

Predictors of expedited hospital discharge in pediatric patients with acute meningoencephalitis admitted to a tertiary care hospital in Karachi, Pakistan

Sobia Muhammad Asad Khan, Syeda Rija Zehra, Sadia Shakoor, Joveria Farooqi, Muhammad Naeem, Erum Khan

The Aga Khan University Hospital, Karachi Pakistan

ABSTRACT

Background: Early/expedited discharge (ED) has been investigated for reducing hospital costs and improved patient outcomes in various medical conditions. Owing to high burden of hospitalization due to meningoencephalitis (ME) in pediatric patients, we evaluated predictors of ED at a tertiary care hospital in Karachi, Pakistan.

Material and Methods: This retrospective cross-sectional study was conducted at a tertiary care hospital in Karachi, May 2017 to January 2023 Pakistan. All patients ≤ 18 years admitted with suspicion of acute infectious ME who underwent CSF multiplex PCR panel (MenP) testing were included. Demographic, clinical and laboratory data were extracted from electronic medical records. Factors contributing to ED were identified by multivariate logistic regression using STATA 13.1 (Stata Corp, College Station, TX, USA).

Results: Among 631 patients, 190 (30 %) achieved early discharge (ED). Viral pathogens were identified in 131 (21 %), tripling the odds of ED (OR 2.99, 95 % CI 1.92–4.66; $p < 0.001$). Infants < 1 month (OR 0.23, 95 % CI 0.08–0.68), altered consciousness (OR 0.30, 95 % CI 0.17–0.67), positive blood cultures, and higher CSF protein (OR 0.99 per unit, 95 % CI 0.98–0.99) independently reduced ED likelihood in multivariate analysis.

Conclusion: Diagnosis of a viral etiology in older children expedites hospital discharge. Thus, CSF molecular testing, particularly enterovirus PCR should be performed in pediatric patients with acute ME.

Keywords: CSF, Early discharge, Enterovirus, Meningoencephalitis, Multiplex PCR, Pediatric, Viral etiology

BACKGROUND

Meningitis and encephalitis are potentially life-threatening clinical conditions that are caused by wide variety of infectious and non-infectious etiologies requiring urgent medical attention. Thus rapid diagnosis is crucial for effective patient management.^{1,2} As of 2019, there have been 2.51 million estimated incident meningitis cases globally, with children < 5 years of age incurring the highest burden especially in countries with lower socioeconomic status.^{3,4} While overall deaths due to meningitis have decreased, hospitalization stay and costs remain of significant concern.¹ Of the 72,000 meningitis-related hospitalizations in the United States, more than half are attributed to viral etiology.⁵ In Pakistan, the overall annual rate of hospitalization from meningoencephalitis (ME) is reported to be 5.7/100,000

population, highest among children < 5 years.⁶ Differentiating viral from bacterial ME is critical, as most patients with viral or aseptic meningitis require only supportive care and can often be discharged early.^{1,7-9} Data from developed countries shows that the median length of hospital stay in ME is four days, with significantly shorter duration for enterovirus, creating an opportunity for early discharge in these patients.¹⁰ Early/ expedited discharge (ED) has been increasingly studied in various medical conditions to optimize resource utilization, reduce hospitalization costs, and mitigate the risk of complications such as hospital acquired infections and immobility associated with prolonged hospital stay.¹¹⁻¹⁵ Therefore, we aimed to evaluate predictors of ED in pediatric patients admitted to a tertiary care hospital in Pakistan with suspicion of infectious ME.

Correspondence: Dr. Sobia Muhammad Asad Khan, Resident Medical Microbiology, The Aga Khan University Hospital, Karachi Pakistan

Email: khan.sobia@aku.edu

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MATERIAL AND METHODS

This retrospective cross-sectional study was conducted at a tertiary care hospital in Karachi, Pakistan. All patients ≤ 18 years, admitted with suspicion of acute ME defined by the criteria as per Justin *et al.*,¹⁶ who underwent CSF multiplex PCR panel (MenP) testing between May 2017- Jan 2023 were included. We excluded patients with nosocomial or iatrogenic meningitis, evidence of ventricular drain or device-

related infections, any history of traumatic brain injury or immunocompromised state and others (Figure-1). Medical records were reviewed for the following variables: age, sex, clinical presentation (fever $\geq 38.0^{\circ}\text{C}$, headache, neck stiffness, altered mental status, seizure, focal neurologic deficit) comorbid conditions, MenP result and etiologic agent, CSF counts i.e. total leucocyte count (TLC), protein and glucose levels, blood C-reactive protein (CRP), electroencephalogram (EEG), concomitant infection (bacteremia, pneumonia, urinary tract infection, intra-abdominal infection), length of stay and clinical outcome at discharge (alive, died).

The institutional review board of Aga Khan University approved the study and the need for informed consent was waived (2023-8937-26598).

CSF samples obtained by lumbar puncture were immediately sent to the College of American Pathologists' accredited clinical microbiology laboratory affiliated with the hospital. Each sample was tested by the MenP, according to the manufacturer's instructions. Briefly, 200 μl CSF sample was mixed with the provided buffer and the tube was inverted several times. Hydration solution was injected into the MenP pouch followed by injection of sample mixture. Pouch was then loaded into the instrument. At the end of the run (~ 1 hour per each sample), results were presented on the computer's software. A clinically relevant positive result was reported to the clinician by a medical microbiologist and guidance provided for appropriate management. As part of routine protocol, in case of a positive cultivable pathogen on MenP, CSF sample was inoculated in brain heart infusion enrichment broth and sheep blood agar and incubated at appropriate conditions.

The primary outcome was early/expedited discharge. No standard definition of expedited discharge exists in context of meningoencephalitis. We adapted the definition used by Tvina *et al* (17) and defined discharge within 72 hours of admission as early or expedited discharge.

Etiology was classified as either bacterial, viral or unspecified based on MenP results reported within 24 hours of CSF sample submission to the laboratory. Among the pathogens tested by the multiplex PCR panel; *Escherichia coli K1*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae* were included in bacterial etiology whereas enterovirus, herpes simplex virus 1 and 2, human herpesvirus 6, human parechovirus and varicella-zoster virus were

included in viral etiology. Any cause of ME other than the ones listed above were classified as unspecified etiology.

Data analysis was conducted using STATA 13.1 (Stata Corp, College Station, TX, USA). Descriptive statistics of all above listed variables were tabulated and proportions compared between patients with early/expedited versus standard discharge. Univariate analysis was done using logistic regression to identify the predictors of ED and odds ratios were calculated. A P -value ≤ 0.05 was considered statistically significant. Multivariate logistic regression model was constructed with a multistage technique using step-wise backward elimination procedures. All variables with a $P \leq 0.2$ in univariate analyses were included in the multivariate model except EEG as it had missing values. Variables with multilinearity were excluded from the final model.

RESULTS

Between May 2017- Jan 2023, MenP was done on 784 pediatric patients admitted to the study site with suspected acute ME. After exclusion, 631 patients remained, of whom, 20.8% ($n=131$) tested positive for any pathogen on MenP (Figure 1). 15.4% and 5.4% ($n=97$ and $n=34$) had viral and bacterial etiology respectively whereas majority i.e. 79.2% ($n=500$) had unspecified etiology (supplementary table 1). Of the 34 patients with bacterial etiology, only 14.7% ($n=5$) were simultaneously positive on culture (*Streptococcus pneumoniae* =3, *Neisseria meningitidis* =1, *Listeria monocytogenes* =1). Early/expedited discharge (ED) was noted in 30.1% ($n=190$) patients. Male to female ratio was 1.3:1 and the median age was 4.73 ± 5.2 years. Most common clinical presentation was fever, and the median length of hospital stay was 6.9 ± 5.5 days. Overall mortality was 3.5% ($n=22$) and none of these were discharged early. Table-I describes the clinical characteristics of patients with early/expedited (ED) versus standard discharge (SD).

Univariate analysis showed that patients with age group <1 month were less likely to be discharged early [OR=0.23 (95% CI=0.08,0.68); $p=0.007$]. Moreover, serious clinical presentation on admission i.e. presence of altered consciousness decreased the likelihood of ED [OR=0.3 (95% CI=0.17,0.67); $p=0.002$]. On the contrary, identification of a viral etiology was significantly associated with ED [OR=2.99 (95% CI=1.92,4.66); $p<0.001$]. Among the biochemical

parameters, CSF glucose and TLC and Blood CRP levels were not associated, whereas for each unit increase in CSF protein, there is an approximately 1% reduction in the likelihood of ED [OR= 0.99 (95% CI=0.98,0.99); p<0.001]. On multivariate logistic

regression; presence of viral etiology was significantly associated with ED, whereas age <1 month, altered consciousness, positive blood culture and high CSF protein were negatively associated with it (Table-II).

Table-I: Baseline characteristics and clinical features of 631 hospitalized pediatric patients with suspected acute infectious ME at a tertiary care hospital in Karachi, Pakistan.

Hospital discharge (N = 631)		
	Early N=190 n (%)	Standard N=441 n (%)
Age Categories		
< 1 month	4 (2.1)	35 (7.9)
>= 1 months to < 5 years	108 (56.8)	248 (56.2)
5 >= years <=18	78 (41.1)	158 (35.8)
Age in years: Median (IQR)	3.00 (0.91-9.00)	2.00 (0.50-8.00)
Sex		
Male	108 (56.8)	251 (56.9)
Female	82 (43.2)	190 (43.1)
Clinical Features		
Fever	154 (81.1)	352 (79.8)
Fits	81 (42.6)	185 (42.0)
Altered Consciousness	10 (5.3)	63 (14.3)
Headache	65 (34.2)	70 (15.9)
EEG^y		
Abnormal	14 (35.9)	126 (68.1)
Normal	25 (64.1)	59 (31.9)
Blood Culture		
Pathogen Isolated	3 (1.6)	40 (9.1)
Etiology		
*Viral	51 (26.8)	46 (10.4)
Bacterial	4 (2.1)	31 (7.0)
Unspecified	135 (71.1)	364 (82.5)
CSF Multiplex PCR Panel		
Positive	55 (28.9)	76 (17.2)
Negative	135 (71.1)	365 (82.8)
Biochemical Parameters		
CSF Glucose (mg/dl): N = 621		
Median (IQR)	70.00 (61.00-83.00)	71.00 (56.00-88.00)
CSF Protein (g/dl): N = 628		
Median (IQR)	29.00 (19.00-43.00)	41.00 (24.00-77.00)
CSF Total Leucocyte Count: N = 626		
Median (IQR)	8.00 (3.00-100.00)	10.00 (2.00-68.50)
CRP (mg/L): N = 241		
Median (IQR)	12.00 (2.53-36.81)	14.05 (4.20-50.00)
Targeted therapy^z		
Yes	4 (2.1)	38 (8.6)
Status at Discharge		
Alive	190 (100.0)	419 (95.0)
Died	0 (0.0)	22 (5.0)

Supplementary Table-I: List of etiological agents detected by CSF multiplex PCR panel in hospitalized pediatric patients (N=631) with suspected acute infectious ME.

Etiological agent ^e	Frequency n (%)
Enterovirus	77 (12.2)
Herpes simplex virus 1	5 (0.8)
Herpes simplex virus 2	1 (0.2)
Human Herpes virus	13 (2.1)

Varicella zoster virus	1 (0.2)
Listeria monocytogenes	2 (0.3)
Neisseria meningitidis	5 (0.8)
Streptococcus agalactiae	3 (0.5)
Streptococcus pneumoniae	20 (3.1)
Escherichia coli	2 (0.3)
Hemophilus influenzae	3 (0.5)
Unspecified etiology	499 (79.0)
Total	631

€ no co-infections detected

Table-II: Predictors of early/expedited discharge in hospitalized pediatric patients (N=631) with suspected acute infectious ME.

	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value
Age Categories						
< 1 month	0.23	(0.08,0.68)	0.007	0.29	(0.09,0.90)	*0.033
>= 1 months to < 5 Years	0.88	(0.62,1.26)	0.486	0.84	(0.57,1.23)	0.381
5 >= Years <=18	1.00			1.00		
Sex						
Female	1.00	(0.71,1.41)	0.986			
Clinical Features						
Fever	1.08	(0.70,1.66)	0.721			
Fits	1.03	(0.73,1.45)	0.874			
Altered Consciousness	0.33	(0.17,0.67)	0.002	0.36	(0.76,0.74)	*0.006
Headache	2.76	(0.17,0.67)	0.002			
EEG						
Abnormal	0.26	(0.13,0.54)	<0.001			
Blood Culture						
Pathogen Isolated	0.16	(0.05,0.53)	0.003	0.23	(0.06,0.77)	*0.017
Etiology						
Viral	2.99	(1.92,4.66)	<0.001	2.79	(1.74,4.46)	*<0.001
Bacterial	0.35	(0.12,1.00)	0.051	0.93	(0.29,2.95)	0.897
CSF Multiplex PCR Panel						
Positive	1.96	(1.31,2.92)	0.001			
Negative	1.00					
Biochemical Parameters						
CSF Glucose (mg/dl)	1.00	(0.99,1.00)	0.184			
CSF Protein (g/dl)	0.99	(0.98,0.99)	<0.001	0.99	(0.98,0.99)	*<0.001
CSF Total Leucocyte Count	1.00	(1.00,1.00)	0.091			
CRP (mg/L)	1.00	(0.99,1.00)	0.345			

*multivariate regression model

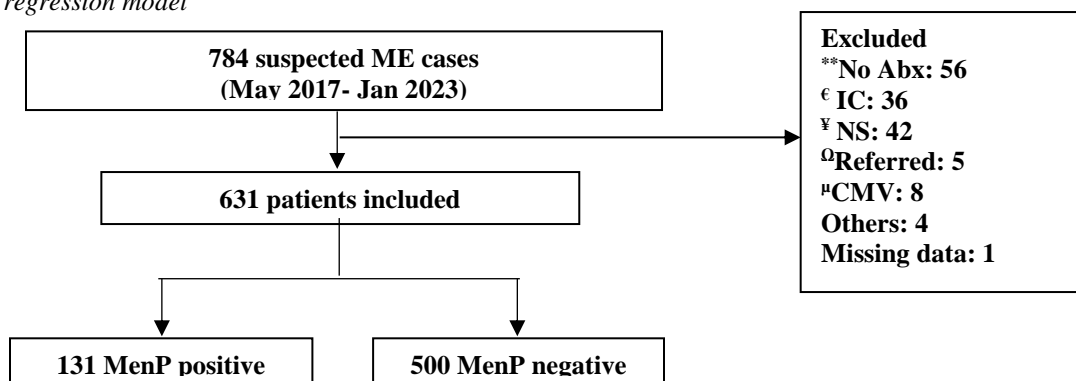


Figure-I: Flow diagram of the included patients with suspicion of acute ME between May 2017 to Jan 2023.

** Abx: antibiotics (patients who did not receive empirical antibiotics on admission); € IC: immunocompromised; ¥ NS: patients with neurosurgical interventions; Ω referred from emergency department; incomplete information; ♯ CMV: Cytomegalovirus, quantitative PCR not evaluated for confirmation of diagnosis

DISCUSSION

Hospitalization due to acute infectious ME in pediatric population is a significant concern. Although a number of studies have evaluated prognostic factors of acute ME, limited data is available on factors associated with ED. Pre-existing comorbid conditions, high CSF leucocyte count, impaired consciousness and positive blood culture have been associated with poor outcome whereas presence of a viral etiology is associated with a favorable outcome.¹⁸⁻²² Thus, we conducted a comprehensive review of five years of data, highlighting important predictors of ED in pediatric patients with suspected infectious ME in a tertiary care hospital in Karachi. Overall, 30.1% were discharged within 72 hours and identification of a viral etiology doubled the likelihood of ED. Our findings are in concordance with other studies reporting a shorter length of stay associated with viral etiology.^{10,23,24} Enterovirus predominated among the cases with viral etiology in this cohort, a finding consistent with studies conducted across the globe.^{23,25,26} Conversely, younger age (<1 month), altered consciousness, positive blood culture, and elevated CSF protein levels were associated with delayed discharge, emphasizing the complexity of managing these patients.

The identification of predictors for ED, particularly a viral etiology, carries substantial economic implications. Shorter hospital stays contribute to reduced healthcare costs, decreased hospital associated infections, improved resource allocation, and increased bed availability in high-burden tertiary care settings.^{27,28} The predominance of enterovirus as the leading viral etiology consistent with global trends, highlights its importance in diagnoses and management of infectious ME. This alignment suggests potential role of targeted enterovirus PCR as a cheaper alternative to the extensive multiplex PCR panels, which may be applicable to resource limited geographic areas like Pakistan. This approach not only optimizes antimicrobial stewardship, leading to early de-escalation of antibiotics, but also shortens hospital stay.²⁹ Our findings emphasize on development of age-specific diagnostic protocols and management strategies, especially for neonates and critically ill patients with severe clinical presentation and elevated CSF protein levels. Moreover, consistent with other studies, we re-emphasize the dilemma of high

proportion of patients with unspecified etiologies (79.2%), which calls for future research advancements in this regard.

Our study had a number of limitations. While the data is derived from a large tertiary care center, it may not be generalizable across geographic areas owing to variable etiological spectrum. Thus, results should be interpreted in context with local epidemiological factors. Furthermore, while early discharge is a significant outcome, the study does not address long-term neurological sequelae owing to its retrospective nature, which are crucial considerations in pediatric ME and should be explored in future studies. Finally, time to appropriate antimicrobial therapy and adjunct therapies such as steroid administration may have impacted the primary outcome but was not explored in the present study.

CONCLUSION.

Viral etiology, particularly enterovirus is a significant cause of pediatric meningoencephalitis and timely detection in older children facilitates early discharge, yielding substantial economic and public health benefits. In resource limited settings, age specific diagnostic protocols may be formulated with incorporation of targeted enterovirus PCR.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Sobia Muhammad Asad Khan: Concept and design of study, acquisition, analysis and interpretation of data, drafting and revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work

Syeda Rija Zehra: Acquisition, analysis and interpretation of data, drafting and revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work

Sadia Shakoor: Design of study, acquisition, analysis and interpretation of data, drafting and revising article critically for important intellectual content, final

approval, agreement to be accountable for all aspects of the work

Joveria Farooqi: Analysis and interpretation of data, drafting and revising article critically for important intellectual, content final approval, agreement to be accountable for all aspects of the work

Muhammad Naem: Analysis and interpretation of data, drafting and revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work

Erum Khan: Analysis and interpretation of data, drafting and revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work.

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