU whereas 28 patients (27.18%) were treated in other ICUs.

Twenty-three patients (22.33%) had thrombocytopenia and 25 (24.27%) were leukopenic. Of the 19 patients (18.45%) who developed SE, 11 (10.70% of the overall population) were pharmacologically treated to induce EEG burst suppression. Radiographic evidence of cerebral edema was seen in 15 patients (14.56%), of whom 4 (3.96% of the overall population) underwent ICP monitoring and 9 (8.74% of the overall population) received hyperosmolar therapy. Univariate analysis was performed to examine clinical and demographic features associated with outcome (table 2).

Predictors of mortality. In our patient cohort, 19 patients (18.45%) died. Multivariate logistic regression analysis demonstrated that the presence of cerebral edema (OR 18.06, 95% CI 3.14–103.92), SE (OR 8.16, 95% CI 1.55–43.10), and thrombocytopenia (OR 6.28, 95% CI 1.41–28.03) were all associated with mortality (see table 3). Mortality was associated with a marginal probability 29% higher with radiologic evidence of cerebral edema ($p < 0.01$), 21% higher with SE ($p = 0.01$), and 19% higher for thrombocytopenic patients compared to those with normal platelet counts ($p = 0.01$). Although there were trends toward slightly increased probability of death among those who were aged 65 years and older (7%; $p = 0.36$), immunocompromised patients (6%; $p = 0.54$) and those with significant comorbid conditions (2%; $p = 0.37$), these findings were not statistically significant. In a separate subset analysis performed comparing infectious (both viral and nonviral) vs autoimmune and unknown causes of encephalitis, an increased likelihood of mortality from infectious causes was observed, but these findings were not significant. In further subset analysis, a trend toward reduced odds of death was seen among patients with cerebral edema receiving ICP monitoring and hyperosmolar therapy.

Furthermore, in our patient cohort, 95% of the patients who died during hospitalization required endotracheal intubation with ventilator support. In our final model predicting mortality, the need for intubation with ventilator support was therefore excluded because it was strongly associated with mortality. However, sensitivity analysis performed with inclusion of endotracheal intubation in our model and addition of other variables including etiology of encephalitis did not differ from our findings using a more parsimonious model.

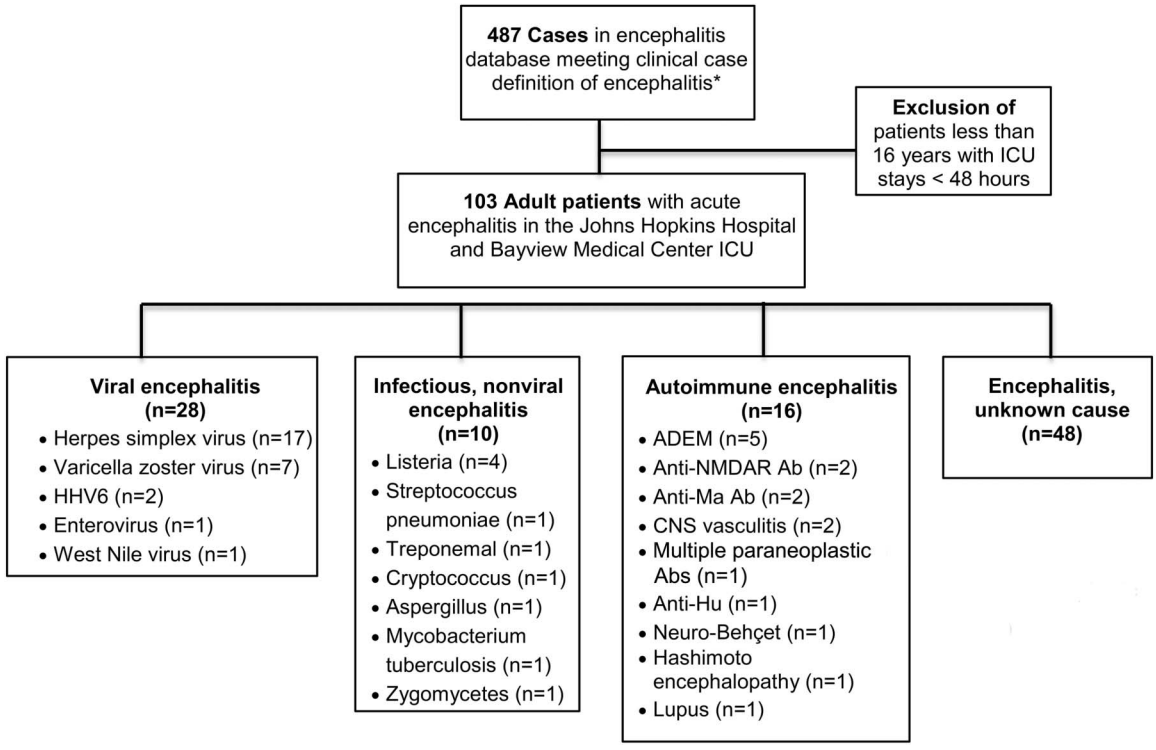
Predictors of outcome among survivors. Of the surviving patients, 37 (35.92%) had favorable outcome (mRS scores 0–3) and 47 (55.95%) had poor outcome

Table 1 Characteristics of the study population (n = 103)

		%
Demographic information		
Male	52	50.49
Female	51	49.51
18–64 y	79	76.70
>65 y	24	23.30
Caucasian	70	67.96
African American	26	25.24
Other race	7	6.80
Immunocompromised[a]	31	30.10
Hospitalization data		
Total length of hospital stay in days, mean	26.17	
Total length of stay in ICU in days, mean	12.53	
Admission to NCCU	75	72.82
Admission to other ICU[b]	28	27.18
Clinical data		
GCS score on admission, mean	10.14	
Thrombocytopenia[c]	23	22.33
Leukopenia[d]	25	24.27
Intubation	61	59.22
Ventilator-associated pneumonia	4	3.88
Intracranial pressure monitoring	4	3.88
Evidence of cerebral edema	15	14.56
Status epilepticus	19	18.45
Pharmacologically burst suppressed	11	10.70

Abbreviations: GCS = Glasgow Coma Scale; ICU = intensive care unit; NCCU = neurosciences critical care unit.
[a] Active malignancy, HIV/AIDs, patients taking chronic immunosuppression medication.
[b] Other ICU defined as medical ICU, surgical ICU, or coronary care unit.
[c] Thrombocytopenia defined as platelet count <100,000/mm^3.
[d] Leukopenia defined as white blood cell count <4,000 cells/mm^3.

Figure 1 Study population and etiologies of encephalitis



One hundred three of the 487 patients in the encephalitis database at The Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center met inclusion criteria. Patients were categorized as viral, infectious nonviral (including bacterial and fungal), autoimmune, and unknown causes of encephalitis. *Case definition of encephalitis: admitted to hospital with encephalopathy and ≥2 of the following: fever (≥38°C), seizures, and/or focal neurologic findings (with evidence of brain parenchyma involvement), CSF pleocytosis (>5 WBCs/mm^3), EEG findings compatible with encephalitis, and abnormal neuroimaging in keeping with encephalitis. Exclusion criteria included delirium or encephalopathy secondary to sepsis, toxic or metabolic causes (hypoglycemia, electrolyte disturbances), or primary psychiatric illness. Ab = antibody; ADEM = acute disseminated encephalomyelitis; HHV6 = human herpesvirus 6; ICU = intensive care unit; NMDAR = NMDA receptor; WBC = white blood cell.

(mRS scores 4 and 5). Twenty-one patients (25% of the surviving patients) were discharged home, 49 (58.33%) discharged to rehabilitation, 10 (11.9%) to a nursing home, and 4 (4.67%) to another hospital (see figure e-1 on the *Neurology*® Web site at www.neurology.org).

Results of the multivariate regression analysis in those patients who survived showed that intubation requirement with ventilator support was associated with poor outcome ($p < 0.001$). In addition, patients with viral (OR 0.09, 95% CI 0.01–0.57), nonviral (OR 0.02, 95% CI 0.01–0.31), and unknown (OR 0.18, 95% CI 0.04–0.91) causes of encephalitis were all less likely to have a poor outcome compared with those patients with an autoimmune etiology (see table 4).

There were 49 patients (47.57%) directly admitted to JHH/JHBMC or with outside hospital stays <24 hours. When analysis was restricted to this subset of patients, our findings were similar to those obtained from the overall study population.

DISCUSSION We assessed outcome at hospital discharge of patients with acute encephalitis who received treatment and supportive care in the ICU. Our goal was to examine patients with acute encephalitis broadly and determine which factors in this critically ill population were predictive of outcome at hospital discharge. Our results show that factors associated with mortality, regardless of etiology, include the potentially reversible conditions of cerebral edema, thrombocytopenia, and SE. In addition, we found that in those patients who survived to hospital discharge, patients with viral, nonviral, and unknown causes of encephalitis were all less likely to have a poor outcome compared with those patients with an autoimmune etiology.

We found that cerebral edema was strongly predictive of mortality in our patient cohort. A nonsignificant trend toward reduced death was seen among patients with cerebral edema receiving ICP monitoring and hyperosmolar therapy, but the number of patients receiving these interventions was too small to draw any definitive conclusions. There have been few previous studies examining the utility of ICP monitoring and management of cerebral edema with hyperosmolar therapy and decompressive

Table 2 Univariate analysis of death, and good and poor outcome in survivors, among patients with all-cause encephalitis

	mRS score <3 (n = 37)		mRS score 4 or 5 (n = 47)		Died (n = 19)		
	freq	%	freq	%	freq	%	*p* Value
Age ≥65 y	5	13.51	12	25.53	7	36.84	0.13
Male	21	56.76	18	38.30	13	68.42	0.05
ICU location (NCCU)	25	67.57	36	76.60	14	73.68	0.65
Cerebral edema	3	8.11	5	10.64	7	36.84	0.01
Status epilepticus	5	13.51	9	19.15	5	26.32	0.50
Burst suppressed	4	10.81	7	14.89	5	26.32	0.31
Need for intubation	14	37.84	29	61.70	18	94.74	<0.01
Leukopenia	8	21.62	11	23.40	6	31.58	0.70
Thrombocytopenia	5	13.51	8	17.02	10	52.63	0.00
GCS score ≤8	10	27.03	18	38.30	11	57.89	0.08
Immunosuppression	11	29.73	11	23.40	9	47.37	0.16

Abbreviations: freq = frequency; GCS = Glasgow Coma Scale; ICU = intensive care unit; mRS = modified Rankin Scale; NCCU = neurosciences critical care unit.

surgery in patients with meningoencephalitis.[12–18] Our results suggest that clinicians must maintain vigilance for any change in pupil reactivity, development of focal neurologic deficits, and changes in level of consciousness. Given evidence that herniation may be reversible with aggressive management, use of hyperosmolar therapy should be initiated emergently, and neurosurgery should be considered if there are signs of mass effect.[19] Further studies in larger cohorts are needed to determine whether there is survival benefit in those critically ill patients with encephalitis who have ICP monitoring, along with aggressive medical and surgical management of cerebral edema.

In addition to the increased mortality seen with cerebral edema, patients in SE were found to have an increased risk of death. Several studies have found a high 30-day mortality risk in patients who develop SE.[20–23] In a previous study evaluating SE in patients with encephalitis and response to antiepileptic drugs and mortality, 36.7% remained refractory to the second antiepileptic drug and approximately one-third of patients died.[24] Studies have shown that encephalitis is a common cause of refractory SE (RSE).[25,26] In our study, 11 patients (57.89% of those patients in SE) had RSE and required pharmacologic burst suppression. The increased likelihood of patients with encephalitis to develop RSE is probably related to the predilection for infections such as HSV and autoimmune encephalitides to target epileptogenic limbic structures and other cortical regions. Ongoing studies of early EEG features may shed further light on prognostication in patients with encephalitis.

The presence of thrombocytopenia was also significantly associated with mortality. The overall incidence of thrombocytopenia among the critically ill is 35% to 44% and may be attributable to a variety of causes including decreased platelet production as a result of bone marrow suppression, increased platelet destruction due to immune and nonimmune causes, hemodilutional effects due to blood loss, or splenic sequestration.[27] In previous studies of critically ill patients, thrombocytopenia was found to be a stronger independent predictor for ICU mortality than were composite scoring systems used in the ICU, such as the APACHE (Acute Physiology and Chronic Health Evaluation) II score or the Multiple Organ Dysfunction Score.[28–30] Our study suggests that this association between thrombocytopenia and mortality in patients who are critically ill extends to those with encephalitis.

Table 3 Multivariate analysis of factors associated with death in patients with all-cause encephalitis[a]

Died before discharge (n = 19)	OR	95% CI	Average marginal effects, %	*p* Value
Age ≥65 y	2.10	0.44–10.02	7.47	0.35
Male	3.63	0.97–13.54	13.00	0.04
Thrombocytopenia	6.28	1.41–28.03	18.54	0.01
Cerebral edema	18.06	3.14–103.92	29.20	<0.01
Status epilepticus	8.16	1.55–43.10	21.19	0.01
Immunosuppression	1.86	0.27–12.6	6.28	0.50
Charlson comorbidity	1.16	0.84–1.60	1.49	0.37

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Hosmer-Lemeshow statistics ($\chi^2 = 2.80$, $p = 0.90$).

Table 4 Multivariate regression analysis of factors associated with good and poor outcome in survivors at discharge in patients with all-cause encephalitis[a]

Disability index at discharge (n = 84)	OR	95% CI	Average marginal effects, %	p Value
Age ≥65 y	2.63	0.58-11.81	18.00	0.19
Male	0.49	0.16-1.46	−13.00	0.18
Etiology of encephalitis				
Autoimmune (ref)	1.00	—	—	—
Viral encephalitis	0.09	0.01-0.57	−41.00	<0.01
Nonviral	0.02	0.01-0.31	−63.00	<0.01
Unknown	0.18	0.04-0.91	−27.00	0.01
Intubation	4.68	1.28-17.05	29.00	0.01
Cerebral edema	1.39	0.21-9.14	6.00	0.73
Thrombocytopenia	2.13	0.36-12.63	14.00	0.4
Status epilepticus	1.40	0.28-7.07	11.00	0.53
Charlson comorbidity	1.15	0.91-1.44	2.00	0.58

Abbreviations: CI = confidence interval; OR = odds ratio; ref = reference.
[a] Hosmer-Lemeshow statistics ($\chi^2 = 8.36$, $p = 0.399$).

Endotracheal intubation requirement with ventilator support was found to be strongly associated with poor prognosis and risk of death. These findings are consistent with previous studies of critically ill patients including those with encephalitis and indicate that physicians must assess the need for mechanical ventilation early with ongoing evaluation of the need for respiratory support.[31–33]

There have been few previous studies in large cohorts on prognostic indicators of encephalitis. In HSV encephalitis, the most frequently studied etiology in adult and pediatric literature, delay in initiation of acyclovir therapy, Simplified Acute Physiology Score II score >27, older age, and GCS score <10 at initiation of therapy were associated with poor outcome.[34] In a prospective study of outcome in acute infectious encephalitis, several factors, including older age, immunosuppression, and mechanical ventilation, were associated with death during hospitalization.[35] In addition to the expanding array of infectious causes, novel antibody-mediated forms of encephalitis have become recognized over the last decade. There is growing interest in factors associated with outcome in this subtype of encephalitis. A recent study of 500 anti-NMDA receptor encephalitis cases showed that almost half of the patients had no improvement in the first month after initiation of immunotherapy or tumor removal, but improvements from severe to slight disability occurred within the first 24 months of treatment in 81% of patients.[36] Results of our study are consistent with previous studies on prognostication in autoimmune encephalitis in that this patient population may experience substantial delays before meaningful functional recovery.

A major limitation of our study is its retrospective nature. We assessed cases of encephalitis at 2 large medical centers, with a large referral base, which may not be representative of encephalitis cases seen in other hospitals. Our study focused on acute encephalitis patients with ICU hospital stays and may not be generalizable to all patients with encephalitis. Despite an increased trend toward mortality observed for those who are immunosuppressed, older than 65 years of age, or with infectious causes of encephalitis, the small size of our study population imposes limitations on any broader conclusions that can be made from these findings. Furthermore, we are also limited in our evaluation of potentially beneficial interventions including ICP monitoring and hyperosmolar therapy on the outcome of patients with encephalitis because of the relatively few numbers of patients undergoing such interventions in our study. In addition, we did not gather long-term data and are therefore unable to comment on long-term outcome in our patient population.

Our study suggests that those patients with autoimmune encephalitis have a higher risk of short-term disability compared with other etiologies of encephalitis, but further studies are needed in larger cohorts to validate this finding. Our study also suggests that regardless of etiology of encephalitis, monitoring for ongoing seizure activity and signs of increased ICP with aggressive treatment of SE, cerebral edema, and platelet derangement in the ICU may decrease mortality and improve functional outcome at hospital discharge. Further prospective studies are needed to determine whether these measures, along with

specialized care in a neurocritical care unit, improve outcome in those with acute encephalitis.

AUTHOR CONTRIBUTIONS

K.T. Thakur, MD, and M. Motta, MD, MPH: design, analysis, and writing of the manuscript. A.O. Asemota, MBBS, MPH: design, statistical analysis, and writing of the manuscript. H.L. Kirsch, BS: analysis and writing of the manuscript. D.R. Benavides, MD, PhD: design, analysis, and writing of the manuscript. E.B. Schneider, PhD: design and statistical analysis of the manuscript. J.C. McArthur, MBBS, MHP: design, review, and review of the manuscript. R.G. Geocadin, MD, FAAN: design, review, and writing of the manuscript. A. Venkatesan, MD, PhD: design, analysis, writing and review of the manuscript.

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DISCLOSURE

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