

Clinical and epidemiological characteristics and in-hospital outcomes of patients with Central Nervous System Infections in a high HIV-burden, resource limited setting: findings from In.Ne.Mo Prospective Cohort Study

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Abstract

Background

Central nervous system (CNS) infections remain a major cause of morbidity and mortality in low-resource settings, particularly in high burden of HIV. Data on clinical presentation and prognostic factors in Mozambique are limited.

Methods

We conducted a prospective cohort study at Maputo Central Hospital, Mozambique, including adults (≥ 18 years) hospitalized with CNS infections between September 2024 and August 2025, with follow-up until September 2026. Demographic, clinical, diagnostic, treatment and outcome data were collected. Cox proportional hazards regression identified independent predictors of death.

Results

Of 281 patients screened, 265 were included. Median age was 39 years (IQR 28–47), 52% were male, and 185 (70%) were living with HIV. Headache (75%) altered mental status (69%), fever (53%) and seizures (39%) were the most frequent presenting features. Half presented approximately one week after symptom onset and 23% after more than one month. Lumbar puncture was performed in 121 (46%). Overall, 84 patients died in hospital (31.7%). Cerebral toxoplasmosis, cryptococcal meningitis and meningoencephalitis were more frequent among the group of deceased, whereas cerebral malaria predominated among survivors ($p < 0.001$). Male sex (adjusted hazard ratio [aHR] 2.24, 95% CI 1.39–3.62), GCS 9–12 (aHR 2.03, 95% CI 1.03–3.97), GCS 3–8 (aHR 4.95, 95% CI 2.48–9.88), HIV infection (aHR 2.39, 95% CI 1.27–4.50), and smoking (aHR 2.18, 95% CI 1.18–4.03) were independently associated with increased hazard of in-hospital death. Antiviral treatment was associated with lower hazard of death (aHR 0.11, 95% CI 0.02–0.45).

Conclusion

CNS infections is associated with high in-hospital case-fatality with approximately one out three patients dying. Severe neurological impairment and HIV infection were major predictors. Delayed presentation limited diagnostic capacity and management emerged as key actionable gaps in care. Improving timely diagnosis and improving management, particularly HIV infection, may reduce case-fatality from CNS infections in Mozambique.

1. Introduction

Central nervous system (CNS) infections impose a substantial global health burden, with the highest incidence occurring in low to median-income settings. There is marked variation of the clinical and epidemiological characteristics across different geographic regions [1]. Globally, the burden of CNS is disproportionately higher in endemic regions for HIV, tuberculosis, and neglected parasitic diseases[2], [3] Meningitis, a largely preventable CNS infection, remains a major cause of neurological disability worldwide, ranking the third leading contributors to neurological disability-adjusted life years (DALYs) accounting for 7.9% (6.6–10.4) of the global burden [4]. Viral, fungal, and parasitic agents are also associated with severe neurological complications and long-term functional sequelae even after specific treatment [5], [6]. In a prospective cohort from Southern Africa, 66.7% of patients investigated for suspected meningitis were HIV-positive, and TB and cryptococcal disease represented important causes of meningeal infection[7]. Similarly, in a tertiary hospital in Zambia, infectious diseases accounted for 38.8% of inpatient neurological diseases diagnosed among people living with HIV, compared with 12.5% in the general inpatient population, highlighting the disproportionate contribution of CNS infections to neurological morbidity in high HIV-burden settings[8]. Despite advances in HIV diagnosis and antiretroviral therapy, outcomes of CNS infections remain poor, particularly among patients presenting with advanced immunosuppression and severe neurological disease. In South Africa, tuberculous meningitis was associated with substantial mortality, with low CD4 cell counts and advanced disease at presentation independently associated with in-hospital death[9]. Contemporary multicentre evidence from Cameroon, Malawi, and Tanzania demonstrated that HIV-associated CNS infections remain associated with substantial early mortality, with 49% of patients dying within two weeks during routine care; However implementation of standardized diagnostic and management pathways reduced two-week mortality to 24%, highlighting both the severity of these infections and the potential for preventable deaths through improved care [10]. The burden of CNS infections is likely underestimated because diagnostic capacity remains limited across many African health systems. Recently, multicentre data from Uganda, Malawi, and Rwanda demonstrated that additional molecular testing identified viral and bacterial CNS infections that were missed by conventional diagnostic approaches and that these infections were associated with poor outcomes[11]. This diagnostic gap is particularly relevant in resource-limited hospitals, where access to neuroimaging, cerebrospinal fluid analysis, microbiological testing, and specialist neurological care may be constrained. Despite recent advances in HIV care and CNS infection management, substantial mortality persists, and the identification of patients at highest risk of death remains an important clinical priority[10], [12]. Data from Mozambique are scarce and the existing evidence suggests that the clinical and epidemiological profile of CNS infections is characterized by a high burden of meningitis, frequent HIV co-infection, and delays in diagnosis [13], [14], [15], [16]. Prospective studies that comprehensively assess the epidemiology, clinical presentation, and short and long term prognostic determinants of CNS infections are critical for informing clinical practice and public health strategies to reduce disease burden [17].

To address this knowledge gap, we conducted a prospective cohort study to investigate the clinical presentation, aetiology, diagnostic findings and predictors of in-hospital outcomes among patients with

CNS infections admitted to Maputo Central Hospital (MCH), the national quaternary referral hospital in Mozambique.

2. Methods

2.1. Study Design and Setting

The *In.Ne.Mo.* Study (from the Portuguese acronym **In**feções **Neurológicas em Moçambique**) is an ongoing prospective cohort study conducted at MCH, Mozambique, that aims to improve the understanding of the epidemiology, clinical presentation, aetiology, management, and outcomes of CNS infections in the country. In this study we report the findings from September 2024 to August 2025. The MCH is a university hospital and the largest hospital of the country, located at Maputo (Fig. 1), with 1500 beds [18], 24/24, seven-day emergency department and admits approximately 4000 patients per month. The hospital serves approximately 1.14 million inhabitants[19].

Due to the high burden of HIV infection in the country, at the hospital there is a low threshold for suspecting CNS infections. Consequently, empirical antimicrobial therapy is routinely initiated whenever a CNS clinically suspected, without waiting for microbiological confirmation. However, diagnostic evaluation is constrained by access to neuroimaging and cerebrospinal fluid (CSF) examinations. Following initial stabilization, patients are typically admitted to the Neurology or Internal Medicine wards for further diagnostic evaluation and management.

Study Procedures

Adult patients (≥ 18 years) hospitalized with suspected CNS infections were consecutively included in the study. Written informed consent was obtained from all participants. For patients with coma, altered mental status, or impaired consciousness, consent was obtained from a legally authorized representative or next of kin.

This study was exclusively observational. All patients received standard clinical care according to institutional protocols and were managed independently of study participation. A *posteriori* diagnostic classification followed a hierarchical algorithm prioritizing microbiological confirmation, followed by compatible clinical syndromes supported by CSF, neuroimaging, and epidemiological context. Clinical evaluation, diagnostic testing, and treatment decisions were made by the attending clinical teams.

2.2. Data Collection and Follow-up

Demographic, clinical, laboratory, neuroimaging, treatment, and outcome data were prospectively collected using standardized case report forms. Variables included age, sex, HIV status, comorbidities, clinical presentation, CSF findings, neuroimaging findings, antimicrobial and adjunctive therapies and in-hospital vital status (outcome).

The study included acute, subacute, and chronic CNS infections.

2.3. Case Definitions

Patients were classified according to predefined diagnostic criteria adapted from international guidelines and consensus definitions for CNS infections[20]. CNS infections were categorized into acute infections (bacterial meningitis, viral meningitis, viral encephalitis, brain abscess, and infection of unknown aetiology) and subacute/chronic infections (tuberculous meningitis, tuberculoma, spinal tuberculosis, cryptococcal meningitis, cerebral toxoplasmosis, neurosyphilis, neuroschistosomiasis, and neurocysticercosis).

HIV-associated CNS opportunistic infections were defined using immunological status, clinical presentation, neuroimaging findings, and microbiological confirmation when available. Detailed diagnostic criteria for individual CNS infections are provided in *the supplement 1*.

2.4. Ethical Considerations

The study was approved by the National Committee for Bioethics in Health (CNBS); approval number: 86/CNBS/2024. This study was carried out in accordance to the Helsinki declaration. Written informed consent was obtained from all participants or from legally authorized representatives when patients were unable to provide consent. All data were anonymized and handled confidentially.

2.5. Statistical analysis

Statistical analyses were performed using R software (version 4.6.1). Continuous variables are presented as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), according to their distribution, while categorical variables are presented as frequencies and percentages.

Baseline characteristics were compared between survivors and non-survivors using the Student's t test or Mann–Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. These analyses were exploratory and intended to describe differences according to in-hospital outcome. Missing data was handled using available case analysis. A two-sided p value < 0.05 was considered statistically significant. Predictors of mortality were identified using univariate and multivariate Cox proportional hazards regression models.

3. Results

3.1. Patient recruitment and selection

A total of 281 patients with clinical syndromic diagnosis of CNS infection were initially identified. Sixteen patients were excluded because an alternative diagnosis was established, including subarachnoid haemorrhages, psychiatric disorders or stroke, leaving a 265 patients for the final analysis (Fig. 2).

Overall, 84 patients (32%) died during hospitalization. HIV-associated opportunistic CNS infections, particularly meningoencephalitis (25%), cerebral toxoplasmosis (24%), cryptococcal meningitis(17%),

CNS tuberculosis (13%) and bacterial meningitis (8%) were major top five contributors to in-hospital deaths.

3.2. Baseline sociodemographic, clinical, and paraclinical characteristics

Baseline sociodemographic characteristics, clinical and laboratorial features are shown in Table 1. Among 265 patients, 137(52%) were males. The median age was 39 (IQR 28–47) years. HIV co-infection was present in 185 (85%) of patients. In the subgroup of CNS infections with co-existent HIV infection, the majority were on receiving antiretroviral therapy for more than one year (n = 78, 67%), with median CD4 T-cell counts of 150 (IQR 68–258) cells/mL. The median CD4 T-cell count was 150 cells/mm³ (IQR: 68–258 cells/mm³).

Table 1

Baseline demographics, selected clinical characteristics, and comparison between the between hospital survivors and deceased after CNS infections in Maputo, Mozambique (1/09/2024 to 30/08/2025).

Sociodemographic and clinical features	Analysed - N	Overall N = 265	Discharged Alive N = 181	In Hospital death N = 84	p-value²
Age (years), median (IQR)	265	39 (28, 47)	37 (27, 45)	41 (31, 53)	< 0.001
Gender					0.063
Female n (%)	128	128 (48%)	95 (52%)	33 (40%)	
Male n (%)	137	137 (52%)	86 (48%)	51 (60%)	
Admission route	263				0.668
Medical emergency department		257 (97.7%)	175 (97.2%)	82 (98.8%)	
Outpatient clinic		6 (2.3%)	5 (2.8%)	1 (1.2%)	
Referred from another facility	78	78 (30.0%)	61 (34.1%)	17 (21.0%)	0.033
Time to onset symptoms					0.079
1 week n (%)		132 (50%)	96 (54%)	36 (42%)	
1 to 2 weeks n (%)		36 (14%)	19 (11%)	17 (20%)	
2 to 4 weeks n (%)		37 (14%)	20 (11%)	17 (20%)	
More than 1 month n (%)		60 (23%)	45 (25%)	15 (18%)	
Length of in-hospital stay in days median (IQR)		8.0 [4.0–15.0]	10.0 [5.0–17.0]	4.5 [3.0–10.0]	< 0.001
HIV status	265				0.013
Negative n (%)		80 (30%)	64 (35%)	16 (19%)	
Positive n (%)		185 (70%)	117 (65%)	68 (81%)	
Clinical manifestations					
Abbreviations: IQR = Inter quartile range, HIV = Human immunodeficiency virus, GCS – Glasgow coma scale.					

Sociodemographic and clinical features	Analysed - N	Overall N = 265	Discharged Alive N = 181	In Hospital death N = 84	p-value²
Glasgow coma scale n	253	30 (12%)	5 (3%)	25 (32%)	< 0.001
GCS 3–8		38 (15%)	15 (9%)	23 (29%)	
GCS 9–12		181 (73%)	154 (89%)	31 (39%)	
GCS 13–15					
Headache n (%)	265	192 (73%)	136 (75%)	56 (66%)	0.151
Seizures n(%)	265	104 (39.2%)	62 (34%)	42 (50%)	0.015
Fever n (%)	265	140 (53%)	92 (51%)	48 (57%)	0.338
Facial Palsy n (%)	7	7 (2.6%)	6 (3.3%)	1 (1%)	0.437
Diplopia n (%)	265	21 (8%)	14 (8%)	7 (8%)	0.867
Motor impairment	61				0.02
Hemiparesis		40 (66%)	20 (53%)	20 (87%)	
Paraparesis		18 (30%)	15 (39%)	3 (13%)	
Monoparesis		3 (4.9%)	3 (7.9%)	0 (0.0%)	
Combine manifestations suggestive of increased intracranial pressure		20 (8%)	8 (4%)	12(14%)	0.003
Altered mental status/delirium	262	181 (69%)	149 (83%)	32 (39%)	< 0.001
Meningeal signs	265	14 (5%)	7 (4%)	7 (8%)	0.146
Abbreviations: IQR = Inter quartile range, HIV = Human immunodeficiency virus, GCS – Glasgow coma scale.					

The most frequent clinical presentation was headache (192, 75%), altered mental status (181, 69%), fever (140, 53%), seizures (104, 39%), motor abnormalities (61, 23%) - hemiparesis (40, 66%), paraparesis (18,30%) (Table 2). The most common comorbidities were hypertension (n = 55, 21%), previous tuberculosis (n = 42, 16%) and diabetes mellitus (n = 10, 4%). Tobacco use was reported by 31 patients (12%) and alcohol use by 76 patients (29%).

Table 2

Admission laboratory results and imaging findings, and comparison between the hospital survivors and deceased after CNS infections in Maputo, Mozambique (1/09/2024 to 30/08/2025)

Findings	Non-missing N	Overall N = 265 ¹	Discharged Alive N = 181	In Hospital death N = 84 ¹	p-value ²
Laboratorial findings					
HB (g/dL) median (IQR)	264	11.0 (9.2, 12.1)	11.0 (9.2, 12.1)	10.2 (8.9, 12.0)	0.388
Leucocytes (x 10 ⁹ /L) median (IQR)	262	8.1 (5.3, 12.3)	7.2 (5.0, 10.9)	9.3 (6.8, 15.0)	0.004
Platelets (x10 ⁹ /L), median (IQR)	255	205 (137, 307)	214 (138, 314)	186 (131, 277)	0.318
Urea (mmol/L), median (IQR)	85	5 (3, 10)	4 (3, 8)	8 (4, 20)	0.010
Creatinine (μmol/L) median (IQR)	140	67 (53, 101)	65 (51, 94)	96 (59, 162)	0.021
Aspartate aminotransferase (U/L)	164	42.0 (30.0–87.0)	42.0 (30.0–76.8)	42.0 (29.2–87.8)	0.77
Alanine aminotransferase (U/L)	167	31.0 (18.4–53.0)	32.0 (19.0–56.0)	28.0 (18.0–50.8)	0.371
Blood glucose (mmol/L)	114	5.2 (4.3–6.2)	3.1 (2.6–3.2)	5.4 (4.9–6.2)	0.358
Erythrocyte sedimentation rate (mm/h)	115	52.0 (33.0–85.0)	53.0 (35.0–76.0)	52.0 (33.0–95.0)	0.821
CD4 count in HIV+ (cells/mL), median (IRQ)	126	150 (71, 257)	167 (74, 295)	115 (74, 181)	0.07
CSF Findings					
Opening Pressure (cmH2O), median (IQR) (n°)	127	20 (20, 30)	20 (20, 30)	29 (20, 40)	0.004
Normal (< 20 cmH2O)		69 (54%)	55 (43%)	14 (11%)	
Increased (> 20 cmH2O)		58 (46%)	38 (30%)	20 (16%)	
Pandy test	55	33(60%)	19(50%)	14(82%)	0.024
Brain imaging findings					
Abbreviations: CSF= cerebrospinal fluid, CT = Computad tomography, IQR= Inter quartile range, HB = haemoglobin,					

Findings	Non-missing N	Overall N = 265 ¹	Discharged Alive N = 181	In Hospital death N = 84 ¹	p-value ²
Laboratorial findings					
CT scan (n = 121)					0.6
Normal		22 (20%)	15 (21%)	7 (18%)	
Pathologic		89 (80%)	56 (79%)	33 (83%)	
Abbreviations: CSF= cerebrospinal fluid, CT = Computad tomography, IQR= Inter quartile range, HB = haemoglobin,					

The time between the onset of neurological symptoms and hospital presentation was within one week in 132 patients (50%) and exceeded one month in 60 (23%) patients.

Brain imaging (CT scan) was performed in 121 patients (46%), and lumbar puncture was initially performed in 127 patients (48%). Laboratorial, CSF and neuroimaging results are summarized in Table 2.

The most frequent aetiology were tuberculous meningitis and cerebral toxoplasmosis (15%), cryptococcal meningitis (14.0%), cerebral malaria (13.0%) and bacterial meningitis (10%). In 19% of patients, the etiology of meningoencephalitis remained unknown (Table 3).

Table 3

Aetiologies of 265 consecutive patients with CNS infections stratified by in-hospital discharge status, Maputo, Mozambique (1 September 2024–30 August 2025).

Characteristic	Overall N = 265 ¹	Discharged Alive N = 181 ¹	In Hospital death N = 84 ¹	p- value ²
Final Diagnosis				< 0.001
Acute CNS Infections				
Cerebral abscess	6 (2.3%)	4 (2.2%)	2 (2.4%)	
Cerebral Malaria	35 (13%)	33 (18%)	2 (2.4%)	
Encephalitis	15 (6%)	14 (8%)	1 (1.2%)	
Bacterial Meningitis	17 (6%)	10 (6%)	7 (8%)	
Meningoencephalitis (unknown aetiology)	56 (21%)	35 (19%)	21 (25%)	
Sub-acute and chronic CNS infections				
Neurocysticercosis	8 (3.0%)	7 (3.9%)	1 (1.2%)	
Neurosyphilis	1 (0.4%)	0 (0%)	1 (1.2%)	
Spinal Schistosoma	1 (0.4%)	1 (0.6%)	0 (0%)	
Transverse myelitis (unknown aetiology)	2 (0.8%)	1 (0.6%)	1 (1.2%)	
Tuberculous Spondilomyelitis	12 (4.5%)	10 (5.6%)	2 (2.4%)	
Cerebral Tuberculoma	5 (2%)	2 (1%)	3 (4%)	
Tuberculous Meningitis	25 (9%)	19 (10.6%)	6 (7%)	
<i>Cryptococcal and Tuberculous Meningitis</i>	2 (0.8%)	2 (1.1%)	0 (0%)	
<i>Cryptococcal meningitis and Cerebral Toxoplasmosis</i>	1 (0.4%)	1 (0.6%)	0 (0%)	
Cryptococcal meningitis	40 (15%)	23 (13.%)	17 (20%)	
Spinal cryptococcal	1 (0.4%)	1 (0.6%)	0 (0%)	
Cerebral Toxoplasmosis	40 (15%)	20 (11%)	20 (24%)	
<i>Cerebral Toxoplasmosis and tuberculoma</i>	2 (0.8%)	2 (1.1%)	0 (0%)	
Abbreviations: CNS = central nervous system;				

The distribution of final diagnoses differed significantly between patients discharged alive and those who died in hospital ($p < 0.001$). In comparison to survivors, the group of deceased patients had a higher proportion of meningoencephalitis of unknown aetiology (25% versus 19%), Cerebral toxoplasmosis, (24% versus 11%), cryptococcal meningitis (20% vs 13%), and bacterial meningitis (8% vs 6%). In contrast, cerebral malaria was markedly less frequent among non-survivors (2.4% vs 18%). Encephalitis was also less frequent among non-survivors (1.2% vs 8%), as were neurocysticercosis (1.2% vs 3.9%), tuberculous spondylomyelitis (2.4% vs 5.6%), and tuberculous meningitis (7% vs 10.6%)

Multiple concomitant CNS infections were found in 2% ($n = 6$). These included cases of concurrent cryptococcal and tuberculous meningitis, cryptococcal meningitis associated with cerebral toxoplasmosis, and cerebral toxoplasmosis coexisting with cerebral tuberculomas.

3.3. Treatment and in-hospital outcomes

All patients received empirical antimicrobial therapy at admission, primarily ceftriaxone and/or metronidazole. Adjunctive corticosteroid therapy was administered in 48 (18%) patients, most commonly prednisolone and dexamethasone. Aetiology-directed treatment included intravenous artesunate for cerebral malaria. Cryptococcal meningitis was treated with liposomal amphotericin B, with fluconazole used according to drug availability. Tuberculous meningitis was managed with standard first-line therapy using a four-drug fixed-dose combination (4FDC).

In-hospital major complications occurred in 34 (12%) patients. The most frequently complications included aspiration pneumonia ($n = 14$, 41%), seizures ($n = 5$, 15%), and decreased level of consciousness ($n = 4$, 12%). Drug-induced hepatitis, acute kidney injury, and malarial nephropathy each occurred in fewer than 5%. Among patients with major complications, 21 (62%) died during hospitalization.

3.4. Predictors of in-hospital case fatality

On multivariable Cox proportional hazards analysis (Table 4), male sex, severe neurological impairment, HIV infection, and smoking were independently associated with a higher hazard of in-hospital death. Male patients had more than twice the hazard of in-hospital death compared with female patients (aHR 2.24, 95% CI 1.39–3.62; $p < 0.001$). A graded association was observed between the severity of neurological impairment and in hospital death. Compared with patients with a normal or mildly impaired a GCS score (13–15, reference), those with GCS 9–12 had approximately twice the hazard of death (aHR 2.03, 95% CI 1.03–3.97; $p = 0.039$), while those with severe impairment (GCS 3–8) had almost five-fold higher hazard (aHR 4.95, 95% CI 2.48–9.88; $p < 0.001$). HIV-positive patients had a higher hazard of in-hospital death (aHR 2.39, 95% CI 1.27–4.50; $p = 0.007$) and smoking (aHR 2.18, 95% CI 1.18–4.03; $p = 0.013$) were also independently associated with a higher hazard of in-hospital death. Antiviral treatment was independently associated with a lower hazard of in-hospital death (aHR 0.11, 95% CI 0.02–0.45; $p = 0.003$). Age, white blood cell count, meningeal signs, inter-facility transfer, seizures, antifungal treatment, antiparasitic treatment, and chronic CNS infection did not emerged and independent predictors of in-hospital death (all $p > 0.05$).

Table 4

Multivariable Cox proportional hazards analysis of factors associated with time to in-hospital death in 265 consecutive patients with CNS infections in Maputo, Mozambique (1/09/2024 to 30/08/2025).

Variable	Adjusted HR	95% CI	p-value
Age, per 10-year increase	1.08	0.91–1.28	0.355
White blood cell count	1.00	0.98–1.03	0.734
Meningeal signs	1.56	0.73–3.33	0.255
Inter-facility transfer	0.79	0.46–1.35	0.391
Male sex	2.24	1.39–3.62	< 0.001
Seizures	0.92	0.59–1.44	0.711
GCS 9–12	2.03	1.03–3.97	0.039
GCS 3–8	4.95	2.48–9.88	< 0.001
Antifungal treatment	0.93	0.50–1.70	0.803
Antiparasitic treatment	0.76	0.43–1.33	0.332
Antiviral treatment	0.11	0.02–0.45	0.003
Chronic ¹ CNS infection	1.12	0.67–1.89	0.662
Smoking	2.18	1.18–4.03	0.013
HIV-positive status	2.39	1.27–4.50	0.007
In hospital complications	1.73	0.99–3.02	0.054
Abbreviations: HR, hazard ratio; CI, confidence interval; GCS, Glasgow Coma Scale; CNS, central nervous system; HIV, human immunodeficiency virus. 1. Tuberculosis, Cryptococcus and Toxoplasmosis.			

4. Discussion

This is the first study describing the distribution and case-fatality of CNS infections in Mozambique. The median age (39 years) and the distribution of the most common CNS infections, for instance, meningoencephalitis, cerebral toxoplasmosis, cryptococcal meningitis, neurotuberculosis and bacterial meningitis are comparable to findings from similar studies conducted in Africa. Approximately one in every three patients died during hospitalization. Comparably high case fatality rates, ranging from 21% to 30%, have also been reported in studies conducted in similar contexts[21], [22], [23]. Several factors may explain the poor vital outcomes observed in our setting. The high prevalence of HIV (70%) shapes the profile of CNS infections in our cohort, which is dominated by opportunistic infections, which are associated with poor outcomes [23], [24], [25]. HIV-positive patients had more than twice the hazard of in-hospital death compared with HIV-negative patients in our study. However, this was not the case for

patients under antiretroviral treatment, which was associated with reduced risk of death. HIV-related immunosuppression increases susceptibility to opportunistic CNS infections and may be associated with atypical presentations, advanced disease and greater diagnostic complexity[26].

The distribution of CNS infection diagnoses also differed between survivors and non-survivors. Cerebral toxoplasmosis, cryptococcal meningitis and meningoencephalitis were more frequent among patients who died, whereas cerebral malaria was substantially more common among survivors. This pattern is consistent with the high mortality associated with HIV-related opportunistic CNS infections reported in African cohorts, particularly cryptococcal meningitis and cerebral toxoplasmosis [10], [26], [27], [28], [29]. However, these comparisons should not be interpreted as independent effects of aetiology, particularly because HIV status, as neurological severity and treatment access may differ substantially across diagnostic categories

The alarming 21% of CNS infections of unknown aetiology merits attention and may reflect limitations in the investigation of specific causes, such as herpesvirus-6, enterovirus for viral infections, and bacterial infections such as streptococcus pneumoniae and Escherichia coli[30] which might demand alternative management that are not available in our context. This is particularly relevant for essential investigations such as CSF analysis or neuroimaging, which were not performed in all patients. In addition, in patients with HIV, overlapping presentations of cryptococcal meningitis, tuberculous meningitis, bacterial meningitis and cerebral toxoplasmosis can make syndromic diagnosis particularly challenging, and delay treatment [31].

Previous work from Uganda demonstrated that delays in diagnosis were associated with poorer outcomes and that an algorithm-based approach substantially reduced the time to diagnosis and treatment of cryptococcal meningitis [32]. These findings are particularly relevant to Mozambique [33], where delays may occur both before referral and after hospital arrival.

The large majority of patients presented late to the hospital, often more than a week after the onset of symptoms, with advanced clinical stage and an impaired level of consciousness. Indeed, a decreased GCS was the strongest risk factor for in-hospital death in our study. This finding should be interpreted taking into account that impaired consciousness captures the cumulative severity of CNS injury resulting from advanced infection and its complications such as cerebral oedema, raised intracranial pressure or seizures. In a limited-resource setting such as ours, the process of care, particularly supportive care for more severe patients, may also account for the observed mortality. Unfortunately, we were unable to explore this potential explanatory variable.

The higher hazard of in-hospital case fatality observed among men may partly reflect gender related differences in healthcare seeking behaviour. Evidence from sub-Saharan Africa suggests that men are more likely than women to present late to healthcare services, particularly in the context of HIV and tuberculosis. Studies from Mozambique report significantly higher odds of late presentation among men with more than twice the odds of late HIV presentation [34], [35]. Qualitative studies from Malawi and Uganda further suggest that socially constructed masculine norms, including perceptions of self-

reliance and reluctance to seek medical care, may contribute to delayed healthcare seeking among men. In our setting, such delays may be particularly consequential given the high burden of HIV-associated and other severe CNS infections[35], [36].

Male gender and adverse outcomes should also be considered in the context of the substantially higher prevalence of tobacco use in sub-Saharan Africa[37]. Recent studies from sub-Saharan African countries including Mozambique, demonstrates high tobacco use among men than women, especially in people living with HIV. In these systematic review and meta-analysis, the smoking prevalence among men living with HIV was 50.3% compared with 36.3% in women[38], [39].

Together, these findings suggest that the high mortality is largely dependent on modifiable factors along the diagnostic and therapeutic pathway, rather than solely reflecting the intrinsic pathogenicity of each CNS infection.

There is evidence from low income countries showing that case-fatality can be reduced through pragmatic interventions involving standardized clinical pathways, rapid diagnostics, staff training and improved coordination of care [10]. Early recognition of CNS infection, access to essential pathogen-specific diagnostics, and standardized treatment pathways may therefore represent realistic targets for Mozambique.

This study has several strengths. It was the first cohort in a referral hospital in Mozambique, which collected prospectively clinical information and evaluated mortality using time-to-event analysis, allowing assessment of the timing of in-hospital death rather than relying solely on a binary outcome. The cohort also included a broad spectrum of CNS infections, reflecting the diagnostic complexity encountered in routine neurological practice at a quaternary referral centre.

Several limitations should be considered. First, the single-centre design limits generalizability to other hospitals and regions of Mozambique, particularly lower-level facilities and rural settings. Second, the cohort may have preferentially included patients with more severe disease because HCM is a national referral hospital. Third, limited availability of diagnostic testing may have resulted in etiological misclassification or a proportion of CNS infections remaining of unknown aetiology. Fourth, information on pre-hospital delays was based on the reported onset of neurological symptoms and may be subject to recall bias.

Conclusion

CNS infections are an important cause of hospital mortality in Mozambique. HIV infection and severe neurological impairment were particularly important prognostic markers. Mortality is likely shaped by other preventable or manageable factors, rather than solely by the intrinsic severity of the CNS infection.

Declarations

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Data Availability Statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request, subject to ethical approval and applicable data protection regulations.

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All authors have read and agreed to the published version of the manuscript

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used gemini.IA for image generation. The author(s) reviewed and edited the output as needed and take full responsibility for the content of the published article.

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Figures

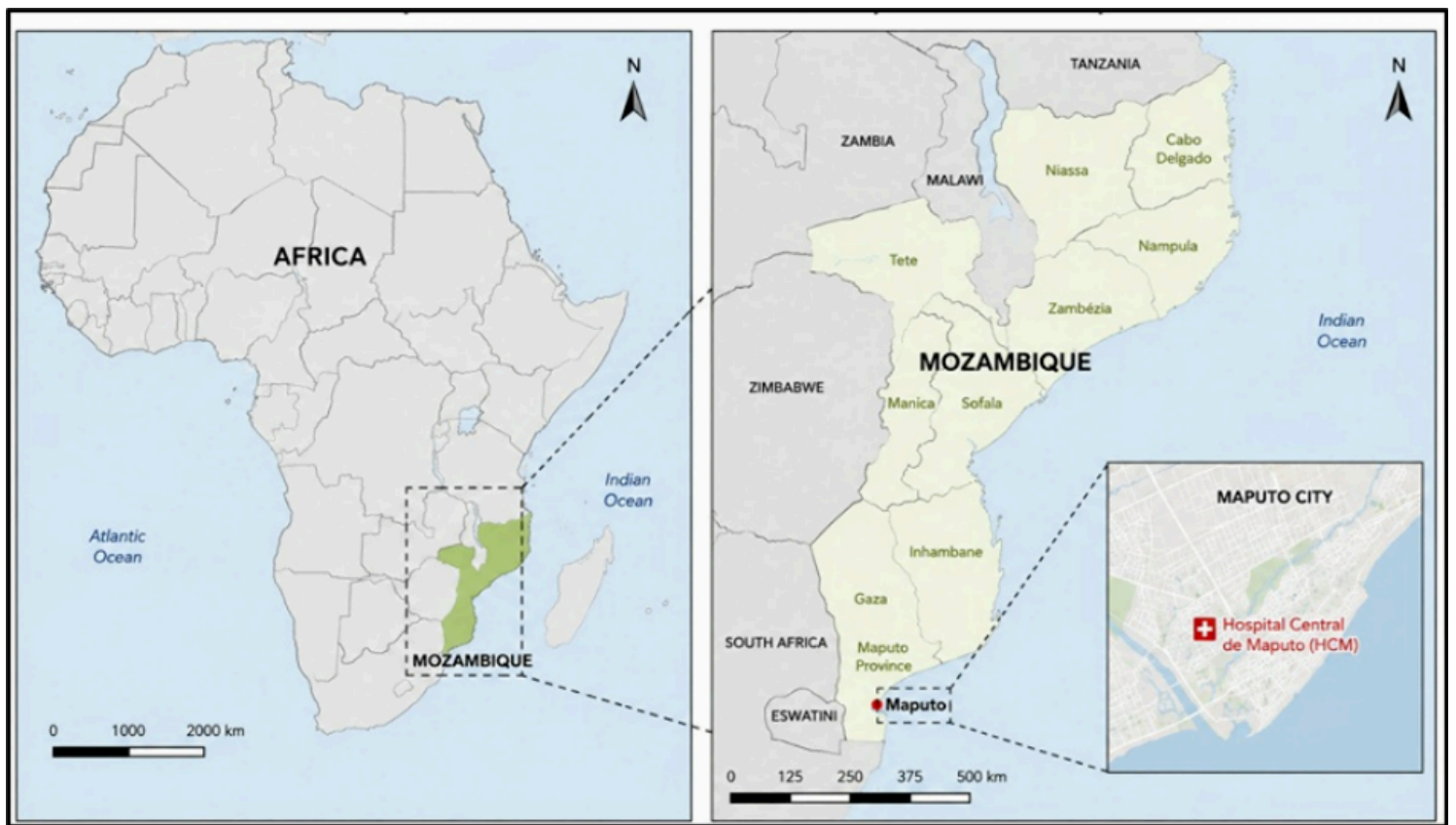


Figure 1

Showing Maputo, where is located Maputo Central Hospital, in Mozambique

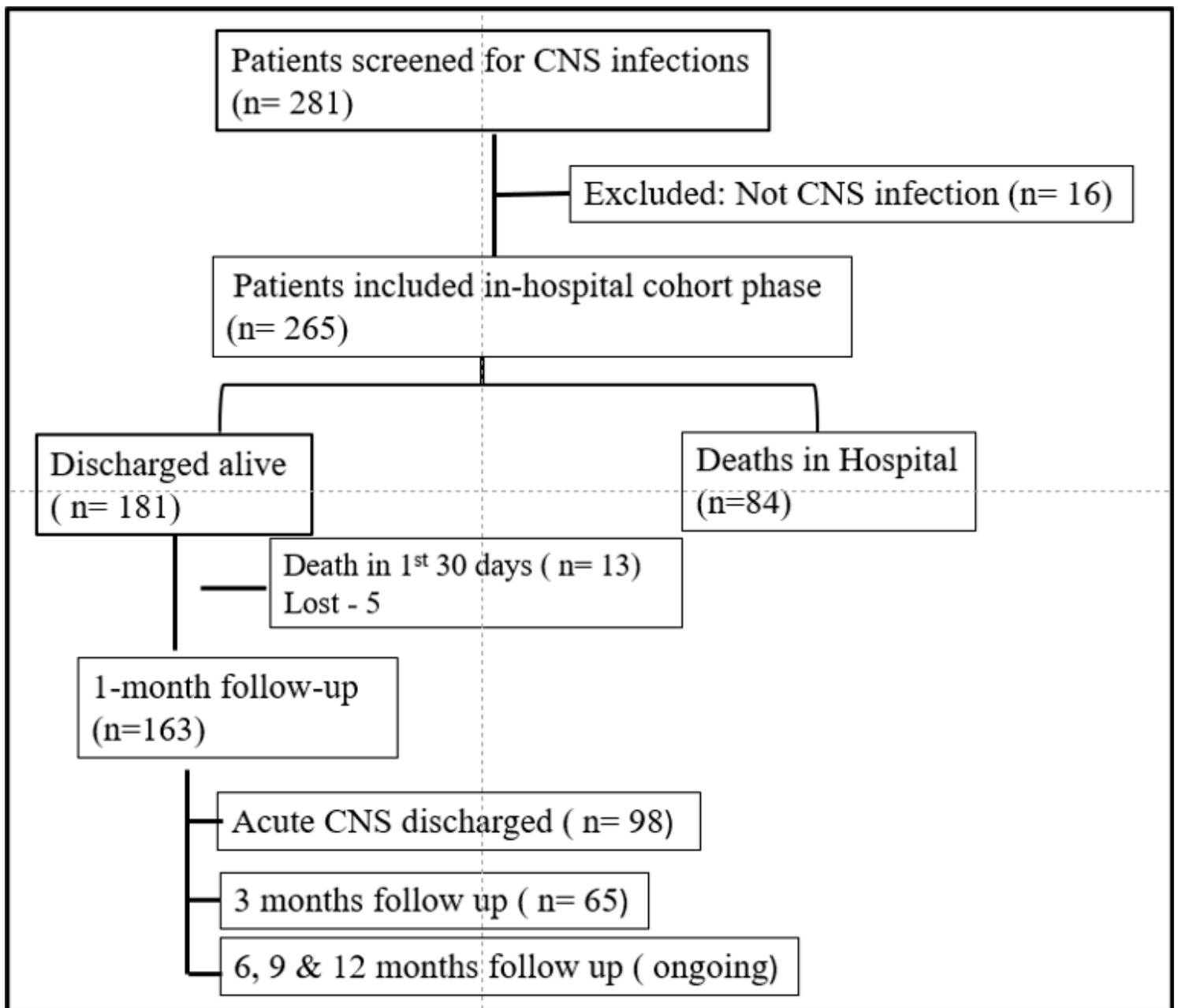


Figure 2

Flow diagram illustrating the identification, screening, and inclusion of patients

Image not available with this version

Figure 3

Figure 3. Graphical abstract InNeMo

Supplementary Files

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