



St. Paul's Hospital Millennium Medical college

Graduate study program

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Clinical Characteristics and outcomes of Cryptococcal Meningitis Among ART-naive HIV-AIDS Patients at SPMMC and Zewiditu memorial hospital: A Retrospective chart review; Addis Ababa, ETHIOPIA

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Acronyms and abbreviations

AIDS: Acquired Immune Deficiency Syndrome

Amb: Ambisom

ART: Antiretroviral Therapy

CBC: Complete Blood Count

CD4 cells: Type of T-lymphocyte, white blood cells

CM: Cryptococcal meningitis

CRAG: Cryptococcal antigen

FLU: Fluconazole

5FC: Fluocytosin

GCS: Glasgow coma scale

HAART: Highly active antiretroviral therapy

HIV: Human Immunodeficiency Virus

ICP: Intracranial pressure

LFT: Liver function test

OIs : Opportunistic Infections

PITC: Provider Initiated Testing and Counselling

RFT: Renal function test

RVI: Retroviral infection

SPHMMC: Saint Paul's Hospital Millennium Medical College

UNAIDS: United Nations Program on HIV/AIDS

WBC : White blood cell WHO: World Health Organization

Abstract

Background: Cryptococcal Meningitis (CM) is one of the top causes of meningitis in adults in Sub-Saharan Africa (SSA) and other regions with a high prevalence of Human Immunodeficiency Virus (HIV), accounting for over 100,000 incident cases of meningitis per year in the region. It was further estimated that 10–20% of HIV related deaths in Africa are due to CM.

Objectives: To assess the clinical characteristics and treatment outcome of cryptococcal meningitis among ART naïve HIV patient at St. Paul's Hospital Millennium Medical College and Zewditu memorial hospital, Addis Ababa Ethiopia.

Methods and material : It is an institutional based retrospective study among new cases of HIV-associated CM who were treated at SPHMMC and Zewditu memorial hospital, Addis Ababa from January 2018 to December 2022. Data was gathered from HMIS unit, manual registration book and patient's charts. The collected data was analyzed using SPSS v. 29.

Result: A total of 32 patients with CM were studied with female predominance of 53.1% (17). The mean age of patient with CM was 42.09 years (range: 23 and 64 years). The main clinical manifestation was headache and fever account for 81.2% (n=26). No significant difference was found in signs and symptoms between those who died and survived, except for lower GCS at disease onset, which had a significant effect on mortality ($p=0.025$). In present study, no statistical difference was detected in the baseline CD 4 count and CSF parameter between survivors and non survivors. Fluconazole was used as monotherapy for all patients except one who used combination therapy with fluconazole and flucytosine. The mortality rate was found to be significantly lower ($p\text{-value} = 0.027$) in patients who had therapeutic lumbar tap. In hospital mortality rate was 34.5%.

Conclusions: To reduce deaths and complication of CM, prompt initiation of effective antifungal treatment in line with WHO 2022 treatment guideline is an effective strategy.

Keywords: Cryptococcal meningitis, HIV, immunocompromised patient, opportunistic infections,

1. INTRODUCTION

1.1. Background

Cryptococcus, a genus of yeast-like fungi, is the etiologic agent of cryptococcosis. Until recently, cryptococcal strains were separated into two species, *Cryptococcus neoformans* and *Cryptococcus gattii*, both of which these species complexes cause indistinguishable disease referred to as cryptococcosis. Cryptococcosis was first described in the 1890s but remained relatively rare until the mid-twentieth century, when advances in diagnosis and increases in the number of immunosuppressed individuals markedly raised its reported prevalence. Although serologic evidence of cryptococcal infection is common among immunocompetent individuals, cryptococcal disease (cryptococcosis) is relatively rare in the absence of impaired immunity.[1]

Individuals at high risk for disease due to *C. neoformans* include patients with advanced HIV infection and CD4+ T lymphocyte counts of $<200/\mu\text{L}$, hematologic malignancies, recipients of solid-organ transplants who require ongoing immunosuppressive therapy, medical conditions necessitate glucocorticoid therapy.[2] The global burden of cryptococcosis was recently estimated ~1 million cases, with $>600,000$ deaths annually. Since the onset of the HIV pandemic in the early 1980s, the overwhelming majority of cryptococcosis cases have occurred in patients with AIDS.[2]

Cryptococcal Meningitis (CM) is one of the top causes of meningitis in adults in Sub-Saharan Africa (SSA) and other regions with a high prevalence of Human Immuno-deficiency Virus (HIV), accounting for over 100,000 incident cases of meningitis per year in the region. It was further estimated that 10–20% of HIV related deaths in Africa are due to CM.[6,15]. In Ethiopia, a known epicenter of HIV, cryptococcal antigenemia is highly prevalent among HIV infected patients with an estimated incidence of 3.4% (Mekelle), 8.4% (Addis Ababa), 10.2% (Oromia), and 11.7% (Bahirdar) [3- 5]

The spectrum of disease caused by *Cryptococcus* species consists predominantly of meningoencephalitis and pneumonia. CNS involvement usually presents as signs and symptoms of chronic meningitis, such as headache, fever, lethargy, sensory deficits, memory deficits, cranial nerve paresis, vision deficits, and meningismus.[2]

CM has a high mortality rate in both HIV-negative and HIV-positive individuals, with a cumulative mortality of about 65% at 1 year. It is commonly diagnosed in HIV-positive patients with a CD4 count lower than 100 cells/ μL . Mortality from the disease has remained high despite increased ART access and this is true for 20–50% of hospitalized patients and commonly in immuno-compromised and those with a history of defaulting or other comorbid condition.[4-7]

Detecting the presence of cryptococcal antigens in the patients' blood, Cryptococcal antigenemia (CrAg) tests, is the commonest method for

diagnosing Cryptococcal meningitis (CM). The CrAg test can detect the target antigen from peripheral blood on average of 22 days prior to the development of CM and it is estimated that about 11% of patients will have positive CrAg test more than 100 days prior to the onset of the disease, CM [1]

Adequate antifungal therapy and physical removal of excess cerebrospinal fluid (CSF) to relieve acute symptoms are the mainstays of CM treatment. Compared to the cost of CM hospitalisation and treatment, CRAG screening and fluconazole treatment are cost effective in resource-limited settings with one study estimating the screen-and-treat strategy to be cost-saving above a CRAG prevalence of 3%.[7-8]

The World Health Organization (WHO) has recommendations of CrAg test and antifungal therapy for HIV infected patients with CD4+T-cell count <100 cells/ μ L. The so-called “targeted screening” of HIV infected patients for CrAg allows early identification of population at high risk and prevention of the establishment of infection, thereby reduction of CM and death. [1]

1.2. Statement of the problem

In 2020, UNAIDS estimated that 36.7 million adults worldwide were living with HIV, of which 23.8 million reside in sub-Saharan Africa. Globally, 27.5 million adults were receiving ART. It is estimated that 4.3 million adults globally had advanced HIV disease (defined as $CD4 < 200$ cells/ μ L and corresponding to 12% of people living with HIV), of whom 2.5 million (58%) live in sub-Saharan Africa. Ethiopia is one of the top ten countries in Sub-Saharan Africa in terms of high incidence of cryptococcal antigenaemia. People at risk of cryptococcal infection have advanced HIV disease.[12]

Although there has been a reduction in the estimated absolute global burden of HIV-associated cryptococcal meningitis since 2014, probably due to ART expansion and, to some degree, CrAg screening programmes, cryptococcosis still results in 19% of AIDS-related deaths. Cryptococcus is a neglected killer [9].

Contributing to the high continued prevalence of cryptococcosis are three key gaps in the HIV care cascade: (1) 27% of people living with HIV are not receiving ART, (2) 39% of people living with HIV do not have suppressed viral loads, and (3) 30% of people living with HIV present for the first time with an initial $CD4$ count of less than 200 cells/ μ L.[12]

A retrospective cohort study conducted between April and October 2011 at Croydon University Hospital and St George's Hospital in London found CM was the HIV-presenting illness in 4% (7/157) of the entire cohort, and 7% (6/91) of patients from Africa. Eight (5%) stored serum samples tested retrospectively were positive for CrAg.[14]

In a 2010–2012 Ugandan cohort of 416 ART-naïve adults with HIV presenting with suspected meningitis, cryptococcal meningitis was diagnosed in 60%, acute bacterial meningitis in 1.6%, and tuberculous meningitis in 2.5%[11]

In a survey done in 2013 from 254 HIV-infected persons from Asella teaching hospital ($n=102$) and from Adama hospital ($n=152$) most of the patients (81%) with cryptococcal antigenemia were among those: newly diagnosed with HIV infection in outpatient setting and diagnosed via provider-initiated HIV counseling and testing as inpatient (PITCH). [16]

FLU monotherapy, though not a standard of care regimen, had continued to be majorly used in Africa. This was possibly perpetuated by the high cost, need for in-hospital administration and need for frequent laboratory monitoring of AmB and 5FC. FLU monotherapy even at high doses continues to be a sub-optimal treatment option for HIV-related CM due to its fungistatic nature that results in a slow fungal clearance rate and consequently a higher 2 and 10-week mortality rate (17).

Cryptococcosis is unique among AIDS-related opportunistic infections in that cryptococcal antigen (CrAg) is detectable in the blood (antigenaemia) weeks to months before the onset of meningitis symptoms. Despite clinical trial data confirming the survival benefit of CrAg screening and pre-emptive treatment, only a few nations have adopted a national CrAg screening programme, with variable uptake from the population.[12]

The above studies shows the prevalenc of CM in newly diagnosed ART naïve patients. In Ethiopia, where the burden of HIV is massive and increasing in number , HIV induced CM in newly diagnosed ART naïve patients is expected to increase. Further studies are needed in different institutions and parts of the country to see the overall picture regarding clinical characterstices and treatement outcomes of the patient .

Therefore, this study tried to assess clinical characterstices and treatement outcomes of the CM in newly diagnosed ART naïve patients, at Saint Paul's Hospital Millennium Medical College (SPHMMC), and Zeweditu memorial hospital, Addis Ababa, Ethiopia, So this study aims to fill the knowledge gap and pave the way for further research.

1.3. Significance of the study

The results of this study showed clinical characteristics and treatment outcomes of the CM in newly diagnosed ART naïve patients at SPHMMC and Zewditu memorial hospital. In addition, this study help as a baseline study to conduct subsequent research and to develop setup-based guidelines in line of WHO treatment guideline for CM .

2. Literature review

Cryptococcal meningitis is the most common cause of meningitis in adults living with HIV in sub-Saharan Africa. In 2014, an estimated 223 100 people developed cryptococcal meningitis globally, resulting in 181 100 deaths, which account for 15% of all AIDS-related deaths. In 2020, UNAIDS estimated that 580 000 AIDS-related deaths occurred among adults globally.[12]

CM usually presents as signs and symptoms of sub acute to chronic meningitis, such as headache, fever, lethargy, sensory deficits, memory deficits, cranial nerve paresis, vision deficits, and meningismus. Diagnosis is supported by CSF analysis and CRAG test.[18]

Mean global cryptococcal antigenaemia prevalence of 4.4% (95% CI 1.6–7.4) among people with CD4 counts of less than 200 cells/ μ L, corresponding to 179 000 cases of cryptococcal antigenaemia globally per year. Annually, it is estimated that there are 152 000 cases of cryptococcal meningitis, resulting in 112 000 cryptococcal-related deaths. [12]

In sub-Saharan African estimated 97000 adults had cryptococcal antigenaemia in 2020, 82 000 adults developed cryptococcal meningitis, and 71000 cryptococcal-related deaths occurred accounting for 63% of all cryptococcal-related deaths. The region with the second highest incidence of cryptococcal meningitis is Asia and Pacific, with 44000 cryptococcal meningitis cases and 26000 cryptococcal-related deaths annually.[12]

A retrospective cohort study conducted between April and October 2011 at Croydon University Hospital and St George's Hospital in London CM was the HIV-presenting illness in 4% (7/157) of the entire cohort, and 7% (6/91) of patients from Africa. Eight (5%) stored serum samples tested retrospectively were positive for CRAG.[14]

A prospective cohort study done at Connaught Hospital in Freetown, Sierra Leone with CD4 count below 100 cells/mm³ from January to April 2018. A total of 170 patients, with median age of 36 and median CD4 count of 45 cells/mm³ were screened. At the time of enrolment, 51% were newly diagnosed with HIV, and 56% were either ART-naïve or newly initiated ($\leq$ 30 days). Eight participants were CrAg positive, giving a prevalence of 4.7%. Six (75%) were newly HIV diagnosed and ART-naïve. On review by a clinician, seven (87.5%) had a history of CM evidenced by at least one of headache, confusion or decreased conscious level. [19]

A cross-sectional study was conducted at Mekelle, Ethiopia, from September 2016 to January 2017, on 267 study participants showed prevalence of cryptococcal antigenemia was 9 (3.4%). All CRAG positive had CD4 count less than 100 cells/mm³. Six of the CrAg positives were ART naïve, and 3 were ART experienced. From 9 peoples with antigenemia, 5 from ART naïve and 1 from ART-experienced groups had CM evidenced by headache, fever, vomiting, neck stiffness.[20]

The mortality of HIV patients with CM in different countries ranges from 10 to 43%. It has been reported that the 2-weeks mortality rate of AIDS patients with CM is 17%, and 10-weeks mortality rate can reach 34%, and the overall 1-year mortality rate is 41%. Even in developed countries, with the best antifungal and ART regimen, the mortality of HIV-associated CM within 10 weeks is still 10 to 25%.[21-23]

Poor prognostic indicators associated with increased mortality in cryptococcus meningitis have been identified as low CD4+ cell count with a high visible cryptococcal count at admission of $> 900 \times 10^3$ /ml, Glasgow coma scale (GCS) < 13 , low body weight on admission < 40 kg, higher systolic blood pressure > 150 mm Hg on admission, a higher BUN, higher CSF protein < 45 g/L and higher CSF opening pressure > 60 cmH₂O.[25-26]

A prospective cohort study done in Latin American countries from a total of 340 patients with CM, of these one hundred and fifty-one (44%) patients was HAART naïve. A total of 142 patients with CM (42%) died during the observation period (median follow-up 0.92 years). Fifty-six (37%) patients were HAART naïve, whereas 86 (45%) of those with CM with HAART ($p = 0.14$). [27]

A Longitudinal, prospective study done in Kisumu District Hospital, Kenya 2013 on 141 subject with cryptococcal meningitis 126 of whom were HAART naïve and 15 were already initiated on HAART (5-12 months), ten patients died within one week.[24]

The main reasons for high death rate include delayed presentation, together with poor availability and high cost of treatment. Furthermore, there are no standardized guidelines applicable to resource-limited settings for the diagnosis and management of cryptococcal disease. Most recently, a randomised controlled trial showed that single-dose liposomal amphotericin B with flucytosine and fluconazole is non-inferior to the WHO-recommended regimen, with significantly reduced side effects. Unfortunately, flucytosine is generally unavailable in sub-Saharan Africa, Asia, and Latin America, although efforts are underway to improve access.[12].

Clinical trials are underway to investigate new treatments and new implementation strategies to improve meningitis care in resource-poor settings. An initiative entitled Ending HIV-associated CM deaths by 2030 has been announced recently, which lays out a comprehensive framework to address cryptococcal related meningitis deaths, including targets and interventions for countries to minimise meningitis deaths.[12]

3. OBJECTIVE OF THE STUDY

3.1. General Objective

To assess the clinical characteristics and treatment outcome of cryptococcal meningitis among ART naïve HIV patient at St. Paul's Hospital Millennium Medical College and Zewditu memorial hospital, Addis Ababa Ethiopia.

3.2. Specific Objectives

To describe the presenting features of adult with cryptococcal meningitis ART naïve HIV patient

To assess associated comorbidity of adult diagnosed with cryptococcal meningitis on ART naïve HIV patient

To evaluate the treatment outcome of adult cryptococcal meningitis on ART naïve HIV patients treated at SPHMMC and Zewditu memorial hospital.

4. Methods

4.1 Study setting

The study was conducted in St. Paul's Hospital Millennium Medical College and Zewditu memorial hospital among adult with CM ART naïve HIV patients treated as Inpatient. St. Paul's hospital is one of the largest specialized tertiary referral public hospitals in the capital under the Ministry of Health. The medical college was opened in 2007, SPHMMC was established through a decree of the Council of Ministers in 2010 and it is being governed by a board under the Federal Ministry of Health. The college has more than 2800 clinical, academic and administrative and support staffs that provide medical specialty services to patients who are referred from all over the country, teaching medicine and nursing students

and doing basic and applied researches. While the inpatient capacity is more than 700 beds, the College sees an average of 1200 emergency and outpatient clients daily. Health care and trainings are given in different biomedical and clinical departments of the college including Internal Medicine, Pediatrics, Gynecology/obstetrics, Surgery, Oncology, Dentistry, Psychiatry, Ophthalmology, hospital pharmacy, Dermatology and Public health departments. Neurology is one of the subspecialty units in the internal medicine department and providing outpatient and inpatient medical care; undergoing academic and research activities. Patients with CM and other patients with neurologic problems are linked to neurology unit from several service delivery units within the hospital or direct external referrals.

Zewditu memorial hospital was one of the sites where the study was conducted. It is located in the capital city, Addis Ababa. It was built, owned and operated by seventh-day Adventists church, but was nationalized during the Derg regime in about 1976. The hospital is named after empress Zewditu the cousin and predecessor on the throne of emperor Haile Selassie. Today the Zewditu hospital is operated by ministry of health. Zewditu hospital is Ethiopia's leading hospital in treatment of ART and currently treats over 7000 people each month.

4.2 Study period

The study was conducted at SPHMMC and Zewditu memorial hospital from March 2023 to November 2023.

4.3 Study design

A hospital based medical record review was conducted to assess the clinical characteristics and treatment outcome of cryptococcal meningitis among ART naïve HIV patient. Chart review was used to collect data.

4.4. Population

4.4.1 Source population

All patients above age of 15 years with CM ART naïve HIV patient at SPHMMC and Zewditu memorial hospital.

4.4.2 Study population

All Patients above age of 15 years with CM ART naïve HIV patient who were admitted and are initiated treatment at SPHMMC and Zewditu memorial hospital and fulfil the inclusion criteria.

4.5 Eligibility criteria

4.5.1 Inclusion criteria:

Patients above 15 years of age who were admitted and initiated treatment at SPHMMC and Zewditu memorial hospital.

- with the diagnosis of CM.
- HIV patients who didn't start ART

4.5.2. Exclusion Criteria:

- Patient with a diagnosis CM who has not infected with HIV
- Patient on HAART

4.6 Sampling

All patients chart with CM from January 2018 to December 2022 who have been treated at SPHMMC and Zewditu memorial hospital. who fulfill the inclusion criteria was reviewed.

4.7. Operational Definition

Advanced HIV disease It is defined as a CD4 cell count <200

Cryptococcal infection Growth of Cryptococcus species in the body documented by direct growth of the organism (culture) or indirect detection (positive antigen test in a person) without prior cryptococcal disease

Cryptococcal disease Infection with Cryptococcus species that impairs normal body function, detected by abnormal clinical symptoms or signs

Cryptococcal antigen positivity(CRAG) Positive serum, plasma, or cerebrospinal fluid cryptococcal antigen. A positive cerebrospinal fluid antigen test indicates cryptococcal meningitis

Meningeal disease Disease presenting with nervous system signs or symptoms, specifically involving the meningeal layer surrounding the brain

Cryptococcal meningitis It is meningeal disease caused by cryptococcal species evidenced by demonstrations of CRAG from CSF or serum, documented growth of the organism from blood or CSF (culture), or detection of Indian ink from CSF

Raised intracranial pressure Cerebrospinal fluid opening pressure ≥ 20 cm H₂O or high opening pressure

Cryptococcoma Localized, solid, tumour-like mass caused by growth of cryptococcal organism and associated inflammatory response; can be intracranial or extracranial

4.8. Study variables

Dependent variable

- Outcome of patient with CM

Independent variable

- Socio demographic factors: age, sex, marital status
- Clinical presentation
- Baseline CD4, Viral load, CRAG positivity, CSF analysis finding
- Co morbidities (DM, renal disease, malignancy, associated CNS OI)
- Treatment regimen

4.9 Data collection tools and techniques

4.9.1 Data collection

The data was collected by using structured checklist, for recording information extracted from patient charts. The data collection format containing the important variables will be developed by the principal investigator in line with the objective of the study based on literature review and will be validated by the research advisors. Data was collected by trained data collectors (medical residents) after being trained ahead of data collection. Data collection was done from June 2023 to September 2023 by retrieving patient cards from central data room. Records of patients who had been diagnosed with CM (ART naïve) from January 2018 to December 2022 will be taken for this study.

4.9.2 Data processing and analysis

At the end of each day, the data was checked manually for completeness, was organized, cleaned and later was carefully coded and analyzed using SPSS version 29. The cleaned data was entered into a computer using Statistical Package for Social Science (SPSS) version 29.0. The data was summarized and described using tables. Descriptive statistics was used to put results of the study in the form of frequency, cross- tabulations between variables and descriptive statistical tests including estimation of mean and chisquare test for association was used. Paragraphs, tables, graphs, charts was used to illustrate findings.

4.10. Ethical Consideration

Prior to conducting the research, permission was obtained from SPHMMC research office and SPHMMC Institutional Review Board (IRB). Letter for cooperation (if needed), from each level was obtained. Names and other identification that was reveal patients' identity was be kept confidential . Scientific objectivity of the study was maintained with honesty and information collected from charts was respected and only used for this study purpose.

4.11. Result dissemination

The results of this study was submitted to the department of internal medicine and public health, SPHMMC in partial fulfillment of the requirement for a specialty certificate in internal medicine. In addition,the thesis will be published on reputable and peer reviewed.

5. Result

5.1 Socio demographic characterstices

A total of 32 patients with established CM who fulfil inclusion criteria were included in the present study. The mean age of the patients was 42.09 years (range: 23 and 64 years). The demographic and clinical characteristics of all patients are shown in Tables 1 and 2. With respect to the sex distribution, female patients accounted for the majority of patient 17(53.1%). Majority of patient were from Addis Ababa 23(71.9%), the remaining were from Oromiya region 7(21.9%) and Amahara region 1(3.1%).

Table.2 Sociodemographic characteristics of studied patients

Variable		Number (n=32)	Percentage(%)
Age	15 -35	8	25
	36-55	19	59.3
	>55	5	15.6
Sex	Male	15	46.9
	Female	17	53.1
Marital status	Married	21	65.6
	Single	8	25
	Divorced	2	6.3
	Widowed	1	3.1
Place of residence	Addis ababa	23	71.9
	Oromiya	7	21.9
	Amahra	2	6.2

5.2 Clinical characteristics

The mean time between the onset of symptoms and hospitalization was 10.44 days.(range: 3 to 21 days). Most of the patients presented with more than one symptoms. The main clinical symptoms were in decreasing order of frequency (Table 2): headache and fever account for 81.2% (n=26) ,followed by body weakness 12.5% (n=4), seizure 28.1% (n=9). With regard to comorbidity, 3 patient (9.3%) had associated OI (2 esophageal candidiasis ,1 oral candidiasis),2 patients had pulmonary tuberculosis on anti tuberclosis, 2 patients (6.3%) had DM, 2 patients (6.3%) had liver disease and 1 had hypertension. 25 patient(78.1%) had positive for menigeal sign.

Table 3 Clinical characteristics of studied patients

Variable		Number(n=32)	Percentage(%)
Presenting symptom	Headache and fever	14	43.75
	Headache ,fever and seizure	9	28.1
	Headache, fever and stiff neck	5	15.6
	Body weakness	4	12.5
Duration of illness	< 7 days	13	40.6
	7– 14 days	16	50
	>15 days	3	9.4
Presence of comorbidity	Diabetic mellitus	2	6.3
	Liver disease	2	6.3
	Associated OI(PCP)	6	18.8
	CNS OI	0	0
	Hypertension	1	3.1
	Absent	21	65.6
Physical finding(GCS)	13- 15	19	59.3
	9 -12	10	31.2
	3-8	3	9.3

5.3 Laboratory investigations

The WBC count ranged from 2600 to 13400, with a mean of 5690/microL (SD 2650). The creatinine level ranged from 0.2 to 1, with a mean of 0.683 (SD 0.2265). The AST level ranged from 11 to 138, with a mean of 41.63 (SD 28.64). The ALT level ranged from 6 to 148, with a

mean of 39.5 (SD 26.76)(Table 3) . For 29 patients (90.62%), CD4 cell count was determined. The baseline CD4 count had a mean of 72.3 (SD 62.45) and ranged from 0 to 292. Twelve individuals underwent the serum cryptococcal antigen test (CRAG); all showed positive results. Baseline viral load was determined for 2 patients ,showed >10,000,000 copies.

In all 32 patients CSF analysis was performed. The CSF WBC count ranged from 0 to 950, with a mean of 124 (SD 201.8). 52.84 mg/dl (SD 18.7) was the mean CSF glucose level (range: 12 and 89). The range of the CSF protein level was 42 to 1769 mg/dl, with a mean of 268.13 mg/dl (SD 299.54). 28 patients had CSF Indian ink; 21 of them had positive results, and 7 were negative results.(Table 4).

29 patients (90.62%) underwent cranial magnetic resonance imaging or computed tomography imaging, and the remaining 3 patients (9.3%) didn't undergo imaging. The results showed 10 patients (34.5%) had abnormalities, including 7 patients (24.1%) showed leptomenigeal enhancement and communicating hydrocephalus, 1 patient showed MCA territory infarction, 1 patient who billateral periventricular and subcortical WM hyperintensities, and 1 patient showed billateral multifocal, cerebral bright lesion primarily in the frontal lobe. The images from the remaining 19 patients were normal (65.5%)

Table 4.Laboratory findings for patients with CM

Variable	Mean(range)
Peripheral blood WBC count (×10 ³ /uL)	5690(2600-13400)
Creatinin level (mg/dl)	0.68(0.2-1)
AST level	41(11-138)
ALT level	39.7(6-148)
Baseline CD4	72(0-292)

CSF WBC count	124(0-950)
CSF glucose level(mg/dl)	52(12-89)
CSF protein level(mg/dl)	268(42-1769)

5.4 Treatment and outcome

Thirty-one patients took fluconazol monotherapy. One patient was treated with combination of fluconazole and flucytocin. Furthermore, 1 patient had anti-PCP (cotrimetaxazol), and 18 patients received antibiotics considering bacterial meningitis coinfection. In 20 patients(59%) therapeutic lumbar tap was done. 11 patient died which showed the hospital mortality rate of 34.5%. 9 patients (81.8%) died within the first two weeks of admission. The mortality rate for female was higher (54.5%) than male (46.27%).

Table 5; Serum CRAG and CSF Indian ink result for patients with CM

Variable		Number(n=32)	Percentage (%)
Serum CRAG	Positive	12	37.5
	Not done	22	62.5
CSF Indian ink	Positive	21	65.6
	Negative	7	21.9
	Not done	4	12.5

The mean stay in hospital was 19.34 days. (range ; 3 -36 days). There was statistical significance in total hospital stay, which was observed that the duration of stay was longer among patients who survived compared to those who died. (Table 5). 15 patients were still alive and receiving care at the ART clinic, whereas six patients were lost to follow-up.

Table 5 ; Association of study variables with patient outcomes

Study variable	Outcome		P value
	Died (n=11)	Survived (n=21)	
Age 15-35	0	8(25%)	0.359
36-55	9(28.1%)	10(31.2%)	
>55	2(6.2%)	3(9.3%)	
Sex male	5(45.4%)	10(31.2%)	0.907
female	6(54.5%)	11(34.3%)	
Presenting symptoms	3(9.3%)	11(34.3%)	0.307

Headache ,fever			
Headache ,fever, seizure	3 (9.3%)	6(18.7%)	
Headache, fever, stiff neck	2(6.25%)	3(9.3%)	
Body weakness	3 (9.4%)	1(3.12%)	
GCS 13-15	3(9.3%)	16(50%)	0.0235
9-12	6(18.7%)	4(12.5%)	
< 9	2(6.2%)	1(3.1%)	
Baseline CD4 count			0.330
<100	9(28.1%)	13(40.6%)	
>100	3(9.3%)	8(25%)	
CSF WBC count			0.389
<20	4(12.5%)	9(28.1%)	
>20	7(21.8%)	12(37.5%)	
CSF protein level (mg/dl)			0.374
<60	0	2(6.2%)	
> 60	11(34.3%)	19(59.3%)	
CSF glucose level (mg/dl)			0.653
<30	2(6.2%)	3(9.3%)	
>30	9(28.1%)	18(56.2%)	
CSF indian ink			0.761
yes	7(25%)	14(50%)	
No	2(6.2%)	2(6.2%)	
Treatment regimen			0.462
Fluconazole monotherapy	11(34.3%)	20(62.5%)	
Fluconazole + flucytocine	0	1(3.1%)	
Lumbar tap done	4(12.5%)	16(50%)	

Not done	7(21.8%)	5(15.6%)	0.027
Hospital stay (in days)			
< 14	8(25%)	24(75%)	
14-21	2(6.25%)	22(68.75)	
>21	1(3.12%)	21(65.6%)	0.052

6. Discussion

In the present study, the mean age of the patients was 42.09 years old. (range: 23 and 64 years). 75 % of the patients were under 45 years old. This average age is slightly higher than that reported in other studies which find an average age of around 37 years [30]. An Ugandan prospective study showed age were not helpful in predicting survival [31]. The mean age of our patients who died from CM was 46.27, while mean age who survived was 37.7. No statistical difference was detected in age between survivors and nonsurvivors (p-value=0.359)

In this study, CM was more common in women (53.1%) than in men (47.4%). The result observed in this study is consistent with the results of other African studies [32]. The difference in incidence between the two sexes could be caused due to the difference in exposure. However, study from Europe showed the proportion of males was higher than that of females (70.9% vs. 29.1%) [33].

The average interval from the start of symptoms to hospital admission was 10.44 days. Around 50 % (16) patients presented with in 7 to 14 days of presentation, 40%(13) patients presented within 7 days of presentation. The observed result in this study is less than the results of other study, specifically 15.7 days and 19 days for Kadjo et al, and Millogo et al. respectively. It is

higher than that of Kilani et al. in Tunisia which is nine days, and also higher than that reported in European studies which is less than a week [34]. This could be due to ease access for health facility and patients's knowledge on HIV infection.

The main clinical symptoms in this study were headache and fever which account for 81.2% , followed by body weakness 12.5% , seizure 25% and loss of consciousness 9.3%. However, study from D.R. Congo showed that headache (100%), fever (100%) and neck stiffness (27.8%) are the most evocative symptoms. [35]. In Romanian study, focal deficit were found in 16.7%, and 20.8% had seizures at disease onset [33]. In our study, no significant difference was found in signs and symptoms between those who died and survived, except for lower GCS at disease onset, which had a significant effect on mortality($p=0.025$). (Table 6)

The CD4 counts of our patients were significantly reduced, with average values 72/mm³. 65.6% of patients had a CD4 count less than 100. Study from Tanzania showed , the median baseline CD4 count was 89 cells/uL, 69% of patients had a CD4 less than 100 [36]. 22% (7) patients had no white blood cell in CSF and 60% (19) patients had CSF white blood cell count of less than 50. In present study, no statistical difference was detected in the baseline CD 4 count between survivors and nonsurvivors ($p\text{-value} > 0.05$). (Table 6). A similar result was found with most CSF parameters, showing insignificant results between survivors and nonsurvivors.

85% patients had India ink test positive in our study. In recent studies, India ink staining was positive for CM in 82%–100% of the patients [37]. Our study result falls within the stated range. Studies from other Asian and African countries showed that low CSF protein level (≤ 60 mg/dl), a low CSF glucose level (≤ 30 mg/dl), a high opening pressure during treatment (> 25 cmH₂O), significantly associated with death [38]. In our patients , 28%(9) of patients had CSF protein less than 100 mg/dl and 41%(13) patients had CSF glucose level less than 40 mg/dl.

In present study, fluconazole was used as monotherapy for all patients except one who used combination therapy with fluconazole and flucytosine. The mortality rate was found to be significantly lower ($p\text{-value} = 0.027$) in patients who had therapeutic lumbar tap. (Table 6). In hospital mortality rate was 34.5%, most death (82%(9)) occurred during the first two weeks of admission. This lethality is greater than those reported in Qatar (9%) [39] ,in Europe 15 % [40] and Burkinafaso (27.8%) [41], but lower than those observed in Democratic Republic of Congo 43.5% [35].

This significant difference in mortality between high and low incomes countries is due to use of fluconazole as monotherapy in low income countries ,since its more affordable and easily available in sub-Saharan Africa countries including Ethiopia. Poor outcomes with fluconazole monotherapy is a key driver of the high mortality from cryptococcal meningitis due to its poor efficacy and , it has been associated with a 10-week mortality as high as 50% [42]. In 2018, after the publication of the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial, the World Health Organization (WHO) updated international guidelines to recommend induction

therapy with the less toxic and more efficacious 1-week regimen of amphotericin B deoxycholate and flucytosine in resource-limited settings [43].

Most recently, a randomised controlled trial showed that single-dose liposomal amphotericin B with flucytosine and fluconazole is non-inferior to the WHO-recommended regimen, with significantly reduced side effects. The single liposomal amphotericin B group study's 2-week and 10-week mortality rates, which were 13.8% and 24.8%, respectively, are among the lowest from trial on cryptococcal meningitis in Africa [44].

7. Conclusion

In conclusion, this study showed sub acute presentation (7- 14 days) of cryptococcal meningitis account for half of the patient. The most common presentation was headache and fever. Lower GCS at disease onset had a significant effect on mortality. Majority of the patient had not comorbidity ,The mortality rate was found to be significantly lower in patients who had therapeutic lumbar tap. All ,except one patient, were on fluconazole monotherapy In hospital mortality rate was high.

8. Recommendation

To reduce death, multiple stakeholders should to be involved;

For physician:

- To decreased intracranial pressure, doing proper therapeutic lumbar tap are necessary to improve care for patients
- prompt initiation of effective antifungal treatment in line with WHO 2022 treatment guideline

For responsible government body:

- To avial effective antifungal medication to the country
- use of routine serum or plasma CrAg screening in ART-naive adults whose CD4 count < 200

For patients:

- Patients should be adhere to HAART

Since this was hospital-based study with a small sample size, a larger study recruiting more patients with a longer duration of follow-up at the national or multiple hospital level are needed for:

- Further identification of factors relating with the severity
- Assessment of treatment outcome

9. Strength and limitation of the study

The importance of this present study is that it provides a reasonable picture of clinical characteristics of CM in HAART naïve patients as well as outcome of treatment. To the best of my knowledge, this will be the first study on patient with CM at SPHMMC and Zewditu memorial hospital. I hope this small sampled study will encourage further study on this disease at both hospital and nationwide level. However, it is not without limitations. The major limitations of the present study are its small sample size as such the results cannot be generalized to the general population since patients that present to this hospital may not represent patients in the country with a very diverse sociocultural background. Hospital-based data may also lead to an overestimation of disease severity. Last but not least, as this study is based mostly on retrospective chart review, the data obtained may be incomplete for some patients and inconsistencies in follow up could be another shortcoming of the present study. The shortcomings of the study include incomplete data completion in some patients, lost of patient's cards and lack of necessary investigation for some patients.

10. References

1. WHO, Rapid Advice: Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children, World Health Organization, Geneva, Switerzland, 2011
2. Harrison's principal of internal medicine, 21st ed., 2022 pp 6229-6233
3. A.Bitew, M.Hassen, T.Getachew, and S.Fentaw, "Prevalence of cryptococcal infection in patients clinically diagnosed to have meningitis in Ethiopia," Clinical Medicine Research, vol. 5, no. 4, pp. 73–76, 2016.
4. [27] P.Pongsai, K.Atamasirikul, and S.Sungkanuparph, "The role of serum cryptococcal antigen screening for the early diagnosis of cryptococcosis in HIV-infected patients with different ranges of CD4 cell counts," Journal of Infection, vol. 60, no. 6, pp. 474–477, 2010.

5. [28] T. Fekade, Y. Woldeamanuel, D. Asrat, G. Ayana, and D. R. Boulware, "Comparison of cryptococcal antigenemia between antiretroviral naïve and antiretroviral experienced HIV positive patients at two hospitals in Ethiopia," *PLoS One*, vol. 8, no. 10, 2013.
6. . Patel RKK, Leeme T, Azzo C, Tlhako N, Tsholo K, Tawanana EO, et al. High mortality in HIV-Associated cryptococcal meningitis patients treated with amphotericin B-Based Therapy Under Routine Care Conditions in Africa. *Open Forum Infect Dis.* (2018) 5:ofy267. doi:10.1093/ofid/ofy267
7. Pinheiro SB, Sousa ES, Cortez ACA, da Silva Rocha DF, Menescal LSF, Chagas VS, et al. Cryptococcal meningitis in non-HIV patients in the State of Amazonas, Northern Brazil. *Braz J Microbiol.* (2020) 52:279–88. doi: 10.1007/s42770-02000383-1
7. Mota G, Pate A, Chastain D, Mann S, Canfield GS, Franco-Paredes C, et al. Increased cryptococcal meningitis mortality among HIV negative, nontransplant patients: a single US center cohort study. *Ther Adv Infect Dis.* (2020) 7:2049936120940881. doi:10.1177/2049936120940881
8. Li M, Liu J, Deng X, Gan Q, Wang Y, Xu X, et al. Triple therapy combined with ventriculoperitoneal shunts can improve neurological function and shorten hospitalization time in non-HIV cryptococcal meningitis patients with increased intracranial pressure. *BMC Infect Dis.* (2020) 20:844. doi: 10.1186/s12879-02005510-9
13. Boyer-Chamard T, Temfack E, Alanio A, Jarvis JN, Harrison TS, Lortholary O. Recent advances in managing HIV-associated cryptococcal meningitis. *F1000Research.* (2019) 8:F1000. doi:10.12688/f1000research.17673.1
9. Jarvis J, Meintjes G (2011) Cryptococcal meningitis—a neglected killer. *S Afr Med J* 101: 244–245.
8. Rajasingham R, Meya DB, Boulware DR (2012) Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care. *J Acquir Immune Defic Syndr* 59: e85–91
10. [29] A. Derbie, W. Ayalew, D. Mekonnen, M. Alemu, and Y. Mulugeta, "Magnitude of cryptococcal antigenemia among HIV infected patients at a referral hospital, northwest Ethiopia," *Ethiopian Journal of Health Sciences*, vol. 28, no. 4, p. 369, 2018.
11. Rajasingham R, Rhein J, Klammer K, et al. Epidemiology of meningitis in an HIV-infected Ugandan cohort. *Am J Trop Med Hyg* 2015; 92:274–9.
12. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis
13. Jarvis J, Meintjes G (2011) Cryptococcal meningitis—a neglected killer. *S Afr Med J* 101: 244–245.
14. The prevalence of cryptococcal antigenemia in newly diagnosed HIV patients in a Southwest London cohort

15. Prevalence of cryptococcal meningitis among people living with human immunodeficiency virus and predictors of mortality in adults on induction therapy in Africa: A systematic review and meta-analysis
16. Comparison of Cryptococcal Antigenemia between Antiretroviral Naive and Antiretroviral Experienced HIV Positive Patients at Two Hospitals in Ethiopia
17. Collaborators GH. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2017, and forecasts to 2030, for 195 countries and territories: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. *Lancet HIV*. (2019) 6:e831–59. doi:10.1016/S2352-3018(19)30196-1
18. National Comprehensive HIV Prevention, Care and Treatment Training for Healthcare Providers pp 221-223, 2021
19. Prevalence and mortality of cryptococcal disease in adults with advanced HIV in an urban tertiary hospital in Sierra Leone: a prospective study, (2020) 20:141
20. Cryptococcal antigenemia and associated risk factors among ART-naïve and ART-experienced HIV-infected peoples at selected health institutions of Mekelle, Northern Ethiopia, 2018
21. Jarvis JN, Harrison TS. HIV-associated cryptococcal meningitis. *AIDS* (London, England). 2007;21(16):2119–29.
22. Jarvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated Cryptococcal meningitis: implications for improving outcomes. *Clin Infect Dis*. 2014;58(5):736–45.
23. Ogundejì AO, Albertyn J, Pohl CH, et al. Method for identification of *Cryptococcus neoformans* and *Cryptococcus gattii* useful in resource-limited settings. *J Clin Pathol*. 2016;69(4):352–7.
24. CRYPTOCOCCUS MENINGITIS IN A COHORT OF HIV POSITIVE KENYAN PATIENTS: OUTCOME AFTER TWO WEEKS OF THERAPY, 2013
25. Clark R.A., Greer D., Atkinson W., Valaines T.G. and Hyslop N. Spectrum of *Cryptococcus Neoformans* infection in 68 patients infected with human immunodeficiency virus. *Rev. Infect. Dis*. 1990; (12): 768 – 777.
26. Wuthiekanun V., Howe P.A., Simpson A.J. et al. Antifungal susceptibilities of cryptococcal *neoformans* in North East Thailand. *Trans. Roy. Soc. Trop Med. Hyg.* 1999; (93): 96-97.
27. Outcomes of HIV-positive patients with cryptococcal meningitis in the Americas, 2017
28. Lortholary et al, 2006
29. Manosuthi et al, 2008)
30. Azambuja AZD, Wissmann Neto G, Wante G, et al. Cryptococcal meningitis: a retrospective cohort of a Brazilian reference hospital in the post-HAART era of universal access. *Canadian Journal of Infectious Diseases and Medical Microbiology*. 2018;2018:Article ID 6512468

31. Clin Infect Dis. 2008 Jun 1; 46(11): 1694–1701.
32. Kadjo K, Ouattara B, Adoubryn KD, et al, current aspects of neuromeningeal cryptococcosis in adults infected with HIV in the internal medicine service of the University Hospital of Treichville Abidjan (Cote d'Ivoire). Journal de mycologie médicale. 2011;21(1):6– 9.
33. Marincu, I.; Citu, C.; Vidican, I.; Bratosin, F.; Mares, M.; Suciu, O.; Frent, S.; Bota, A.V.; Timircan, M.; Bratu, M.L.; et al, 2022
34. Kadjo K, Ouattara B, Adoubryn KD, et al
35. Katabwa JK, Mukuku O, Lwamba GK, et al, 2021
36. Matobogolo M. Boaz et al. 2017
37. Naik KR, Saroja AO, Doshi DK. Hospital-based Retrospective Study of Cryptococcal Meningitis in a Large Cohort from India. Ann Indian Acad Neurol 2017;20:225-8.
38. Somnuek Sungkanuparph, *et al*, 2017
39. Khan, et al (2020)
40. Suciu, O.; Frent, S.; Bota, A.V.; Timircan, M.; Bratu, M.L.; et al, 2021
41. Bamba S, Barro-Traoré F, Sawadogo E, et al, 2012
42. Tenforde MW, Gertz AM, Lawrence DS, et al. Mortality from HIV-associated meningitis in sub-Saharan Africa: a systematic review and meta-analysis. J Int AIDS Soc 2020;23(1):e25416)
43. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization, March 1, 2018
44. N Engl J Med 2022;386:1109-20

Annex I: Information sheet

Title of the Research proposal: Clinical characteristics and response to treatment of adult CM ART naïve RVI patients at St. Paul's hospital millennium medical college and Zewiditu memorial hospital: a retrospective chart review; Addis Ababa, Ethiopia

Name of Investigator: Dr. Bereket Mesele (MD,internal medicin resident)

Name of the Organization: St. Paul's Hospital Millennium Medical College, Department of Internal Medicine

Name of the Sponsor: SPHMMC research office

Introduction: this information sheet is prepared for SPHMMC department of internal medicine Addis Ababa, Ethiopia. The aim of this information sheet is, to be clear about the purpose of research with the concerned office about data collection procedures and to get permission in order to conduct the study.

Purpose of the Research thesis: To assess Clinical charterstices and response to treatment of adult CM ART naïve RVI patient at St. Paul's Hospital Millennium Medical College and Zewiditu memorial hospital ; Addis Ababa, Ethiopia

Procedure: In order to achieve the above objective, information, will be taken from medical records of patients' with CM ART naïve patient from June 1st 2023 to September 30th 2023.

Risk and /or Discomfort: As this study is retrospective and non-interventional; it will not inflict any harm on the study participants. The Privacy, confidentiality and anonymity information collected from patients' chart will be maintained.

Benefits: The study participants will not benefit from this study directly; but as the result of this study may benefit for service improvement in the future.

Confidentiality: To ensure confidentiality the data will be collected by trained internal medicine residents data will be handled anonymously, will be coded and entered to secure software.

Person to contact: This research project will be reviewed and approved by the institutional review board of SPHMMC.

For further information, the PI and advisors can be contacted:

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Annex II: Data Collection Tool

Name of data collector----- Date of data collection-----

Code of patients chart -----

SN	Questions	Response and categories	Remark
101	Age (years)		
102	Sex	1. Male 2. Female	

103	Marital Status	1. Single 3. Separated 4. Widowed	2. Married 5. Divorced	
104	Region	1. Addis Ababa 2. Amhara 3. SNNPR	4. Oromiya 5. Tigray 6. Others	
105	Place of residence			

106	Presenting symptom(major symptom)	1. Headache 2. Fever 3. Seizure 4. Loss of consciousness 5. Body weakness 6. Stiff neck, 7. photophobia 8. Other_____	
107	Duration of illness		
108	Presence of known comorbid illness	1. DM 2. Renal disease 3. Liver disease 4. Malignancy 5. Tuberculosis 6. Other, ...	

		7. Absent	
108	Physical finding	1. GCS 2. Muscle power 3. Menigeal sign 4. Any skin lesion	

109	laboratory studies	1. CBC 2. RFT 3. LFT 4. Serum CRAG (if done) 5. Baseline CD4 6. Baseline viral load	
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110	CSF analysis	1. WBC with differential 2. .glucose 3. Protein 4. Indian ink 5. Opening pressure	
111	Brain imaging result(if done)		
112	Treatement regimen	1. Fluconazole monotherapy 2. Fluconazole with amphotricin	
113	Any treatement for associated illness?	1. Anti TB 2. Antibiotices 3. Other ,specify	

114	Is there any sign of increased ICP?	1. Assymteric pupil size 2. Persisistant vomiting 3. Bradycardia 4. No sign of increased ICP 5. Other specify	
115	Lumbar tap done if above sign present?	1. Yes 2. No	
116	Transfer to ICU for mechanical venilation	1. Yes 2. No	
117	If yes to the above question(116),what was the indication?		
117	Total stay in hospital		
118	Outcome	1. Death 2. On follow ups 3. Lost to follow ups	
119	Immediate cause of death if he/she passed away		
118	On how many days of admission death occurred?		

Annex III. Assurance of Investigator

I the undersigned resident agree to accept all responsibilities for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the Research and Publication Directorate and /or Department of Public Health of St. Paul's Hospital Millennium Medical College.

Name of the Resident: _____

Signature: _____

Date: _____

Approval of Advisors

Name of Public Health Advisor: _____

Signature: _____

Date: _____

Name of Clinical Advisor: _____

Signature: _____

Date: _____