# The Clinical Features and Therapeutic Outcomes of Young Adults with Cryptococcal Meningitis

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**Abstract**

***Objective:*** No previous study has reported on the clinical characteristics of cryptococcal meningitis (CM) focusing solely on young adults.

***Patients and methods:*** Ninety-nine adult patients with CM (64 men and 35 women) were enrolled, of whom 26 were classified into the young adult group (≤ 40 years) and 73 into the non-young adult group (> 40 years). The modified Rankin scale (mRS) was used to evaluate the outcomes of the survivors at the time of discharge and at 1 year of follow-up. The clinical characteristics and laboratory data between 1) the young adult CM patients with and without acquired immune-compromised syndrome and 2) the male and female young adult CM patients were compared. The prognostic factors of the young adult CM patients were also analyzed.

***Results:*** The young adult group had a higher incidence of headache as the clinical presentation which may have been due to the higher intracranial pressure in this group. The overall mortality rate of the young adults with CM was high (38.5%, 10/26), but no significant prognostic factors were found. In follow-up studies of the neurologic deficits, the young adult survivors had better outcomes (mRS scores = 0-2) than the non-young adult group at discharge and 1 year after discharge.

***Conclusion:*** The young adult CM patients had a higher incidence of headache as the clinical presentation. Although the mortality rate in the young adult CM patients was high, the survivors had better neurologic outcomes..

***Keywords:*** cryptococcal meningitis, young adult, AIDS, headache, therapeutic outcome, intracranial pressure.

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## INTRODUCTION

Many factors including age may influence the epidemiologic trend of central nervous system (CNS) infections, and this age-associated epidemiologic change has also been observed in different age groups with cryptococcal meningitis (CM) [1-5]. CM is a serious CNS infection caused by *Cryptococcus (C.) neoformans* [1,6], and

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because of its grave prognosis, CM has a severe economic impact on healthcare systems [6,7]. Because of the aging population worldwide, the health condition of young adults, who are the cornerstone of the family and society, has become more important. Young adults (≤ 40 years old) are considered to be more physically healthy than very young or old individuals. Many reports [1,5,6,8-10] have shown the clinical characteristics and therapeutic outcomes of CM, however no previous study has focused solely on the clinical characteristics of CM in young adults. In this study, we examined the clinical and laboratory features and therapeutic outcomes of young adults with CM in order to delineate the clinical characteristics of this specific group of CM patients.

## MATERIALS AND METHODS

***Patient enrollment***

We retrospectively reviewed the clinical manifestations, laboratory data and initial neuroimaging features of adult patients (> 18 years of age) with a new diagnosis of CM admitted to Kaohsiung Chang Gung Memorial Hospital during a 15-year study period (2002–2016). During this period, 99 adult patients with CM were identified, of whom 26 were classified into the young adult group (≤ 40 years of age) and the other 73 were classified into the non-young adult group (> 40 years of age). The therapeutic outcomes of these patients were evaluated at discharge and at 1 year using the modified Rankin scale (mRS) [11], with the results being defined as a good outcome (mRS score = 0-2) or a poor outcome (mRS score ≥ 3). This study was approved by the Ethics Committee of Kaohsiung Chang Gung Memorial Hospital (IRB No: 1608300002).

***Diagnostic criteria and management of CM***

In this study, CM was defined as either (1) isolation of *C. neoformans* in one or more cerebrospinal fluid (CSF) cultures, a positive CSF cryptococcal antigen titer, or positive CSF India ink staining and clinical features of meningitis; or (2) isolation of *C. neoformans* in a blood culture with clinical presentations of meningitis and typical CSF features [1,12]. The neuroimaging findings used for analysis were derived from initial cranial magnetic resonance imaging and/or cranial computed tomography studies as previously described [1]. During the study period, the main antifungal regimen was amphotericin B +/- flucytosine +/- fluconazole. Extra-ventricular drainage and/or ventriculo-peritoneal shunts were used to relieve hydrocephalus and/or increased intracranial pressure [1]. In the initial stage of management, most of the CM patients were treated in the intensive care unit to allow for better monitoring of neurological and medical conditions.

***Statistical analysis***

We performed four separate statistical analyses. First, we compared the clinical characteristics, laboratory data and neuroimaging findings between the young adult and non-young adult groups. Second, we compared the clinical characteristics and laboratory data between the young adult CM patients with and without acquired immune-compromised syndrome (AIDS). Third, we compared the clinical and laboratory features between the male and female young adult CM patients. Fourth, we investigated the potential prognostic factors for the young adult CM patients who survived and died. Categorical variables were analyzed using the chi-square test or Fisher's exact test, and continuous variables were analyzed using the t-test or Mann-Whitney U-test. In the first analysis, variables with a $P$ value < 0.05 were further analyzed using multivariate logistic regression analysis. The therapeutic results of the enrolled patients were divided into two groups: good outcome group (mRS score 0-2) and poor outcome group (mRS score ≥ 3). We also compared the therapeutic results at the time of discharge and after 1 year of follow-up between the survivors in the young and non-young adult groups using the Mann-Whitney U-test.

## RESULTS

***Demographic data of the 99 adult patients with CM***

Of the 99 included adult CM patients (64 men and 35 women), 26 were ≤ 40 years of age (young adult group) and 73 were > 40 years of age (non-young adult group). The clinical characteristics, laboratory findings and neuroimaging features of these 99 adult CM patients are listed in Table 1. The young adult group included 21 men and five women with a mean age of 30.58 years (range: 20-38 years).

***Underlying conditions and clinical presentations of the 26 young adults with CM***

AIDS was the most common underlying condition found in eight patients, followed by autoimmune disorders (3), hematologic disorders (2), diabetes mellitus (DM) (1), and liver cirrhosis (1). Headache was the most common clinical presentation in 23 patients, followed by fever [19], altered consciousness (8), seizure (7), visual disturbance (7), and hearing impairment (3).

***Comparative results***

Table 1 shows the comparative results of clinical

**Table 1.** Clinical characteristics, cerebrospinal fluid and neuroimaging data in young adult (≤40 years old) and non-young adult (> 40 years old) cryptococcal meningitis patients

| | ≤40 y/o (n=26) | >40 y/o (n=73) | *p*-value |
|---|---|---|---|
| Gender | | | |
| Male | 21 | 43 | |
| Female | 5 | 30 | 0.045 |
| Mortality at discharge | 10 | 23 | 0.547 |
| Underlying disease | | | |
| AIDS | 8 | 4 | 0.002 |
| Diabetes mellitus | 1 | 22 | 0.006 |
| Liver cirrhosis | 1 | 8 | 0.438 |
| Hematologic disorders | 2 | 10 | 0.727 |
| Autoimmune disorders | 3 | 7 | 0.720 |
| Malignancy | 0 | 9 | 0.107 |
| Chronic obstructive pulmonary disease | 0 | 5 | 0.322 |
| Adrenal insufficiency | 1 | 7 | 0.677 |
| Organ transplantation | 0 | 1 | 1.000 |
| Initial presentation | | | |
| Headache | 23 | 42 | 0.004 |
| Altered consciousness | 8 | 41 | 0.026 |
| Fever | 19 | 41 | 0.130 |
| Seizure | 7 | 8 | 0.063 |
| Visual disturbance | 7 | 9 | 0.119 |
| Hearing impairment | 3 | 3 | 0.184 |
| Cerebrospinal fluid (CSF) data | | | |
| Opening pressure of ICP ($mmH_2O$) | 290.00 | 200.00 | 0.013 |
| White blood cell count ($10^9$/L) | 0.12 | 0.08 | 0.598 |
| CSF/ blood glucose ratio | 0.248 | 0.273 | 0.728 |
| Protein (g/L) | 0.71 | 1.21 | 0.003 |
| Lactate (mmol/L) | 4.01 | 4.52 | 0.744 |
| Positive India ink stain | 12 | 19 | 0.018 |
| CSF Cryptococcus antigen titer (≥1: 1024) | 14 | 24 | 0.062 |
| Positive culture result | 22 | 55 | 0.104 |
| Serum Cryptococcus antigen titer (≥1: 1024) | 11 | 23 | 0.245 |
| Cryptococcemia | 13 | 17 | 0.011 |
| Extraneural involvement | 2 | 8 | 1.000 |
| Neuroimaging finding | | | |
| Basal meningeal enhancement | 10 | 24 | 0.880 |
| Pseudocyst/VRS dilatation | 5 | 27 | 0.089 |
| Hydrocephalus | 7 | 26 | 0.395 |
| Cerebral infarct | 2 | 12 | 0.505 |
| Cryptococcoma | 1 | 5 | 1.000 |

AIDS: acquired immunodeficiency syndrome; ICP= intracranial pressure; VRS: Virchow-Robin space

**Table 2.** Clinical and aboratory data and neuroimaging features of the young adult cryptococcal meningitis patients with or without AIDS

| | AIDS (n=8) | Without AIDS (n=18) | *p*-value |
|---|---|---|---|
| Gender | | | |
| Male | 8 | 13 | |
| Female | 0 | 5 | 0.281 |
| Mortality at discharge | 3 | 7 | 1.000 |
| Underlying disease | | | |
| Diabetes mellitus | 0 | 1 | 1.000 |
| Liver cirrhosis | 0 | 1 | 1.000 |
| Hematologic disorders | 0 | 2 | 1.000 |
| Autoimmune disorders | 0 | 3 | 0.529 |
| Adrenal insufficiency | 0 | 1 | 1.000 |
| Initial presentation | | | |
| Headache | 7 | 16 | 1.000 |
| Altered consciousness | 1 | 7 | 0.360 |
| Fever | 6 | 13 | 1.000 |
| Seizure | 1 | 6 | 0.375 |
| Visual disturbance | 2 | 5 | 1.000 |
| Hearing impairment | 0 | 3 | 0.529 |
| Cerebrospinal fluid (CSF) data | | | |
| Opening pressure of ICP (mmH2O) | 290.40 | 322.17 | 0.637 |
| White blood cell count (109/L) | 0.005 | 0.137 | 0.055 |
| CSF/ blood glucose ratio | 0.353 | 0.185 | 0.237 |
| Protein (g/L) | 0.51 | 0.84 | 0.024 |
| Lactate (mmol/L) | 2.90 | 5.55 | 0.011 |
| Positive India ink stain | 5 | 7 | 0.642 |
| CSF Cryptococcus antigen titre (≥1: 1024) | 6 | 8 | 0.388 |
| Positive culture result | 6 | 16 | 1.000 |
| Serum Cryptococcus antigen titre (≥1: 1024) | 5 | 6 | 0.035 |
| Cryptococcemia | 7 | 6 | 0.030 |
| Neuroimaging findings | | | |
| Basal meningeal enhancement | 2 | 8 | 1.000 |
| Pseudocyst/VRS dilatation | 0 | 5 | 0.281 |
| Hydrocephalus | 1 | 6 | 0.375 |
| Cerebral infarct | 1 | 1 | 1.000 |
| Cryptococcoma | 0 | 1 | 1.000 |

AIDS: acquired immunodeficiency syndrome; ICP= intracranial pressure; VRS: Virchow-Robin space

features and therapeutic outcomes between the young and non-young adult groups. The results showed that gender, AIDS, DM, the presence of headache, altered consciousness, opening intracranial pressure, level of CSF protein, presence of positive India ink stain, and presence of cryptococcemia were all potentially different between the two groups. However, after multivariate logistic regression analysis of these potential factors, only the presence of headache was significant ($P$ = 0.047, OR = 6.228; 95% CI = 1.028-37.739). Because eight of the 26 young adult CM patients had AIDS as the underlying condition, we compared clinical and laboratory data

**Table 3.** Clinical and laboratory data and neuroimaging features of the male and female young adults (≤40 years old) with cryptococcal meningitis

| | male (n=21) | female (n=5) | *p*-value |
|---|---|---|---|
| Mortality at discharge | 9 | 1 | 0.617 |
| Underlying disease | | | |
| AIDS | 8 | 0 | 0.281 |
| Diabetes mellitus | 1 | 0 | 1.000 |
| Liver cirrhosis | 1 | 0 | 1.000 |
| Hematologic disorders | 2 | 0 | 1.000 |
| Autoimmune disorders | 1 | 2 | 0.085 |
| Adrenal insufficiency | 0 | 1 | 0.192 |
| Initial presentation | | | |
| Headache | 20 | 3 | 0.085 |
| Altered consciousness | 8 | 0 | 0.281 |
| Fever | 16 | 3 | 0.588 |
| Seizure | 6 | 1 | 1.000 |
| Visual disturbance | 7 | 0 | 0.278 |
| Hearing impairment | 3 | 0 | 1.000 |
| Cerebrospinal fluid (CSF) data | | | |
| Opening pressure of ICP (mmH2O) | 285 | 290 | 0.432 |
| White blood cell count (109/L) | 0.12 | 0.012 | 0.208 |
| CSF/ blood glucose ratio | 0.302 | 0.164 | 0.786 |
| Protein (g/L) | 0.72 | 0.709 | 1.000 |
| Lactate (mmol/L) | 4.207 | 3.585 | 0.787 |
| Positive India ink stain | 11 | 1 | 0.553 |
| CSF Cryptococcus antigen titer (≥1: 1024) | 13 | 1 | 0.272 |
| Positive culture result | 18 | 4 | 0.217 |
| Serum Cryptococcus antigen titer (≥1: 1024) | 11 | 0 | 0.035 |
| Cryptococcemia | 12 | 1 | 0.322 |
| Extraneural involvement | 2 | 1 | 0.488 |
| Neuroimaging finding | | | |
| Basal meningeal enhancement | 9 | 1 | 1.000 |
| Pseudocyst/VRS dilatation | 3 | 2 | 0.236 |
| Hydrocephalus | 5 | 2 | 0.588 |
| Cerebral infarct | 2 | 0 | 1.000 |
| Cryptococcoma | 1 | 0 | 1.000 |

AIDS= acquired immune-deficiency syndrome; ICP= intracranial pressure; VRS= Virchow-Robin space

between the patients with and without AIDS (Table 2). The results showed that the patients with AIDS had lower CSF total protein and lactate levels, higher incidence of serum cryptococcal antigen level ≥ 1:1024, and cryptococcemia. However, none of these potential factors were significant in multivariate logistic regression analysis. There was a gender discrepancy among the 26 young adult CM patients, with a male:female ratio of 21:5. Table 3 shows the comparative results of clinical and laboratory features between the male and female young adults with CM. The results showed that the incidence of high serum cryptococcal Ag titer (> 1:1024) was different between the two groups.

***Therapeutic results and prognosis***

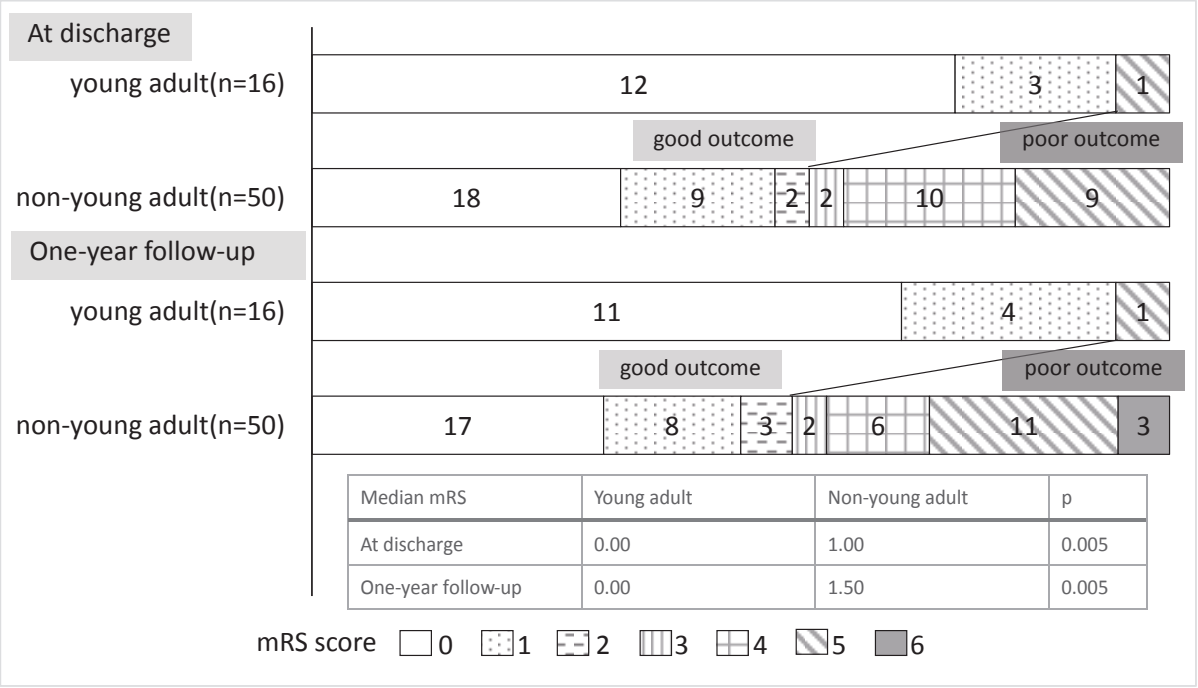
Despite treatment, 10 of the 26 young adult CM

**Table 4.** The prognostic factors of the young adult (≤ 40 years old) cryptococcal meningitis patients

| | Survived (n=16) | Expired (n=10) | *p*-value |
|---|---|---|---|
| Gender | | | |
| Male | 12 | 9 | |
| Female | 4 | 1 | 0.617 |
| Underlying disease | | | |
| AIDS | 5 | 3 | 1.000 |
| Diabetes mellitus | 0 | 1 | 0.385 |
| Liver cirrhosis | 0 | 1 | 0.385 |
| Hematologic disorders | 0 | 2 | 0.138 |
| Autoimmune disorders | 1 | 2 | 0.538 |
| Adrenal insufficiency | 1 | 0 | 1.000 |
| Initial presentation | | | |
| Headache | 14 | 9 | 1.000 |
| Altered consciousness | 3 | 5 | 0.189 |
| Fever | 11 | 8 | 0.668 |
| Seizure | 2 | 5 | 0.069 |
| Visual change | 3 | 4 | 0.369 |
| Hearing impairment | 1 | 2 | 0.538 |
| Cerebrospinal fluid (CSF) data | | | |
| Opening pressure of ICP (mmH2O) | 292.45 | 350.17 | 0.364 |
| White blood cell count (109/L) | 0.094 | 0.158 | 0.452 |
| CSF/ blood glucose ratio | 0.376 | 0.027 | 0.036 |
| Protein (g/L) | 0.69 | 0.76 | 0.928 |
| Lactate (mmol/L) | 3.47 | 6.45 | 0.006 |
| Positive India ink stain | 7 | 5 | 1.000 |
| CSF Cryptococcus antigen titre (≥1: 1024) | 8 | 6 | 0.678 |
| Positive culture result | 14 | 8 | 1.000 |
| Serum Cryptococcus antigen titre (≥1: 1024) | 7 | 4 | 1.000 |
| Cryptococcemia | 7 | 6 | 0.420 |
| Neuroimaging finding | | | |
| Basal meningeal enhancement | 8 | 2 | 0.628 |
| Pseudocyst/VRS dilatation | 1 | 4 | 0.055 |
| Hydrocephalus | 4 | 3 | 1.000 |
| Cerebral infarct | 1 | 1 | 1.000 |
| Cryptococcoma | 1 | 0 | 1.000 |

AIDS: acquired immunodeficiency syndrome; ICP= intracranial pressure; VRS: Virchow-Robin space

patients died. Analysis of the prognostic factors is shown in Table 4. The results showed that CSF/blood glucose ratio and CSF lactate level were potential factors, however none were significant in multivariate logistic regression analysis. The mRS scores of the 16 survivors in the young adult group and the 50 survivors in the non-young adult group at discharge are shown in Figure 1. Fifteen of the young adult CM survivors had a good outcome and one had a poor outcome at discharge and after 1 year of follow-up. With regards to the 50 non-young adult CM survivors, 21 had a poor outcome at discharge and 22 had a poor outcome (including three deaths) after 1 year of follow-up. Comparisons of the median mRS scores at discharge and 1 year after discharge between the young and non-young adult CM survivors all showed significant differences (Figure 1).




| Median mRS | Young adult | Non-young adult | p |
|---|---|---|---|
| At discharge | 0.00 | 1.00 | 0.005 |
| One-year follow-up | 0.00 | 1.50 | 0.005 |

**Figure 1.** The distribution of modified Rankin scale (mRS) scores of the survivors of young adult and non-young adult cryptococcal meningitis patients at discharge and at 1 year after discharge.

## DISCUSSION

The clinical features of CM are protean and may vary in different age groups of patients [1-5]. In China, the majority of pediatric CM patients have been reported to be apparently normal, with only 23.5% having identifiable underlying conditions [4]. *Joshi et al*.[3] and Likasitwattanakul *et al*. [6] reported pediatric cryptococcosis in both HIV-negative and HIV-positive patients, however other immunocompromising medical conditions are usually seen in HIV-negative patients. We recently investigated CM in elderly adults [7], and found that the elderly CM patients were predominantly female, had higher rates of altered consciousness and acute/subacute cerebral infarction as the clinical presentation, and the presence of cryptococcemia as the significant prognostic factor.

In the current study, 80.8% (21/26) of the young adult CM patients were male, which is higher than that (58.9%, 43/73) of the non-young adult CM patients. This male predominance in the young adult CM patients is in contrast to the female predominance in the elderly CM patients in our recent study [7]. Compared with the epidemiologic trend of CM in Western countries [13] in which being HIV-positive is the most common cause of CM, most adult patients with CM in Taiwan are not HIV-positive [1,14]. In the current study, 30.8% (8/26) of the young adult CM patients had AIDS as the underlying condition compared to only 5.5% (4/73) of the non-young adult CM patients. This finding is consistent with the study by Liao et al. [14] who reported that HIV seropositive CM patients in Taiwan were usually young males, and this finding is also consistent with that of the study by Lee et al. in which CM was found to occur more frequently in young and male populations who were HIV-positive [15]. Nevertheless, in the current study, there were no significant differences in the clinical characteristics and laboratory findings between the young adult CM patients with and without AIDS (Table 2). As shown in Tables 2 and 3, none of the five female young adult CM patients was HIV-positive, and none of the female patients had a serum cryptococcal Ag titer > 1:1024, which is an important prognostic factor

of CM [16,17]. DM is an important and rapidly growing medical disorder in Taiwan [18], and 10.9% of adults have been reported to have DM [19]. In the current study, 30.1% (22/73) of the non-young adult CM patients had DM as the underlying condition, which is higher than that (3.85%, 1/26) of the young adult CM patients. Nevertheless, there were no significant differences in the presence of DM between the two groups of adult CM patients (Table 1).

Headache is an important clinical manifestation as well as an important prognostic factor of CM [1,20-22]. In the current study, headache was a significant factor to differentiate the two groups of adult CM patients, with a higher incidence in the young adult group. In CM, increased intracranial pressure is an important cause of headache and may influence the therapeutic outcome [23,24]. It is well known that there is a significant age-associated decrease in brain volume [25,26]; therefore it is possible that the younger patients with CM had a greater increase in intracranial pressure assuming that the volume of the intracranial space was fixed. Although the difference in opening pressure did not reach statistical significance, it was higher in the young adult CM group than in the non-young adult group, which may have resulted in a higher incidence of headache. In our previous study of geriatric CM patients, we found that the elderly CM patients had a lower incidence of headache as the clinical presentation [7]. This difference in the incidence of headache in different age groups of adult CM patients may imply that older CM patients have a lower incidence of headache as the clinical presentation and younger CM patients have a higher incidence of headache as the clinical presentation.

As shown in Table 1, the most common clinical manifestations in the young adult CM patients were headache, altered consciousness and fever, which is similar to the non-young adult CM patients and to other CNS infectious diseases such as bacterial meningitis in adults [27]. Patients with CM usually have a subacute or chronic onset of clinical presentations, however none of these clinical features are unique, and therefore the diagnosis of CM can only be confirmed by positive culture results of clinical specimens and/or an elevated CSF cryptococcal antigen titer regardless of the age of the patients.

In the current study, the mortality rate of the young adult CM patients was 38.5% (10/26), which is higher than that (31.6%, 23/73) of the non-young adult group, but the difference did not reach statistical significance. Among the young adult group, no significant prognostic factors were found for the prediction of mortality. Despite the higher mortality rate in the young adult CM group, unlike the non-young adult CM patients who survived, the young adult CM patients who survived at discharge had a better clinical outcome, and this better outcome was also noted 1 year after discharge from the hospital (Figure 1). This better clinical outcome of the young adult group of CM patients may be explained by the finding that the non-young adult group of CM patients had more medical comorbidities, even though this difference was not significant.

## CONCLUSIONS

This is a preliminary study of clinical characteristics, therapeutic outcome and therapeutic result of this specific group CM patients. Compared with the non-young adult CM patients, the young adult CM patients had a significantly higher incidence of headache as the clinical manifestation, which may have been related to a higher intracranial pressure in this group of patients. Although there were differences in the underlying condition and mortality rate, these factors did not show statistical significance between the young and non-young adult groups of CM patients. However, the therapeutic and follow-up results showed that the young adult CM patients who survived had a better clinical outcome at discharge and after 1 year of follow-up compared to the non-young adult patients who survived. This is a preliminary study of the clinical characteristics and therapeutic outcomes of young adult CM patients. Because of the limitation of the small number of cases, further large-scale studies are needed to better delineate this specific group of patients.

**Declaration of conflict of interest statement**

The authors declare that they have no conflict of interest.

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## REFERENCES


1. Tsai WC, Lien CY, Lee JJ, Lin WC, Hsu CW, Huang CR, Tsai NW, Chang CC, Lu CH, Chang WN. The prognostic factors of HIV-negative adult cryptococcal meningitis with a focus on cranial MRI-based neuroimaging findings. J Clin Neurosci 2018;55:57-61.
2. Mourad A, Perfect JR. Present and future therapy of cryptococcal infections. J Fungi (Basel) 2018;4:pli. E33
3. Charalambous LT, Premji A, Tybout C, Hunt A, Cutshaw D, Elsamadicy AA, Yang S, Xie J, Giamberardino C, Pagadala P, Perfect JR, Lad SP. Prevalence, healthcare resource utilization and overall burden of fungal meningitis in the United States. J Med Microbiol 2018;67:215-227.
4. Guo LY, Liu LL, Liu Y, Chen TM, Li SY, Yang YH, Liu G. Characteristics and outcome of cryptococcal meningitis in HIV seronegative children in Beijing, China, 2002-2013. BMC Infect Dis 2016;16:635.
5. Joshi NS, Fisher BT, Prasad PA, Zaoutis TE. Epidemiology of cryptococcal infection in hospitalized children. Pediatr Infect Dis J 2010;29:e91-95.
6. Likasitwattanakul S, Poneprasert B, Sirisanthana V. Cryptococcosis in HIV-infected children. Southeast Asian J Trop Med Public Health 2004;35:935-939.
7. Tsai WC, Lien CY, Lee JJ, Hsiao WC, Huang CR, Tsai NW, Chang CC, Lu CH, Chang WN. The clinical characteristics and therapeutic outcomes of cryptococcal meningitis in elderly patients: a hospital-based study. BMC Geriatrics 2019; 19:91.
8. Lawrence DS, Boyer-Chammard T, Jarvis JN. Emerging concepts n HIV-associated cryptococcal meningitis. CurrOpin Infect Dis 2019;32:16-23.
9. Nyazika TK, Tatuene JK, Kenfak-Foguena A, Verweij PE, Meis JF, Robertson VJ, Hagen F. Epidemiology and aetiologies of cryptococcal meningitis in Africa, 1950-2017: protocol; for a systematic review. BMJ Open 2018;8:e020654.
10. Henao-Martinez AF, Chastain DB, Franco-Paredes C. Treatment of cryptococcosis in non-HIV immunocompromised patients. Curr Opin Infect Dis 2018;31:278-285.
11. Farrell B, Godwin J, Richards S. The United Kingdom transient ischemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044-1054.
12. Chang WN, Lu CH, Chang HW, Lui CC, Tsai NW, Huang CR, Wang HC, Chuang YC, Chen SF, Chang CC. Time course of cerebral hemodynamics in cryptococcal meningitis in HIV-negative adults. Eur J Neurol 2007;14:770–776.
13. Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol 2017; 13: 13-24.
14. Liao CH, Chi CY, Wang YJ, Tseng SW, Chou CH, Ho CM, Lin PC, Ho MW, Wang JH. Different presentations and outcomes between HIV-infected and HIV-uninfected patients with cryptococcal meningitis. J Microbiol Immuno Infect 2012;45:296-304.
15. Lee YC, Wang JT, Sun HY, Chen YC. Comparisons of the clinical features and mortality of cryptococcal meningitis between patients with and without human immunodeficiency virus infection. J Microbiol Immunol Infect 2011; 44: 338-345.
16. Anekthananon T, Manosuthi W, Chetchotisakd P, Kiertiburanakul S, Supparatpinyo K, Ratanasuwan W, Pappas PG, Filler SG, Kopetskie HA, Nolen TL, Kendrick AS, Larsen RA; BAMSG 3-01 Study Team. Predictors of poor clinical outcome of cryptococcal meningitis in HIV-infected patients. Int J STD AIDS 2011; 22: 665-670.
17. Qu J, Zhou T, Zhong C, Deng R, Lü X. Comparison of clinical features and prognostic factors in HIV-negative adults with cryptococcal meningitis and tuberculous meningitis: a retrospective study. BMC Infect Dis 2017; 17: 51.
18. Jiang YD, Chang CH, Tai TY, Chen JF, Chuang LM. Incidence and prevalence rates of diabetes mellitus in Taiwan: analysis of the 2000-2009 nationwide health insurance database. J Formosan Med Assoc 2012;111:599-604.
19. https://www.idf.org/our-network/regions-members/western-pacific/members/114-taiwan.html
20. de Azambuza AZ, WissmannNeto G, Watte G, Antoniolli L, Goldani LZ. Cryptococcal meningitis; a retrospective cohort of a Brazilian reference hospital in the post-HAART era of universal access. Can J

Infect Dis Med Microbiol 2018; 2018: 6512468.
21. Graybill JR, Sobel J, Saag M, van Der Horst C, Powderly W, Cloud G, Riser L, Hamill R, Dismukes W. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis 2000;30:47-54.
22. Chen CH, Sy HN, Lin LJ, Yen HC, Wang SH, Chen WL, Chen YM, Chang YJ: Epidemiological characterization and prognostic factors in patients with confirmed cerebral cryptococcosis in central Taiwan. J Venom Anim Toxins Incl Trop Dis 2015;21:12.
23. Liliang PC, Liang CL, Chang WN, Lu K, Lu CH. Use of ventriculoperitoneal shunts to treat uncontrollable intracranial hypertension in patients who have cryptococcal meningitis without hydrocephalus. Clin Infect Dis 2002; 34: e64-68.
24. Liu L, Zhang R, Tang Y, Lu H. The use of ventriculoperitoneal shunts for uncontrollable intracranial hypertension in patients with HIV-associated cryptococcal meningitis with or without hydrocephalus. Biosci Trends 2014; 8: 327-332.
25. Scahill RI, Frost C, Jenkins R, Whitewell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Arch Neurol 2003; 60: 989-994.
26. Peters R. Ageing and brain. Postgrad Med J 2006; 82: 84-88.
27. Lien CY, Huang CR, Tsai WC, Hsu CW, Tsai NW, Chang CC, Lu CH, Chien CC, Chang WN. Epidemiologic trend of adult bacterial meningitis in southern Taiwan. J Clin Neurosci 2017; 42: 59-65.