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Research Article

PREDICTORS OF CLINICAL OUTCOMES IN INDIAN PATIENTS WITH ACUTE ENCEPHALOPATHY: A PROSPECTIVE OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTER IN INDIA

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ABSTRACT

Objective: Objective of the study was to evaluate the predictors of poor disease outcome at discharge and at 1 month in patients with acute encephalopathy.

Methods: This prospective, observational, single center study included adult patients meeting the diagnostic criteria for acute confusion state and admitted in the intensive care unit of a tertiary care hospital. A modified Rankin Scale (mRS) score of <3 was considered as "good outcome," while mRS ≥3 was considered as an indicator of "poor outcome."

Results: Among the total population of 219, 52.5% (n=115) were male, the mean age was 41.58 (±18.10) years and mean disease duration was 14.30 (±10.05) days (range: 1–30 days). Lethargy was the most common history at presentation (84.93%), while sleep abnormalities were least common (4.57%), and tuberculous meningitis was the most common etiology (21%). Diminution of vision, diplopia, dysarthria, cranial nerve symptoms, abdominal pain, difficulty in breathing, seizures, high-risk behavior, loss of appetite and the diagnosis of posterior reversible encephalopathy, retroviral disease, stroke and tuberculous meningitis were significant predictors of "poor outcome" at discharge ($p<0.05$). A diagnosis of tuberculous meningitis, history of headache, diminution of vision, diplopia, dysarthria, seizures, sensory deficits and loss of appetite and neuroimaging findings of atrophy, intracranial bleeding, demyelination, and space-occupying lesion were found to be significant predictors of "poor outcome" at 1 month post-discharge in this population ($p<0.05$).

Conclusion: In patients with acute encephalopathy, tuberculous etiology, the presence of focal brainstem deficits and specific neuroimaging findings indicate poor outcomes at discharge as well as at 1 month follow-up.

Keywords: Brain diseases, Central nervous system, India, Meningitis, Neuroimaging, Observational study.

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INTRODUCTION

Encephalopathy is a broad term referring to altered mental status due to focal or global brain insults, which may lead to cognitive and/or arousal changes [1]. Although the American Association of Psychiatry defines encephalopathy as "altered consciousness with change in cognition and/or with a perceptual disturbance developing over hours or days and that which was not better accounted for by a pre-existing or evolving chronic dementia," [2] there is lack of consensus on definition of encephalopathy among neurology fraternity due to the involvement of a wide variety of physiological dysfunctions (e.g., trauma, ischemia, hemorrhage, tumor, etc.) and non-structural derangements (which could be metabolism, toxin or infection-related) [1]. The determination of underlying etiology relies on history (mainly the onset speed, progression, and duration of symptoms), mental status examination and radiological/biochemical investigations [1].

In a study by Ashish *et al*., primary central nervous system (CNS) infection was found to be the commonest etiology, reported in 70% of patients (n=127) with acute febrile encephalopathy. 33% of this study population had meningitis, 29.9% had evidence of meningoencephalitis, 12.7% were diagnosed to have sepsis-associated encephalopathy, while 11% remained devoid of final diagnosis despite extensive investigation – demonstrating the heterogeneous nature of this syndrome [3]. Delirium is a predominantly reported feature in critically ill patients with encephalopathy and is related with long-term cognitive impairment. Moreover, it is also found to be significantly associated with higher mortality rate, longer durations of mechanical ventilation, and prolonged lengths of stay in the intensive care unit (ICU) [4].

The epidemiological data on clinical profile of encephalopathy in Indian patients are very sparse, and there also lies scarcity of studies analyzing the correlation of disease characteristics and final diagnosis with disease outcomes in such patients. Hence, this naturalistic study was planned to evaluate the interplay between clinico-demographic features, and the disease outcomes in acute encephalopathy patients admitted at a tertiary care center in India.

METHODS

This was a prospective, observational, single-center study conducted at the ICU of Victoria Hospital, Bangalore which is attached to Bangalore Medical College and Research Institute (Bangalore) during January 2017 - December 2018. The study was approved by the Bangalore Medical College and Research Institute ethics committee. Patients aged ≥ 18 years, meeting the diagnostic criteria for acute confusion state as per the Confusion Assessment Method for the ICU criteria [5] and admitted in the hospital were included in the study. A signed informed consent form was received from each participant for utilizing their data in the study. The objective of the present analysis was to identify the predictors of "poor outcome" in acute encephalopathy patients at discharge and at 1 month follow-up, through evaluation of the correlation of patients' demographic features, clinical characteristics, history of presenting

Table 1: Demographic and clinical profile of study population

Category	Total (n=219) n (%)
Age group*	
<20 years	23 (10.5)
21–35 years	72 (32.88)
36–50 years	61 (27.85)
51–65 years	38 (17.35)
>65 years	25 (11.42)
Gender	
Male	115 (52.51)
Female	104 (47.49)
Duration of disease*	
1–4 days	50 (22.83)
5–8 days	29 (13.24)
9–12 days	28 (12.79)
13–16 days	36 (16.44)
17–30 days	76 (34.7)
Altered sensorium	
Hypo	185 (84.47)
Hyper	34 (15.53)
Focal motor deficits*	
None	185 (84.47)
Right Hemiparesis	7 (3.2)
Left Hemiparesis	8 (3.65)
Paraparesis	1 (0.46)
Quadriparesis	18 (8.22)
History of presenting illness	
Headache	182 (83.11)
Diminution of Vision	78 (35.62)
Diplopia	63 (28.77)
Dysarthria	43 (19.63)
Cranial Nerve Symptoms	101 (46.12)
Ataxia	62 (28.31)
Neck Stiffness	144 (65.75)
Fever	163 (74.43)
Vomiting	168 (76.71)
Loose Motion	33 (15.07)
Drug Intake	44 (20.09)
Lethargy	186 (84.93)
Chest Pain	14 (6.39)
Abdominal Pain	21 (9.59)
Difficulty in Breathing	22 (10.05)
Seizures	109 (49.77)
Sensory Deficits	6 (2.74)
Decreased Urine Output	18 (8.22)
Involuntary Movement	34 (15.53)
High-Risk Behavior	33 (15.07)
Loss of Appetite	73 (33.33)
Psychiatric Illness	18 (8.22)
Sleep Abnormalities	10 (4.57)

*p-values are calculated after Bonferroni adjustment

illness, neuroimaging findings, CNS examination and final diagnosis with the score of modified Rankin Scale (mRS) of degree of disability. Patients with an mRS score <3 were considered to have "good outcome," whereas the mRS value of ≥3 was considered indicative of "poor outcome."

Statistical analysis

Data were analyzed with Epi info CDC version 7. Continuous variables are expressed as mean and standard deviation (±). Categorical variables are expressed with absolute numbers and percentages. The Chi-square test was used to find an association between categorical variables. Bonferroni corrections were used in case of more than two categories. A p<0.05 was considered statistically significant.

RESULTS

Clinico-demographic findings

The study population comprised 219 patients with mean age of 41.58 (±18.10) years, mean disease duration of 14.30 (±10.05) days (range: 1–30 days) and 52.5% (n=115) of them were male (Table 1). Lethargy

Table 2: Correlation of presenting history and diagnosis with mRS at discharge

Variable	mRS (<3) (n=63) (%)	mRS (≥3) (n=156) (%)	p-value
History of Presenting Illness			
Headache	54 (29.67)	128 (70.33)	0.56
Diminution of Vision	14 (17.95)	64 (82.05)	0.012
Diplopia	9 (14.29)	54 (85.71)	0.003
Dysarthria	6 (13.95)	37 (86.05)	0.017
Cranial Nerve Symptoms	22 (21.78)	79 (78.22)	0.035
Ataxia	14 (22.58)	48 (77.42)	0.204
Neck Stiffness	41 (28.47)	103 (71.53)	0.89
Fever	43 (26.38)	120 (73.62)	0.183
Vomiting	45 (26.79)	123 (73.21)	0.24
Loose Motion	5 (15.15)	28 (84.85)	0.061
Drug Intake	11 (25)	33 (75)	0.54
Lethargy	53 (28.49)	133 (71.51)	0.83
Chest Pain	4 (28.57)	10 (71.43)	0.98
Abdominal Pain	1 (4.76)	20 (95.24)	0.011
Difficulty in Breathing	2 (9.09)	20 (90.91)	0.032
Seizures	42 (38.53)	67 (61.47)	0.001
Sensory Deficits	0 (0)	6 (100)	0.114
Decreased Urine Output	5 (27.78)	13 (72.22)	0.92
Involuntary Movement	11 (32.35)	23 (67.65)	0.615
High-Risk Behavior	1 (3.03)	32 (96.97)	0.001
Loss of Appetite	7 (9.59)	66 (90.41)	0.001
Psychiatric Illness	3 (16.67)	15 (83.33)	0.24
Sleep Abnormalities	2 (20)	8 (80)	0.531
Final diagnosis*			
Autoimmune encephalitis	5 (50)	5 (50)	0.13
CNS demyelination	3 (37.5)	5 (62.5)	0.55
Epileptic encephalopathy	1 (25)	3 (75)	0.84
Fungal CNS infection	0 (0)	4 (100)	0.19
Hydrocephalus	1 (100)	0 (0)	0.11
Hypertensive Encephalopathy	2 (33.33)	4 (66.67)	0.76
Intracranial Space Occupying Lesion	2 (40)	3 (60)	0.55
Meningoencephalitis	8 (29.63)	19 (70.37)	0.92
Metabolic Encephalopathy	7 (30.43)	16 (69.57)	0.84
Mitochondrial Encephalopathy	0 (0)	1 (100)	0.545
Mixed Encephalopathy	6 (35.29)	11 (64.71)	0.55
Posterior Reversible Encephalopathy	4 (100)	0 (0)	0.001
Retroviral disease	0 (0)	11 (100)	0.02
Seizure disorder	6 (42.86)	8 (57.14)	0.23
Stroke	6 (66.67)	3 (33.33)	<0.05
Tuberculous Meningitis	6 (13.04)	40 (86.96)	<0.05
Venous Stroke	2 (50)	2 (50)	0.37
Viral Encephalitis	4 (16)	21 (84)	0.13

*p-values are calculated after Bonferroni adjustment, mRS: Modified Rankin Scale

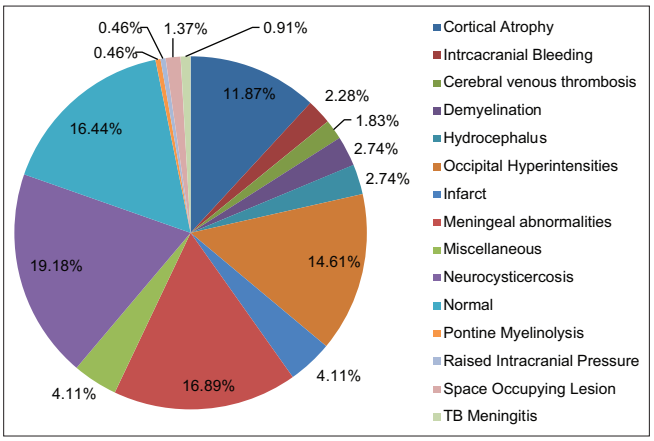

Fig. 1: Neuroimaging findings

was the most common history at presentation (84.93%), while sleep abnormalities were least common (4.57%). Focal motor deficits were reported in 16.08% of patients, quadriparesis being the most prevalent (8.22%). Detailed disposition of clinico-demographic features is demonstrated in Table 1.

Neuroimaging findings and diagnosis

Fig. 1 demonstrates the distribution of neuroimaging findings among the study population. With 19.18% prevalence, neurocysticercosis was the most common neuroimaging observation, while pontine myelinolysis and raised intracranial pressure were least commonly reported (0.46% each).

As seen in Fig. 2, tuberculous meningitis was the most commonly diagnosed etiology (21%), while hydrocephalus and mitochondrial encephalopathy were reported least (0.46% each).

mRS score at discharge

Mean mRS score at discharge in this population was 3.11 (±1.02) as seen in Table 2. The presenting history of diminution of vision, diplopia, dysarthria, cranial nerve symptoms, abdominal pain, difficulty in breathing, seizures, high-risk behavior and loss of appetite was significantly associated with poor clinical outcome at discharge as indicated by mRS score ≥3. Moreover, the patients with a diagnosis of posterior reversible encephalopathy, retroviral disease, stroke, and tuberculous meningitis were also found to have significantly higher rate of poor clinical outcome at discharge. No other disease characteristic showed difference in the rate of "good outcome" and "poor outcome" at discharge.

As depicted in Table 3, patients with abnormal optic fundi and pupillary reactions as well as absence of oculoencephalic, oculovestibular, and motor responses showed significantly higher rate of "poor outcome" at discharge.

mRS score at 1 month

At 1 month, the mean mRS score was 2.47 (±1.72) among total population. The rate of "poor outcome" as indicated by the % of patients with mRS ≥3 at 1 month was significantly higher among males as compared to females. Besides, a presenting history of headache, diminution of vision, diplopia, dysarthria, seizures, sensory deficits, and loss of appetite was also associated with significantly higher rate of "poor outcome." No specific diagnosis, except tuberculous meningitis, showed difference in the rate of "good" or "poor" outcomes, while the neuroimaging findings of atrophy, intracranial bleeding, demyelination, and space occupying lesion were associated with significantly higher rate of mRS ≥3 (Table 4).

As depicted in Table 4, patients with abnormal optic fundi and pupillary reactions as well as absence of oculoencephalic, oculovestibular, and motor responses showed significantly higher rate of "poor outcome" at 1 month.

DISCUSSION

In this prospective study, we evaluated the demographic characteristics, clinical features, CNS examination findings, neuroimaging findings,

Table 3: Correlation of CNS examination findings with mRS at discharge

Variable	mRS (<3) (n=63) (%)	mRS (≥3) (n=156) (%)	p-value
Optic fundi			
Normal	44 (35.8)	79 (64.2)	0.009
Abnormal	19 (19.8)	77 (80.2)	
Pupillary reactions			
Normal	60 (32.8)	123 (67.2)	0.003
Abnormal	03 (8.3)	33 (91.7)	
Oculocephalic responses			
Absent	0 (0)	8 (100)	0.06
Present	63 (29.9)	148 (70.14)	
Oculovestibular responses			
Absent	0 (0)	8 (100)	0.06
Present	63 (29.9)	148 (70.1)	
Corneal responses			
Absent	0 (0)	9 (100)	0.052
Present	63 (30)	147 (70)	
Motor response			
Absent	2 (6.3)	30 (93.8)	0.002
Present	61 (32.6)	126 (67.4)	
Meningeal signs			
Absent	26 (29.2)	63 (70.8)	0.904
Present	37 (28.5)	93 (71.5)	
Cerebellar signs			
Absent	58 (30.4)	133 (69.6)	0.172
Present	5 (17.9)	23 (82.1)	

CNS: Central nervous system, mRS: Modified Rankin Scale

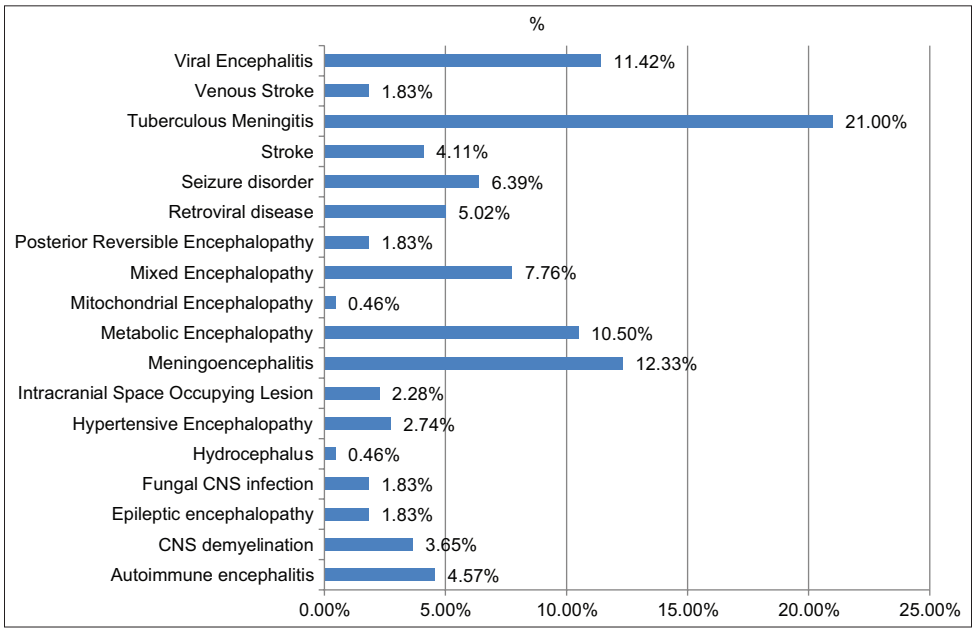

Fig. 2: Final diagnosis

Table 4: Correlation of gender, presenting history, and neuroimaging findings with mRS at 1 month after discharge

Variables	mRS (<3)	mRS (≥3)	p-value
	n=123 (%)	n=95 (%)	
Gender			
Male	56 (48.70)	59 (51.30)	0.011
Female	68 (65.38)	36 (34.62)	
History of Presenting Illness			
Headache	108 (59.34)	74 (40.66)	0.051
Diminution of Vision	36 (46.15)	42 (53.85)	0.022
Diplopia	22 (34.92)	41 (65.08)	<0.001
Dysarthria	17 ((40.48)	25 (59.52)	0.020
Cranial Nerve Symptoms	52 (52)	48 (48)	0.225
Ataxia	35 (57.38)	26 (42.62)	0.86
Neck Stiffness	84 (58.33)	60 (41.67)	0.427
Fever	88 (53.99)	75 (46.01)	0.212
Vomiting	99 (59.28)	68 (40.72)	0.123
Loose Motion	17 (51.52)	16 (48.48)	0.537
Drug Intake	22 (51.16)	21 (48.84)	0.44
Lethargy	100 (54.05)	85 (45.95)	0.095
Chest Pain	10 (71.43)	4 (28.57)	0.242
Abdominal Pain	10 (47.62)	11 (52.38)	0.392
Difficulty in Breathing	11 (50)	11 (50)	0.522
Seizures	69 (63.89)	39 (36.11)	0.028
Sensory Deficits	1 (16.67)	5 (83.33)	0.046
Decreased Urine Output	9 (50)	9 (50)	0.57
Involuntary Movement	24 (70.59)	10 (29.41)	0.070
High-Risk Behavior	14 (42.42)	19 (57.58)	0.078
Loss of Appetite	29 (39.73)	44 (60.27)	<0.001
Psychiatric Illness	13 (72.22)	5 (27.78)	0.158
Sleep Abnormalities	4 (40)	6 (60)	0.284
Neuroimaging findings*			
Atrophy	21 (80.77)	5 (19.23)	0.007
Bleeding	5 (100)	0 (0)	0.04
Cerebral venous thrombosis	2 (50)	2 (50)	0.795
Demyelination	0 (0)	6 (100)	0.004
Hydrocephalus	3 (50)	3 (50)	0.75
Hyper-intensities	20 (62.5)	12 (37.5)	0.45
Infarct	3 (33.33)	6 (66.67)	0.15
Meningeal abnormalities	23 (62.16)	14 (37.84)	0.44
Miscellaneous	2 (22.22)	7 (77.78)	0.035
Neurocysticercosis	19 (45.24)	23 (54.76)	0.10
Normal	25 (69.44)	11 (30.56)	0.11
Pontine Myelinolysis	1 (100)	0 (0)	0.38
Raised Intracranial Pressure	0 (0)	1 (100)	0.25
Space Occupying Lesion	0 (0)	3 (100)	0.047
Tuberculous Meningitis	0 (0)	2 (100)	0.10

mRS: Modified Rankin Scale. *p-values are calculated after Bonferroni adjustment

and final diagnosis in patients with acute encephalopathy for their correlation with disease outcome in terms of mRS score at discharge and at 1 month. The mean age and male: female proportion in this study population are in line with those reported by an observational study in Indian patients with acute febrile encephalopathy by Modi *et al*., depicting the mean age of 31.89 years and 63% male population [6]. Apart from altered sensorium (100%), lethargy (84%), headache (83%), and vomiting (76%) were the most common presenting history in the present study, which are similar to the findings of the study by Modi *et al*., in which fever (100%), headache (100%), and altered mental state (100%) were most commonly reported. In another prospective observational study by Feng *et al*., focal neurological deficits (p=0.014) and total length of hospital stay (p=0.045) were significantly associated with poor outcome at discharge (mRS ≥3) in 216 patients with viral encephalitis [7]. Contrastingly, none

Table 5: Correlation of CNS examination findings with mRS at 1 month

Variables	mRS (<3)	mRS (≥3)	p-value
	n=123 (%)	n=95 (%)	
Optic fundi			
Normal	83 (67.5)	40 (62.5)	<0.001
Abnormal	41 (42.71)	55 (57.29)	
Pupillary reactions			
Normal	116 (63.4)	67 (36.6)	<0.001
Abnormal	8 (22.22)	28 (77.78)	
Oculocephalic responses			
Absent	0 (0)	08 (100)	0.001
Present	124 (58.8)	87 (41.2)	
Oculovestibular responses			
Absent	0 (0)	08 (100)	0.001
Present	124 (58.8)	87 (41.2)	
Corneal responses			
Absent	0 (0)	9 (100)	<0.001
Present	124 (59.05)	86 (40.95)	
Motor response			
Absent	5 (15.6)	27 (84.4)	<0.001
Present	119 (63.6)	68 (36.4)	
Meningeal signs			
Absent	50 (56.2)	39 (43.8)	0.913
Present	74 (56.9)	56 (43.1)	
Cerebellar signs			
Absent	106 (55.5)	85 (44.5)	0.381
Present	18 (64.3)	10 (35.7)	

CNS: Central nervous system, mRS: Modified Rankin Scale

of these parameters were found associated with poor outcome in our study. This could be explained by the involvement of multiple etiologies in our study population along with the influence of focal motor deficits which (as characterized by diminution of vision, diplopia, dysarthria, cranial nervous symptoms and seizures in this population) predicted poor outcome at discharge.

The association of magnetic resonance imaging (MRI) abnormalities and clinical outcome in encephalopathy is disputed as demonstrated by contrasting results of various studies. In patients with autoimmune encephalopathy, MRI abnormalities are found to have no impact on mRS score at discharge as depicted by a multicenter registry of 120 patients by Schubert *et al*. [8]. However, abnormal MRI findings were found significantly associated with higher mRS score in 50 patients with autoimmune encephalitis (p=0.003) [9].Considering the high preponderance of pathological signals found to be present in cerebral cortex and basal ganglia, brain MRI is considered to be the most valuable evaluation in patients with acute encephalopathy in addition to clinical and neurophysiological examination [10]. The current study depicts association of varied types of MRI abnormalities with disease outcome in encephalopathy of multiple etiologies. Specifically, the patients with posterior reversible encephalopathy (p=0.001), retroviral disease (p=0.02), stroke (p<0.05) and tuberculous meningitis (p<0.05) had significantly higher rate of "poor outcome" at discharge in this population. Interestingly, the neuroimaging findings did not impart significant effect on the rate of poor outcome at discharge, while the type of etiology did not have significant relation with poor outcome at 1 month.

However, particular features of presenting history and CNS examination significantly predicted poor outcome at both discharge as well at 1 month. We found a significant association of abnormalities in optic fundi, pupillary reactions and absence of oculocephalic responses, oculovestibular responses and motor responses significantly associated with "poor outcome" at discharge and at 1 month (Table 5). This can potentially be explained by the focal brainstem lesions which are often associated with poor clinical and mortality outcomes in patients with altered consciousness [11].

Major strengths of our study are its naturalistic nature and inclusion of patients with a wide spectrum of etiological presentations with acute encephalopathy. This may enable generalizability of the findings and be of value for enhancing clinical understanding of acute encephalopathy in Indian patients. Moreover, we could identify specific predictors of "poor outcome" in these groups of patients regardless of their age and ongoing treatment.

One important limitation of this study in our opinion is not having analyzed the correlation of biochemical characteristics and management pattern with disease outcome. Considering the scarcity of real-world clinical data on Indian patients with encephalopathy, the findings of this study are expected to form the basis for further extensive research in this field.

CONCLUSION

From this prospective, observational study, we conclude that tuberculous meningitis is the most common etiology behind acute encephalopathy in the studied population. Diminution of vision, diplopia, dysarthria, cranial nerve symptoms, abdominal pain, difficulty in breathing, seizures, high-risk behavior, loss of appetite, the diagnosis of posterior reversible encephalopathy, retroviral disease, stroke, and tuberculous meningitis are significant predictors of "poor outcome" at discharge. Moreover, a diagnosis of tuberculous meningitis, history of headache, diminution of vision, diplopia, dysarthria, seizures, sensory deficits, and loss of appetite as well as the neuroimaging findings of atrophy, intracranial bleeding, demyelination and space occupying lesion were found to be significant predictors of "poor outcome" at 1 month post-discharge in this population. These features should be looked out for and addressed promptly to improve the prognosis in patients with encephalopathy.

AUTHORS CONTRIBUTION

Suhana S and Murali S conceptualized, designed, and conducted the study. Raval N contributed to data analysis and drafted, edited, and finalized the manuscript of this paper.

AUTHORS FUNDING

Nil.

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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