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ORIGINAL ARTICLE

Prediction of unfavorable outcomes in cryptococcal meningitis: results of the multicenter Infectious Diseases International Research Initiative (ID-IRI) cryptococcal meningitis study

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Abstract

Cryptococcal meningitis (CM) is mostly seen in immunocompromised patients, particularly human immunodeficiency virus (HIV)-positive patients, but CM may also occur in apparently immunocompetent individuals. Outcome analyses have been performed in such patients but, due to the high prevalence of HIV infection worldwide, CM patients today may be admitted to hospitals with unknown HIV status, particularly in underdeveloped countries. The objective of this multicenter study was to analyze all types of CM cases in an aggregate cohort to disclose unfavorable outcomes. We retrospectively reviewed the hospitalized CM patients from 2000 to 2015 in 26 medical centers from 11 countries. Demographics, clinical, microbiological, radiological, therapeutic data, and outcomes were included. Death, neurological sequelae, or relapse were unfavorable outcomes. Seventy (43.8%) out of 160 study cases were identified as unfavorable and 104 (65%) were HIV infected. On multivariate analysis, the higher Glasgow Coma Scale (GCS) scores ($p = 0.021$), cerebrospinal fluid (CSF) leukocyte counts > 20 ($p = 0.038$), and higher CSF glucose levels ($p = 0.048$) were associated with favorable outcomes. On the other hand, malignancy ($p = 0.026$) was associated with poor outcomes. Although all CM patients require prompt and rational fungal management, those with significant risks for poor outcomes need to be closely monitored.

Introduction

Cryptococcosis is a global invasive fungal infection with substantial therapeutic challenges. The disease has a predilection to invade the lungs and the central nervous system (CNS). Cryptococcal meningitis (CM) is usually seen with human immunodeficiency virus (HIV) infection, but may also affect healthy individuals [1, 2]. It is estimated that approximately one million cases and 625,000 deaths occur annually worldwide, with more than 70% of these occurring in sub-Saharan Africa [3]. The 1-year mortality rate of CM remains at 1025% in developed countries, while mortality can reach 75% at 6 months in countries with limited resources [4, 5]. In a study performed in 20 countries in the northern hemisphere, 3% of all patients with community-acquired CNS infections were HIV positive and CM was the leading CNS infection among the HIV-positive group. However, CM had a 1% share in the entire cohort. This was probably due to the higher economic status and the better infrastructures of the participating centers compared to Africa [6].

Since CM is more prevalent particularly in HIV patients, comparative studies have gained weight in this group of patients and, thus, outcome analyses have often been based on the comparison of immunological statuses. Comparative outcome analyses have been scarce in the literature for CM and were mostly restricted to HIV-positive patients. However, HIV patients today may present with any kind of opportunistic infections to the hospitals preceding HIV diagnosis and the clinician may diagnose CM in patients with unknown HIV status. Therefore, the determination of predictive markers of unfavorable outcome in CM in the absence of HIV data is important in decision making. Hence, in this study, we

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included all CM patients, both HIV positives and negatives as a unique cohort, and we aimed to analyze CM and its predictors of mortality in a large multicenter study, which is of global importance since the data come from 26 centers in 11 countries.

Materials and methods

Design and participants

This retrospective multicenter cohort study included all consecutive hospitalized adult patients (age over 16 years) with CM between 2000 and 2015. It included 26 referral centers from 11 countries, including Denmark, Egypt, France, Israel, Italy, Portugal, Romania, Saudi Arabia, Switzerland, USA, and Turkey.

Definitions

The definitions used in this study according hospital admission data were as follows:

Cryptococcal meningitis was defined as isolation of *Cryptococcus* species from cerebrospinal fluid (CSF) culture, positive CSF India ink or positive CSF cryptococcal antigen (CrAg) titer, and consistent clinical features of meningitis, including fever, headache, altered mental status, meningismus signs, and focal neurological deficits [7]. The positivity of one of these tests from the CSF at the minimum was mandatory for microbiological confirmation.

Favorable outcome was defined as survival without neurological sequelae.

Unfavorable outcome was defined as death due to CM or survival with sequelae or relapses [3, 8].

Relapse was defined as reappearance of symptoms with the positive CSF culture/India ink after 4 weeks of improvement with sterile cultures [9].

The underlying illnesses were classified according to the modified McCabe and Jackson classification scheme [10].

Charlson comorbidity index (CCI) was used to describe comorbidities [11].

Elapsed time was defined as the time period between the onset of symptoms and the start of CM treatment.

Immune reconstitution inflammatory syndrome (IRIS) was identified by the modified criteria [12].

Glasgow Coma Scale (GCS) was used to describe the level of consciousness. Scores of 13–15 were recorded as mild, 9–12 as moderate, and ≤ 8 as poor [13].

Type of CNS involvement. Patients with symptoms for less than 2 weeks at the time of diagnosis were included in the acute meningitis category, 2–4 weeks were classified as subacute meningitis, and over 4 weeks were classified as chronic meningitis [6].

Exclusion criteria

Evidence for the presence of any CNS infection other than CM were excluded from the study.

Data collection and procedures

This an Infectious Diseases International Research Initiative (ID-IRI) study. The ID-IRI is an international platform, which serves as a network for clinical researches on infectious diseases and clinical microbiology (https://infectdisiri.wordpress.com). A questionnaire was sent to participating centers, which ultimately submitted their data in an Excel file format. Data on demographic characteristics (age, gender, occupation, place of residence), underlying diseases (such as HIV, malignancy, diabetes, steroid use, organ transplantation, renal insufficiency, and sarcoidosis), type of CNS involvement, clinical signs/symptoms, HIV status (antiretroviral therapy, CD4 cell count), IRIS development, the presence of other opportunistic infections, routine blood parameters, serum CrAg titers, imaging findings [magnetic resonance imaging (MRI), computed tomography (CT), chest X-ray), CSF analysis [cell count/type, glucose, protein, Indian ink stain, Sabouraud dextrose agar (SDA) culture, CrAg, and cryptococcal polymerase chain reaction (PCR)], length of hospital stay, therapeutic agents, and patient outcomes were recorded. At the end of the study period, the centers submitted their data. These data were merged to form the final database. All enrolled patients were divided into favorable and unfavorable outcome groups. Factors that would predict unfavorable outcomes were evaluated between these two groups.

Microbiological investigations

Microbiological data included the results of India ink stain, mycological cultures, cryptococcal PCR of CSF, and CrAg titers (latex agglutination or ELISA) of CSF and serum. All specimens were inoculated onto SDA agar containing chloromycetin. SDA culture plates were incubated at 30 °C and examined daily for 4 weeks.

Statistical analysis

For quantitative variables, the results were expressed as median and minimum–maximum (min; max), or mean and standard deviation (SD), as indicated. Qualitative variables were expressed as effective and percentage. The characteristics of the patients according to their outcomes were compared by the

Chi-square test or Fisher's exact test for categorical variables and by the unpaired Student's *t*-test (or Mann–Whitney *U*-test in case of non-normal distribution). Normality of distributions was assessed using histograms and the Shapiro–Wilk test. With some variables being specific for a subgroup of patients or some variables having an important proportion of missing variables, for multivariate analysis, we first selected variables with less than 20% of missing values and variables concerning all the patients. To select variables with a potential influence on the outcome a priori, we used classification techniques (random forest and lasso). Then, we used an automatic stepwise selection based on the Akaike information criteria (AIC) to obtain our final model.

Results

Patients' characteristics, underlying diseases, and clinical features

A total of 185 CM patients was enrolled. Twenty-five cases were excluded from the outcome analysis because of lack of follow-up data after discharge from the hospital. Seventy (43.8%) out of 160 cases included in the outcome analysis had unfavorable outcomes. Of these, 42 (26.3%) died, 19 (11.9%) survived with sequelae, and 9 (5.6%) experienced relapses.

The median (interquartile range, IQR) age of the 160 patients was 41 (33–52) years. Of the study group, 122 (76.3%) patients were men. Eighty-three (54.9%) patients lived in urban and 44 (29.1%) in suburban areas. One hundred and four (65%) cases were found to be HIV infected. Most of the CM cases presented with 103 (64.4%) acute, others 34 (21.2%) subacute, and 23 (14.4%) chronic infection, respectively. Forty-two (26.3%) cases were admitted to the intensive care unit (ICU).

In 89 of 104 HIV-infected cases, viral load testing was carried out. In 50 (56.2%) cases, the HIV-RNA level was > 100,000 copies/mL. The median (IQR) CD4 count was 27 (10–60) cells/μL and it was < 200 cells/μL in 84 (84.8%) cases. Fever [118 (73.8%)], headache [130 (61.4%)], nausea/vomiting [82 (51.3%)], and altered mental status [77 (48.1%)] were the most common symptoms. The CCI score was < 6 points in 121 (75.6%) cases.

The characteristics of the patients, underlying diseases, and clinical features were compared according to the outcomes in Table 1.

Predictors of unfavorable outcome

CD4 count < 200 cells/μL at the time of diagnosis for CM and short duration of antiretroviral therapy (ART) usage (before CM diagnosis) had significantly more frequent unfavorable outcomes ($p < 0.05$). Advanced age, admission to the ICU, and recent hospitalization within 3 months were found to be associated with unfavorable outcomes ($p < 0.05$ for all comparisons). There were no significant relationships between outcome and gender, the area of residence, recent antibiotic use, history of brain surgery, feeding birds, other opportunistic infections, types of CNS involvement, and underlying diseases.

Cranial nerve involvement, focal neurological deficits, speech disorders, level of consciousness, neck stiffness, urinary involvement, and low GCS scores (0–8) were significantly more frequent in the unfavorable outcome group ($p < 0.05$ for all comparisons).

Laboratory and radiological findings

It was observed that 93 (78.1%) of 119 cases were positive by India ink staining. Culture on SDA agar was positive in 140 (93.3%) of 150 cases within 72 h of inoculation. CrAg was positive in the CSF in 98 (90.7%) of 108 cases tested. In 91 cases for which it is known, CSF CrAg was determined by latex in 83 (91.2%) and by ELISA in 8 (8.8%). The total CSF leukocyte counts ranged between 0 and 1750 cells/mm^3, with a median of 56 (10–167) cells/mm^3 in 157 cases.

In the unfavorable outcome group, serum lymphocyte percentage and CSF leukocyte counts were significantly lower, while the serum neutrophils to lymphocyte ratio, serum CrAg titers, CSF CrAg positivity, cryptococcal PCR positivity, and delayed lumbar puncture (LP) after admission were significantly higher ($p < 0.05$ for all comparisons). The comparisons of initial abnormal imaging studies between the two groups are presented in Table 2. Cerebral infarcts were found only in patients with unfavorable outcome ($p = 0.016$).

Antifungal treatment

Empiric antifungal treatment was performed for 76 (47.5%) patients, while in 84 (52.5%) patients, the antifungal treatment was given according to the microbiological data. There was no correlation between outcome and empirical antifungal use, drug regimen, duration of treatment, and drug modification. In addition, no correlation existed between the outcome and the use of induction, consolidation, or suppression phase regimens. The doses of corticosteroids used were significantly higher in the group with unfavorable outcome ($p = 0.01$). No correlation was found between outcome and repeated LPs, the number of LPs, temporary drains, permanent shunt devices, and development of IRIS. The total antifungal treatment duration was significantly shorter for patients with unfavorable outcomes (Table 3) ($p < 0.001$).

Table 1 Patients' characteristics, underlying diseases, and clinical features at presentation

Characteristics	Unfavorable outcome, $n = 70$ (%)	Favorable outcome, $n = 90$ (%)	p-Value
Age (years)[b]	46.1 ± 15.9	41.2 ± 14.0	0.047*
Male gender	53 (75.7)	69 (76.7)	1.000
Weight (kg)[b]	63.3 ± 11.9	64.5 ± 11.2	0.667
Area of residence (urban/suburb/rural)	35 (54.7)/17 (26.6)/12 (18.8)	48 (55.2)/27 (31.0)/12 (13.8)	0.690
Admission to intensive care unit	29 (41.4)	13 (14.4)	**< 0.001***
Recent hospitalization (< 3 months)	29 (41.4)	22 (24.4)	**0.034***
Recent antibiotic use (< 3 months)	22 (31.4)	23 (25.6)	0.521
History of brain surgery	4 (5.7)	3 (3.3)	0.700
History of feeding birds	3 (4.3)	2 (2.2)	0.654
Other opportunistic infections	15 (21.4)	16 (17.8)	0.687
Type of CNS involvement (acute/subacute/chronic)	46 (65.7)/14 (20.0)/10 (14.3)	57 (63.3)/20 (22.0)/13 (14.4)	0.972
Underlying diseases			
HIV infection	40 (57.1)	64 (71.1)	0.095
HIV-RNA > 100,000 copies/mL (at the diagnosis of CM)	13 (44.8) ($n = 29$)	37 (61.7) ($n = 60$)	0.203
CD4 count < 200 cells/μL (at the diagnosis of CM)	34 (97.1) ($n = 35$)	50 (78.1) ($n = 64$)	**0.035***
ART use (before CM diagnosis)	13 (32.5) ($n = 40$)	14 (21.9) ($n = 64$)	0.331
ART duration (before CM diagnosis) (months)[a]	2 (1–48) ($n = 11$)	19 (1–88) ($n = 14$)	**0.029***
ART duration (> 1 months) (after CM diagnosis)	5 (38.5) ($n = 13$)	11 (28.2) ($n = 39$)	0.506
Malignancy (all)	9 (12.9)	7 (7.8)	0.426
Hematologic malignancy	3 (4.3)	4 (4.4)	1.000
Chronic liver disease	10 (14.3)	14 (15.6)	1.000
Cirrhosis	5 (7.1)	5 (5.6)	0.749
Alcoholism	12 (17.1)	10 (11.1)	0.386
Renal insufficiency	10 (14.3)	7 (7.8)	0.286
Drug addiction	13 (18.6)	10 (11.1)	0.268
Diabetes mellitus	11 (15.7)	5 (5.5)	0.063
Corticosteroids (immunosuppressive dose)	6 (8.6)	9 (10.0)	0.973
Immunosuppressed	58 (82.9)	80 (88.9)	0.386
History of transplantation	7 (10.0)	4 (4.4)	0.213
Hypertension	11 (15.7)	11 (12.2)	0.686
Chronic obstructive pulmonary disease	3 (4.3)	2 (2.2)	0.654
Use of tacrolimus	6 (8.6)	3 (3.3)	0.181
Sarcoidosis	0	2 (2.2)	0.505
HIV-negative CD4 lymphopenia	0	3 (3.3)	0.257
Charlson comorbidity index score < 6	53 (75.7)	68 (75.6)	1.000
Clinical presentations			
Fever (temperature ≥ 38 °C)	42 (60.0)	76 (84.4)	**< 0.001***
Headache	48 (68.6)	82 (91.1)	**< 0.001***
Altered mental status	41 (58.6)	36 (40.0)	**0.030**
Nausea/vomiting	29 (41.4)	53 (58.9)	**0.042***
Dizziness	23 (32.9)	29 (32.2)	1.000
Pulmonary symptoms (cough, dyspnea)	14 (20.0)	18 (20.0)	1.000
Cranial nerve palsies	22 (31.4)	13 (14.4)	**0.017***
Focal neurological deficit	22 (31.4)	14 (15.6)	**0.028***

Table 1 (continued)

Characteristics	Unfavorable outcome, $n = 70$ (%)	Favorable outcome, $n = 90$ (%)	p-Value
Visual disorder	11 (15.7)	11 (12.2)	0.686
Speech disorders	12 (17.1)	5 (5.6)	**0.036***
Hearing disorders	2 (2.9)	4 (4.4)	0.697
State of consciousness (conscious)	41 (58.6)	67 (74.4)	**0.014***
Personality changes	26 (37.1)	23 (25.6)	0.160
Depression	5 (7.1)	12 (13.3)	0.316
Seizures	8 (11.1)	3 (3.3)	0.060
Neck stiffness	14 (20.0)	36 (40.0)	**0.011***
Kernig's/Brudzinski's signs	9 (12.9)	10 (11.1)	0.926
Papilledema	4 (5.7)	6 (6.7)	1.000
Cutaneous	5 (7.1)	2 (2.2)	0.241
Pulmonary	15 (21.4)	13 (14.4)	0.345
Urinary	4 (5.7)	0	**0.035***
Bloodstream	24 (34.3)	24 (26.7)	0.385
Glasgow Coma Scale score (0–8)/(9–12)/(13–15)	10 (14.7)/8 (11.8)/50 (73.5)	3 (3.4)/11 (12.5)/74 (84.1)	**0.041***

CNS central nervous system; *HIV* human immunodeficiency virus; *ART* antiretroviral therapy

[a] Median (min–max)

[b] Mean ± standard deviation (SD)

*$p < 0.05$

Multivariate analysis

The higher GCS scores were associated with better outcomes and, accordingly, CSF leukocyte counts > 20 and higher CSF glucose levels were associated with favorable outcome (Table 4). On the other hand, malignancy was associated with poor outcomes. CrAg was not associated with the outcomes (probably by the lack of power due to missing data), but the model was always better with the quantitative variables than with the cut-off value, whatever the cut-off level was.

Discussion

There is a significant number of studies evaluating unfavorable outcomes in CM [3, 14–19]. It is commonly recognized that CM is an opportunistic infection; however, it occurs in previously healthy persons too [4]. Advanced age, malignancy, liver cirrhosis, iatrogenic Cushing syndrome, respiratory failure, increased length of stay in the ICU, corticosteroid therapy, abnormal mental status, seizures, cranial nerve palsies, low CSF leukocyte counts, low CSF glucose levels, high CSF CrAg titers, hematogenous dissemination of cryptococci, hydrocephalus, and cerebral infarction have previously been reported to be associated with poor outcomes in various CM cohorts [3, 17, 20–24]. In this study, we found that a combination of clinical, diagnostic, and host factors contributed to the outcomes in CM patients. The presence of malignities and low GCS score were associated with unfavorable outcomes. On the other hand, high CSF leukocyte counts (> 20 cells/mm^3) and CSF glucose levels were associated with better prognosis. We could not disclose that HIV infection contributed to unfavorable outcome in CM patients.

The control of underlying diseases contributes to therapeutic success in CM treatment. Although there are reports that could not find any association between malignant diseases and the development of CM [19], neoplasms were known to be associated with increased mortality in CM patients [1, 20, 24, 25]. CM was reported rarely in patients with solid tumors, while hematological malignancies constitute the great majority and higher mortality rates [26]. CM patients with malignancies have shorter survival periods than those with the acquired immunodeficiency syndrome (AIDS) in several reports [4, 27]. In our multicenter study, there was no significant association between hematological malignancies and poor outcome in CM patients. However, our data showed that there was a significant correlation between malignant disease and poor outcomes.

GCS score, the indicator of conscious state, is the most significant predictor of mortality in many types of CNS infections [8, 28, 29] in general and in CM in particular [13, 15, 17, 22, 30]. The outcome was worse in those who had a GCS score of < 9 [31]. Accordingly, lower GCS scores were related to increased unfavorable outcome according to our data. Moreover, the absence of prominent clinical manifestations causes delays in diagnosis in CM cases, but data are scarce on their relations to outcome. The absence of headache is one

Table 2 Serum/cerebrospinal fluid (CSF) and radiological findings of the cases

Characteristics	Unfavorable outcome, $n = 70$ (%)	Favorable outcome, $n = 90$ (%)	p-Value
Laboratory findings on admission			
Serum leukocyte count (cells/mm^3)[a]	6200 (1000–122,000)	5000 (1200–90,480)	0.446
Serum lymphocyte percentage (%)[a]	12.0 (1.0–75.0)	20.0 (1.0–79.0)	< **0.001***
Serum neutrophil/lymphocyte ratio[a]	6.5 (0.2–98)	3.4 (0.1–71)	**0.044***
Hemoglobin (mg/dL)[b]	11.8 ± 2.5	11.6 ± 2.2	0.925
Platelet (/mm^3)[b]	211,100 ± 109,120.3	197,200 ± 94,713.7	0.403
Serum CRP (mg/dL)[a]	4.6 (0.9–17.0)	4.8 (0.3–18.5)	0.542
Serum ALT (U/L)[a]	32.0 (10.0–199.0)	26.0 (4.0–409.0)	0.067
Serum creatinine (mg/dL)[a]	0.8 (0.3–6.0)	0.9 (0.2–2.4)	0.101
Serum albumin (g/dL)[a]	3.3 (1.8–4.8)	3.5 (1.3–4.9)	0.157
Serum CrAg	41 (58.6)	43 (47.8)	0.231
Serum CrAg titer[a]	1:512 (1:2–1:32,770) ($n = 41$)	1:128 (1:2–1:8192) ($n = 42$)	**0.025***
CSF appearance (clear)	50 (87.7) ($n = 57$)	58 (70.7) ($n = 82$)	0.093
CSF leukocyte count (cells/mm^3)[a]	29 (0–1584)	76 (0–1750)	**0.018***
CSF leukocyte count >20 cells/mm^3	40 (58.8) ($n = 68$)	66 (74.2) ($n = 89$)	0.063
CSF lymphocyte ratio (%)[a]	84.0 (7.0–99.0) ($n = 31$)	70.0 (10.0–99.0) ($n = 47$)	0.385
CSF neutrophil/lymphocyte ratio[a]	0.1 (0–13.3) ($n = 31$)	0.4 (0–8.0) ($n = 47$)	0.314
CSF glucose (mg/dL)[b]	37.5 ± 25.1 ($n = 58$)	41.8 ± 24.9 ($n = 86$)	0.317
CSF/blood glucose ratio[b]	0.3 ± 0.2 ($n = 58$)	0.4 ± 0.2 ($n = 86$)	0.054
CSF protein (mg/dL)[a]	58.0 (0.96–1251.0)	56.0 (0.6–1012.0)	0.341
CSF Indian ink	40 (57.1)	53 (58.9)	0.480
CSF SDA culture	61 (87.1)	79 (87.8)	0.937
SDA culture outside of CSF	28 (40.0)	27 (30.0)	0.114
CSF CrAg	50 (71.4)	48 (53.3)	**0.025***
CSF CrAg titer[a]	1:512 (1:2–1:16,380)	1:128 (1–1:65,540)	0.058
CSF PCR positivity	5 (71.4) ($n = 7$)	3 (16.6) ($n = 18$)	**0.008***
LP after admission (h)[a]	4.5 (0.5–1632)	3.0 (0.2–540)	< **0.001***
Radiological assessment			
Normal chest X-ray	41 (64.1) ($n = 64$)	59 (72.8) ($n = 81$)	0.340
Pulmonary nodule	9 (14.1) ($n = 64$)	3 (3.7) ($n = 81$)	0.052
Pulmonary infiltration	18 28.1) ($n = 64$)	18 (22.2) ($n = 81$)	0.533
Normal CT/MRI	28 (42.4) ($n = 66$)	47 (56.0) ($n = 84$)	0.139
Hydrocephalus	8 (12.1) ($n = 66$)	7 (8.3) ($n = 84$)	0.622
Cerebral edema	16 (24.2) ($n = 66$)	16 (19.0) ($n = 84$)	0.569
Cerebral infarct	12 (18.5) ($n = 65$)	4 (4.8) ($n = 84$)	**0.016***
Pseudocyst/cryptococcoma	12 (18.2) ($n = 66$)	9 (10.7) ($n = 84$)	0.284
Leptomeningeal involvement	12 (18.2) ($n = 66$)	8 (9.5) ($n = 84$)	0.191

CSF cerebrospinal fluid; *CRP* C-reactive protein; *ALT* alanine aminotransferase; *CrAg* cryptococcal antigen; *SDA* Sabouraud dextrose agar; *PCR* polymerase chain reaction; *LP* lumbar puncture; *CT* computed tomography; *MRI* magnetic resonance imaging

[a] Median (min–max)

[b] Mean ± standard deviation (SD)

*$p < 0.05$

Table 3 Antifungal treatment strategies and adjunct managements

Characteristics	Unfavorable outcome, $n = 70$ (%)	Favorable outcome, $n = 90$ (%)	p-Value
Elapsed time (days)[a]	9.0 (1.0–112.0)	10.0 (1.0–288.0)	0.777
Empirical antifungal use	33 (47.1) ($n = 70$)	43 (47.8) ($n = 90$)	1.000
FLU/AmB/AmB + 5FC/AmB + FLU	15 (45.5)/11 (33.3)/7 (21.2)/0	10 (23.3)/23 (53.5)/9 (20.9)/1 (2.3)	0.118
Empirical antifungal duration (days)[a]	3 (0–15)	3 (0–30)	0.310
Empirical antifungal changed	5 (11.9) ($n = 42$)	7 (9.7) ($n = 72$)	0.757
Induction antifungal therapy (initial)			
FLU/AmB/AmB + 5FC/AmB + FLU/FLU + 5FC	9 (12.9)/23 (32.9)/27 (38.6)/8 (11.4)/3 (4.2)	19 (21.1)/29 (32.2)/32 (35.6)/9 (10.0)/1 (0.1)	0.530
Consolidation therapy (FLU) ($n = 117/123$)	36 (97.3) ($n = 37$)	81 (94.2) ($n = 86$)	1.000
Suppression therapy (FLU) ($n = 82/85$)	23 (95.8) ($n = 24$)	59 (96.7) ($n = 61$)	0.636
Corticosteroid use (prednisone equivalence)	22 (31.4)	28 (31.1)	1.000
Corticosteroid dose (mg)[a]	60.0 (5.0–1250.0) ($n = 22$)	13.75 (5.0–100.0) ($n = 24$)	**0.010***
Corticosteroid duration (days)[a]	7.0 (1.0–53.0)	7.0 (1.0–71.0)	0.714
Repeated lumbar puncture	45 (64.3)	69 (76.7)	0.123
Number of lumbar punctures[a]	2.0 (1.0–25.0)	2.0 (1.0–10.0)	0.116
Temporary drain	6 (8.6)	4 (4.4)	0.335
Permanent shunt device	4 (5.7)	2 (2.2)	0.405
Immune reconstitution inflammatory syndrome	0	3 (3.3)	0.257
Antifungal therapy total duration (days)[a]	32.5 (1.0–1331.0) ($n = 50$)	87.0 (8.0–1305.0) ($n = 70$)	**< 0.001***

FLU fluconazole; *AmB* amphotericin B; *5FC* 5-fluorocytosine

[a] Median (min–max)

*$p < 0.05$

of the factors predicting poor outcome in CM [25, 32, 33]. Likewise, nausea and vomiting was associated with increased mortality in the literature [34]. In our study, headache and nausea/vomiting were not related to unfavorable outcomes, which might be related with the heterogeneity of our patients including both HIV positives and negatives, and at various stages of immunosuppression.

The fungal burden reflected by CrAg titers has prognostic importance in patients with CM [1]. High CSF CrAg titers (especially > 1:1024) have been identified as poor outcome

Table 4 Multivariate model with predictors for outcome

Variable	Coefficient**	Standard error	p-Value
Glasgow Coma Scale	0.934	0.403	**0.021***
Malignancy	− 2.857	1.281	**0.026***
CSF leukocytes count (> 20 cells/mm^3)	1.807	0.872	**0.038***
Headache	1.846	1.012	0.068
Nausea/vomiting	1.263	0.749	0.092
Hypertension	− 1.610	1.027	0.117
Serum CrAg titer	− 0.0007	0.0004	0.077
CSF CrAg titer	0.00004	0.00005	0.470
CSF glucose	0.031	0.016	**0.048***

**A positive value expresses the predictor of a favorable outcome, while a negative value expresses a predictor of unfavorable outcome

*$p < 0.05$

signs [18, 20]. In other studies, high CSF CrAg titers at baseline were predictors for the unfavorable clinical outcome [16, 35, 36]. In another study, high (≥ 1:512) serum CrAg levels were associated with mortality. In this study, however, higher CrAg levels were not shown to be associated with outcome. The potential reason for this was that the immune status of our patients varied from severely immunocompromised to apparently healthy, leading to differences in CrAg clearance. Added to that, low CSF leukocyte counts have been identified as poor outcome indicators [20, 32]. There are many reports on the association of CSF leukocyte counts and favorable outcome. Lower CSF leukocyte counts were associated with poor outcomes [35], while higher CSF leukocyte counts were associated with better prognosis [14, 22, 37]. In addition, depressed CSF glucose levels in CM have been known to correlate with poor prognosis in various studies [20, 21]. Accordingly, two laboratory parameters, high leukocyte counts over 20 cells/mm^3 and high CSF glucose levels, were associated with favorable outcomes in CM.

There were some limitations concerning this study. First, CM is a rare disease and it was difficult to provide a prospective cohort. Hence, the major limitation of our study was its retrospective design. Second, because most serotypes of *Cryptococcus* species were not identified, analysis could not be performed in this study. Third, participating countries may not all have the same levels for healthcare and management of diseases, and that could influence the results.

In conclusion, patients with CM with substantial risks for mortality and sequelae require early diagnosis and prompt antifungal therapy. We found that CM patients with lower GCS scores, malignancy, lower CSF leukocyte counts, and lower CSF glucose levels are at increased risk of unfavorable outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict interest.

Ethics approval The study obtained approval by the review board of the Fatih Sultan Mehmet Education and Research Hospital in Istanbul.

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