Predictors of Unfavorable Outcome in Meningitis Patients

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The main objective is to study the predictors of unfavorable outcome in meningitis patients.

This is a prospective analytic study of 100 patients with different types of meningitis admitted in Tribhuvan University teaching hospital (TUTH) during 2005/2006. Patients were followed up at 2 weeks, 6 weeks and 12 weeks. Thirty variables were evaluated at presentation and during hospital stay as predictors of unfavorable outcome. Data analysis was done using SPSS version 11.5. The prognostic rule was derived from significant variables.

Among 100 patients (62 males and 38 females), 23 died in Hospital. Univariate analysis yielded 15 variables as significant risk factors for mortality. Among them, according to logistic regression analysis, 12 variables were independent predictors of mortality. Patients with 0 to 3 risk factors had no risk of death. Patients with 4 to 6 risk factors, moderate risk group, had mortality rate of 23.1% and patients with 7 or more risk factors, high risk group, had 100% mortality rate. This prediction tool has 100% sensitivity, 100% specificity , 100% positive predictive value and 100% negative predictive value.

Risk stratification of patients with meningitis is possible from simple clinical and laboratory variables on admission.

Keywords: meningitis, predictors, prognosis

Meningitis is an inflammation of the leptomeninges and the underlying subarachnoid cerebrospinal fluid caused by different pathogens resulting in cerebrospinal fluid (CSF) pleocytosis. It is associated with a central nervous system (CNS) inflammatory reaction that may result in decreased consciousness, seizures, raised ICP and stroke. The meninges, subarachnoid space and the brain parenchyma are all often frequently involved in the inflammatory reaction (meningoencephalitis). These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, tuberculous, fungal and various other meningitis on the basis of etiology. It may present with a non specific prodromal fever, headache, neck stiffness, altered mental status, also occasional focal neurological signs and seizures appear.

Meningitis is one of the major problems worldwide including Nepal, it accounts for many deaths and disabilities. In spite of advances in medical science and technology and treatment modalities, it remains as a significant problem to diagnose and treat. Globally 1.2 million people suffer from bacterial meningitis each year and that 135,000 of these patients die. Approximately 500,000 of these cases and 50,000 of the deaths are due to meningococci.[7] Out breaks of epidemic Menigococcal meningitis occasionally occur more in Meningitis belt of central Africa where 40,000 cases were reported in 1989 out break in Ethiopia.[7] When the disease is diagnosed early and adequate therapy is instituted, the case-fatality event rate ranges from 5-10% and may exceed 40% in patients with meningococcal sepsis.[3] In a review of 493 episodes of

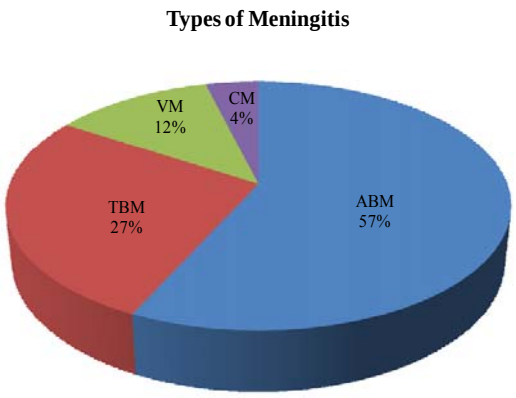

Figure 1: Distribution of patients according to etiological diagnosis.

GCS score	Expired	Survived	Total
15	1	32	33
12-14	8	35	43
9-11	13	8	21
3-8	1	2	3
Total	23	77	100

Table 1: Outcome according to GCS score on presentation.

CSF opening pressure (Cm of CSF)	Expired	Survived	Total (%)
6-18	6	53	59
>18-29	11	18	29
>29	6	6	12
Total	23	77	100

Table 2:Outcome according to CSF opening pressure.

bacterial meningitis in adults done by Marlene L. Durand et al, the overall case fatality rate was 25%.[4]

Several studies have been performed to describe the clinical features and to find out prognostic factors in adults with different types of meningitis. Diederik Van de Beek et al performed a large prospective study of meningitis,[16] Several characteristics were found to be significantly associated with an unfavorable outcome such as advanced age (> 65 Yrs), presence of otitis or sinusitis, absence of rash, heart rate of more than 120 beats per minute, low score on the Glasgow coma scale (GCS) on admission, CSF white cell count of fewer than 1000 per cu.mm, positive blood culture, elevated erythrocyte sedimentation rate and reduced platelet count.

Other factors with statistically significant unfavorable outcome were presence of symptoms for less than 24 hours before admission, seizures, pneumonia, an immunocompromised state (use of immunosuppressive drugs or splenectomy, diabetes mellitus, or alcoholism, patients infected with the human immunodeficiency virus (HIV)), heart rate below 60 beats per minute and hypotension (defined as a diastolic blood pressure of less than 60 mmHg) at the time of admission.[5, 16] The odds of an unfavorable outcome was 6 times as high (95% CI, $p<0.001$) among patients infected with S. pneumoniae as compared to patients infected with N. meningitidis, even after adjustment for other clinical predictors.

CSF glucose level of less than 1.9 mmol per liter, a ratio of CSF glucose to blood glucose of less than 0.23, a protein level of more than 220mg per dl were also found to be significant predictors of unfavorable outcome in Van de Beek et al's study. Presence of focal neurological deficits, low GCS, cranial nerve palsy, cerebral abnormality like aphasia, hemiparesis, paraparesis were also predictors of unfavorable outcome.[5]

Materials and methods

This study was conducted at Tribhuvan University Teaching Hospital, Kathmandu, Nepal between 15th of March 2005 and 20th of August 2006. This is a prospective observational study to analyze the predictors of unfavorable outcome in different types of meningitis. Total of 100 patients who were admitted with a primary diagnosis of meningitis were studied. Patients were examined at the emergency room if they presented with features suggestive of meningitis (any two of four features: fever, headache, neck stiffness and altered sensorium). Lumbar puncture with cerebrospinal fluid pressure measurement was done and the proforma was filled up by the investigator. Written consent was taken from the every patient or patient party for Lumbar puncture and study. Follow up of patients continued at 2 weeks , 6 weeks and 12 weeks by direct observation or telephone contact.The inclusion criteria for study were, i) age more than 14 years, ii) Neutrophilic or lymphocytic pleocytosis with altered level of protein/sugar ratio in cerebrospinal fluid, iii) positive CSF culture, positive gram stain/AFB stain or demonstration of organism in India Ink smear. Similarly, the exclusion criteria were i) age less than 14 years, ii) Normal CSF findings, iii) patients unwilling to do basic investigations according to protocol, iv) patient left against medical advice,

In all patients history regarding presenting complaints, any associated comorbidity and duration and past history of any illness were recorded. All patients were evaluated for vitals, level of consciousness and

SN	Variables	No. of pts. with the variable	Death	P value
2	Duration of symptoms >24 Hrs	4	3	0.037*
3	Otitis or sinusitis	3	2	0.118
4	Pneumonia	5	2	0.332
5	HIV positive	4	4	0.002*
6	Headache	99	23	1
7	Neck stiffness	97	23	1
8	Rashes	4	2	0.226
9	Papilledema	15	12	<0.01*
10	Heart rate>100/min	16	15	<0.01*
11	Diastolic BP<60 mmHg	7	6	0.001*
12	GCS(14 or below)	67	22	0.007*
13	Triad#	69	21	0.017*
14	Cranial nerve palsy	16	9	0.001*
15	Cerebral abnormality#	18	6	0.403
16	Positive india ink preparation	4	4	0.002*
17	CSF WBC count <2000/cumm	68	16	0.854
18	Protien mg/dl>220 mg/dl	7	2	0.66
19	CSF:Blood Glucose ratio<0.23	25	9	0.075
20	Positive blood culture	1	1	0.23
21	ESR>25mm/hr	80	20	0.553
22	Platelets count<1,00,000/ cumm	18	13	<0.01*
23	Exposure with TB/treated	4	3	0.037*
24	H/O alcohol consumption	36	16	0.001*
25	Immunosuppressive drugs	2	2	0.051
26	Diabetes	9	1	0.68
27	Photophobia	72	21	0.037*
28	Abnormal CT head finding	26	12	0.012*
29	CSF opening pressure>18cm CSF	41	17	0.001*
30	Seizures	32	15	<0.01*

*Table 3: Mortality analysed according to risk factors by univariate analysis technique. Triad#: Triad of fever, neck stiffness and altered sensorium; Cerebral abnormality#: Aphasia, hemiparasis, paraparesis, quadriparesis; *: significant variables.*

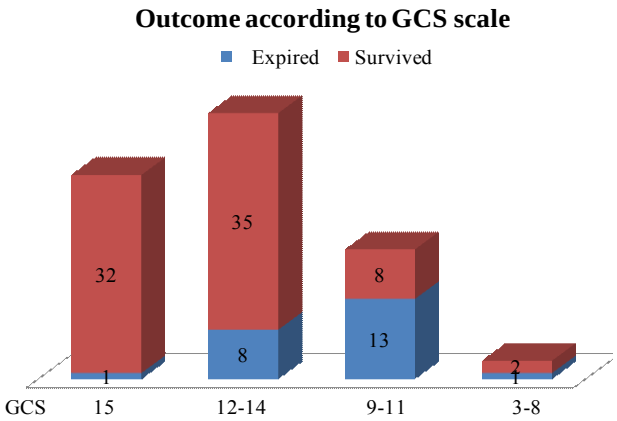

Figure 2: Outcome of patients according to GCS score.

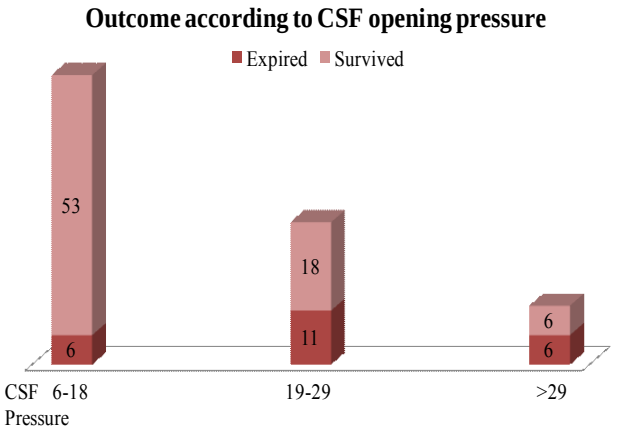

Figure 3: Outcome according to CSF opening pressure.

neurological findings at the time of presentation. Altered sensorium was defined as per GCS scale. All the patients were evaluated to find out any coexisting conditions like otitis or sinusitis, pneumonia, immunocompromised status.

The followings were regarded as primary investigations:

1. Routine Haematology and Biochemistry,
2. Cerebrospinal fluid (CSF) analysis
   - Total leukocyte count, differential leukocyte count,
   - Protien level, sugar level,
   - Gram stain, Acid fast bacillus (AFB) stain, India Ink preparation
   - Culture and sensitivity pattern
3. Chest x-ray- postero anterior (P/A)view, lateral view on requirement
4. Computed tomography (CT) head (plain/contrast)
5. Magnetic Resonance Imaging (MRI) head on requirement basis

Variables present at the time of admission	Odds ratio	*p* value
Duration of symptoms<24 hrs	11.4	0.039
Heart rate>100/min	142.5	<0.001
Diastolic BP<60 mHg	26.8	0.003
Triad of fever,neckstiffness, altered	6.3	0.017
sensorium		
GCS(14 or below)	12.6	0.016
Papilledema	12.2	<0.010
Seizures	6.6	<0.001
CSF opening pressure>18 cm of CSF	6.3	0.001
Cranial nerve palsy	6.4	0.001
Platelets counts<1,00,000/cumm	215.3	<0.001
HIV positive	24.2	0.012

Table 4: Significance of independent predictors of mortality.

No. of risk factors	Survived	Dead	Total	Mortality %
0	7	0	7	0
1	10	0	10	0
2	16	0	16	0
3	14	0	14	0
4	19	0	19	0
5	6	2	8	25
6	5	7	12	58.3
7	0	7	7	100
8	0	3	3	100
9	0	1	1	100
10	0	2	2	100
11	0	1	1	100
Total	77	23	100	

Table 5: Mortality according to prognostic rule (based on patients having 0 to 12 of the independent predictors).

Criteria for diagnosis

Diagnosis of bacterial meningitis was based on a compatible clinical picture with one of the following:

i. positive CSF culture ,
ii. negative CSF culture but with neutrophilic pleocytosis with total cells more than 5/cumm
iii. positive CSF gram stain,
iv. negative CSF culture without neutrophilic pleocytosis if elevated CSF protein, decreased CSF glucose.

Tuberculous Meningitis

Diagnosis was based on a compatible clinical picture plus one of the following pictures:

1. mycobacterial culture/AFB stain +ve in the CSF,
2. lymphocytic pleocytosis with cells more than 5/ cumm with high CSF protein and normal or decreased CSF glucose level
3. findings in CT head suggestive of TBM:

i. basilar meningeal thickening,
ii. abnormal leptomeningeal enhancement,
iii. dilatation of ventricles (hydrocephalus),
iv. effacement of basal cisterns,
v. cerebral infarction and edema,
vi. tuberculomas

Viral Meningitis

Risk stratification	No.of predictors	No.of patients	No.of death	Mortality %
Low risk group	≤3	47	0	0
Moderate risk group	4-6	39	9	23.1
High risk group	≥7	14	14	100
Total		100	23	23

Table6: Prognostic tool according to the prognostic rule.

Compatible clinical picture plus lymphocytic pleocytosis (25 to 500 cells/dl), a normal or slightly elevated protein concentration (20 to 80 mg/dl), a normal glucose concentration in CSF.

Fungal Meningitis

Diagnosis on the basis of compatible clinical picture and the followings

1. mononuclear or lymphocytic pleocytosis
2. increased CSF protein and decreased glucose level,
3. occasional eosinophils in the CSF

Stratification	Dead	Survived	Total	Validity
High risk	14	0	14	Sensitivity =100%
				Specificity =100%
				Positive predictive value =100%
				Negative predictive value =100%
Low risk	0	47	47	
	14	47	61	

Table7: Sensitivity, specificity, positive and negative predictive value

4. demonstration of organism in CSF India Ink smear or organism in culture

CSF analysis was repeated on 10th day in tuberculous meningitis cases to see the drug response and exclude other meningitis. CSF repeat analysis was also done if the admitted patient did not improve by the third day of admission. CT head was done if indicated by clinical evaluation.

Outcome measures

Only two outcome measures were analyzed in this study, i) survival and ii) mortality

Statistical analysis

Statistical analysis was performed using the Statistical package for the Social Sciences (SPSS v11.5; SPSS Inc, Chicago, USA). Death in hospital was used as the end point. Univariate correlation between death and clinical or laboratory features at the time of admission as well as during hospital stay were evaluated using Pearson's chi-square test or Fischer's exact test. All tests of significance were two-tailed and a P-value less than 0.05 was considered to be significant.

Variables with a significant univariate correlation with death in hospital or prolonged hospital stay were considered for a logistic regression analysis using a backward selection algorithm to identify the independent correlates of mortality. For the multivariable analysis, all continuous variables were considered categorically, using clinically and statistically appropriate cut-off points, in order to achieve the necessary simplicity of a prediction rule for clinical use.

Results

A total of 100 patients were enrolled in the study and followed up from the time of admission till discharge. Among them 62 patients were male and 38 patients were female with a male: female ratio of 1.6:1. The age of the patients ranged from 15 years to 82 years. When sub group based on age was analyzed, maximum numbers of patients were in 15-24 years age group (38%).

Among 100 patients, 57 were acute bacterial meningitis (ABM), 27 were tuberculous meningitis (TM), 12 were viral meningitis (VM) and 4 cryptococcal meningitis (CM) **(Figure 1)**.

Among 100 patients, most of the patients presented with fever (99%), headache (99%), followed by vomiting (86%), photophobia (72%), altered sensorium (71%) and seizures (32%). Three patients had focal and 29 patients had generalized tonic clonic seizures.

Regarding cardinal signs on presentation neck stiffness was present in 97%, kernig's sign in 68%, Brudzinski's sign in 3%, papilledema in 15%. However, cushing's reflex was not found in any patient. All three signs, neckstiffness, kernig's sign and brudzinski's sign were present in 3%.

Overall mortality rate was 23%. Mortality in bacterial meningitis was 19.3%, tuberculous meningitis 22.2%, viral meningitis 16.7% and 100% in cryptococcal meningitis.

All the 4 HIV positive patients, 3 admitted with cryptococcal meningitis and 1 with bacterial meningitis, died.

Among 100 patients, 33 patients had GCS of 15 on admission, 43 patients had 12-14, 21 patients had 9-11 and 3 patients had 3-8 **(Table 1)**. Out of 33 patients having GCS 15 on admission, 32 survived and 1 expired. Out of 3 patients with GCS 3-8 range, 1 patient expired and 2 survived in **(Figure 2, Table 1)**.

Among 59 patients who had CSF opening pressure of 6-18 cm of CSF, 53 patients (89.8%) survived and 6 (10.1%) expired. Among 29 patients who had CSF pressure of >18-29 cm of CSF pressure,11 patients (37.9%) died and 18 (62.06%) survived. Among 12 patients who had CSF pressure >29cm, 6 survived (50%) and 6 expired (50%) **(Table 2)**.

Regarding predictors of unfavorable outcome; 30 variables were studied at presentation and during hospital stay. Univariate analysis identified 15 distinct variables associated ($p<0.05$) with mortality **(Table 3)**. Logistic regression analysis of significant variables in univariate analysis yielded following 12 variables as independent predictors of mortality. They were duration of symptoms <24 hours ($p=0.039$), heart rate >100/min ($p<0.001$), diastolic BP <60 mmHg ($p=0.003$), Triad of fever, neckstiffness and altered sensorium ($p=0.017$), GCS (14 or below) ($p=0.016$), cranial nerve palsy ($p=0.001$), seizures ($p<0.001$), platelets counts <1,00,000/cumm ($p<0.001$) on presentation and HIV positive ($p=0.002$). Other independent predictors of mortality were papilledema ($p<0.01$), abnormal CT head findings ($p<0.01$), CSF opening pressure > 18 cm of CSF ($p=0.001$).

Prognostic rule was derived based on patients having 0 to 12 of these independent predictors. As shown in table 5; patients having 0 to 4 of these risk factors had no risk of in hospital death. The group with 5, 6 and 7 risk factors

comprised 8, 12 and 7 patients respectively, who had corresponding mortality rates of 25%, 58.3% and 100%. The group with 8, 9, 10 and 11 risk factors comprised 3, 1, 2 and 1 patients respectively, who had corresponding mortality rate of 100% in all groups.

Prognostic tool was developed dividing the patients into low risk group, comprising 47 patients with less than or equal to 3 risk factors having 0% mortality rate, moderate risk group, comprising 39 patients with 4 to 6 risk factors having mortality rate of 23.1% and high risk group, comprising 14 patients with 7 or more risk factors, having overall mortality rate of 100% **(Table 6)**.

Considering this cut off points, this model had 100% sensitivity, 100% specificity, 100% positive predictive value and 100% negative predictive value. This was statistically analyzed through the prediction for mortality by sensitivity, specificity, positive and negative predictive value **(Table 7)**.

Discussion

In the present study, male: female ratio was 1.6:1.The maximum number of patients were in 15-24 age groups (38 patients, 38%).The classic triad of fever, neck stiffness and altered sensorium was present in 69% of patients and at least two of four symptoms: headache, fever, neck stiffness and altered sensorium was present in 100%. Diederik vande Beek et.al found the classic triad in 44% and at least 2 of four symptoms in 95% of patients.[16]

In our study; low GCS (14 or below) on admission had high mortality which is significant and consistent with other studies.[8, 16]

Cerebrospinal fluid opening pressure more than 18 cm of CSF was significant variable for mortality in our study as shown by other studies.[3, 14]

Despite advances in antimicrobial agents and prompt administration of these therapies, an overall mortality rate of meningitis was 23% in present study. Highest mortality was found among cryptococcal meningitis (100%), 22.2% among tuberculous meningitis, 19.3 among bacterial meningitis and lowest in viral meningitis (16.7%). In addition, viral meningitis had less frequent neurological deficits among all. Cryptococcal meningitis due to its frequent association with HIV had worse outcome as reflected in other studies.[5, 14] Viral meningitis has very low mortality rates among meningitis and good outcome.[10] Overall mortality rate of meningitis is similar to rates quoted in other studies.[8,]

Fatalities were mainly in young adults, age was not the risk factor for mortality (p =0.49) in our study. Other study shows age above 65 years as a significant risk factor for mortality in meningitis.[16] In addition septic shock on admission has been known to adversely affect the prognosis reflected by thrombocytopenia and diastolic blood pressure <60mHg,[2] which is consistent with our study.

Diabetes mellitus is a significant predictor of poor outcome in meningitis.[6, 12] Our study didn't show any significance of diabetes mellitus for poor outcome in meningitis. Hypotension, altered mental status and seizures were significantly associated with adverse clinical outcome in meningitis[13] , which is reflected in our study also.

Coexisting conditions like AIDS had shown worse outcome. All four patients with HIV died during hospital stay in our study. 3 cryptococcal meningitis and 1 bacterial meningitis patients were HIV positive.

Hydrocephalus, infarctions and cerebral edema seen in CT-head played significant role in evaluating the prognostic outcome of patients in our study which matches to study done by S.H. Lan et al.[11]

Though cerebrospinal fluid parameters play key role in diagnosis meningitis, our study didn't find any significance of low CSF glucose or high level of CSF protein in terms of mortality. Neither any significance of CSF total WBC counts was found. This is not consistent with Diderik Vande Beek et. al's study.[16]

We evaluated 30 variables at presentation and during hospital stay as predictors of unfavorable outcome. In univariate analysis 15 factors were found to be significant (Table 3). Logistic regression analysis of significant variables in univariate analysis yielded following 12 variables as independent predictors of unfavorable outcome: these were duration of symptoms <24 hours (p =0.039), heart rate >100/min (p <0.001), diastolic BP <60 mmHg (p =0.003), Triad of fever, neck stiffness and altered sensorium (p=0.017), GCS (14 or below) (p =0.016), cranial nerve palsy (p =0.001), seizures (p<0.001), platelets counts <1,00,000/cumm (p <0.001) on presentation and HIV positive (p =0.002). Our results are similar with Diederik Vande Beek et al. study.[5]

Other independent predictors of mortality were papilledema (p <0.01), abnormal CT head findings (p <0.01), CSF opening pressure > 18 cm of CSF (p =0.001). Similar findings are quoted in different studies.[9, 4, 1]

Prognostic rule was derived based on patients having 0 to 12 of these independent predictors. As shown in table 5; patients having 0 to 4 of these risk factors had no risk of in hospital death. The group with 5, 6 and 7 risk factors comprised 8, 12 and 7 patients respectively, who had corresponding mortality rates of 25%, 58.3% and 100%. The group with 8, 9, 10 and 11 risk factors comprised 3, 1, 2 and 1 patient respectively, who had corresponding mortality rate of 100% in all groups.

Prognostic tool was developed dividing the patients into low risk groups comprising 47 patients with less than or equal to 3 risk factors having 0% mortality rate, moderate risk group comprising 39 patients with 4 to 6 risk factors and corresponding mortality rate of 23.1% and high risk group comprising 14 patients with 7 or more risk factors, having overall mortality of 100% **(Table 6)**.

Considering this cut off points, this model had 100% sensitivity, 100% specificity, 100% positive predictive value and 100% negative predictive value **(Table 7)**.

It is a simple prediction tool for clinical practice and reflects the relative importance of the predictors for the

stratification of patients in terms of risk. The proposed classification tool, derived from a limited amount of readily available information, may be helpful for management of patients with meningitis.

It is obvious that the proposed model requires validation in population based prospective studies with sufficiently large sample sizes. As our system has been evaluated only in the population from which it was derived, its performance has to be assessed in completely independent, external databases. Because the proposed prognostic rule was developed at a single institution, its usefulness at hospitals in different settings needs to be proven.

Conclusions

Patients with meningitis can be divided into low moderate and high risk group according to prognostic factors. Cryptococcal meningitis had the worst outcome and viral meningitis had the best outcome. Overall mortality in meningitis was 23%.The findings of the present study suggest that simple clinical and laboratory parameters on admission hleps in idnetifying risk factors, thus ensuring prompt management of high risky patients and directing those at low risk to less intensive and expensive level of care. This attitude is definitely more cost effective especially in a country like Nepal.

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