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REVIEW ARTICLE

Long-term Mortality and Disability in Cryptococcal Meningitis: A Systematic Literature Review

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Cryptococcal meningitis (CM) is the primary cause of meningitis in adults with human immunodeficiency virus (HIV) infection and an emerging disease in HIV-seronegative individuals. No literature review has studied the long-term outcome of CM. We performed a systematic review on the long-term (≥3-month) impact of CM (*Cryptococcus neoformans* and *Cryptococcus gattii*) on mortality and disability in HIV-infected and non–HIV-infected adults. Although the quality of current evidence is limited, the long-term impact of CM on survival and disability seems to be high. One-year mortality ranged from 13% in an Australian non–HIV-infected *C. gattii*–infected cohort to 78% in a Malawian HIV-infected cohort treated with fluconazole monotherapy. One-year impairment proportions among survivors ranged from 19% in an Australian *C. gattii* cohort to >70% in a Taiwanese non–HIV- and HIV-infected cohorts. Ongoing early therapeutic interventions, early detection of impairments and access to rehabilitation services may significantly improve patients' survival and quality of life.

Keywords. cryptococcal meningitis; long-term outcome; mortality; disability; risk factors.

Cryptococcal meningitis (CM) is a leading cause of meningitis in many low- and middle-income countries (LMICs), where it accounts for 15%–20% of all human immunodeficiency virus (HIV)–related deaths [1]. Despite the expansion of antiretroviral therapy (ART) programs, rates of CM remain high, because many HIV-infected persons begin ART late and face difficulties maintaining effective treatment [2]. Moreover, sustainable access to the current reference induction treatment, flucytosine (5-FC) and amphotericin B (AmB), is a major challenge in these settings [3]. Fluconazole monotherapy is the only alternative but is associated with higher short-term mortality, even at high dosages [4]. Consequently, CM mortality remain high in LMICs, ranging from 22% to 96% [5, 6] at 10–12 weeks. In contrast, it has been estimated to range from 9% to 15% in Western Europe and North America [7, 8].

In addition, a growing number of CM-associated deaths occur in non-HIV patients in high-income countries (HICs) [9]. CM caused by *Cryptococcus neoformans,* is increasingly observed among patients with non-HIV immunosuppression [9]. In parallel, *Cryptococcus gattii* CM, endemic in Australia, appeared recently as an outbreak in North America, mainly among patients without apparent immunosuppression (up to 72% of cases). Mortality outcomes for non–HIV-associated CM (non-HIV-CM) seem to be no better than those for HIV-associated CM (HIV-CM) in similar settings [9].

Beyond mortality, CM survivors may experience long-term (≥3 months after CM diagnosis) neurological and sensorial impairment, resulting in disability and poor quality of life [7, 10].

However, data on long-term outcomes in CM remain scarce [11, 12]. Indeed, while short-term mortality for HIV-CM has been well reviewed [8, 9, 13, 14], literature reviews including longer-term overall cryptococcosis mortality are limited [9, 14], and none have reported on long-term CM-related neurosensorial impairment and disability.

To address this gap, we exhaustively reviewed published data on the long-term mortality, impairment, and disability associated with CM caused by *C. neoformans* or *C. gattii* in either immunodeficient or immunocompetent adults. We addressed the following questions: What are the proportions/rates and predictive factors for death occurring ≥3 months after CM diagnosis or treatment induction? What are the nature, frequency, and predictive factors for CM sequelae/impairment, disability and decreased quality of life ≥3 months after CM treatment induction? Finally, are there differences in ≥3-month prognosis between HIV-infected and non-HIV infected patients?

METHODS

This systematic review was conducted in line with the PRISMA Statement [15].

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Search Strategy and Study Selection

PubMed/Medline, Web of Science, Cochrane Library, Embase, Global Health, LILACS and World Health Organization (WHO) online libraries were searched for studies published in English, French, or Spanish between 1 January 2005 and 30 June 2015 (Figure 1). The search combined 2 groups of words, including synonyms and MeSH terms for "cryptococcal meningitis" (group 1) and "outcome and risk factors" (group 2) (see Supplementary Table S1).

All types of study design were considered for eligibility. Studies were included if they fulfilled the following criteria: (1) reporting the mortality rate/proportion and/or the proportion of sequelae/impairments/disability occurring ≥3 months after CM diagnosis or after induction treatment, (2) participants ≥18 years-old, and (3) documented first episode of CM diagnosis based on positive india ink and/or positive cryptococcal antigen (CrAg) results and/or positive culture (*C. neoformans* or *C. gattii*), in cerebrospinal fluid (CSF). Both immunodeficient and apparently immunocompetent patients were considered. Studies on cryptococcomas without CM and studies where CM data could not be individualized from other causes of meningitis were excluded. Additional studies were manually searched for from reference lists of all identified articles.

Quality Assessment

The quality of the selected studies was assessed at outcome level [15] using the Critical Appraisal Skills Programme (CASP) tools [16]. Three domains were assessed: (1) validity: appropriate design, appropriate sampling methods, risk of bias and confounding; (2) importance: effect size, power, precision of study; and (3) comparability/generalizability. Studies that fulfilled >70% of criteria were considered of good quality and those that fulfilled <50% of CASP criteria were excluded for providing weak evidence.

Data Extraction and Synthesis

For each study included, the following data were extracted: (1) study characteristics (setting, design, sample size, statistical method used, potential bias and confounding), (2) participant characteristics (eligibility criteria; age; sex; immunological, mental and ART status at diagnosis; timing of ART initiation), (3) *Cryptococcus* species, (4) outcome (mortality proportion/rate, impairments/disability proportion, and quality of life) stratified by outcome timing (6, 12, and >12 months after diagnosis), and (5) predictive factors (age, immunological status, viral load, CSF characteristics, clinical presentation, mental and ART status at diagnosis, antifungal and ART treatment received, adjunctive therapy, setting, *Cryptococcus* species, occurrence of immune reconstitution inflammatory syndrome (IRIS), opportunistic coinfections/affections).

Quality assessment of included studies showed high heterogeneity; we therefore decided to undertake a qualitative synthesis rather than a meta-analysis, which included describing the studies and their results and limitations without pooling estimates. Further synthesis of the results was done with predefined subgroups by patients' immunological status (HIV infected or non–HIV infected).

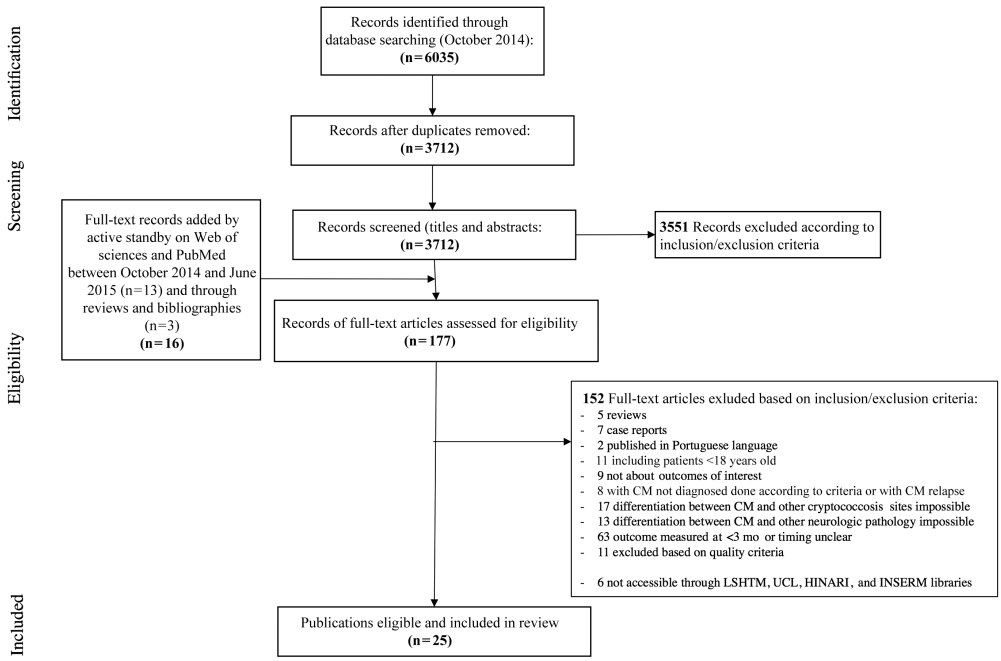

Figure 1. Flow diagram of the articles inclusion/exclusion process (inspired by PRISMA 2009 flow diagram [15]). Abbreviations: CM, cryptococcal meningitis; INSERM: Institut National de la Santé et de la Recherche Médicale (France); LSHTM, London School of Hygiene and Tropical Medicine; UCL, University College London.

Table 1. Overview of the 25 Articles Included in this Review

	Article	Setting	Design	Sample size - number	Mean Age (except when mentioned) – years (IQR)	Information on		
						Mortality	Sequelae/Impairments	Disability/quality of life
HIV-CM								
1	Bicanic (2008)[19]	LMIC (South Africa)	RCT	64 (30 in AmB 0.7mg arm, 34 in AmB 1 mg arm)	33 (28–38)	x		
2	Day (2013)[11]	LMIC (Vietnam)	RCT	298 (99 in AmB arm, 100 in AmB+5-FC arm, 99 in AmB+Fluconazole arm)	Median: 28 (24–31) (Children 14–18 years old included)	x		x
3	Makadzange (2010)[28]	LMIC (Zimbabwe)	RCT	54 (28 in early ART arm and 26 in late ART arm)	37 +/-7.7	x		
4	Boulware (2014)[20]	LMIC (South Africa) LMIC (Uganda)	RCT	177 (88 in early ART arm and 89 in late ART arm)	Median: Early ART: 35 (28–40) Late ART: 36 (30–40)	x		
5	Kambugu (2008)[18]	LMIC (Uganda)	PC	44	36 (31–42)	x		
6	Bicanic (2007)[26]	LMIC (South Africa)	PC	54 (36 ART Naïve, 18 ART experienced)	34 (29–39)	x		
7	Bicanic (2009)[29]	LMIC (South Africa)	PC	100 (65 survived for analysis on IRIS: 11 in IRIS arm and 54 in non-IRIS arm))	NA	x		
8	Boulware (2010)[30]	LMIC (Uganda)	PC	101 (56 in IRIS arm, 45 in non-IRIS arm)	NA	x		
9	Butler (2012)[17]	LMIC (Uganda)	PC	189	36.2 (SD +/-8.8)	x		
10	Rothe (2013)[27]	LMIC (Malawi)	PC	60	Median: 32 (29–39)	x		
11	Chaiwarith (2014)[25]	LMIC (Thailand)	RC	79	35.1 +/-7.2	x		
12	Carlson (2014)[33]	LMIC (Uganda)	PC	78	35 +/-8		x	x
13	Lizarazo (2012)[36]	LMIC (Columbia)	RC	63	34 +/-9.2	x	x	
14	Jarvis (2014)[21]	LMIC (South Africa)	PC	263	Median: 34 (29–39)	x		
15	Lanoy (2011)[22]	HIC (France)	PC	1020	<30y: 16% 30–40: 50% 40–50: 24% >50: 11%	x		
16	Mathiesen (2012)[24]	HIC (Denmark)	RC	45	40 (33–46)	x		
17	Cachay (2010)[42]	HIC (USA)	RC	82	38 (19–57)	x		

Table 1. *Continued*

	Article	Setting	Design	Sample size (number)	Age (years)	Information on		
						Mortality	Sequelae/Impairments	Disability/quality of life
HIV and non-HIV-CM								
18	Liao (2012)[23]	HIC (Taiwan)	RC	*HIV:* 19 72 *non-HIV:* 53	*HIV:* 33.3 +/-7.4 *non-HIV:* 55.3 +/-15.7	x	x	
19	Lee (2011)[37]	HIC (Taiwan)	RC	*HIV:* 37 88 *non-HIV:* 51	*HIV:* 38.19 +/-12.12 *non-HIV:* 59.57 +/-14.17	x		
Non-HIV-CM								
20	Zhu (2010)[32]	LMIC (China)	RC	154	Median: 38.5	x		
21	Wang (2005)[35]	HIC (Taiwan)	PC	26	No Hearing loss group: 47 +/-21 Hearing loss group: 57 +/-17		x	
22	Phillips (2015)[34] (*C. gattii*)	HIC (British Columbia, Canada)	RC	47	Median: 50 (range 21–89)	x	x	
23 and 24	Chen (2012)[12] and (2013)[31] (*C. gattii*)	HIC (Australia)	RC	73	NA	x	x	
25	Sun (2009)[51]	HIC/MIC (USA, France, Spain, Canada, India)	PC	75	51.5 (43–60)	x		

Abbreviations: AmB, amphotericin B; ART, antiretroviral therapy; HIC, high income countries; HIV, human immunodeficiency virus; HIV-CM, human immunodeficiency virus-associated cryptococcal meningitis; IQR, interquartile range; IRIS, immune reconstitution inflammatory syndrome; LMIC, low and middle income countries; MIC, middle-income country; NA, Non Available; PC, prospective cohort; RC, retrospective cohort; RCT, randomized control trial; SD, standard deviation.

RESULTS

Study Characteristics

Of the 6035 records identified during the study period, 177 were selected for full-text review, and 25 articles (24 studies: 4 randomized controlled trials [RCTs], 11 prospective cohort studies, and 9 retrospective cohort studies) were eventually retained (Figure 1) [11, 12 17–39]. Only 1 of the studies [11] was included despite not fulfilling the inclusion criteria, because it provided key results on disability. Twenty-one studies provided information on mortality outcomes, 6 on impairments, 2 on disability, and none on quality of life. All continents were represented, with 15 studies from LMICs and 9 from HICs. Only 6 studies (25%) fulfilled ≥70% of quality criteria: 2 RCT and 4 cohort studies (Table 1).

Long-term Mortality and Predictive Factors

In HIV-CM, 17 articles provided information on CM mortality outcome (5 from HICs and 12 from LMICs), and 10 examined risk factors (Table 2). Five articles (28%) fulfilled ≥70% of quality criteria. Available data suggest that the high mortality rate in the first 10 weeks of treatment continues to rise slowly, leveling off after 6 months of treatment [11–17]. However, evidence was weak, with few studies and difference in CM management across studies. Two studies using survival analysis showed that with the use of both AmB-based combination therapy and appropriately timed ART, the survival curve strongly flattens after 3 months [20, 21]. There was important variation in the 1-year mortality according to both setting and period: in HICs, the mortality was about 50% in the pre-ART period [22] and 20% in the late ART period [22–24], whereas it ranged from 39.5% to 78% in LMICs [17–21, 25–27]. The 1-year mortality also varied according to the induction treatment received, with fluconazole performing worse than AmB monotherapies, which, in turn, performed worse than AmB-based combined therapy (Figure 2). Nevertheless, even with the latter, the 1-year mortality was about 40% [19, 20] in LMICs and about 20% [22–24] in HICs. Other protective factors included the use of ART, as shown in France [22] and Denmark [24], and, in ART-naive patients, delaying the introduction of ART to 5–10 weeks after induction therapy compared with an introduction between 3 days and 2 weeks [20, 28]. In LMICs, the 1-year mortality observed in patients with aggressive management of intracranial pressure was lower than in those without such management (40% [19, 20] vs 59% [18], respectively).

In HIV-CM, the main independent risk factors for long-term mortality were altered neurological status [11, 25], low CD4 cell count [23], high CSF fungal/CrAg burden [11, 25], and older age [24] at diagnosis (Table 3). Finally, the association between IRIS and higher long-term mortality is still unclear [20, 29, 30] with only 1 study of the 3 that addressed this question showing a significant association [30]. This may result from the small study sizes or from the IRIS definition adopted, which may miss early IRIS, leading to an ascertainment bias, as suggested by Boulware et al [20].

In non-HIV-CM, evidence on long-term mortality is weaker; only 6 articles were identified (including none from LMICs), and none fulfilled ≥70% of quality criteria (Table 4). One-year mortality ranged from 13.7%, in an Australian cohort infected by C. *gattii* with underlying conditions in only 28% of patients [12, 31] to 42.3%, in a Taiwanese study with underlying conditions in all patients [23]. Non–HIV-CM mortality may continue to rise after 3 months, as suggested by data from Liao et al [23].

The main independent risk factors for 1-year mortality in non–HIV-infected patients were delayed diagnosis [32], age >60 years [32], altered initial neurological status [23, 32], high CSF CrAg level [23] and non–AmB-based versus AmB-based induction therapy [32, 39] (Table 5). In patients with *C. gattii* CM, only high CSF CrAg levels were found to be independently associated with 1-year mortality [12].

Long-term Neurosensorial Impairments and Disability and Their Predictive Factors

Seven studies provided evidence on neurosensorial impairment and disability (3 for HIV-CM and 4 for non–HIV-CM), and only 1 fulfilled ≥70% of quality criteria [33] (Supplementary Table S2).

In HIV-CM, up to 69.2% of survivors from a Taiwanese cohort had neurosensorial sequelae 1 year after diagnosis [23] mainly residual headache (38%), motor deficit (15%), and vertigo (15%). In a Ugandan study, cognitive function remained impaired in 41% of survivors, although the contribution of HIV encephalitis should also be questioned [33].

Only 2 studies assessed long-term disability related to HIV-CM [11, 33], and none used the WHO International Classification of Functioning definition [10]. In the clinical trial reported by Day et al [11], 40% of the survivors reported having some form of "disability" at 6 months, and in the cohort study reported by Carlson et al [33], 11% of survivors declared themselves unable to work at 1 year.

Few predictive factors of long-term impairments and disability were found. Carlson et al [33] demonstrated that the risk of 12-month impaired cognition was increased in HIV-CM patients with lower CD4 cell counts at induction. Paradoxically, persons with sterile CSF cultures after 14 days of AmB therapy had worse neurocognitive outcomes than those who were still culture positive. At 6 months, Day et al demonstrated that patients treated with AmB plus 5-FC were half as likely to report a disability as patients treated with AmB monotherapy [11].

In non-HIV CM, findings were heterogeneous. In 2 cohorts of patients infected with *C. gattii* without underlying conditions, the rates of neurosensorial sequelae among 1-year survivors were between 19% and 24% [12, 34]. This proportion reached 73.3% in a cohort of patients with underlying conditions (*Cryptococcus* species not known) [23]. The main

Table 2. Long-term Mortality in Human Immunodeficiency Virus–Associated Cryptococcal Meningitis

Study	Setting	Design	Sample Size, No.	*Cryptococcus gattii* or *Cryptococcus neoformans*	Mortality Rate (SA) or Proportion (PD), %, (No./Total) or (95% Confidence Interval)[a]	Quality Score, %[b]
>3 to 4 mo after diagnosis or induction treatment						
Liao et al (2012) [23]	HIC (Taiwan)	RC	19	No data	5.3 (1/19) (PD; d90)	54
Lee et al (2011) [37]	HIC (Taiwan)	RC	37	No data	29.7 (11/37) (PD; d90)	58
Chaiwarith et al (2014) [25]	LMIC (Thailand)	RC	79	*C. neoformans* (92%)	32.4 (24/74) (PD; d90)	65
Lizarazo et al (2012) [36]	LMIC (Columbia)	RC	63	*C. neoformans*	54 (SA; d120)	50
6 mo after diagnosis or induction treatment						
Cachay et al (2010) [38]	HIC (United States)	RC	82	No data	6.1 (5/82) (PD)	64
Bicanic et al (2008) [19]	LMIC (South Africa)	RCT	64	No data	32 (PD)	55
Boulware et al (2014) [20]	LMICs (South Africa and Uganda)	RCT	177	No data	37.9 (67/177) (PD)	82
Day et al (2013) [11]	LMIC (Vietnam)	RCT	298	*C. neoformans*	45 (132/291) (PD)	82
Butler et al (2012) [17]	LMIC (Uganda)	PC	189	No data	52 (95% CI, 45–59) (SA)	58
Bicanic et al (2009) [29]	LMIC (South Africa)	PC	100	No data	53 (53/100) (PD)	54
Kambugu et al (2008) [18]	LMIC (Uganda)	PC	44	No data	59.1 (26/44) (PD)	73
1 y after diagnosis or induction treatment						
Lanoy et al (2011) [22]	HIC (France)	PC	1020	No data	50 (95% CI, 45–54) (SA) during pre-cART period (1992–1995); 24 (18–29) (SA) during early cART period (1996–1998); 17 (12–22) (SA) during late cART period (1999–2004)	64
Liao et al (2012) [23]	HIC (Taiwan)	RC	19	No data	22.2 (4/18) (PD)	54
Mathiesen et al (2012) [24]	HIC (Denmark)	RC	45	No data	44.2 (SA) during full period (1988–2008); 23 (SA) during cART period (1997–2008)	81
Boulware et al (2010) [30]	LMIC (Uganda)	PC	101	No data	27.7 (28/101); deaths in 1st week excluded (PD)	77
Boulware et al (2014) [20]	LMICs (South Africa and Uganda)	RCT	177	No data	39.5 (70/177) (PD)	82
Bicanic et al (2008) [19]	LMIC (South Africa)	RCT	64	No data	40 (PD)	55
Jarvis et al (2014) [21]	LMIC (South Africa)	PC	263	No data	41 (PD)	57
Chaiwarith et al (2014) [25]	LMIC (Thailand)	RC	79	No data	52.2 (36/69) (PD)	65
Butler et al (2012) [17]	LMIC (Uganda)	PC	189	No data	55 (95% CI, 48-62) (SA)	58
Kambugu et al (2008) [18]	LMIC (Uganda)	PC	44	No data	59.1 (26/44) (PD)	73
Bicanic et al (2007) [26]	LMIC (South Africa)	PC	54	No data	64.7 (33/51) (PD)	69
Rothe et al (2013) [27]	LMIC (Malawi)	PC	60	No data	78 (95% CI, 64–86) (SA)	69

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; d90, day 90 after diagnosis or induction treatment; d120, day 120 after diagnosis or induction treatment; HIC, high-income country; HIV-CM, human immunodeficiency virus–associated cryptococcal meningitis; LMIC, low- or middle-income country; PC, prospective cohort; PD, percentage of deaths; RC, retrospective cohort; RCT, randomized controlled trial; SA, survival analysis.

[a]Mortality expressed as PD at the time point (those lost to follow-up excluded when known) or as SA (probability of death at a time point, those lost to follow-up censored). Parenthetical numbers represent No./total when mortality is expressed as PD and provided, or 95% confidence intervals when mortality is expressed as SA and provided.

[b]Quality score : percentage of quality criteria of the Critical Appraisal Skills Program (CASP) tools that are fulfilled by the study [16].

impairments were vertigo (13%–24%), visual loss (13%–23%), hearing impairment (6%–17%), and motor deficit (3%–16%). Sylvian fissure enhancement seen with magnetic resonance imaging and CSF CrAg titers >1/256 at induction were, respectively, independently associated with hearing loss in any non-HIV-CM [35], and neurological sequelae in *C. gattii* cohorts [12].

Comparison Between HIV-CM and Non-HIV-CM

The 3 studies comparing long-term mortality between HIV-CM and non-HIV-CM [23, 36, 37] gave contradictory results. Nevertheless, valid comparisons are prevented by the studies' heterogeneity in terms of proportions of ART-naive patients for HIV-CM and proportions of patients with underlying conditions for non-HIV-CM.

DISCUSSION

Long-term Impact of CM on Mortality, Impairment, and Disability

To our knowledge, this is the first literature review focusing on long-term outcomes of CM, including death, neurosensorial impairment, and disability. Our review shows that the mortality

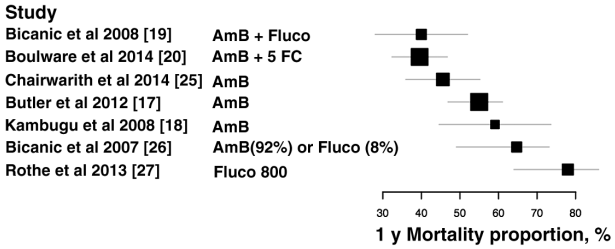

Figure 2. Forest plot of 1-year mortality proportions in human immunodeficiency virus (HIV)–associated cryptococcal meningitis (CM) according to induction therapy received. Four studies are excluded from this forest plot. One is the 2010 study by Boulware et al [30], in which the mortality rate is probably underestimated; the patients were included after antiretroviral therapy initiation at a median of 34 days (interquartile range, 24–41 days) after CM diagnosis, missing all deaths occurring during the first weeks. The studies by Lanoy et al (2011) [22], Liao et al (2012) [23], and Mathiesen et al (2012) [24] were omitted because no information was available or extractable for the treatment received by the HIV-infected patients or for the dichotomized periods. In the 2007 study by Bicanic et al [26], 92% of patients were treated with amphotericin B monotherapy, and 8% of patients were treated with fluconazole monotherapy. 5-FC, flucytosine; AmB, amphotericin B; Fluco, Fluconazole.

can reach 78% in HIV-CM [27] and 42% in non-HIV-CM [23] at 1 year. In addition, regardless of the species studied (*C. neoformans*, *C. gattii*), we found supportive evidence for an important long-term burden of CM on impairments and disability, with proportions reaching up to 70% in both HIV-infected and non–HIV-infected survivors [23]. These findings demonstrate that the long-term prognosis of CM in adults may be at least as poor as that associated with other causes of encephalitis in France (33% with impairment at 3 years) [40] or with tuberculosis meningitis (mortality, 20%–60%; impairment among survivors, 20%–50%) [41, 42].

Prevention of Risk Factors for Long-term Adverse CM Outcomes

Evidence regarding risk factors for long-term outcomes was limited, showing an important gap in knowledge. Each risk factor for long-term outcomes identified was found to be predictive in only 1–3 studies. Some studies did not adjust for confounders (ART [22] and IRIS [20, 29] in HIV-CM, underlying conditions [12, 32] and high CSF antigen titers [35] in non-HIV-CM). Some important potential predictive factors have not been studied (eg, *Cryptococcus* species, phenotypes and genotypes, intracranial pressure management) and discordant results regarding the effect of IRIS in HIV-CM or underlying conditions in non-HIV-CM were reported. Moreover, definitions of some risk factors varied between studies (neurological abnormalities, fungal burden assessment tools and threshold, underlying disease) limiting the potential for comparison. Therefore, future research should systematically assess the long-term impact of all these risk factors using standardized and validated definitions and tools. Nevertheless, some key actions can be identified to reduce long-term mortality and prevent long-term impairment and disability.

In HIV-CM, some of the well-known short-term mortality risk factors (baseline altered neurological status, high fungal burden, or immunosuppression) [21] also seem to be predictive of long-term adverse outcomes. Their identification could orient clinicians in providing closer clinical follow-up. More importantly, our review identified some evidence for a protective effect of AmB-based combined antifungal regimens with long-term mortality and combined AmB + 5-FC therapy with long-term disability. It has to be noted that only 1 [33] of the 7 cohorts assessing impairments and disability in this review provided AmB-based combined therapy to all patients. Moreover, though ART does not seem to influence short-term HIV-CM mortality [43], it plays a key role in reducing long-term mortality [20, 22, 24, 26, 28, 38]. As in tuberculosis meningitis [44], if introduced appropriately (after 4–5 weeks), ART might protect against other opportunistic infections [20]. Therefore, to prevent not only short-term but also longer-term adverse outcomes, there is an urgent need to scale up access to and coverage of ART, AmB, and especially 5-FC therapy, usually not available in LMICs [45]. In addition, future research on antifungal therapy, as well as adjuvant therapy (especially IRIS and intracranial pressure management), should assess the effect on long-term outcomes, including disability.

In non-HIV-CM, the limited number and heterogeneity of studies preclude firm conclusions on long-term mortality risk factors. In *C. gattii* cohorts, our results suggest that underlying conditions and altered mental status at induction might be poor long-term prognostic factors [12, 34]. However, these univariable associations might be confounded by other factors. For instance, experimental studies have shown that a difference in virulence of the *C. gattii* genotype infecting Australian patients (mainly VGI) [46] compared to that infecting of Canadian patients (mainly VGII A) [47] might be another explanation for the difference in mortality. In general, the identified long-term mortality risk factors for non-HIV-CM advocate for early CM diagnosis in persons aged >60 years with underlying conditions. Nevertheless, management guidelines are based on results from trials involving patients with HIV-CM, which may not apply to those with non-HIV-CM. Further multicentric cohorts/trials, as already conducted for solid organ transplant recipients [48], should therefore be proposed, to further assess these potential predisposing factors and look for the best therapeutic options.

Poor Attention to Impairment and Disability

Although many studies were initially identified, few had high-quality data on long-term outcomes, and only 7 assessed long-term impairments and disability. Only 3 studies assessed impairments/disability and their predictive factors as a primary outcome, and 5 did not describe the method of outcome measurement [12, 23, 31, 34, 36]. None used the WHO definition of disability [10] or assessed quality of life. Similarly, reviews of long-term outcomes of other meningoencephalitis causes

Table 3. HIV-CM Predictive Factors for Long-term Mortality Identified By Review

Predictive Factors	No. of Studies	Study	Design (Quality Score, %)[a]	Outcome Measure of Association (95% CI)
Protective factors				
ART vs no ART at induction	2	Mathiesen et al (2012) [24]	RC (81)-	Adjusted rate ratio[c] (Cox) for 1-y mortality, 0.22 (.06–.77) (P = .02)
		Lanoy et al (2011) [22][b]	PC (69)	1-y mortality (Kaplan-Meier), 50% (45%–54%) for pre-ART vs 17% (12%–22%) for late ART
Early vs late ART initiation after induction (for ART- naive patients)	2	Boulware et al (2014) [20]	RCT (82)	ART initiation at 2 vs 5 wk: hazard ratio[d] (Cox) for 11-mo mortality, 1.66 (1.03–2.68) (P = .04)
		Makadzange et al (2010) [28]	RCT (50)	ART initiation at <72 h vs 10 wk: aHR[e] (Cox) for 3-y mortality, 2.85 (1.1–7.23) (P = .03)
AmB-based bitherapy vs monotherapy	1	Day et al (2013) [11]	RCT (82)	AmB + 5-FC vs AmB: aHR[f] (Cox) for 6-mo mortality, 0.56 (.36–.87) (P = .01)
				AmB + 5-FC vs AmB + fluconazole: aHR[f] (Cox) for 6-mo mortality, 0.55 (.35–.88) (P = .01)
		Bicanic et al (2008) [19][b]	RCT (55)	AmB 0.7 vs 1 mg/kg (+ 5-FC) for 6- and 12-mo mortality: no difference (Fisher exact test, no data and no P value provided)
Risk factors				
Older age	1	Mathiesen et al (2012) [24]	RC (81)	Adjusted rate ratio[h] (Cox) for 1-y mortality for each 1-y increase (in age), 1.05 (.99–1.11) (P = .054)
Altered neurological status at induction vs no altered status (with different items according to studies)	2	Chaiwarith et al (2014) [25]	RC (65)	aOR[g] (logistic) for 1-y mortality, 5.27 (1.26–24.05)
		Day et al (2013) [11]	RCT 82)	aHR[e] (Cox) for 6-mo mortality, 2.30 (1.57–3.36) (P < .001)
Baseline elevated fungal burden (CSF CrAg titers or fungal load)	2	Chaiwarith et al (2014) [25]	RC (65)	aOR[g] (logistic) elevated CrAg for 1-y mortality, 7.08 (1.62–31)
		Day et al (2013) [11]	RCT 82)	aHR[e] (Cox) elevated fungal load for 6-mo mortality, 1.33 (1.08–1.65) (P = .01) for each increase of 1 $\log_{10}$ CFUs/mL
Low CD4 cell count at induction (<20 vs >20 cells/mm^3)	1	Liao et al (2012) [23]	RC (54)	aOR[f] (logistic) for death or relapse at >1 y, 18 (1.19–71.46) (P = .04)
Contradictory results				
IRIS vs no IRIS during CM episode	3	Boulware et al (2010) [30]	PC (77)	aHR[i] (Cox) for 1-y mortality, 2.3 (1.1–1.51) (P = .04)
		Bicanic et al (2009) [29][b]	PC (54)	No association (Fisher exact test) as 36% of 6-mo mortality in IRIS vs 26% in non-IRIS, (P = .49)
		Boulware et al (2014) [20][b]	RCT (82)	IRIS in early vs late ART: 20% (17 of 87) vs 13% (9 of 69), respectively, (P = .32) (mortality significantly higher in early ART)

Abbreviations: 5-FC, flucytosine; aHR, adjusted hazard ratio; AmB, amphotericin B; aOR, adjusted odds ratio; ART, antiretroviral therapy; CFUs, colony-forming units; CI, confidence interval; CM, cryptococcal meningitis; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; HIV-CM, human immunodeficiency virus–associated CM; IRIS, immune reconstitution inflammatory syndrome; PC, prospective cohort; RC, retrospective cohort; RCT, randomized controlled trial.

[a]Quality score: percentage of quality criteria of the Critical Appraisal Skills Program (CASP) tools that are fulfilled by the study [16].

[b]Evidence based on univariate analysis. (In all other studies, evidence is based on multivariate analysis.)

[c]Variables included in model: age, sex, mental status, CD4, time-updated initiation of ART, antifungal regimen, flucytosine induction, nationality, time-period (88-96/97-08), hospital centre (variables with P < .1 were included in the model).

[d]Not adjusted because RCT with similar characteristic in both arms (P > .1 for all characteristics).

[e]Adjusted for age, sex, CSF CrAG titer, and CD4 cell count.

[f]Adjusted on age, sex, headache, fever, neck stiffness, seizure, glasgow coma score, cranial-nerve palsy, papilledema, cerebrospinal liquid opening pressure >18 cm H_2O, white blood cell count in cerebrospinal liquid, cerebrospinal liquid and plasma glucose levels.

[g]Variables included in model (P < .10 in univariate analysis): altered mental status, seizures, CSF CrAg titer, and year of diagnosis (2005–2010).

[h]Variables included in the model: clinical and laboratory variables at presentation + antifungal treatment given.

[i]Adjusted for baseline CD4 cell count, all other characteristic similar in both groups (body mass index, time from CM diagnosis to ART, opportunistic infection, baseline CD8 cell count, baseline and subsequent viral load, subsequent CD4 cell count, eosinophil count, and initial median serum CrAG titer).

identified a paucity of studies and very few data on morbidity and impairment [40, 49]. This is indicative of the low value placed on the collection of long-term meningoencephalitis outcomes, especially data on impairment and disability. Very few studies conducted systematic screening for impairments with validated tools, which may lead to misclassifications and underreporting. Indeed, the 2 studies that systematically assessed patients with validated tools found much higher proportions of impairments than the other studies (impaired cognition in 41% of HIV-CM survivors [33] and hearing impairment in 31% of non-HIV-CM survivors [35]). Therefore, future CM research should focus not only on short-term medical outcomes but also on longer-term impairments, disability, and quality of life. WHO definitions of disability [10] as well as validated neurocognitive, sensorial, and quality-of-life assessment tools should be used as in studies of other forms of encephalitis [40, 49].

Table 4. Long-term Mortality for Non–Human Immunodeficiency Virus–Associated Cryptococcal Meningitis

Study	Setting	Design	Sample Size	*Cryptococcus gattii* or *Cryptococcus neoformans*	Immune Status	Mortality Proportions, % (No./Total)[a]	Quality Score, %[b]
>3 to 4 mo after diagnosis or induction treatment							
Sun et al (2009) [39]	HICs (United States, Canada, France, Spain) plus India	PC	75	No data	100% Solid organ transplant	18.7 (14/75) (d90)	69
Liao et al (2012) [23]	HIC (Taiwan)	RC	53	No data	100% with underlying conditions	30.8 (16/52) (d90)	54
Lee et al (2011) [37]	HIC (Taiwan)	RC	51	No data	92% with underlying conditions	33.3 (17/51) (d90)	58
1 y after diagnosis or induction treatment							
Chen et al (2012) [12]	HIC (Australia)	RC	73	*C. gattii*	28% with underlying conditions	13 (10/73)	68
Phillips et al (2015) [34]	HIC (Canada)	RC	47	*C. gattii*	45% with underlying conditions	27.7 (13/47)	64
Zhu et al (2010) [32]	LMIC (China)	RC	154	No data	33% with underlying conditions	28.7 (41/143)	62
Liao et al (2012) [23]	HIC (Taiwan)	RC	53	No data	100% with underlying conditions	42.3 (22/52)	54

Abbreviations: d90, day 90 after diagnosis or induction treatment; HIC, high-income country; LMIC, low- or middle-income country; PC, prospective cohort, RC, retrospective cohort.
[a]Mortality expressed as percentage of deaths at the time point (those lost to follow-up excluded when known).
[b]Quality score : percentage of quality criteria of the Critical Appraisal Skills Program (CASP) tools that are fulfilled by the study [16].

Table 5. Non–Human Immunodeficiency Virus–Associated Cryptococcal Meningitis Predictive Factors of Long-term Mortality Identified By the Review

Predictive Factors	No. of Studies	Study	Design (Quality Score, %)[a]	Outcome Measure of Association (95% CI)
Protective factors				
AmB-based therapy	2	Zhu et al (2010) [32]	RC (62)	Non AmB-based vs AmB based: aHR[b] (Cox) for 1-y mortality, 8.87 (3.53–22.25) ($P < .001$)
		Sun et al (2009) [39]	PC (69)	AmB lipid vs AmB deoxylate: aOR[c] (logistic) for 3-mo mortality, 0.11 (.02–.57) ($P = .008$)
Risk factors				
Delayed diagnosis vs no delay	1	Zhu et al (2010) [32]	RC (62)	aHR[b] (Cox), 6.3 (2.41–16.53) ($P < .001$)
Older age	1	Zhu et al (2010) [32]	RC 62)	No data shown
Altered neurological status at induction vs no altered status (with different definitions according to studies[e])	3	Zhu et al (2010) [32], Liao et al (2012) [23], Chen et al (2012) [12] (*Cryptococcus gattii*)[f]	RC 62) RC (54) RC (68)	aHR[b] (Cox), 8.08 (2.96–16.95) ($P < .001$) aOR[d] (logistic) for death or relapse at >1 y, 8.7 (2.23–28.98) ($P = .003$) 1-y mortality 19% in abnormal vs 3% in normal neurological status, (Fisher exact test) ($P = .05$)
Baseline elevated fungal burden (CSF CrAg titers)	1	Liao et al (2012) [23]	RC (54)	>1/512 vs <1/512: aOR[d] (logistic) for death or relapse at >1 y, 16.2 (1.37–192.02) ($P = .03$)
		Chen et al (2012) [11] (*C. gattii*)	RC (68)	>1/256 vs <1/256: aOR for 1-y mortality, 1.8 (1–26) ($P = .05$)
Fungemia vs no fungemia in SOT	1	Sun et al (2009) [39]	PC (69)	aOR[c] (logistic) for 3-mo mortality, 10.6 (2.08–54.55) ($P = .004$)
Renal failure vs no renal failure in SOT	1	Sun et al (2009) [39]	PC (69)	aOR[c] (logistic) for 3-mo mortality, 4.61 (1.02–20.8) ($P = .047$)
Contradictory results				
Underlying conditions vs healthy	2	Chen et al (2012) [11] (*C. gattii*)[f]	RC (68)	1-y mortality 26% in predisposed vs 7.4% in healthy (log-rank test) (P = .03)
		Zhu et al (2010) [32][f]	RC (62)	1-y mortality 26.5% in predisposed vs 29.8% in healthy (Fisher exact test) (P = .69)

Abbreviations: aHR, adjusted hazard ratio; AmB, amphotericin B; aOR, adjusted odds ratio; CI, confidence interval; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; non-HIV-CM, non–human immunodeficiency virus–associated cryptococcal meningitis; PC, prospective cohort; RC, retrospective cohort; SOT, solid organ transplantation.
[a]Quality score : percentage of quality criteria of the Critical Appraisal Skills Program (CASP) tools that are fulfilled by the study [16].
[b]Variables included in model: age, sex, time to diagnosis>4 months, pulmonary cryptococcosis, auto-immune disease, hematological malignancy, solid cancer, corticotherapy, transplantation, no underlying conditions, altered mental status, coma, seizure, cerebral herniation, non–AmB-based initial therapy, inclusion of 5-FC in the induction antifungal regimen, intrathecal AmB treatment, and ommaya implantation.
[c]Variables included in model ($P < .20$ in univariate analysis): receipt of Calcineurin inhibitors, renal failure at baseline, abnormal mental status, fungemia, and receipt of lipid AmB (backward strategy).
[d]Variables included in model: clinical, laboratory variables at presentation, and antifungal treatment given.
[e]Definitions included focal neurological signs, hydrocephalus, low coma Glasgow score, and herniation.
[f]Evidence based on univariate analysis. (In all other studies, evidence is based on multivariate analysis.).

Implication for Rehabilitation

Despite the limited amount of evidence, it is alarming to see that at 1 year, 20%–70% of survivors have long-term impairments limiting cognitive, motor, visual, and/or hearing function, for both HIV-CM and non-HIV-CM in both LMICs and HICs. Moreover, while research and guidelines focus mainly on management of the acute phase of CM to prevent death in this phase [50], little attention is given to long-term follow-up and the identification of, and support for, impairments and disability. Therefore, ensuring access to physical, occupational, sensorial, and cognitive rehabilitation services is as important as enhancing prevention by fluconazole preemptive treatment and access to ART and AmB-based therapy [10]. Although these services are routinely accessible in developed countries, they are limited in LMICs owing to a lack of rehabilitation personnel and high costs [51]. For this reason, the development and adaptation of context-specific rehabilitation models should be one of the global research priorities for CM and central nervous system infections, as already advocated by John et al [51].

Limitations

In addition to the limitations related to the quality and heterogeneity of included studies, our review has some external limitations. Our inclusion and exclusion criteria might have restricted the panel of literature found. Eleven studies have been excluded because they included patients aged <18 years (Supplementary Table S3). Moreover, the chosen threshold of quality is arbitrary, because the CASP group has yet to propose a validated scoring system. This has led to exclusion of an additional 11 articles to decrease the risk of inaccurate conclusions (Supplementary Table S3). Nevertheless, each article excluded owing to patient age or study quality was carefully examined and the impact of its exclusion assessed. One article was subsequently reintroduced in our review based on this assessment [11].

CONCLUSION

CM has an important long-term impact on mortality and disability. Nevertheless, the quality of evidence is limited, and future CM research should focus not only on short-term medical outcomes but also on longer-term mortality, impairments, disability, and quality of life. In the meantime, fluconazole preemptive treatment, early diagnosis, and improved access to timely effective combined antifungal therapy should be implemented to prevent death and other long-term consequences of CM. In addition, early detection of impairments and access to rehabilitation services will improve quality of life in CM survivors.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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