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Original Research Article

Clinical Outcome Using Standard Therapeutic Regimen in Adult Patients with Tubercular Meningitis at A North Indian Tertiary Care Centre

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Abstract:

Tuberculous Meningitis is a dreaded medical condition with high mortality and morbidity. Survivors are left with severe medical conditions. Its therapeutic interventions are also equally challenging because of adverse drug reactions as well as compliance issues. Timely intervention and early diagnosis significantly determines mortality and morbidity in a resource poor and endemic country. Identifying prognostic factors and administration of standard therapeutic regimen are directly related to the survival of patients.

Keywords: Tuberculous Meningitis, Therapeutic Regimen, Clinical Outcome.

Introduction

CNS tuberculosis accounts for 1% of all tuberculosis cases and 6% of extra pulmonary tuberculosis in immunological competent people. With an increase in TB infection, CNS TB incidence rises. According to estimates, the CNS is affected in 10% of all tuberculosis patients.[1] Considering that 10% of cases are CNS TB, the incidence of CNS TB in India in 2016 was almost 21.2/100,000 people.[2] The prevalence and frequency of tuberculosis in the community are typically reflected in the incidence of CNS tuberculosis. The estimated mortality rate from tuberculous meningitis in India is 1.5 per 100,000. HIV infection raises the risk of complications and case fatality rates for extra pulmonary tuberculosis, especially tuberculous meningitis.[3] About 1% of people with active tuberculosis who develop central nervous system (CNS) tuberculosis, caused by the haematogenous spread of Mycobacterium tuberculosis from initial lung infection leads to the formation of small subpial and subependymal foci (Rich foci) in the brain and spinal cord.[4]

In some cases, foci rupture and discharge bacteria into the subarachnoid region, causing meningitis. In others, foci enlarge to form tuberculomas without meningitis. Before the infection has been subdued by the adaptive immune response, hematogenous dissemination most likely takes place early in the illness. This early haematogenous dissemination in humans explains why people with impaired T-cell responses (such as those with untreated

HIV infection) are especially susceptible to disseminated disease; why children with BCG-primed T-cell responses are protected against miliary tuberculosis and meningitis; and why polymorphisms in early, innate immune response genes (TIRAP, 14 TLR215) are linked to the development of tuberculous meningitis[4].

The most severe form of tuberculosis, tuberculous meningitis, significantly increases morbidity and morbidity in both adults and children. The prognosis is often poor and left patient with disabilities especially in immunocompromised[5]. Overall hospital mortality rates for individuals with drug-susceptible TBM can reach 50%, and long-term five-year mortality rates can reach 58%. Due to illness complications such infarction, vasculitis, and hydrocephalus, people with TBM very frequently experience long-term neurological consequences. Delays in diagnosis and subsequent early initiation of anti-TB treatment, as well as limited CSF penetration of many anti-TB agents like rifampin, are contributing factors to the high rates of morbidity and mortality among TBM patients[6].

Age of the patient, the intensity and characteristics of the illness, the time of therapy started, Latency time between the onset of symptoms and the introduction of therapy as well as type of treatment received all affect case fatality rates[7]. Despite descriptive literature on the pathological findings in TBM and drugs being available for more than 50 years, the morbidity and mortality in TBM remain unacceptable high. Currently, the main obstacles to effective management of TBM include an early TBM diagnosis (Clinical symptoms that are vague and diverse and paucity in high-performance diagnostic and laboratory measures), An efficient TBM treatment and managing the complications[8]. The most significant diagnostic and therapeutic gaps are brought on by delayed presentation, reliance on complementary or conventional medicine, inability to perform or refusal of lumbar puncture, absence of laboratory facilities, and lack of access to or cost of antibiotics. TBM is challenging to diagnose, hence underreported[9].

Aerosolized droplets containing M. tuberculosis is inhaled to cause the primary infection. This is followed by the activation of neutrophils, dendritic cells, and alveolar macrophages, which engulf the mycobacteria in the terminal alveoli. Infected cells then migrate to lymphoid tissue, leading to Th1 cells activation and pro inflammatory cytokines production, thus inflammatory changes in parenchyma of lung and vasculature. If the mycobacteria enter the vasculature, haematogenous spread may take place, with a potential of CNS invasion[10–14].

A diagnosis of tuberculous meningitis is established when AFB are seen, M TB is cultured, or M tuberculosis is detected by a validated molecular method from the CSF in a patient with symptoms or signs indicative of the disease[5].

WHO treatment recommendations for TBM include for 2 months of a four-drug regimen (rifampicin, isoniazid, pyrazinamide, and ethambutol) in both adults and children, followed by 7 to 10 months of isoniazid and rifampicin. [14]

The most recent WHO recommendations is 2 month HRZS phase, followed by a 10-month HR continuation phase. The RNTCP recommendations suggest two months of HRZE and nine to twelve months of HRE. Two months of HRZE and seven months of HRE are recommended by the Index TB guidelines. According to the index TB panel, TBM should be treated for at least 12 to 18 months. It is hypothesized that adjunct corticosteroids reduces the inflammation in TBM and thereby increase patient outcomes[9]. The strongest predictor of TBM survival is the introduction of this regimen before the onset of coma[15].

According to a 2016 Cochrane Systematic Review and Meta-analysis, corticosteroids improve survival in TBM (children and adults) who are HIV-1 negative For the recommended dosage of steroids in TBM, the Index TB guidelines states that "In hospital: intravenous dexamethasone 0.4 mg/kg/24 hr in 3–4 divided doses may be preferred with a slow switch to oral therapy and taper".

In our set up as a standard regimen,HRZS for 3month and HRZ for 7 to 10 month along with corticosteroid 8mg IV TDS given.

Aim

To study treatment regimen outcome and ADR monitoring in adult patients with tubercular meningitis treated at Department of Neurology and Department of Respiratory Medicine, King George's Medical University, Lucknow, India.

Objectives

- To describe demographic and health characteristics of patients treated for Tuberculous Meningitis under therapeutic regimen.
- To assess the outcome in patients treated for Tuberculous Meningitis under therapeutic regimen
- To find out the factors determining the outcome in patients treated for Tuberculous Meningitis under therapeutic
- To assess the causality of the adverse drug reaction in patients treated for Tuberculous Meningitis under the treatment regimen using WHO –UMC causality scale.
- To assess the severity of the adverse drug reaction of the patients treated for Tuberculous Meningitis under treatment regimen using Hartwig and Siegel severity scale.

Materials & Methods

The study as was conducted at the Department of Neurology and Department of Respiratory Medicine, King George's Medical University , Lucknow. It started after the ethical clearance from the University's Institutional Ethics Committee (vide no: VII-PGTSC-IIA/P2,) All patients with diagnosed case of tuberculous meningitis were recruited from the Departments of Neurology and Respiratory Medicine, KGMU. The study duration was 12 month i.e October 2021 to September 2022.

Subject selection:

All the patients with diagnosed or proven tuberculous meningitis were screened for the study. Those who satisfied our inclusion/exclusion criteria were included in the study after the written consent is taken.

Setting

Study will be conducted in the Department of Pharmacology in collaboration with Department of Neurology and Respiratory Medicine and cases taken from IPD or OPD.

Inclusion criteria

- Age >18yrs
- Both gender(male and female)
- With written consent
- Diagnosed case of TBM based on laboratory, neuroimaging and clinical features
- TBM cases with hydrocephalus
- TBM cases with tuberculoma
- Cases of pulmonary TB with TBM as a complication

Exclusion criteria

- Age <18yrs
- Patients who were unwilling to participate and did not give consent in the study.
- Pregnant and Lactating women
- Patients with viral and bacterial meningitis (except tuberculous meningitis), cerebral abscess, meningeal metastasis and Lymphoma.
- TBM infected with HIV

- drug resistant TBM i.e MDR and XDR cases.
- Patients with chronic liver disease and renal diseases as these affects ADR monitoring
- Patients with incomplete medical record
- Patients lost to follow up.

Study design

It is a Prospective observational study. Diagnosis of TBM is made on the basis of presence of mycobacterium tuberculosis in CSF, clinical and radiological imaging .Patients who satisfy above criteria are categorized into three group A, B and C .Group A consist of TBM patients without tuberculoma without hydrocephalus, Group B consist of TBM patients with tuberculoma, Group C consist of TBM patients with hydrocephalus. Further sub grouping of these groups are done on the basis severity of the disease using British Medical Research Council Criteria (BMRCC, into stage I, stage II and stage III. On admission demographic details are taken and a baseline neurological status of the patients of each group is noted on the basis of Modified Rankin Score(Appendix 4) before the initiation of the treatment regimen. Now patients are monitored for 12 months . On follow up after one year of treatment, neurological status is measured as Outcome using Modified Rankin Score (MRS). The classification of outcome is defined as 'good' (a score of 0), 'intermediate' (a score of 1 or 2) or 'poor' (score 3-5 and death) .It is applicable for both baseline outcome and follow up outcome.

Baselines as well as follow up outcome of group A, B, and C are compared.

Study variables

- Age
- Gender
- Residence
- Past history of TB
- Co morbidities
- Presenting symptoms
- Stage of TBM
- MRS outcome
- Causality assessment of ADR
- Severity assessment of ADR

Sample Size

Sample Size at 90% Power

Sample size is calculated on the basis of maximum variation in modified Rankin Score among various groups of TBM based on diagnosis using the formula,

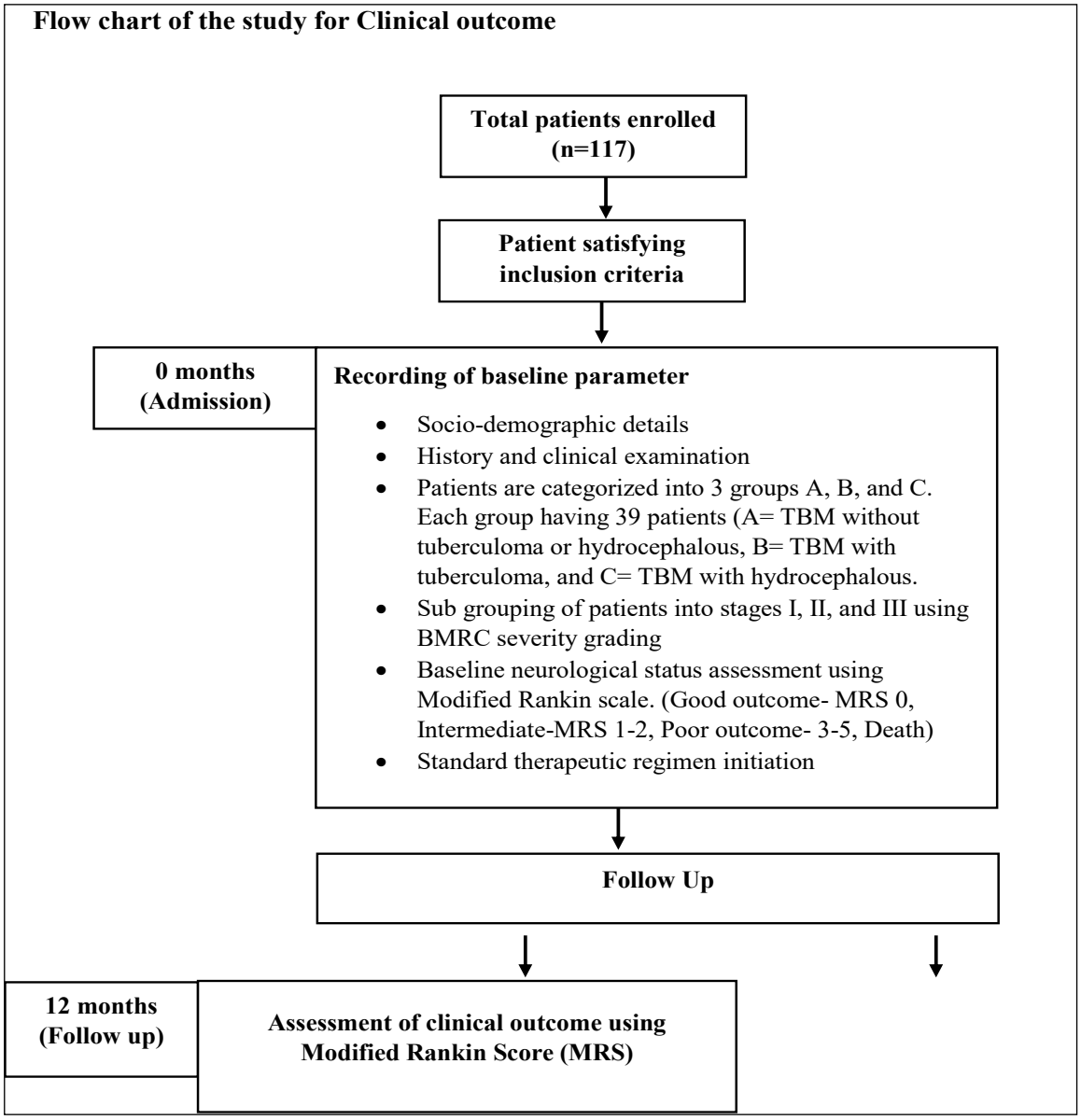
$$n = k\frac{\left(z_\alpha + z_\beta\right)^2\left(\sigma^2\right)}{d^2}$$

Where σ = 1.3, The max SD of modified Rankin Score among various groups of TBM. d = 50% of mean MRS score of group having maximum variation (=1.3), the difference considered to be statistically significant. (Ref. RAJENDRAN, Santhosh et al. Outcomes of patients presenting with central nervous system tuberculosis at a tertiary care center in India. International Journal Of Community Medicine And Public Health, [S.l.], v. 8, n. 1, p. 138-146, dec. 2020. ISSN 2394-6040.)

- Design effect k = 2 for considering multiple within groups
- type I error α = 5% corresponding to 95% confidence level
- type II error β = 10% for detecting results with 90% power of study
- Data loss factor = 10% So the required sample size is calculated to be n = 117
- Each group will have 39 patients

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean and SD. Qualitative variables were compared using Chi-Square test /Fisher's exact test as appropriate. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 23.0.



Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring 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 requiring constant nursing care and attention
6	Dead

Table 1: MRSA Score

Stage I	Fully conscious, no definite neurological symptoms, GCS>/=15
Stage II	Decreased level of consciousness, meningeal irritation, minor (cranial palsy) or no neurological deficit, GCS 11-14
Stage 3	Severe clouding of sensorium, convulsions, focal neurological deficits, involuntary movements, GCS</=10

Table 2 BMRC Stages

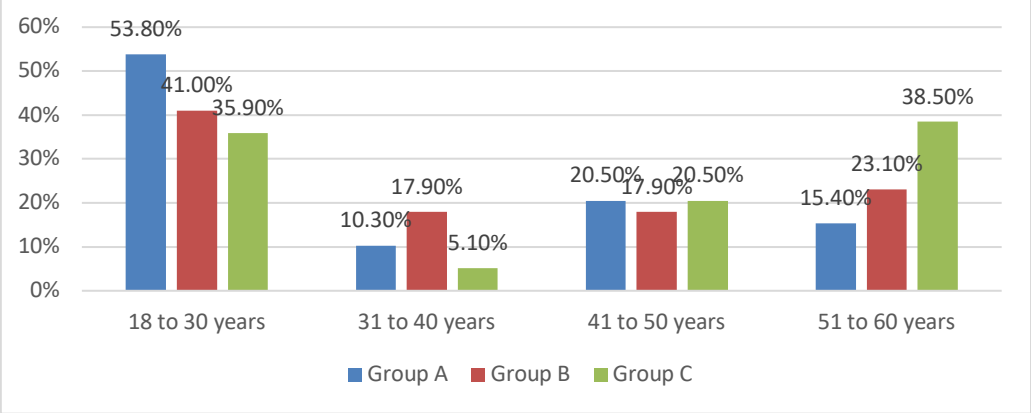
Results

Table 1: Age wise distribution of the patients enrolled

Age Intervals	Groups					
	A		B		C	
	N	%	N	%	N	%
18 to 30 years	21	53.8%	16	41.0%	14	35.9%
31 to 40 years	4	10.3%	7	17.9%	2	5.1%
41 to 50 years	8	20.5%	7	17.9%	8	20.5%
51 to 60 years	6	15.4%	9	23.1%	15	38.5%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.189

Above table shows the frequency distribution and association of age intervals of the study subjects according to the groups. The following data was concluded from the above association; subjects in the age range of 18 to 30 years were 53.8% in group A, 41% in group B and 35.9% in group C. Age range 31 to 40 years was 10.3%, 17.9% and 5.1% in respective groups. 41 to 50 years subject were 20.5% in A, 17.9% in B and 20.5% in C. At last, 51 to 60 years subjects were 15.4% in A, 23.1 in B and 38.5% in C.



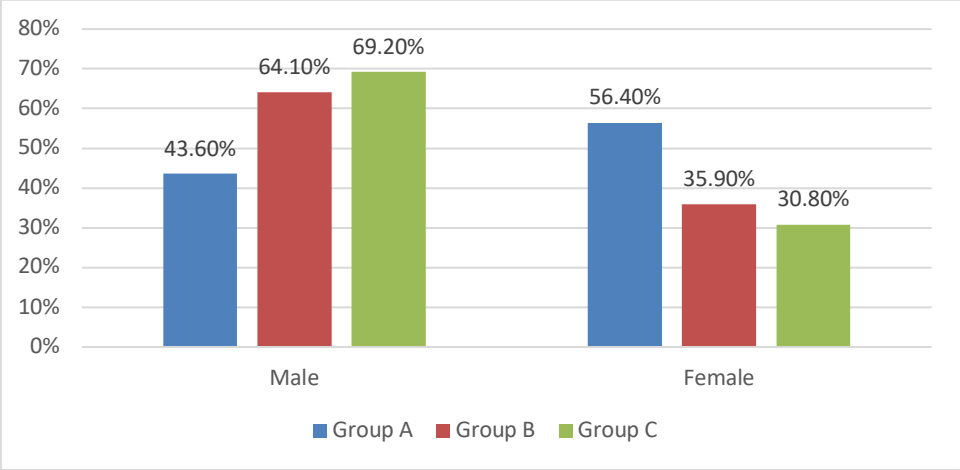
Graph: 1

Table 2: Gender wise distribution of the patients enrolled

Sex	Group					
	A		B		C	
	N	%	N	%	N	%
Male	17	43.6%	25	64.1%	27	69.2%
Female	22	56.4%	14	35.9%	12	30.8%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.051.

Above table shows the frequency distribution and association of sex of the study subjects according to the groups. Group A consist of 43.6% male and 56.4% females, group B consists 64.1% males and 35.9% females while group c consists of 69.2% males and 30.8% females.



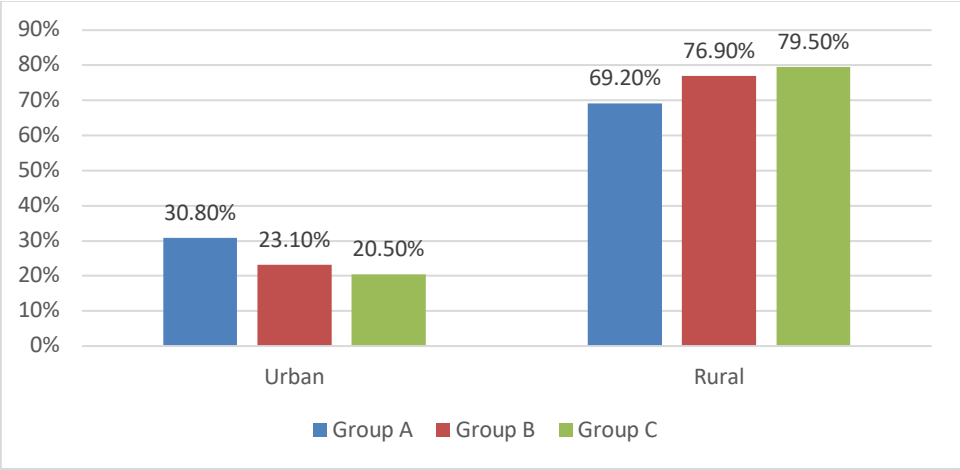
Graph: 2

Table 3: Residence wise distribution of the patients enrolled

Residence	Group					
	A		B		C	
	N	%	N	%	N	%
Urban	12	30.8%	9	23.1%	8	20.5%
Rural	27	69.2%	30	76.9%	31	79.5%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.551

Above table shows the frequency distribution and association of residence of the study subjects according to the groups. Group A consist of 30.8% urban and 69.2% rural, group B consists 23.1% urban and 76.9% rural while group C consists of 20.5% urban and 79.5% rural.



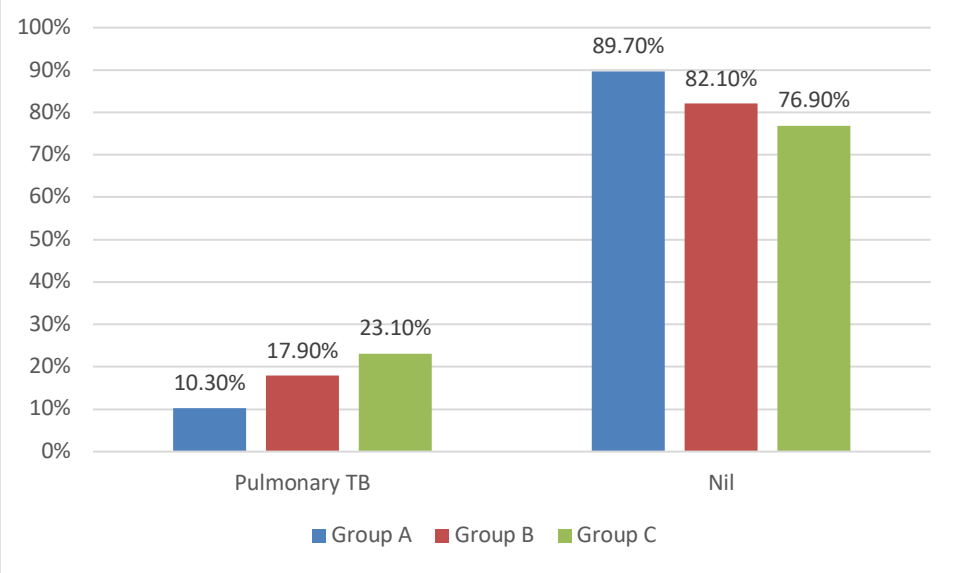
Graph: 3

Table 4: Distribution as per past history of pulmonary TB

Past history	Group					
	A		B		C	
	N	%	N	%	N	%
Pulmonary TB	4	10.3%	7	17.9%	9	23.1%
Nil	35	89.7%	32	82.1%	30	76.9%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.318

Above table shows the frequency distribution and association of past history of the study subjects according to the groups. Group A consist of 10.3% pulmonary TB and 89.7% Nil, group B consists 17.9% pulmonary TB and 82.1% Nil while group c consists of 23.1% pulmonary TB and 76.9% Nil.



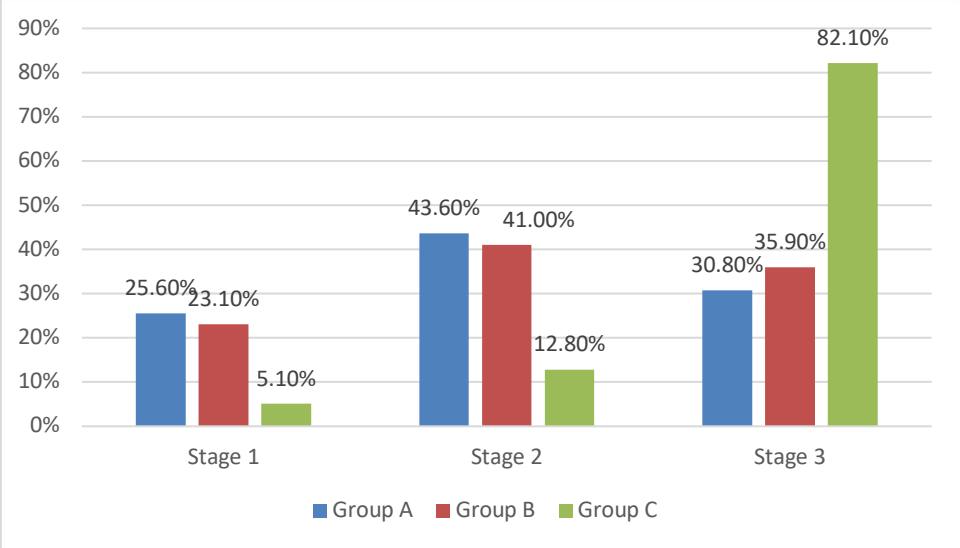
Graph: 4

Table 5: Distribution of the patients as per BMRC criteria at the time of admission

BMRC TBM staging for severity(group)	Group					
	A		B		C	
	N	%	N	%	N	%
Stage I	10	25.6%	9	23.1%	2	5.1%
Stage II	17	43.6%	16	41.0%	5	12.8%
Stage III	12	30.8%	14	35.9%	32	82.1%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = <0.001

Above table shows the frequency distribution and association of BMRC TBM staging for severity(group)of the study subjects according to the groups. Group A consist of 25.6%stage I, 43.6% stage I and 30.8% stage III;group B consist of 23.1% stage I, 41% stage II and 35.9% stage III while group C consist of 5.1% stage 1, 12.8% stage II and 82.1% stage III.

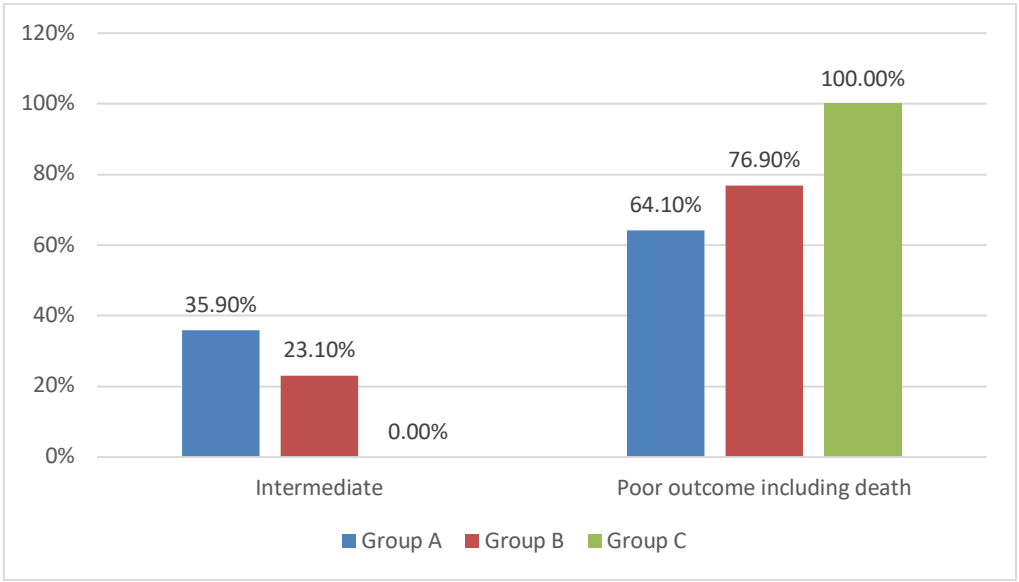


Graph: 5

Table 6: Distribution of baseline neurological status(outcome) of the patients at the time of admission before initiation of therapeutic regimen as per Modified Ranking Score

Modified ranking score on admission(Neurological status)	Group					
	A		B		C	
	N	%	N	%	N	%
Good outcome	0	0.0%	0	0.0%	0	0.0%
Intermediate outcome	14	35.9%	9	23.1%	0	0.0%
Poor outcome including death	25	64.1%	30	76.9%	39	100.0%
Total	39	100.0%	39	100.0%	39	100.0%

Above table shows the frequency distribution and association of Modified ranking score on admission of the study subjects according to the groups. Group A consist of 35.9% intermediate and 64.1% poor outcome; group B consist of 23.1% intermediate and 76.9% poor outcome while group C consist of 100% poor outcome.



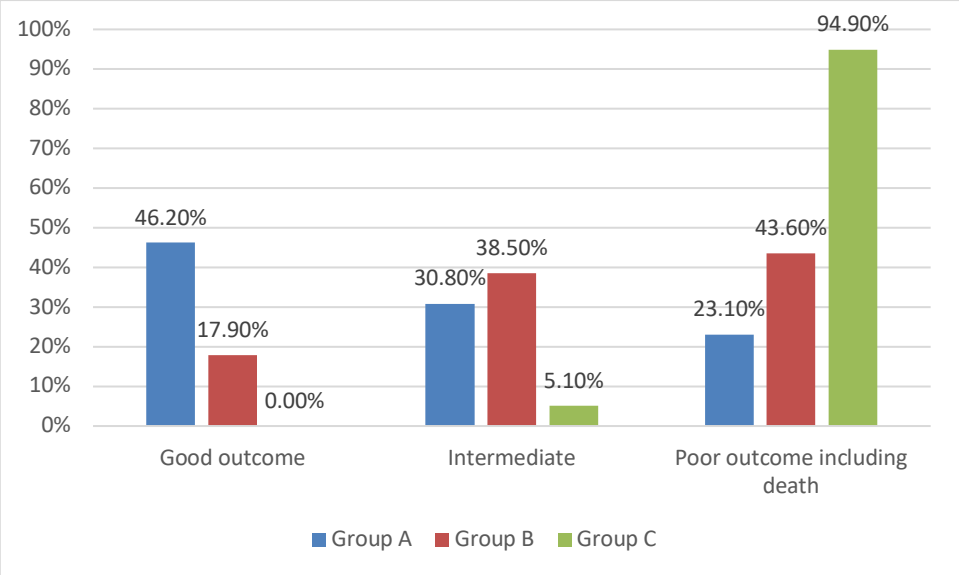
Graph: 6

Table 7: Distribution of the neurological status(Outcome) of the patients after the initiation of therapeutic regimen at the time of follow up

Modified ranking score on follow up(Neurological status)	Group					
	A		B		C	
	N	%	N	%	N	%
Good outcome	18	46.2%	7	17.9%	0	.0%
Intermediate outcome	12	30.8%	15	38.5%	2	5.1%
Poor outcome including death	9	23.1%	17	43.6%	37	94.9%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = <0.001

Above table shows the frequency distribution and association of Modified ranking score on follow up of the study subjects according to the groups. Group A consist of 46.2% good outcome, 30.8% intermediate and 23.1% poor outcome; group B consist of 17.9% good outcome, 38.5% intermediate and 43.6% poor outcome while group C consist of 5.1% intermediate and 94.9% poor outcome



Graph: 7

Discussion

The present study was conducted from October 2021 to September 2022 at Department of Pharmacology in collaboration with Department of Neurology and Department of Respiratory medicine, KGMU, Lucknow. 117 patients who met inclusion criteria were studied during these one year time frame. In our study 58.97% comprised of male and female 41.03% this goes in tune with study conducted by H K Anuradha et al[16] where it has been shown that 59% were male and 41% were male. Similarly study conducted by Verajit Chotmongkol et al[17] found 55.6% male and 44.4% female. Similarly, Chia Peck Kee et al[18] found 60.7% male whereas female constituted 39.3%. 60% males were also found in the study conducted by Emily E. Evans et al[6]. Most common presenting age found was 18 to 30 years which is similar to study conducted by L Mathukumalli N et al[19] where 56.5% were of the same age group similar to the finding by Stephen Kent et al[20].

Maximum population in all the group were from rural background compared to urban

population, 69.2%, 76.9%, and 79.5% respectively in group A, B and C. This can be attributed due to lack of awareness, poverty, nutrition issues and lack of easy accessibility to better health facilities. It is similar to the finding by Abdul Majid Wani et al[21] where study in Kashmir valley shown 76.3% TBM cases were from rural areas.

89.7% in group A, 82.1% in group in group B, and 76.9% in group C had no past history of pulmonary TB which implies that there may be extrapulmonary causes to tuberculous meningitis in addition to most commonly thought pulmonary origin. It is in the same tune with findings demonstrated by Amrut Savadkar et al[22].

BMRC staging is used to assess and group patients in our study. It segregates patients into different grades based on the severity. On admission, before the initiation of the therapeutic regimen 25.6% of patients of group A, 23.1% group B and 5.1% patients of group C were found to be in stage I. In stage II, 43.6% group A, 41% group B, and 12.8% from group C reported .Similarly 30.8% from group A, 35.9% group B and 82.1% from group C reported in stage III. Maximum patients in group A and group B reported in stage II whereas in group C majority were in stage III. Factor behind delayed presentation in advanced stages could be explained by the fact that maximum patients in our study belong to rural background with illiteracy and poor socio economical strata late. Moreover, ours is a tertiary care centre therefore referred and complicated cases which present in advanced stage of TBM can be another factor. In group A and B i.e TBM patients without tuberculoma without hydrocephalus and group B (TBM with tuberculoma), maximum presentation seen at stage II. This finding is consistent with the study conducted by R K Garg et al[23] at King George's Medical University, Lucknow, in which 43.3% patients with TBM and 32.6% TBM with tuberculoma reported at stage II. Similarly study conducted at SGPGI, Lucknow by U K Mishra et al[24] observed 57.0% patients in stage II compared to stage I and III. On similar note Sruthi Kola Reddy et al[19] in a work done at Nizams Institute of Medical Sciences, Hyderabad found 53% patient at the time of presentation in stage II. A systematic analysis done by Ming Gui Wang et al[25] observed that among 17 studies stratified patient by severity of TBM had 41.4% to 52.4% patients in stage II. Chinese study done Heping Xiao et al[26] reported 51% patient in stage II. Turkish study conducted by S. Hosoglu et al[27] also reported 39.5% stage II patients. 82.1% patients of group C i.e TBM with hydrocephalus reported in stage III in our study. Mehak Fatima et al noted 65.52% Pakistani patients with TBM in stage III. In contrast to our finding, R K Garg et al[28] found 38% TBM patients with hydrocephalus in stage III at work done at KGMU, Lucknow. Similarly Mohammed Humble Raza et al[29] noted 58.3% patients in Stage III. Davendran Kanesen et al[30] found 22.4% patients ,and Anum Khan et al[31] 16.66% patients in stage III respectively. The reason for higher percentage of TBM patients with hydrocephalus reported in stage III in our setup might be due to majority of our patients are from poor socio economical background as well as KGMU being a tertiary care centre receives referred patients in advanced stages and complications from peripheral and other secondary health centre.

On follow up, outcome in the form of neurological status is measured using modified Ranking score. Good outcome noticed in 46.2% patients of group A, 17.9% in group B and nil in group C. Intermediate outcome observed in 30.8% patients of group A, 38.5% of group B and 5.1% patients of group C. Poor prognosis which includes death is seen in 23.1% of group A, 43.6% group B and 94.9% patients of group C. Majority of good

outcome observed in group A, group B had majority of intermediate outcome while group C consist of highest number of poor outcome patients. Maximum number of stage I and stage III were reported in group A(TBM without tuberculoma or hydrocephalus) and group C (TBM with hydrocephalus)respectively. Patients having majority of intermediate outcome were associated with group B(TBM patients with tuberculoma). Therefore it appears that stage of TBM at the time of presentation have a crucial role in determination of the outcome during follow up after the administration of the therapeutic regimen. This finding goes in sync with the meta analysis conducted by Wang et al[25] showing poor outcome in stage III patients and dependency of the outcome upon BMRC stages at the time of presentation.

Work done by R K Garg et al[23] demonstrates good outcome (MRS 0) in TBM patients without tuberculoma to be 41.8% compared to TBM patients with tuberculoma. Poor outcome (MRS 3-5 including death) was reported 22.4% .Intermediate outcome(MRS 1-2) found to be 34.9% in TBM with tuberculoma patients compared to TBM patients without tuberculoma. These observations are near findings of our study.

In another study conducted in 2008-09 at KGMU by H K Anuradha et al[32] noted good outcome only in 35% of TBM patients which is lower than our finding (46.2%)indicates the improvement in therapeutic and diagnostic modality regarding TBM management in due course of time. In another study conducted during 2009 by U K Mishra et al[24] shown 35.4% TBM patients with poor outcome compared to our finding 23.1%, which further supports recent improvements in TBM management.

TBM patients with hydrocephalus i.e group C had 82.1% stage III patients and 87.3% reported poor prognosis including death. Total 94.9% patients had poor outcome in group C. Hyrocephalus is one of the well-known complications in TBM that contributes to mortality and morbidity significantly. Advanced stage of TBM hydrocephalus and its association with poor outcome appears to be the reason for the observation mentioned above. Our study is in the similar note with work done by Muthukumalli et al [19]showing 92.7% poor outcome in TBM hydrocephalus grade 3.Devendra Kanesen et[30] al reported 65.2% patients had poor outcome with advanced stage .Systematic analysis done by Yiek wong et al[33] shows 63.11% patient had poor prognosis as the stage advances explaining the pathological basis of poor prognosis in TBM hydrocephalus due to vasculitic infarct especially in brain stem and deep gray nuclei.

Conclusion

- Out of 117 patients, male (58.97%) constituted more as compared to females.
- Age group of 18 to 30 yrs was most vulnerable except in TBM with hydrocephalus where 51 to 60 yrs age group found to be more susceptible due immunological factors and co morbidities.
- Prevalence of TBM found more in rural population because of lack of awareness and delay in diagnosis and treatment as access to better health facilities is difficult
- Majority of TBM patients reported in stage II except TBM patients with hydrocephalus where maximum reported at stage III
- Most of the TBM patients presented in stage II except TBM patient with hydrocephalus where maximum presented at stage III.
- Good outcome at follow up seen maximum in TBM patients without tuberculoma without hydrocephalus followed by TBM patient with tuberculoma.

- Maximum poor outcome seen in TBM patients with hydrocephalus followed by TBM patients with tuberculoma
- BMRC stage determines the outcome at follow up. Early stage at admission i.e. stage I patients had good outcome compared to the stage III patients having advanced stage where maximum poor outcome is seen.It highlights the importance a high index of suspicion in endemic areas, early diagnosis and treatment in TBM patients.
- Stage of TBM (BMRC) as well as functional neurological status (Modified Rankin Score) are two most important determinants of prognosis.
- Total mortality was 23.9%, all in stage III, maximum in TBM patients with hydrocephalus. It indicates that alternate therapeutic approach should be explored so far medical management of TBM patients with hydrocephalus is concerned
- Hydrocephalus is associated with poor prognosis in the patients with TBM both in term of morbidity and mortality

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