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A Prospective Study to Assess the Significance of Serum and Cerebrospinal Fluid C-Reactive Protein (CRP) Level in Meningitis in Adults and its Role differentiating Pyogenic from Non-Pyogenic Meningitis

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Abstract
Introduction: *Acute Pyogenic Meningitis is the most common cause of suppurative infection in the central nervous system. The prognosis of pyogenic meningitis is critically dependant on a rapid and causal implementation of immediate treatment. However, clinical and biochemical parameters are not reliable enough except when bacteria are found in the CSF under a microscope.*
Therefore, the treatment of acute pyogenic meningitis is most of the time presumptive. Use of biological markers, especially lymphokines and acute phase reactants has been proposed to facilitate the initial diagnosis. Today C-reactive protein is one of the most widely used inflammatory markers in the emergency department to distinguish bacterial from non-bacterial infections.
Aims and Objectives: *To evaluate the utility of C- reactive protein levels in serum and CSF as rapid screening test in meningitis patient to differentiate pyogenic and non-pyogenic meningitis.*
Materials and Methods:
Source of Data: *Patients who were admitted in the general medicine wards and intensive medical care unit in the Department of General medicine, Government Thiruvannamalai Medical College Hospital, for the complaints suggestive of meningitis such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium, signs of meningeal irritation and focal neurologic deficits regardless of their past treatment status with the fulfilment of the inclusion and exclusion criteria included in the study.*
Sample Size: *50 patients admitted to our Department of General medicine, Government Thiruvannamalai Medical College Hospital, with clinical syndrome suggestive of Acute meningitis such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium, signs of meningism and focal neurologic deficit regardless of their past treatment status are enrolled in our study. Informed consent was obtained from the patients or the attenders if the patient is sick enough to give the consent.*
Study Design*: Prospective and observational study*
Study Duration*: 6 months*
Statistical Methods: *Following statistical methods have been employed in the present study*
• Independent sample't' test - Unpaired
• One-way analysis of variance (ANOVA)
• Fischer's exact test
Conclusion:
1. *The Cerebrospinal fluid level of CRP is elevated in acute pyogenic meningitis and hence it is useful to differentiate it from viral meningitis/encephalitis.*
2. *Therefore, the CRP assays in Cerebrospinal fluid is highly useful in the management aspects whenever the diagnosis is uncertain by conventional methods.*
3. *The Cerebrospinal fluid level of CRP is significantly elevated in patients who expired and in patients with post meningitis sequelae than in patients recovered uneventfully. So, it may be used as a marker of prognostication in acute pyogenic meningitis.*
4. *The Cerebrospinal fluid level of Lactate is significantly elevated in patients who expired than in patients with post meningitis sequelae and is even lower in patients who recovered uneventfully. Hence it predicts the clinical outcome better and it can be used as a marker of prognostication in acute pyogenic meningitis.*

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I. Introduction

Acute Pyogenic Meningitis is the most common cause of suppurative infection in the central nervous system. The prognosis of pyogenic meningitis is critically dependant on a rapid and causal implementation of immediate treatment. However, clinical and biochemical parameters are not reliable enough except when bacteria are found in the CSF under a microscope.

Therefore, the treatment of acute pyogenic meningitis is most of the time presumptive. Use of biological markers, especially lymphokines and acute phase reactants has been proposed to facilitate the initial diagnosis. Today C-reactive protein is one of the most widely used inflammatory markers in the emergency department to distinguish bacterial from non-bacterial infections.

Large number of studies conducted worldwide suggests that CRP level in the CSF is higher in pyogenic meningitis as compared to non-pyogenic meningitis and hence aids in the differential diagnosis and management of meningitis. Among the pyogenic group the raised CRP was observed mostly among gram negative organisms when compared to gram positive organisms. Other parameters like reduced CSF glucose, elevated CSF proteins were also taken into consideration in this study to correlate raised C-reactive protein in cerebrospinal fluid and bacterial meningitis.

Further it is easier and quicker to perform sensitive reliable and rapid diagnostic test for timely therapeutic intervention. The detection of CRP in CSF also helps in the choice of appropriate antibiotic and the duration of therapy. So in this study we tried to find positive association between raised CSF CRP and raised CSF/Serum CRP ratio in cases of meningitis and used it to differentiate pyogenic from non-pyogenic infections.

Infectious diseases of CNS have always been a major cause of mortality and morbidity for millions of people around the world. CNS infection can result in devastating consequences and in many cases, may result in both medical and neurological emergencies. Meningitis is an inflammation of the membranes that surround the brain and spinal cord. It is associated with a central nervous system inflammatory reaction that may result in decreased consciousness, varied intracranial pressure and stroke. The meninges, the subarachnoid space and the brain parenchyma are all frequently involved in the inflammatory reaction (Meningoencephalitis).

Meningitis can be caused by many agents which includes bacteria, virus, fungi, protozoa, and helminth and even by non-infectious agents such as malignancy, chemical compounds, drug hypersensitivity etc. Etiological diagnosis of meningitis remains a problem in clinical practice as CSF biochemical analysis & cellular response often overlap. Reliable, rapid and cost effective diagnostic tests which can be performed in any standard pathology laboratory and can be of help in differentiating the various types of meningitis is the need of the hour. In this regard, C-reactive protein level and Adenosine deaminase activity can be used as rapid tests in the differential diagnosis of meningitis. ADA estimation is useful in the diagnosis of tubercular meningitis. CRP estimation has been documented to be useful in the diagnosis of pyogenic meningitis. The level of both ADA and CRP are found to be low in cases of viral meningitis.

Infections of the central nervous system are common in adult practice. The clinical profile is protean. A high index of suspicion of the treating physician is essential to make an early diagnosis. The need for early diagnosis is imperative. Potent antibiotics have reduced mortality, but do not prevent sequelae especially if therapy is delayed. The newer rapid diagnostic tests and imaging modalities have improved the holistic management of children with CNS infections. Pre-treatment with antibiotics of patients with purulent meningitis can modify the clinical picture and CSF findings. So distinctive etiological diagnosis becomes difficult. Gram staining of CSF can provide a rapid preliminary identification of infective organism, but is liable to misinterpretation especially in inexperienced hands.

Culture of CSF takes 24 to 48 hours for isolating the causative organism. Furthermore, culture may not always be positive in adults who have received antibiotics prior to hospitalization.

According to various studies Bacterial polysaccharide antigen of microorganisms can be detected by newer immunological tests like counter immune electrophoresis, Latex agglutination tests etc. Since antigen may be present in the CSF even after lysis of bacteria, these immunological tests could prove useful even in partially treated patients. The present study was therefore designed to evaluate the utility of CRP in CSF in diagnosing cases of pyogenic meningitis, to study the spectrum of bacterial pathogens causing acute bacterial meningitis and to analyse the clinical profile of bacterial meningitis. Given its dire consequences, the prompt diagnosis and the timely identification of the species causing meningitis is crucial, which is challenged by the various confounding factors that influence the accuracy of CSF results. The lumbar puncture is the indispensable part of the management of acute meningitis which should not be delayed unless absolute contraindications exist.

The currently used conventional methods for differentiation of the various types of meningitis have serious limitations. CSF gram stain is often not contributory and operator dependent. It is not reliable if the organisms are scarce in the spinal fluid or if the therapy has been started. The CSF cultures often need a day or two and even longer or comes negative in partially treated cases. According to various Indian workers the sensitivity of the CSF culture is 30-60%. Therefore, the treatment of meningitis, most of the time is presumptive.

The glucose value in CSF is difficult to interpret since it is influenced by the plasma glucose level in the circulation, as hyperglycaemia falsely increases the CSF glucose concentration even in bacterial meningitis and hypoglycaemia is associated with low glucose level in CSF. This issue can be addressed by concurrent sampling of blood for plasma glucose along with lumbar puncture and the CSF/serum glucose ratio is used, which is highly diagnostic of bacterial meningitis if it is below 0.4.

Partially treated patients with use of inappropriate antibiotics can obscure the cytological and biochemical status of the spinal fluid and the chance of recovery of organisms from the spinal fluid will also become less likely. They also simulate the CSF picture of viral meningoencephalitis. In Enteroviral meningitis; the polymorphs can flood the CSF in first 6 hours along with normal CSF glucose. In immunosuppressed patients, the mounting of CSF inflammatory response is suboptimal and can also simulate the viral picture. Hence a quick and reliable method for differentiating the bacterial and viral meningitis is essential for optimal management outcome.

Reliable, cost effective, rapid screening tests which can be performed in any standard pathology laboratory could be of help in the differentiation of various types of meningitis in adults. Apart from CSF CRP, the CSF lactic acid is considered as a good biomarker to differentiate between the pyogenic and the viral meningitis. The mechanism of lactate production in brain is due to the meningitis associated cerebral ischemia and anaerobic metabolism. Unlike glucose, the blood lactate level will not influence the CSF lactate level and they are largely independent of each other since the CSF lactate level depends upon the local production in the brain. This is an advantage over the CSF glucose. CSF lactate is highly useful in the diagnosis of post-surgical meningitis which is not accompanied by specific cells and proteins.

The C-reactive protein is an acute phase reactant and is a globulin chiefly produced by hepatocytes in response to various stimuli such as infection, malignancy and tissue necrosis. It was discovered by Tilletee of France in 1951. The CRP production is also induced locally by lipopolysacharides of gram negative bacilli in neurons and various other extra hepatic sites. Kiezsolwski et al found out that the CSF CRP levels is elevated in pyogenic meningitis significantly when compared to non-pyogenic meningitis. Vaishnavidevi387 et al and Tanidawale60 et al agreed with this observation. GojanmohanRaj42 et al observed that the CSF CRP level is significantly elevated in gram negative bacillary meningitis when compared to gram positive ones. Hence the use of CSF CRP latex immunoassay will rapidly differentiate the bacterial and the viral meningitis and thereby guide the management with confidence.

II. Aims And Objectives

To evaluate the utility of C- reactive protein levels in serum and CSF as rapid screening test in meningitis patient to differentiate pyogenic and non-pyogenic meningitis.

III. Materials And Methods

Source of data: Patients who were admitted in the general medicine wards and intensive medical care unit in the Department of General medicine, Government Thiruvannamalai Medical College Hospital, for the complaints suggestive of meningitis such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium, signs of meningeal irritation and focal neurologic deficits regardless of their past treatment status with the fulfilment of the inclusion and exclusion criteria included in the study.

Sample size: 50 patients admitted to our Department of General medicine, Government Thiruvannamalai Medical College Hospital, with clinical syndrome suggestive of Acute meningitis such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium, signs of meningism and focal neurologic deficit regardless of their past treatment status are enrolled in our study. Informed consent was obtained from the patients or the attenders if the patient is sick enough to give the consent.

Study design*:* Prospective and observational study

Study duration*:* 6 months

Inclusion criteria:

- Patients with complaints of fever, headache, vomiting, altered sensorium with or without loss of consciousness in the age group of 18 - 65 years
- CSF protein > 45mg/dl
- CSF gram stain and culture positive

- CSF glucose < 40 mg/dl

Exclusion criteria:
- Patients less the 18 years and greater than 65 years
- Acute infections at sites other than CNS
- Patients with severe hepatic dysfunction and severe dyslipidaemia
- Females on OCP's and Intrauterine devices
- Patients on steroids
- Traumatic or dry tap

Procedure:

A questionnaire prepared noted the duration and detail of illness. The clinical constellation of symptoms suggestive of acute meningeal infection such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium and focal neurological deficit such as blindness, double vision, hemiparesis, bulbar symptoms etc. were noted. History of Diabetes, Tuberculosis and immunodeficient states and drug history was elicited. Personal history of smoking, alcohol abuse and substance abuse, if any, was elicited. A detailed physical examination was conducted which included the vitals, hydration status, pulse oximetry, skin besides a thorough systemic examination. Screening neurological examination was done to document the signs of meningeal irritation and to evaluate the focal neurological deficit. Complete blood count, random blood sugar, renal and liver function test, serum electrolytes, urine routine and ECG were done. Chest x ray was done to rule out the infective foci like pneumonia, Koch's. An urgent coagulation profile was performed to rule out coagulopathy. Adequate amount of blood was sampled for culture and sensitivity emergently prior to the administration of steroids and empirical antibiotics.

If there were no features like coma on presentation, focal neurological deficit or immunocompromised state features, a lumbar puncture was performed without delaying unduly for imaging. The procedure was done after getting the informed consent. The patient was put in the universal flexion position with assistance and L_3 - L_4 space was identified and lumbar puncture was done with the optimal gauge spinal needle under sterile precaution with draping. Adequate amount was sampled and its appearance was noted. The sample was sent for cell count, cytology, protein, sugar, gram stain, AFB stain, lactic acid and high sensitive CRP level, India ink preparation and PCR (if clinically indicated). Separate sample was drawn with sterile precaution in a culture broth for culture and sensitivity. Emergent CT or MRI if needed, as indicated by clinical scenario, with contrast, was done to note the meningeal enhancement and to evaluate for the complications of meningitis. Optimal fluid therapy and nursing care were provided.

Instruments

Chest x ray: A Chest x ray postero-anterior view is done to rule out the infective foci such as Koch's, pneumonia etc.

CT/MRI with contrast +/- angiogram: To document the post contrast meningeal enhancement and to evaluate for the various complications, as clinically indicated.

Lumbar puncture

After getting informed consent, patient is placed in the universal flexion position. With thorough cleaning by povidone iodine and draping, lumbar puncture was performed with aseptic precaution after identifying the L_3 - L_4 space with the help of the iliac crest. When the spinal needle enters the subarachnoid space the cerebrospinal fluid comes out and the opening pressure is measured. Then adequate sample is drawn and sent for cytological, biochemical and microbiological analysis including high sensitive CRP along with special investigations, as clinically indicated.

Laboratory methods: CSF CRP level estimation

All specimens for investigations were collected before introduction of antibiotics. Immunoturbidimetric assay using the Dimension RxL analyser (Siemens) with calibrators and internal controls provided by Siemens and according to manufacturer's recommendations was used to analyse CRP levels. This is a latex immunoassay developed to accurately and reproducibly measure CRP. The CRP present in the sample reacts with the anti-CRP antibody adsorbed into latex causing agglutination. This agglutination is identified as an absorbance change (572 nm), with the rate of change being proportional to the quantity of CRP in the sample.

IV. Statistical Methods

Following statistical methods have been employed in the present study
• Independent sample't' test - Unpaired
• One-way analysis of variance (ANOVA)

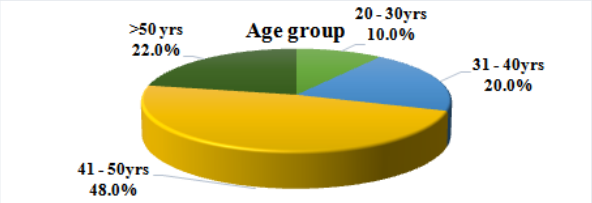
• Fischer's exact test
Variables were significant if p value < 0.05

To compare three mean values one-way ANOVA is applied. To compare two mean values independent sample't' test is applied. ROC curve analysis is used to find optimal cut-off values. Sensitivity and specificity analysis is done to find the diagnosis accuracy. To analyse the data SPSS (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. Released 2013) is used. Significance level is fixed as 5 % ($\alpha = 0.05$).

V. Observation And Results

1: Age wise distribution:

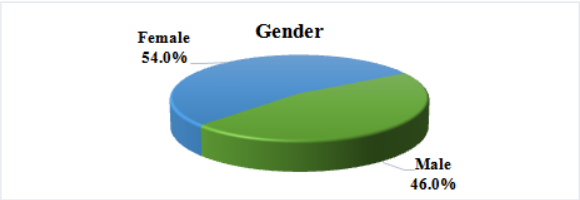
Age group	N	%
20 - 30yrs	5	10.0%
31 - 40yrs	10	20.0%
41 - 50yrs	24	48.0%
> 50 yrs	11	22.0%
Total	50	100.0%



In the study group of 50 patients with meningitis, 20 % were in the age group of 30-40, 48 % in the age group of 40-50, 10 % in the age group of 20-30 and 22 % in the age group of above 50 years. The maximum incidence of meningitis was seen in the age group of 41 – 50 years

2: Sex wise distribution:

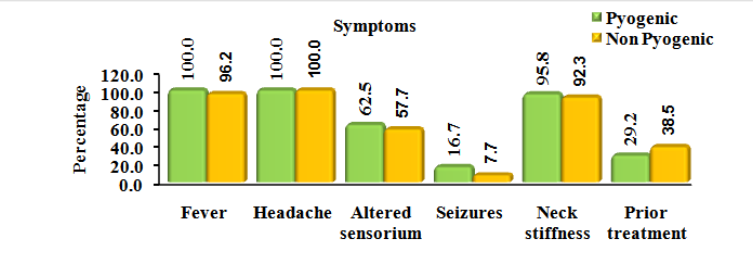
Gender	N	%
Male	23	46.0%
Female	27	54.0%
Total	50	100.0%



In the study group of 50 patients with meningitis, 46 % were males and 54 % were females. In both the sex, maximum incidence was seen in of 41 – 50 years.

3: Distribution of symptoms among the different types of meningitis:

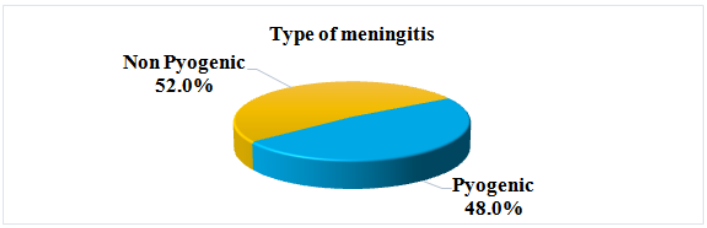
Symptoms	Type of meningitis					
	Pyogenic		Non- Pyogenic		Total	
	N	%	N	%	N	%
Fever	24	100.0%	25	96.2%	49	98.0%
Headache	24	100.0%	26	100.0%	50	100.0%
Altered sensorium	15	62.5%	15	57.7%	30	60.0%
Seizures	4	16.7%	2	7.7%	6	12.0%
Neck stiffness	23	95.8%	24	92.3%	47	94.0%
Prior treatment	7	29.2%	10	38.5%	17	34.0%
Total	24	100.0%	26	100.0%	50	100.0%



Fever, headache, neck stiffness was significantly associated with bacterial meningitis.

4: Incidence of type of meningitis in the study group:

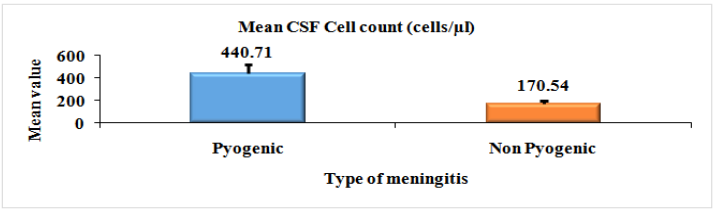
Type of meningitis	N	%
Pyogenic	24	48.0%
Non- Pyogenic	26	52.0%
Total	50	100.0%



Among the study group in pyogenic and non-pyogenic meningitis, 52 % of the patients belong to the non-pyogenic group and 48 % belong to the pyogenic group.

5: CSF cell count in different types of meningitis:

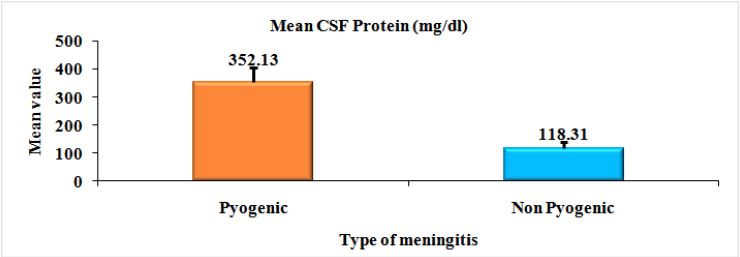
Type of meningitis	N	Mean CSF Cell count (cells/µl)	Std. Error
Pyogenic	24	440.71	75.693
Non- Pyogenic	26	170.54	22.923



In the case of pyogenic meningitis, the mean cell count was found to be 440.71 when compared to the cases of non-pyogenic meningitis which was found to have 170.54. Hence the CSF cell count was higher in pyogenic meningitis compared to non-pyogenic meningitis.

6: CSF protein in different types of meningitis:

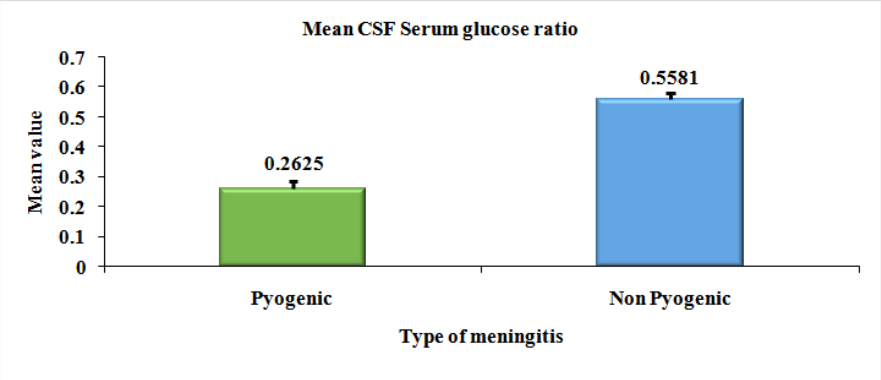
Type of meningitis	N	Mean CSF Protein (mg/dl)	Std. Error
Pyogenic	24	352.13	54.290
Non- Pyogenic	26	118.31	19.341



In the case of pyogenic meningitis, the mean CSF protein count was found to be 352.13, when compared to the cases of non-pyogenic meningitis which was found to have 118.31. Hence the CSF protein will be higher in pyogenic meningitis.

7: CSF/Serum Glucose ratio in different types of meningitis:

Type of meningitis	N	Mean CSF Serum glucose ratio	Std. Error
Pyogenic	24	.2625	.02358
Non- Pyogenic	26	.5581	.02356



In the case of pyogenic meningitis, the mean CSF glucose was found to be 0.2625 when compared to the non-pyogenic cases whose mean was found to have been 0.5581. Hence in pyogenic meningitis it was found to have overall low CSF glucose level.

8: CSF cultures in different types of pyogenic meningitis:

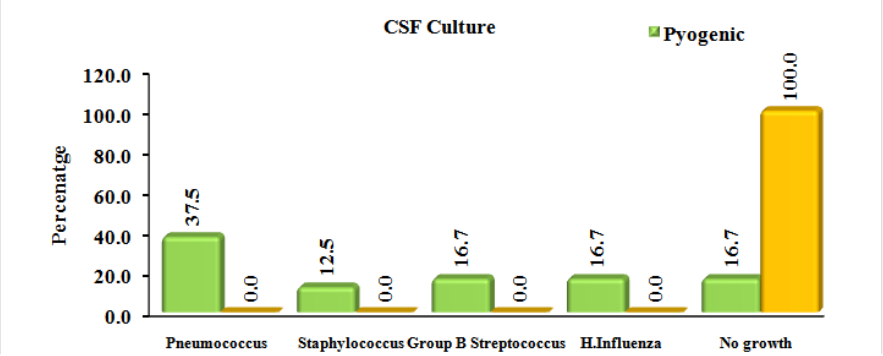
CSF Culture	Type of meningitis					
	Pyogenic		Non- Pyogenic		Total	
	N	%	N	%	N	%
Pneumococcus	9	37.5%	0	0.0%	9	18.0%
Staphylococcus	3	12.5%	0	0.0%	3	6.0%
Group B Streptococcus	4	16.7%	0	0.0%	4	8.0%
H. Influenza	4	16.7%	0	0.0%	4	8.0%
No growth	4	16.7%	26	100.0%	30	60.0%
Total	24	100.0%	26	100.0%	50	100.0%

Among the organisms grown in the cultures Pneumococcus is the most commonly isolated one accounting for about 37.5 % of the positive cases. The next common organism was Group B streptococcus and H. Influenza accounting for about 16.7 % of the positive cases each.

9: Various parameters and their mean values used for differentiation of pyogenic and non-pyogenic meningitis:

Gender	Type of meningitis					
	Pyogenic		Non- Pyogenic		Total	
	N	%	N	%	N	%
Male	11	47.8	12	52.2	23	100.0%
Female	13	48.1	14	51.9	27	100.0%
Total	24	48.0%	26	52.0%	50	100.0%

Variables	Type of meningitis	N	Mean	Std. Error
Age (yrs)	**Pyogenic**	24	46.54	1.943
	Non- Pyogenic	26	42.12	1.904
CSF Serum glucose ratio	**Pyogenic**	24	.2625	.02358
	Non- Pyogenic	26	.5581	.02356
CSF Protein (mg/dl)	**Pyogenic**	24	352.13	54.290
	Non- Pyogenic	26	118.31	19.341
CSF Cell count (cells/µl)	**Pyogenic**	24	440.71	75.693
	Non- Pyogenic	26	170.54	22.923

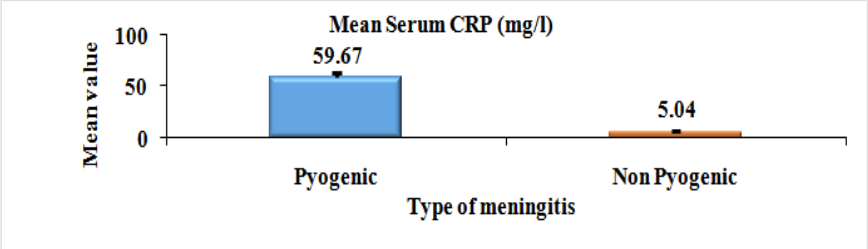


In these tables we have showed the mean CSF parameters (cell count, protein, serum glucose ratio) in pyogenic and non-pyogenic meningitis as below: In the study mean age at presentation for the patient presented with pyogenic meningitis were found to be 46.5 and for the non-pyogenic meningitis patients were found to be 42.1. Among the glucose values in pyogenic meningitis were found to have been 0.26 and for the non-pyogenic meningitis were found to have 0.56.

Protein studies shows that in the case of pyogenic meningitis mean values were higher that is 352.1 when compared to the cases in non-pyogenic meningitis where the mean was 118.3 which is low. In the case of cell count in the case of pyogenic meningitis cell count was found to be increased that is 440.7 when compared to the case in non-pyogenic meningitis which is low that is 170.5

10: Serum CRP in different types of meningitis:

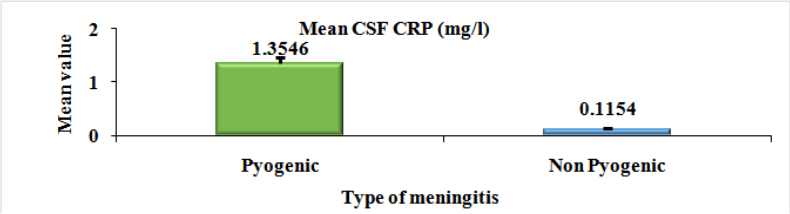
Type of meningitis	N	Mean Serum CRP (mg/l)	Std. Error
Pyogenic	24	59.67	4.184
Non- Pyogenic	26	5.04	1.122



In the case of pyogenic meningitis, the mean serum CRP was found to be 59.67 when compared to the non-pyogenic cases in which it was 5.04. Hence it was found to be statistically significant that the serum CRP level was elevated in the pyogenic category cases.

11: CSF CRP in different types of meningitis:

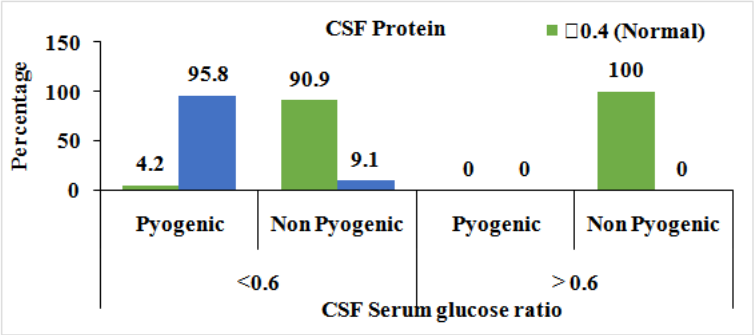
Type of meningitis	N	Mean CSF CRP (mg/l)	Std. Error
Pyogenic	24	1.3546	.10418
Non- Pyogenic	26	.1154	.02942



In the case of pyogenic meningitis, the mean CSF CRP was found to be 1.3546 when compared to the non-pyogenic cases in which it was 0.1154. Hence it was found to be statically significant that the CSF CRP level was elevated in the pyogenic category cases.

12: Comparison between CSF CRP values and Serum / CSF glucose ratio:

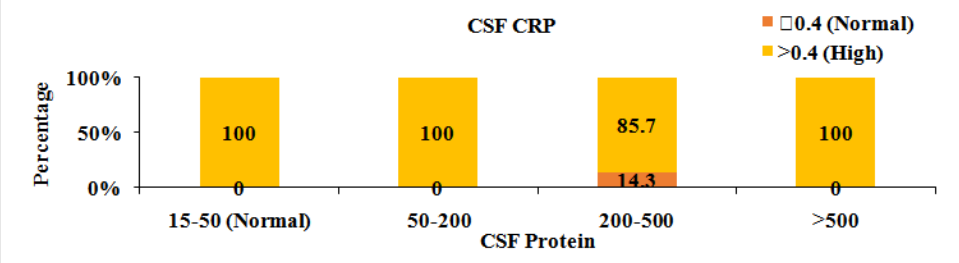
CSF CRP	CSF Serum glucose ratio							
	<0.6				> 0.6			
	Pyogenic		Non- Pyogenic		Pyogenic		Non- Pyogenic	
	N	%	N	%	N	%	N	%
≤0.4 (Normal)	1	4.2%	10	90.9%	0	0.0%	15	100.0%
>0.4 (High)	23	95.8%	1	9.1%	0	0.0%	0	0.0%



In the above tables ang pi-chart it is evident that the patients whose CSF CRP values <0.4 that is the normal range the glucose ratio was low in the case of non-pyogenic meningitis (90.9 %) when compared to the percentage in pyogenic cases which is 4.2 %. When the CRP values is higher that is > 0.4 the glucose ratio is higher in pyogenic cases about 95.8 % whereas the percentage of cases with low glucose ratio in non-pyogenic cases were only 9.1 %.This implies that there is a positive correlation in the diagnosis of pyogenic meningitis with low serum / CSF glucose ratio and high CRP values.

13: Comparison between CSF CRP values and CSF protein in the case of pyogenic meningitis:

Pyogenic	CSF CRP	CSF Protein							
		15 - 50 (Normal)		50 - 200		200 - 500		➢ 500	
		N	%	N	%	N	%	N	%
	≤0.4 (Normal)	0	0.0%	0	0.0%	1	14.3%	0	0.0%
	>0.4 (High)	2	100.0%	9	100.0%	6	85.7%	6	100.0%

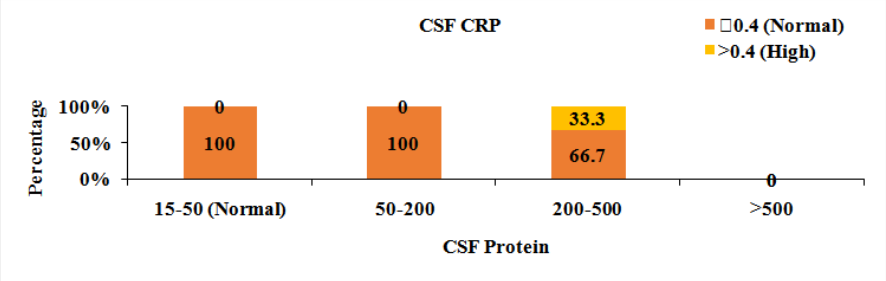


In the above tables ang pi-chart it is evident that the patients whose CSF CRP values < 0.4 that is the normal range, the CSF protein in the case of pyogenic meningitis was 14.3 % in the range of protein 200 – 500. When the CRP values is higher that is > 0.4 the CSF protein in pyogenic cases were higher 2 cases in the range of 15 – 50, 9 cases were in the range 50 – 200, 6 cases in the range of 200 – 500 (higher) and 6 cases in the range of > 500.

This implies that there is a positive correlation in the diagnosis of pyogenic meningitis with high protein values in CSF and high CSF CRP values.

14: Comparison between CSF CRP values and CSF protein in the case of non-pyogenic meningitis:

Non- Pyogenic	CSF CRP	CSF Protein							
		15 - 50 (Normal)		50 - 200		200 - 500		> 500	
		N	%	N	%	N	%	N	%
	≤0.4 (Normal)	2	100.0%	21	100.0%	2	66.7%	0	0.0%
	>0.4 (High)	0	0.0%	0	0.0%	1	33.3%	0	0.0%

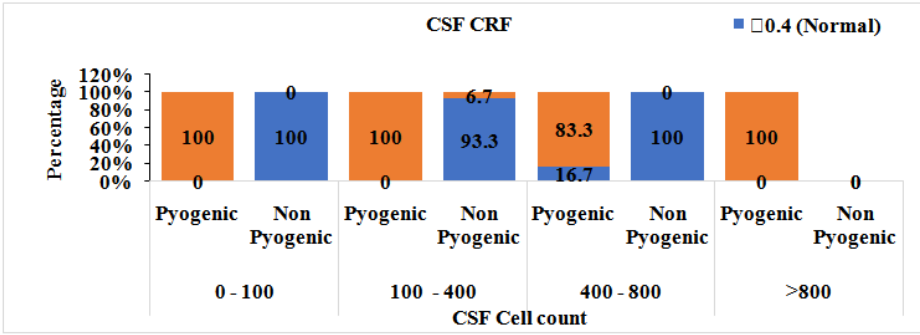


In the above tables ang pi-chart it is evident that the patients whose CSF CRP values <0.4 that is the normal range, the CSF protein in the case of non-pyogenic meningitis presentation was 2 cases in the range of 15 – 50, 21 cases were in the range 50 – 200, 2 cases in the range of 200 – 500 and no cases in the range of > 500. Whereas when the CSF CRP values higher that is > 0.4 only one case was presented with increased CSF protein count in the 200 – 500 range.

This implies that there is no correlation in the diagnosis of non-pyogenic meningitis with high protein values in CSF and high CSF CRP values.

15: Comparison between CSF CRP values and CSF cell count:

CSF CRP	CSF Cell count															
	0 - 100				100 - 400				400 - 800				>800			
	Pyogenic		Non-Pyogenic		Pyogenic		Non-Pyogenic		Pyogenic		Non-Pyogenic		Pyogenic		Non-Pyogenic	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
≤0.4 (Normal)	0	0%	10	100%	0	0%	14	93.3%	1	16.7%	1	100%	0	0%	0	0%
>0.4 (High)	3	100%	0	0%	11	100%	1	6.7%	5	83.3%	0	0%	4	100%	0	0%



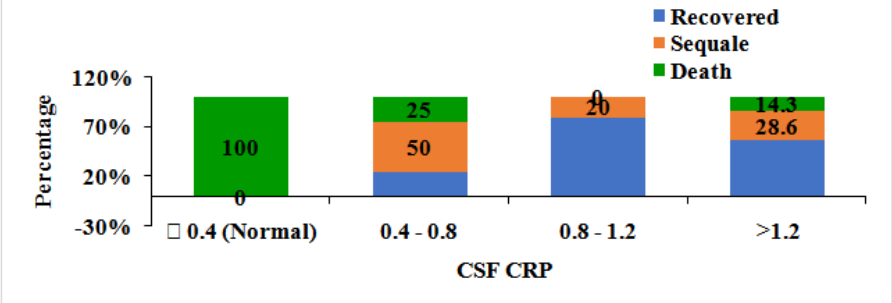
In the above table comparison between CSF cell count and the CSF CRP are done. It is evident that when the CSF CRP is lower that is < 0.4 in the case of pyogenic meningitis only one case (16.7 %) have high cell count (400 – 800), whereas in the case of non-pyogenic meningitis 10 cases (100 %) have cell count in the range of 0 – 100, 14 (93.3 %) cases have the cell count in the range of 100 – 400, 1 case (100 %) in the range of 400 – 800.

In the case when the CSF CRP value is > 0.4, in the case of pyogenic meningitis 3 cases (100 %) have CSF protein count in the range of 0-100, 11 (100 %) cases have the cell count in the range of 100 – 400, 5 (83.3 %) cases have protein count in the range of 40 – 800, and four cases (100 %) have protein count in the range of >800. In the case of non-pyogenic meningitis, only one case (6.7 %) presented in the range of 100 – 400.

This implies that the elevated CSF CRP values have high cell count that is correlated with the diagnosis of pyogenic meningitis, and there is no specific correlation between the CSF CRP values and CSF cell count in the case of non-pyogenic meningitis.

16: Comparison between CSF CRP values and the outcome in the patient with meningitis:

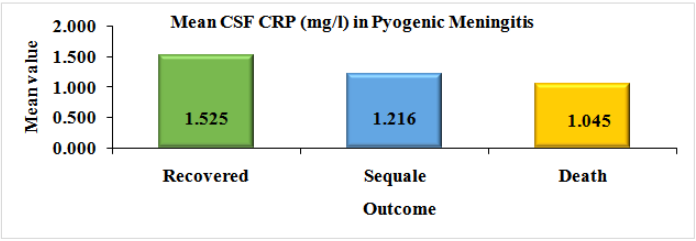
CSF CRP	Outcome					
	Recovered		Sequelae		Death	
	N	%	N	%	N	%
≤ 0.4 (Normal)	0	0.0%	0	0.0%	1	100.0%
0.4 - 0.8	1	25.0%	2	50.0%	1	25.0%
0.8 - 1.2	4	80.0%	1	20.0%	0	0.0%
>1.2	8	57.1%	4	28.6%	2	14.3%



In the above tables it is evident that, when the CSF CRP value is > 1.2, 8 patients have recovered (57.1 %), 4 patients have post meningitis sequelae (28.6 %), 2 have expired (14.3 %). In the CSF CRP range 0.8 – 1.2 recoveries was about 4 patients (80.0 %), post meningitis sequelae was about 20.0 % one case, and no death. Hence the early instillation of antibiotics with the initial high CSF CRP values even before the results of blood or CSF culture lead to the more recovery of patients.

17: Mean CSF CRP values in various outcomes in all cases of pyogenic meningitis:

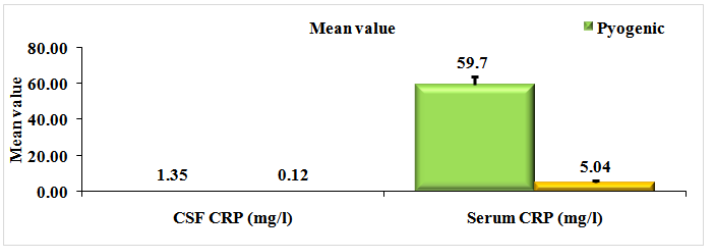
Type of meningitis	Outcome	N	Mean CSF CRP (mg/l)	Std. Error
Pyogenic	**Recovered**	13	1.5246	.11201
	Sequelae	7	1.2157	.17364
	Death	4	1.0450	.39511
	Total	24	1.3546	.10418



In the case of high CSF CRP values in all cases of pyogenic meningitis the mean values of patients who were recovered from the illness are 1.525, those who have post meningitis sequelae were found to have 1.216 and the mean values of patients who were expired were 1.045 (lowest). Hence from this table it is evident that high CSF CRP a marker for diagnosis of pyogenic meningitis without the evidence from CSF culture is evident, with this evidence early instillation of antibiotics resulted more recovery of patients and less post meningitis sequelae and death from meningitis.

18: Mean CSF CRP and the Serum CRP values in differentiating pyogenic from non-pyogenic meningitis: (p – value):

Variables	Type of meningitis	N	Mean	Std. Error	P - Value
CSF CRP (mg/l)	**Pyogenic**	24	1.3546	.10418	**< 0.001**
	Non- Pyogenic	26	.1154	.02942	
Serum CRP (mg/l)	**Pyogenic**	24	59.67	4.184	**< 0.001**
	Non- Pyogenic	26	5.04	1.122	



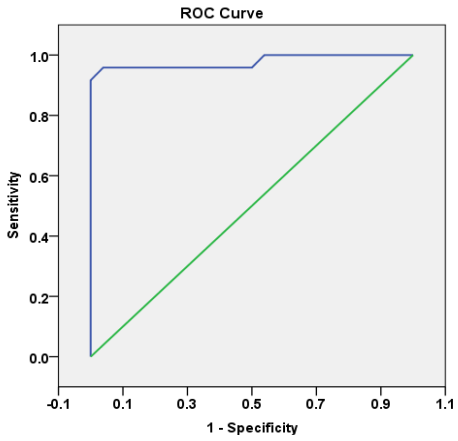
The mean CSF CRP levels in pyogenic and non-pyogenic were differentiated by Conventional methods was 1.35 and 0.12 mg/dl respectively. The mean serum CRP levels in pyogenic and non-pyogenic was differentiated by Conventional methods was 59.7 and 5.04 mg/dl respectively. To compare three mean values **one-way ANOVA** is applied. To compare two men values **independent sample t-test** is applied. **ROC curve analysis** is used to find optimal cut-off values. Sensitivity and specificity analysis is done to find the diagnosis accuracy.

To analyse the data SPSS (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. Released 2013) is used. Significance level is fixed as 5% ($\alpha = 0.05$).The reference normal range significance was analysed and the **P value was < 0.0001, extremely significant.**

19: Sensitivity and Specificity of CSF CRP in the differentiation of pyogenic and non-pyogenic meningitis:

		Type of meningitis		Total
		Pyogenic	Non- Pyogenic	
CSF CRP (mg/l)	> 0.46	23	1	24
	≤ 0.46	1	25	26
Total		24	26	50

ROC curve analysis:



Area under the Curve 0.978 (SE=0.022, P<0.001)

Parameter	Estimate
Sensitivity	95.83%
Specificity	96.15%
Positive Predictive Value	95.83%
Negative Predictive Value	96.15%
Diagnostic Accuracy	96.00%

VI. Discussion

Comprehensive analysis of 50 cases of acute meningitis:

We have analysed 50 patients admitted with various symptoms and signs of meningitis like fever, headache, altered sensorium, seizures, and neck stiffness. These patients were admitted in our Government Thiruvannamalai Medical College Hospital in various medical wards and intensive medical care unit. Patients with contraindications for lumbar puncture like those with coagulopathy, documented Intracranial space occupying mass lesion and local infection at sites of lumbar puncture, and patients with pyogenic infections elsewhere with tissue necrosis and those with malignancy, those with severe hepatic failure and dyslipidaemia, patients on long term steroids and OCP, patients with recent history of stroke were excluded from the study as these would cause elevation of the biomarkers.

Patients with altered sensorium were subjected to CT Brain / MRI brain before doing LP. Other patients were subjected to LP after sending blood culture samples. CSF analysis for glucose, CSF/serum glucose ratio, protein, cell count, cytology, Gram staining, AFB staining, Bacterial and blood culture were used. Serum CRP and CSFCRP assay were done in all patients.

In the study group of 50 patients with meningitis, 20% were in the age group of 30-40, 48 % in the age group of 40-50, 10 % in the age group of 20-30 and 22% in the age group above 50 years. The maximum incidence of meningitis was seen in the age group of 41 – 50 years. 46% were males and 54% were females.

Out of the 50 patients, 48% were found to have pyogenic meningitis and 52 % have found to be non-pyogenic meningitis. The CSF culture was positive for 20 patients and Gram staining was positive for about 11 patients. The organisms identified by culture were Pneumococci in 9 patients, H. Influenza in 4 patients and Group B Streptococci in 4 and staphylococcus in about 3 patients.

Among other cases 16 patients were differentiated as having viral meningitis / encephalitis. Patients were diagnosed to have viral aetiology based on the typical CSF findings of normal glucose, slightly elevated protein and lymphocytic pleocytosis and the negative gram stain, the absence of bacterial growth in CSF cultures.

Out of the 3 patients found to have TB meningitis, 2 patients had history of prolonged fever with chest X ray showing military mottling and MRI brain showing basal exudates. The third patient had history of pulmonary tuberculosis on ATT intensive phase and his MRI brain also showed exudates. One patient was diagnosed as a case of fungal meningitis. He was positive for HIV ELISA testing and hence CSF was sent for India ink staining and found positive. 6 patients could not be differentiated as to the type of meningitis.

Among patients with pyogenic patients, the mean age in years was 46. Out of the 24 patients, 11 were males and 13 were females. The mean CSF/serum glucose ratio was 0.3318 and mean CSF protein was 368.72 mg/dl and the mean CSF cell count was 1270 cells/ µl. 16 were found to have viral meningitis/encephalitis. The mean age in years was 35.5. Out of the 16patients, 10 were males and 6 were females. The mean CSF/serum glucose ratio was 0.265 and mean CSF protein was 352.13 mg/dl and the mean CSF cell count was 440 cells / µl.

There was no significant difference in age and incidence among the two groups, patients with pyogenic and non-pyogenic meningitis. There was a significant difference in CSF protein level and CSF/serum glucose ratio between the two groups. The difference in cell count between the two groups was not significant. The mean CSF CRP and Serum CRP values among patients differentiated as pyogenic and non-pyogenic were 1.3546, 0.1154 mg / dl and 59.67, 5.04 mg/dl respectively.

The significance of difference between these two values was analysed using the unpaired t test and it was found to be extremely significant with a P value < 0.0001. Hence we could infer that CSF CRP and serum CRP differed markedly in patients with pyogenic and non-pyogenic meningitis and both are useful markers for early identification of pyogenic meningitis and its prompt treatment. This result is like the results of studies on the significance of CSF CRP for differentiating pyogenic and non – pyogenic meningitis conducted by Vaishnavi et al69, kieslowskii et al68, Anil shindae etal67, Tankhiwale et al70. Studies conducted by Ali Hassan Abro et al65, Smith etal71, Genton et al72, Klien et al53 showed similar results using CSF Lactate.

Out of the 6 patients undifferentiated by conventional methods, 6 patients had no elevated CSF CRP or either serum CRP. These 6 patients were treated as pyogenic meningitis empirically but only four patients recovered and other patients one expired and one have post meningitis sequelae. Hence, out of the 24 patients differentiated as pyogenic by conventional methods, all the patients had elevated CSF CRP levels and serum CRP levels. Out of the 26 patients differentiated to be non-pyogenic (16 viral, 3 TB, 1 fungal) one of the patient had high CRP values which were treated with antibiotics and the patient recovered from the illness. Hence in this case it is established that the raised CRP can be taken significant for starting the antibiotics even if the patients had the viral picture.

Hence the Sensitivity CSF CRP for differentiating Pyogenic from non- pyogenic meningitis was 95.83 % and the Specificity was 96.15 %. The Predictive value of a positive test was 95.83 % and the predictive value of a negative test was 96.15 %.The diagnostic accuracy was found to be 96.00%

The two-sided P value using the Fischer's exact test was < 0.0001, considered extremely significant. This is in par with the EFNS guideline on the management of community-acquired bacterial meningitis published in the American Journal of Neurology 2008.

Among the 24 patients of pyogenic meningitis differentiated by conventional methods, the mean CSF CRP values of patients who recovered completely, who survived with sequelae, who expired were 0.7317, 0.6936, 0.6543 mg/dl respectively. The significance of means was analysed using the ANOVA and the P value was 0.0965, considered significant. Though the mean CSF CRP levels in patients who survived with sequelae and those who recovered did not differ much, there was a significant difference in mean CRP levels among patients who recovered completely and the other two categories. Hence it is concluded that CSF CRP can also be used as a marker of prognostication in pyogenic meningitis. Similar results were found out by Saint Nouirahk et al 85 in their study.

In summary though the CSF biomarkers like CSF CRP and serum CRP are not used routinely to aid in the differential diagnosis of meningitis, several studies have shown that these biomarkers are valuable in the differential diagnosis. Our study has also shown that CSF CRP and serum CRP are not only useful in the differential diagnosis but also as prognostication markers.

Our study had certain limitations. The sample size of our study was less. We could not use controls to show the normal CSF reference values of CRP as doing LP and drawing CSF from healthy people is not acceptable.

VII. Conclusion

1. The Cerebrospinal fluid level of CRP is elevated in acute pyogenic meningitis and hence it is useful to differentiate it from viral meningitis/encephalitis.
2. Therefore, the CRP assays in Cerebrospinal fluid is highly useful in the management aspects whenever the diagnosis is uncertain by conventional methods.
3. The Cerebrospinal fluid level of CRP is significantly elevated in patients who expired and in patients with post meningitis sequelae than in patients recovered uneventfully. So, it may be used as a marker of prognostication in acute pyogenic meningitis.
4. The Cerebrospinal fluid level of Lactate is significantly elevated in patients who expired than in patients with post meningitis sequelae and is even lower in patients who recovered uneventfully. Hence it predicts the clinical outcome better and it can be used as a marker of prognostication in acute pyogenic meningitis.

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