Risk Stratification for the need of mechanical ventilation in adults presenting with encephalitis.

Ashley Heck, Denisse Ramirez, Alejandro Granillo Ibanez, Rodrigo Hasbun

Department of Medicine, Section of Infectious Disease, McGovern Medical School, UTHealth Science Center, Houston, TX

UTHealth | McGovern Medical School
The University of Texas Health Science Center at Houston

Introduction

Encephalitis is an inflammation of the brain caused by a viral infection, such as herpes simplex virus, or an autoimmune response, such as anti-N-Methyl-D-Aspartate (NMDA) receptors. Even though it is known these are the most common causes, the etiology of encephalitis in adults unknown in a substantial proportion of patients. Mechanical Ventilation is used in many patients with encephalitis most commonly due to the necessity of protecting the patient's airways. This study evaluated risk factors for mechanical ventilation and created a risk score to identify subgroups at higher risk so that they can be monitored in an intensive care unit.

Table 1: Baseline and clinical characteristics of 271 adults with encephalitis with or without the need for mechanical ventilation

Variables	Mechanical Ventilation N = 91 (%)	No Mechanical Ventilation N = 180 (%)	P-value [a]
Median Age, years (range)	48 (18-93)	49 (18-90)	0.542
Male gender, n/N (%)	51/91 (56.04)	92/180 (51.11)	.442
Race, n/N (%)			.237
White	29/91 (31.87)	69/180 (38.33)	
African American	24/91 (26.37)	52/180 (28.89)	
Hispanic	28/91 (30.77)	33/180 (18.33)	
Asian	6/91 (6.59)	11/180 (6.11)	
Not Specified	4/91 (4.40)	13/180 (7.22)	
Immunocompromised [b], n/N(%)	23/91 (25.27)	41/180 (22.78)	.648
HIV positive, n/N (%)	11/87 (12.64)	28/166 (16.87)	.377
Comorbidity [c], n/N (%)	52/89 (58.43)	110/177 (62.14)	.577
Symptoms, n/N (%)			
Acute onset [d]	51/90 (56.67)	83/178 (46.63)	.121
Headache	37/71 (52.11)	86/161 (53.42)	.855
Neck Stiffness	9/69 (13.04)	23/151 (15.23)	.669
Nausea	22/72 (30.56)	61/161 (37.89)	.280
Photophobia	3/54 (5.56)	13/129 (10.08)	.323
Psychiatric Symptoms	28/91 (30.77)	72/180 (40.00)	.137
Memory Deficits	21/91 (23.07)	61/180 (33.89)	0.067
Movement Disorders	8/27 (29.63)	19/27 (70.37)	.902
Physical exam, n/N (%)			
Fever [e]	59/91 (64.84)	104/180 (57.78)	.262
Focal Neurological deficits [f]	41/91 (45.05)	75/180 (41.67)	.594
Seizures	47/91 (51.65)	61/180 (33.89)	0.005
GCS [g] <8	13/91 (14.29)	29/180(16.11)	.695
GCS<13	33/91 (36.26)	67/180 (37.22)	.877
SOFA [h] > 3	68/91 (74.73)	62/180 (34.44)	<0.001

[a] p-Value comparing mechanical ventilation use to no mechanical ventilation groups,
[b] Immunocompromised is defined as Human immunodeficiency virus (HIV), recent chemotherapy (<1 month), solid organ or bone marrow transplantation, receiving ≥20 mg of prednisone or equivalent for >1 month, or congenital immunodeficiency.
[c] Charlson comorbidity index score >1,
[d] acute onset defined as symptoms lasting less than or equal to 5 days before presentation
[e] Temperature > 38.4F,
[f] Focal neurological deficits defined as acute-onset cranial nerve abnormalities or acute defects in sensorimotor abilities including aphasia,
[g] Glasgow coma scale,
[h] Sequential Organ Failure Assessment

Table 2: Laboratory findings, Microbiology testing and Neuroimaging findings on 271 adults with encephalitis with or without the need for mechanical ventilation

Variables, n/N (%)	Mechanical Ventilation N= 91(%)	No Mechanical Ventilation N=180 (%)	P value [a]
Laboratory findings			
Hyponatremia (<135mg/dl)	10/36 (27.78)	24/87 (27.59)	.983
Serum WBC (>11,000/mm³)	45/91 (49.45)	59/180 (32.78)	.008
CSF WBC (cells/mm³)	38 (0-15,900)	41 (0-25,000)	.926
CSF glucose (mg/dl) [b]	64 (6-253)	58 (9-320)	.863
CSF protein (mg/dl) [b]	83 (19.7-662)	76 (22-782.4)	.260
Microbiology testing			
CSF Herpes Simplex Virus PCR	2/81 (2.47)	16/154 (10.39)	.030
CSF Varicella Zoster Virus PCR	6/40 (15.00)	12/68 (17.65)	.722
CSF Cytomegalovirus PCR	2/19 (10.53)	4/29 (13.79)	.738
CSF Enterovirus PCR	0/65 (0.00)	2/102 (1.96)	.256
West Nile serologies	13/49 (26.53)	22/91 (24.18)	.759
Anti-NMDA antibodies [c]	7/22 (31.82)	15/38 (39.47)	.553
Neuroimaging findings			
Abnormal CT [d]	29/89 (32.58)	46/163 (28.22)	.469
Abnormal MRI [e]	61/82 (74.39)	95/139 (68.35)	.341
Abnormal EEG [f]	75/83 (90.36)	104/130 (80.00)	.044
Cerebral Edema [f]	17/66 (25.76)	19/120 (15.83)	.101

[a] p-Value comparing mechanical ventilation use to no mechanical ventilation groups
[b] Median values (range)
[c] NMDA = N-Methyl-D-Acetyl
[d] CT abnormalities seen include hemorrhagic or ischemic stroke, postoperative changes, hypodensity, hyperintensity, mass, edema, transtentorial herniation, leptomeningeal process, or white matter abnormalities, or subarachnoid hemorrhage
[e] MRI abnormalities seen include restricted diffusions, intraparenchymal lesions, demyelination, leukoencephalopathy, gliosis, ring enhancing lesions, or Dural enhancement
[f] EEG abnormalities seen include hemorrhage, mass, or cerebral infarction

Table 3: Clinical management, etiologies, and outcomes of 271 adults with encephalitis with or without the need for mechanical ventilation.

Variables	Mechanical Ventilation N=91 (%)	No Mechanical Ventilation N=180 (%)	P value [a]
Clinical management, n/N (%)			
Antiviral therapy	70/85 (82.35)	123/148 (83.11)	.778
Autoimmune therapy [b]	53/91 (58.24)	91/180 (50.56)	.231
Adjunctive steroids [c]	53/91 (58.24)	84/180 (46.67)	.086
Intensive care unit admission	91/91 (100)	47/176 (26.70)	<.001
Etiologies, n/N (%)			
Viral Encephalitis	27/91 (29.67)	60/180 (33.33)	.542
Autoimmune	9/91 (9.89)	27/180 (15.00)	.242
Unknown	44/91 (48.35)	76/180 (42.22)	.337
Miscellaneous	11/91 (12.09)	17/180 (9.44)	.500
Outcomes, n/N (%)			
Glasgow outcome scale<4	55/88 (62.50)	106/178 (59.55)	.643
In hospital mortality	22/91(24.18)	7/180 (3.89)	<0.001
Readmitted [d]	17/91 (18.68)	46/180 (25.56)	0.039

[a] p-Value comparing mechanical ventilation use to no mechanical ventilation groups
[b] Autoimmune therapy includes steroids, PLEX, IVIG, or a combination of steroids and PLEX or steroids and IVIG
[c] Adjunctive steroids include prednisone, methylprednisone, dexamethasone, or hydrocortisone
[d] Readmitted from admission to data collection in 2021

Methods

Adults > 18 years of age, who presented to one of two hospital systems in Houston, Texas between February 2005 and December 2015 with the presence of an encephalitis related discharge diagnosis identified with the International Classification of Disease (ICD-9) discharge diagnosis codes were included in this study. There were a total of 1241 patients admitted that fit those criteria to the two hospital systems composed of 16 different facilities and included Memorial Hermann Health System (14 hospitals) and Harris Health System (2 hospitals).

Our study population was comprised of a total 271 patients. The patient's paper or electrical medical records were analyzed to determine the presentations and outcomes for each patient.

Statistical Analysis

The data was entered into the IBM (International Business Machines Corporation) SPSS software. Descriptive analysis based on meaningful features of the patient such as basic demographics, patient's presentation, and clinical management (Tables 1-4) was performed. Individual bivariant analysis of the variables seen in Tables 1-4 were compared using a chi-square test, ANOVA test, and a risk assessment. The variables that had statistical significance (P < 0.05) were then analyzed using a binary logistic regression. A risk score was developed that classified patients as low, intermediate, or high risks of being placed on mechanical ventilation with a confidence interval of 95%. Goodness-of-fit of the predictive model was determined using Hosmer - Lemeshow Test. The model was validated using bootstrapping. The diagnostic accuracy for the risk score was determined by calculating the area under the receiver operating characteristic (ROC) curve.

Results

A total of 271 patients were included based on guidelines from the ICD-9. These 271 patients were then further divided into two groups: 91 patients (33.58 %) that required mechanical ventilation (MV) and 180 patients (66.42 %) that did not require MV.

Of the variables, only presence of seizures, serum WBC > 11,000/mm³, SOFA score >3 , and abnormal EEG were found to be significant variables seen at admission. After bootstrapping this data, seizures failed to be significant. The Hosmer and Lemeshow Test showed a significance of 0.046. The risk score was divided into a low risk (none of the 3 variables = serum WBC > 11,000/mm³, SOFA score > 3, or an abnormal EEG), intermediate risk (1 of the 3 variables) or high risk (2 or 3 of the variables). There were 3.13% of patients in the low risk, 17.92% of patients in the intermediate risk and 52.21% of patents in the high-risk group. (Table 5) The ROC curve showed an area under the curve (AUC) to be 0.728. (Graph 1)

Table 4: Bivariate and Logistic Regression Analyses of Baseline and clinical characteristics of 271 adults with encephalitis

Variable	Bivariant Analysis Odds Ratio (95% Confidence Interval) P-value [a]	Logistic Regression
Baseline Characteristic		
Immunocompromised [b]	1.147 (0.637 – 2.063) 0.648	
Comorbidity [c]	0.856 (0.509 – 1.439) 0.557	
Clinical Characteristic		
Seizures	2.084 (1.246-3.484) 0.005	0.532 (-0.136 – 1.159) 0.089
Fever [d]	1.347 (0.799 – 2.271) 0.262	
Focal Neurological deficits	1.148 (0.691 – 1.908) 0.594	
SOFA >3 [e]	5.627 (3.202 – 9.890) <0.001	1.609 (0.996 – 2.421) < 0.001
GCS [f]		
GCS < 8	0.868 (0.427 – 1.763) 0.695	
GCS < 13	0.960 (0.569 – 1.620) 0.877	
Cerebral Edema	1.844 (0.882 – 3.858) 0.101	
Serum WBC (>11,000/mm³) [g]	2.006 (1.198 – 3.359) 0.008	0.671 (0.22 – 1.381) 0.038
Abnormal EEG [h]	2.344 (1.006-5.463) 0.044	1.003 (0.111 – 2.246) 0.033
Management		
Steroid use [i]	1.561 (0.937-2.599) 0.086	

[a] p-Value comparing mechanical ventilation use to no mechanical ventilation groups
[b] Immunocompromised is defined as Human immunodeficiency virus (HIV), recent chemotherapy (<1 month), solid organ or bone marrow transplantation, receiving ≥20 mg of prednisone or equivalent for >1 month, or congenital immunodeficiency.
[c] Charlson comorbidity index score >1,
[d] Temperature > 38.4F,
[e] Sequential Organ Failure Assessment
[f] Glasgow coma scale,
[g] White Blood Cell Count
[h] EEG abnormalities seen include hemorrhage, mass, or cerebral infarction
[i] Adjunctive steroids include prednisone, methylprednisone, dexamethasone, or hydrocortisone

Conclusions

This study found that patients presenting with serum white blood cell counts > 11,000/mm³, SOFA scores > 3, and abnormal EEG are at a significant increase in the need for mechanical ventilation.

A risk score was derived that stratified patients into 3 subgroups:

Low risk (3.13%): none of these three findings,
Intermediate risk (17.9%): patients with 1 of these risk factors; and
High risk (52.2%): patients with 2 or 3 risk factors.

This risk score could be helpful in identifying which patients need more intense monitoring and be considered for ICU admission.

ROC Curve

Source of the Curve: Low =0, Intermediate = 1, High = 2/3
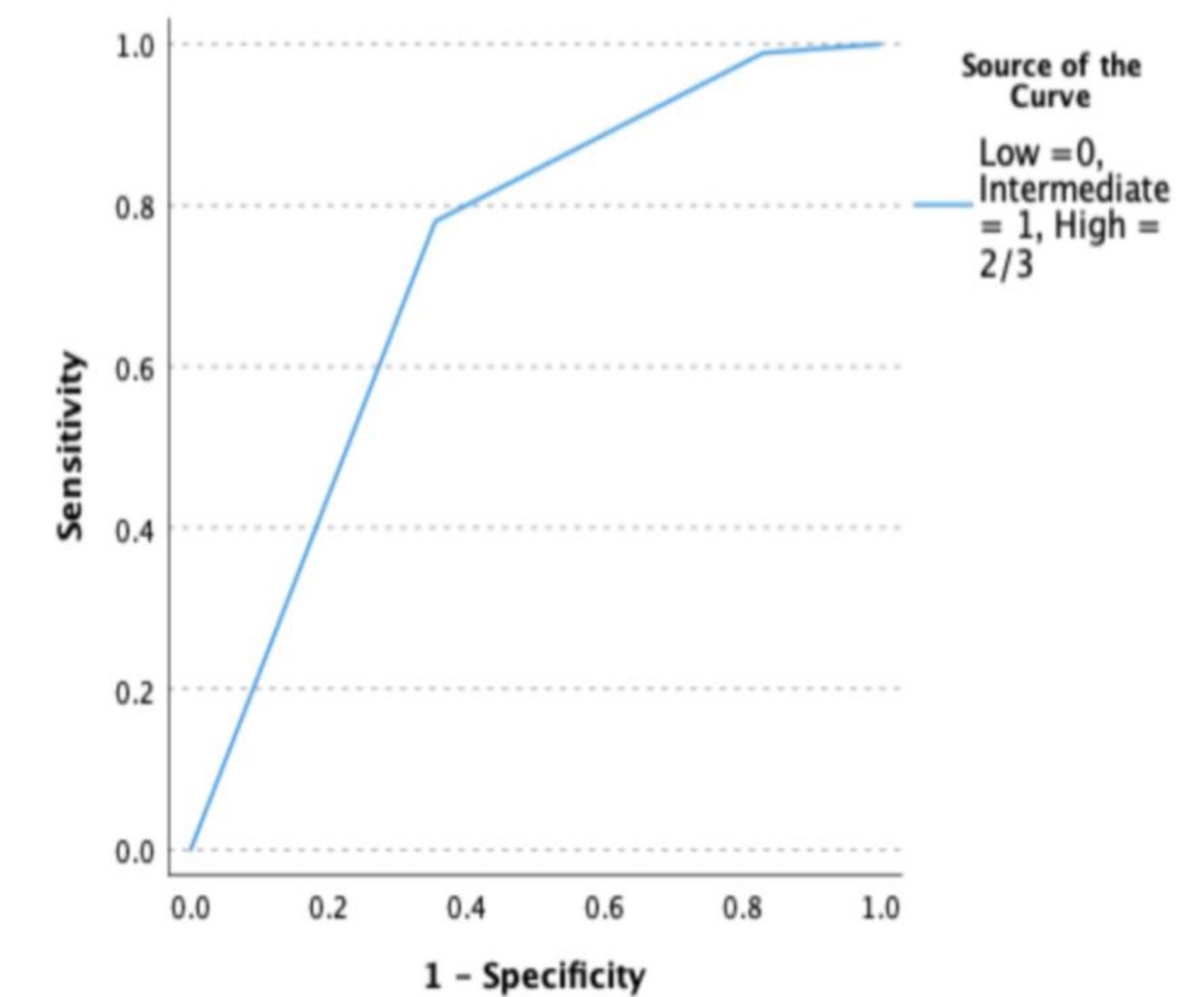
Receiver Operating Characteristic (ROC) curve of risk score (Low =0 variables seen in the patients, Intermediate = 1 variable seen, and High = 2 or 3 variables seen).
Area under the curve = 0.728.

Table 5: Risk Classification for Mechanical ventilation in patients with encephalitis.

Risk Group	No. Predictors for Mechanical ventilation [a]	Patients on mechanical ventilation/ total in the risk group (%)	P value
Low	0 of 3	1/32 (3.13)	<0.001
Intermediate	1 of 3	19/106 (17.92)	<0.001
High	2 or 3 of 3	71/136 (52.21)	<0.001

[a] Predictors include serum white blood cell count > 11,000/mm³, Sequential Organ Failure Assessment (SOFA) scores > 3 or abnormal Electroencephalogram (EEG)