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Risk Factors for Cryptococcal Meningitis in People Living with HIV Who Test Positive for Cryptococcal Antigens in Blood: A Single-Center Study in a Resource-Limited Setting

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Abstract

Objective

Cryptococcal infection is a common opportunistic infection among people living with HIV; if not effectively diagnosed, it can progress to cryptococcal meningitis (CM), which has a high mortality rate. High cryptococcal antigen (CrAG) titers in the blood predict CM in HIV patients; however, hospitals in resource-limited areas lack the means to measure these titers.

Methods

We manually collected data from the hospital information system on 107 HIV-infected patients aged ≥ 18 years who were admitted to Hangzhou Xixi Hospital between January 2012 and August 2023 and who tested positive for serum CrAGs via colloidal gold immunochromatographic assay. The data were divided into two groups (meningitis group and nonmeningitis group) to conduct a retrospective observational cohort study. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for the progression of patients with positive serological CrAG test results to CM, and ROC curves were constructed to further evaluate the predictive performance.

Results

Multivariate logistic regression analysis revealed that positive blood culture results (OR = 239.637; 95% CI: 15.838–3625.923; P < 0.001), the CD4/CD8 ratio (OR = 0.95; 95% CI: 0–0.084; P = 0.02), and headache (OR = 475.208; 95% CI: 30.611–7,377.148; P < 0.001) were significantly associated with progression to CM. ROC curve analysis of these three factors demonstrated moderately good predictive performance. The predictive probability of the overall model was high, with an AUC of 0.984 (95% CI: 0.965–1.000). The cutoff value for the CD4/CD8 ratio was 0.095, with a Youden index of 0.403, a sensitivity of 85%, and a specificity of 55.32%.

Conclusion

In resource-limited settings, among patients with HIV who test positive for blood CrAg, cryptococcemia, the CD4/CD8 ratio, and headache are significant independent risk factors for the development of CM. These findings have broad applicability and clinical utility in similar regions worldwide where blood CrAG titration testing is not available.

Background

Cryptococcus is one of the most characteristic opportunistic pathogens in patients with advanced HIV infection[1]; the risk of disseminated infection is significantly increased, and the case-fatality rate approaches 100% in patients with central nervous system involvement if timely and effective antifungal treatment is not administered. Despite the widespread adoption of HIV testing, the expanded use of antiretroviral therapy (ART), and the availability of new antifungal drugs in modern medicine, the case-fatality rate remains high at 60% [2].

Cryptococcal antigens (CrAGs) are the main component of the cryptococcal capsule; compared with culture and histopathological examination, CrAG testing is rapid and simple. Studies have shown that the prevalence of cryptococcal antigenemia among outpatient HIV-infected patients with a CD4 cell count < 100 cells/μL is approximately 6.0%[3]. Among people living with HIV, those who test positive for CrAGs are seven times more likely to develop cryptococcal meningitis (CM) than those who test negative[4]. Therefore, the World Health Organization (WHO) recommends serum CrAg screening in individuals with a CD4 cell count < 100 cells/μL[5].

Current research suggests that high CrAG titers in the blood are predictors of CM and CM mortality in people living with HIV[6, 7]. However, other risk factors remain unclear. In China, clinical laboratories in general hospitals are typically only able to perform qualitative CrAG testing in whole blood or plasma and are unable to conduct quantitative testing. Many samples must be sent to specialized testing facilities for analysis; however, the high cost and lengthy turnaround time of these tests have limited their widespread use in China. Whether evaluation systems other than CrAG titers exist to identify early predictors of progression from a positive qualitative CrAG blood test to meningitis—thereby enabling clinicians to develop more aggressive antifungal treatment plans or place greater emphasis on diagnostic lumbar puncture (LP) [8]—is an effective way to reduce early mortality and is also highly important for understanding the pathogenesis of cryptococcal infection.

Methods

Study population

We conducted a retrospective observational cohort study of 107 HIV-positive patients with seropositive CrAG test results who were admitted to Xixi Hospital in Hangzhou, Zhejiang Province (this center serves as the Hangzhou Public Health Clinical Center and is one of the national key tertiary-level specialized infectious disease hospitals responsible for the clinical diagnosis and treatment of HIV/AIDS cases as mandated by the government). The inclusion criteria were as follows: (1) age > 18 years; (2) HIV-infected individuals (confirmed positive by the clinical laboratory's HIV preliminary screening test and the CDC laboratory's HIV antibody test); (3) positive for serum CrAGs as determined by qualitative colloidal gold immunochromatography (Genobio Pharmaceutical Co., Ltd.); and (4) blood culture performed concurrently during hospitalization. The exclusion criterion was a history of treatment for cryptococcal disease. All patients with positive serum CrAG results underwent LP screening and were subsequently divided into two groups: the meningitis group and the nonmeningitis group. See the flowchart (Fig. 1) for details.

Diagnostic criteria

Cryptococcemia is defined as a positive blood culture for *Cryptococcus*.

CM is defined as the isolation of *Cryptococcus* from cerebrospinal fluid (CSF) cultures, a positive CSF India ink stain, and/or a positive CSF CrAG test.

Data collection

We collected the following data by manually retrieving records from the hospital's medical records system: baseline demographic characteristics (sex, age, body mass index (BMI), and history of underlying medical

conditions); symptoms; and baseline laboratory test results, including complete blood counts, blood chemistry, coagulation tests, peripheral blood T-lymphocyte subsets, and HIV-RNA testing for all of these patients. Regardless of the symptoms or severity of the clinical condition, with the patient's consent, all patients underwent a LP to measure CSF pressure and to collect CSF samples for white blood cell, glucose, protein, and chloride measurements; qualitative CSF CrAG testing, India ink staining, and *Cryptococcus* culture. Patients also underwent blood culture, a chest CT scan and cranial imaging (CT or MRI) at admission to identify potential, clinically relevant cryptococcal disease.

Statistical analysis

Analysis was performed using SPSS version 22.0. Continuous variables are expressed as medians and interquartile ranges; normally distributed data were compared using t tests. Data that did not follow a normal distribution were compared using the Mann–Whitney U test. Logistic regression models were used to assess independent risk factors for the progression of patients with qualitatively positive CrAG test results to CM. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated using the ROC curve, and data analysis was performed using R version 4.1.2 (The R Foundation). A P value < 0.05 was considered to indicate statistical significance.

Ethical considerations

This study protocol was approved by the Ethics Committee of Hangzhou Xixi Hospital (Clinical Research Ethics Committee of Hangzhou Xixi Hospital, No: 2026-042). Since this study was entirely retrospective, we did not obtain written informed consent from the patients. This study was conducted in accordance with the Declaration of Helsinki.

Results

Patient characteristics and demographic information

Among the 107 HIV-infected individuals who tested positive for CrAGs according to a qualitative serological assay, 60 had concurrent CM; 51 were male (85%), and 9 were female (15%), with a mean age of 40 years (29, 49.75) and a mean BMI of 19.82 kg/m² (17.3, 21.45). Fourteen patients (23.33%) had chronic underlying conditions, including 3 with diabetes, 4 with chronic hepatitis B virus infection, 3 with hypertension, 1 with chronic hepatitis C virus infection, 1 with partial gastrectomy, 1 with cirrhosis complicated by chronic kidney disease and hypertension, and 1 with hypertension complicated by chronic obstructive pulmonary disease (COPD). There were 47 cases of nonCM, including 40 males (85.11%) and 7 females (14.89%). The mean age was 42 years (30, 54), and the mean BMI was 19.92 kg/m² (18.44, 65.8). Fifteen patients (31.91%) had underlying chronic conditions, including 2 cases of diabetes, 6 cases of chronic hepatitis B virus infection, 4 cases of malignant tumors, 1 case of chronic kidney disease, 1 case of chronic hepatitis B virus infection combined with diabetes, and 1 case of chronic hepatitis B virus infection combined with hypertension (Table 1).

Clinical presentation

In terms of clinical manifestations, compared with patients in the non CM group, patients in the CM group had a significantly greater prevalence of fever (81.67% vs. 63.83%, P=0.037), headache (83.33% vs. 4.26%, P<0.001),

nausea and vomiting (55% vs. 4.26%, P<0.001), altered mental status (33% vs. 0, P<0.001), decreased vision (16.67% vs. 0, P=0.009), papilledema (16.67% vs. 0, P=0.009), seizures (10% vs. 0, P=0.034), and neck resistance (46.67% vs. 2.13%, P<0.001). (Table 1)

Laboratory and Radiographic Findings

In laboratory tests, patients in the CM group had significantly greater proportions of positive blood cultures (75% vs. 8.51%, P< 0.001), as well as higher D-dimer levels(1.79 (0.77, 4.7) vs. 1.14 (0.54, 2.66), P=0.048), baseline intracranial pressure (267.5 (175, 350) vs. 130 (100, 170), P<0.001), CSF cell counts (8 (2.25, 30) vs. 2 (1, 4), P<0.001), and CSF protein levels (831 (502, 1352) vs. 449 (346, 637), P<0.001) and lower CD4+ cell counts (16 (7.25, 36.5) vs. 38 (18, 93), P<0.001), CD4/CD8 ratios (0.055 (0.02, 0.08) vs. 0.1 (0.06, 0.19), P<0.001), and platelet counts (178 (118.5, 231.75) vs. 204 (146, 276) (Table 1).

Multivariable analysis

We performed univariate and multivariate logistic regression analyses on factors associated with progression to CM on the basis of the clinical manifestations and laboratory findings (Table 2). According to the univariate logistic regression analysis, a high number of positive blood cultures, a high incidence of headache, a high incidence of cranial imaging, and high levels of C-reactive protein (CRP), as well as low a $CD4^+$ T-cell count, $CD8^+$ T-cell count, CD4/CD8 ratio, platelet count, aspartate aminotransferase (AST) level, and serum sodium level, were significantly associated with progression to CM. Multivariate logistic regression analysis revealed that only a positive cryptococcal blood culture (OR = 239.637; 95% CI: 15.838–3625.923; P < 0.001), the CD4/CD8 ratio (OR = 0; 95% CI: 0–0.084; P=0.02), and headache (OR = 475.208; 95% CI: 30.611–7377.148; P<0.001) remained significantly associated with progression to CM. (Table 2)

ROC curves were used to further evaluate the ability of positive cryptococcal blood culture results, the CD4/CD8 ratio, and headache to predict the development of CM in patients with positive qualitative CrAG test results (Table 3, Figure 2). The results revealed that the CD4/CD8 ratio (AUC = 0.754; 95% CI: 0.662–0.845), headache (AUC = 0.895; 95% CI: 0.830–0.961), and a positive blood culture for *Cryptococcus* (AUC = 0.832; 95% CI: 0.752–0.913) demonstrated moderately good predictive performance. The predictive probability of the overall model was high, with an AUC of 0.984 (95% CI: 0.965–1.000). The cutoff value for the CD4/CD8 ratio was 0.095, with a Youdan index of 0.403, a sensitivity of 85%, and a specificity of 55.32%.

Discussion

CM is an opportunistic fungal infection associated with advanced HIV and is estimated to account for 15% of AIDS-related deaths worldwide [9]. In resource-limited areas where titers are unavailable and qualitative screening is the only option, developing precise screening and intervention strategies is equally critical.

There are three methods for detecting CrAGs: latex agglutination, enzyme-linked immunosorbent assay (EIA), and lateral flow assay (LFA). Compared with the traditional latex agglutination test, the LFA offers the advantages of high accuracy, rapid results, ease of interpretation, and low cost[10–12], making it suitable for use in resource-limited settings. The colloidal gold immunochromatographic assay we used is a type of LFA.

Our study revealed that the presence of headache symptoms in patients with serum CrAG positivity is one of the predictors of progression to CM, which is consistent with the findings of previous studies[7]. CSF analysis is essential for the diagnosis of CM; previous studies have recommended that all HIV-infected patients with evidence of cryptococcal infection undergo a LP to screen for CM[6, 13]. However, as an invasive procedure, LP is met with limited acceptance among patients, particularly those with mild symptoms. Our study confirms that, in clinical practice, when patients present with headaches as a neurological symptom, rapid follow-up and early LP to rule out CM are strongly recommended, even if cryptococcal blood antigen titers cannot be detected.

In this study, the CD4 cell counts in both the crypt-positive and crypt-negative groups were predominantly <100 cells/μL, which is consistent with the findings of previous studies[14, 15]. The CD4/CD8 ratio is an important indicator of the balance between $CD4^+$ and $CD8^+$ T cells; it reflects the homeostasis of the immune system and indicates the body's ability to combat infections and regulate the immune response[16]. Following HIV infection, the human immune system is compromised. This is accompanied by progressive depletion of $CD4^+$ T cells and compensatory activation and proliferation of $CD8^+$ T cells, resulting in a decrease in $CD4^+$ T-cell counts and an increase in $CD8^+$ T-cell counts, which in turn leads to an abnormally low CD4/CD8 ratio[17]. Studies have shown that the CD4/CD8 ratio can also serve as a prognostic indicator for AIDS and is closely associated with an increased risk of death in people living with HIV/AIDS [18, 19]. This study suggests that a significantly low CD4/CD8 ratio in people living with HIV is a high-risk warning sign for the development of CM. This may be due to impaired cellular immune function, which can reduce the recruitment of macrophages and neutrophils to the site of infection, thereby decreasing the clearance rate of *Cryptococcus*[20].

Previous studies have shown that 23.2%–68.0% of HIV-infected patients with concomitant CM test positive for cryptococcemia[21, 22]. Our study also revealed that cryptococcemia is a predictor of progression to CM in HIV-infected patients. This further supports the guideline recommendation that patients with disseminated cryptococcosis (including cryptococcemia) require the same systemic antifungal treatment regimen as those with CM do[5]. Therefore, clinicians must remain vigilant regarding cryptococcemia and ensure early diagnosis and prompt treatment.

Our results highlight that among patients with advanced HIV infection and positive blood CrAG test results, positive cryptococcal blood culture results, headache, and the CD4/CD8 ratio are predictive of progression to meningitis. This study is the first to systematically analyze risk factors for CM in settings where only qualitative blood CrAg testing is available. A practical predictive model based on clinical findings combined with basic laboratory tests is proposed to help clinicians identify "high-risk positive patients," which can be used to guide decisions regarding LP and the early implementation of more aggressive antifungal treatment regimens. To provide localized evidence for the implementation of the WHO's "Early Diagnosis and Intervention" strategy at the community level. This study may help inform future efforts to explore optimal management strategies for people living with HIV who test positive for CrAGs.

This study has several limitations. First, this was a retrospective, single-center study with a relatively small sample size, which may have led to selection bias. However, such limitations are common in real-world studies conducted in resource-limited settings. Nevertheless, the purpose of this study is to provide valuable evidence for clinical practice in regions and healthcare institutions lacking advanced diagnostic tools.

Conclusion

In resource-limited settings, among patients with HIV and a positive CrAg test, a positive cryptococcal blood culture, headache, and the CD4/CD8 ratio are predictive factors for progression to meningitis. These findings have broad applicability and clinical utility in similar regions worldwide where cryptococcal blood antigen titration testing is not available.

Abbreviations

AIDS
Acquired Immunodeficiency Syndrome
ART
Anti-Retroviral Therapy (orTreatment)
CD
Cluster of Differentiation
CI
Confidence Interval
CM
Cryptococcal Meningitis
CNS
Central Nervous System
CrAg
Cryptococcal Antigen
CSF
Cerebrospinal Fluid
EIA
Enzyme Immunoassay
HIV
Human Immunodeficiency Virus
LFA
Lateral Flow Assay
WHO
World HealthOrganization.

Declarations

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Availability of data and materials

All the generated data in this review are included in the manuscript.

Ethics approval and consent to participate

Not applicable in this section.

Consent for publication

Not applicable in this section.

Competing interests

Authors declare that they have no competing interests.

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Tables

Table 1. Basic Demographic, Clinical, and Laboratory Characteristics of Patients with and without CM

Characteristic	CM (n=60)	Not CM (n=47)	*Z/χ2*	*P*-value
general situation				
Male,n(%)	51(85)	40(85.11)	<0.001	0.988
Age(year),median(IQR)	40(29,49.75)	42(30,54)	0.741	0.459
underlying medical conditions,n(%)	14(23.33)	15(31.91)	0.982	0.322
BMI(kg/²),median(IQR)	19.82(17.3,21.45)	19.92(18.44,65.8)	1.273	0.206
Clinical Symptoms				
Fever,n(%)	49(81.67)	30(63.83)	4.34	0.037
Headache,n(%)	50(83.33)	2(4.26)	65.975	<0.001
Nausea and vomiting,n(%)	33(55)	2(4.26)	30.833	<0.001
Change of consciousness,n(%)	20(33)	0(0)	19.268	<0.001
Vision loss,n(%)	10(16.67)	0(0)	6.786	0.009
Hearing loss,n(%)	2(3.33)	0(0)	/	0.495
Optic papillar edema,n(%)	10(16.67)	0(0)	6.786	0.009
seizures,n(%)	6(10)	0(0)	/	0.034
Signs				
Neck resistance,n(%)	28(46.67)	1(2.13)	26.462	<0.001
Pathological signs,n(%)	5(8.33)	1(2.13)	/	0.227
Baseline laboratory data				
Positive blood culture,n(%)	45(75)	4(8.51)	46.937	<0.001
Log_{10} HIV,median(IQR)	4.67(3.36,5.21)	4.47(2.44,5.42)	0.612	0.54
ART	4(6.67)	7(14.89)	1.145	0.285
WBC(10^9/L),median(IQR)	4.9(3.14,6.68)	5.49(3.07,7.2)	0.229	0.819
CRP(mg/L),median(IQR)	15.8(8.07,35.75)	13(4.28,63)	0.584	0.559
PCT(ng/ml),median(IQR)	0.09(0.05,0.14)	0.12(0.06,0.37)	1.695	0.09
Hb(g/L),median(IQR)	116.5(109.5,133.75)	116(100,129)	1.242	0.217
LDH(U/L),median(IQR)	239(191.5,323)	241(190,412)	0.37	0.711
Alb(g/L),median(IQR)	33.8(31.2,37.05)	35.3(28.6,38.3)	0.105	0.917
$CD4^+$Tcellcount(cells/ul),media(IQR)	16(7.25,36.5)	38(18,93)	4.442	<0.001
$CD8^+$Tcellcount(cells/ul),media(IQR)	365.5(265.25,570.75)	397(248,795)	1.174	0.24

CD4/CD8 ratio,media(IQR)	0.055(0.02,0.08)	0.1(0.06,0.19)	4.506	<0.001
B cellcount(cells/ul),media(IQR)	59(26.25,109.25)	59(35,119)	0.292	0.77
NK cellcount(cells/ul),media(IQR)	68.5(42.75,153.75)	85(61,156)	1.284	0.199
neutrophil(10^9/L),median(IQR)	3.82(2.16,5.71)	3.4(1.95,5.27)	0.549	0.583
lymphocyte(10^9/L),median(IQR)	0.61(0.41,0.88)	0.65(0.38,1.13)	0.725	0.468
NLR,median (IQR)	5.93(3.16,9.07)	4.42(2.91,10.64)	1.039	0.299
monocyte(109/L),median(IQR)	0.3(0.19,0.43)	0.35(0.25,0.47)	1.303	0.193
MLR,median (IQR)	0.5(0.28,0.8)	0.45(0.31,0.85)	0.163	0.87
PLT(10^9/L),median (IQR)	178(118.5,231.75)	204(146,276)	2.027	0.045
PLR,median (IQR)	286.51(180.55,427.44)	322.64(167.27,513.16)	0.361	0.718
globulin(g/L),median(IQR)	38.2(33.5,43.1)	37.2(33.8,43.9)	0.151	0.88
Creatinine(umol/L),median(IQR)	63(53,70)	65(59,80)	1.846	0.065
urea nitrogen(mmol/L),median(IQR)	4.45(2.95,5.78)	4.3(3.6,5.7)	0.672	0.502
Total bilirubin(umol/L),median(IQR)	9.23(5.4,11.95)	8(5.86,10.9)	0.65	0.516
ALT(U/L), median(IQR)	26.5(15.5,46.75)	26(13,44)	0.753	0.451
AST(U/L), median(IQR)	29(20,40.75)	30(25,53)	1.595	0.111
Sodium(mmol/L),median (IQR)	134(130.65,137.78)	136.5(134,140)	2.583	0.011
PT(S), median (IQR)	11.95(11.4,12.7)	12.2(11.4,12.8)	0.716	0.474
APTT(S), median (IQR)	28.4(26.1,31.3)	28.8(25.9,31.3)	0.157	0.875
FIB(g/L) , median (IQR)	3.4(2.83,4.29)	3.38(2.63,4.31)	0.27	0.788
D-dimer(mg/L),median(IQR)	1.79(0.77,4.7)	1.14(0.54,2.66)	1.974	0.048
CSF data				
Opening pressure,median(IQR)	267.5(175,350)	130(100,170)	6.334	<0.001
Cell number(10^6/L),median(IQR)	8(2.25,30)	2(1,4)	5.097	<0.001
Proteins(mg/L),median(IQR)	831(502,1352)	449(346,637)	4.155	<0.001
Glucose(mmol/L),median(IQR)	2.3(1.53,2.7)	2.9(2.5,3.3)	4.21	<0.001
Chlorine(mmol/L),median(IQR)	118(115.25,122)	122(116,123)	2.473	<0.001
Baseline imaging data				
Cranial imaging	27(45)	13(27.66)	3.39	0.065
Pulmonary imaging	45(75)	35(74.47)	0.004	0.95

Outcomes improved,n(%)	58(96.67)	43(91.49)	/	0.401

Abbreviations:ART,antiretroviral treatment;WBC,White blood cell count; CRP,C reactive protein;PCT,Procalcitonin;BMI,Body Mass Index;Hb,haemoglobin;ART, antiretroviral treatment;LDH,lactate dehydrogenase;Alb,albumin;CSF, cerebrospinal fluid;PLT,blood platelet;PT,Prothrombin time; APTT,Activated partial thromboplastin ime;FIB,Fibrinogen;NLR,Neutrophil-to-Lymphocyte Ratio;MLR,Monocyte-to-Lymphocyte Ratio;PLR,Platelet-to-Lymphocyte Ratio;ALT, alanine aminotransferase;AST, aspartate aminotransferase;

Table2 Logistic Regression Analysis and Advances in Baseline Indicators Associated with Cryptococcal Meningitis

Variables	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value
Positive blood culture	32.25(9.915,104.899)	<0.001	239.637(15.838,3625.923)	<0.001
CRP	0.993(0.982,1.004)	0.191		
$CD4^+$T cell count	0.973(0.958,0.988)	<0.001		
$CD8^+$T cell count	0.999(0.997,1)	0.062		
CD4/CD8 ratio	0(0,0.02)	<0.001	0(0,0.084)	0.02
PLT	0.996(0.991,1)	0.052		
AST	0.985(0.972,0.999)	0.03		
Sodium	0.893(0.816,0.977)	0.014		
Fever	2.524(1.043,6.111)	0.04		
Headache	112.5(23.389,541.122)	<0.001	475.208(30.611,7377.148)	<0.001
Cranial imaging	2.14(0.945,4.843)	0.068		

Abbreviations:CRP,C reactive protein; PLT,blood platelet; AST, aspartate aminotransferase;

Table3 CD4/CD8 Ratio, Headache, and Positive Blood Culture in Predicting Progression from *Cryptococcal* Antigen-Positive to *Cryptococcal* Meningitis

Variable	AUC	Standard Deviation	*P*	Lower CI	Upper CI
CD4/CD8 ratio	.754	.047	.000	.662	.845
Headache	.895	.033	.000	.830	.961
Positive blood culture	.832	.041	.000	.752	.913
Probability of Prediction	.984	.010	.000	.965	1.000

Figures

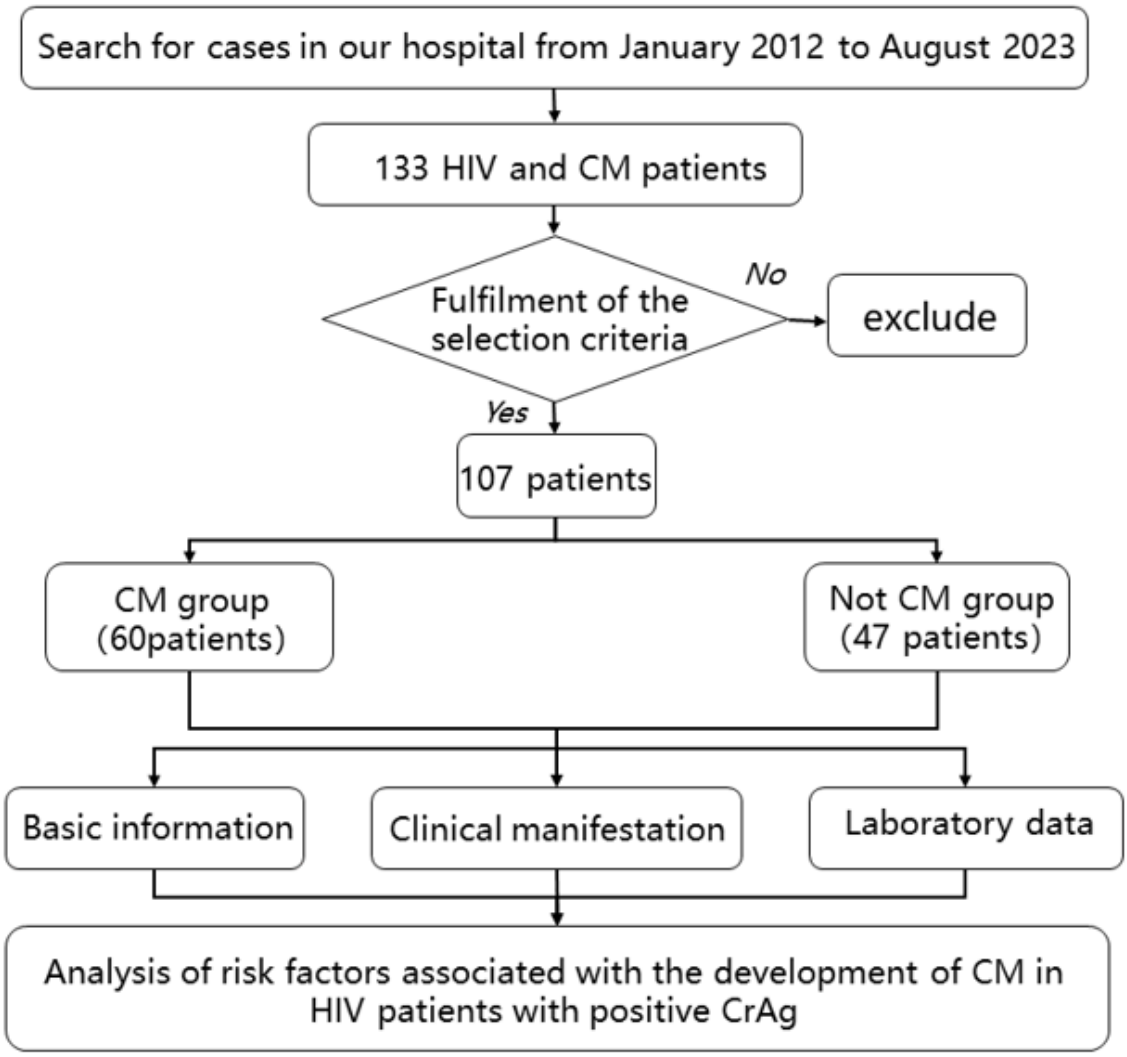


Figure 1

Flow chart of the study design

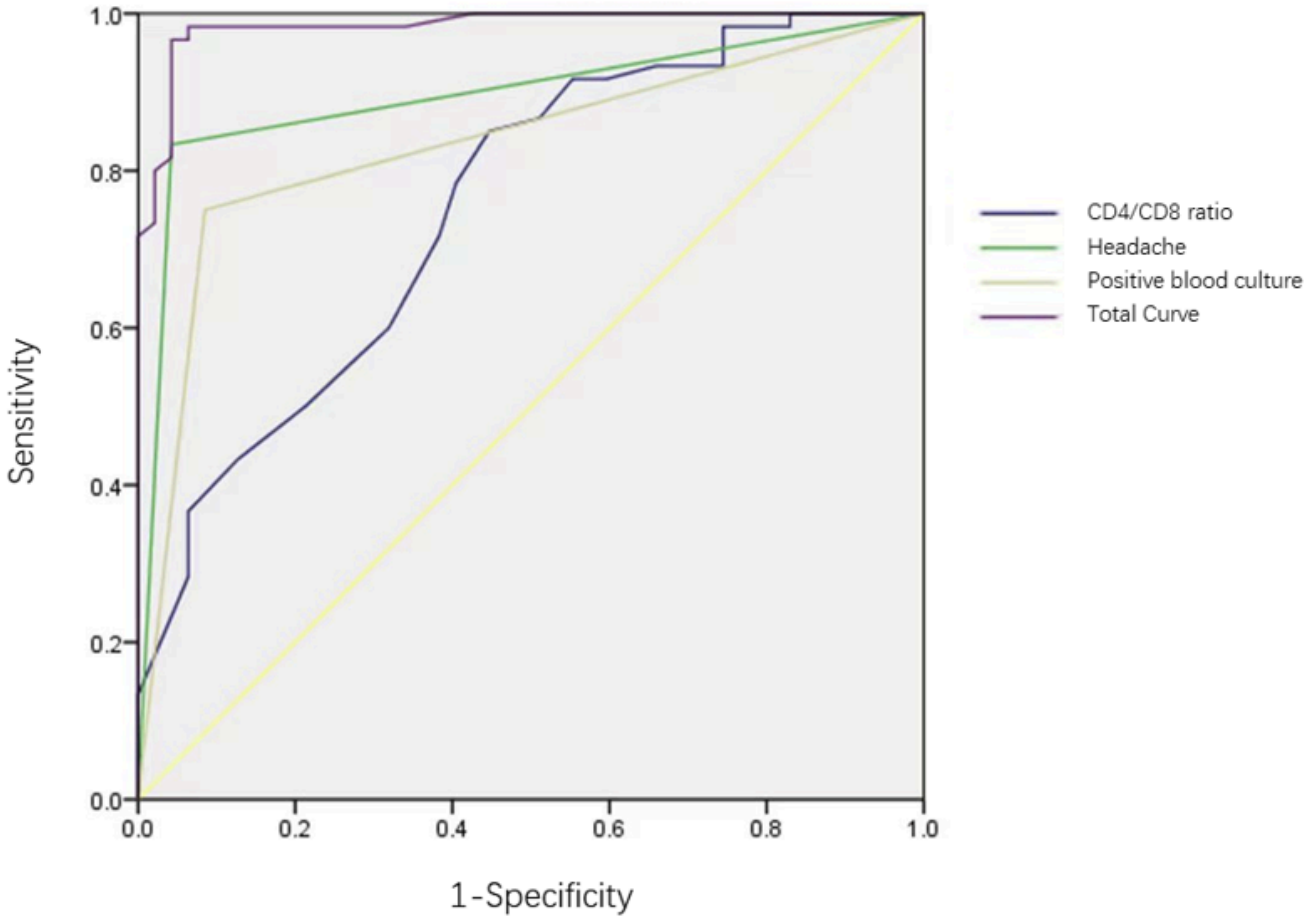


Figure 2

Receiver operating characteristic(ROC) curve of positive cryptococcal blood culture results, the CD4/CD8 ratio, and headache to predict the development of CM in patients with positive qualitative CrAG test results