RISK FACTOR PROFILE AND OUTCOME ASSESSMENT OF PATIENTS PRESENTING WITH MENINGITIS: A PROSPECTIVE OBSERVATIONAL STUDY

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(GENERAL MEDICINE)

JULY, 2020 **DR. PANKAJ SUKHADIYA**

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DECLARATION

I hereby declare that the thesis titled **"RISK FACTOR PROFILE AND OUTCOME ASSESSMENT OF PATIENTS PRESENTING WITH MENINGITIS: A PROSPECTIVE OBSERVATIONAL STUDY"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled "**RISK FACTOR PROFILE AND OUTCOME ASSESSMENT OF PATIENTS PRESENTING WITH MENINGITIS: A PROSPECTIVE OBSERVATIONAL STUDY**" is the bonafide work of Dr. Pankaj Sukhadiya carried out under our guidance and supervision, in the Department of General Medicine, All India Institute of Medical Sciences, Jodhpur.

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The power of God is with you at all times; through the activities of mind, senses, breathing and emotions, and is constantly doing all the work using you as a mere instrument.

Shrimad Bhagavad Geeta

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Dedicated to Lord Krishna and my beloved family

INDEX

LIST OF ABBREVIATIONS

ABM	Acute Bacterial Meningitis
ADA	Adenosine Deaminase
AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
AIIMS	All India Institute of Medical Sciences
ALP	Alkaline Phosphatase
AM	Aseptic Meningitis
ANOVA	Analysis Of Variance
AUC	Area Under the Curve
BCE	Before Common Era
BMI	Basal Metabolic Index
BP	Blood Pressure
CAM	Community-Acquired Meningitis
CBNAAT	Cartridge- Based Nucleic Acid Amplification Test
CECT	Contrast-Enhanced Computed Tomography
CFR	Case Fatality Rate
CI	Confidence Interval
CM	Chronic Meningitis
CMV	Cytomegalovirus
CN	Cranial Nerve
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease
COX	Cyclooxygenase
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DIC	Disseminated Intravascular Coagulation

DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
ELISA	Enzyme-Linked Immunoassay
ESR	Erythrocyte Sedimentation Rate
GBD	Global Burden of Disease
GCS	Glasgow Coma Scale
GI	Gastrointestinal
GOS	Glasgow Outcome Score
HB	Haemoglobin
HBA1C	Glycated Hemoglobin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HSCRP	High Sensitivity C-Reactive Protein
HSV	Herpes Simplex Virus
i.e.,	Id Est (That Is)
ICP	Intracranial Pressure
ICT	Intracranial Tension
ICU	Intensive Care Unit
IL	Interleukin
INH	Isoniazid
INR	International Normalized Ratio
IPD	In Patient Department
IQR	Interquartile Range
IV	Intravenous
KFT	Kidney Function Test
KOH	Potassium Hydroxide
LCMV	Lymphocytic Choriomeningitis Virus
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LMICS	Low- And Middle-Income Countries

LP	Lumbar Puncture
MM	Meningococcal Meningitis
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
MSSA	Methicillin Sensitive *Staphylococcus aureus*
MRSA	Methicillin Resistant *Staphylococcus aureus*
MTBC	Mycobacterium Tuberculosis Complex
n	Number Of Samples
NAAT	Nucleic Acid-Based Amplification Technique
NPV	Negative Predictive Value
PAF	Platelet Activation Factor
PCR	Polymerase Chain Reaction
PGE2	Prostaglandin E2
PM	Pyogenic Meningitis
PPV	Positive Predictive Value
PT	Prothrombin Time
RBC	Red Blood Cells
RBG	Random Blood Glucose
RFT	Renal Function Test
RMSF	Rocky Mountain Spotted Fever
ROC	Receiver Operating characteristic curve
SAM	Subacute Meningitis
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
SGR	Serum Glucose Ratio
SLEV	Saint Louise Encephalitis Virus
SOFA	Sequential Organ Failure Assessment
SPSS	Statistical Package For The Social Sciences

TB	Tuberculosis
TBM	Tubercular Meningitis
TLC	Total Leukocyte Count
TLRS	Toll-Like Receptors
TNF	Tumor Necrosis Factor
UK	United Kingdom
USA	United States Of America
UTI	Urinary Tract Infection
VE	Viral Encephalitis
VM	Viral Meningitis
VZV	Varicella-Zoster Virus
WBC	White Blood Cells
WHO	World Health Organization
WNE	West Nile Encephalitis
WNV	West Nile Virus
ZN	Ziehl-Neelsen

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SUMMARY OF THE PROJECT

Background

Previous studies have mainly focused on the pediatric population, with studies on the adult population being limited. Hence, it is of particular importance to study the risk factors for poor outcomes of meningitis occurring in the adult population. Therefore, this study was done to explore the various clinical features with which patients present in a tertiary care setting, CSF abnormalities including biochemical analysis (protein, glucose, chloride ADA) followed by specific biomarkers analysis (CSF TNF-alpha and IL-8), cytological analysis and microbiological analysis), diagnostic scoring systems assessment anddetermine the risk factors for poor outcomes in patients presenting with meningitis.

Aims and Objectives

1. To determine the risk factors associated with poor outcomes (mortality and sequelae)in patients presenting with meningitis.
2. To describe the clinical, laboratory profile and outcomes of patients presenting with meningitis at All India Institute of Medical Sciences, Jodhpur.
3. To determine the utility of cerebrospinal fluid Tumor Necrosis Factor-Alpha (TNF-alpha) and Interlukin-8 (IL-8) levels as diagnostic or prognostic biomarkers for meningitis.
4. To determine the sensitivity and specificity of standard scoring systems in tubercularmeningitis in our settings.

Results

In this study, a total of 209 patients with clinical features of meningitis were enrolled who were ≥ 18 years of age. The mean age of 209 patients was 48.15 ± 20.48 years. Cases were most prevalent in younger age group of 18-25 years. Altered sensorium, fever &headache were most common symptoms with frequencies of 78%, 70% & 65% and classical triad of fever, headache & neck stiffness was present in 24% of patients(n=209). Tubercular meningoencephalitis is the most common etiology with a frequency of 36% (n=154) followed byviral meningoencephalitis 21% (n=154), dengue

encephalitis 18 % (n=154) & bacterial meningoencephalitis 12% (n=154). CSF analysis was done for 141 confirmed meningoencephalitis patients, out of which CSF abnormality was present in 133 patients (86%)(n=154). In proven TBM patients, ROC was constructed for CSF ADA levels, AUC was 0.89. The original 10 IU/L cut-off had 40% sensitivity and 97% specificity. Here wepropose a cut-off value of 05 IU/L with 83% specificity and 87% sensitivity. CSF TNF-alpha and IL-8 are not significant markers for diagnosis or predicting prognosis among meningoencephalitis patients (P-value>0.05). One hundred forty-nine (97%) of 154 meningoencephalitis patients in our study had brain imaging. CT Brain was done in 149 (97%), MRI Brain in 121 (79%) and 77% of patients had abnormal brain imaging. ROC was constructed for Thwaites' diagnostic score and Lancet consensus scoring system & it showed that the diagnostic utility of Thwaites' diagnostic score (AUC-0.75) and Lancet consensus scoring system (AUC-0.96) in TBM was significant (P-value <0.01). Proposed novel cut-off value of new cut-off value of (0) in Thwaites' score and 8 in the lancet score had sensitivity of 75% & a specificity of 79% and sensitivity of 92% & specificity of 96%, respectively. In our study, 30% of patients (N=209) died. Among these 62 individuals, 44 (29%) have proven meningoencephalitis (n=154). 13 individuals (46%) died from dengue encephalitis. 17 patients (30%) died from tubercular meningoencephalitis. It was found that low GCS (P- value-<0.01), sepsis (P-value-<0.05) and focal neurological deficit (P-value-<0.05) at the timeof admission and raised HsCRP (P-value-<0.05) levels are significant predictors of mortality in patients presenting with meningitis and low GCS (P-value-<0.01) and diagnosis of tubercular meningoencephalitis (P-value-<0.05), are significant predictors of disability and development of complications in patients presenting with meningitis.

Conclusion

Our observational study found that low GCS, sepsis, and focal neurological deficit at admission, raised HsCRP levels, and tubercular meningoencephalitis are predictors of mortality and disability and complications in meningitis patients. CSF ADA, chloride, and its ratio with serum value can distinguish TBM from other etiologies, and our work suggests 05 IU/L as a novel diagnostic criterion for ADA in TBM. CSF cytokines, TNF-alpha, and IL-8 are not diagnostic or prognostic biomarkers for meningoencephalitis. MRI is possibly superior to CT scan for diagnosing meningoencephalitis. Value of diagnostic scoring approaches such as Thwaites' diagnostic score and the Lancet

consensus scoring system for the diagnosis of TBM was evaluated and found to be substantial. Our analysis suggests a new cutoff value of (0) in Thwaites' score with a sensitivity of 75% and specificity of 79% and 8in Lancet score with a sensitivity of 92% and specificity of 96%.

INTRODUCTION

Meningitis refers to inflammation of the membranous covering of the brain and spinal cord with an associated abnormal leukocyte count in the cerebrospinal fluid (CSF). It is a clinical syndrome characterized by the classic triad of symptoms - fever, headache and neck stiffness (1,2). The causes are classified based on etiology into infectious (bacterial, viral, fungal and parasitic) and noninfectious (neoplastic, vasculitis, drug-induced, head trauma and neurosurgery) (3). There were 8.7 million reported cases of meningitis worldwide, with 379,000 subsequent deaths (4–6).

Several risk factors and predisposing conditions have been identified that increase susceptibility to meningitis. This includes elderly age, chronic diseases leading to immunosuppression (diabetes mellitus, chronic kidney disease, HIV/AIDS, malignancy), iatrogenic (post-splenectomy, head surgery and immunosuppressive therapy), addiction [alcoholism and smoking], anatomical defects, lack of vaccination and organ transplant recipient patients (7–9).

Elderly age, presence of pneumonia, otitis or sinusitis, a low Glasgow Coma Scale (GCS) score on admission, tachycardia, a positive blood culture, an elevated erythrocyte sedimentation rate, thrombocytopenia, a low cerebrospinal fluid white-cell count, delaying antimicrobial therapy, shock and ICU admission were found asmarkers for poor outcomes in bacterial meningitis (10–23). The advanced age, altered sensorium, low GCS score on admission, high APACHE II, modified Rankin Scale(mRS) & SOFA score, focal neurological deficit, disseminated tuberculosis infection, hyponatremia, presence of tubercle bacillus in CSF, meningeal enhancement on brain imaging and concomitant hydrocephalus were found as poor prognostic factors in tubercular meningitis (TBM) (24–37). Timely administration of anti-tubercular therapy and steroid therapy predicted a favorable outcome (27, 38, 39).

The most common types of meningitis include bacterial meningitis and tuberculous meningitis (TBM). One systematic review on the prevalence and etiology of meningitis among hospitalized patients in India showed that total 38 studies reported prevalence of meningitis and 21 studies reported data on etiology between year 1990 to 2020. The confirmed bacterial meningitis prevalence in the pediatric population (0-14 years) ranged between 0.5% and 61.8%. Only 7 studies reported the prevalence in patients of all age groups (0-75 years), ranging between 8.68% and 78.85% (40). The most

commonly identified bacterial organisms responsible for pyogenic meningitis are *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Listeria monocytogenes* and *Staphylococcus aureus.* Tuberculous meningitis is caused by Mycobacterium tuberculosis. The most common viral organisms implicated are Enterovirus and Herpes simplex virus. Aseptic meningitis is a blanket term used when an organism cannot be isolated from CSF. Fungal and parasitic meningitis usually affects immunodeficient people (1-3,9,40-43).

Meningitis is classified as acute and subacute based on duration of symptoms. Acute meningitis is defined as duration of illness less than 5 days, subacute meningitis (SAM) greater than 5 days and less than 30 days and chronic meningitis(CM) as greater than 30 days (44). CSF examination is considered gold standard in the diagnosis of meningitis (45, 46). Interpretation of etiology is based upon analysis of CSF appearance, opening pressure (cm CSF), white blood cell concentration (cells per μL), predominant cell type, protein (g/L), glucose (mg/dL or mmoL/L) and CSF glucose serum glucose ratio (43, 47–49). CSF neutrophilic pleocytosis, CSF glucose concentration <40 mg/dL (<2.22 mmol/L), a CSF to serum glucose ratio of ≤0.4 and protein concentration >100 mg/dL (>1000 mg/L) is characteristically present in pyogenic meningitis. (48, 49) CSF culture and isolation of bacteria is considered definitive diagnosis, however, Indian studies have reported low CSF culture positivity rates in meningitis. A positive CSFculture has been found to have a wide range from 6–50% in the cases discovered to be suffering from meningitis (3). CSF in viral meningitis patients reveals pleocytosis with lymphocytic and monocytic predominance, elevated protein concentration (50-100 mg/dl) and normal CSF glucose concentration (9).

CSF profile in tubercular meningitis (TBM) patients demonstrate pleocytosis with lymphocytic predominance, elevated protein concentration (>100 mg/dl) and low CSF glucose concentration (50, 51). The diagnostic methods used to confirm the diagnosis of tubercular meningitis (TBM) - light microscopy to demonstrate acid fast bacilli (AFB) in CSF smears, mycobacterial culture in CSF and nucleic acid amplification tests. But it is difficult to demonstrate AFB and CSF cultures are usually negative (52–55).

There is a need to differentiate the type of meningitis based on the clinical features and

the CSF biochemistry because of the urgency and different treatment strategiesinvolved in the management of each type of meningitis. CSF cytology, CSF protein concentrations and CSF/serum glucose ratio were found to show no significant differences in TBM and pyogenic meningitis. Several CSF biomarkers have been explored for early diagnosis and differentiation of type meningitis. CSF adenosine deaminase (ADA) levels are significantly high in Tubercular meningitis (TBM) patients in comparison to other etiologies. CSF - ADA level of >10 U/L is considered as diagnostic hallmark in TBM (55–62).

Several studies have indicated that CSF TNF alfa levels can be utilized to distinguish bacterial meningitis from non-bacterial meningitis. High CSF TNF-alfa levels are associated with adverse outcomes (63–65). CSF Interlukin-8 Levels havealso been used to differentiate pyogenic meningitis from aseptic meningitis at cut off value of 1.685 ng/dL (66). CSF TNF-alfa and IL-8 levels correlated with CSF pleocytosis, protein and glucose concentration in a prior study (65).

Apart from single biomarker several scoring systems have been applied for early differentiation of TBM from pyogenic meningitis. Thwaites' diagnostic score is used to differentiate TBM from pyogenic meningitis. The Thwaites' system has 5 parameters including age, duration of illness, total white blood cell count, CSF cellcount and the CSF neutrophilic percent, with a maximum score of 13. The patientis classified as Possible TBM with a total score of 4 or less, and with possible bacterial meningitis if the score is greater than 4 (67). The Lancet consensus scoring system has 20 parameters, which are divided in 4 categories (clinical, CSF,CNS imaging and evidence of TB elsewhere) with a maximum score of 20. Diagnosis of TBM is either definite, probable, possible or no TBM based on assigned score (68).

Previous studies have mainly focused on the pediatric population, with studies on the adult population being limited. Hence, it is of particular importance to study the risk factors for poor outcomes of meningitis occurring in adult population (40).Therefore, this study was done to explore the various clinical features with which patients present in a tertiary care setting, CSF abnormalities including biochemical analysis (protein, glucose, chloride ADA) followed by special biomarkers analysis (CSF TNF-alpha and IL-8) , cytological analysis and microbiological analysis), diagnostic scoring systems assessment and determinethe risk factors for poor outcomes in patients presenting with meningitis.

REVIEW OF LITERATURE

History of Meningitis

Research was done on historical literatures as well as reviews of them. A detailed assessment of the historical literature was carried out by Kenneth L. Tyler, Eelco F. M. Wijdicks, P. N. Tandon, and Olivier Walusinski. The review focused on developing concepts surrounding the classification of meningitis, its clinical aspects, pathology, and management (69–72). The Carlsberg Glyptothek in Copenhagen has an Egyptian burial stele from the 18th dynasty (1580-1350 BCE) that portrays one of the earliest and most well-known renderings of central nervous system (CNS) illness symptoms. The Hippocratic literature describes several cases of severe headache, febrile sickness, and mental status changes, which today would be diagnosed as encephalitis or meningitis (73). Due to the relative stereotypy of its three principal clinical symptoms — headache, fever, and altered sensorium — bacterial meningitis is likely the "archetype" of all CNS infections and one of the simplest CNS infectious diseases to trace through historical records.

Thomas Willis (1621–1675), an English physician, is regarded as a significant figure in the history of neurology and the neurosciences. Willis was well aware, based on his clinical observations, that many individuals with "phrensy" never developed hyperactive features and clinically progressed into a hypoactive condition of lethargy or coma that might result in death.

Robert Whytt (1714–1766) and his contemporaries coined the terms "acute hydrocephalus (hydrocephalus acuta)" and "dropsy in the brain" in the 18th century. Whytt first detailed this condition-*Although Hippocrates and Celsus had described similar situations, no one had "provided us with the signs by which we may recognize dropsy of the brain's ventricles from other illnesses affecting that organ"*(74). He fixed this by dividing cerebral dropsy symptoms into three stages. *The first stage began 4-6 weeks before death, when "they [the children] lose their appetite and spirits; they appear pale and fall away in flesh; they always have a quick pulse and a degree of fever"*(74). *Continuing, "They get a headache or forehead pain. Candlelight irritates them." The pulse slowed and became erratic two to three weeks before death in the second stage. The initial stage's symptoms remained, making kids lethargic. He detailed*

extraocular paralysis and oculomotor nerve palsies. The third phase made kids drowsy and comatose.

Another contemporary, John Fothergill (1712–1780), confirmed with Whytt's report, noting that patients complained of *"great, deep-seated pain in the head, extending from temple to temple, and the patient is sometimes quite ill, crying alternately, "Oh, my head!"* John Cheyne(1777–1836), a physician from Edinburgh, dedicated his 1808 work *Hydrocephalus Acutus orDropsy of the Brain* to Charles Bell. His instances resembled those recorded under the label *"apoplexia hydrocephalica"* by William Cullen, a prominent member of the Edinburgh school(1710–1780). In contrast to Whytt and Fothergill, he believed that the extra fluid in the brain was a consequence of an antecedent event, which he hypothesized was disturbed vascular circulation. Abercrombie (1828) stated -*Meningitis indicates inflammation of the arachnoid, pia mater or both as opposed to inflammation of the dura mater, he says in the introductionto this section.* Although Herpin most likely coined the term meningitis in 1803, it did not reach popular usage until Abercrombie's widely distributed research. Louis Odier (1748– 1814) of Geneva is credited for recognizing the relevance of meningeal suppuration inmeningitis patients, but the term "meningitis" was not often used to describe this illness until much later (75).

Louis Guersent (1777–1848) was able to propose a classification of meningitis that began to reflect modern views of the disease in 1839, separating acute meningitis, chronic meningitis, meningitis due to trauma, epidemic meningitis and a subset of cases associated with mental illness (likely including cases of the syndrome of syphilitic general paresis described by Antoine Bayle [1799–1858] in 1822). *Tuberculous meningitis has a distinct preliminary phase that ends in a sudden onset of symptoms and tubercles in the meninges and other organs. Non-tuberculous meningitis. A.: Acute form, epidemically or without reason after head injuries. B.: Chronic, mental illness or not* (75).

Gaspard Vieusseux (1746–1814), a Genevan physician, wrote the first comprehensive clinicaldescription of epidemic meningitis, which was likely caused by meningococcal infection. Twenty years after the discovery of meningococcal meningitis by Gaspard Vieusseux, the French physician Louis Senn (1799–1873) recognized a more chronic type of infantile basilarmeningitis.

Although Robert Whytt in England had recorded instances that most certainly constituted tuberculous meningitis in 1768, the examples described by Senn are conclusive. At autopsy, itwas discovered that some of the affected infants had lung cavitation, miliary illness, or even tubercles in the brain that are diagnostic of tuberculosis. Even more astonishing is the fact that Senn's paper was published in the same year as Pierre Louis' (1787–1872) fundamental work on pulmonary TB.

Until the end of the 19th century, meningitis was diagnosed based only on clinical symptoms,with confirmation required inspection of the brain and meninges after death. The introduction of cerebrospinal fluid (CSF) testing as a routine neurodiagnostic tool greatly expanded the ability to conclusively detect meningitis premortem and further subcategorize variants. James Leonard Corning (1855–1923) was the first to study spinal fluid in 1885, which led to Heinrich Quincke's (1842–1903) invention of the present lumbar puncture technique. InDecember 1890, he performed his first lumbar puncture on a one-year-and-nine-month-old boy suspected of suffering from tuberculous meningitis. Quincke was the first to notice the existence of pleocytosis and hypoglycorrhachia in CSF acquired by lumbar puncture, as well as to identify bacteria in CSF taken from patients with purulent meningitis.

The association of bacterial meningitis with a low CSF glucose level and pleocytosis was established in early reports by Ludwig Lichtheim (1845–1928) (Lichtheim, 1893), Georges Deniges (1859–1951), Jean Sabrazes (1867–1940) (Deniges and Sabrazes, 1896), and Arnold Netter (1855–1936) (Netter, 1898) and subsequently confirmed by William Mestrezat (1883).Mestrezat proposed that hypoglycorrhac most likely resulted from both the consumption of glucose by bacteria in the cerebrospinal fluid (CSF) and its degradation by the associated cellular exudates, an opinion that predominated until 20th-century research indicated that interference with the action of glucose transporters was the more likely cause.

Merritt and Fremont-Smith discovered that the cerebrospinal fluid alterations are largely the same regardless of the organism, consisting mostly of an increase in pressure, a pleocytosis,an increase in protein and a drop in the sugar and chloride contents. The presence of a low sugar content in a purulent fluid is a significant indicator of bacterial meningitis, and organisms are virtually always found on smear or culture. The majority of instances of community-acquired acute bacterial meningitis

are caused by infection with *Neisseria meningitidis (meningococcus), Streptococcus pneumoniae (pneumococcus) or Listeria monocytogenes*, according to several recent studies.Prior to the development of the Hibvaccine, *Haemophilus influenzae* was a significant cause of bacterial meningitis(69).In 1887, Anton Weichselbaum (1845–1920) isolated *Neisseria meningitidis* (then known as Diplococcus *intracellularis meningitides of Weichselbaum*) from the cerebrospinal fluid (CSF) of cerebrospinal meningitis patients.

Neck stiffness (nuchal rigidity), one of the distinguishing features of bacterial meningitis,may have been detected by Hippocratic writers in the fifth century BCE, characterised by Vesalius and artistically depicted by William Blake. Despite the fact that many clinical aspects of meningitis had been accurately described by the middle of the 19th century, thekey eponymic indicators (Kernig's and Brudzinski's signs) were not documented until the end of the century.

Kernig stated – "*In cases of meningitis, I have seen for a number of years a symptom that appears to be underrecognized but is, in my opinion, of tremendous utility. I am referring about flexion contracture of the legs or, on occasion, the arms, which is only visible when the patient sits up... If one attempts to extend the patient's knees while sat on the edge of the bed with his or her legs dangling, he or she will only be able to attain an angle of approximately degrees."*

Large outbreaks of meningococcal meningitis in military encampments during World War I, as well as later epidemics in Detroit, Milwaukee, and Indianapolis between 1928 and 1931, all occurred in the early 20th century. These epidemics provided an abundance of clinical and pathological material for study and served as a major impetus for early immunotherapy trials. In the 1930s, Arnold Rich (1893–1968) and Howard McCordock (1895–1938) conducted pivotal pathological studies on tuberculous meningitis, which led to the realisation that the disease typically resulted from the release of mycobacteria into the subarachnoid space from alocal caseous focus in the brain or meninges.

Georg Jochmann (1874–1915) in Germany and Simon Flexner (1863–1946) in the United States treated meningococcal meningitis with horse antisera as the first effective specialized therapy for bacterial meningitis. Flexner's account of the effective use of serum therapy in 1300 instances of epidemic meningitis, which reduced mortality to

31% for this hitherto mainly deadly condition, is a milestone in the history of medicine. However, the results of serum therapy for *Hemophilus influenza* meningitis were far less impressive than for meningococcal meningitis, with a mortality rate of 85 percent in treated children compared to 98 percent in untreated children.

Antibiotics, beginning with the introduction of sulfonamides, ultimately superseded serum therapy for bacterial meningitis. Schwentker et al. stated low dose penicillin treatment for meningococcal meningitis was less effective than treatment with sulfonamides and its derivatives remained the treatment of choice. The emergence of resistant meningococci forced the use of high-dose penicillin and subsequently, third-generation cephalosporin therapy.

The efficacy of antibiotics in the prevention of meningococcal meningitis was first demonstrated with sulfadiazine in 1943. Although the earliest results in the treatment of pneumococcal meningitis with the low doses of penicillin initially available were inferior to those of sulfanilamide, the availability of higher doses of penicillin and its derivatives becamethe treatment of choice. As pneumococcal resistance to penicillin and cephalosporins became more prevalent, the current treatment for pneumococcal meningitis has evolved to incorporatevancomycin to cover these resistant strains.

Cooke et al. reported for the first time after WWII that streptomycin was effective in treating tuberculous meningitis in a one-year-old newborn. Isoniazid (INH) became the standard TB treatment in 1952. Cortisone therapy of tuberculous meningitis patients was shown in the early 1950s to resolve CSF pleocytosis and raised protein concentration more rapidly. Bacterial meningitis is one of the great archetypes of central nervous system (CNS) infectionsand tracing its historical development provides context for understanding the historical development of other CNS bacterial infections (e.g., abscess, empyema) and sets the stage for the later identification of "aseptic meningitis," in which viruses rather than bacteria cause the infection. Infections affecting the subarachnoid space (viral meningitis) were distinguished from those affecting the brain parenchyma with the identification of viruses as a cause of CNS disease (viral encephalitis).

MENINGITIS

Definition

Meningitis is a condition characterized by inflammation of the meninges, the membranes thatsurround the brain and spinal cord. An aberrant laboratory profile of the cerebrospinal fluid is one of the defining characteristics of meningitis (2). Meningitis is considered to be a major threat to public health on a global scale due to the fact that it can affect those who have recovered from the disease and is associated with dangerous complications. Meningitisepidemics are seen as a global threat requiring immediate attention (76).

Epidemiology

According to the findings of the Global Burden of Disease (GBD) Study conducted in 2016, the number of incident cases of meningitis in the world has increased from 2.50 million (2.19–2.91) in the year 1990 to 2.82 million (2.46–3.31) in the year 2016 (76,77). Each year, bacterial meningitis affects more than one million and two hundred fifty thousand people all over the world (78). As a result of the significantly increased disease burden, resource-poor countries may show an incidence of meningitis that is even ten times higher than that of resource-rich countries (79,80). The World Health Organization estimates that approximately 290,000 people lost their lives to meningitis in 2015 and this number is expected to rise in thecoming years (76). Without treatment, the mortality rate associated with meningitis can reach as high as 70 percent; this number varies greatly depending on factors such as location, country, age, and the causative agent (78).

In spite of a decrease of 21% from 1990 to 2016 in the overall mortality rate that was caused by meningitis, the overall burden of meningitis is still very high. In addition to a high mortality rate, infections with the potential to cause life-threatening complications, such as bacterial meningitis, can leave survivors with a significant degree of disability (81–83). One out of every five people who survive bacterial meningitis may be left with permanent neurological sequelae and prolonged neurological sequelae. These can include cranial nerve palsies, hydrocephalus, seizures, hemiparesis, and impaired vision and hearing. It's possible that this will have a negative effect on the survivors' overall quality of life (78,81). Meningitisis responsible for 5.6 million disability-adjusted life years around the world, with 98% of cases occurring in

low-income and middle-income countries (83).

Canna J. Ghia and Gautam S. Rambhad (40) did a systematic review on the prevalence of meningitis among hospitalized patients in India. A total of 38 of 51 studies reported meningitis prevalence in India. These studies included individuals with pyogenic meningitis, sick or hospitalized patients with tuberculosis, acute febrile encephalopathy syndrome, septicemia or invasive pneumococcal disease and patients with comorbidities. Eighteen studies carried out in different parts of India,reported their findings exclusively on the pediatric population. Seven studies were conducted in northern India, four in the southern region two in the western region and four in several cities/states. One study was carried out innorth-east India. The study participants were 1–14 years old. Two studies found 5.41% and 10% of neonates/newborns had hospital-acquired meningitis. Bacterial meningitis prevalence ranged from 0.5% (15 instances out of 2904 research participants) to 35% in several states (78 cases out of 226 study participants). Bacterial meningitis prevalence in north India ranges from 3% (four cases out of 147 research participants) to 21.81% (484 cases out of 2219). The prevalence of tubercular meningitis in pediatric patients was reported in two investigations, with rates of 7.9% (12 cases out of 151 patients with acute febrile encephalopathy syndrome) and 20.97% (13 cases out of 62 patients with tuberculosis), respectively. Meningitis prevalence was 12%–20.25% in the west and 8.28%–38% in the south. Pneumococcal meningitis was found in 21.81%, 35%, and 61.8% of IPD patients from southern, multiple states, and north-east India, respectively.

Seven studies reviewed all-age patient data. In contrast to the vast majority of studies that have reported the incidence of bacterial meningitis, Yerramilli et al. (3) in an observational analysis, discovered a significant prevalence of aseptic/viral meningitis (39%). Meningitis was found in 34.3% of the patients who enrolled in a prospective surveillance research that was carried out in 1037 adult individuals who were thought to be suffering from an invasive bacterial infection. Meningitis was shown to be 24.3% prevalent among 408 persons with IPDin a prospective, laboratory-based research.

Yerramili A et al. carried out an observational study among 147 patients. In this study, male patients had a greater incidence of meningitis. Meningitis cases were most prevalent in those between the ages of 21 and 40 years. Their research cohort had a mean age of 50±15 years.

Dodd et al did a comprehensive review on global burden of tuberculous meningitis in adults. In 2019, 164,000 persons acquired TBM, 118,000 of whom were diagnosed and treated (72%). 39% of incident TBM cases were female, totaling 63,200 (95% CI: 35,300-91,000), and 37,800 (95% CI: 19,700-55,900) incident TBM cases were HIV positive. The 25-34 and 35-44 age categories had the highest incidence: 31,900 (95% CI; 18,800–45,000) and 32,700 (95%; 19,600–45,900), respectively. However, significant incidence was observed across all age groups, with the population over 65 years old having the highest incidence rate (22,400; 95% confidence interval [CI], 12,000–32,900). The WHO region with the highest incidence of incident TBM was Southeast Asia with 65,900 (95% CI; 34,600–97,100), followed by Africa with 48,100 (95%; 41,400–54,800).

Although the exact prevalence of CNS TB in India is unknown, it is estimated to account for 1% of all TB cases or about 17 000 cases in India in 2014. (WHO, 2015). The most prevalent form of CNS TB, TB meningitis, has a significant case fatality rate. All types of CNS TB can cause long-term complications in survivors.

Etiology of Meningitis

Systematic review of Canna J. Ghia and Gautam S. Rambhad, also addressed frequency of etiology among meningitis patients. Twenty-one of the 51 included studies provided information on the etiology of meningitis. These studies involved mixed patient populations: (a) Pyogenic meningitis and (b) meningitis in individuals with fever, TB hydrocephalus or respiratory compromise. Out of 21 total studies there were a total of 12 studies that presented data on the pediatric population, however only 8 articles reported data on patients of all ages, including newborns, older children, adolescents, and adults. In these studies, *S. pneumoniae* was found to be the most prevalent cause of meningitis. The studies were conducted in various parts of India and the incidence of *S. pneumoniae* infection ranged from 12% to82.9% in children and from 4% to 61.8% in patients of all age groups. Eight of the twelve studies conducted on the pediatric population identified *S. pneumoniae* as the causativeorganism. In nine studies with a frequency ranging from 4.5% to 70%, the second most prevalent causal bacteria in the pediatric population was *H. influenza*, mostly type b. In 56% of cases of aseptic meningitis in a study involving 25 children, enterovirus was shown to be the causal

agent. In one study, group B Streptococcus was identified as the causal pathogen in more than 49 percent of children aged one to 59 months. Sixty-seven percent of the children in a retrospective analysis of 100 with group A meningococcal infection developed meningococcal meningitis.

In studies reporting data on patients belonging to all age groups, *Staphylococcus aureus* (seven studies; frequency range: 1.8–41.38%), *N. meningitidis* (five studies; frequency range: 1–27.59%) were found to be the most common causes of bacterial meningitis, other than *S. pneumoniae*. Other causal organisms included *Klebsiella pneumoniae* (five studies; frequencyrange of 5.5–20.7%), *Escherichia coli* (five studies; frequency range of 4.76–27.08%), *H. influenzae* (four studies; frequency range of 1.8-19.4%).

Yerramilli A et al discovered that the most prevalent kind of meningitis that was found intheir study was viral or aseptic meningitis, followed by the pyogenic and tuberculous meningitis (TBM). There were much fewer incidences of fungal meningitis and other formsof meningitis as well, such as chemical meningitis or meningitis caused by malignancy.

Etiology of meningitis can be broadly classified into a) Infectious b) Non-infectious

Infectious -

1. Bacterial
2. Viral
3. Tubercular
4. Fungal
5. Parasitic

Non-infectious -

1. Neoplastic & Paraneoplastic
2. Autoimmune
3. Traumatic
4. Iatrogenic

Bacterial meningitis can be contracted either in the community or in a healthcare

setting. In the case of community-acquired bacterial meningitis, the condition is caused by the invasion of bacteria into the meninges, either as a direct extension of a local infection oras a result of bacteremia. The most prevalent bacterial cause changes with age. *Neisseria meningitidis* is still the most common cause of meningitis in people aged 11 to 17 years old. *Streptococcus pneumoniae* is the most common cause of meningitis in all other age groups. *Group B Streptococcus* is common in infants younger than two months of age. Other, less prevalent pathogens include *Listeria monocytogenes* and gram-negative bacteria such as *Escherichia coli, Klebsiella, Enterobacter* and *Pseudomonas aeruginosa*. *Hemophilus influenzae* is not completely eradicated from the population of those whohave not been immunized against it. In hospitals, *S. pneumonia, Staphylococcus aureus, Staphylococcus albus* and gram-negative bacilli are the most common pathogens that lead to nosocomial infections (2).

Enteroviruses, particularly those belonging to the Coxsackie or Echovirus family, are the agents that are responsible for the majority of cases of viral meningitis in people of all ages. Parechoviruses are also common in children. Herpes simplex virus types 1 and 2, varicella-zoster virus and human herpesvirus 6 are examples of herpesviruses that can cause meningitis. Cytomegalovirus, Epstein-Barr virus, Adenovirus, lymphocytic choriomeningitis virus (LCMV), influenza, parainfluenza and mumps are some of the additional viruses that can cause this condition. West Nile virus (WNV), Zika virus, chikungunya virus, dengue virus, LaCross virus, Saint Louise encephalitis virus, Powassan virus, and eastern equine encephalitis virus are all examples of arboviruses that have the potential to cause viral meningitis (84–87).

Mycobacterium tuberculosis is the organism responsible for tuberculous meningitis (TBM). Robert Whytt is credited with providing the first description of TBM inhis monograph titled Observations on Dropsy in the Brain, which was published in 1768. TBM was first characterised as a separate clinical entity in the year 1836 and in 1882, Robert Koch established that M. tuberculosis was the causative agent of tuberculosis.

Fungal pathogens that affect the CNS include yeasts, dimorphic fungi, and moulds. The predominant clinical condition linked with a fungal infection depends on the fungus's morphology, but these syndromes sometimes overlap. Leptomeningitis is caused by small pseudomycetes (yeasts) like cryptococcus, blastomycosis, histoplasmosis, coccidiomycosis, and sporotrichosis. Large pseudomycetes like candida cause brain

abscesses or granulomas. Aspergillosis and zygomycosis, which produce huge branched hyphae, can infiltrate blood vessels and orbits, sinuses and cranial bone producing stroke. Fungi seed the CNS after being inhaled as an aerosol and infecting the lungs and lymph nodes. Inhalation can infect the paranasal sinuses. Hematogenous dissemination from the lungs causes systemic infection and CNS involvement. The CNS may be directly affected by paranasal sinuses, orbits or other facial sites. Cryptoccocus causes 70% of fungal meningitis in the US and worldwide, followed by coccidoimycosis (16.4%), candidiasis (7.6%), and histoplasmosis (6%). Candida is the most prevalent histologically proven brain fungal infection in several autopsy samples and may go undetected.

These organisms infect patients based on their geographic location and immune status. HIV/AIDS, organ transplantation, chemotherapy or corticosteroids, and hematologic malignancy are the main risk factors for fungal infection.

Pathophysiology

The majority of meningitis cases are brought on by an infectious pathogen that has been colonized or developed a localized infection elsewhere within the host. The skin, the nasopharynx, the respiratory tract, the gastrointestinal (GI) tract and the genitourinary tract are all potential locations for colonization or infection. An infectious agent (i.e., a bacterium, virus, fungus, or parasite) can enter the CNS and result in meningeal illness through any of the three main paths listed below:

1. Bloodstream infection (such as bacteremia, viremia, fungemia, or parasitemia) followed byhematogenous seeding of the central nervous system.
2. A retrograde neural route, such as the olfactory and peripheral nerves (eg, Naegleria fowlerior Gnathostoma spinigerum).
3. Contiguous direct spread (eg, sinusitis, otitis media, congenital malformations, trauma ordirect inoculation during intracranial manipulation)

A frequent cause is local extension from an adjacent extra cerebral infection (such as sinusitis, mastoiditis, or otitis media). The following are potential routes by which infections could go from the middle ear to the meninges:

The following are potential routes by which infections could go from the middle ear to

the meninges:

1. The bloodstream
2. Existing tissue planes (e.g. posterior fossa)
3. Temporal fractures of the bones
4. The labyrinths' round or oval window membranes

The meninges barrier between the bloodstream and the brain serves as the brain's natural defense against the body's immune system. The blood-brain barrier, however, can be damaged in cases of meningitis; once bacteria or other organisms have entered the brain, they are mostly shielded from the immune system and can propagate.

When the body attempts to combat an infection, the condition can deteriorate; blood vessels become permeable, allowing fluid, white blood cells and other inflammatory factors to enter the meninges and brain. In turn, this process results in brain swelling and may ultimately lead to decreased blood flow to certain regions of the brain, aggravating the infection symptoms. Depending on the severity of bacterial meningitis, inflammation may be limited to the subarachnoid area. In less severe cases, the pial barrier stays intact and the underlyingparenchyma is unaffected. In more severe cases of bacterial meningitis, the pial barrier is compromised and the underlying parenchyma is penetrated by the inflammation reaction. Consequently, bacterial meningitis may result in extensive cortical degeneration, especially if neglected. Bacterial meningitis spreads through replicating bacteria, inflammatory cells, cytokine-induced membrane transport disturbances, and enhanced vascular and membrane permeability. In this condition, these processes cause CSF cell count, pH, lactate, protein and glucose alterations (88).

Exudates penetrate deeply into the basal cisterns and throughout the CSF, causing the following symptoms:

1. Cranial nerve damage (e.g., cranial nerve VIII, with resultant hearing loss)
2. CSF pathway blockage (causing obstructive hydrocephalus)
3. Vasculitis and thrombophlebitis induction (causing local brain ischemia)

Signs, symptoms and complications of tuberculous meningitis (TBM) are the outcomes

of an immunologically directed inflammatory response. Droplet inhalation infects alveolar macrophages with Mycobacterium tuberculosis. Localized infection in the lungs spreads to regional lymph nodes, leading to a primary complex. During this phase, a transient but considerable bacteremia might spread bacilli to other organs. The bacilli may travel to the central nervous system (CNS) and results in forms of CNS Tuberculosis- tuberculous meningitis, intracranial tuberculoma or spinal tuberculous arachnoiditis. If miliary TB develops, there is severe bacteremia, which increases CNS spread. Rich foci of metastatic caseous lesions can arise in the brain from bacilli. Rich foci grow and rupture into the subarachnoid space, causing meningitis. Tubercles rupturing into the subarachnoid space produce meningitis, while those deeper in the brain parenchyma or spinal cord generate tuberculomas or abscesses. Rich foci do not rupture into the ventricle like abscesses or tuberculomas. A thick gelatinous exudate may infiltrate cortical or meningeal blood vessels, causing irritation, blockage or infarction. TBM, unlike most forms of bacterial meningitis, tends to occur at the base of the skull (basal meningitis), which explains the widespread impairment of cranial nerves (particularly III, VI, and VII) and obstructive hydrocephalus dueto congestion of basilar cisterns. Adhesion development, obliterative vasculitis, and encephalitis or myelitis cause subsequent neurological disease (50).

Viruses may reach the meninges via the circulation, retrograde spreading from nerve endings or reactivation from a dormant state in the nervous system. When a virus enters the central nervous system (CNS) and spreads across the subarachnoid space, it triggers an inflammatory response that results in meningitis. Encephalitis occurs when the brain parenchyma is inflamed and is associated with a worse prognosis Enteroviruses reproduce outside of the CNS and enter the CNS by hematogenous dissemination (1).

Clinical Features

Community-acquired meningitis (CAM) is acute or subacute if symptoms last more than five days. Subacute and chronic presentations are more common in tuberculous and fungal meningitis, while acute presentations are more likely to be bacterial or viral. Acute bacterial meningitis (ABM) is associated with significant mortality and neurologic sequelae, requiring immediate antibiotic and corticosteroid treatment, especially in pneumococcal cases (44).

Chronic meningitis is defined as a set of signs and symptoms of meningeal irritation coupled with CSF pleocytosis that lasts more than 30 days. There are numerous infectious and non- infectious etiologies that can lead to chronic meningitis.

Only around 44% of adults with bacterial meningitis have the classical triad of fever, headache, and neck stiffness. These symptoms might appear over a period of several hours or up to two days. Van de Beek et al observed that 95% of people with bacterial meningitis exhibited two of the following four symptoms: fever, headache, stiff neck, and impaired mental status in a large prospective analysis of 696 cases (13). Other symptoms include nausea, vomiting, seizures, photophobia, drowsiness and eventually coma.

Yerramilli et al. discovered in their study that 26% of the study population had the typical triad of headache with fever, stiff neck, and disturbed mental state. The majority (83%) of the patients had at least two of the four symptoms—headache, stiff neck, fever, and altered senses—present. Apart from headache, which was the primary symptom in nearly half of the enrolled individuals, other frequent symptoms included seizures, vomiting and sleepiness.

Certain groups may present differently. Elderly patients, particularly those with underlying comorbidities (e.g., diabetes, renal and hepatic illness), may exhibit lethargy and the absence of meningeal symptoms.

Viral meningitis patients may have previous systemic symptoms (e.g., myalgia, fatigue, or anorexia). Mumps-related meningitis usually causes fever, vomiting, and headache. Parotitis, which causes salivary gland swelling in 50% of patients, resolves in 7–10 days. Fever and meningeal inflammation may be mild in immunosuppressed people.

Meningitis' typical triad includes fever, nuchal stiffness, and altered mental status, but most patients only suffer from headache. Mood changes can include irritation, somnolence, psychosis, and coma. In most cases, no focal neurologic abnormalities are found. The majority of patients with bacterial meningitis also experience stiff necks, although meningeal symptoms are not sensitive enough to diagnose meningitis. High blood pressure and bradycardia may also occur.

In otherwise healthy, non-elderly patients, acute bacterial meningitis is clinically evident. In contrast, the majority of subacute bacterial meningitis patients present diagnostic difficulties. A pulmonary or otitis media coinfection may be found on systemic examination. Extracranialinfections such sinusitis, otitis media, mastoiditis, pneumonia, and UTI may be present. Endotoxic shock with vascular collapse characterises severe *N. meningitidis* (meningococcal) infection.

All causative agents of viral meningitis have similar physical characteristics, but some have specific clinical symptoms that help narrow the diagnosis. The following suggest enteroviral infection: Exanthemas, pericarditis, myocarditis, conjunctivitis, pleurodynia, herpangina, and hand-foot-and-mouth disease symptoms.

Non blanching petechiae and cutaneous haemorrhages may occur in *N meningitides* meningitis. A petechial purpuric rash may be caused by enteroviral illness, RMSF, West Nile encephalitis, bacterial endocarditis with meningeal involvement (50%), *H.influenzae, S.pneumoniae*, or *S. aureus*. Arthritis is more common in meningococcal and *M. pneumoniae* infections than in other bacteria. Movement problems (tremor, myoclonus, Parkinsonism) andacute flaccid paralysis are common in West Nile meningoencephalitis patients.

In 10% to 20% of patients, focal neurologic symptoms include specific cranial nerve abnormalities (mostly of cranial nerves III, IV, VI, and VII). These are caused by elevated intracranial pressure (ICP) or the presence of exudates surrounding nerve roots. In 10% to 20% of patients, focal cerebral symptoms may occur due to ischemia caused by vascular inflammation and thrombosis. Papilledema is a rare feature (1% of patients) that also implies elevated ICP, but it is neither sensitive nor specific: it occurs in only one-third of meningitis patients with elevated ICP and is also present in brain abscess and other illnesses.

Clinicians have relied on meningeal symptoms (nuchal rigidity, Kernig sign, and Brudzinski sign) for more than a century to evaluate patients with suspected meningitis and determine who should receive a lumbar puncture (LP). A prospective analysis of 297 individuals with suspected meningitis revealed, however, that these indicators have very low sensitivities: 5% for the Kernig sign, 5% for the Brudzinski sign, and 30% for nuchal rigidity. Therefore, the absence of meningeal symptoms should not delay the lumbar puncture.

Systemic signs on physical examination may indicate meningitis etiology. A morbilliform rash accompanied by pharyngitis and lymphadenopathy may indicate a viral cause (e.g., Epstein-Barr virus [EBV], cytomegalovirus [CMV], adenovirus, or HIV). Rapid transformation of macules and petechiae into purpura suggests meningococcal disease (withor without meningitis). Vesicular lesions in a dermatomal distribution suggest VZV. Genital vesicles are indicative of HSV-2 meningitis.

Sinusitis or otitis indicates direct invasion into the meninges, typically due to *S. pneumoniae* or, less frequently, *H. influenzae*. Rhinorrhea and otorrhea are indicative of a cerebrospinal fluid (CSF) leak from a basilar skull fracture, with *S. pneumoniae* being the most prevalent cause of meningitis.

Hepatosplenomegaly and lymphadenopathy indicate a systemic disease, such as viral (e.g., mononucleosis-like syndrome in EBV, CMV, and HIV) and fungal (e.g., candidiasis) infections (e.g., disseminated histoplasmosis). The presence of a cardiac murmur is indicative of infectious endocarditis with subsequent bacterial inoculation of the meninges. Due to fulminant meningococcemia, the Waterhouse-Friderichsen syndrome can cause massive petechial/bullous haemorrhages in the skin and mucous membranes, DIC, and septic shock (13,45,49).

Risk Factors associated with diagnosis and prognosis

Yerramilli et al. observed that in contrast to the other risk factors, it was shown that individuals with diabetes mellitus and those who had undergone a neurosurgical surgery, particularly a ventriculoperitoneal shunt, had a considerably greater tendency for developing meningitis (P-value <0.0001).

Multiple studies have evaluated risk factors associated with poor outcomes in bacterial meningoencephalitis. Hypotension, altered mental status and seizures at presentation were found to be independent risk factors associated with poor outcomes in the study carried out byAronin et al. A prognostic model was created using these baseline clinical features. Katenbauer S et al. found factors associated with bad outcome using Glasgow outcome score (GOS). Chronic debilitating illnesses, low Glasgow Coma Scale Score and localized neurological impairments on admission, low CSF leucocyte counts, pneumonia, bacteremia and meningitis-related intracranial and systemic problems were linked with a poor outcome (GOS /= 4). Age > or =60 was related with a greater mortality rate, although the GOS of the survivors was equivalent to that of the younger survivors. Vibha D et al. discovered that patients with advanced age, female gender, illness duration >1 day, and rural domicile demonstrated a significant association with mortality. At the time of admission, patients witha lower Glasgow Coma Scale (GCS) or hypotension had a decreased survival rate. Diabetes, papilledema and seizures were related with mortality. The presence of rash, herpes labialis, or sequelae such as hemiparesis, cranial nerve (CN) palsy or myelopathy did not substantially alter the result. The presence of decreased haemoglobin (Hb), total leukocytes 15,000/cc, low platelet count, or multiorgan involvement in the form of compromised renal or hepatic function was associated with a bad prognosis. It was discovered that the presence of clear CSF, CSF neutrophils 75%, and a lower CSF/blood glucose ratio was associated with unfavourable outcome. A CSF cell count 900 cells/cc or the presence of CSF proteins did not affect the result. CT examination revealed cerebral edema, meningeal enlargement, hydrocephalus, and infarct. All of these characteristics excluding hydrocephalus were strongly linked with mortality.

The Study done by Van de beek et al. also used Glasgow outcome scale for predicting poor outcomes. They found that advanced age, the presence of otitis or sinusitis, the absence of rash, a low Glasgow Coma Scale score on admission, tachycardia, a positive blood culture, anelevated erythrocyte sedimentation rate, thrombocytopenia and a low cerebrospinal fluid white-cell count were risk factors for an unfavourable outcome. Gu J et al. discovered that advanced age, altered sensorium, a poor GCS score at admission and concurrent hydrocephalus are independent risk factors for TBM. A study by Mishra UK et al. has found several factors contributing to poor outcomes in tubercular meningoencephalitis. They have assessed outcomes using Modified rankin Scale (mRS $\leq$ 2- good and mRS > 2 - poor). It was discovered that advanced age, altered sensorium, low GCS & comorbidities at presentation, seizures, hyponatremia, leukocytosis, HIV co-infection, AFB in CSF, culture positivity, hydrocephalus & infarction on brain imaging, are associated with poor outcomes.

Diagnosis

Mcgill F et al. published The UK joint specialist societies' guideline on the diagnosis and management of acute meningitis (45) and meningococcal sepsis in immunocompetent adults. They have mentioned the utility of blood tests & CSF analysis in the diagnosis of meningitis of various etiologies.

Blood Tests

In all cases of suspected bacterial meningitis or meningococcal sepsis, blood cultures must be obtained. Optimally, this should be done before any antibiotics are administered, so the yield can reach 74%. If a patient has received antibiotics prior to hospitalization, blood cultures should be obtained as soon as possible upon admission. Serological tests can also be done to determine the cause of meningitis, such as mumps, syphilis, or Lyme disease. CSF glucose interpretation requires taking blood glucose with the LP. Lactate measurement is beneficial inthe care of patients with suspected sepsis and, if elevated, can give valuable suggestions for resuscitation. The serum procalcitonin can distinguish between bacterial and viral illnesses. In adults, it has a sensitivity of 95% and a specificity of 100% (PPV - 97-100%; NPV- 93.9- 100%) for discriminating bacterial from viral meningitis.

CSF Analysis

According to Mcgill F et al. initial CSF examination of cells, protein, and glucose aids in determining the probable cause of meningitis; subsequent microscopy and culture can confirm the etiology and antibiotic susceptibility. Frequently, insufficient amounts of CSF are collected, limiting the number of possible investigations. As CSF is generated at a rate of around 22 ml/h, it is safe to withdraw at least 15 ml from adults.

Unless done in the sitting position, CSF opening pressure should always be monitored during a lumbar puncture. In bacterial meningitis, the opening pressure is typically greater than 20 cm CSF and is frequently even higher.

There are often polymorphonuclear pleocytosis in the cerebrospinal fluid (CSF) in acute bacterial meningitis, although there are always variations. In the early stages of the disease, there may be few or no white blood cells. In some types of bacterial meningitis, such as listeria or inadequately treated bacterial meningitis, lymphocytes may predominate. In early viral meningitis, especially enteroviral illness, a predominance of neutrophils may also be observed, but such individuals are unlikely to have a total CSF white cell count more than 2,000 cells per mm3. CSF glucose, protein, and lactate can distinguish viral, bacterial and other meningitis causes. The numbers can provide useful hints to the potential etiology, but in most cases, they are unable to provide conclusive answers because of overlap across the diseases. A patient is unlikely to have bacterial illness if the CSF protein is less than 0.6 g/L. In bacterial meningitis, the concentration of glucose in the cerebrospinal fluid (CSF) is decreased; however, the concentration also fluctuates based on the plasma glucose, hence the CSF: plasma glucose ratio should be considered. Typically, CSF glucose is approximately two-thirds of plasma glucose. The ratio is typically much lower in bacterial meningitis; a CSF: plasma glucose ratio cutoff of 0.36 provides a high sensitivity and specificity (93%) for identifying bacterial meningitis. Any CSF abnormality need to be evaluated in light of the patient's clinical presentation, as none of the CSF parameters provide a definitive indication of the underlying etiology.

If antibiotics had not been used beforehand, CSF lactate had a high sensitivity and specificity (93% and 96%, respectively) in discriminating between bacterial and viral meningitis. It has been claimed that a CSF lactate cutoff of 35 mg/dl provides the highest sensitivity for discriminating between bacterial and viral meningitis. If

individuals have been treated with antibiotics, the sensitivity decreases below 50%. If performed prior to starting antibiotics, the test's strong negative predictive value makes it useful for ruling out bacterial meningitis and providing assurance to halt or withhold antimicrobials.

Gram staining of the cerebrospinal fluid (CSF) is a rapid method for identifying bacteria with a sensitivity between 50 and 99% (depending on the organism and preceding antibiotics) anda specificity of 97-100%. CSF yields can be increased using cytospin centrifugation. CSF culture is the gold standard for diagnosing bacterial meningitis. In 70% to 85% of instances ofbacterial meningitis, this test is diagnostic, depending on whether antibiotics wereadministered beforehand and the infecting organism. For meningococci, CSF may sterlize during the first 2 hours of antibiotic therapy and within 4 hours for pneumococci. However, even if cultures are negative, CSF analysis may be useful up to 48 hours after parenteral antibiotics have been administered.

Cantu RM et al. and Mcgill F et al. assessed CSF laboratory profile in patients presenting with viral meningitis and it as observed that CSF in viral meningitis patients shows pleocytosis with lymphocytic and monocytic predominance, with elevated protein concentration (50-100 mg/dL) & normal CSF Glucose/ Plasma Glucose Ratio.

Some viral meningitis causes, including enterovirus, VZV, and HSV, can be identified by polymerase chain reaction (PCR) assays. C-reactive protein and serum white blood cell count cannot consistently discriminate between viral and bacterial meningitis. CSF Procalcitonin and CRP levels have not been found helpful in distinguishing viral meningitis from bacterial, in comparison to serum values.

Leonard JM did a comprehensive review on diagnosis of CNS tuberculosis. It was observed that the initial CSF pressure is typically increased. The fluid has a transparent or "ground- glass" appearance, and a thin web-like clot frequently forms on the surface. Typically, the CSF profile reveals a mononuclear pleocytosis along with high protein and low glucose levels. In the majority of cases, the total cell count is between 100 and 500/mm3, while in 15% of instances it is between 500 and 1,500/mm3. Early in the course of a disease, the cellular response may be atypical, with few cells, a mixed pleocytosis, or a transient polymorphonuclear predominance, which evolves in the direction of the expected lymphocytic response on subsequent examinations.

The CSF protein concentration ranges from 100 to 500 mg/dl in the majority of patients, is below 100 mg/dl in 25%, and exceeds 500 mg/dl in approximately 10% of reported cases. A protein concentration between 2 and 6 g/dl is indicative of subarachnoid block and is associated with a poor prognosis. In 80% of cases, the CSF glucose concentration is abnormally low, less than 45 mg/dl; given that the patient typically presents with subacute or chronic meningitis, this characteristic constitutes strong evidence of a granulomatous infection of the CNS.

By demonstrating M. tuberculosis via stained smear and culture, diagnosis is confirmed. 75% of cultures are positive, but it takes between 3 and 6 weeks to detect growth. Therefore, the demonstration of acid-fast bacilli (AFB) by stained smear of cerebrospinal fluid (CSF) sediment remains the quickest method for making an early diagnosis. The sensitivity of the AFB smear and culture is variable, influenced in part by the selection and quantity of the specimen submitted by the clinician, as well as the diligence with which laboratory personnel execute the procedure. Multiple CSF specimens obtained from multiple lumbar punctures have diagnostic value. In the clinical series reported by Kennedy and Fallon, the yields on smear and culture for the initial CSF specimen were 37% (smear) and 56% (culture), but increased to 87% (smear) and 83% (culture) when two additional specimens were examined. Importantly, additional 30% of cases were diagnosed from CSF obtained 1 to 3 days after therapy initiation. In a separate study done by Thwaites et al. involving 132 adult patients specifically designed to evaluate the efficacy of careful microbiological technique, 58% of smears were positive and 71% of cultures were positive. 82% was the combined sensitivity ofsmear and culture. On the basis of these findings, it is recommended to obtain a minimum of three serial CSF samples for smear and culture. It is not necessary to delay anti-tuberculosis treatment because the yield remains high a few days after treatment has begun.Interpretation of etiology is based upon analysis of CSF appearance, opening pressure (cm of CSF), CSF WBC count (cells/uL), predominant cell type, protein concentration (gm/L) & CSF glucose / Plasma glucose ratio.

[Table no. 1- Interpretation of CSF profile in different etiologies]

	Appearance	Opening Pressure (cm CSF)	WBC (Cells/µL)	Predominant cell type	CSF protein (gms/L)	Serum Glucose (mmol/L)	CSF Glucose / Plasma Glucose ratio
Normal	Clear	10-20	< 5	-	<0.4	2.6-4.5	>0.66
Bacterial	Cloudy / Turbid / Purulent	Raised	Raised (>100)	Neutrophils	Raised (>1.0)	Low	Very Low
Viral	Clear	Normal or Mildly raised	Raised (<1000)	Lymphocytes	Mildly Raised (0.5-1.0)	Normal or Slightly Low	Normal or Slightly Low
Tuberculous	Clear, Cloudy	Raised	Raised (<500)	Lymphocytes	Greatly Raised	Low	Very Low

SPECIFIC CSF TESTS

CSF CBNAAT

The nucleic acid-based amplification technique (NAAT) based on PCR, can quickly detect specific microbial DNA in clinical specimens. Due to laboratory sensitivity and specificity differences, PCR detection for M. tuberculosis DNA in CSF is inconsistent. In a comparison study of seven facilities done by Noordhoek et al., sensitivity varied greatly and false-positivetest results ranged from 3 to 20%. Pai et al. in their systematic review & meta-analysis observed that TB meningitis NAATs had 56% sensitivity and 98% specificity. When clinical suspicion supports empirical therapy for CNS TB and initial AFB stains are negative, CSF specimens should be analyzed for PCR. A negative result neither precludes the diagnosis nor justifies discontinuing therapy. The World Health Organization recommends the Xpert MTB/RIF assay for TBM-suspected CSF specimens. This cartridge-based NAAT identifies M. tuberculosis and RIF resistance in under 2 hours. A meta-analysis of 13 trials (839 CSF samples) done by WHO comparing Xpert MTB/RIF to the culture found 80.5% sensitivityand 97.8% specificity.

The results of a cross-sectional study that was carried out by Paul A. and colleagues showed that the sensitivity and specificity of CSF CBNAAT were, respectively, 77% and 96%. Gene Xpert was shown to have a sensitivity of 67% in a study conducted by Patel et al., while another study conducted by Nhu et al. indicated that Gene Xpert had a sensitivity of 59% and a specificity of 99%.

CSF ADA

ADA is ubiquitously present in the body, but primarily in lymphoid tissue, where levels are particularly high in active T-Lymphocytes; hence, it is linked to illnesses that elicit T-cell- mediated immune responses. It has been shown that ADA is useful in distinguishing tuberculous pleural effusions. ADA assay may be relevant in confirming TBM; however, elevated levels may also be detected in other Central Nervous System (CNS) illnesses (such as Sarcoidosis, Meningeal lymphoma, Subarachnoid haemorrhage, and Neurobrucellosis), making it too non-specific to be useful. During the cell-mediated immune response to a tuberculosis infection, it is assumed that T-lymphocytes are responsible for releasing ADA into the CSF.

According to a study by Gupta BK et al. (19 patients), a CSF - ADA level of 10 U/L can distinguish tuberculous from nontuberculous meningitis. They noticed a statisticallysignificant distinction between the CSF - ADA levels of tuberculous and non-tuberculous meningitis (P <0.01). Results of the study reveal that ADA levels in CSF are of great utility inthe diagnosis of TBM and in differentiating this disease from others, as a cut-off CSF - ADA level of 10 U/L exhibited pretty high accuracy with sensitivity of 94.73% and specificity of 90.47 % for the diagnosis of tuberculous meningitis.

Agarwal A. et al. found in a study of 32 tuberculous meningitis patients that ADA level 10 U/L as a cut-off value had a sensitivity of 87.5%, specificity of 83.33%, positive predictive value of 87.5%, and negative predictive value of 83.3%.

For the diagnosis of tuberculous meningitis, a study conducted by Goswami k et al. on 22 TBM patients revealed that the cutoff value for ADA activity levels in CSF should be approximately 5 IU/l, with an approximate sensitivity of > 90% and specificity of approximately 85%. In the study, the cutoff level of CSF ADA activity was approximately or greater than 20 IU/l in tuberculous meningitis. CSF ADA activities (about greater than 20 IU/l) were 4 times higher in Tubercular meningitis than in other groups of meningitis with a typical cut-off value of approximately 5 IU/l. In pyogenic meningitis, the typical CSF ADA cutoff value is 10 IU/l, whereas the cutoff level of CSF ADA activity is 5 in both aseptic and fungal meningitis. Thus, different cut-off levels of CSF ADA activities were identified, and substantial discrimination ($p<0.001$) was observed between tuberculosis and non-tuberculous meningitis.

CSF Chloride and Ratio

Tan et al. found that the chloride content of CSF and plasma samples, as well as the ratio of CSF to plasma chlorides, reduced in patients with tuberculous meningitis (102.150mmol/L, 101.75mmol/L, and 1.164, respectively), which supported the diagnosis of tuberculous meningitis. The combination of the chloride concentration in cerebrospinal fluid (CSF) andthe ratio of CSF chlorides to plasma chlorides could increase diagnostic sensitivity to 97 % orspecificity to 87 %. When the chloride content in CSF is less than 121.70 mmol/L, plasma chlorides are greater than 101.45 mmol/L, and the ratio of CSF to plasma chlorides is greater than 1.200, cryptococcal meningitis may be suspected. The combination of chloride contentin CSF and the ratio of CSF to plasma chloride has a diagnostic sensitivity of 94.2 % and a specificity of 91.6%. The

chloride concentrations in cerebrospinal fluid (CSF) and plasma, as well as the ratio of CSF chloride to plasma chloride, had little diagnostic significance for viralmeningitis. The CSF chloride concentration was substantially lower in patients with tuberculous and cryptococcal meningitis than in patients with viral meningitis. Chloridelevels in plasma decreased significantly in patients with cryptococcal meningitis than in those with tuberculous or viral meningitis. The ratio of CSF to plasma chlorides decreased in patients with tuberculous meningitis, but it increased in individuals with cryptococcal meningitis.

CSF Cytokines (Tumor necrosis factor-alpha and Interleukin-8)

In bacterial meningitis, cytokines (e.g., Tumor necrosis factor-alpha and Interleukin-1), chemokines (Interlukin-8), and other proinflammatory molecules cause pleocytosis and neuronal injury. Patients with bacterial meningitis typically exhibit elevated CSF concentrations of TNF-, IL-1, IL-6, and IL-8. In individuals with aseptic meningitis, cytokine levels, particularly those of IL-6, TNF-, and interferon gamma, are high. Cells (e.g., endothelial cells, leukocytes, microglia, astrocytes, and meningeal macrophages) are exposed to bacterial products generated during replication and death; this exposure stimulates the generation of cytokines and proinflammatory mediators. This process is presumably triggeredby the binding of bacterial components (such as peptidoglycan and lipopolysaccharide) to pattern-recognition receptors, such as Toll-like receptors (TLRs). TNF- and IL-1 are the most important cytokines involved in mediating this inflammatory cascade. The glycoprotein TNF- is produced by activated monocyte-macrophages, lymphocytes, astrocytes, and microglial cells. IL-1, formerly known as endogenous pyrogen, is largely produced by activated mononuclear phagocytes and is responsible for inducing fever during bacterial infections. Both IL-1 and TNF- have been identified in the CSF of bacterial meningitis patients. In experimental types of meningitis, they are found within 30 to 45 minutes of intracisternal endotoxin administration.

Multiple secondary mediators, such as IL-6, IL-8, nitric oxide, prostaglandins (e.g. prostaglandin E2 [PGE2]), and platelet activation factor (PAF), are believed to increase this inflammatory process, either independently or in conjunction with IL-1. IL-6 stimulates the production of acute-phase reactants in response to bacterial infection. The chemokine IL-8 mediates TNF- and IL-1-induced neutrophil chemoattractant responses.

Nitric oxide is a free radical molecule that, when created in large quantities, can induce cytotoxicity. PGE2, which is a byproduct of cyclooxygenase (COX), appears to contribute to the production of enhanced blood-brain barrier permeability. It is hypothesized that PAF, by its diverse biological activities, mediates the development of thrombi and the activation of clotting factors inside the vasculature. However, the specific functions of each of thesesecondary mediators in meningeal inflammation remain unknown.

Injuries to the vascular endothelium and an increase in the permeability of the blood-brain barrier result in the entrance of several blood components into the subarachnoid space. This contributes to vasogenic edema and high CSF protein levels in many cases. In reaction to cytokines and chemotactic chemicals, neutrophils move from the bloodstream and penetrate the compromised blood-brain barrier, resulting in the intense neutrophilic pleocytosis that is characteristic of bacterial meningitis.

Patients with aseptic meningitis (AM) and acute bacterial meningitis (ABM) had elevated levels of interleukin-6 ($p < 0.05$), according to a case-control research by Junior P et al. ABM had greater CSF IL-8 levels than AM and controls ($p < 0.05$). Using a cutoff of 1.685 ng/dL, the area under the receiver operator curve (ROC) for IL-8 in ABM demonstrated a discriminatory power of 0.951 (100% sensitivity and 94% specificity). In the presence of meningeal inflammation, the CSF concentrations of both IL-6 and IL-8 are elevated; IL-8may be an important tool for distinguishing ABM from AM.

According to a study by Bociaga-Jasik et al., the mean concentration of TNF-alpha, IL-1 beta,and IL-8 in CSF of patients with bacterial meningitis was considerably higher than that of the control group (viral meningitis: 7.93 pg/ml, 31.89 pg/ml, 405.28 pg/ml, and without meningitis: 0.38 pg/ml, 2.55 pg/ml, 32.56 pg/ml. Pleocytosis, protein levels, and glucose levels were all associated with TNF-alpha, IL-8, and pleocytosis, whereas pleocytosis and CSF protein levels were correlated with IL-1 beta. A considerable risk of patient death was linked to high levels of TNF-alpha in the CSF (median value 953 pg/ml).IL-1 beta is a more accurate prognostic predictor. Patients with neurological sequelae had a median IL-1 beta level of 401.3 pg/ml, while those who died had a median level of 585.9 pg/ml, compared to 244.7 pg/ml in the group of patients who did not experience any difficulties. Analysis of the ROC curve showed that cases with a concentration of IL-1 beta > or = 289.9 pg/ml may be distinguished from those without it with 88.9% sensitivity and 67.7% specificity. For TNF- alpha, the cut-off was 538.9 pg/ml or more. The specificity for the determined critical point was 68.7%, and the sensitivity was 77%.

Brain-imaging

The most crucial function of CT scanning in imaging meningitis patients is to spot sequelae such symptomatic hydrocephalus, subdural empyema, and cerebral abscess that call for immediate neurosurgical intervention and are contraindications for lumbar puncture.

Contrast-enhanced CT scans may also aid in the early detection of conditions such ventriculitis, infarction, and venous thrombosis. A common consequence of bacterial meningitis in newborns is ventriculitis. Contrast-enhanced CT scans can reveal ependymal enhancement.

A study by Nagra et al. to assess the results of CT brain scans in meningitis patients. In total, 111 patients were admitted during the first time frame, while 47 patients were admitted during the second time frame. Compared to 36 patients (80%) in the second group, 67 patients (61% of the first group) received CT. In the initial group, there were eight abnormal scans (12%), including three individuals who had radiological signs of cerebral edema. Oneof these patients received a lumbar puncture and experienced no neurological aftereffects. Five aberrant scans (14% of the total) were found in the second group, one of which presented a lumbar puncture contraindication due to mild ventricular dilatation. This patient underwent a lumbar puncture without incident. Clinical characteristics in every patient with abnormal scans suggested elevated intracranial pressure.

Contrast-enhanced MRI Brain detects meningeal inflammation and sequelae, making it the most sensitive imaging technique for bacterial meningitis. A study conducted by Lummel et al. on 136 patients with bacterial meningitis revealed that the bacterial pathogen agent was confirmed in 114 cases, and an MRI was available for 75 patients. On MRI, meningitis- associated pathologic imaging abnormalities were present in 62 of 75 (82.7%) individuals.

Comprehensive review of neuroimaging in tubercular meningitis done by Marais et al. showed hydrocephalus and basal meningeal enlargement are the most frequent radiological manifestations of tuberculous meningitis as detected by CT. Approximately 80% of children have hydrocephalus and 75% have basal meningeal augmentation; whereas approximately 45% of adolescents and adults have

hydrocephalus and 8–34% have basal meningeal enhancement. Many patients additionally exhibit infarcts (8–44% of cases) and tuberculosis (8–31%). The presence of pre-contrast hyperdensity in the basal cisterns was 100% specific for tuberculous meningitis in children, according to Andronikou, but this finding has not been confirmed by other studies. The combination of basal meningeal enhancement, infarcts, and hydrocephalus was also 100% specific; the most sensitive feature was basal meningeal enhancement (89%). Kumar also reported comparable results. MRI has greater sensitivity than CT for detecting abnormalities such as meningeal enhancement, infarcts, and tuberculomas, particularly brainstem lesions. Thwaites reported MRI findings in adult patients with tuberculous meningitis; 82% exhibited basal meningeal enlargement and 77% exhibited hydrocephalus. 74% of patients in the same trial developed tuberculoma during treatment, the majority of whom were asymptomatic. HIV-positive children and adults with tuberculous meningitis have a lower incidence of hydrocephalus and basal meningeal enhancement and a higher incidence of infarcts, gyral enhancement, and mass lesions compared to HIV-negative patients. Patients with HIV and tuberculous meningitis are also more prone to develop cerebral atrophy, which is difficult to differentiate from communicative hydrocephalus. However, these findings are inconsistent, and some studies found no difference in imaging between HIV-positive and HIV-negative adults. Alternative causes of meningitis, such as cryptococcal meningitis, CMV encephalitis, toxoplasmosis, sarcoidosis, meningeal metastases, and lymphoma, are more common in HIV-positive patients and can produce comparable radiological findings.

In his exhaustive analysis of CNS tuberculosis, Leonard JM explored the role of neuroimaging in diagnosing tuberculous meningoencephalitis. The use of computed tomography (CT) and magnetic resonance imaging (MRI) has substantially eased the evaluation and management of CNS TB patients. These imaging studies are helpful for determining the presence and severity of basal arachnoiditis, cerebral edema and infarction, as well as the presence and progression of hydrocephalus. CT scans revealed hydrocephalus in 75% of patients, basal meningeal enhancement in 38%, cerebral infarcts in 15-30%, and tuberculomas in 5-10%, according to community-based studies by Bhargava S et al. and Ozateş M et al. A study of selected neuroimaging research published within the previous two decades can yield a number of important clinical observations. CT evidence of basal enlargement paired with any degree of

hydrocephalus is extremely indicative of TBM in patients with similar clinical symptoms. If the CT scan is normal at the time treatment begins,the prognosis for a full recovery is excellent. The combination of hydrocephalus and substantial basal enlargement is symptomatic of advanced illness with a bad prognosis. The presence of vasculitis and, consequently, the risk for basal ganglia infarction corresponds wellwith substantial basal enhancement. MRI is the method of choice for identifying lesions of the brain stem, midbrain, and basal ganglia in patients of all ages.

DIAGNOSTIC SCORING SYSTEMS

Thwaites' Diagnostic Score

Thwaites GE et al. evaluated the clinical and laboratory parameters of 251 Vietnamese individuals admitted to an infectious disease hospital who met diagnostic criteria for tubercular (n=143) or bacterial (n=108) meningitis. Using multivariate logistic regression and the classification tree approach, independently predictive features of tuberculous meningitis were modelled as a diagnostic rule. Resubstitution and prospective test data approaches were used to evaluate the performance of these diagnostic tools. Age, length of history, white- blood-cell count, total cerebrospinal fluid white-cell count and cerebrospinal fluid neutrophil proportion were predictive of a diagnosis of tuberculous meningitis. The established diagnostic criteria was 97% sensitive and 91% specific by resubstitution and 86% sensitive and 79% specific when used prospectively to an additional 42 people with tuberculousmeningitis and 33 with bacterial meningitis. The comparable results for the classification tree were 99 percent and 93 percent for resubstitution and 88 percent and 70 percent for future testdata. In the ROC analysis, a cutoff of 4 was chosen since it provides the highest sensitivity (97%) with adequate specificity (91%).

Lancet Consensus Scoring System

A consensus case definition for tubercular meningitis was formed for use in clinical research by Marais et al. The Lancet consensus scoring system consists of 20 parameters, which are grouped into 4 categories (clinical, CSF, CNS imaging, and evidence of TB elsewhere), witha maximum score of 20. If there is evidence of AFB in a CSF smear, culture, or brain orspinal cord histopathology, a definitive diagnosis of TBM is made. If the overall score is greater than 10 points in patients without imaging or 12 points with imaging, a probable diagnosis is given. Scores between 6 and 9 without imaging or 6–11 with imaging indicate a possible diagnosis. On the basis of the overall scores, the diagnosis of TBM is either definite, probable, possible or non-existent.

Sulaiman T et al. executed a multicenter study to assess the diagnostic value of "Thwaites' system" and "lancet consensus scoring system" in subacute and chronic tuberculous versus nontuberculous meningitis. Both scores were able to separate TBM

from bacterial meningitis;however, only the Lancet score was able to discriminate TBM from fungal, viral, and unknown etiologies, despite significant overlap ($P < 0.0001$). Both criteria demonstrated low diagnostic accuracy in distinguishing TBM from non-TBM etiologies (AUC-ROC < 0.5), however, the Lancet consensus scoring system performed fairly in diagnosing TBM (AUC-ROC =.738, sensitivity = 50%, specificity = 89.3%).

Mortality

In 2015, the World Health Organization reported that over 290,000 individuals died from meningitis. According to the latest WHO data published in 2020 Meningitis Deaths in India reached 33,337 or 0.39% of total deaths. The age adjusted Death Rate is 2.52 per 100,000 of population ranks India #55 in the world.

McIntyre PB et al., Jayaraman Y et al., Oordt-Speets AM et al. & Van de Beek D et al. evaluated and found that in high-income countries, meningitis is one of the top 10 causes of death among children younger than 14 years old. In high-resource countries, the mortality rate associated with meningitis caused by *S. pneumoniae* and *N. meningitidis* was 30% and 7%, respectively. After the introduction of the Hib and *S. pneumoniae* vaccines, bacterial meningitis caused by these bacteria has decreased significantly in high-income countries. In low- and middle-income countries (LMICs), where bacterial meningitis remains a serious concern, the situation is different. Inadequate vaccine coverage and the lack of availability of these vaccines in national immunization programmes are among the causes of this crisis. In terms of mortality and morbidity, meningitis has a greater impact on children under the age offive, particularly in settings where national immunization programmes *for H. influenzae type b, S. pneumoniae,* and N. meningitidis are not properly implemented.

Dodd et al did a comprehensive review on global burden of tuberculous meningitis in adults. According to this review, 78,200 (95% UI; 52,300-104,000) adults died from TBM in 2019.A total of 31,700 (95% CI; 10,100-53,300) of the 118,000 incident TBM patients who were diagnosed and treated died, resulting in a CFR of 27%. All 46,500 (95% CI; 32,200–60,900) incident TBM patients who went undiagnosed were assumed to die, accounting for 59% of TBM deaths. 27,200 persons with HIV died from TBM, 35% of all TBM deaths, and 36% (28,300, 95% CI; 18,400–38,300) were women. With 14,900 deaths (95% CI; 9,920–19,900),
the 35–45 age group had the highest deaths. The African and Southeast Asian WHO areashad the most deaths, 30,900 (95% CI; 25,600–36,200) and 26,600 (95%; 4,350–48,800), respectively.

Complications

Van de Beek, D. et al., Weisfelt, M. et al., Hoogman, M. et al. & Roed, C. et al completed a comprehensive review on morbidity in bacterial meningitis patients. It was discovered that patients with bacterial meningitis (especially pneumococcal meningitis) are at a high risk for neurological problems that reduce their quality of life. Approximately fifty percent of survivors have specific neuro- logical abnormalities, such as hearing loss, seizures, andcognitive impairment. A meta-analysis revealed that the risk of serious sequelae in low- income nations was twice as high as in high-income countries.

Hearing loss (in 34% of patients), seizures (13%), motor impairments (12%), cognitive abnormalities (9%) and hydrocephalus (7%) were the most prevalent sequelae of bacterial meningitis in 18,183 children. Patients with *S. pneumoniae, H. influenzae,* and *S. suis* meningitis frequently have hearing loss, perhaps due to the direct spread of bacterial products and inflammatory mediators from the meninges to the cochlea. Cognitive impairment (lower processing speed) can be detected in roughly one-third of patients who have had pneumococcal or meningococcal meningitis in survivors of bacterial meningitis.

According to review analysis done by Soleiman-Meigooni, Kumar Garg R & Gupta G, complications of tuberculous meningitis (TBM) include Hydrocephalus, cranial nerve palsies, Visual impairment and blindness, stroke (ischemic or hemorrhagic), seizures, spinal TB, tuberculous radiculomyelitis, hyponatremia, arachnoiditis, tuberculoma formation & permanent neurological disability.

METHODOLOGY

OBJECTIVES

Primary Objective

To determine the risk factors associated with poor outcomes (mortality and sequelae) in patients presenting with meningitis.

Secondary Objectives

1. To describe the clinical, laboratory profile and outcomes of patients presenting with meningitis at All India Institute of Medical Sciences, Jodhpur.
2. To determine the utility of cerebrospinal fluid Tumor Necrosis Factor-alpha (TNF-alpha) and Interlukin-8 (IL-8) levels as diagnostic or prognostic biomarkers for meningitis.
3. To determine the sensitivity and specificity of standard scoring systems in tubercularmeningitis in our settings.

STUDY SETTING

Patients attending the out-patient/emergency and in-patient services of the Department of Internal Medicine of All India Institute of Medical Sciences, Jodhpur, Rajasthan.

STUDY DURATION

The study duration is 1.5 years spanning from 13th of March 2021 to 13th of Sept. 2022 at the outpatient and inpatient services of the Department of Internal Medicine, All India Institute ofMedical Sciences, Jodhpur, Rajasthan.

STUDY PARTICIPANTS

INCLUSION CRITERIA

All adult patients (≥18 years) with a clinical definition of meningitis was included.

EXCLUSION CRITERIA

Patients not giving consent was excluded from the study.

STUDY DESIGN

A hospital-based prospective observational study was conducted at AIIMS Jodhpur for a period of 1.5 years from 13th March 2021 to 13th September 2022 after getting institute's ethical committee approval in ethical certificate reference number AIIMS/IEC/2021/3364. Written consent was taken from study participants. A structured data form was designed to collect the information from the patients.

For the purpose of this study, meningitis was be defined as:

1. Presence of signs and symptoms compatible with meningitis {Fever, headache, signs of meningeal irritation (neck stiffness/ Brudzinski's or Kernig's sign) or symptoms of Raised Intracranial Tension (ICT)}.
2. CSF pleocytosis ≥ 5 WBC/microliter

On the visit to the hospital, a baseline assessment of various variables was done which includes: Socio-demographic - Name, age, gender, educational status and employment status, socioeconomic status.

1. History: A detailed medical history was taken. Particular attention was given to thepresence, type and duration of classical symptoms such as fever, seizures, headache and neck stiffness. The presence of features of raised ICT and focal neurological deficit was noted. Vaccination history was also considered.
2. Co-morbidities: Comorbid conditions such as diabetes, hypertension, HIV infection, past history of pulmonary/extrapulmonary tuberculosis, recent surgery or stroke/ heart disease was noted along with addictions: alcohol, smoking or IV drug abuse etc. A patient was consideredimmunocompromised if the patient is presented with uncontrolled diabetes mellitus (DM) or HIV co-infection or taking immunosuppressant medications for some other cause. Clinical suspicion of sepsis was based on initial clinical findings and SOFA score assessment.
3. A detailed general physical and systemic examination was done and recorded including presence of clinical signs of meningeal irritation and presence of external source of infection such as sinus or ear discharge was noted.

4. Investigations required for routine clinical management was performed including routine blood investigations: Complete hemogram, High Sensitivity C-Reactive Protein(HsCRP), procalcitonin, Erythrocyte Sedimentation Rate (ESR), Liver function test, Kidney Function test, Serum Electrolytes, Random Plasma Glucose, Blood, Sputum and Urine Cultures.
5. CSF Examination was performed to include routine parameters such as:
    a. Biochemistry- CSF/Blood Glucose Ratio, Proteins, Chloride, CSF Chloride/ Serum Chloride Ratio, CSF Adenosine Deaminase (ADA), CSF TNF-alpha & IL-8 levels
    b. Cytology- Total count and Differential count
    c. Microbiology- Gram staining, ZN staining, Culture, India ink for Cryptococcus, KOH mount for fungal hyphae, PCR for TB/viral pathogens as clinically indicated.
6. Chest X-ray
7. Brain Imaging: CT-Brain or MRI Brain- As per clinical indication
8. Clinical scoring with Thwaites' Diagnostic score and Lancet Consensus scores for tubercular meningitis (Appendix 5) was done for all.

Patients was classified as acute (≤ 5 days), subacute (>5 days to 30 days) and chronic meningitis (>30 days) based on the duration of symptoms. The management received by the patient and the clinical course will be followed up during the hospital stay. Outcomes such as mortality,

ICU admission, duration of hospital stay and CNS sequelae was noted.

Patients was followed up after 1 month of discharge to evaluate outcomes & the development of complications, by applying the Modified Rankin Score (MRS) and Glasgow Coma Scale (GCS).

DATA COLLECTION

Data was collected on the first visit after obtaining informed written consent for the baseline assessment using socio-demographic and clinical proforma.

Blood samples were taken on the same day and were collected in Vacutainer™ serum separator tubes containing spray-coated silica and clot activator and serum separator gel for serum separation. Blood, urine and sputum or bronchial aspirate sample for culture and sensitivity, was collected using sterile techniques.

CSF was collected in a universal sterile container by means of lumbar puncture. CSF TNF- alpha levels and CSF IL-8 levels were estimated by ELISA-based kits, made by the company ImmunoTag, Ltd, conducted in the biochemistry lab under supervision from experts of AIIMS Jodhpur. CT brain and MRI brain was done in the department of Radiodiagnosis.

All the data regarding clinical, laboratory and imaging profile & related to treatment and outcomes, was maintained in excel sheet.

STATISTICAL ANALYSIS

Statistical analysis was carried out using software program SPSS version 25.0. (SPSS Inc. Chicago, USA). Data was presented as mean ± standard deviation for parametric data or number (%) and median with IQR for extreme values of data. Adjusted odds ratios was calculated for respective risk factors for mortality and sequelae in meningitis patients using multivariable logistic regression. For determining risk factors, we performed univariablelogistic regression analysis followed by multivariable logistic regression with mortality and sequelae as the dependent variable and other risk factors as independent variables. The resultsof the multivariable analysis were reported as adjusted Odds Ratio with 95% Confidence Intervals. A two tailed p value less than 0.05 was considered significant. Differences in mean values of CSF markers with respect to various etiologies were compared with One- way ANOVA. ROC curve was constructed for Thwaites' diagnostic score, Lancet consensusscoring system and CSF adenosine deaminase (ADA) and AUC was calculated for Tubercular meningitis patients with sensitivity and specificity of specific cut-off value.

RESULTS

1. Patient population description

Total of two hundred and nine (209) patients with clinical features of meningitis were enrolled. Out of 209 patients, 128 (61.2%) were males and 81 (38.8%) were females.

The mean age was 48.15 ± 20.48 years (range 18-92). The mean age of male patients was 49.86 ± 19.94 years (range 18-86 years). While the mean age for female patients was 45.44 ± 21.14 years (18-92).

These 209 patients were categorized into different age groups. The highest number of patientsgot enrolled in above 65 years followed by, in descending order 18-25 years,46-55 years, 26- 35 years and least number of patients got enrolled in age group between 36 to 45 years of age.

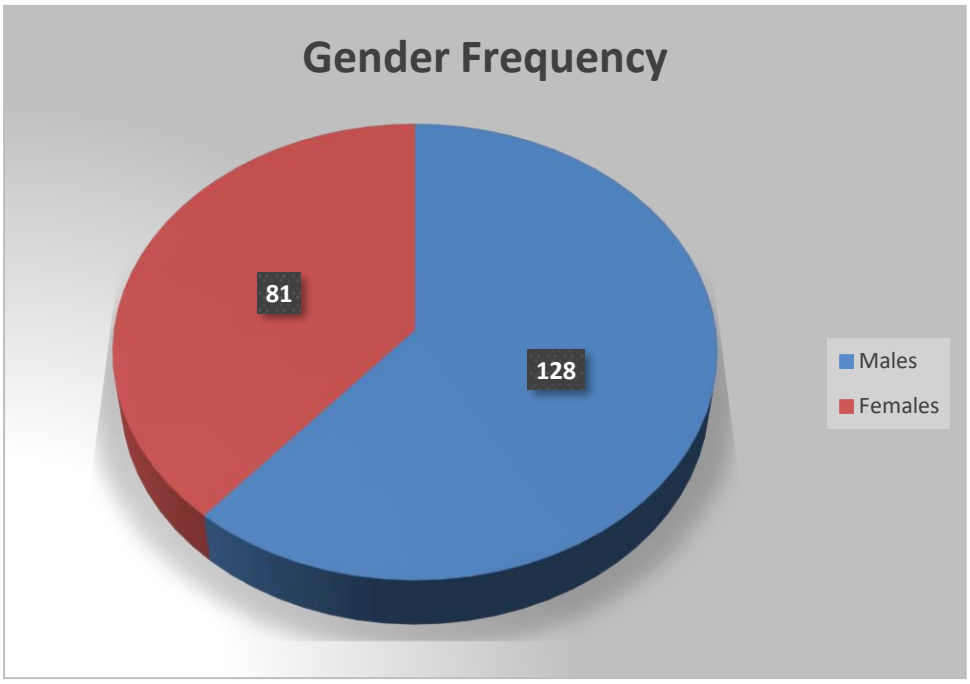


Figure No. 01 Gender Frequency in Suspected Meningoencephalitis Patients (n=209)

Table No. 02 Gender wise age distribution (n=209)

	Mean	Range
Males (n=128)	49.86±19.94	(18-86)
Females (n=81)	45.44±21.14	(18-92)
Total (n=209)	48.15±20.48	(18-92)

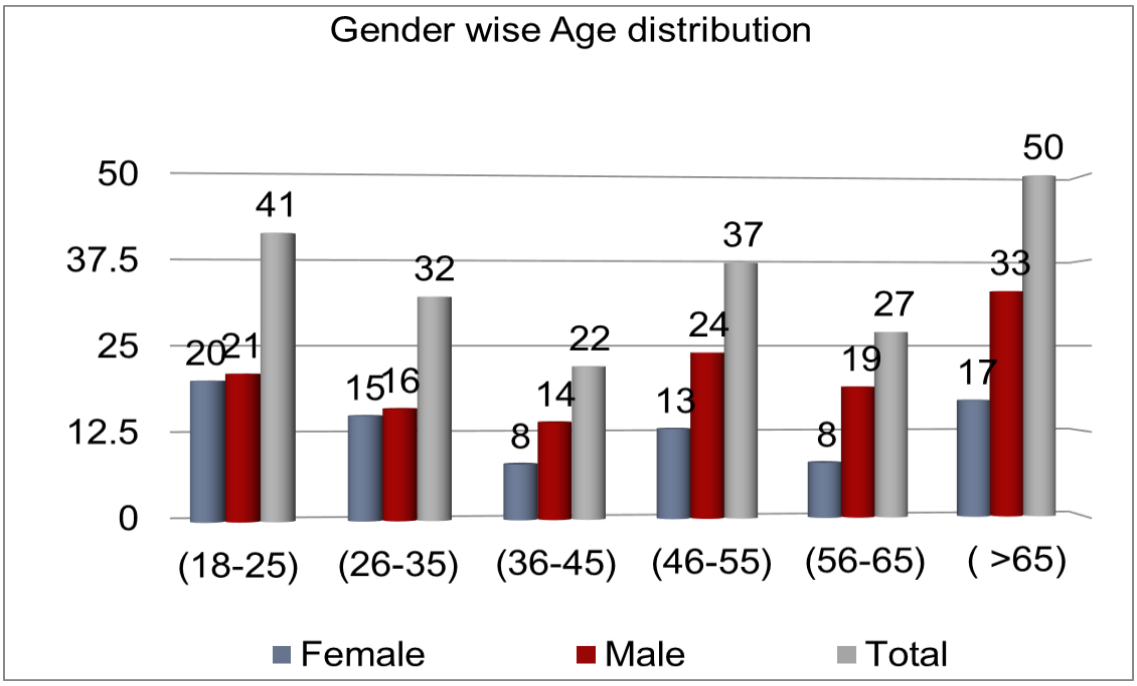


Figure No. 02 Gender wise age distribution in suspected meningoencephalitis patients (n=209)

A total of 154 patients were diagnosed as proven meningoencephalitis. Mean age of these patients was 44±20 years with a range of 18 to 86 years. Out of these 154, 94 patients weremale (61%) & 60 patients were female (39%).Mean age for male patients was 51±21 years with a range of 18 to 86 years. Mean age for female patients was 40±18 years with a range of18 to 76 years.

2. Classification of diagnosis

After complete diagnostic evaluation (CSF analysis & brain imaging), these 209 patients were broadly classified into categories of meningoencephalitis and other

diagnosis. Out of total 209 patients, 154 patients were categorized into the broad diagnosis of meningoencephalitis. These 154 patients were further classified into 7 sub-diagnoses- tubercular meningoencephalitis, viral meningoencephalitis, dengue encephalitis, bacterial meningoencephalitis, fungal meningoencephalitis, paraneoplastic meningoencephalitis and other forms of meningoencephalitis in respective order of frequency.

Other meningoencephalitis included chronic meningitis (2), autoimmune encephalitis (1) & cerebellitis (1), CNS toxoplasmosis (1), Scrub (1) & Lyme's meningoencephalitis (1) and CNS mucormycosis (1).

Other forms of diagnosis were consisting of cerebrovascular accident (09), septic encephalopathy (09), metabolic encephalopathy (09), brain metastasis (03), hypertensive encephalopathy (02) & progressive multifocal leukoencephalopathy (02). Rest 21 patients were diagnosed into various other causes of altered sensorium.

Table no. 3- Frequency of patients in different diagnostic categories (n=209)

S.no.	Diagnosis Category (n=209)	Frequency
1.	Tubercular Meningoencephalitis	**56(26.8%)**
2.	Viral Meningoencephalitis	**33(15.8%)**
3.	Bacterial Meningoencephalitis	**18(8.6%)**
4.	Dengue Encephalitis	**28(13.4%)**
5.	Fungal Meningoencephalitis	**05(2.4%)**
6.	Paraneoplastic Meningoencephalitis	**05(2.4%)**
7.	Other Meningoencephalitis	**09(4.3%)**
8.	Other Diagnosis	**55(26.3%)**

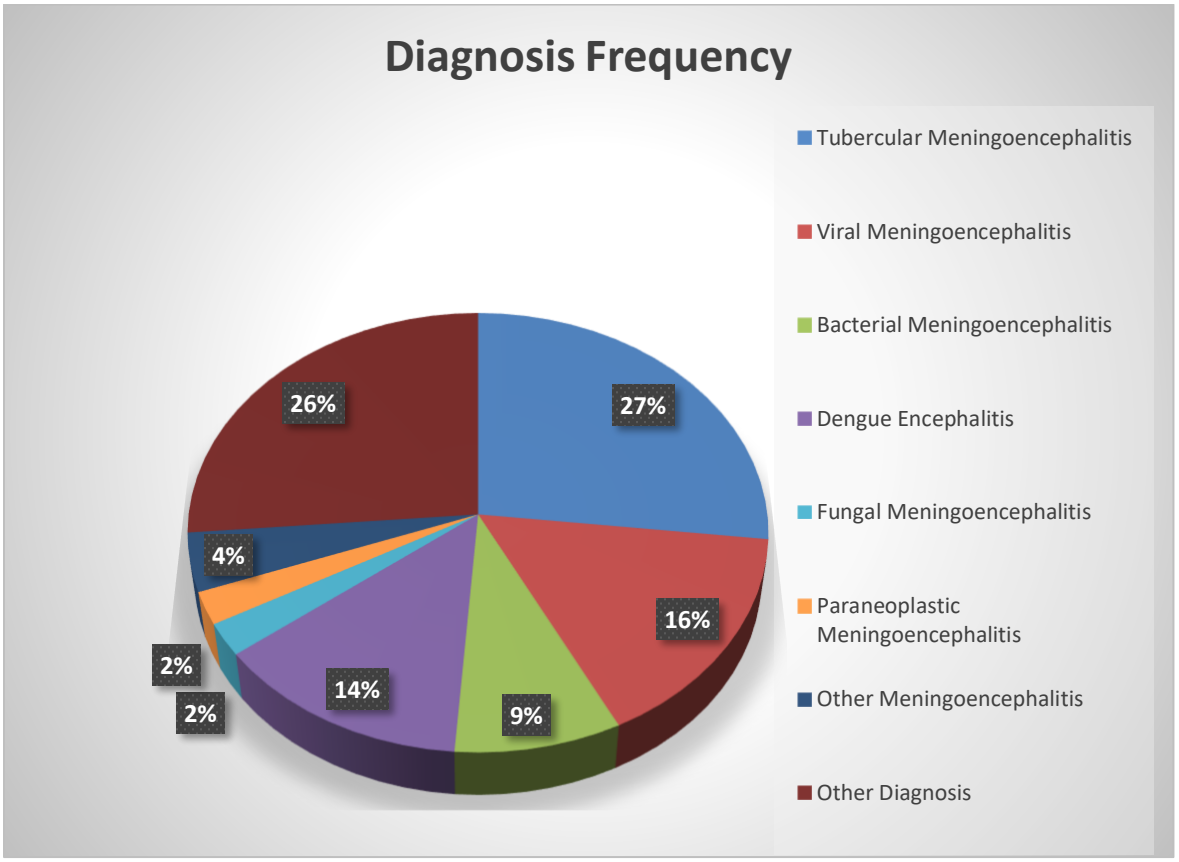
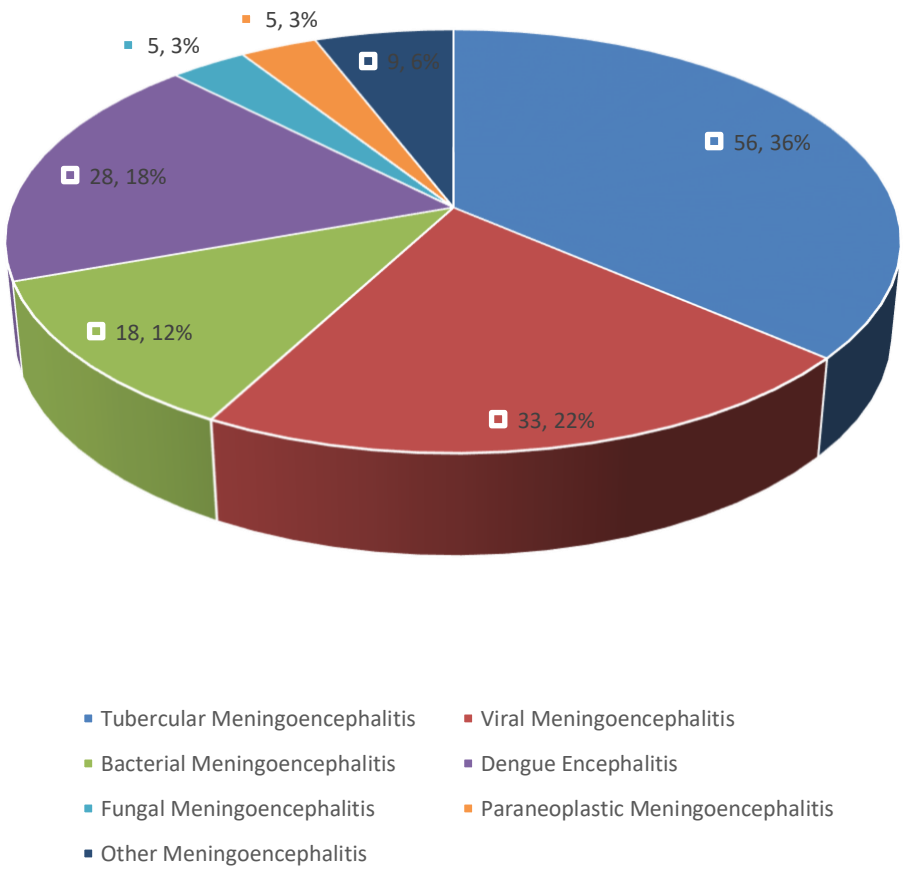


Fig no. 3- Frequency of patients in different diagnostic categories (n=209)

Fig no. 4 -Frequency of etiology in confirmed Meningoencephalitis Patents (n=154)



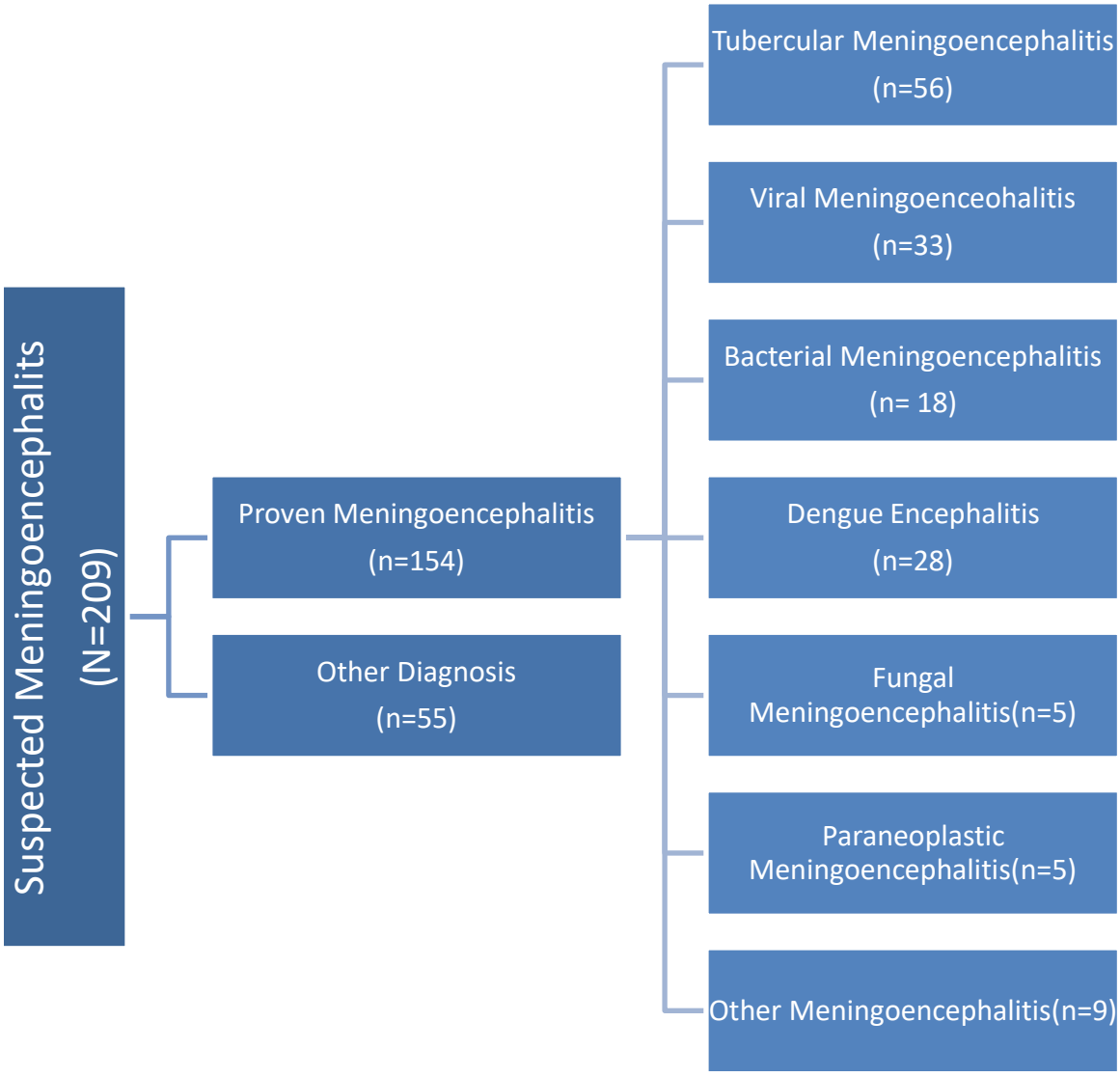


Fig no. 05 – Flow chart: Distribution of patients in diagnostic categories (n=209)

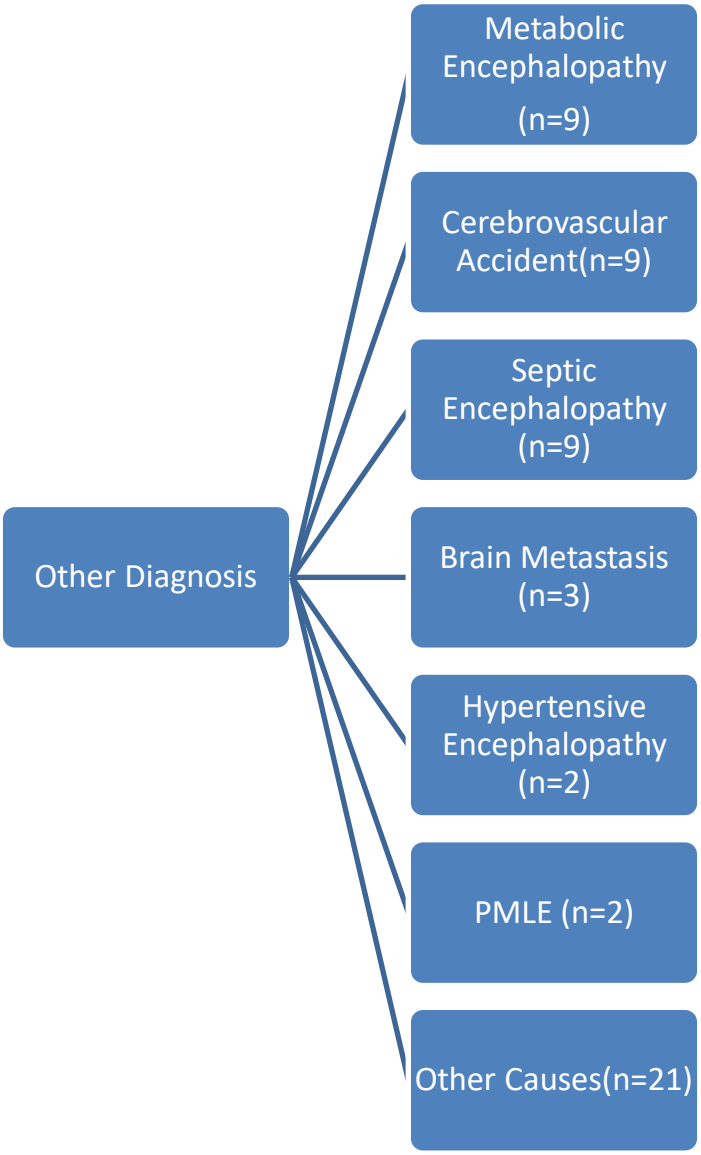


Fig no. 06 – Flow chart: Distribution of patients of other diagnostic category (n=55)

3. Clinical features at the time of admission

Two hundred and nine patients were evaluated & clinically diagnosed as meningitis, based on the presenting symptoms. Altered sensorium remained the most common symptom with 163 patients (78%) presented with the same. Fever and headache were 2nd and 3rd most common symptoms, which were presented in 147(70.3%) & 136(65.1%) patients relatively.

Other common presenting symptoms in descending order of frequency were neck

stiffness (36.4%), vomiting (25.8%) & seizures (23%), which were there in 76, 54 & 48 patients relatively. Less frequent clinical features were nausea, focal neurological deficit, neurologicalweakness, coma, weight loss & shortness of breath presenting in 46(22%, 46(22%), 41(19.6%), 22(10.5%), 21(10%) & 19(9.1%). The least common symptoms were otorrhea, CSF rhinorrhoea, blurring of vision & delirium presenting in 4(1.9%), 3(1.4%), 2(1.0%) & 1(0.5%).

Mean duration of illness at presentation was 10±13 days with a range of 1-90 days.

Table no. 4: Frequency of clinical features in enrolled patients (n=209)

Sr.no.	Presenting Symptom	Number of patients(%)(n=209)
1.	Altered sensorium	163 (78%)
2.	Fever	147 (70.3%)
3.	Headache	136 (65.10%)
4.	Neck Stiffness	76 (36.40%)
5.	Vomiting	54(25.80%)
6.	Seizures	48(23.00%)
7.	Nausea	46(22.00%)
8.	Focal neurological deficit	46(22.00%)
9.	Paralysis	41(19.60%)
10.	Coma	22(10.50%)
11.	Weight Loss	21(10.00%)
12.	Shortness of breath	19(9.10%)
13.	Otorrhea	4(1.90%)
14.	CSF Rhinorrhea	3(1.40%)
15.	Blurring of vision	2(1.00%)
16.	Delirium	1(0.50%)
17.	Photophobia	0(0.00%)

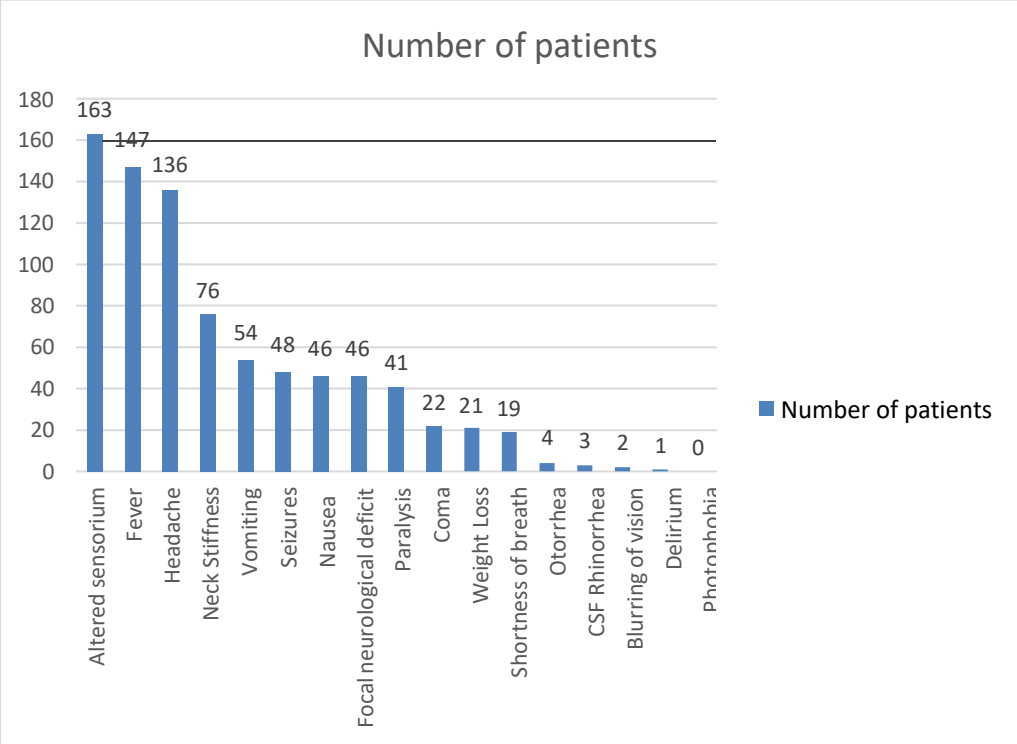


Fig No. 07 – Frequency of clinical features in enrolled patients (n=209)

4. Co-morbidities at presentation

The coexistence of comorbidities at the time of admission were evaluated. Diabetes mellitus emerged as the most common comorbidity at the time of admission being present in 48 oftotal patients (23%). Immunodeficiency and sepsis were the 2nd and 3rd most common comorbidities, presented in 39 (18.7%) & 34 (16.3%) patients relatively. Recent evidence & past history of dengue fever, respiratory tract infection, tuberculosis, urinary tract infection, COVID-19 infection, HIV, hepatitis B & hepatitis C were recorded in 30(14.4%),26(12.4%),21(10.0%),11(5.3%),07(3.3%),10(4.8%),01(0.5%) & 01(0.5%) patients in respective order. Current or past history of COPD, hypertension, renal dysfunction, stroke, malignancy, heart disease & chronic liver disease was present in 24(11.5%), 21(10%), 14(6.7%), 09(4.3%), 08(3.8%) & 03 (1.4%) patients. Addiction history of tobacco smoking and alcohol consumption were also noted among patients with frequency of 11.5% (n=24) & 3.8% (n=08) in respective order. It was also noticed that 3.3% (n=07) & 1.9% (n=04) of the population comprising of 07 & 04 patients had recent or past history of any neurosurgery & head trauma respectively.

Table No. 5. Frequency & percentages of Co-morbidities of enrolled patients (n=209)

Sr.no	Co-morbidities	Number of patients (n=209)
1.	Diabetes mellitus	48(23%)
2.	Immunodeficiency	39(18.70%)
3.	Sepsis	34(16.30%)
4.	Dengue Fever	30(14.40%)
5.	Respiratory Tract Infection	26(12.40%)
6.	COPD	24(11.50%)
7.	Smoking	24(11.50%)
8.	Hypertension	21(10.00%)
9.	Tuberculosis	21(10.00%)
10.	Renal Dysfunction	19(9.10%)
11.	Stroke	14(6.70%)
12.	Urinary Tract Infection	11(5.30%)

13.	HIV/AIDS	10(4.80%)
14.	Malignancy	09(4.30%)
15.	Heart Disease	08(3.80%)
16.	Alcohol	08(3.80%)
17.	Neurosurgery/VP Shunt	07(3.30%)
18.	COVID-19	07(3.30%)
19.	Head Trauma	04(1.90%)
20.	Chronic Liver Disease	03(1.40%)
21.	Hepatitis B	01(0.50%)
22.	Hepatitis C	01(0.50%)

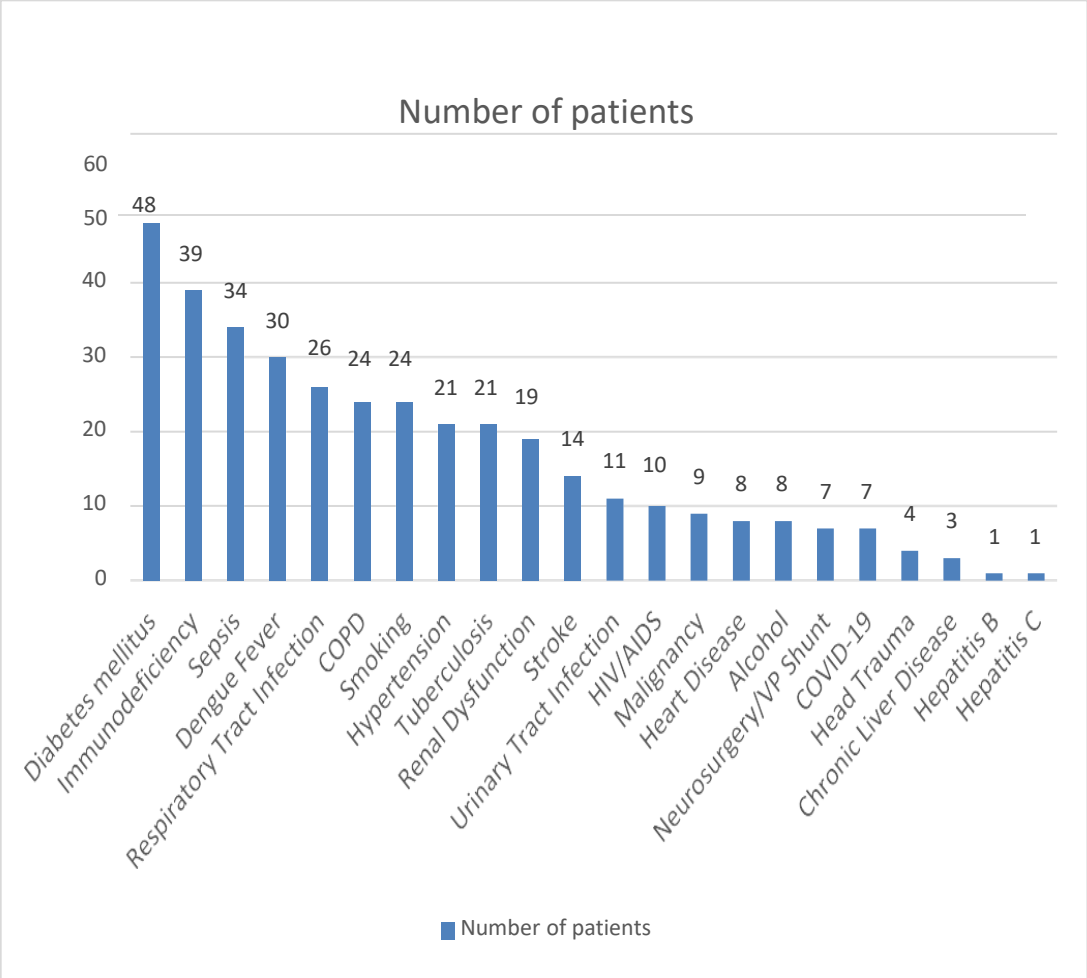


Fig. No. 08 – Frequency of comorbidities in enrolled patients (n=209)

5. Investigations

5.1 Haematological profile

Haematological profile consisting of haemoglobin, total leukocyte count & platelet count wasevaluated among patients.

Mean Hb of population is 11.52±2.7 g/dl which ranged between 5 to 19.5. Mean TLC value is13.3x 10^3cells/µL±26.9 x 10^3 with a range of 0.81 X 10^3cells/µL to 391.00 X 10^3cells/µL.Analyzed mean platelet value is 255.77 X 10^3 /µL ±139.45 X 10^3 /µL with range of 7 X 10^3 /µL to 631 X 10^3 /µL.

5.2 Inflammatory Markers

Inflammatory markers consisting of serum High sensitivity C-reactive protein (HsCRP), Erythrocyte sedimentation rate (ESR) & Procalcitonin were evaluated among 184 (88.03%), 177 (84.68%) & 119 (56.93) patients respectively. Mean HsCRP is 63.19±64.04 mg/L which ranged between 0.14 to 278.00 mg/L.Mean ESR value is 44±31 mm in 1 hour ranging between 2 to 194.Mean Procalcitonin value is 13.93±76.01 ng/mL with a range of 0.02-803.00 ng/mL.

5.3 Renal Profile

Renal profile comprising of serum urea and serum creatinine, was evaluated among 209 patients. Mean serum urea value is 51±43 mg/dL with a range of 6.00-294.Mean serum creatinine value is 1.46±1.36 mg/L which ranged between 0.27 to 9.12 mg/dL.

Rest all blood investigations comprising of liver function tests, serum electrolytes, venous plasma glucose & HbA1c, are mentioned in table with mean±standard deviation and range.

Table No. 6- Haematological profile of suspected meningoencephalitis patients (n=209)

Parameter	Mean±SD	Range
Hb(gm/dL)(n=209)	11.5±2.7	5.0-19.5
TLC(cells/µL) (n=209)	13.3±26.9	0.81-391.2
Platelet(cells/µL) (n=209)	255.77±139.45	7-631
HsCRP(mg/L) (n=184)	63.19±64.04	0.14-278.00
ESR(mm in 1st hour) (n=177)	44±31	2-194
Procalcitonin(n=119)	13.95±76.00	.02-803.00
Urea(mg/dL) (n=209)	51±43	6-294
Creatinine(mg/dL) (n=209)	1.46±1.36	.27-9.12
SGOT(IU/L) (n=209)	202±806	2-8216
SGPT(IU/L) (n=209)	146±665	2-8235
ALP IU/L) (n=209)	162±196	39-1998
Total Bilirubin(mg/dL) (n=209)	1.14±1.88	.07-22.59
Direct Bilirubin(mg/dL)(n=209)	0.59±1.12	.02-12.9
Indirect Bilirubin (mg/dL)(n=209)	0.68±0.83	.02-9.71
Total Protein(g/dL) (n=208)	6.31±1.18	.54-9.35
Albumin(g/dL) (n=209)	3.21±0.76	1.32-4.82
Globulin(g/dL) (n=209)	3.11±0.70	.31-5.74
Sodium(mEq/L) (n=209)	134±08	109-171
Potassium(mEq/L) (n=209)	4.10±0.73	1.70-7.01
Chlorides(mEq/L) (n=209)	100±08	60-125
Plasma Glucose (mg/dL)(n=194)	122±39	74-290
HbA1c (n=30)	8.6±2.4	4.7-15.5

Cultures of body fluids- Blood, urine & sputum/bronchial aspirate

Out of total 209 patients, blood, urine & sputum or bronchial cultures were obtained for 199 patients (95%).
Culture positivity rate for blood, urine& sputum/bronchial aspirate was 10.6% (n=21), 10.6% (n=21) & 12.1% (n=24) respectively.

Various bacterial organisms were cultured in automated blood culture system comprising of Methicillin Resistant *Staphylococcus aureus* (MRSA) (n=2), Methicillin Sensitive Staphylococcus*aureus* (MSSA) (n=2), *Escherichia coli* (n=2), *Klebsiella pneumonia* (n=2), *Enterococcus faecium*(n=2), *Streptococcus pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Burkholderiacenocepacia, Providencia rettgeri, Serratia marscences* & *Staphylococcus epidermidis.*

Total frequency of gram-positive organisms was 8(38.1 %) and for gram-negative organisms, it was 9(42.8%).

Multiple times multiple bacterial organisms were cultured in single blood culture. Though most common finding was presence of 'Gram positive cocci', which became sterile in further reporting (n=5) (23.8%) & same as with 'Gram negative bacilli' (n=1) (4.8%).

On the other aspect, urine culture showed growth of only gram negative bacteria, comprising of Escherichia coli (n=11) (52.3%), *Pseudomonas aeruginosa*(n=6) (28.6%), *Klebsiella pneumoniae* (n=3) (14.3%), *Klebsiella oxytoca* (n=1) (4.8%) &*Proteus vulgaris* (n=1)(4.8%).

Sputum or bronchial aspirate culture showed *Acinetobacter baumannii* (n=8) (33.3%), *Klebsiella pneumoniae* (n=4) (16.16%), *Escherichia coli* (n=03) (12.5%), *Pseudomonas aeruginosa*(n=03) (12.5%) & Methicillin Resistant *Staphylococcus aureus* (MRSA) (n=3) (12.5%).

Mycobacterium tuberculosis was also cultured in 3 of samples out of 24(12.5%).

CSF ANALYSIS

Diagnostic lumbar puncture was done in 195 patients out of 209 patients (95%). Cerebrospinal fluid analysis was done on the basis of biochemical, cytological & microbiological profile.

CSF abnormality was detected in 173 samples out of 195 samples (89%). CSF biochemical & cytological profile is depicted below in table.

Table No. 07 – CSF Profile of suspected meningoencephalitis patients (n=195)

Sr.no.	Parameters(n=195)	Range	Mean±SD
1.	Protein(mg/dL)	19-778	147±171
2.	Chloride(mEq/L)	90-147	122±10
3.	CSF Chloride/Plasma Chloride	0.85-1.62	1.22±0.01
4.	Glucose(mg/dL)	1-254	67±38
5.	CSF Glucose/Plasma Glucose	0.01-0.96	0.54±0.22
6.	ADA (IU/L)	0-91	4±9
7.	WBC(Cells/µL)	0-1471	87±205
8.	RBC(Cells/µL)	0-10000	376±1459

In 154 confirmed meningoencephalitis patients, CSF analysis was done for 141 patients, outof which CSF abnormality was present in 133 patients (86%).

CSF biochemical & cytological profile is depicted below in table.

Table No. 08 – CSF Profile of confirmed meningoencephalitis patients (n=141)

Sr.no.	Parameters(n=141)	Range	Mean±SD
1.	Protein(mg/dL)	19-778	147±171
2.	Chloride(mEq/L)	92-147	122±10
3.	CSF Chloride/Plasma Chloride	0.94-1.62	1.22±0.01
4.	Glucose(mg/dL)	1-254	63±42
5.	CSF Glucose/Plasma Glucose	0.01-0.96	0.51±0.24
6.	ADA (IU/L)(n=121)	0-91	6±10
7.	WBC(Cells/µL)	0-1472	117±234
8.	RBC(Cells/µL)	0-10000	506±1699

Compare Means

Mean values of CSF findings were compared within different diagnostic categories by One-Way ANOVA test.

CSF Protein

Mean difference was significant between tubercular meningoencephalitis & viral meningoencephalitis (P- value < 0.05). Mean difference was significant between bacterialmeningoencephalitis & viral meningoencephalitis. (P- value < 0.05)

CSF GLUCOSE/PLASMA GLUCOSE RATIO

Mean difference was significant among tubercular meningoencephalitis, viral meningoencephalitis & dengue encephalitis (P- value < 0.01). Mean difference was significant between bacterial meningoencephalitis & dengue encephalitis (P- value < 0.01).

CSF Chloride

Mean difference was significant among tubercular meningoencephalitis, viral meningoencephalitis & dengue encephalitis (P- value< 0.01).

CSF Chloride/Serum Chloride ratio

Mean difference was significant between tubercular meningoencephalitis & viral meningoencephalitis (P- value< 0.01).

Here it was observed that mean ratio difference was not significant between TBM & dengueencephalitis. It can be attributed to circulating volume depletion in dengue fever patients leading to increase in serum chloride levels.

CSF Adenosine deaminase

Mean difference was significant between tubercular meningoencephalitis & viral meningoencephalitis (P- value< 0.05).

CSF WBC Count

Mean difference was significant between tubercular meningoencephalitis & bacterial meningoencephalitis (P- value< 0.05). Bacterial meningoencephalitis: Mean difference was significant in comparison to TBM, viral meningoencephalitis, dengue encephalitis & paraneoplastic meningoencephalitis (P- value< 0.01).

Table No. 09 – CSF Protein description among different etiologies

Diagnosis	Mean ± SD	Range
Tubercular Meningoencephalitis(n=56)	235 ± 28	19-778
Bacterial Meningoencephalitis(n=18)	286 ± 55	46-735
Viral Meningoencephalitis(n=33)	105 ± 19	25-553
Dengue Meningoencephalitis(n=16)	106 ± 29	22-374
Fungal Meningoencephalitis(n=05)	192 ± 75	86-484

Table No. 10 – CSF glucose/Plasma glucose ratio description among different etiologies

Diagnosis	Mean ± SD	Range
Tubercular Meningoencephalitis(n=56)	0.40± 0.03	0.01-0.92
Bacterial Meningoencephalitis(n=18)	0.43± 0.03	0.01-0.88
Viral Meningoencephalitis(n=33)	0.62± 0.03	0.30-0.94
Dengue Meningoencephalitis(n=16)	0.71 ± 0.03	0.50-0.96
Fungal Meningoencephalitis(n=05)	0.52 ± 0.13	0.04-0.75

Table No. 11 – CSF chloride/Serum chloride ratio description among different etiologies

Diagnosis	Mean ± SD	Range
Tubercular Meningoencephalitis(n=56)	1.18± 0.10	0.94-1.40
Bacterial Meningoencephalitis(n=18)	1.24± 0.02	1.12-1.61
Viral Meningoencephalitis(n=33)	1.25± 0.01	1.08-1.41
Dengue Meningoencephalitis(n=16)	1.22± 0.01	1.12-1.31
Fungal Meningoencephalitis(n=05)	1.28 ± 0.04	1.20-1.42

Table No. 12 – CSF ADA Level description among different etiologies

Diagnosis	Mean ± SD	Range
Tubercular Meningoencephalitis(n=51)	10 ± 2	0-91
Bacterial Meningoencephalitis(n=15)	03 ± 0.4	01-06
Viral Meningoencephalitis(n=30)	02 ± 0.3	0-07
Dengue Meningoencephalitis(n=09)	01 ± 00	01-01
Fungal Meningoencephalitis(n=04)	1.5 ± 0.5	01-03

Table No. 13 – CSF WBC Count description among different etiologies

Diagnosis	Mean ± SD	Range
Tubercular Meningoencephalitis(n=56)	121 ± 19	0-455
Bacterial Meningoencephalitis(n=18)	348 ± 99	0-1472
Viral Meningoencephalitis(n=33)	80 ± 43	0-1440
Dengue Meningoencephalitis(n=16)	03 ± 01	0-10
Fungal Meningoencephalitis(n=05)	110 ± 93	0-480

CSF Microbiological analysis

Gram staining did not show any results in the 195 obtained CSF samples. One sample demonstrated acid fast bacilli (0.01%). One sample grew *Acinetobacter baumannii* in automated bacterial culture system. Mycobacterium tuberculosis was cultured in 3 samples and demonstrated by MPT-64 Antigen testing.

Fungal elements were demonstrated in 4 of the samples by the means of KOH mount. Molecular diagnosis for tuberculosis (Gene-Xpert/Gene Xpert Ultra) demonstrated M.tuberculosis in 19 samples. Out of 19, 17 samples showed rifampicin sensitivity, 1 showed indeterminate sensitivity & 1 samples showed resistance to rifampicin.

Brain Imaging

Brain imaging were obtained in 202 patients out of 207. It was done by the means of CT-scan& MRI. MRI brain was performed on 158 patients out of 202(78%) and CT scan was performed in all 202 patients except 7 (97%). One hundred and fifty patient showed imaging abnormality out of 202 patients (74%).

Out of 154 confirmed meningoencephalitis patients, 149 patients (97%) underwent brain imaging. CT Brain was performed in 149 patients (97%) & MRI Brain was performed in 121 patients (79%).Brain imaging abnormality was observed in 118 patients (77 %).

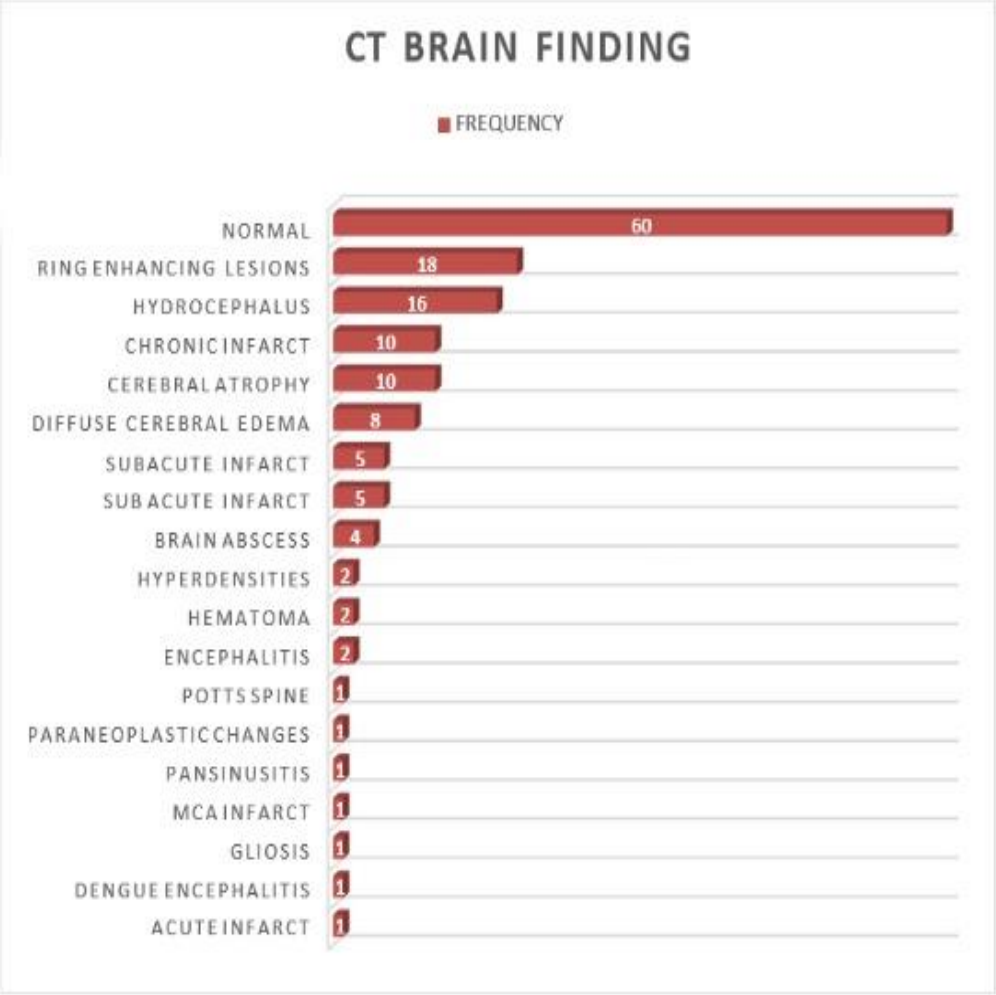


Fig No. 09 -CT- Brain findings with their frequency in confirmed meningoencephalitis (n=149)

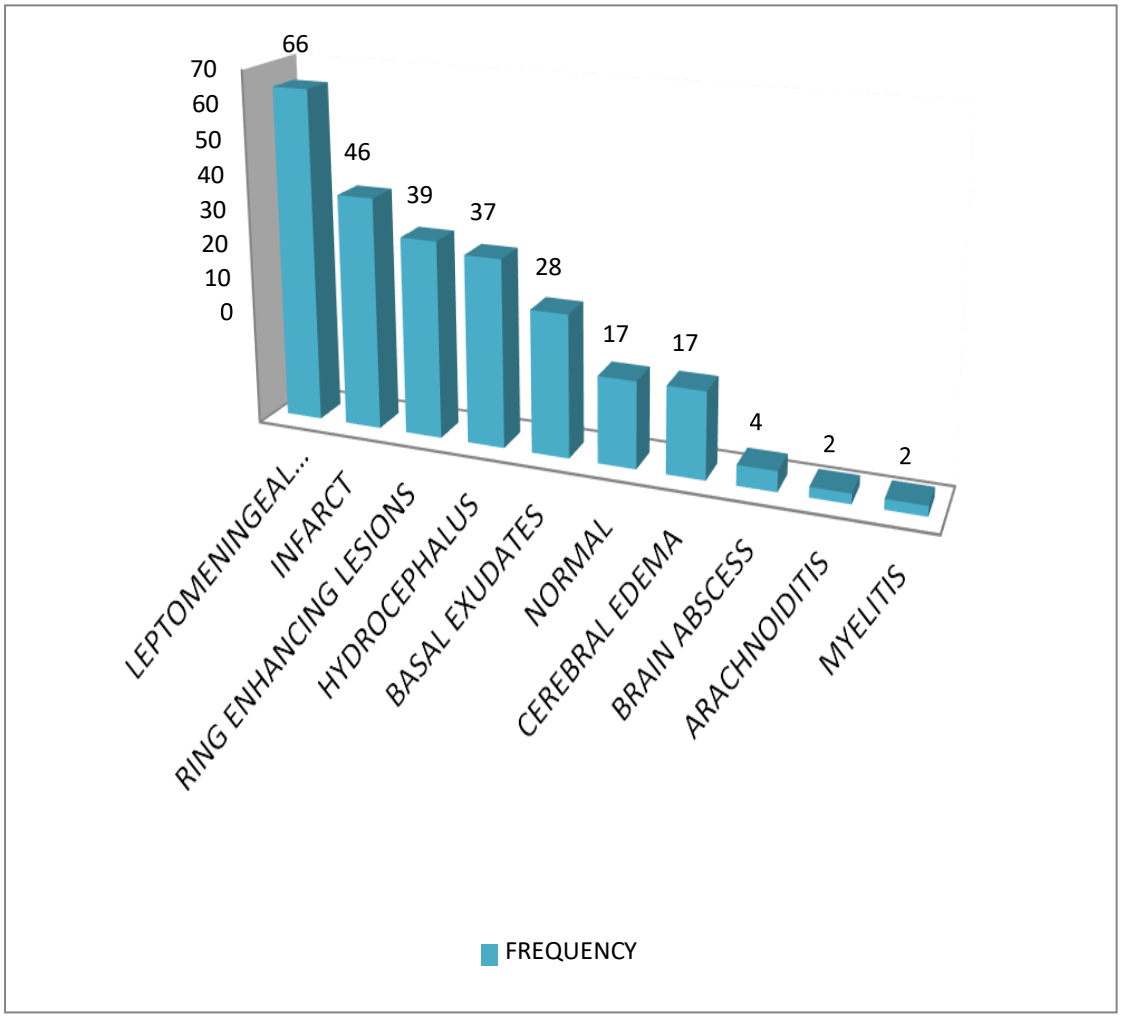


Fig No. 10-MRI Brain findings with their frequency in confirmed meningoencephalitis (n=121)

ANTIBIOTICS

A total of 192 patients (92%) out of 209 with clinical suspicion of infectious meningoencephalitis received empirical antimicrobials.

Eventually 149 patients (78%) were identified with infectious etiology & management continued with antimicrobials.

Table No. 14 – Frequency of antimicrobials among suspected meningoencephalitis

Sr. No.	Anti-Microbials	Suspected Infectious Meningoencephalitis	Proven Infectious Meningoencephalitis
1.	CEFTRIAXONE	109(57%)	80(54%)
2.	PIPERACILLIN-TAZOBACTAM	48(25%)	30(20%)
3.	MEROPENAM	33(17%)	20(13.5%)
4.	VANCOMYCIN	21(11%)	21(14%)
5.	DOXYCYCLINE	05(2.6%)	05(3.3%)
6.	LINEZOLID	05(2.6%)	05(3.3%)
7.	TMP-SMX	02(01%)	02(1.5%)
8.	ATT	55(29%)	55(37%)
9.	MODIFIED ATT	32(17%)	32(21%)
10.	MDR-ATT	3(1.5%)	3(02%)
11.	ACYCLOVIR	86(45%)	67(45%)
12.	ART	09(4.5%)	09(06%)
13.	AMPHOTERICIN B	07(3.5%)	07(4.5%)
14.	VORICONAZOLE	04(2.00%)	04(2.5%)

DURATION OF ANTIBIOTICS

Patients received antimicrobials according to the respective etiology. Data of antimicrobial duration was collected comprising both inpatient and outpatient coverage. Tubercular meningoencephalitis patients received ATT for a duration upto 12 months. Therefore, it generated extreme values of data & test of normality [Shapiro-Wilk test] was applied.

Median duration of antimicrobial coverage in total 209 patients, was 10 days with interquartile range of 19 days.

Median duration of antimicrobial coverage among proven meningoencephalitis (n=154) was 14 days with IQR of 34 days. Meningoencephalitis patients of viral etiology (n=61) received antimicrobials with a mean duration of 11±6 days with a range of 3-28 days. Meningoencephalitis patients of bacterial etiology (n=18) received antimicrobials with amean duration of 15±8 days with a range of 6-42 days.

STEROIDS

A total of 127 patients (60%) received steroids comprising dexamethasone (125 patients) & methylprednisolone (02 patients) either oral or parenteral.

Tubercular meningoencephalitis patients (n=154) received steroids up to 12 weeks of duration,creating extreme values of data. Therefore, median duration with interquartile range was calculated & test of normality [Shapiro-Wilk test] was applied.

Median duration was 4 days with IQR of 12 days.

ANTIEPILEPTICS

A total of 30 patients (14%) out of 209 patients received antiepileptics during the course of admission. Out of these 30, 26 patients were of proven meningoencephalitis category. (26/154)

DURATION OF HOSPITAL STAY

Extreme values of data were observed during calculation. Therefore, median duration with IQR was calculated. Median duration of hospital stay in total population was 14 days with IQR of 128 days.

Median duration of hospital stays in proven meningoencephalitis patients (n=154) was 14 days with IQR of 127 days.

Mean duration of hospital stay in meningoencephalitis patients of viral etiology (n=61) was13±10 days with range of 3-60 days.

Mean duration of hospital stay in meningoencephalitis patients of bacterial etiology (n=18)was 16±10 days with range of 6-50 days.

ICU REQUIREMENT

A total of 88 patients (42%) out of 209 patients had ICU requirement during course ofadmission with mean duration of 9±1 days & range of 1 to 35 days.

Sixty-five patients (42%) of proven meningoencephalitis (n=154) category required ICU carewith mean duration of 10±1 days & range of 1 to 35 days.

A total of 24 tubercular meningoencephalitis patients (n=56) (43%) required ICU care meanduration of 12±2 days & range of 1 to 35 days.

A total of 05 bacterial meningoencephalitis patients (n=18) (28%) required ICU care

mean duration of 06±2 days & range of 03 to 15 days.

A total of 28 meningoencephalitis patients of viral etiology (n=61) (46%) required ICU caremean duration of 08±01 days & range of 3 to 26 days.

NEUROSURGICAL PROCEDURE

A total of 11 patients required any neurosurgical procedure, all of these patients belonged toproven meningoencephalitis category (n=154) (07%).

MODIFIED RANKIN SCALE

MRS score was calculated at the time of admission, discharge & after 1 month of follow up.Respective frequencies are depicted below in graphs.

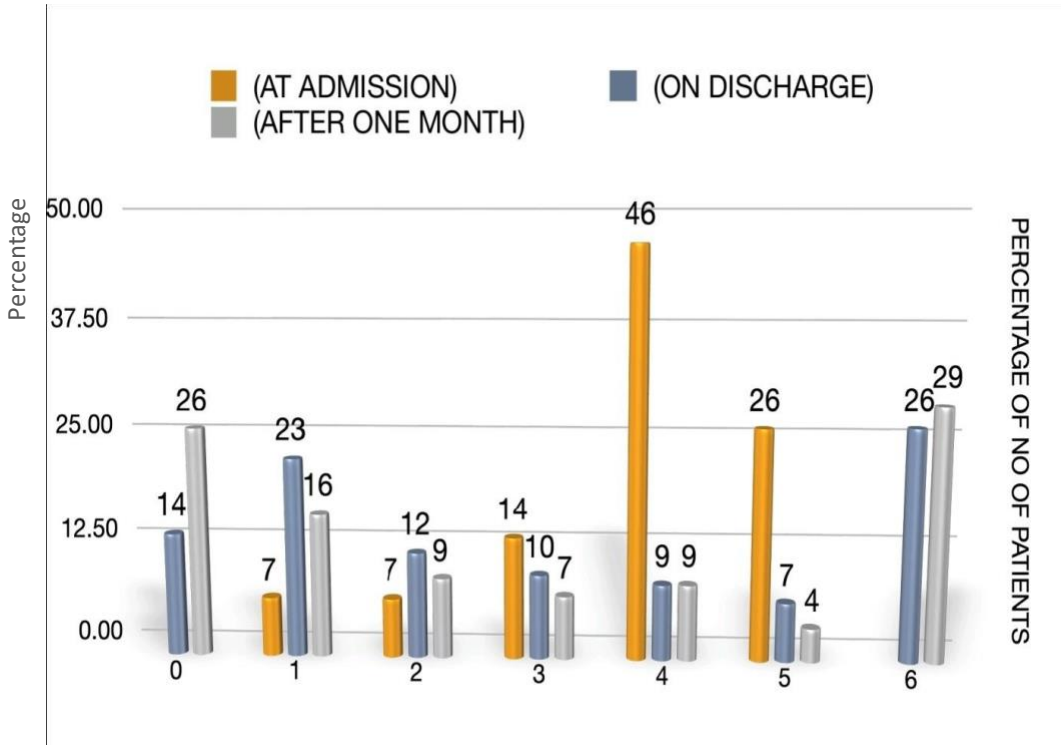


Fig No. 11 – MRS Score at admission, on discharge and at 1 month follow up insuspected meningoencephalitis (n=209)

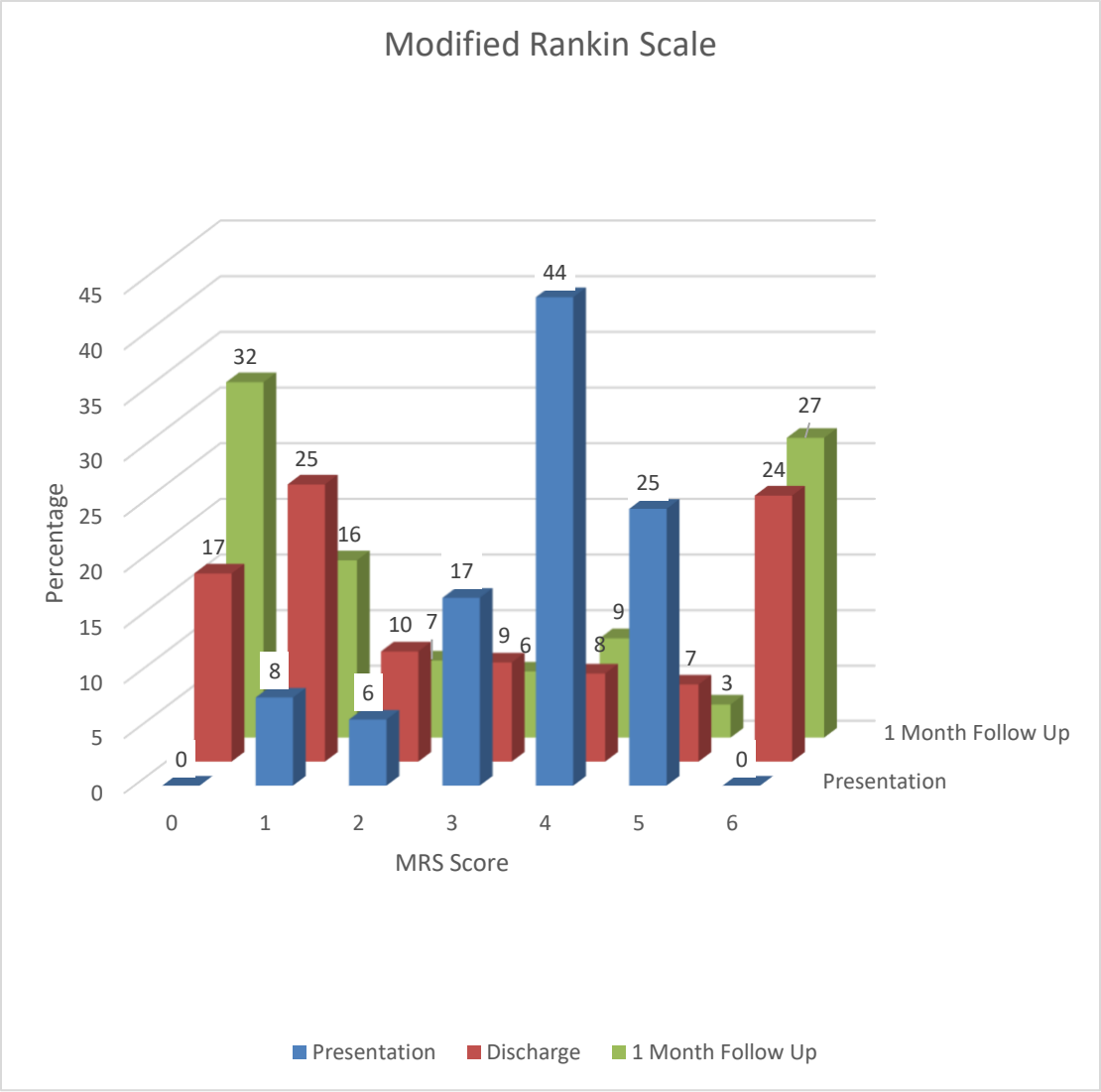
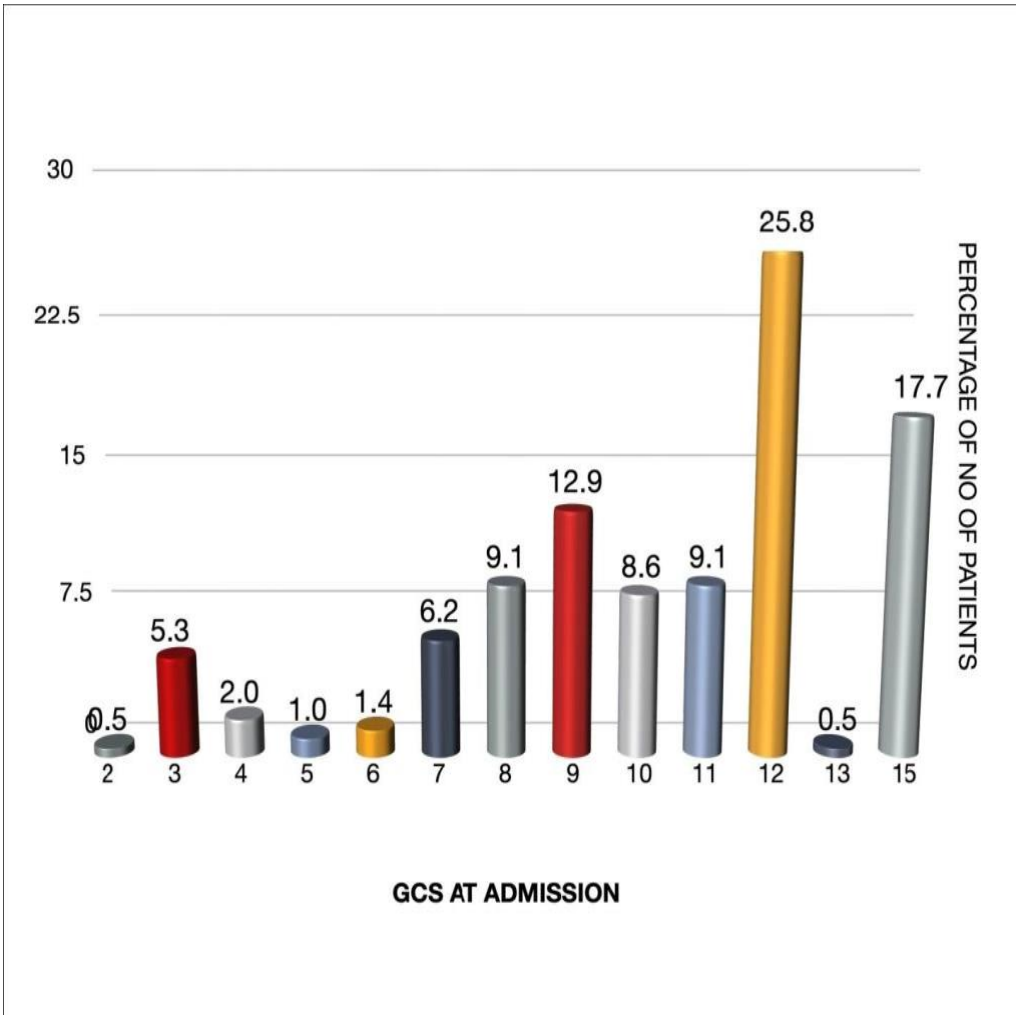


Fig No. 12 – MRS Score at admission, on discharge and at 1 month follow up inconfirmed meningoencephalitis (n=154)

GLASGOW COMA SCALE



GCS was calculated at the time of admission; discharge & 1 month follow up.

Fig No. 13 - GCS at admission in suspected meningoencephalitis (n=209)

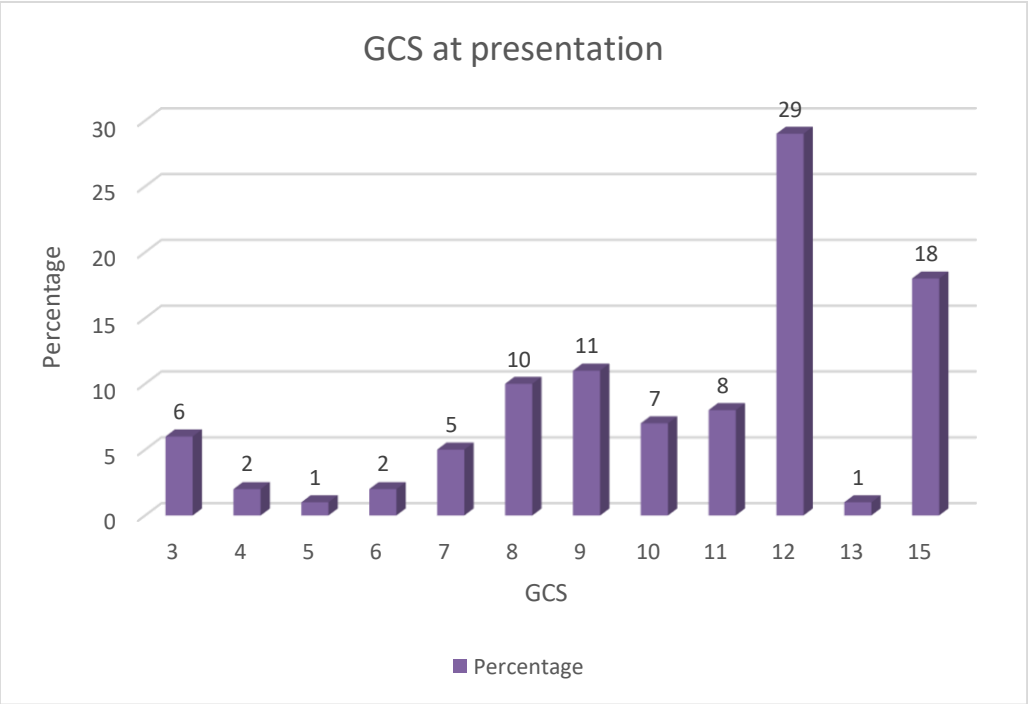


Fig No. 14 - GCS at admission in confirmed meningoencephalitis (n=154)

MORTALITY

Statistics related to mortality is depicted below in table.

Table No. 15 – Mortality Frequency in enrolled patients

Sr. No.	Diagnosis	Mortality
1.	Suspected meningoencephalitis(n=209)	62(30%)
2.	Proven meningoencephalitis(n=154)	44(29%)
3.	Tubercular meningoencephalitis(n=56)	17(30%)
4.	Viral meningoencephalitis(n=33)	04(12%)
5.	Bacterial meningoencephalitis(n=18)	05(29%)
6.	Dengue meningoencephalitis(n=28)	13(46%)

MORBIDITY/ SEQUELAE/ COMPLICATIONS

Patients were followed up for a duration of 1 month & were evaluated for development of complications. Complications were categorized into CNS complications (Category 1), complications outside CNS(Category 2) & Both (Category 3).

A total of 133 patients (64%) developed complications out of 209 patients. 75% patients belonged to Cat. 1, 20 % belonged to Cat. 3 & remaining 5 % belonged to Cat. 2.

One hundred & five patients out of 154 patients of proven meningoencephalitis developed any sort of complication. Out of these 70% belonged to Cat.1, 26% belonged to Cat. 3 & remaining 4 % belonged to Cat. 2.

Table No. 16– Frequency of complications in different etiologies

Diagnosis	Number	No Complication	CNS	Extra CNS	Both
TBM	56	09(16%)	18(32%)	5(09%)	24(43%)
Bacterial Meningoencephalitis	18	09(50%)	08(44%)	0(00%)	01(06%)
Viral Etiology	61	26(43%)	33(54%)	01(1.5%)	01(1.5%)

ATT INDUCED HEPATITIS

Thirty-two patients in total population of 209 developed AIH (15%).

In tubercular meningitis population (n=56), 29 patients (52%) developed AIH.

Association of Risk factors with Poor Outcomes in Confirmed Meningoencephalitis Patients

PREDICTORS OF MORTALITY

Table No. 17 Predictors of Mortality in confirmed Meningoencephalitis (n=154)

Sr. No.	Predictor	OR (95%)	P- value
1.	Age (n=154)	0.71(0.99-1.02)	0.71
2.	Gender (Male) (n=94)	1.56(0.75-3.28)	0.23
3.	TB Meningoencephalitis (n=56)	1.13(0.55-2.33)	0.74
4.	Viral Meningoencephalitis (n=61)	0.93(0.32-2.83)	0.84
5.	Bacterial Meningoencephalitis (n=18)	0.94(0.32-2.83)	0.92
6.	Diabetes Mellitus (n=34)	0.86(0.37-2.04)	0.74
7.	Hypertension (n=12)	1.26(0.36-4.42)	0.72
8.	Renal Dysfunction (n=11)	0.53(0.11-2.55)	0.43
9.	Sepsis (n=24)	9.18(3.45-24.37)	<0.01
10.	Immunocompromised (n =32)	1.40(0.61-3.21)	0.43
11.	HIV AIDS (n=06)	0.48(0.05-4.26)	0.51
12.	Duration (n=154)	0.99(0.96-1.02)	0.49
13.	Seizures (n=41)	1.42(0.66-3.06)	0.37
14.	Focal Neurological Deficit (n=35)	2.31(1.23-5.96)	0.01
15.	Alcoholism (n=03)	0.33	0.30
16.	Hb (n=154)	0.93(0.82-1.06)	0.31
17.	TLC (n=154)	1.00(0.98-1.02)	0.78
18.	Thrombocytopenia (n=154)	1.00(0.99-1.00)	0.04
19.	HsCRP (n=154)	1.01(1.00-1.01)	<0.01
20.	ESR (n=154)	1.00(0.99-1.02)	0.56
21.	Procalcitonin (n=83)	1.01(0.99-1.3)	0.33
22.	Hypoalbuminemia (n=154)	0.42(0.25-0.69)	<0.01
23.	Plasma Glucose (n=154)	1.00(0.99-1.01)	0.33
24.	CSF Protein (n=141)	1.00(0.99-1.00)	0.17

25.	CSF Chloride (n=141)	0.99(0.96-1.03)	0.76
26.	Chloride Ratio (n=141)	0.53(0.01-37.04)	0.77
27.	ADA (n=121)	1.04(0.99-1.09)	0.11
28.	CSF Glucose / Plasma Glucose Ratio (n=141)	1.02(0.22-4.71)	0.98
29.	WBC (n=141)	1.00(0.99-1.00)	0.52
30.	Imaging Abnormality (n=118)	1.83(0.69-4.85)	0.23
31.	Ring Enhancing Lesion (n=39)	1.14(0.51-2.52)	0.75
32.	Leptomeningeal Enhancement (n=66)	1.14(0.56-2.31)	0.71
33.	Basal Exudates (n=28)	0.64(0.24-1.71)	0.37
34.	Hydrocephalus (n=37)	2.04(0.94-4.46)	0.07
35.	Infarct (n=46)	1.73(0.83-3.64)	0.14
36.	CSF Abnormality (n=133)	0.21(0.05-0.92)	0.04
37.	Low GCS (n=154)	0.67(0.58-0.77)	<0.01

Binary logistic regression analysis was done to find the predictors of mortality in cases of proven meningoencephalitis. Univariate analysis showed low GCS, sepsis & immunocompromised condition at admission as significant predictors along with thrombocytopenia, hypoalbuminemia, CSF abnormality and raised HsCRP levels.

Table No. 18 – Multivariate analysis: Mortality Predictor (n=154)

Sr. No.	Predictor	OR(95% CI)	P- value
1.	Sepsis	4.35(1.17-16.15)	.03
2.	Focal Neurological Deficit	5.01(1.47-17.10)	.01
3.	Platelet Count	.99(0.99-1.00)	.21
4.	Serum HsCRP	1.01(1.00-1.01)	.02
5.	Serum Albumin	.601(0.26-1.40)	.24
6.	Low GCS	.77(0.65-0.92)	<0.01
7.	CSF abnormality	.14(0.01-1.34)	.09

Multivariate analysis was done to find independent predictors of mortality. It showed sepsis, focal neurological deficit & low GCS on admission and raised HsCRP levels as independent predictors of mortality.

PREDICTORS OF DISABILITY

Table No. 19 – Predictors of disability in confirmed meningoencephalitis (n=154)

Sr. No.	Predictor	OR (95%)	P- value
1.	Age (n=154)	1.03(1.01-1.04)	<0.01
2.	Gender (Male) (n=94)	2.30(1.16-4.54)	0.02
3.	TB Meningoencephalitis (n=56)	1.20(0.62-2.34)	0.58
4.	Viral Meningoencephalitis (n=61)	0.66(0.34-1.29)	0.23
5.	Bacterial Meningoencephalitis (n=18)	1.00(0.37-2.70)	0.99
6.	Diabetes Mellitus (n=34)	1.44(0.67-3.13)	0.35
7.	Hypertension (n=12)	4.20(1.09-16.15)	0.04
8.	Renal Dysfunction (n=11)	1.31(0.11-3.60)	0.94
9.	Sepsis(n=24)	8.51(2.74-26.40)	<0.01
10.	Immunocompromised(n =32)	1.56(0.71-3.42)	0.26
11.	HIV AIDS (n=06)	1.27(0.25-6.48)	0.78
12.	Duration (n=154)	1.00(0.98-1.03)	0.69
13.	Seizures (n=41)	1.12(0.54-2.30)	0.77
14.	Focal Neurological Deficit (n=35)	2.28(1.05-4.94)	0.04
15.	Hb (n=154)	0.92(0.82-1.04)	0.20
16.	TLC (n=154)	1.00(0.98-1.01)	0.63
17.	Platelet (n=154)	1.00(0.99-1.00)	0.60
18.	HsCRP (n=154)	1.01(1.00-1.01)	<0.01
19.	ESR (n=154)	1.00(1.00-1.02)	0.03
20.	Procalcitonin (n=83)	1.01(0.99-1.01)	0.46
21.	Hypoalbuminemia (n=154)	0.42(0.26-0.69)	<0.01
22.	Plasma Glucose (n=154)	1.00(0.99-1.01)	0.23
23.	CSF Protein (n=141)	1.00(0.99-1.00)	0.04
24.	CSF Chloride (n=141)	0.98(0.95-1.01)	0.19
25.	Chloride Ratio (n=141)	1.03(0.02-46.81)	0.99
26.	ADA (n=121)	1.06(0.99-1.13)	0.05

27.	CSF Glucose / Plasma Glucose Ratio (n=141)	0.45(0.11-1.80)	0.26
28.	WBC (n=141)	1.00(0.99-1.00)	0.15
29.	Imaging Abnormality (n=118)	3.17(1.26-7.98)	0.02
30.	Ring Enhancing Lesion (n=39)	2.22(1.06-4.67)	0.03
31.	Leptomeningeal Enhancement (n=66)	1.07(0.56-2.04)	0.84
32.	Basal Exudates (n=28)	0.94(0.41-2.16)	0.89
33.	Hydrocephalus (n=37)	0.38(0.18-0.82)	0.14
34.	Infarct (n=46)	2.83(1.38-5.81)	0.01
35.	CSF Abnormality (n=133)	0.48(0.11-2.11)	0.33
36.	GCS (n=154)	0.67(0.58-0.77)	<0.01

Binary logistic regression analysis was done to find the predictors of disability by identifyingthe relationship between MRS score at 1 month of follow up & selected factors. Age, male gender, low GCS, sepsis & focal neurological deficit at presentation are found as significant predictors of disability along with hypertension as a comorbidity and raised levels of serum HsCRP, ESR, hypoalbuminemia, raised CSF protein & ADA levels. Brain imaging abnormality with findings of ring enhancing lesions & infarct are also found to be significant.

Table No. 20 – Multivariate Analysis – Predictors of disability (n=154)

Sr. No.	Predictors	OR(95% CI)	P- value
1.	Sepsis	3.92 (0.55-27.95)	0.17
2.	Focal Neurological Deficit	3.753(0.77-18.31)	0.10
3.	HsCRP	1.00(0.99-1.01)	0.83
4.	Albumin	0.38(0.13-1.15)	0.09
5.	Low GCS	0.694(0.56-0.86)	<.01
6.	Age	1.02(0.99-1.05)	0.18
7.	Gender	0.46(0.90-2.32)	0.34
8.	Hypertension	10.74(0.46-251	0.14

9.	ESR	1.01(0.99-1.04)	0.23
10.	Brain Imaging Abnormality	1.38(0.15-12.71)	0.12
11.	Ring Enhancing Lesions	1.85(0.28-12.40)	0.17
12.	Infarct	.60(0.12-3.10)	0.10
13.	Protein	1.00(0.00-1.00)	0.83
14.	ADA	1.09(0.96-1.23)	0.09

Multivariate analysis showed that out of these significant parameters, only low GCS on presentation is independent predictor of disability on follow up of proven meningoencephalitis patients.

PREDICTORS OF CNS COMPLICATIONS

Table no. 21 – Predictors of CNS Complications in confirmed meningoencephalitis (n=154)

Sr. No.	Age (n=154)	OR (95%)	P- value
1.	Gender (Male) (n=94)	0.01 (0.99-1.03)	0.24
2.	TB Meningoencephalitis (n=56)	0.73 (0.37-1.46)	0.38
3.	Viral Meningoencephalitis (n=61)	2.20 (1.06-4.54)	0.03
4.	Bacterial Meningoencephalitis (n=18)	0.55 (0.28-1.08)	0.08
5.	Diabetes Mellitus(n=34)	0.52 (0.19-1.39)	0.19
6.	Hypertension(n=12)	1.75 (0.75-4.08)	0.20
7.	Renal Dysfunction(n=11)	0.77 (0.23-2.55)	0.67
8.	Sepsis(n=24)	0.65 (0.19-2.24)	0.50
9.	Immunocompromised(n =32)	1.44 (0.56-3.72)	0.45
10.	HIV AIDS (n=06)	0.92 (0.41-2.05)	0.84
11.	Duration (n=154)	0.55 (0.11-2.81)	0.47
12..	Seizures (n=41)	1.01 (0.99-1.04)	0.36
13.	Focal Neurological Deficit (n=35)	1.77 (0.80-3.88)	0.16
14.	Alcoholism (n=03)	28.69 (3.80-216.53)	<0.01
15.	Hb (n=154)	1.13 (0.10-12.70)	0.92
16.	TLC (n=154)	0.93 (0.83-1.05)	0.26
17.	Platelet (n=154)	0.99 (0.98-1.01)	0.40
18.	HsCRP (n=154)	1.00 (0.99-1.00)	0.80
19.	ESR (n=154)	1.00 (0.99-1.01)	0.18
20.	Procalcitonin (n=83)	1.00 (0.99-1.01)	0.91
21.	SerumAlbumin (n=154)	1.01 (0.98-1.03)	0.49
22.	Plasma Glucose (n=154)	0.86 (0.55-1.34)	0.51
23.	CSF Protein (n=141)	1.01 (1.00-1.02)	0.14
24.	CSF Chloride (n=141)	1.00 (0.99-1.00)	0.14
25.	Chloride Ratio (n=141)	0.98 (0.94-1.01)	0.15

26.	ADA (n=121)	0.03 (0.00-2.05)	0.10
27.	CSF Glucose / Plasma Glucose Ratio (n=141)	1.13 (1.02-1.26)	0.03
28.	WBC (n=141)	1.00 (0.99-1.01)	0.25
29.	Imaging Abnormality (n=118)	1.00 (0.99-1.00)	0.21
30.	Ring Enhancing Lesion (n=39)	1.77 (0.79-4.00)	0.17
31.	Leptomeningeal Enhancement (n=66)	2.72 (1.15-6.44)	0.02
32.	Basal Exudates (n=28)	1.75 (0.88-3.46)	0.11
33.	Age (n=154)	3.11 (1.11-8.72)	0.03
34.	Infarct (n=46)	2.22 (1.02-4.84)	0.05
35.	CSF Abnormality (n=133)	0.58 (0.11-3.01)	0.52
36.	Low GCS (n=154)	0.90(0.82-0.99)	0.03

Binary logistic regression analysis was done to find predictors of CNS complications in patients of proven meningoencephalitis. Low GCS & focal neurological deficit at presentation are found as significant predictors of CNS complications along with diagnosis oftubercular meningoencephalitis & raised CSF ADA levels. Findings of ring enhancing lesions, basal exudates & infarct on brain imaging, are also found to be significant.

Table no. 22 – Multivariate analysis – Predictors of CNS Complications (n=154)

Sr. No.	Predictor	OR(95% CI)	P- value
1.	TBM	6.10(1.58-23.55)	.009
2.	Focal Neurological Deficit	1471594808.319	.998
3.	ADA	1.04(0.91-1.20)	.542
4.	Ring Enhancing Lesions	0.87(0.20-4.20)	.863
5.	Basal Exudates	0.59(0.09-4.01)	.587
6.	Infarct	1.26(0.42-3.81)	.682
7.	Low GCS	0.79(0.68-0.93)	.005

Multivariate analysis showed that out of these significant parameters, only low GCS on presentation and diagnosis of tubercular meningoencephalitis, are independent predictors of CNS complications in proven meningoencephalitis patients.

ANALYSIS OF CSF TUMOR NECROSIS FACTOR – alpha (TNF-alpha) & INTERLUKIN - 8 (IL-8)

INTERLUKIN - 8 (IL-8)

Levels of interlukin-8 were measured in CSF by means of ELISA. Analysis of 83 samples was done among 209 clinically suspected meningoencephalitis.Mean value of CSF IL-8 is 68±66 pg/mL with range of 0 to 329 pg/mL.

A total of 57 samples were analyzed among proven meningoencephalitis patients.Mean value of CSF IL-8 is 70±64 pg/mL with range of 0 to 329 pg/mL. Twenty-two samples of tubercular meningoencephalitis were analyzed & showed mean value of 65±37 pg/mL with range of 0 to 159 pg/mL.

Binary logistic regression analysis was done in relation to diagnosis and it was non-significant (P- value=0.60).

Nineteen samples of meningoencephalitis of viral etiology were analyzed & showed meanvalue of 92±91 pg/mL with range of 0 to 329 pg/mL.

Binary logistic regression analysis was done in relation to diagnosis and it was non-significant (P- value=0.08).

Nine samples of bacterial meningoencephalitis were analyzed & showed mean value of 74±57 pg/mL with range of 0 to 187 pg/mL.

Binary logistic regression analysis was done in relation to diagnosis and it was non-significant. (P- value=0.87)

Twenty-six samples of not confirmed meningoencephalitis were analyzed & showed mean valueof 62±70 pg/mL with range of 0 to 224 pg/mL.

Significance of IL-8→

Not significant as predictor of mortality in suspected meningoencephalitis (P-value=0.06)(OR=0.99) (95%CI=0.99-1.00). Not significant as predictor of disability in suspected meningoencephalitis (P- value=0.80) (OR=0.99) (95%CI=0.99-1.00). Not

significant as predictor of complications in suspected meningoencephalitis (P-value=0.41) (OR=0.99) (95%CI=0.99-1.00).

Not significant as predictor of mortality in proven meningoencephalitis (P- value=0.69) (OR=0.99) (95%CI=0.99-1.00). Not significant as predictor of disability in proven meningoencephalitis (P- value=0.32) (OR=1.00) (95%CI=0.98-1.01). Not significant as predictor of CNS complications in proven meningoencephalitis (P- value=0.08) (OR=0.99)(95%CI=0.99-1.00).

Therefore, CSF IL-8 is not a significant marker for diagnosis or predicting prognosis among meningoencephalitis patients.

Tumor necrosis factor – alpha (TNF-alpha)

Levels of Tumor necrosis factor alpha were measured in CSF by means of ELISA. Analysis of 83 samples was done among 209 clinically suspected meningoencephalitis. Mean value of CSF TNF-alpha is 26±18 pg/mL with range of 0.25 to 143 pg/mL.

A total of 57 samples were analyzed among proven meningoencephalitis patients. Mean value of CSF TNF-alpha is 27±20 pg/mL with range of 0 to 143 pg/mL. Binary logistic regression analysis was done in relation to diagnosis and it was non-significant(P-value=0.48).

Twenty-two samples of tubercular meningoencephalitis were analyzed & showed mean value of 26.40±17.75 pg/mL with range of 0.25 to 95.60 pg/mL. Binary logistic regression analysis was done in relation to diagnosis and it was non-significant(P-value=0.89).

Nineteen samples of meningoencephalitis of viral etiology were analyzed & showed mean value of 21.31±5.74 pg/mL with range of 1.00 to 26.10 pg/mL. Binary logistic regression analysis was done in relation to diagnosis and it was non- significant. (P-value=0.58).

Nine samples of bacterial meningoencephalitis were analyzed & showed mean value of 34.80±41.38 pg/mL with range of 0.50 to 143 pg/mL. Binary logisticregression analysis was done in relation to diagnosis and it was non-significant. (P- Value=0.16)

Twenty-six samples of not proven meningoencephalitis were analyzed & showed mean valueof 23.85±12.51 pg/mL with range of 0.25 to 61.38 pg/mL.

Significance of TNF-alpha →

Not significant as predictor of mortality in suspected meningoencephalitis (P-value=0.44)(OR=0.99) (95%CI=0.95-1.02). Not significant as predictor of disability in suspected meningoencephalitis (P- value=0.52) (OR=1.01) (95%CI=0.98-1.04). Not significant as predictor of complications in suspected meningoencephalitis (P-value=0.73) (OR=0.99) (95%CI=0.97-1.02).

Not significant as predictor of mortality in proven meningoencephalitis (P- value=0.99) (OR=1.00) (95%CI=0.97-1.03). Not significant as predictor of disability in proven meningoencephalitis (P- value=0.27) (OR=1.02) (95%CI=0.98-1.06). Not significant as predictor of CNS complications in proven meningoencephalitis (P- value=0.54) (OR=0.99)(95%CI=0.96-1.02).

Therefore, CSF TNF-alpha is not a significant marker for diagnosis or predicting prognosis amongmeningoencephalitis patients.

Independent samples t Test was applied and it showed CSF TNF-alpha & IL-8 cannot differentiate among suspected meningoencephalitis & proven meningoencephalitis.

Table No. 23. Mean and standard deviation of TNF-alpha and CSF IL-8 (n=83)

	Proven Meningoencephalitis	**N**	**Mean**	**Std. Error Mean**
TNF - ALPHA	0	26	23.85±12.51	2.45381
	1	57	26.91±20.30	2.68888
CSFIL8	0	26	61.69±69.70	13.668
	1	57	70.26±64.32	8.520

Table No. 24 Independent Samples "t" Test of TNF-alpha and CSF IL-8 (n=83)

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	P- value	t	df	P- value (2- tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
TNF-ALPHA	Equal variance assumed	.479	.491	.709	81	.481	3.06170	4.32007	11.65729	5.53389
	Equal variances not assumed			.841	73.667	.403	3.06170	3.64022	10.31555	4.19215
CSF IL-8	Equal variances assumed	.873	.353	.549	81	.585	-8.571	15.626	-39.661	22.520
	Equal variances not assumed			.532	45.158	.597	-8.571	16.106	-41.007	23.866

Table No. 25 ANOVA Table between TNF alpha and Diagnosis categories (n=83)

			Sum of Squares	df	Mean Square	F	P-value
TNF-ALPHA DIAGNOSIS CATEGORIES	Between Groups	(Combined)	1786.661	6	297.777	.881	.513
		Linearity	44.426	1	44.426	.131	.718
		Deviation from Linearity	1742.235	5	348.447	1.030	.406
	Within Groups		25363.756	75	338.183		
	Total		27150.417	81			

Table No. 26 ANOVA Table between IL8 and diagnostic categories (n=83)

			Sum of Squares	df	Mean Square	F	P-value
IL-8 DIAGNOSIS CATEGORIES	Between Groups	(Combined)	25273.808	6	4212.301	.963	.456
		Linearity	5098.278	1	5098.278	1.165	.284
		Deviation from Linearity	20175.530	5	4035.106	.922	.471
	Within Groups		328163.082	75	4375.508		
	Total		353436.890	81			

SENSITIVITY & SPECIFICITY OF DIAGNOSTIC SCORING SYSTEMS

("Thwaites' scoring system and "Lancet consensus scoring system")

Previous literature showed that "Thwaites' scoring system" and "Lancet consensus scoring system" have been used in diagnosis tubercular meningitis & differentiating from other formsof meningitis.

"Thwaites' scoring system" suggests high probability of TBM with score of ≤4.

"Lancet consensus scoring system" suggests probable diagnosis of TBM if score >10 & possible TBM if score is between 6-9, without brain imaging and probable TBM if score > 12& possible TBM if score is between 6-11.

"Thwaites' scoring system" was applied to 142 patients among 154 proven meningoencephalitis patients. It showed mean value of 0±4 with a range of (-5) to 13.

In TBM, mean value is (-2) ±3 with a range of (-5) to 02.

Binary logistic regression analysis showed that decreasing values of scoring are significantpredictor tubercular meningoencephalitis. (P- value = <0.01) (OR=0.66) (CI=0.57-0.76)

In bacterial meningoencephalitis, mean value is 06±4 with a range of (-5) to 13.

Binary logistic regression analysis showed that increasing values of scoring are significant predictor bacterial meningoencephalitis. (P- value = <0.01) (OR=1.70) (CI=1.36-2.13)

"Lancet consensus scoring system" was applied to 142 patients among 154 proven meningoencephalitis patients. It showed mean value of 8±6 with a range of 0 to 20.

In TBM, mean value is 15±4 with a range of 5 to 20.

Binary logistic regression analysis showed that increasing values of scoring are significantpredictor of TBM. (P- value = <0.01) (OR=2.45) (CI=1.66-3.57)

In bacterial meningoencephalitis, mean value is 03±1 with a range of 01 to 05.

Binary logistic regression analysis showed that decreasing values of scoring are significant predictor bacterial meningoencephalitis. (P- value = <0.01) (OR=0.60) (CI=0.43-0.84)

LANCET CONSENSUS SCORING SYSTEM

Clinically diagnosed TBM

Area under curve was calculated for “Lancet consensus scoring system” in Clinically diagnosed TBM patients (Possible and Probable) and it was 0.987.

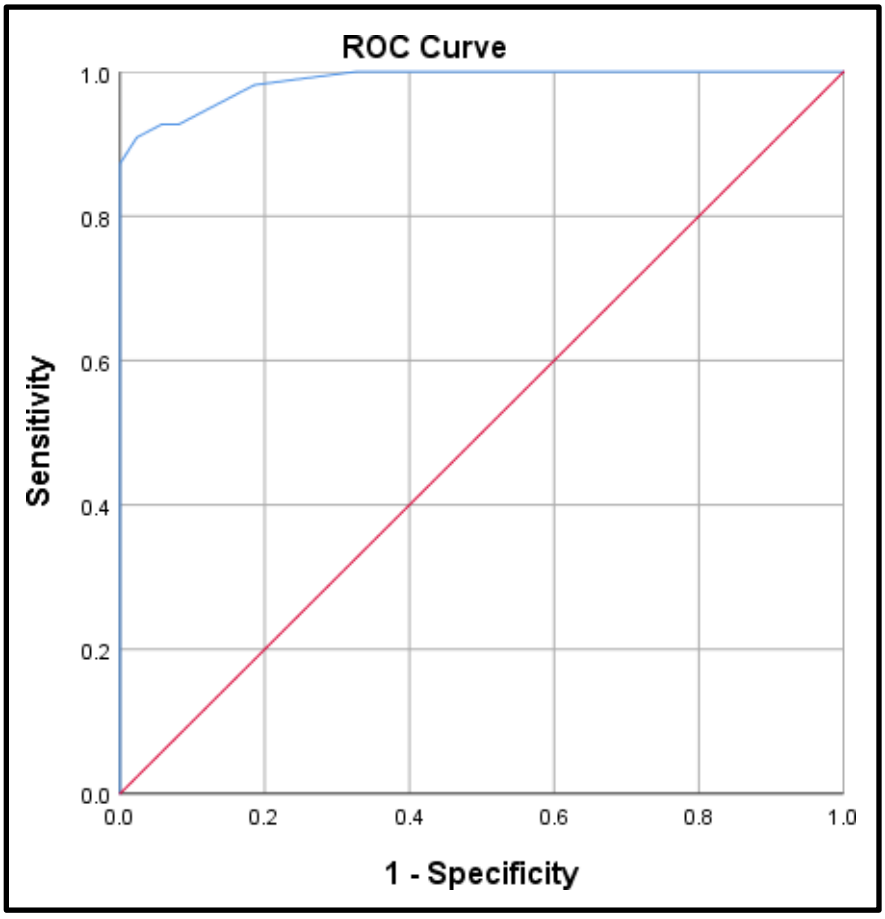


Fig. 15 ROC for Lancet consensus scoring system in Clinically diagnosed TBM patients (n=56)

Table No. 27 Co-ordinations for ROC for Lancet consensus scoring system in Clinically diagnosed TBM patients (n=56)

Coordinates of the Curve		
Lancet Consensus Scoring System		
Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
-1.00	1.000	1.000
.50	1.000	.977
1.50	1.000	.919
2.50	1.000	.744
3.50	1.000	.523
4.50	1.000	.326
5.50	.982	.186
6.50	.927	.081
7.50	.927	.058
8.50	.909	.023
9.50	.873	.000
10.50	.855	.000
11.50	.836	.000
12.50	.782	.000
13.50	.673	.000
14.50	.655	.000
15.50	.618	.000
16.50	.509	.000
17.50	.455	.000
18.50	.236	.000
19.50	.200	.000
21.00	.000	.000

The original value of 12 of probable TBM showed 80% sensitivity & 100% specificity. Here we can suggest new value of 8 for probable TBM with sensitivity of 92 % & specificity of 96 %.

Confirmed TBM (Definite TBM)

Area under curve was calculated for "Lancet consensus scoring system" in Confirmed TBM patients and it was 0.961.

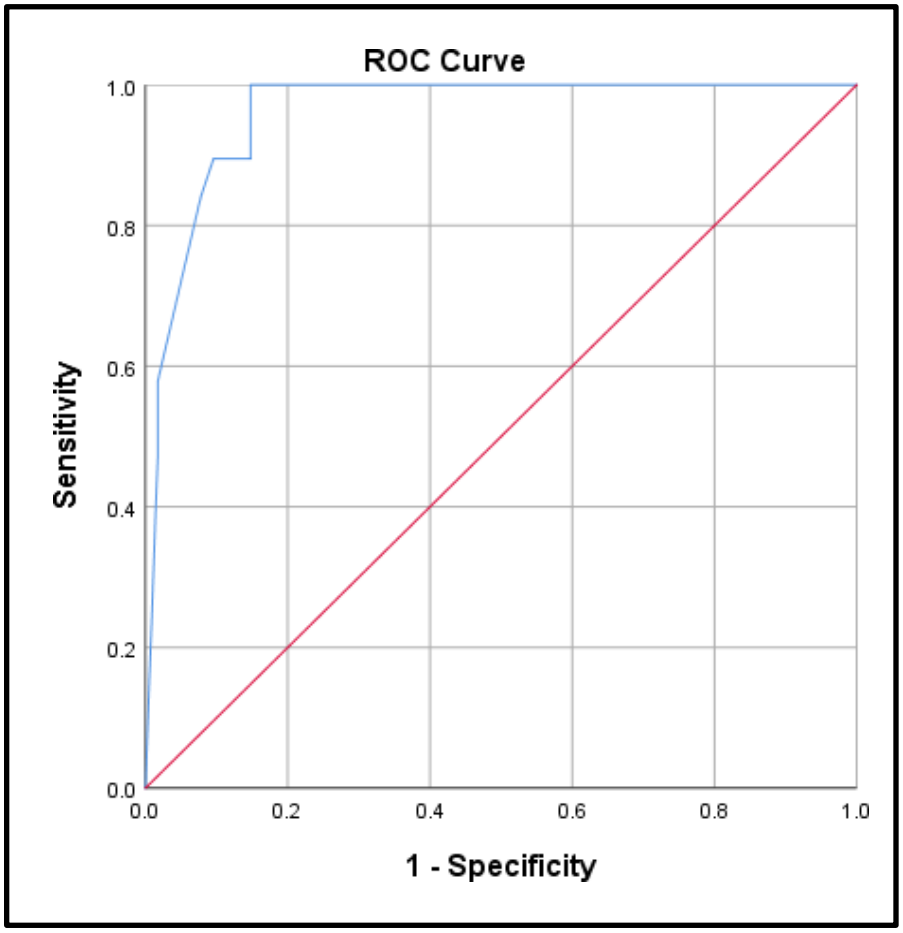


Fig. 16 ROC for Lancet consensus scoring system in confirmed cases of TBM (n=20)

Table No. 28 Co-ordinates for ROC for Lancet consensus scoring system in confirmed cases of TBM (n=20)

Coordinates of the Curve		
Test Result Variable(s): Lancet Consensus Scoring System		
Positive if Greater Than or Equal To	Sensitivity	1 – Specificity
-1.00	1.000	1.000
.50	1.000	.991
1.50	1.000	.948
2.50	1.000	.843
3.50	1.000	.678
4.50	1.000	.548
5.50	1.000	.435
6.50	1.000	.330
7.50	1.000	.313
8.50	1.000	.278
9.50	1.000	.243
10.50	1.000	.235
11.50	1.000	.226
12.50	1.000	.200
14.00	1.000	.148
15.50	.895	.148
16.50	.895	.096
17.50	.842	.078
18.50	.579	.017
19.50	.474	.017
21.00	.000	.000

Original value of 12, showed sensitivity of 100 % & specificity of 79%.

Our proposed score of 8, showed sensitivity of 100 % & specificity of 71%.

THWAITES' DIAGNOSTIC SCORING SYSTEM

Clinically diagnosed TBM

Area under curve was calculated for "Thwaites' scoring system" in Clinically diagnosed TBM patients and it was 0.827.

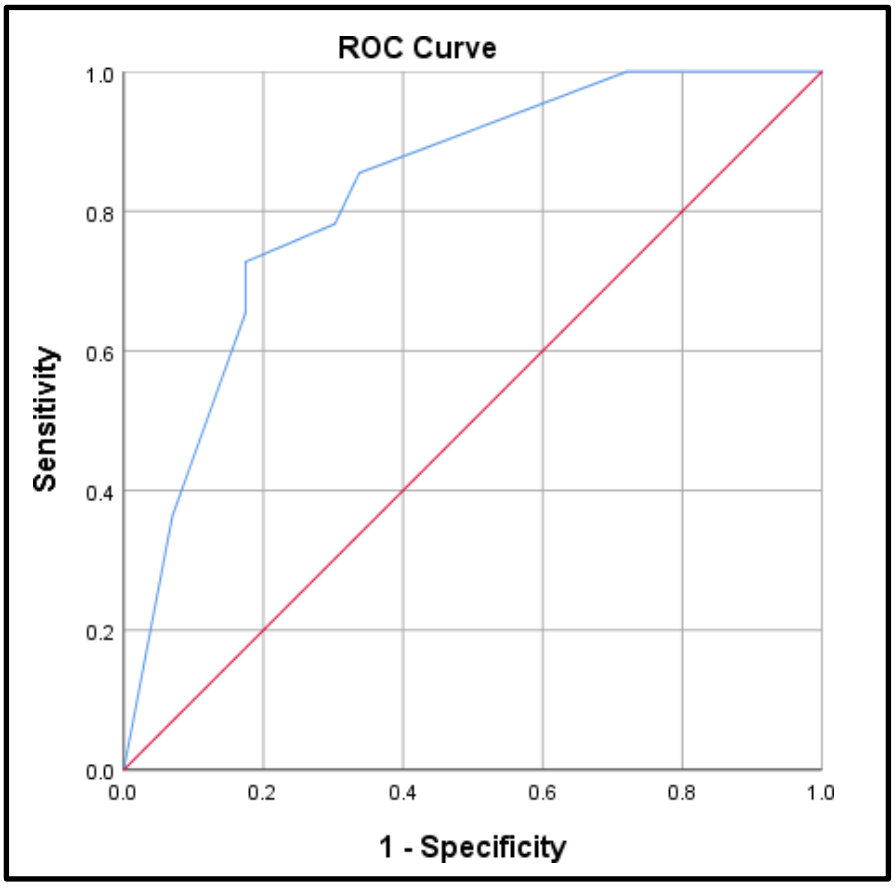


Fig. 17 ROC for Thwaites' Diagnostic Scoring System in Clinically diagnosed TBM patients (n=56)

Table No. 29 Co-ordinates for Thwaites' Diagnostic Scoring System in Clinically diagnosed TBM patients (n=56)

Coordinates of the Curve		
Thwaites' Diagnostic Scoring System		
Positive if Less Than or Equal To	Sensitivity	1 - Specificity
-6.00	.000	.000
-4.00	.364	.070
-2.00	.655	.174
-.50	.727	.174
.50	.782	.302
1.50	.855	.337
2.50	1.000	.721
3.50	1.000	.733
4.50	1.000	.756
5.50	1.000	.767
6.50	1.000	.930
7.50	1.000	.942
9.00	1.000	.953
11.50	1.000	.988
14.00	1.000	1.000

The original value of ≤ 4 showed sensitivity of 100 % & specificity of 26 %. Here we can suggest a new value of (0) for diagnosis of TBM with sensitivity of 75 % & specificity of 79 %.

Confirmed TBM

Area under curve was calculated for "Thwaites' scoring system" in Confirmed TBM patients and it was 0.746.

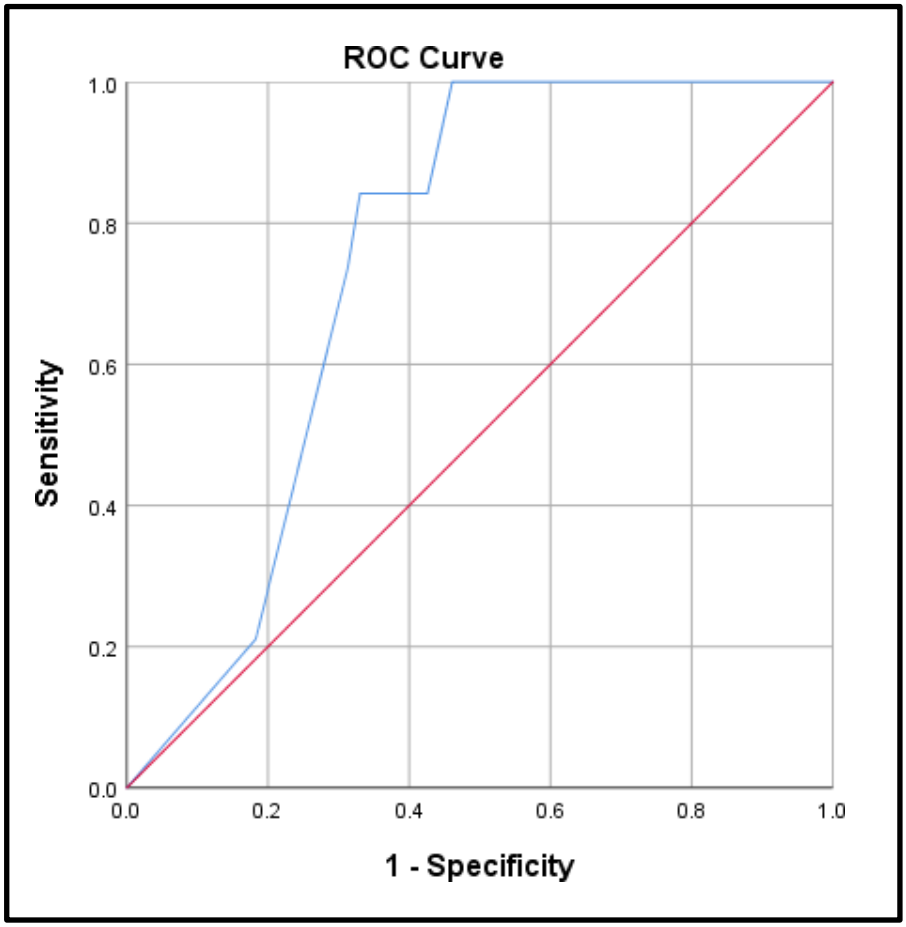


Fig. 18 ROC for Thwaites' Diagnostic Scoring System in Confirmed TBM patients (n=20)

Table No. 30 Co-ordinate for ROC for Thwaites' Diagnostic Scoring System in Confirmed TBM patients (n=20)

Coordinates of the Curve		
Test Result Variable(s): Thwaites' Diagnostic Scoring System		
Positive if Less Than or Equal To	Sensitivity	1 - Specificity
-6.00	.000	.000
-4.00	.211	.183
-2.00	.737	.313
-.50	.842	.330
.50	.842	.426
1.50	1.000	.461
2.50	1.000	.800
3.50	1.000	.809
4.50	1.000	.826
5.50	1.000	.835
6.50	1.000	.948
7.50	1.000	.957
9.00	1.000	.965
11.50	1.000	.991
14.00	1.000	1.000

The original value of ≤ 4 showed sensitivity of 100 % & specificity of 22%.

Our proposed cut-off value of 0 showed sensitivity of 100 % & specificity of 62.5%.

CSF- Adenosine Deaminase (ADA) Level

Confirmed TBM

Area under curve was calculated for CSF ADA levels in confirmed meningoencephalitis patients and it was 0.892.

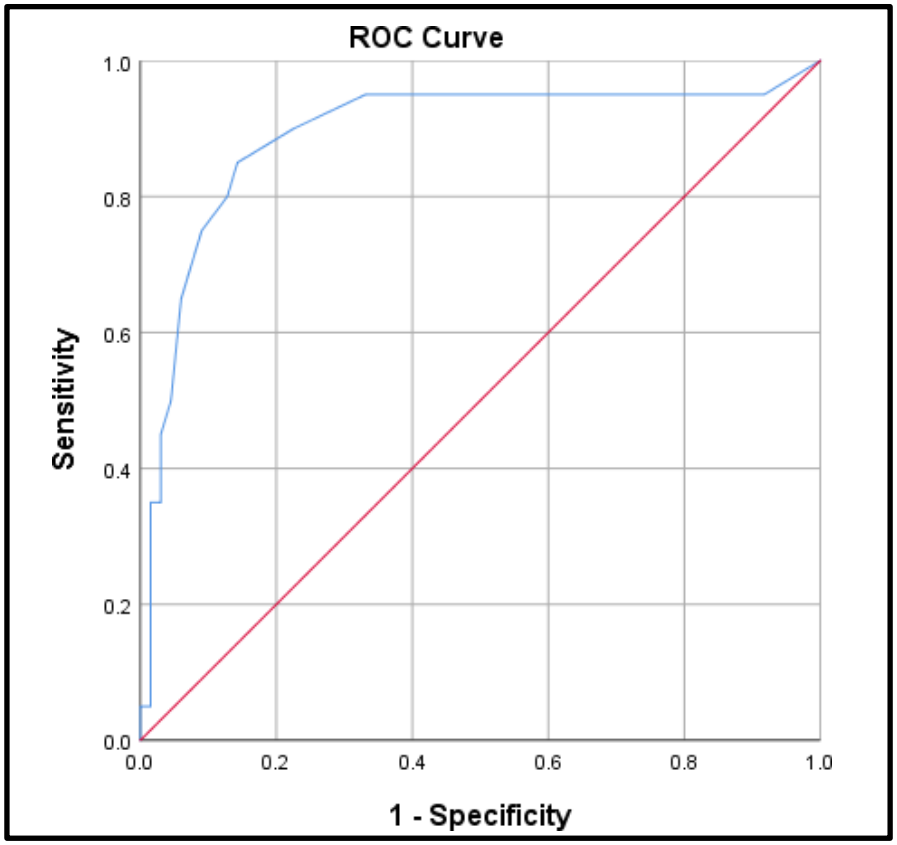


Fig. 19 Area Under the Curve for CSF ADA in Confirmed TBM patients (n=20)

Table No. 31 Co-ordinates for ROC for CSF ADA in confirmed TBM patients (n=20)

Coordinates of the Curve		
Test Result Variable(s): ADA		
Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
-1.00	1.000	1.000
.50	.950	.917
1.50	.950	.466
2.50	.950	.331
3.50	.900	.226
4.50	.850	.143
5.50	.800	.128
6.50	.750	.090
7.50	.650	.060
8.50	.500	.045
9.50	.450	.030
10.50	.350	.030
12.50	.350	.015
15.50	.300	.015
18.00	.250	.015
19.50	.200	.015
24.00	.150	.015
31.50	.050	.015
35.50	.050	.008
63.50	.050	.000
92.00	.000	.000

Previous described cut-off value of 10 IU/L showed sensitivity of 40 % and specificity of 97 %. Here we can propose new cut-off value of 05 IU/L, which showed sensitivity of 87.5% and specificity of 82%.

DISCUSSION

EPIDEMIOLOGY

In our study, mean age in confirmed meningoencephalitis patients was 44±20 years and gender ratio was 1.6: 1 (Male > Female). Cases of acute meningoencephalitis were 57% and subacute meningoencephalitis were 43% (n=154). A study done by Sulaiman T et al. on 611 meningitis patients showed acute meningitis patients consisted of 75% (458/611) of total cases, with a median age of 36 years, whereas subacute meningitis patients consisted of 25% (153/611), with a median age of 38 years. Out of 458 patients with acute meningitis 256 patients (56%) were female & 74 patients (48%) were female out of 153 patients with subacute meningitis, making a total of 330 female patients (54%) out of 611 patients. An opposite finding was observed in our study where the male population was predominant.

The study done by Yerramilli et al. on 147 cases of meningitis of all age groups observed thatthe mean age of their population was 50±15 years. Gender distribution was similar to our study with male patient frequency of 59% (87/147) and female patient frequency of 41% (60/147) (92,93).

In our study, out of 209 with clinical suspicion of meningoencephalitis highest number of patients (24%) got enrolled in the age group > 65 years (50/209) followed by the age group of 18-25 years (20%) (41/209). This pattern got reversed in patients with confirmed meningoencephalitis, 25% of patients (39/154) belonged to age group of 18-25 years & 18.6% of patients (29/154) belonged to age group of > 65 years. The study by Yerramilli A et al. showed somewhat similar findings with the maximum proportion of their study population belonged to the age group of 21-40 years, with frequency of 39% (57/147) and 25% of patients (36/147) belonged to age group of > 60 years. The study by Sulaiman T showed a frequency of 12% of patients from age group of > 65 years (75/611).

The studies on meningitis have mainly focused upon pediatric population or all age population, with studies on only adult population being limited. The available adult studiesare specific & were mainly carried out on HIV/AIDS patients (40).

CLINICAL FEATURES

In our study altered sensorium was the most common symptom with 163 patients (78%) presented with the same. Fever and headache were 2nd and 3rd most common symptoms, which were presented in 147(70.3%) & 136(65.1%) patients relatively. Other predominant symptom was neck stiffness presented in 36.4 % of patients. Classical triad of fever, headache & neck stiffness was present in 24% of patients (51/209). Other symptoms were related focal neurological deficit or weakness, nausea, vomiting & seizures.

A prospective national study of 1,268 adults with community-acquired bacterial meningitis in the Netherlands by Bijlsma, M. W. et al. revealed that a high proportion of patients exhibited classic meningitis symptoms, such as headache (83% of patients), neck stiffness (74%), fever (74%), and impairment of consciousness (71%).

Yerramilli et al. found that 26% of the study group exhibited the classic triad of headache with fever, neck stiffness, and altered mental status comparable to our findings. The majority of patients (83%) exhibited at least two of the four symptoms, including headache, neck stiffness, fever, and altered sensorium. Nonetheless, according to the study by van de beek et al., 41% of patients had the 'typical triad' symptoms (neck stiffness, fever, and disturbed mental status). Photophobia is a significant clinical feature, which has been described in relation to meningitis in previous study by Sulaiman T et al., however this specific symptom was not present in our patient population.

ETIOLOGY

In our study, it was found that tubercular meningoencephalitis is the most common etiology with a frequency of 36 % (n=154) followed by viral meningoencephalitis 21 % (n=154) & dengue encephalitis 18 % (n = 154). The frequency of bacterial meningoencephalitis remained low, 12 % of 154 patients. Other less frequent etiologies were fungal, scrub typhus, lymes' disease, CNS toxoplasmosis, paraneoplastic & autoimmune. In comparison to that previous studies providing information on etiology related to meningitis, exhibited that bacterial meningitis is the most common etiology with *S. pneumoniae* being the most prevalent organism (40). Yerramilli A et al

discovered that the most prevalent kind of meningitis that was found in their study was viral or aseptic meningitis, followed by the pyogenic and tuberculous meningitis (TBM).

COMORBIDITIES

In our study, Diabetes mellitus emerged as the most common comorbidity at the time of admission being present in 48 of total patients (23%). Immunodeficiency and sepsis were the 2nd and 3rd most common comorbidities, presented in 39 (18.7%) & 34 (16.3%) patients relatively. These comorbidities were statistically non-significant (P- value <0.05) in relation todiagnosis of meningitis. Yerramilli et al. found that patients with diabetes mellitus and those who had undergone a neurosurgical surgery, primarily a ventriculoperitoneal shunt, had a greater risk of developing meningitis compared to those with other risk factors. (P- value> 0.0001).

CSF ANALYSIS

In our study, CSF analysis was done for diagnostic evaluation of patients. Biochemical, cytological & microbiological findings were assessed for diagnosis. Empirical parenteral antibiotics were started irrespective of lumbar puncture. After initiating empirical parenteral antibiotics, CSF sterilization may occur more rapidly. If the clinical presentation and laboratory data cannot demonstrate the presence of bacterial meningitis, an insufficient culture may result in an unnecessary prolongation of treatment. The yield of bacteria on a gram stain is dependent on a variety of factors, including the amount of organisms present,the prior use of antibiotics, the technique employed for smear preparation, the stainingtechniques applied and the ability and expertise of the observer.

In our study, CSF analysis was done for 141 patients, out of which CSF abnormality was present in 133 patients (86%). Mean values of CSF protein, glucose & leucocyte count were 147 mg/dL with SD of 171, 63 mg/dL with SD of 42 & 117 cells/uL with SD of 234. CSF protein concentration & cell count was elevated according to the UK joint societies' guideline by F Mcgill et. al. Mean CSF protein concentration was more elevated in comparison to studyby Sulaiman T et. al., which was 81 mg/dL. Elevated CSF leucocyte counts were comparable.Same study showed positive gram staining &

positive bacterial culture in 42 & 44 patients respectfully. In comparison to that our study did not show any finding on CSF gram staining and culture was positive in only 1 patient. It can be attributed to administration of antibiotics outside our center, empirical antibiotic use before lumbar puncture or low load of organisms.

In our study, CSF protein was significantly elevated in tubercular, bacterial and fungal meningoencephalitis. Compared to earlier research, concentration levels were higher. Levels of CSF protein was also elevated in viral meningoencephalitis, which is equally comparable to previous studies (1–3,13,44,45,49,67,84,90). Mean difference was significant betweentubercular meningoencephalitis & viral meningoencephalitis and bacterial meningoencephalitis & viral meningoencephalitis. It signifies that CSF protein can be used as a marker to differentiate viral meningoencephalitis from tubercular and bacterial meningoencephalitis, but cannot differentiate tubercular from bacterial. Study by Shekhar Ret al. showed significant difference between CSF protein level in bacterial and tubercular meningoencephalitis, which was contrary to our study.

We observed that CSF Glucose/ Plasma Glucose ratio was decreased in tubercular and bacterial meningoencephalitis and was equally comparable to previous studies (2,3,13,44,45,49,67).

We found that CSF Glucose/ Plasma Glucose ratio can be used to differentiate viral and dengue encephalitis from tubercular meningoencephalitis and viral meningoencephalitis from bacterial meningoencephalitis. According to our study CSF leucocyte count was significantly elevated in patients with bacterial meningoencephalitis and mildly elevated in tubercular & viral meningoencephalitis. Previously studies revealed similar findings (1- 3,13,45,49,50,67,84)

It was our observation that high levels of CSF leucocyte count signify bacterial meningoencephalitis and can used to differentiate bacterial meningoencephalitis from other causes of meningoencephalitis.

According to our analysis levels of CSF chloride are reduced in cases of tubercular meningoencephalitis and it can be used to differentiate tubercular meningoencephalitis from viral & dengue encephalitis, so do CSF chloride/Serum Chloride ratio, but it can only differentiate tubercular from viral meningoencephalitis. Similar findings were shown in a study by Tan et al. (91).

It has been demonstrated that Adenosine deaminase levels (ADA) is useful in differentiating tuberculous pleural effusions. CSF ADA levels have been useful in diagnosis of TBM. In our study, ADA level of 10 IU/L was used as diagnostic cut-off level for TBM. ADA levels were elevated in proven TBM cases. This level has also been used in various observational studies in TBM patients (55,58,61).
In our population, AUC was calculated for CSF ADA in proven TBM patients & it was 0.892. Original cut-off level of 10 IU/L showed sensitivity of 40% and specificity of 97%.

Opposite results were observed in previous studies in which sensitivity ranged from 87-94% and specificity ranged from 83 – 90% (55,58,61).

Here we are suggesting a new cut off value of 05 IU/L with a specificity of 82% and sensitivity of 87.5%. Same cut off value was suggested by Goswami K et al. with sensitivity of 90% and specificity of 85%.

Previous studies have assessed the role of CSF cytokines in diagnosis and prognosis in meningoencephalitis patients. Studies by Junior P et. al. and Bociaga-Jasik et al. showed diagnostic and prognostic value of CSF IL-8 and TNF-alpha levels. Our study suggests that CSF TNF-alpha and IL-8 are not significant markers for diagnosis or predicting prognosis among meningoencephalitis patients.

In our study, a total of 56 patients out of 154 patients suspected with diagnosis of TBM after assessment of clinical features, initial CSF profile and brain imaging findings. Out of these 56 suspected TBM patients, 20 patients were diagnosed as confirmed TBM by means of CSF CBNAAT and mycobacterial culture. CSF ZN staining was positive in only one sample. Mycobacterium tuberculosis was cultured in 3 samples and demonstrated by MPT-64 Antigentesting. Molecular diagnosis for tuberculosis (Gene-Xpert/Gene Xpert Ultra) demonstrated M.tuberculosis in 19 samples. Out of 19, 17 samples showed rifampicin sensitivity, 1 showed indeterminate sensitivity & 1 samples showed resistance to rifampicin. Yield rate of ZN staining and mycobacterial culture was 2% and 5%, which is too low in comparison to previous studies by Thwaite's et al. and Kennedy & Fallon. On the basis of these findings, it isrecommended to obtain a minimum of three serial CSF samples for smear and culture, which was suggested by these studies.

BRAIN IMAGING

Out of, 149 confirmed meningoencephalitis patients (97%) who underwent brain imaging, CTBrain was performed in 149 patients (97%) & MRI Brain was performed in 121 patients (79%). Brain imaging abnormality was observed in 118 patients (77%). In comparison to our findings, Sulaiman T et al. observed that CT brain was available for 87% of patients and MRIbrain was available for 47% of patients, while brain imaging abnormality was detected in 37% of patients. Which is too low compared to our study. However, Lummel et al. showed that MRI brain findings were normal only in 17% while Nagra et al. showed that CT brain findings were normal in 86% of patients. As many patients with MRI abnormalities had a normal CT brain, we can reach the conclusion that in the diagnosis of meningoencephalitis, MRI brain is probably better than CT brain.

Most common CT brain findings were ring enhancing lesions (12%), hydrocephalus, chronic infarct, cerebral atrophy & cerebral edema and most common observed MRI brain findings were leptomeningeal enhancement (55%), infarct, ring enhancing lesion, hydrocephalus & basal exudates. Comprehensive review of neuroimaging in tubercular meningitis done by Marais et al. showed hydrocephalus and basal meningeal enlargement are the most frequent radiological manifestations of tuberculous meningitis as detected by CT. Similar finding was observed in this study also that MRI has greater sensitivity than CT for detecting abnormalities such as meningeal enhancement, infarcts, and tuberculomas, particularly brainstem lesions. Thwaites reported MRI findings in adult patients with tuberculous meningitis; 82% exhibited basal meningeal enlargement and 77% exhibited hydrocephalus.

Diagnostic Scoring Methods

Thwaites' diagnostic score and Lancet consensus scoring system were used in our study inthe diagnosis of TBM. It was observed that decreasing values of Thwaites' diagnostic score are significant predictor of tubercular meningoencephalitis (P- value = <0.01) (OR=0.66)(CI=0.57-0.76) and increasing values are significant predictor of bacterial meningoencephalitis (P- value = <0.01) (OR=1.70) (CI=1.36-2.13). Area under curve was calculated for "Thwaites' scoring system" in TBM patients and it was 0.83. The original value of ≤ 4 showed sensitivity of 100% & specificity of 26%.

Original study by Thwaites' et al. concluded that a cut-off score of 4 showed sensitivity of 97% and specificity of 91%. Herewe can suggest a new cut off score of (0) for diagnosis of TBM with sensitivity of 75% & specificity of 79%. Area under curve was calculated for Thwaites' scoring system in proven TBM patients and it was 0.746. The original value of ≤ 4 showed sensitivity of 100% & specificity of 22%. Our proposed cut-off value showed sensitivity of 84% and specificity of 63%.

Our study showed that increasing values of Lancet consensus scoring are significant predictorof TBM (P- value = <0.01) (OR=2.45) (CI=1.66-3.57) and decreasing values of scoring are significant predictor bacterial meningoencephalitis (P- value = <0.01) (OR=0.60) (CI=0.43- 0.84). Area under curve was calculated for Lancet consensus scoring system in clinically diagnosed TBM patients and it was 0.987. The original value of 12 of probable TBM showed 80% sensitivity & 100% specificity. Here we can suggest new value of 8 for probable TBM with sensitivity of 92% & specificity of 96%. Area under curve was calculated for Lancet consensus scoring system in Proven TBM patients and it was 0.961. Original value of 12 of probable TBM with sensitivity of 100% & specificity of 79%. Here our proposed value of 8 showed sensitivity of 100% and specificity of 71%.

Multicentre analysis by Sulaiman T et al. assessed the scores and it showed that both scores were able to separate TBM from bacterial meningitis; however, only the Lancet score was able to discriminate TBM from fungal, viral, and unknown aetiologies, despite significant overlap (P <0.0001).

ANTIBIOTICS & STEROIDS

In our study, 92% patients (n=192) received empirical parenteral antibiotics and out of most common antibiotic received was ceftriaxone. Similar finding was observed in the study by Yerramilli et al.

MORTALITY

In our study, a total of 62 patients (30%) suffered mortality in whole population (N=209). Out of these 62 patients, 44 patients (29%) belong to confirmed meningoencephalitis group (n=154). Most common etiology of mortality was Dengue

encephalitis, 13 patients (46%) out of 28 patients. Tubercular meningoencephalitis remained the 2nd most common cause of mortality, leading to death of 17 patients (30%) out of 56. Similar to that, review by Dodd et al. observed CFR of 27% (n=1,18,000) in TBM patients in year 2019. In comparison to our findings, previous study by Yerramilli A showed contrary results, they observed that frequency of mortality was 5.4% (n=147) and TBM remained the most common causeleading to death of 7.5% (n=41) patients. The reasons for higher mortality in our study hastwo possible explanations, as there was a dengue epidemic during the study period, dengue encephalitis remained a significant contributor to the mortality. Secondly, population selection in prior studies was different predominantly including pediatric population while our population which might have affected mortality.

COMPLICATIONS, OUTCOMES & PREDICTORS OF OUTCOME

In our study, the modified Rankin scale score and the Glasgow Coma Scale were calculated atthe time of admission, at discharge, and after one month of follow-up in order to evaluate complications. The maximum number of patients with an MRS score of 4 was around 44% (n=67) out of 154 patients. Consequently, 26% of 154 patients died during admission, resulting in an MRS score of 6, and at 1 month of follow-up, 3% more patients (n=154) died, resulting in an MRS score of 6 for 29% of patients (n=154). MRS score of 0, correspondingto symptom-free life, was given to 17% of patients out of 154 at the time of discharge and to 32% of patients out of 154 at the time of the 1-month follow-up, indicating that 17% of the patient population had recovered from their illness at the time of discharge, and this proportion increased to 32% at the time of the 1-month follow-up. At the time of admission, aGCS score of 12 was recorded for the majority of patients, 26% (n=154). Modified rankin Scale (mRS ≤ 2- good and mRS > 2 - poor) was used as a tool to measure outcomes and disability, similar to study done by Mishra UK et al. in TBM patients. In our study, 54% of patients (n=83) had good outcomes and 46% (n=71) had poor outcomes.

In our study, complications comprised of CNS complications and extra CNS complications. TBM was the etiology associated with highest frequency of complications, being present in 84% of TBM patients out of 56. However, CNS complications were present in only 32%. Frequency of CNS complications was highest in cases of meningoencephalitis of viral etiology, which was 54% (n=61).

ATT induced hepatitis was observed in 52% of TBM patients (n=56) in our study. Frequency was significantly higher than previous studies by Mishra U et. al. (43%)(n=150) and Kumar M et al. (32.8%)(n=67), though number of TBM patients were lower in our study.

Our study analyzed multiple predictors affecting the outcomes of patients presenting with meningitis. Regression analysis showed low GCS, sepsis & immunocompromised conditionat admission as significant dependent predictors along with thrombocytopenia, hypoalbuminemia, CSF abnormality and raised HsCRP levels

(P- value <0.05). Out of these, sepsis, focal neurological deficit & low GCS on admission and raised HsCRP levels were found as independent predictors of mortality (P- value <0.05).

In our analysis, age, male gender, low GCS, sepsis & focal neurological deficit at presentation are found as significant dependent predictors of disability along with hypertension as a comorbidity and raised levels of serum HsCRP, ESR, hypoalbuminemia, raised CSF protein &ADA levels. Brain imaging abnormality with findings of ring enhancing lesions & infarct are also found to be significant (P- value <0.05). Out of these dependent significant parameters, only low GCS on presentation is independent predictor of disability on follow up of proven meningoencephalitis patients (P- value <0.05).

Our study revealed that low GCS & focal neurological deficit at presentation are found as dependent significant predictors of CNS complications along with diagnosis of tubercular meningoencephalitis & raised CSF ADA levels. Findings of ring enhancing lesions, basal exudates & infarct on brain imaging, are also found to be significant (P-value <0.05). Out of these significant parameters, only low GCS on presentation and diagnosis of tubercular meningoencephalitis, are independent predictors of CNS complications in proven meningoencephalitis patients (P- value <0.05). Similar findings were observed in previously (10-27,30-37).

Raised levels of HsCRP, male gender, raised levels of ADA & ring enhancing lesions on brain imaging found as new predictors of poor outcomes in meningitis patients in comparison to previous studies. Waikar SS et al. showed association of hyponatremia with TBM in their study, which was not observed in our study.

CONCLUSION

Based on the observational study done to assess the risk factors associated with poor outcomes (mortality and sequelae) in patients presenting with meningitis, it was found that low GCS, sepsis and focal neurological deficit at the time of admission and raised HsCRP levels are predictors of mortality in patients presenting with meningitis and low GCS and diagnosis of tubercular meningoencephalitis, are predictors of disability and development of complications in patients presenting with meningitis. It was observed that the male/female ratio was 1.6:1 in our study population of meningoencephalitis with the highest prevalence in 18-25 years of age. The most common clinical feature was altered sensorium with classical triad of headache, fever & neck stiffness was present in only 23% of our study population. It was found that the most common etiology for meningitis among our study population was tuberculosis.

Analysis of the CSF profile showed elevated CSF protein was elevated in all cases of meningoencephalitis, the highest being in TBM and similarly, CSF WBC count was elevated except in dengue encephalitis cases and the highest being in bacterial meningoencephalitis. CSF Glucose/ Plasma Glucose ratio was found reduced in cases of TBM and bacterialmeningoencephalitis. CSF ADA level, chloride level and its ratio with serum value can be used to distinguish TBM from other etiology and our study has suggested 05 IU/L as a new diagnostic cutoff for ADA in TBM. It was also found that CSF cytokines, CSF TNF-alpha and IL-8 are not useful as diagnostic or prognostic markers among meningoencephalitis patients. Brain imaging is useful in diagnosing and differentiating various causes of meningoencephalitis and it was found that MRI is a better diagnostic modality than CT scan.

Diagnostic scoring methods like Thwaites' diagnostic score and Lancet consensus scoring system were analyzed and their utility in the diagnosis of TBM is significant. Our study has suggested a new cutoff value of "0" in thwaites' score with a sensitivity of 75% & a specificity of 79 % and "8" in the lancet score with a sensitivity of 92% & specificity of 96%.

This is one of the very few studies that describes the clinical symptoms, laboratory features, imaging features, diagnostic score comparison, therapeutic decisions and prognostic factors for all meningitis in adults.

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IEC Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3529 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3364**

Project title: **"Risk factor profile and outcome assessment of patient presenting with meningitis: A prospective observational study"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Pankaj Sukhadiya**
Guide:	**Dr. Mahendra Kumar Garg**
Co-Guide:	**Dr. Gopal Krishna Bohra, Dr. Maya Gopalakrishnan, Dr. Ashwini Agarwal & Dr. Kamla Kant Shukla**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

Appendix 1

All India Institute of Medical Sciences

Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation: **RISK FACTOR PROFILE AND OUTCOME ASSESSMENT OF PATIENTS PRESENTING WITH MENINGITIS- A PROSPECTIVE OBSERVATIONAL STUDY**

Name of PG Student: Dr Pankaj Sukhadiya Tel. No. 9782887695

Patient/Volunteer Identification No.:_____ I, S/o_____ or D/o_____ R/o_____ give my full, free, voluntary consent to be a part of the study **"RISK FACTOR PROFILE AND OUTCOME ASSESSMENT OF PATIENTS PRESENTING WITH MENINGITIS- A PROSPECTIVE OBSERVATIONAL STUDY",** the procedure and nature of which has been explained to me in my own language to myfull satisfaction. I confirm that I have had the opportunity to ask questions. I understand that my participation is voluntary and am aware of my right to opt out of thestudy at any time without giving any reason. I understand that the information collected about me and any of my medical records may be looked at by responsible individual from_____or from regulatory authorities. I give permission for these individuals to have access to my records. For future references and studies if needed, the samples collected will be stored understringent conditions.

Date :_____ _____

Place : _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date :

Place : Signature of PG Student

Witness 1 Witness 2

Signature Signature

Name:_____ Name:_____

Address:_____ Address:_____

APPENDIX-2

अखिल भारतीय आयुर्विज्ञान संस्थान

जोधपुर, राजस्थान

सूचित सहमति प्रपत्र

थीसिस का शीर्षक: मेनिन्जाइटिस मरीजों का जोखिम कारक प्रालेख एवं परिणाम मूल्यांकन : एक संभावित अवलोकन अध्ययन पीजी छात्र का नाम: डॉ पंकज सुखाड़िया, दूरभाष।संख्या :9782887695

रोगी / स्वयंसेवी पहचान संख्या.: _____

मैं,_____पुत्र /पुत्री_____

निवासी_____,मेरी स्वतंत्र स्वैच्छिक सहमति देता हू निम्नलिखित अध्ययन का हिस्सा बनने के लिए मेनिन्जाइटिस मरीजों का जोखिम कारक प्रालेख एवं परिणाम मूल्यांकन : एक संभावित अवलोकन अध्ययन जिसकी प्रक्रिया और प्रकृति मेरी पूरी संतुष्टि के लिए अपनी भाषा में मुझे समझाया गया है।मैं पुष्टि करता हूं कि मेरे पास प्रश्न पूछने का अवसर था। मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और किसी भी कारण के बिना ,किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं।

.मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्र की गई जानकारी एम्स जोधपुर से या नियामक प्राधिकरणों से जिम्मेदार व्यक्ति द्वारा देखी जा सकती है। मैं इन व्यक्तियों के लिए अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

यदि आवश्यक हो तो भविष्य के संदर्भों और अध्ययनों के लिए, एकत्र किए गए नमूने कड़े परिस्थितियों में संग्रहित किए जाएंगे ।

दिनांक: _____ _____

स्थान : _____ हस्ताक्षर/बाएंअंगूठेकीछाप

यह प्रमाणित करने के लिए कि उपर्युक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।

तारीख :_____ _____

स्थान: _____ हस्ताक्षरपीजी छात्र

साक्षी 1	साक्षी 2
हस्ताक्षर	हस्ताक्षर
नाम: _____	नाम: _____
स्थान : _____	स्थान : _____

APPENDIX-3

PATIENT INFORMATION SHEET

Name of the patient: **Patient ID.:**

- **RISK FACTOR PROFILE AND OUTCOME ASSESSMENT OF PATIENTS PRESENTING WITH MENINGITIS- A PROSPECTIVE OBSERVATIONALSTUDY**
- **Aim of the study**: To describe the clinical, laboratory profile and outcomes of patients presenting with meningitis at All India Institute of Medical Sciences, Jodhpur
- **Study site:** Out Patient and in-patient services of Department of Internal Medicine,All India Institute of Medical Sciences, Jodhpur, Rajasthan.
- **Study procedure:** All the above-mentioned variables will be assessed by detailedhistory, clinical examination and laboratory investigations.
- **Likely benefit:** This study will help to distinguish between the type of meningitis based on the clinical features and the CSF biochemistry as there are varying grades of urgency as well as different treatment strategies involved in the management of each type of meningitis.
- Confidentiality: All the data collected from each study participant will be kept highly confidential and will be preserved for future use if found suitable by the Head of Department of General Medicine, AIIMS, Jodhpur
- **Risk:** Enrollment in above study poses no substantial risk to any of the study participant and if any point of time participant wants to withdraw himself/ herself, he/ she can do so voluntarily at any point of time during the study.

For further information / questions, the following personnel can be contacted: Dr. Pankaj Sukhadiya, Junior Resident, Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Ph: 9782887695

APPENDIX-4

(a) SOCIO-DEMOGRAPHIC AND CLINICAL PROFORMA

Patient ID:

Name of patient:

Age/Gender:

Address:

Contact number:

CLINICAL PROFILE:

(b) Data Collection Proforma

Symptoms	Duration
Fever	
Headache	
Neck Stiffness	
Nausea	
Vomiting	
Photophobia	
Seizures	
Altered sensorium	
Sleepiness	
Confusion	
Irritability	
Delirium	
Paralysis	
Coma	
Focal Neurological Deficit	

Risk Factors	Present/Absent	
Diabetes mellitus		
Hypertension		
Respiratory tract infection		
Otorrhea		
CSF Rhinorrhea		
Immunocompromised Status		
Head Trauma		
Neurosurgery/Ventriculoperitoneal Shunt		
Tuberculous		
Stroke		
Heart Disease		
Hydrocephalus		
Smoking		
Alcoholism		

(c) Routine blood investigations

1.Complete Hemogram		
Hb		
TLC		
DLC(N/L/M/E)		
Platelets		
Hct/MCV/MCH		
2.Inflammatory markers		
HsCRP		
ESR		
Procalcitonin		
3.KFT **Urea/Creatinine**		
4.LFT **SGOT/SGPT/ALP**		
Total Bil./Direct/Indirect		
Total Protein/Albumin/Globulin		
5.Serum Electrolytes		
Sodium/Potassium/Chlorides		
6.HIV/HBsAg/HCV		
7.Plasma Glucose		
Blood Culture and sensitivity		
Urine Culture and sensitivity		
Sputum Culture and sensitivity		

(d) CSF examination

Cerebrospinal Fluid Examination		
1.Biochemistry		
Proteins		
Glucose		
CSF Glucose/Plasma Glucose Ratio		
CSF IL-8 and TNF-alpha		
2. Cytology		
WBC		
RBC		
3. Microbiology		
Gram Staining		
ZN Staining		
Culture and sensitivity		
India Ink Staining		
KOH Mount		
4.PCR		

(e) Radio imaging

Brain Imaging

Chest Xray

(f) Treatment history sheet

	Dose	Duration and Timing
Antimicrobials		
1. **2.** **3.**		
Steroids		
Antipileptics		

Hospital Stay	
Requirement of ICU	
Requirement of VP Shunt/Neurosurgery	
Requirement of Repeat Lumbar Puncture	
Condition at discharge	

(g) Clinical scoring system proforma

Clinical Score	Value
1.Thwaites' Diagnostic Scoring System	
2.Lancet Consensus Scoring System	
3.Modified Rankin Scale	
4.Glasgow Coma Scale	

(h) Follow-up proforma

Follow up: Follow up of the patients will be done after 1 month from the date of discharge, which will be based on Modified Rankin scale, cranial nerve examination, Glasgow coma scale (GCS) and CSF examination if clinically indicated.

Parameter	**at the time of discharge**	**at 1 month follow up**
Modified Rankin scale		
Cranial nerve examination		
GCS		
CSF examination		

APPENDIX -5 Clinical Scoring Systems

1. Thwaites' Diagnostic Scoring

Variable	Score
Age (years)	
≥36	2
<36	0
Blood WCC (10^3/ml)	
≥15,000	4
<15,000	0
History of illness (days)	
≥6	−5
<6	0
CSF total WCC (10^3/ml)	
≥750	3
<750	0
CSF % neutrophils	
≥90	4
<90	0

Suggested rule for diagnosis: total score ≤ 4 = TBM; total score > 4 = non-TBM. TBM, tuberculous meningitis; WCC, white cell count; CSF, cerebrospinal fluid.

2. Lancet Consensus Scoring System

Clinical criteria	**Score (Maximum category score = 6)**
Symptom duration of more than 5 days	4
Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks	2
History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children < 10 years of age)	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
Altered consciousness	1
CSF criteria	**(Maximum category score = 4)**
Clear appearance	1
Cells: 10–500 per µl	1
Lymphocytic predominance (> 50%)	1
Protein concentration greater than 1 g/L	1
CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2·2 mmol/L	1
Cerebral imaging criteria	**(Maximum category score = 6)**
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Pre-contrast basal hyperdensity	2
Evidence of tuberculosis elsewhere	**(Maximum category score = 4)**
Chest radiograph suggestive of active tuberculosis: signs of tuberculosis = 2; miliary tuberculosis = 4	2/4
CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS	2
AFB identified or *Mycobacterium tuberculosis* cultured from another source—i.e., sputum lymph node, gastric washing, urine, blood culture	4
Positive commercial *M tuberculosis* NAAT from extra-neural specimen	4

3. **Modified Rankin Scale**

Modified Rankin Scale (MRS)
0 No symptoms
1 No significant disability, despite symptoms; able to perform all usual duties and activities
2 Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3 Moderate disability; requires some help, but able to walk without assistance
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent, and requires constant nursing care and attention
6 Death

4. **Glasgow Coma Scale**

GLASGOW COMA SCORE

Eye(s) Opening	
Spontaneous	4
To speech	3
To pain	2
No response	1
Verbal Response	
Oriented to time, place, person	5
Confused/disorientated	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1
Best Motor Response	
Obeys commands	6
Moves to localised pain	5
Flexion withdraws from pain	4
Abnormal flexion	3
Abnormal extension	2
No response	1
Best response	15
Comatose patient	8 or less
Totally unresponsive	3