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Etiology, Clinical Profile and In-Hospital Outcome of Adult Patients Presenting with Altered Sensorium to a Tertiary Care Hospital - A Prospective Cross-Sectional Study

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Abstract

Background: Altered sensorium is among the commonest presentations to the medical emergency department and carries a substantial in-hospital mortality, yet its etiological spectrum and prognostic determinants vary widely between healthcare settings.

Objectives: To study the clinical profile and etiology of adult patients presenting with non-traumatic altered sensorium, and to assess their in-hospital outcome.

Methods: A hospital-based prospective cross-sectional study was conducted between February 2021 and August 2022 in hospitals attached to Bangalore Medical College and Research Institute. Two hundred and seventy consecutive patients aged 18 years and above presenting with altered sensorium to the medical emergency department or admitted to the intensive care unit were enrolled after informed consent. Patients with head injury, primary psychiatric illness and postoperative altered sensorium were excluded. All patients underwent detailed history, clinical examination, Glasgow Coma Scale (GCS) scoring, biochemical evaluation and neuroimaging, and were followed until discharge or death. Data were analysed using SPSS version 20, with p less than 0.05 taken as significant.

Results: The mean age was 54.8 (16.4) years and 184 patients (68.1%) were male. One hundred and fifty-six patients (57.8%) were discharged and 114 (42.2%) died. Focal neurological deficit was the commonest presenting complaint (115, 42.6%). Cerebrovascular accident was the commonest etiology (109, 40.4%), followed by metabolic encephalopathy (64, 23.7%) and septic encephalopathy (50, 18.5%). Etiology was significantly

associated with outcome (p less than 0.001), with septic encephalopathy carrying the highest case fatality (37/50, 74.0%). Mortality was 68.9% in patients with admission GCS 3 to 8 versus 10.2% in those with GCS 13 to 15 (p less than 0.001). Discharge rates fell from 72.4% among patients presenting within 6 hours of symptom onset to 33.3% beyond 48 hours.

Conclusion: Cerebrovascular accident was the commonest cause of altered sensorium, but septic encephalopathy was the commonest cause of death. Early presentation, higher admission GCS and a preserved level of consciousness were the strongest favourable prognostic markers.

Keywords: Altered Sensorium, Encephalopathy, Glasgow Coma Scale, Cerebrovascular Accident, Septic encephalopathy, In-hospital mortality.

Introduction

Consciousness is conventionally described along two independent axes: arousal, or the level of wakefulness, and content, which encompasses awareness of the self and the environment. Impairment of either axis produces the clinical state loosely termed altered sensorium, an umbrella expression that spans acute confusion, drowsiness, stupor and coma. Because the descriptive vocabulary applied to these states has never been fully standardised, the same patient may be labelled confused by one clinician, encephalopathic by another and obtunded by a third, and this terminological drift has historically hampered comparison across published series.[1,3] What unites these presentations is a shared final common pathway: diffuse or bilateral cerebral dysfunction, brainstem dysfunction, or a systemic derangement severe enough to compromise the substrate supply on which cortical function depends.

Anatomically, the maintenance of normal consciousness depends on the integrity of the ascending reticular activating system (ARAS), a diffuse neuronal network arising in the paramedian tegmentum of the rostral pons and midbrain, relaying through the thalamus and projecting widely to the cerebral cortex, together with the functional integrity of both cerebral hemispheres. Coma may therefore arise from a lesion damaging the ARAS or its thalamic projections, from bilateral hemispheric injury of sufficient extent, or from a drug, toxin or metabolic abnormality that suppresses reticular and cortical function globally. Unilateral hemispheric lesions do not by themselves produce coma unless they generate mass effect and secondary brainstem compression.[1,3] This anatomical framework has direct bedside utility, since the presence of asymmetrical neurological signs, anisocoria or disconjugate eye movements points towards a structural cause requiring urgent imaging, whereas symmetrical findings with preserved pupillary reactivity favour a toxic or metabolic process.

Altered mental status is not an uncommon reason for emergency attendance. Depending on the case definition applied and the age structure of the population served, it accounts for approximately 4% to 10% of adult emergency department visits. In the prospective series reported by Kanich and colleagues from a university hospital in the United States, 317 patients with altered mental status represented about 5% of the emergency department census over the study period, and the commonest discharge diagnoses were neurological in 28% and toxicological in 21%, followed by trauma and psychiatric syndromes in 14% each and infection in 10%.[4] Xiao and colleagues, reporting on 1934 patients from a tertiary centre in Beijing, similarly found that

primary neurological disorders, intoxications, organ system dysfunction and endocrine or metabolic disease accounted for the bulk of presentations, and emphasised the high emergency department mortality associated with the syndrome.[5] In an urban Singaporean emergency department, Lim Beng Leong and colleagues prospectively recruited 967 patients with a mean age of 66.5 years and documented the resource intensity and diagnostic difficulty that this heterogeneous group imposes on emergency services.[6]

The etiological distribution, however, is far from constant across geography. A systematic review of 14 observational studies of non-traumatic coma in emergency and critical care settings by Horsting and colleagues found stroke in 6% to 54% of patients, post-anoxic coma in 3% to 42%, poisoning in less than 1% to 39% and metabolic causes in 1% to 29%, while infection accounted for 10% to 51% of cases in African cohorts. The reported mortality across those studies ranged from 25% to 87%, and a further 5% to 25% of survivors remained moderately or severely disabled or in a persistent vegetative state.[8]

This extraordinary heterogeneity reflects genuine differences in disease burden, in the availability of prehospital care and in the thresholds at which patients reach hospital, and it means that etiological data generated in one health system cannot simply be transposed to another.

The Indian picture differs from most Western series in several respects. The burden of communicable disease remains high, alcohol-related liver disease and chronic kidney disease are common, organophosphate and other agricultural poisonings are frequent, and a substantial proportion of patients reach tertiary care after a considerable prehospital delay.

John and colleagues, studying 251 elderly Indian patients with encephalopathy, reported neurological causes in 38.7%, infection or sepsis in 36.5% and metabolic causes in 33.5%, with hyponatraemia the commonest metabolic derangement and pneumonia the commonest infective source; overall mortality in that cohort was 19.1%, and better outcomes were seen in patients presenting within six hours of symptom onset.[7] Rai and colleagues, in a north Indian series of patients with acute confusional state, similarly highlighted the contribution of infection and metabolic derangement and the prognostic weight of admission mental status.[16] A more recent multicentre Korean study of new-onset altered level of consciousness has again underlined that the diagnostic label assigned in the emergency department frequently changes once inpatient evaluation is complete.[15]

Metabolic encephalopathies deserve particular attention because they are, in principle, the most reversible group. Hepatic encephalopathy arises from hyperammonaemia with astrocytic glutamine accumulation, osmotic swelling, mitochondrial dysfunction and enhanced GABAergic tone, and is usually precipitated by an identifiable event such as infection, gastrointestinal bleeding, hypokalaemia or volume depletion. Uraemic encephalopathy reflects the accumulation of guanidino compounds and other retained solutes that antagonise GABA receptors while acting as agonists at N – methyl –D–aspartate receptors, producing cortical hyperexcitability. Hypoglycaemia deprives the brain of its principal substrate within minutes of exhaustion of a glycogen reserve sufficient for only about half an hour of cerebral activity, and rapid correction is the single most rewarding intervention in the emergency department. Acute hyponatraemia below 125 mmol/L commonly

causes confusion, and levels below 120 mmol/L are frequently associated with seizures and coma. The clinical importance of this group lies less in their individual pathophysiology than in the fact that a bedside glucose measurement, a serum sodium and a set of liver and renal function tests will identify most of them within an hour of arrival.[2]

Sepsis-associated encephalopathy is the least well recognised and arguably the most lethal category. It is defined as diffuse cerebral dysfunction induced by the systemic inflammatory response to infection in the absence of direct central nervous system infection or another identifiable encephalopathy. Its pathogenesis is multifactorial and involves endothelial activation and blood brain barrier breakdown, microglial activation with local production of nitric oxide and reactive oxygen species, impaired cerebral autoregulation with consequent hypoperfusion, cholinergic and other neurotransmitter dysfunction, and mitochondrial failure with neuronal apoptosis.[13] It occurs in up to 70% of patients admitted to intensive care with sepsis and is independently associated with higher intensive care and hospital mortality as well as with poorer long-term cognitive and functional outcomes.[14] Because the encephalopathy may precede overt haemodynamic decompensation, altered sensorium in a febrile or hypotensive patient should prompt an aggressive search for a septic focus rather than a neurological work-up alone.

Objective grading of the depth of impairment remains central to both communication and prognostication. The Glasgow Coma Scale, described by Teasdale and Jennett in 1974 for the assessment of traumatic brain injury, has become the most widely used and best validated instrument for this purpose, and has been extended well beyond its original indication to intracranial haemorrhage, poisoning, cardiac arrest and central nervous system infection.[10] Its limitations are equally well documented: the verbal component cannot be scored in intubated or aphasic patients, the eye component is unreliable in periorbital swelling, the subscales are unequally weighted, and it contains no direct assessment of brainstem function. The Full Outline of UnResponsiveness (FOUR) score was devised to address these deficiencies by substituting a verbal-independent motor task and adding explicit brainstem reflex and respiratory pattern components.[11] In a study of medical patients with altered sensorium, Gujjar and colleagues found both scales to have good interrater reliability and comparable relation to outcome, so that the choice between them remains largely one of local familiarity.[12] The classical prognostic work of Levy and colleagues in 500 patients with non-traumatic coma established that recovery was related more to the cause of coma and to the depth and duration of impairment than to age, with cerebrovascular causes carrying the worst functional recovery.[9]

Time to presentation is a further modifiable determinant. Many causes of altered sensorium are reversible if identified promptly, and the list of conditions in which delay converts a salvageable patient into a fatal one is long: hypoglycaemia, opioid intoxication, bacterial meningitis, non-convulsive status epilepticus, basilar artery occlusion and acute obstructive hydrocephalus among them.[2] A structured airway, breathing and circulation approach with immediate capillary glucose measurement, early empirical thiamine and naloxone where indicated, and early broad-spectrum antibiotics where sepsis is suspected, has been shown to improve outcomes.[3] Yet in resource-constrained settings the

interval between symptom onset and arrival at a tertiary centre is often measured in days rather than hours, and quantifying the outcome penalty attached to that delay is of direct public health relevance.

Despite the frequency of the presentation, prospective Indian data describing the full etiological spectrum of altered sensorium across all adult age groups, together with objectively documented in-hospital outcomes, remain limited. Most published Indian series have been retrospective, restricted to the elderly, restricted to non-traumatic coma with a Glasgow Coma Scale threshold, or based on modest sample sizes. The present study was therefore designed to prospectively characterise the etiology, clinical profile and in-hospital outcome of an unselected cohort of 270 adult patients presenting with altered sensorium to a large public tertiary care teaching hospital in southern India, and to identify the clinical and laboratory variables at presentation that are associated with mortality.

Aims and Objectives

1. To study the clinical profile and etiology of adult patients presenting with altered sensorium to a tertiary care hospital.
2. To assess the in-hospital outcome, defined as discharge or death, in patients presenting with altered sensorium, and to identify clinical and laboratory variables at presentation associated with that outcome.

Materials and Methods

Study design and setting

This was a hospital-based prospective cross-sectional observational study conducted in the Department of General Medicine and its attached hospitals under Bangalore Medical College and Research Institute, Bangalore, Karnataka, India. The institution is a public tertiary care teaching hospital serving a large urban and periurban catchment and receiving both direct emergency attendances and referrals from peripheral centres.

Study period

Patients were recruited over a period of nineteen months, from February 2021 to August 2022. Each enrolled patient was followed prospectively from the point of emergency department presentation until the terminal in-hospital event, that is, discharge from hospital or death.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Bangalore Medical College and Research Institute before commencement of recruitment. Because the index presentation itself precluded valid consent from most participants, written informed consent was obtained from the legally acceptable representative or attending caregiver of every patient in a language the representative understood. Consent forms were made available in English, Kannada and Hindi. Participants and their representatives were informed of their right to withdraw at any stage without any effect on the treatment provided. Patient identity was not recorded in the analysis dataset. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study population and eligibility criteria

Consecutive patients presenting with altered sensorium to the medical emergency department, and patients admitted to the medical intensive care unit with altered sensorium, were screened for eligibility.

Inclusion criteria were: age 18 years or above; presentation with altered sensorium to the medical emergency department or admission to the intensive care unit with altered sensorium; and availability of a

caregiver willing and competent to provide informed consent.

Exclusion criteria were: age below 18 years; altered sensorium attributable to head injury; patients with a primary psychiatric illness accounting for the altered mental state; postoperative patients; and patients whose caregivers declined consent.

Sample size estimation

The sample size was estimated using the formula n = Z squared x p x q / d squared, where Z was the standard normal deviate at a 95% confidence level (1.96). The expected proportion of neurological etiology among patients with altered sensorium was taken as 38.6% on the basis of the previously published series by John and colleagues.[7] Accordingly p was 38.6, q was 61.4, and the relative precision d was set at 15% of p, that is 5.8. Substitution yielded a required sample size of 270.5, and 270 patients were therefore enrolled.

Study procedure and data collection

After enrolment, a structured study proforma was completed for every patient. A detailed history was obtained from the accompanying caregiver and covered the circumstances and rapidity of onset of the altered sensorium, the interval between symptom onset and arrival at the emergency department, antecedent symptoms such as fever, headache, vomiting, seizures, focal weakness or behavioural change, history of ingestion of drugs, alcohol or poison, current medications, and pre-existing comorbid illness including diabetes mellitus, hypertension, chronic kidney disease, ischaemic heart disease, chronic liver disease and seizure disorder.

A complete general physical examination was performed, recording pulse rate, blood pressure, respiratory rate and pattern, temperature, oxygen saturation, hydration, pallor, icterus, cyanosis, clubbing, lymphadenopathy, pedal oedema and cutaneous findings including petechiae and injection marks. Systemic examination covered the cardiovascular, respiratory, abdominal and central nervous systems. Neurological assessment included the level of consciousness, pupillary size and reactivity, extraocular movements, oculocephalic response, corneal reflex, fundoscopy, motor power, deep tendon reflexes, plantar responses and signs of meningeal irritation.

The level of consciousness was recorded descriptively as confused, drowsy, stuporous or comatose, and was in addition graded objectively using the Glasgow Coma Scale, which was scored at the time of first assessment in the emergency department and categorised as severe (3 to 8), moderate (9 to 12) or mild (13 to 15) impairment.[10]

Investigations

Capillary blood glucose was measured at the bedside in every patient at the time of first contact. Venous blood was drawn for complete blood count, blood urea, serum creatinine, serum electrolytes including sodium, potassium and chloride, liver function tests comprising total and direct bilirubin, total protein, albumin, globulin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase, prothrombin time with international normalised ratio, random blood sugar, and serology for hepatitis B surface antigen and hepatitis C virus. Arterial blood gas analysis, serum ammonia, thyroid function tests, blood and urine cultures, sputum culture, cerebrospinal fluid analysis by lumbar puncture, chest radiography, electrocardiography and electroencephalography were performed where clinically indicated. Non-contrast computed tomography of the brain was obtained in all patients in whom a

structural cause was considered, and magnetic resonance imaging was performed when computed tomography was uninformative and clinical suspicion of a structural lesion persisted.

Outcome definitions and etiological classification

The final etiological diagnosis for each patient was assigned at the end of the hospital stay by the treating unit on the basis of the composite of clinical, laboratory, microbiological and radiological data, and was classified into one of nine mutually exclusive categories: ischaemic stroke, haemorrhagic stroke, cerebral venous thrombosis, metabolic encephalopathy, septic encephalopathy, neuroinfection, poisoning or toxin exposure, seizure disorder, and multifactorial. Septic encephalopathy was diagnosed when there was clinical and laboratory evidence of systemic infection with encephalopathy in the absence of direct central nervous system infection or an alternative metabolic explanation. The primary outcome was in-hospital status at the end of the admission, categorised as discharge or death.

Statistical analysis

Data were entered into a Microsoft Excel spreadsheet and analysed using the Statistical Package for the Social Sciences (SPSS) version 20 (IBM Corporation, Armonk, New York, United States). Continuous variables were summarised as mean and standard deviation where the distribution approximated normality, and as median with interquartile range where it did not. Categorical variables were summarised as frequencies and percentages. Comparison of continuous variables between the discharged and deceased groups was performed using the independent samples t test or the Mann-Whitney U test as appropriate to the distribution. Categorical variables were compared using the Pearson chi-square test, with the Fisher exact test substituted where expected cell counts were small. A two-sided p value of less than 0.05 was considered statistically significant throughout.

Results

Demographic profile and overall outcome

Two hundred and seventy patients presenting with altered sensorium were enrolled and followed to a terminal in-hospital event. One hundred and fifty-six patients (57.8%) were discharged alive and 114 (42.2%) died in hospital, giving an overall in-hospital case fatality of 42.2%.

The mean age of the cohort was 54.8 (16.4) years, with a minimum of 18 years and a maximum of 90 years. The largest single age stratum was 51 to 60 years, which contained 60 patients (22.2%), followed by 41 to 50 years with 58 patients (21.5%). Two hundred and fifteen patients (79.6%) were above 40 years of age. Mean age did not differ between the discharged group (54.6 (15.9) years) and the deceased group (55.2 (16.0) years), p = 0.99, and no age stratum showed a significant excess of mortality. One hundred and eighty-four patients (68.1%) were male and 86 (31.9%) were female; the proportion of males among those discharged (106/156, 67.9%) and among those who died (78/114, 68.4%) was almost identical, p = 0.934 (Table 1).

Table 1: Baseline demographic characteristics of the study population and their distribution by in-hospital outcome (N = 270)

Variable	Total (n = 270)	Discharged (n = 156)	Died (n = 114)	p value
Age in years, mean (SD)	54.8 (16.4)	54.6 (15.9)	55.2 (16.0)	0.99
18 to 30 years, n (%)	19 (7.0)	12 (7.7)	7 (6.1)	

31 to 40 years, n (%)	36 (13.3)	21 (13.5)	15 (13.2)	
41 to 50 years, n (%)	58 (21.5)	35 (22.4)	23 (20.2)	
51 to 60 years, n (%)	60 (22.2)	34 (21.8)	26 (22.8)	
61 to 70 years, n (%)	52 (19.3)	28 (17.9)	24 (21.1)	
71 to 80 years, n (%)	32 (11.9)	19 (12.2)	13 (11.4)	
Above 80 years, n (%)	13 (4.8)	7 (4.5)	6 (5.3)	
Male, n (%)	184 (68.1)	106 (67.9)	78 (68.4)	0.934
Female, n (%)	86 (31.9)	50 (32.1)	36 (31.6)	

SD, standard deviation. Percentages for age strata and sex are column percentages.

Presenting complaints and delay to presentation

In addition to the altered sensorium that defined eligibility, focal neurological deficit was the commonest accompanying presenting complaint, documented in 115 patients (42.6%). Vomiting was reported in 50 patients (18.5%), fever in 30 (11.1%), headache in 27 (10.0%), abdominal pain in 23 (8.5%), abdominal distension in 17 (6.3%), breathlessness in 16 (5.9%), convulsions in 14 (5.2%), pedal oedema in 9 (3.3%) and jaundice in 8 (3.0%).

Individual patients frequently reported more than one complaint, so the percentages sum to more than 100.

The interval between symptom onset and arrival at the emergency department was strongly associated with survival. One hundred and twenty-seven patients (47.0%) reached hospital within 6 hours of symptom onset and 92 of them (72.4%) were discharged alive. Eighty-one patients (30.0%) presented between 6 and 24 hours, of whom 43 (53.1%) survived.

Forty-four patients (16.3%) presented between 24 and 48 hours, of whom only 15 (34.1%) survived, and 18 patients (6.7%) presented beyond 48 hours, of whom 6 (33.3%) survived. Mortality therefore rose progressively from 27.6% in the earliest-presenting group to 66.7% in the latest (Table 2).

Table 2: Presenting complaints and interval from symptom onset to emergency department arrival, with associated outcome

Variable	n	% of 270	Discharged, n	Died, n	Discharge rate (%)
Presenting complaint					
Focal neurological deficit	115	42.6			
Vomiting	50	18.5			
Fever	30	11.1			
Headache	27	10.0			
Abdominal pain	23	8.5			
Abdominal distension	17	6.3			
Breathlessness	16	5.9			
Convulsions	14	5.2			

Pedal oedema	9	3.3			
Jaundice	8	3.0			
Interval to presentation					
Within 6 hours	127	47.0	92	35	72.4
6 to 24 hours	81	30.0	43	38	53.1
24 to 48 hours	44	16.3	15	29	34.1
Beyond 48 hours	18	6.7	6	12	33.3

Complaints are not mutually exclusive; a patient could report more than one, so percentages exceed 100 in aggregate.

Level of consciousness and Glasgow Coma Scale at admission

At the time of first assessment, 123 patients (45.6%) were drowsy, 80 (29.6%) were stuporous, 49 (18.1%) were confused and 18 (6.7%) were comatose. The descriptive level of consciousness discriminated outcome sharply.

Forty-three of the 49 confused patients (87.8%) and 89 of the 123 drowsy patients (72.4%) were discharged alive, whereas only 22 of the 80 stuporous patients (27.5%) and 2 of the 18 comatose patients (11.1%) survived.

The same gradient was evident with objective Glasgow Coma Scale scoring. One hundred and thirty-four patients (49.6%) had an admission score of 9 to 12, 87 (32.2%) scored 3 to 8 and 49 (18.1%) scored 13 to 15. Mortality was 68.9% (60/87) in the 3 to 8 band, 36.6% (49/134) in the 9 to 12 band and 10.2% (5/49) in the 13 to 15 band. The association between admission Glasgow Coma Scale category and in-hospital outcome was highly significant, p less than 0.001 (Table 3).

Table 3: Level of consciousness and Glasgow Coma Scale category at admission in relation to in-hospital outcome (N = 270)

Variable	Total n (%)	Discharged n	Died n	Mortality (%)	p value
Level of consciousness					Not tested
Confused	49 (18.1)	43	6	12.2	
Drowsy	123 (45.6)	89	34	27.6	
Stuporous	80 (29.6)	22	58	72.5	
Comatose	18 (6.7)	2	16	88.9	
Glasgow Coma Scale					Less than 0.001
3 to 8 (severe)	87 (32.2)	27	60	69.0	
9 to 12 (moderate)	134 (49.6)	85	49	36.6	
13 to 15 (mild)	49 (18.1)	44	5	10.2	

Glasgow Coma Scale recorded at first assessment in the emergency department. p value derived from the Pearson chi-square test across the three score bands.

Comorbid illness

Hypertension was the commonest comorbidity, present in 119 patients (44.1%), followed by diabetes mellitus in 89 (33.0%). Chronic kidney disease was documented in 16 patients (5.9%), ischaemic heart disease in 11 (4.1%) and other comorbid conditions, principally chronic liver disease, seizure disorder and hypothyroidism, in 17 (6.3%). None of the individual comorbidities showed a statistically significant association with in-hospital mortality on univariate analysis (Table 4).

Table 4: Distribution of comorbid illness and its relationship with in-hospital outcome (N = 270)

Comorbidity	Present, n (%)	Discharged n	Died n	p value
Hypertension	119 (44.1)	69	50	0.952
Diabetes mellitus	89 (33.0)	50	39	0.709
Chronic kidney disease	16 (5.9)	8	8	0.516
Ischaemic heart disease	11 (4.1)	5	6	0.398
Other comorbidity	17 (6.3)	11	6	0.550

Comorbidities are not mutually exclusive. p values derived from the Pearson chi-square test comparing presence versus absence of each comorbidity across outcome groups.

Etiological spectrum and its relation to outcome

Taken as a single category, cerebrovascular accident was the commonest cause of altered sensorium, accounting for 109 patients (40.4%). Within this group, ischaemic stroke predominated with 83 patients (76.1% of cerebrovascular accidents and 30.7% of the whole cohort), followed by haemorrhagic stroke in 23 (21.1% and 8.5% respectively) and cerebral venous thrombosis in 3 (2.8% and 1.1%).

Metabolic encephalopathy was the second commonest category with 64 patients (23.7%), and septic encephalopathy the third with 50 patients (18.5%). Neuroinfection accounted for 23 patients (8.5%), poisoning or toxin exposure for 13 (4.8%), multifactorial causes for 7 (2.6%) and seizure disorder for 4 (1.5%).

Etiology was very strongly associated with outcome, p less than 0.001. Case fatality was highest in septic encephalopathy at 74.0% (37/50) and in the multifactorial group at 85.7% (6/7), intermediate in metabolic encephalopathy at 53.1% (34/64), haemorrhagic stroke at 47.8% (11/23) and seizure disorder at 75.0% (3/4), and lowest in neuroinfection at 13.0% (3/23) and ischaemic stroke at 15.7% (13/83). Two of the three patients with cerebral venous thrombosis died (Table 5).

Table 5: Etiological distribution of altered sensorium and its relationship with in-hospital outcome (N = 270)

Etiology	Total n (%)	Discharged n	Died n	Case fatality (%)	p value
Ischaemic stroke	83 (30.7)	70	13	15.7	Less than 0.001
Metabolic encephalopathy	64 (23.7)	30	34	53.1	
Septic encephalopathy	50 (18.5)	13	37	74.0	
Haemorrhagic stroke	23 (8.5)	12	11	47.8	
Neuroinfection	23 (8.5)	20	3	13.0	
Poisoning or toxin	13 (4.8)	8	5	38.5	

Multifactorial	7 (2.6)	1	6	85.7	
Seizure disorder	4 (1.5)	1	3	75.0	
Cerebral venous thrombosis	3 (1.1)	1	2	66.7	
Total	270 (100.0)	156	114	42.2	

p value derived from the Pearson chi-square test for the association between etiological category and outcome across the whole table.

Composition of the major etiological subgroups

Among the 64 patients with metabolic encephalopathy, hepatic encephalopathy was the commonest single cause with 21 patients (32.8%), followed by hypoglycaemic and uraemic encephalopathy with 13 patients each (20.3% each), hyponatraemic encephalopathy in 8 (12.5%), carbon dioxide narcosis in 5 (7.8%) and hypernatraemic encephalopathy in 4 (6.3%). The lowest recorded blood glucose in the cohort was 21 mg/dL and the lowest recorded serum sodium was 104 mEq/L. Within this subgroup, hepatic encephalopathy accounted for the largest share of deaths (15 of 34 metabolic deaths, 44.1%), followed by uraemic encephalopathy with 6 deaths, whereas patients with hypoglycaemia and hyponatraemia showed comparatively good survival.

Among the 50 patients with septic encephalopathy, pneumonia was the commonest source, identified in 30 patients (60.0%), followed by urinary tract infection in 14 (28.0%) and skin and soft tissue infection in 6 (12.0%). Gastrointestinal infection, lung abscess, pelvic inflammatory disease and catheter-related bloodstream infection accounted for one patient each. Sputum culture in patients with bronchopneumonia grew Klebsiella species in 5 patients and Acinetobacter baumannii in 2, with commensal flora only in 6. Urine culture grew Escherichia coli in 8 of the 14 patients with urosepsis.

Among the 23 patients with neuroinfection, bacterial meningitis was commonest with 10 patients, followed by viral meningitis in 8, tuberculous meningitis in 4 and cryptococcal meningitis in 1. Among the 13 patients with poisoning or toxin exposure, alcohol intoxication accounted for 5 (38.5%) and organophosphate compound poisoning for 3 (23.1%), with one patient each following amlodipine overdose, barbiturate overdose, antipsychotic overdose, cypermethrin poisoning and rodenticide ingestion. Eight of these 13 patients (61.5%) recovered fully (Table 6).

Table 6: Composition of the major etiological subgroups

Subgroup and component	n	% within subgroup	Deaths n
Cerebrovascular accident (n = 109)			
Ischaemic stroke	83	76.1	13
Haemorrhagic stroke	23	21.1	11
Cerebral venous thrombosis	3	2.8	2
Metabolic encephalopathy (n = 64)			
Hepatic encephalopathy	21	32.8	15
Hypoglycaemic encephalopathy	13	20.3	5
Uraemic encephalopathy	13	20.3	6

Hyponatraemic encephalopathy	8	12.5	2
Carbon dioxide narcosis	5	7.8	3
Hypernatraemic encephalopathy	4	6.3	3
Source of sepsis (n = 50)			
Pneumonia	30	60.0	21
Urinary tract infection	14	28.0	8
Skin and soft tissue infection	6	12.0	5
Gastrointestinal infection	1	2.0	
Lung abscess	1	2.0	
Pelvic inflammatory disease	1	2.0	
Catheter-related bloodstream infection	1	2.0	
Neuroinfection (n = 23)			
Bacterial meningitis	10	43.5	
Viral meningitis	8	34.8	
Tuberculous meningitis	4	17.4	
Cryptococcal meningitis	1	4.3	
Poisoning or toxin (n = 13)			
Alcohol intoxication	5	38.5	2
Organophosphate compound	3	23.1	1
Barbiturate overdose	1	7.7	1
Amlodipine overdose	1	7.7	1
Antipsychotic overdose	1	7.7	
Cypermethrin poisoning	1	7.7	
Rodenticide ingestion	1	7.7	

Some patients with sepsis had more than one identifiable source, so the source counts exceed the subgroup total of 50. Deaths within the sepsis subgroup are shown by the source recorded at the time of death (bedsores in 3 patients and diabetic foot in 2 patients were additional sources identified among fatal cases).

Distribution of deaths by etiology

Although cerebrovascular accident was the commonest cause of presentation, septic encephalopathy was the commonest cause of death, accounting for 37 of the 114 deaths (32.5%). Metabolic encephalopathy followed with 34 deaths (29.8%), then ischaemic stroke with 13 (11.4%) and haemorrhagic stroke with 11 (9.6%). Considered as a single group, cerebrovascular accident contributed 26 deaths (22.8%). Multi factorial causes accounted for 6 deaths (5.3%), poisoning or toxin exposure for 5 (4.4%), and neuro infection, seizure disorder and cerebral venous thrombosis for 3, 3 and 2 deaths respectively.

Among the 37 deaths attributed to septic encephalopathy, pneumonia was the source in 21 patients, of whom 15 had bronchopneumonia and 6 had

aspiration pneumonia, urosepsis in 8, bedsores in 3 and diabetic foot infection in 2. Among the 34 deaths from metabolic encephalopathy, hepatic encephalopathy accounted for 15 and uraemic encephalopathy for 6.

Most patients with cerebral infarction who survived were discharged with moderate residual disability, while those who died characteristically had large territorial infarcts with radiological midline shift (Table 7).

Table 7: Distribution of in-hospital deaths by etiology (n = 114)

Etiology	Deaths n	% of all deaths	Case fatality within etiology (%)
Septic encephalopathy	37	32.5	74.0
Metabolic encephalopathy	34	29.8	53.1
Ischaemic stroke	13	11.4	15.7
Haemorrhagic stroke	11	9.6	47.8
Multifactorial	6	5.3	85.7
Poisoning or toxin	5	4.4	38.5
Neuroinfection	3	2.6	13.0
Seizure disorder	3	2.6	75.0
Cerebral venous thrombosis	2	1.8	66.7
Total	114	100.0	42.2

Several laboratory parameters measured at admission differed significantly between survivors and non-survivors. Blood urea was higher in the deceased group at 68.2 (62.1) mg/dL compared with 46.8 (45.2) mg/dL in survivors, p = 0.002, and serum creatinine was likewise higher at 1.64 (1.73) mg/dL versus 1.15 (1.24) mg/dL, p less than 0.001.

Markers of hepatic dysfunction showed the same pattern: median total bilirubin was 1.10 (0.60 to 2.40) micromol/L in the deceased group versus 0.70 (0.50 to 1.13) in survivors, median direct bilirubin was 0.62 (0.20 to 1.40) versus 0.30 (0.19 to 0.50), median alkaline phosphatase was 96.0 (56.0 to 136.0) U/L versus 45.0 (23.0 to 78.0) U/L, median aspartate aminotransferase was 34.0 (19.0 to 64.3) U/L versus 23.0 (18.0 to 46.0) U/L, and median alanine aminotransferase was 29.0 (17.8 to 64.0) U/L versus 15.5 (7.0 to 32.5) U/L, all with p = 0.001.

Synthetic hepatic function was similarly discriminatory. Serum total protein was lower in the deceased group at 5.90 (1.26) g/dL versus 6.34 (1.05) g/dL, and serum albumin was lower at 2.90 (0.87) g/dL versus 3.38 (0.78) g/dL, both p = 0.001, while the international normalised ratio was higher at 1.22 (0.42) versus 1.00 (0.39), p less than 0.0001. Haemoglobin was significantly lower in the deceased group, p less than 0.001.

In contrast, total leucocyte count, platelet count, serum sodium, potassium, chloride, globulin and random blood sugar did not differ significantly between the two groups.

Three patients (1.1%) were positive for hepatitis B surface antigen and none was positive for hepatitis C virus, a difference that was not statistically significant, p = 0.278 (Table 8).

Table 8: Admission laboratory parameters in relation to in-hospital outcome (N = 270)

Parameter	Discharged (n = 156)	Died (n = 114)	p value
Total leucocyte count, per cubic mm	10684 (5540.8)	13160 (5082.3)	0.541
Platelet count, x 10 to the 5 per microlitre	2.46 (2.48)	2.25 (1.13)	0.312
Blood urea, mg/dL	46.8 (45.2)	68.2 (62.1)	0.002
Serum creatinine, mg/dL	1.15 (1.24)	1.64 (1.73)	Less than 0.001
Serum sodium, mmol/L	135.6 (8.6)	136.1 (7.4)	0.849
Serum potassium, mmol/L	4.15 (0.80)	4.22 (0.96)	0.928
Serum chloride, mmol/L	99.5 (6.2)	98.9 (7.2)	0.571
Total bilirubin, median (IQR)	0.70 (0.50 to 1.13)	1.10 (0.60 to 2.40)	0.001
Direct bilirubin, median (IQR)	0.30 (0.19 to 0.50)	0.62 (0.20 to 1.40)	0.001
Total protein, g/dL	6.34 (1.05)	5.90 (1.26)	0.001
Serum albumin, g/dL	3.38 (0.78)	2.90 (0.87)	0.001
Serum globulin, g/dL	3.10 (0.67)	3.04 (0.85)	0.469
Alkaline phosphatase, U/L, median (IQR)	45.0 (23.0 to 78.0)	96.0 (56.0 to 136.0)	0.001
Aspartate aminotransferase, U/L, median (IQR)	23.0 (18.0 to 46.0)	34.0 (19.0 to 64.3)	0.001
Alanine aminotransferase, U/L, median (IQR)	15.5 (7.0 to 32.5)	29.0 (17.8 to 64.0)	0.001
Random blood sugar, mg/dL	149.6 (101.3)	126.3 (79.9)	0.069
International normalised ratio	1.00 (0.39)	1.22 (0.42)	Less than 0.0001
Hepatitis B surface antigen positive, n (%)	3 (1.9)	0 (0)	0.278

Values are mean (standard deviation) unless stated otherwise. IQR, interquartile range. Comparisons by independent samples t test for normally distributed variables and Mann-Whitney U test for skewed variables.

Discussion

This prospective study of 270 consecutive adults presenting with non-traumatic altered sensorium to a public tertiary care hospital in southern India found cerebrovascular accident to be the commonest etiology, metabolic and septic encephalopathy the next two, and an overall in-hospital mortality of 42.2%. The single most clinically useful observation is the dissociation between the commonest cause of presentation and the commonest cause of death: cerebrovascular accident accounted for 40.4% of admissions but only 22.8% of deaths, whereas septic encephalopathy accounted for 18.5% of admissions but 32.5% of deaths.

The demographic profile of the cohort is consistent with published series. The mean age of 54.8 years and the male preponderance of 68.1% are close to those reported by Xiao and colleagues from Beijing, where the mean age was 51 years and the largest stratum was 60 years and above, comprising 41.2% of the 1934 patients studied.[5] Our cohort was younger than the Singaporean series of Lim Beng Leong and colleagues, in which 967 patients had a mean age of 66.5 years, a difference attributable to the fact that theirs was drawn from a population with a substantially higher median age.[6] Neither age nor sex was associated with outcome in our data, and this is concordant with the classical prognostic

study of Levy and colleagues, who found in 500 patients with non-traumatic coma that functional recovery did not depend on age but was related to the cause of coma and to the depth and duration of unconsciousness.[9]

The etiological distribution we observed sits comfortably within the wide range documented in the systematic review by Horsting and colleagues, which found stroke in 6% to 54% and metabolic causes in 1% to 29% of patients with non-traumatic coma across 14 studies, with infection responsible for 10% to 51% in African cohorts.[8] Our figures of 40.4% for cerebrovascular accident and 23.7% for metabolic encephalopathy fall towards the upper end of the stroke range and within the metabolic range. Notably, post-anoxic coma, which accounted for 3% to 42% of cases in that review, was not a discrete category in our cohort, most likely because patients with out-of-hospital cardiac arrest in this setting rarely survive transport to a tertiary emergency department. Conversely, poisoning accounted for only 4.8% of our cases, at the low end of the reported range of less than 1% to 39%, reflecting the fact that acute poisonings in this catchment are commonly triaged directly to dedicated toxicology or surgical emergency services.

Our findings diverge in an instructive way from the Western literature. Kanich and colleagues, in a university hospital emergency department in the United States, reported neurological causes in 28% and toxicological causes in 21%, followed by trauma and psychiatric syndromes in 14% each and infection in only 10%.[4] Toxicological and psychiatric causes together made up more than a third of that cohort but a far smaller fraction of ours, while the infective burden in our series was nearly double theirs. This is the expected signature of a middle-income tertiary referral setting with a high communicable disease burden, a substantial population of patients with decompensated chronic liver and kidney disease, and a filter effect whereby milder toxicological and psychiatric presentations are managed elsewhere. The recent multicentre Korean study of new-onset altered level of consciousness makes a related point, namely that the etiological label assigned at first contact in the emergency department is frequently revised once the inpatient evaluation is complete, which supports our decision to assign the final diagnosis at the end of the hospital stay rather than at admission.[15]

Comparison with the Indian series by John and colleagues, on which our sample size calculation was based, is particularly informative. That study of 251 elderly patients found neurological causes in 38.7%, infection or sepsis in 36.5% and metabolic causes in 33.5%, with hyponatraemia the commonest metabolic derangement at 45.2% of that subgroup and hypoglycaemia next at 29.8%.[7] Our neurological proportion of 40.4% is almost identical, but our metabolic subgroup was dominated by hepatic encephalopathy at 32.8% rather than by hyponatraemia, which accounted for only 12.5% of our metabolic cases. The most plausible explanation is the difference in age structure: their cohort was exclusively elderly, in whom drug-induced and idiopathic hyponatraemia is common, whereas ours spanned all adult ages and included a large number of patients with alcohol-related cirrhosis in the fourth and fifth decades. Rai and colleagues, in a north Indian cohort with acute confusional state, similarly identified infection and metabolic derangement as dominant contributors and confirmed the prognostic weight of the mental status at admission.[16]

Our overall mortality of 42.2% was more than twice the 19.1% reported by John and colleagues.[7] Several factors

are likely to contribute. First, our institution is a public tertiary referral centre receiving a disproportionate share of patients who have already failed treatment at peripheral facilities, and 23.0% of our patients arrived more than 24 hours after symptom onset. Second, 32.2% of our patients had an admission Glasgow Coma Scale of 8 or less, indicating a cohort of considerable severity. Third, the recruitment period spanned the second and third waves of the COVID-19 pandemic, during which access to elective and semi-urgent care in this region was substantially curtailed. It should be emphasised, however, that a mortality of 42.2% remains within the 25% to 87% range documented across the studies pooled by Horsting and colleagues, and is by no means an outlier.[8]

The single strongest prognostic variable in our data was the depth of impairment at presentation. Mortality rose from 10.2% in patients with an admission Glasgow Coma Scale of 13 to 15, through 36.6% at 9 to 12, to 68.9% at 3 to 8, p less than 0.001. The descriptive level of consciousness showed the same gradient, with 87.8% of confused patients surviving compared with 11.1% of comatose patients. This reproduces one of the most consistent findings in the literature on impaired consciousness and validates the continued use of a simple bedside score for triage and family counselling.[10] The Full Outline of UnResponsiveness score offers theoretical advantages in intubated and aphasic patients, since it substitutes a verbal-independent motor task and adds brainstem reflex and respiratory pattern components,[11] but the comparative study by Gujjar and colleagues in medical patients with altered sensorium found broadly equivalent interrater reliability and outcome prediction for the two instruments, so the Glasgow Coma Scale remains a defensible choice where familiarity is high.[12]

The relationship between delay in presentation and mortality deserves emphasis because it is the one variable in this study that is genuinely modifiable at a system level. Discharge rates fell from 72.4% among patients reaching hospital within 6 hours to 33.3% among those presenting beyond 48 hours. John and colleagues reported a comparable finding, with 87% of patients presenting within 6 hours achieving a good outcome.[7] Some of this association is undoubtedly confounded by indication, in that catastrophic presentations such as large intracerebral haemorrhage bring patients to hospital quickly while indolent metabolic decompensation does not. Nevertheless, the therapeutic window for several of the commonest causes in our cohort, including ischaemic stroke, bacterial meningitis and sepsis, is measured in hours, and the observed gradient is consistent with a genuine causal contribution. Structured emergency assessment with immediate capillary glucose measurement, early empirical thiamine and naloxone where indicated, and early broad-spectrum antibiotics where sepsis is suspected, is the intervention set most likely to translate earlier arrival into survival.[2,3]

The disproportionate lethality of septic encephalopathy in our series, at a case fatality of 74.0%, is the finding with the greatest immediate clinical implication. Sepsis-associated encephalopathy occurs in up to 70% of patients admitted to intensive care with sepsis and is independently associated with higher intensive care and hospital mortality as well as poorer long-term cognitive outcomes.[14] Its pathogenesis involves endothelial activation and blood brain barrier breakdown, microglial activation with local generation of nitric oxide and

reactive oxygen species, impaired cerebral autoregulation with resultant hypoperfusion, cholinergic dysfunction and mitochondrial failure with neuronal apoptosis.[13] Because the encephalopathy is frequently hypoactive rather than hyperactive, and may precede overt haemodynamic decompensation, it is easily attributed to a primary neurological process, with the consequence that antimicrobial therapy and source control are delayed. Pneumonia was the source in 30 of our 50 septic patients and in 21 of the 37 deaths from sepsis, and in 6 of those fatal cases the pneumonia was aspiration pneumonia, that is, a complication of the altered sensorium itself rather than its cause. This observation argues strongly for early attention to airway protection and aspiration prophylaxis in every patient with a depressed level of consciousness, and supports the case for adult pneumococcal and influenza vaccination in patients with the chronic comorbidities that predominated in this cohort.

The metabolic subgroup illustrates a second important gradient. Hepatic encephalopathy carried 15 of the 34 metabolic deaths despite representing only a third of that subgroup, and uraemic encephalopathy a further 6, whereas patients with hypoglycaemia and hyponatraemia showed comparatively good survival. This is coherent with the laboratory findings, in which urea, creatinine, bilirubin, alkaline phosphatase, transaminases and international normalised ratio were all significantly higher, and total protein and albumin significantly lower, in the deceased group. Taken together these variables describe end-organ failure rather than a transient biochemical derangement, and they suggest that the prognostic distinction within metabolic encephalopathy is best drawn between a reversible single-analyte abnormality and encephalopathy that is the terminal manifestation of established organ failure.

Neuroinfection carried a case fatality of only 13.0% in our series, which compares favourably with much of the literature and is likely to reflect the predominance of bacterial and viral meningitis, which respond well to prompt therapy, over the more lethal encephalitides. Ischaemic stroke likewise carried a case fatality of 15.7%, considerably lower than the haemorrhagic stroke figure of 47.8%. Most patients with cerebral infarction who survived were discharged with moderate residual disability, while fatal cases characteristically had large territorial infarcts with midline shift, reinforcing the conventional understanding that mortality in ischaemic stroke is driven principally by infarct volume and secondary mass effect rather than by the vascular event itself.

Strengths and limitations

The strengths of this study include its prospective design, its enrolment of consecutive unselected adult patients across the whole spectrum of severity rather than only those meeting a coma threshold, its adequate sample size derived from a formal calculation, and the assignment of the final etiological diagnosis on the composite of clinical, laboratory, microbiological and radiological data at the end of the hospital stay rather than at first contact.

Several limitations should be acknowledged. First, this was a single-centre study conducted at a public tertiary referral hospital, so referral bias is likely and the etiological proportions may not be generalisable to primary or secondary care. Second, the outcome assessed was restricted to in-hospital status; no functional outcome measure such as the modified Rankin Scale was applied at discharge, and there was no

post-discharge follow-up, so the substantial burden of survivors with residual disability documented in other series could not be quantified. Third, the analysis was univariate, and no multivariable model was constructed to adjust for confounding between admission Glasgow Coma Scale, etiology and time to presentation, which are plainly interrelated. Fourth, the etiological categories were assigned to be mutually exclusive, which necessarily oversimplifies the common clinical reality of a patient with, for example, sepsis precipitating hepatic encephalopathy. Fifth, electroencephalography was performed only where clinically indicated, so non-convulsive status epilepticus may have been under-diagnosed. Finally, the recruitment period coincided with the COVID-19 pandemic, which is likely to have affected both the case mix reaching hospital and the Delay to Presentation.

Conclusion

In this prospective study of 270 adults presenting with non-traumatic altered sensorium to a tertiary care hospital, cerebrovascular accident was the commonest etiology, accounting for 40.4% of cases, with ischaemic stroke predominating within that group. Metabolic encephalopathy accounted for 23.7% of cases, with hepatic encephalopathy the commonest single metabolic cause, and septic encephalopathy for 18.5%. Overall in-hospital mortality was 42.2%.

Despite being only the third commonest cause of presentation, septic encephalopathy was the commonest cause of death, contributing 32.5% of all mortality with a case fatality of 74.0%, and pneumonia was the commonest septic source both overall and among fatal cases. Metabolic encephalopathy contributed a further 29.8% of deaths, driven predominantly by hepatic and uraemic causes.

Three variables available at the bedside within minutes of arrival identified patients at highest risk of death: a low admission Glasgow Coma Scale, with mortality of 68.9% at a score of 3 to 8 compared with 10.2% at 13 to 15; a depressed descriptive level of consciousness, with mortality of 88.9% in comatose patients compared with 12.2% in confused patients; and a longer interval between symptom onset and arrival, with mortality rising from 27.6% within 6 hours to 66.7% beyond 48 hours. Admission markers of hepatic and renal end-organ failure, specifically urea, creatinine, bilirubin, alkaline phosphatase, transaminases, albumin and international normalised ratio, were also significantly associated with death.

These findings support three practical recommendations. Every patient presenting with altered sensorium should be systematically evaluated for a septic focus regardless of how neurological the presentation appears, since sepsis was the largest single contributor to mortality and its encephalopathy is characteristically hypoactive. Airway protection and aspiration prophylaxis should be instituted early in every patient with a depressed level of consciousness, given that aspiration pneumonia was a source of fatal sepsis in six patients in this cohort. Finally, public health measures aimed at shortening the interval between symptom onset and arrival at a facility capable of definitive evaluation, together with adult pneumococcal and influenza vaccination in patients with chronic comorbidity, represent the interventions most likely to reduce mortality in this population.

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