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ORIGINAL ARTICLE

Comparisons of clinical features and mortality of cryptococcal meningitis between patients with and without human immunodeficiency virus infection

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Background: Cryptococcosis is a systemic infection caused by *Cryptococcus neoformans*, and cryptococcal meningitis can occur in patients with late-stage human immunodeficiency virus (HIV) infection and other forms of immunosuppressive status. This study was designed to compare clinical features and laboratory findings of cryptococcal meningitis in HIV-positive and HIV-negative patients.
Methods: From January 1, 2000 to December 31, 2009, all patients aged more than 18 years hospitalized at National Taiwan University Hospital with a diagnosis of cryptococcal meningitis were analyzed retrospectively.
Results: In total, 88 patients with cryptococcal meningitis were identified and 37 (42%) were HIV infected. Cryptococcal meningitis occurred in young (mean, 38 *vs.* 60; $p < 0.001$) and male (97% *vs.* 63%, $p < 0.001$) populations more frequently among HIV-positive group with higher Charlson comorbidity score (mean, 7 *vs.* 4; $p < 0.001$), higher initial complaint of cough (36% *vs.* 16%; $p = 0.032$), lower cerebrospinal fluid (CSF) white count (mean, 26 *vs.* 86; $p = 0.024$), lower total protein of the CSF (mean, 88 *vs.* 149; $p = 0.012$), higher percentage of serum latex agglutination cryptococcal antigen titer exceeding 1:512 (77% *vs.* 50%; $p = 0.026$), more extraneural involvement (70% *vs.* 49%; $p = 0.046$), more cryptococcemia (68% *vs.* 35%; $p = 0.003$), and higher proportion of normal brain images (44% *vs.* 13%; $p = 0.003$) than HIV-negative group. The all-cause mortality rates on Day 30 and Day 90 were 23.9% and 31.8%, respectively. The independent risk factors for Day 30 mortality were altered mental status, extraneural involvement, absence of lymphocyte predominance, and absence of leptomeningeal enhancement (odds ratio: 7.84, 9.71, 0.22, and 0.07, respectively; 95% confidence interval): 2.03–30.27, 2.01–46.94, 0.06–0.80, and 0.01–0.49, respectively). Those for Day 90 mortality were serum white count more than 11,000/μL, higher Charlson

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comorbidity score, and absence of normal brain images (odds ratio: 5.39, 1.40, and 0.09, respectively; 95% confidence interval: 1.22—23.72, 1.11—1.76, and 0.01—0.78, respectively).
Conclusions: The clinical features of cryptococcal meningitis between HIV and non-HIV patients have some divergences, including age, sex, underlying diseases, CSF parameters, extraneural site involvement, fungemia, and so on. We also identified risk factors for mortality of this disease. However, the mortality of cryptococcal meningitis was not different in HIV-positive and HIV-negative patients in terms of Day 30 and Day 90 mortality.

Introduction

Cryptococcosis is a systemic infection caused by *Cryptococcus neoformans*, an encapsulated yeast-like organism that can be isolated from the environment. Cryptococcal meningitis is a common opportunistic infection and acquired immunodeficiency syndrome (AIDS)-defining illness in patients with late-stage human immunodeficiency virus (HIV) infection, particularly in Southeast Asia and Southern and East Africa.[1,2] Cryptococcal meningitis also occurs in patients with other forms of immunosuppression, including corticosteroids use, organ transplantations, chronic leukemias, lymphomas and sarcoidosis,[3] and in apparently immunocompetent individuals.[4] Although the natural history of cryptococcal meningitis in patients with AIDS had been well documented in developed countries,[5—7] there were few updated publications about cryptococcal meningitis in HIV-negative patients. We hypothesize that patient characteristics, clinical features, and outcomes of cryptococcal meningitis in HIV-positive patients may be different from those in HIV-negative patients. In this retrospective study, we aimed to compare the clinical presentations, laboratory data, radiographic findings, and outcomes of cryptococcal meningitis between HIV-positive and HIV-negative patients who were admitted to a university hospital from 2000 to 2009.

Patients and methods

Study population

We retrospectively reviewed the medical and microbiological records of hospitalized patients aged 18 years or older with a diagnosis of cryptococcal meningitis from 2000 to 2009. Cryptococcal meningitis was defined as positive cerebrospinal fluid (CSF) culture for *C neoformans*.

All enrolled patients were divided into HIV-positive and HIV-negative groups. A standardized case collection form was used to record age, sex, underlying diseases, Charlson comorbidity score, initial presentations, duration of initial symptoms to diagnosis, laboratory data, radiographic findings, and intrahospital mortality. Factors that would predict a poor outcome were also evaluated between these two groups.

Laboratory studies

HIV infection was detected by positive enzyme-linked immunosorbent assay method (Abbott Axsym System, Wiesbaden, Germany) and confirmed by Western blotting (NEW LAV Blot, Bio-rad, Marnes-la-Coquette, France). CSF was routinely sent for complete white blood cell counts and differential counts, glucose, protein, and India ink stain and cultures. Urine, pus, lung, ascites, pleural effusion, lymph node, and/or other biopsy tissues and aspiration specimens were performed and submitted for cultures when indicated. Brain imaging, including computed tomography (CT) or magnetic resonance imaging (MRI) was done when indicated and the results were reviewed. Neuroimage findings included leptomeningeal enhancement, cerebral infarction, hydrocephalus, abscess, and other presentations. The serum and CSF cryptococcal antigen titers were determined using commercial latex agglutination tests (LATEX-CRYPTOCOCCUS ANTIGEN DETECTION SYSTEM, Immuno-Mycologics, Inc., Norman, USA).

Treatment strategies and outcome

Amphotericin B, 0.7—1 mg/kg/d, was the drug of choice in both HIV-positive and HIV-negative patients with cryptococcal meningitis.[8] Flucytosine was not available at National Taiwan University Hospital (NTUH) until 2008, so our treatment strategies were as follows: the first antifungal agent chosen was amphotericin B and at least 1 week of duration was prescribed.

Beside, time to sterile CSF, the duration from positive culture for *C neoformans* to mortality, and the period of starting antifungal agents after presentation at NTUH were all recorded for analysis of treatment outcomes, defined by all-cause mortality on Day 30 and Day 90. The factors for poor prognosis were included in the univariate and multivariate analyses.

Statistical analysis

Continuous variables were described as mean $\pm$ standard deviation and compared using Student's *t* test. Categorical variables were compared with a χ^2 test or Fisher exact test if the expected values were below 10. Risk factors for all-cause Day 30 and/or Day 90 mortality were identified using a logistic regression model. All parameters were initially tested by univariate analysis and those with a p value <0.05 were used for multivariate analysis. Parameters with collinearity (tested by correlation matrix) were not simultaneously considered in the final model. Stepwise model comparison and Akaike's Information Criterion were used to determine the best model of multiple variables analysis. Statistical analyses were performed using SAS 9.1.3 (SAS

Institute, Cary, NC, USA). All tests were two-tailed and a p value <0.05 was considered statistically significant.

Results

Patient population

From 2000 to 2009, 88 patients with cryptococcal meningitis were identified. Of these 88 patients, 37 (42%) were HIV infected. Comparisons of the demographic and clinical features in the HIV-positive and HIV-negative groups are shown in Table 1. Compared with HIV-uninfected patients, HIV-infected patients were more likely to be male and younger. Among HIV-negative group, 45 (91.8%) had at least one underlying disease, and the most frequently recorded underlying diseases included hepatobiliary diseases, hypertension, hematology, and oncologic diseases (Table 1). Although less underlying diseases are associated with HIV-infected patients, higher percentage of these patients present with Charlson comorbidity score above 6 ($p = 0.02$). There was no significant difference in initial presentations between HIV-positive and HIV-negative patients, except cough, which was more frequent in the former group (36% *vs.* 16%, $p = 0.03$). The most commonly complained symptoms were fever (67%), followed by headache (65%), and altered mental status (43%). Other initial presentations include hearing impairment, incoherent speech, and unilateral decrease in muscle power. About 75% and 74% of the patients were diagnosed as having cryptococcal meningitis in less than 1 month from the initial onset of symptoms in HIV-infected and non–HIV-infected groups, respectively. Overall, the in-hospital mortality was 29.7% and 33.3% in HIV-positive and HIV-negative patients, respectively ($p = 0.720$).

Laboratory data

The results of laboratory data and radiological findings are also shown in Table 2. The mean CSF leukocyte count was 26 cells/mm^3 in HIV-infected patients, which was significantly lower than that in the non–HIV-infected group (86 cells/mm^3, $p = 0.02$). About 83.8% of patients with HIV infection had white count below 20 in CSF in contrast to 36% of patients without HIV infection. Among HIV-positive patients, there was significantly lower average total protein level in CSF (88 mg/dL *vs.* 149 mg/dL, $p = 0.012$) and fewer cases with CSF glucose below 40 mg/dL (38.9% *vs.* 61.2%, $p = 0.042$) than those in HIV-negative patients. There was no statistical difference in opening pressure on spinal tap between the two groups. *C neoformans* was detected by India ink preparation in 24 patients (of 35) with HIV infection and 21 of 42 patients without HIV infection. In 67% (59 of 88) of the patients, blood and CSF samples for cryptococcal Ag tests were collected simultaneously and processed in parallel. CSF latex agglutination cryptococcal antigen titer (LACT) more than 1:512 in HIV-positive and HIV-negative groups was demonstrated in 24 and 22 patients, respectively. A higher percentage of the patients with HIV infection had serum LACT exceeding 1:512 than those without HIV infection ($p = 0.026$). However, there were three and two cases with LACT in CSF and serum less than 1:8 for HIV-positive group, respectively, and four and one patients for HIV-negative group, respectively. Twenty-six of 37 patients among HIV-positive group and 25 of 51 patients among HIV-negative group had *C neoformans* isolated from specimens other than CSF, including blood (25 *vs.* 18), lung specimens (3 *vs.* 4), urine (2 *vs.* 4), lymph node (1 *vs.* 0), ascites (0 *vs.* 2), pleural effusion (0 *vs.* 1), and wound (0 *vs.* 1). Brain images were performed in only 73 patients. The most common presentations were cerebral infarction (30), leptomeningeal enhancement (27), and hydrocephalus (11), but 17 patients had normal image findings. Higher percentage of patients without HIV infection presented with cerebral infarction than those with HIV infection ($p = 0.008$), but normal presentations were revealed in the HIV-positive group significantly much more than HIV-negative group ($p = 0.003$).

Treatment and outcome

Thirty patients were treated with amphotericin B-based therapy initially and 25 patients had received amphotericin B for more than 1 week in HIV-positive group. Among non-HIV cases, amphotericin B-based regimen was prescribed initially in 29 patients and at least 1 week of treatment was used in 93% (27 of 29) of these patients. The average days of starting antifungal agents after arrival at the hospital were 2.6 days and 9.5 days in the HIV-infected group and non-HIV group, respectively ($p = 0.012$). Of the 31 HIV-infected patients whose CD4 cell counts were determined, the count was <100/mm^3 in most cases (28 of 31, 90.3%), and the average count was 41/mm^3 (range, 2–267). About 68.8% (22 of 32) of these HIV-positive patients had plasma HIV viral load above 10^5 copies/mL. The all-cause mortality rate on Day 30 was 23.9% (21 deaths) and on Day 90 was 31.8% (28 deaths). There were 26 patients with HIV infection and 34 patients without HIV infection who survived. For those survived, the mean duration of antifungal treatment to sterile CSF was 18 days versus 14 days in the HIV-positive group and the HIV-negative group without statistical significance. In univariate analysis, factors associated with mortality at Day 30 were CSF white count below 20 cells/mm^3, absence of lymphocyte predominance, higher Charlson comorbidity score, absence of headache, altered mental status, cryptococcemia, extraneural involvement, and absence of leptomeningeal enhancement on brain images (Table 3). In multivariate analysis, absence of lymphocyte predominance [odds ratio (OR) 0.22, 95% confidence interval (CI): 0.06–0.80, $p = 0.022$], altered mental status (OR 7.84, 95% CI: 2.03–30.27, $p = 0.003$), extraneural involvement (OR 9.71, 95% CI: 2.01–46.94, $p = 0.005$), and absence of leptomeningeal enhancement on brain images (OR 0.07, 95% CI: 0.01–0.49, $p = 0.007$) were found to be independent predictors of mortality at Day 30. On the other hand, age above 50 years, absence of lymphocyte predominance, initial serum white count more than 11,000/μL, presence of hepatobiliary diseases, presence of renal diseases, higher Charlson comorbidity score, absence of headache, dyspnea, cryptococcemia, extraneural involvement, and absence of normal brain images had strong association with mortality at Day 90 in univariate analysis (Table 4). The multivariate analysis demonstrated that initial serum white count more than 11,000/μL (OR 5.39, 95% CI: 1.22–23.72, $p = 0.026$), Charlson comorbidity score (OR 1.40, 95% CI: 1.11–1.76, $p = 0.004$), and absence

Table 1 Demographic and clinical features in HIV-positive and HIV-negative patients with *Cryptococcus neoformans* meningitis

Variables	HIV positive	HIV negative	*p*
	N = 37	*N* = 51	
Age, yr			
Mean ± SD	38.19 ± 12.12	59.57 ± 14.17	
Range	23–81	31–88	<0.001
Sex (male, %)	36 (97.3%)	32 (62.7%)	<0.001
Underlying diseases	37	49	
Hepatobiliary diseases	2 (5.4%)	17 (34.7%)	0.001
Hypertension	1 (2.7%)	15 (30.6%)	<0.001
Hematology and oncology	5 (13.5%)	14 (28.6%)	0.096
Diabetes mellitus	1 (2.7%)	12 (24.5%)	0.005
Neurological diseases	3 (8.1%)	12 (24.5%)	0.047
Autoimmune diseases	0	9 (18.4%)	0.009
Renal diseases	1 (2.7%)	8 (16.3%)	0.082
Respiratory diseases	3 (8.1%)	8 (16.3%)	0.426
Cardiovascular diseases	1 (2.7%)	5 (10.2%)	0.360
Endocrine diseases	0	3 (6.1%)	
Others	0	5 (10.2%)	
Nil	0	4 (8.2%)	
Charlson comorbidity score	7 ± 1.55	4 ± 2.80	<0.001
>6	16 (43.2%)	10 (20.4%)	0.022
Initial presentation	36	50	
Headache	24 (66.7%)	32 (64%)	0.798
Fever	28 (77.8%)	30 (60%)	0.083
Altered mental status	13 (36.1%)	24 (48%)	0.273
Vomiting	17 (47.2%)	14 (28%)	0.067
Unsteady gait	5 (13.9%)	11 (22%)	0.340
Cough	13 (36.1%)	8 (16%)	0.032
Stiff neck	6 (16.7%)	7 (14%)	0.733
Abnormal vision	4 (11.1%)	6 (12%)	>0.999
Dyspnea	7 (19.4%)	6 (12%)	0.342
Seizure	4 (11.1%)	4 (8%)	0.897
Others	10 (27.8%)	10 (20%)	
Duration of initial symptoms to diagnosis	36	50	
≤1 mo	27 (75%)	37 (74%)	0.917
In-hospital mortality	11 (29.7%)	17 (33.3%)	0.720

HIV = human immunodeficiency virus; SD = standard deviation.
Neurological diseases included cerebrovascular diseases, hydrocephalus; autoimmune diseases, ankylosing spondylodiskitis, dermatomyositis/polymyositis, systemic lupus erythematosus, Sjogren's syndrome, microscopic polyangitis, autoimmune pancreatitis; respiratory diseases, pulmonary tuberculosis, bronchiectasis, pneumoconiosis; cardiovascular diseases, sick sinus syndrome, cardiomyopathy, arrhythmia, coronary artery diseases, valvular heart diseases; endocrine diseases, adrenal insufficiency, Graves' disease; other underlying diseases, transplant recipient, trisomy X.
Other initial presentations included hearing impairment, incoherent speech and unilateral decrease in muscle power, and memory impairment.

of normal brain images (OR 0.09, 95% CI: 0.01–0.78, $p = 0.029$) were independent risk factors for mortality at Day 90 in cryptococcal meningitis. The Kaplan-Meier survival curve for all 88 patients is showed in the Fig. 1, which demonstrates no significant difference in mortality hazard between HIV-infected and non–HIV-infected group (Log-rank test, $p = 0.832$).

Discussion

Cryptococcal meningitis has been described as an opportunistic infection in immunocompromised patients, but is also known to affect apparently healthy individuals.[9] Of the 88 patients identified with cryptococcal meningitis in

Table 2 Laboratory data and radiographic findings in HIV-positive and HIV-negative patients with *Cryptococcus neoformans* meningitis

Variables	HIV positive	HIV negative	*p*
	N = 37	*N* = 51	
CSF white blood cell count (median, interquartile range, minimum-maximum), cells/mm^3	3 (8, 0–291)	43.5 (82, 0–1,100)	<0.001
<20	31 (83.8%)	18 (36%)	<0.001
Lymphocyte predominant	24 (64.9%)	35 (68.60%)	0.711
CSF protein (median, interquartile range, minimum-maximum), mg/dL	59 (68.9, 0–443)	111 (133.4, 1–767.4)	0.003
>45	25 (67.6%)	41 (83.7%)	0.080
CSF glucose (mean ± SD), mg/dL	46.22 ± 24.39	36.02 ± 26.73	0.075
<40	14 (38.9%)	30 (61.2%)	0.042
Open pressure (mean ± SD), mmH_2O	283.04 ± 116.05	275.39 ± 138.04	0.824
>200	23 (79.3%)	24 (64.9%)	0.199
CSF positive India ink	24/35 (68.6%)	21/42 (50%)	0.100
CSF LACT, >1:512	24/34 (70.6%)	22/41 (53.7%)	0.134
Serum LACT, >1:512	23/30 (76.7%)	18/36 (50%)	0.026
Serum white blood cell count (mean ± SD), /μL	6236.29 ± 6268.23	8,374 ± 4386.63	0.056
>11,000	3 (8.1%)	8 (16%)	0.447
Serum sodium (mean ± SD), mmol/L	135.82 ± 6.95	134 ± 8.05	0.274
Extraneural involvement	26 (70.3%)	25 (49%)	0.046
Fungemia	25 (67.6%)	18 (35.3%)	0.003
Brain images (CT or MRI)	25	48	
Enhancement	11 (44%)	16 (33.3%)	0.370
Cerebral infarction	5 (20%)	25 (52.1%)	0.008
Hydrocephalus	2 (8%)	9 (18.8%)	0.387
Abscess	1 (4%)	1 (2.1%)	>0.999
Others	7 (28%)	7 (14.6%)	
Normal	11 (44%)	6 (12.5%)	0.003

CSF = cerebrospinal fluid; CT = computed tomography; HIV = human immunodeficiency virus; LACT = latex agglutination cryptococcal antigen titer; MRI = magnetic resonance imaging; SD = standard deviation.
Extraneural involvement defined as *C neoformans* isolated from specimens other than CSF, including any one of the followings: blood, lung specimens, urine, lymph node, ascites, pleural effusion, and wound.
Normal brain images on CT or MRI were defined as no obvious intracranial lesions demonstrated; other brain image findings included encephalitis, gelatinous pseudocyst, brain edema, and hemorrhage.

the present study, 37 (42%) were documented with HIV infection. In a series of 306 HIV-negative patients with cryptococcosis, the predisposing conditions were steroids (28%), organ transplant (18%), chronic organ failure (liver, lung, kidney) (18%), malignancy (18%), and rheumatological disease (13%).[4] Shih et al.[10] reported that 42 of 94 patients with cryptococcal meningitis in non–HIV-infected status had documented underlying diseases, including lymphoma (12%), rheumatological diseases (11%), diabetes mellitus (9%), transplantation (6%), cancers (6%), cirrhosis of the liver (6%), and chronic renal failure (5%). We found that there seemed to be higher proportion of patients with the above predisposing conditions in recent years. Cryptococcal meningitis affects people of any age and men are more affected than women.[11–13] The nationwide survey by the French Cryptococcosis Study Group found that the male-to-female ratio was much greater for HIV-infected patients compared with those without HIV (8:1 *vs.* 1.7:1).[14] HIV affects mainly the young and sexually active.[15] Charlson comorbidity score was calculated in our study and was significantly higher in the HIV-positive group, probably because of the inherent characteristics of the scoring system.

Patients with cryptococcal meningitis commonly present with a subacute or chronic course more than weeks to months. In a 130-case study of patients with cryptococcal meningoencephalitis, the duration of symptoms before admission less than 1 month was 48% and 52% in AIDS and non-AIDS group, respectively ($p = 0.599$).[11] Interestingly, there was no difference in duration of initial symptoms to diagnosis between these two groups in our study; 75% and 74% of the patients in HIV-positive and HIV-negative group, respectively, were diagnosed within 1 month. This might imply that accessibility to hospital care in Taiwan is very convenient. Although less typical clinical manifestations of cryptococcal meningitis in HIV-infected patients (such as headache, altered mental status, and stiff neck) were reported previously,[5,6,16] no significant difference in the above-mentioned presentations between both groups was seen in our series.

Table 3 Factors associated with death at Day 30 in cryptococcal meningitis

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age (>50 yr)	1.78	0.65–4.84	0.261			
India ink	1.16	0.39–3.40	0.793			
CSF WBC < 20 cells/mm^3	4.52	1.37–14.86	0.013			
CSF Glu < 40 mg/dL	0.91	0.34–2.49	0.857			
CSF TP > 45 mg/dL	0.50	0.17–1.49	0.430			
CSF LACT, >1:512	2.10	0.67–6.63	0.206			
Open pressure > 200 mmH_2O	0.57	0.16–2.05	0.393			
Lymphocyte predominant	0.33	0.12–0.92	0.034	0.22	0.06–0.80	0.022
Initial serum WBC > 11,000/μL	3.13	0.84–11.57	0.088			
Hepatobiliary diseases	2.21	0.73–6.65	0.159			
Renal diseases	2.82	0.68–11.69	0.152			
HIV infection	1.35	0.50–3.61	0.554			
Charlson comorbidity score	1.32	1.06–1.64	0.013			
Headache	0.38	0.14–1.03	0.057			
Fever	2.49	0.75–8.26	0.137			
Altered mental status	3.65	1.29–10.33	0.015	7.84	2.03–30.27	0.003
Dyspnea	2.23	0.64–7.75	0.209			
Cryptococcemia	4.74	1.55–14.48	0.006			
Extraneural involvement	6.18	1.66–22.97	0.007	9.71	2.01–46.94	0.005
Leptomeningeal enhancement	0.18	0.04–0.82	0.027	0.07	0.01–0.49	0.007

CSF = cerebrospinal fluid; CI = confidence interval; Glu = glucose; HIV = human immunodeficiency virus; LACT = latex agglutination cryptococcal antigen titer; TP = total protein; WBC = white blood cell.

The CSF indices (cell count, protein, and glucose) were almost always abnormal in HIV-negative patients with cryptococcal meningitis whereas they may be normal or only mildly abnormal in patients with AIDS,[17,18] which were consistent with our observations. Beside, the presentation of HIV-infected patients with *C neoformans* meningitis was characterized by positive India ink smears, positive LACT of CSF and serum, and the isolation of cryptococci from extraneural sites,[3,16,18] the former two indicating an increased fungal load in all patients with cryptococcal

Table 4 Factors associated with death at Day 90 in cryptococcal meningitis

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age (>50 yr)	2.76	1.08–7.09	0.035			
India ink	0.86	0.33–2.26	0.763			
CSF WBC < 20 cells/mm^3	2.04	0.80–5.24	0.138			
CSF Glu < 40 mg/dL	0.81	0.32–2.02	0.649			
CSF TP > 45 mg/dL	0.65	0.23–1.84	0.419			
CSF LACT, >1:512	2.46	0.84–7.23	0.100			
Open pressure > 200 mmH_2O	0.52	0.17–1.66	0.271			
Lymphocyte predominant	0.33	0.13–0.86	0.023			
Initial serum WBC > 11,000/μL	4.58	1.22–17.28	0.025	5.39	1.22–23.72	0.026
Hepatobiliary diseases	3.02	1.06–8.64	0.039			
Renal diseases	9.33	1.79–48.58	0.008			
HIV infection	0.85	0.34–2.11	0.720			
Charlson comorbidity score	1.32	1.08–1.62	0.007	1.40	1.11–1.76	0.004
Headache	0.30	0.12–0.78	0.013			
Fever	1.70	0.62–4.67	0.301			
Altered mental status	2.35	0.94–5.90	0.069			
Dyspnea	4.24	1.24–14.51	0.021			
Cryptococcemia	2.52	1–6.37	0.051			
Extraneural involvement	3	1.11–8.11	0.030			
Normal brain images	0.10	0.01–0.81	0.031	0.09	0.01–0.78	0.029

CSF = cerebrospinal fluid; CI = confidence interval; Glu = glucose; HIV = human immunodeficiency virus; LACT = latex agglutination cryptococcal antigen titer; TP = total protein; WBC = white blood cell.

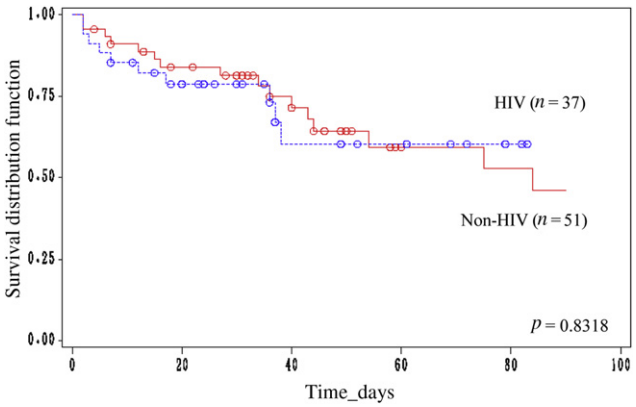

Figure 1. Kaplan-Meier survival curve for cryptococcal meningitis according to HIV infection status. HIV = human immunodeficiency virus.

meningitis.[17,18] Indeed, our study confirmed that the greater frequency in which *C neoformans* was isolated from extraneural sites, including blood, in the HIV-positive group was significant ($p = 0.046$). Although there was no significant difference in the India ink positivity between the two groups (69% *vs.* 50% in HIV positive and HIV negative, respectively), it might be because of small number of cases in our study. In comparing the brain images of HIV-infected and non−HIV-infected groups, the higher proportion of normal images among HIV-positive patients in the present study is compatible with previous reports.[6,16,17] In contrast, the scans of 87.5% of the 48 HIV-negative patients who underwent brain CT or MRI were abnormal, with hydrocephalus being detected in 21.4% (9 of 42). This possibly reflects the more aggressive inflammatory response in the subarachnoid space in this group.[14] Although cerebral infarction on brain images was more common among HIV-negative group in our cases, it is difficult to document that the above finding is directly related to cryptococcal meningitis, and less cerebral infarction occurring in HIV-infected patients might be resulted from their younger age.

Generally, the 3-month mortality rate during management of acute cryptococcal meningoencephalitis approximates 20% despite access to advanced medical care and the availability of highly active antiretroviral therapy.[19,20] In HIV-negative patients, overall mortality rates have varied from 9 to 31%.[15,21,22] Beside, Sun et al.[7] reported that the mortality rate within 2 weeks and 10 weeks of hospitalization with cryptococcosis was 10.3% and 20.7%, respectively in HIV-infected patients responding to highly active antiretroviral therapy. A higher proportion of patients in the HIV-negative group died, which could be explained by the longer delay in starting antifungal agents after arrival at the hospital (9.5 days in HIV-negative group *vs.* 2.6 days in HIV-positive group).

The poor prognostic factors for cryptococcal meningitis reported by prior studies included (1) Cryptococcus growth from sites other than CSF, (2) alteration in mental status, (3) elevated opening pressure > 200 mmH_2O, (4) CSF glucose < 40 mg/dL, (5) CSF cell count < 20 cells/mm^3, (6) high CSF LACT titer,[13,23,24] and (7) positive India ink smear.[12,25] Our data showed that altered mental status, extraneural involvement, absence of CSF lymphocyte predominance, and absence of leptomeningeal enhancement on brain images were independent risk factors for 30-day mortality, the former two factors comparable to previous studies. Cryptococcal meningitis, an example of chronic meningitis, is the most common cause of fungal meningitis, and lymphocytic pleocytosis is usually presented in CSF finding.[26]. Thus absence of CSF lymphocyte predominance on CSF finding might contribute to the delayed administration of antifungal agents. There is no pathognomonic brain image of cryptococcal meningitis, and CT scans or MRI may be normal or reveal meningeal enhancement, single or multiple nodules (cryptococcomas), cerebral edema or hydrocephalus.[27] In our series, higher proportion of patients with leptomeningeal enhancement on brain images had received lumbar puncture within 3 days than those without such a radiological finding (70.4% *vs.* 63.8%, $p = 0.567$), probably implicating that leptomeningeal enhancement on brain images alerted the clinician for early diagnosis of CNS infection. In the present study, initial serum white count more than 11,000/μL, higher Charlson comorbidity score, and abnormal brain images were documented as independent risk factors for 90-day mortality, which indicated that underlying diseases (Charlson comorbidity score) and severe inflammatory response either systemic or in subarachnoid space[14] (abnormal brain images) were important. On the other hand, HIV infection doesnot play a role in mortality at Day 30 and Day 90 in our cases, similar to the previous study by Jean et al.[28] But Ganiem et al.[29] reported that 1-month mortality was higher and strongly associated with HIV infection in adult meningitis, including cryptococcal meningitis, in Indonesia. This difference in mortality could be explained by the fact that patients with HIV-positive cryptococcal meningitis admitted at NTUH routinely receive repeated lumbar puncture to relieve increased intracranial pressure (IICP), as reported by Sun et al.[30]

As for management of cryptococcal meningitis, the duration of induction therapy with amphotericin B in HIV-infected and non−HIV-infected individuals was different (2 weeks *vs.* 4−6 weeks).[31] Beside, objective of treatment in either HIV-positive or HIV-negative cryptococcal meningitis could be different, too. In HIV-positive cryptococcal meningitis, control of elevated intracranial pressure, long-term control of infection, and resolution of clinical evidence of disease are the principal goals, although failing eradication of this infection is common in HIV disease. In HIV-negative cryptococcal meningitis, the goal of treatment includes both (1) cure of the infection (CSF sterilization) and (2) prevention of long-term CNS system sequelae, such as cranial nerve palsies, hearing loss, and blindness. In our cases, the information was not recorded because of its retrospective entity.

There were limitations in the present study. First, our study was a retrospective research by using secondary data source (patients' medical records). Usually there are missing data and misclassification in this kind of study. However, these factors would only make the results become more conservative. Second, not all patients were checked for HIV status because some patients died before they could be screened for HIV, and HIV screening is still not well accepted by Taiwanese. Third, flucytosine was not available at NTUH in the past 10 years, so it was not included in our study of its effect on mortality. Finally, it is

difficult to confirm those patients with infarctions were newly onset or old events because not all patients received diffusion-weighted imaging of MRI.

In summary, our study demonstrated that among patients with cryptococcal meningitis, those in HIV-positive group were younger, more likely to be male gender, more likely to have cough, more likely to have an initial serum LACT exceeding 1:512, more likely to have extraneural involvement, had higher Charlson comorbidity score, and less likely to have abnormal brain images than those in HIV-negative group. Altered mental status, extraneural involvement, absence of CSF lymphocyte predominance, and absence of leptomeningeal enhancement on brain images were independent risk factors for 30-day mortality. Serum white blood cell count of more than 11,000/μL, Charlson comorbidity score, and absence of normal brain images were documented as independent risk factors for 90-day mortality. Presence of HIV infection is not a risk factor for 30-day, 90-day, and in-hospital mortality of patients with cryptococcal meningitis.

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