Systematic Review

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Cryptococcus Osteomyelitis in Humans—A Systematic Review

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Background: *Cryptococcus* spp. is an opportunistic fungal pathogen rarely infecting immunocompetent individuals. Cryptococcal osteomyelitis is an uncommon disease characterized by the invasion of bone tissue by *Cryptococcus*. It typically arises in disseminated infection, while isolated cryptococcal osteomyelitis is scarcely diagnosed. This study seeks to review all published *Cryptococcus* spp. osteomyelitis cases in humans, focusing on epidemiology, microbiology, clinical complications, treatment, and clinical outcomes.

Methods: A systematic review was conducted through a literature search of PubMed and Scopus databases. The protocol was registered in Prospero (ID: CRD42024627780).

Results: In total, 106 studies provided data on 118 patients with *Cryptococcus* spp. osteomyelitis. The mean age of patients was 41.83 years and 56.41% were male. Immunosuppression constituted the most common predisposing risk factor (17.8%), followed by history of tuberculosis (15.25%) or diabetes mellitus (12.71%). The most frequently infected bone structures included the thorax (24.58%), vertebrae, and upper extremities (15.25% respectively), while in 16.1%, multiple bones were involved. *Cryptococcus neoformans* was the identified pathogen in most cases (97.22%). Fluconazole (72.41%), amphotericin B (62.93%), and flucytosine (34.48%) were the most commonly used antifungals. In 47.41%, a combination of antifungals was administered. Overall mortality was relatively low (7.63%), while only 4.24% of deaths were attributed to the infection.

Conclusions: Given the potential of *Cryptococcus* spp. to cause severe bone infection, clinicians should include this disease in the differential when encountering yeast microorganisms in microbiological specimens, especially in patients with significant comorbidities or immunodeficiency. This is essential for ensuring accurate diagnosis and appropriate treatment.

Keywords: *Cryptococcus*; osteomyelitis; spondylodiscitis; fungal infection

Introduction

Cryptococcus spp. constitutes an encapsulated opportunistic fungal pathogen commonly found in environments such as soil, decomposing organic matter, and bird excrement, particularly pigeon droppings [1,2]. This fungus rarely leads to infection in individuals with healthy immune system but primarily affects those with immunosuppression, including patients with Acquired Immunodeficiency Synrome (AIDS), lymphoma, tuberculosis, organ transplants, or those undergoing steroid therapy [3,4]. Research suggests that cryptococcosis occurs in approximately 5–10% of immunocompromised patients and up to 30% of patients with AIDS, while its occurrence in immunocompetent individuals is as rare as one case per 100,000 individuals [2,3].

The respiratory system serves as the primary entry point for *Cryptococcus* spp. [5]. Once inhaled, the fungus can be established in the lungs, potentially leading to cryptococcal pneumonia or spreading through the bloodstream to infect other parts of the body [6]. While the lungs and central nervous system are the most frequent targets, infections can also manifest in various other organs and tissues; infection of the kidneys, skin, eyes, prostate, and colon have been reported [7]. In rare cases, the skeletal system may be affected as well, resulting in cryptococcal osteomyelitis, which typically arises due to hematogenous dissemination from a primary lung infection [1]. This condition is

uncommon, particularly in immunocompetent individuals, accounting for only about 5% of all cryptococcal infections [8,9]. Most instances of cryptococcal osteomyelitis occur as part of systemic infection rather than as isolated one [10]. Given the uncommon clinical presentation of cryptococcal osteomyelitis, this entity is often misdiagnosed, resembling several other conditions, including malignancy or tuberculosis. Therefore, clinicians should maintain a high index of suspicion for cryptococcal infections in patients presenting with bone lesions to prevent misdiagnosis and delay in appropriate treatment.

This systematic review sought to review all reported cases of osteomyelitis caused by *Cryptococcus* species, focusing on its epidemiology, clinical presentation, microbiological features, treatment approaches, and clinical outcomes. The rationale for this review lies in the rarity and diagnostic complexity of cryptococcal osteomyelitis, especially in immunocompetent individuals. There is currently a lack of comprehensive, synthesized data on this condition in the literature; this review aims to address these knowledge gaps by consolidating existing case reports and studies to better understand its presentation, diagnosis, and management, thereby aiding clinicians in recognizing and appropriately treating this uncommon infection.

Materials and Methods

Search Strategy and Inclusion and Exclusion Criteria

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines following a predefined protocol agreed upon by all authors (**Supplementary file 1**) [11]. The protocol was registered in Prospero (ID: CRD42024627780). The principal aim of this review is to gather and present all published data regarding osteomyelitis caused by *Cryptococcus* species in humans and to note mortality rates and epidemiological trends associated with this infection. Additionally, the review sought to document the specific infection sites, provide detailed clinical profiles of affected patients, and summarize microbiological findings alongside treatment approaches for *Cryptococcus* spp. osteomyelitis. A comprehensive literature search was conducted independently by two researchers (AZ and AG) using the PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov) and Scopus (https://www.scopus.com) databases, covering publications available up to 15 December 2024. A predefined search strategy was applied, incorporating the keywords "*Cryptococcus*" OR "Cryptococcal" AND "osteomyelitis" OR "bone". Any discrepancies in the selection process were resolved with the guidance of a senior investigator (PI). The inclusion criteria required studies presenting original data, such as case reports, case series, and cohort studies that focused on the epidemiology and clinical outcomes of *Cryptococcus* spp. osteomyelitis in humans. Only articles published in English were considered. Systematic reviews, narrative reviews summarizing aggregated data, animal studies, and papers lacking full-text availability or sufficient details on patient mortality and epidemiology were excluded from the present review. To ensure a comprehensive search, the reference lists of all included studies were examined for additional relevant publications that may not have been identified in the initial search.

Data Extraction and Definitions

The extracted data from each selected study included the year of publication, study type, country of origin and patient demographics such as age and gender. Additionally, relevant medical history, microbiological findings, and infection details were documented. These encompassed the specific bone involved, diagnostic methods used, associated complications, identified pathogens, patterns of antibiotic resistance, treatment strategies, and clinical outcomes, including survival or mortality. The connection between mortality and the initial infection was determined based on the observations reported by each study's authors.

Quality Assessment of Included Studies

The quality of the included studies was assessed independently by two reviewers (AZ and AG) using established tools such as the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports and case series. These tools were used to evaluate the studies based on criteria like study design, sample size, methodological rigor and potential biases. Any discrepancies between the reviewers were resolved through discussion and, in cases where consensus could not be reached, a senior investigator (PI) was consulted. Studies that did not meet a predefined quality threshold were excluded from the review to ensure that the findings were based on robust evidence.

Statistical Analysis

Categorical data are displayed as counts and corresponding percentages, while continuous data are summarized using either median with interquartile range (IQR) or mean with standard deviation based on their distribution. The normality of continuous data distribution was assessed using the Shapiro–Wilk test, supplemented by visual inspection of histograms and Q–Q plots. To compare continuous variables, the Mann–Whitney U-test was applied for non-normally distributed data, whereas the *t*-test was used for normally distributed data. To compare categorical variables between groups, either the Chi-square test or Fisher's exact test was used. A stepwise logistic regression analysis was conducted to identify independent predictors of mortality. Variables with a p-value < 0.10 in univariate analysis or those considered clinically relevant, such as age and sex, were included in the multivariable model. Results were reported as odds ratios (aORs) with 95% confidence intervals (CIs). Statistical significance was defined as a two-tailed p-value of <0.05. All statistical these analyses were

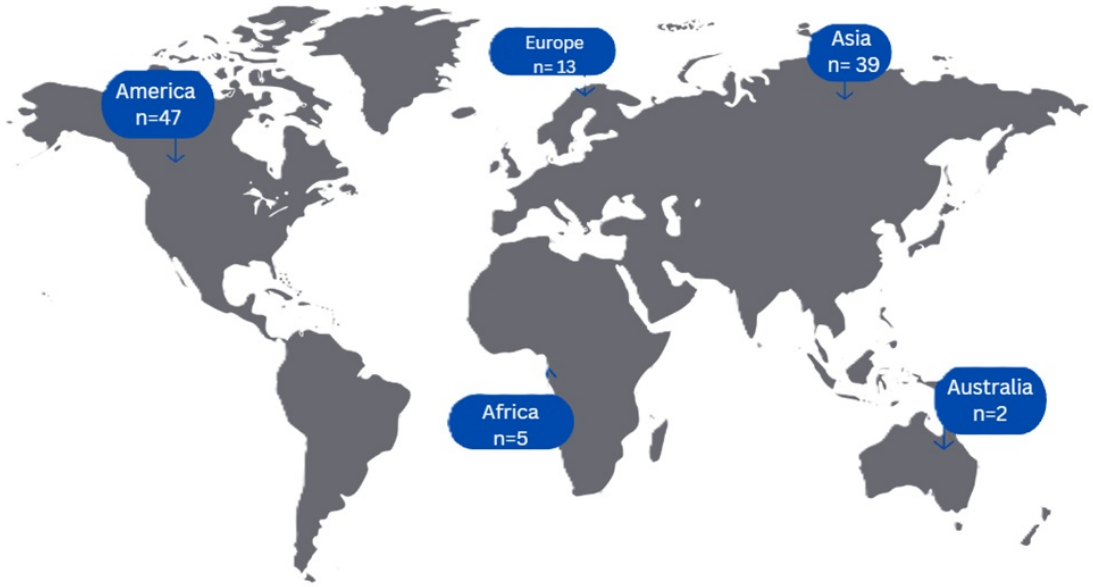

Fig. 1. Geographical distribution of cryptococcal osteomyelitis cases worldwide (n = number of cases). This image created by the authors using the canva website (www.canva.com).

conducted using GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA, USA). Stepwise logistic regression analysis was performed to identify factors associated with mortality. This statistic analysis was conducted using Stata 15.0 (StataCorp LLC, College Station, TX, USA).

Results

Included Studies' Characteristics

A total of 745 articles from PubMed and Scopus databases were screened, with 106 ultimately meeting the inclusion criteria for this study. These 106 studies included in the present systematic review involved a total of 118 patients [1–3,5–9,12–109]. Geographically, 47 studies were conducted in North and South America, 39 in Asia, 13 in Europe, 5 in Africa, and 2 in Oceania. The study types comprised 104 case reports and two case series. Fig. 1 illustrates the global distribution of cryptococcal osteomyelitis cases, while Fig. 2 presents the study inclusion flow diagram.

Epidemiology of Cryptococcal Osteomyelitis

The mean age of patients with cryptococcal osteomyelitis was 41.83 years (ranging from 1 to 84 years), with 56.41% (66 patients) being male. Regarding medical history and risk factors, 21 patients (17.80%) were immunosuppressed, while 18 (15.25%) were diagnosed with tuberculosis. Additionally, a history of diabetes mellitus was present in 15 patients (12.71%) and malignancy in 11 (9.32%). Notably, hematological malignancies (7 patients) were more commonly observed than solid organ tumors (4 patients), and amongst these patients, 5 were receiving chemotherapy. Sarcoidosis or trauma was noted in 8 patients each (6.78%), respectively, while 6 (5.08%) had undergone organ transplantation. Autoimmune syndromes or human immunodeficiency virus (HIV) were diagnosed in 5 patients each (4.24%) respectively. In 4 patients (3.39%) antimicrobial agents were administered within the past three months prior to infection. Interestingly, in 26 patients (22.03%) no predisposing factors were identified. Table 1 provides a detailed overview of the demographic and clinical characteristics of *Cryptococcus* osteomyelitis patients.

Microbiology and Antimicrobial Resistance of Cryptococcal Osteomyelitis

Cryptococcus spp. was identified in bone cultures in 99 out of 114 patients (86.84%, with available data). In 8 out of 114 patients (7.02%), the pathogen was isolated in pus cultures, received from abscess or wound formation, while in 16 (14.04%), it was retrieved from various biological specimens, including the cerebrospinal fluid (CSF), bloodstream, sputum or urine. Among the identified species *Cryptococcus neoformans* was the most prevalent (97.22%, in 105 out of 108 patients, where the isolated species is reported). Of note, in one case infection was caused by *Cryptococcus gattii.* Concomitant infection was documented in 12 patients (10.17%), and in three of those (25%), *Mycobacterium tuberculosis* was the responsible pathogen. Identification was primarily achieved through histology, based on the pathogen's unique microbiological characteristics, while more advanced molecular methods, including Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) or next-generation sequenc-

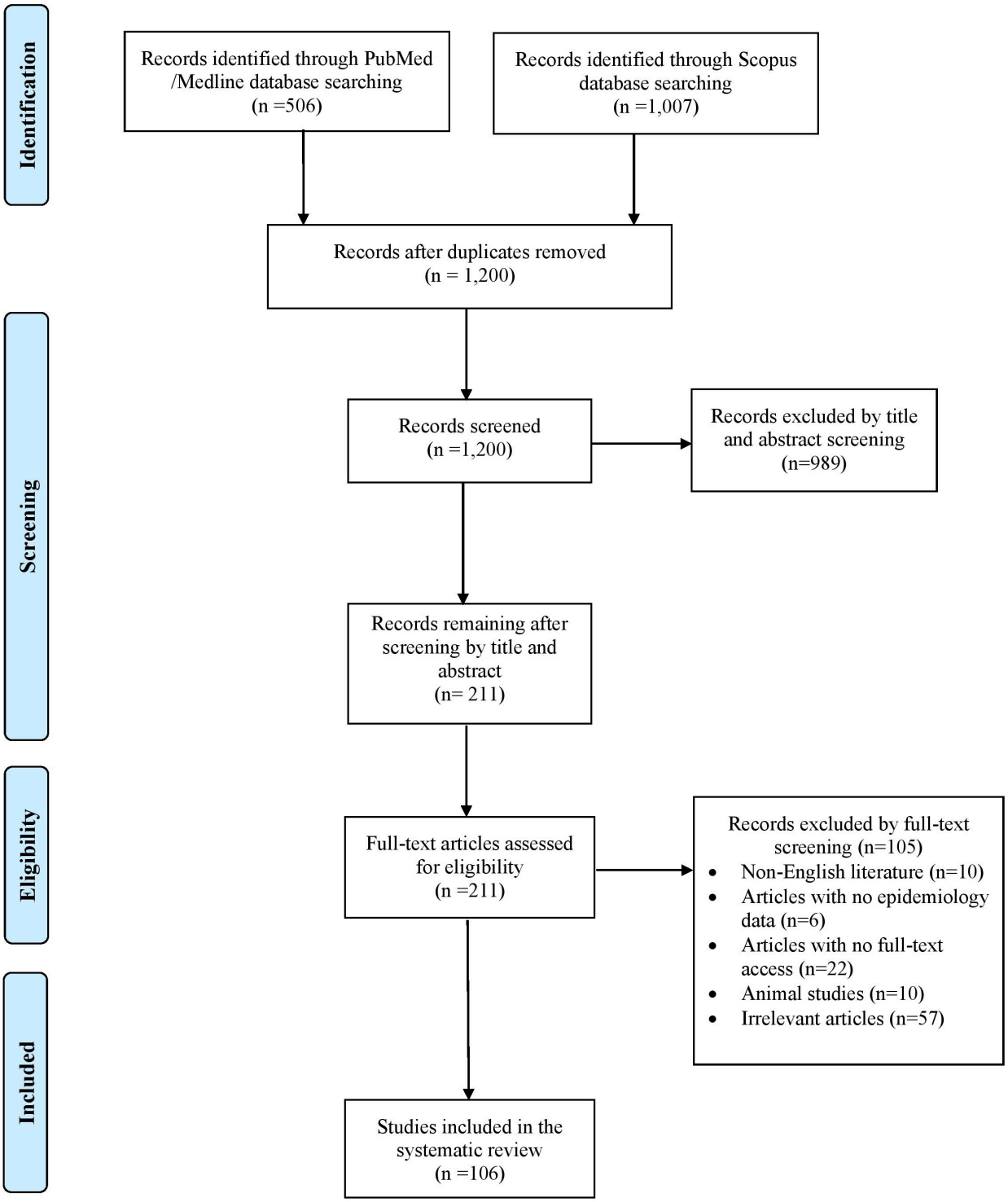

Fig. 2. Trial flow of this systematic review. Created using Microsoft Word, version 16.0 (Microsoft Corporation, Redmond, WA, USA).

ing (NGS), were applied in four (8.33%) and two patients (4.17%, with a total of 48 patients) respectively. Moreover, PCR was effectively used as an identification method in two cases (4.17%).

Antimicrobial susceptibility was tested only in 19 patients (16.1%) and revealed resistance to antifungal agents only in two (10.52%). More specifically, regarding these two patients, resistance to caspofungin and fluconazole was observed in the first patient and resistance to itraconazole in the second one.

Table 1. Characteristics of patients with cryptococcal osteomyelitis.

Characteristic	All patients (n = 118)*	Survived (n = 109)*	Died (n = 9)*
Age, years, median (IQR)	41.5 (Q1–Q3: 27–56)	41 (Q1–Q3: 26.3–55)	45 (Q1–Q3: 28.2–57)
Male gender, n (%)	66/117 (56.41)	61 (55.96)	5/8 (62.5)
Predisposing factors			
Immunosuppression, n (%)	21 (17.80)	19 (17.43)	2 (22.22)
Tuberculosis, n (%)	18 (15.25)	14 (12.84)	4 (44.44)
Diabetes mellitus, n (%)	15 (12.71)	12 (11.01)	3 (33.33)
Malignancy, n (%)	11 (9.32)	10 (9.17)	1 (11.11)
Sarcoidosis, n (%)	8 (6.78)	7 (6.42)	1 (11.11)
Trauma, n (%)	8 (6.78)	8 (7.34)	0
Organ transplantation, n (%)	6 (5.08)	5 (4.59)	1 (11.11)
Autoimmune syndrome, n (%)	5 (4.24)	5 (4.59)	0
HIV, n (%)	5 (4.24)	4 (3.67)	1 (11.11)
No predisposing factors, n (%)	26 (22.03)	26 (23.85)	0
Clinical characteristics			
Fever, n (%)	36 (30.51)	33 (30.27)	3 (33.33)
Sepsis, n (%)	8 (6.78)	6 (5.5)	2 (22.22)
Treatment			
Fluconazole, n (%)	84/116 (72.41)	80/108 (74.07)	4 (44.44)
Amphotericin, n (%)	73/116 (62.93)	65/108 (60.19)	8 (88.88)
Flucytosine, n (%)	40/116 (34.48)	34/108 (31.48)	6 (66.66)
Antifungal combination, n (%)	55/116 (47.41)	49/108 (45.37)	6 (66.66)
Outcomes			
Deaths due to infection, n (%)	5 (4.24)	NA	NA
Deaths overall, n (%)	9 (7.63)	NA	NA

HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; *, data refer to the number of patients mentioned on top unless otherwise described, all percentages were calculated based on reported data.

Clinical Presentation of Cryptococcal Osteomyelitis

The most commonly infected bone structure was the thorax in 29 patients (24.58%), followed by the vertebrae and the upper extremities' bones in 18 patients each, respectively (15.25%). Osteomyelitis of the skull was observed in 15 patients (12.71%), pelvic bones in 13 (11.02%), tibia or fibula in 12 (10.17%), and femoral bone in 11 (9.32%). Less frequently infected bones included those of the foot in 9 patients (7.63%), the patella and scapula in 6 (5.08%) as well as the bones of the hands in 4 (3.39%). Intriguingly, in 19 patients (16.10%) osteomyelitis was multifocal. Infection of the skin was present in 38 patients (32.20%), while the central nervous system (CNS) and lower respiratory system were also involved, in 10 each (8.47%), respectively.

The most common clinical complications associated with cryptococcal osteomyelitis included abscess formation in 41 patients (34.75%), fever in 36 (30.51%) and bone fracture in 13 (11.02%). Additionally, ulceration was noted in 10 patients (8.47%), while sepsis and renal failure occurred in 8 patients each (6.78%), respectively. Admission to intensive care units or septic shock occurred only in 2 (1.69%) and 1 (0.85%) patients respectively.

Treatment and Outcome of Cryptococcal Osteomyelitis

Out of the 118 available patients, 113 patients (95.76%) underwent antifungal therapy. Fluconazole constituted the most commonly prescribed antifungal agent, given to 84 patients (72.41%), followed by amphotericin B and flucytosine, administered to 73 (62.93%) and 40 (34.48%) patients respectively. Voriconazole was given in 7 patients (6.03%), while itraconazole in 4 (3.45%). Antifungal combination was given to 55 patients (47.41%), while in 5 (4.31%), antifungals were not administered. In 71 patients (60.17%), surgical procedures were performed alongside antimicrobial treatment, including mainly debridement of the infected bone. The median duration of therapy for survivors was 6 months. The overall mortality rate was calculated at 7.63% (9 patients), while deaths specifically linked to cryptococcal osteomyelitis accounted for 4.24% (5 patients).

Univariable and Multivariable Statistical Analysis

In univariable analysis, logistic regression models were used to evaluate the association between mortality of

Table 2. Results of logistic regression analysis in regard to mortality.

Risk factors		Univariable analysis		Multivariable analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years)		1 (0.97–1.04)	0.735	0.98 (0.93–1.03)	0.562
Sex	Females	-	-	-	-
	Males	1.31 (0.3–5.76)	0.720	1.45 (0.21–9.8)	0.705
Diabetes mellitus	No	-	-	-	-
	Yes	4.04 (0.89–18.29)	0.07	5.35 (0.24 –117.86)	0.288
CNS	No	-	-	-	-
	Yes	13.73 (2.91–64.78)	0.001	78.81 (4.93–1260.89)	0.003
Organ dysfunction	No	-	-	-	-
	Yes	17.67 (2.92–106.8)	0.002	11.67 (0.65 –210.69)	0.096
Treatments with fluconazole	No	-	-	-	-
	Yes	0.11 (0.07–1.13)	0.074	0.19 (0.11–3.39)	0.263

CNS, central nervous system; OR, odds ratio; CI, confidence interval.

cryptococcal osteomyelitis and various risk factors. This analysis provided odds ratios (ORs) with 95% confidence intervals (CIs) to estimate the incidence of death based on different factors. Location of infection in the CNS (OR: 13.73, 95% CI: 2.91–64.78, $p = 0.001$) and development of organ dysfunction (OR: 17.67, 95% CI: 2.92–106.8, $p = 0.002$) showed a statistically significant association with mortality. Renal failure, diabetes mellitus and treatment with fluconazole were also associated with mortality, although not in a statistically significant manner. Multivariable logistic regression models were then applied to control potential confounders and provide a more accurate estimation of the effect of each risk factor. The analysis revealed statistically significant association between mortality and location of infection in the CNS (OR: 78.81, 95% CI: 4.93–1260.89, $p = 0.003$). Results of univariable and multivariable analysis are depicted in Table 2. Due to missing data on patients' follow-up estimation of cox proportional hazard in order to investigate any association between patients' survival, based on a time to event analysis, could not be performed.

Discussion

The present systematic review examined osteomyelitis caused by *Cryptococcus* species, drawing from multiple studies to offer a comprehensive analysis of their epidemiology, microbiology, clinical presentation, treatment approaches, and outcomes. Given the rarity of this condition and the scattered nature of existing evidence, a clear synthesis of available data is urgently needed to guide clinical recognition and management. The most commonly infected bone structure was the thorax, followed by the vertebrae and the upper extremities' bones. These findings are consistent with prior studies reporting a predilection for thoracic and vertebral involvement, which may reflect both pathogen dissemination patterns and the vascular architecture of these bones. However, the higher frequency of upper extremity and skull involvement observed in this review expands the anatomical spectrum previously underrecognized in the literature. Among the identified species, *Cryptococcus neoformans* was the most prevalent. The most common clinical complications associated with cryptococcal osteomyelitis included abscess formation and fever, while fluconazole constituted the most widely administered antifungal agent. Overall mortality was 7.63%.

A major rationale for conducting this review is the significant underreporting and under recognition of cryptococcal osteomyelitis in both immunocompromised and immunocompetent populations. Despite its potentially serious consequences, this condition is often misdiagnosed due to its nonspecific presentation and similarity to more common bone infections or malignancies. The limited number of reported cases of cryptococcal osteomyelitis in the existing literature renders the establishing of precise epidemiological data for this infection particularly challenging [53]. In this review, most cases were observed in male patients, with a median age of 41.5 years. Interestingly, the majority of cases were described in North and South America and Asia. The higher prevalence of the infection in these countries may be linked to their climate, as *Cryptococcus* species thrive in warm, humid environments, as well as to the abundant bird populations, especially pigeons, whose excreta are a major source of the fungus. Moreover, the elevated rates of HIV infection, particularly in Southeast Asia and parts of North and South America, contribute to an increased risk of cryptococcal infections [110]. Conversely, the cooler or drier climates, which are more common in parts of Europe, are not favourable for fungal proliferation. The advent of antiretroviral therapy has also reduced the incidence of cryptococcosis in developed countries [111]. Regional disparities in reported cases, such as the relatively lower number from Africa, may also reflect differences in diagnostic capacity, access to healthcare or publication trends rather than true epidemiological variation. However, the lack of consolidated global data and absence of standardized diag-

nostic or treatment protocols represent a major knowledge gap that this review aims to begin addressing.

Formerly referred to as European blastomycosis, torulosis, or Busse-Buschke disease, cryptococcosis is an opportunistic infection caused by *Cryptococcus* species [23]. Cryptococcus spp., initially described in 1894, constitutes a dimorphic, heterobasidiomycetous, encapsulated fungal species that has been identified as both environmental fungus and opportunistic pathogen, frequently found in avian excreta, soil, and trees [112]. More than 95% of cryptococcal infections are caused by *Cryptococcus neoformans*, typically causing systemic cryptococcosis in individuals with immunosuppression, whereas *Cryptococcus gattii* accounts for the remaining cases, primarily affecting immunocompetent individuals [113,114]. Although *Cryptococcus gattii* was considered confined to tropical and subtropical climates, over the past decade, cases of *Cryptococcus gattii* have been reported globally, with the fungus occupying a unique ecological niche in trees and tree hollows [115]. Inhalation of spores or desiccated yeast cells is a common yet asymptomatic occurrence in the general population; however, in immunocompromised individuals, such exposure may lead to pulmonary or systemic cryptococcosis [112]. The infection typically enters the body through the lungs, often leading to pneumonia and meningitis [116]. Cryptococcal osteomyelitis is rare and usually arises from a primary pulmonary infection that disseminates through the bloodstream, though in rare cases, it may result from direct traumatic inoculation through the skin [3,64]. It is observed in 5–10% of patients with widespread disease, while isolated bone infection is even less frequent [69]. Despite advances in fungal diagnostics, the limited awareness and absence of tailored diagnostic algorithms for skeletal involvement remain significant barriers to timely diagnosis.

Cryptococcal virulence is driven by three key processes: adaptation to the host environment, immune evasion, and the production of numerous virulence factors. While these mechanisms are found in many fungal pathogens, *Cryptococcus* spp. is distinctive in its ability to utilize a wide range of strategies for host adaptation, immune system avoidance, and virulence factor production [117]. Surviving in the host requires *Cryptococcus* spp. to adapt to factors such as temperature, nutrients, pH, and oxidative stress. This adaptation involves metabolic changes and activation of signalling pathways like mitogen-activated protein kinases (MAPKs) [118]. A key aspect of this adaptation is its ability to grow at the body's physiological temperature of 37 °C, which is typically intolerable for most environmental fungi. This temperature tolerance is likely a critical factor in its pathogenicity, especially in immunosuppressed hosts [119]. Additionally, *Cryptococcus* spp. produces enzymes like proteases, lipases, and urease as virulence factors. Of note, urease breaks down urea into CO_2 and ammonia, which is essential for nitrogen use and is produced in large amounts by *Cryptococcus* spp. Urease activity is also used in diagnosing cryptococcosis, highlighting its role as a virulence factor [120]. Finally, the pathogen's capsule and melanin constitute two additional virulence factors. The capsule protects against phagocytosis, stress factors like dehydration, and free radicals. It also influences the host's immune response [121,122]. Melanin is crucial for virulence, with melanization mutants showing reduced pathogenicity. This pigment helps the fungus resist stress factors like free radicals, radiation, and heat, and can also reduce antifungal drug effectiveness [123,124].

This systematic review highlights immunosuppression as the most common predisposing risk factor for cryptococcal osteomyelitis. During periods of severe cell-mediated immunodeficiency, the fungal organism may translocate into the bloodstream, leading to disseminated disease [125]. Notably, 5 patients with HIV infection were identified in the present review. A decrease in CD4+ T cells level, as well as chronic inflammation and treatment with immunosuppressive drugs, render HIV patients more prone to cryptococcal osteomyelitis. Intriguingly, in HIV patients who begin antiretroviral therapy, the infection may remain dormant and later re-emerge as part of immune reconstitution inflammatory syndrome (IRIS) [55]. Tuberculosis (TB) represented the second most common predisposing factor (15.25%) for cryptococcal osteomyelitis encountered in the present review. Tuberculosis and cryptococcosis are both serious opportunistic infections that especially affect individuals with compromised cell-mediated immunity [126]. Despite their similarities, concurrent infection with *Cryptococcus neoformans* and *Mycobacterium tuberculosis* is uncommon and often undiagnosed. In the present study 12 patients (10%) were misdiagnosed and their bone lesions were considered to be bone TB. Most documented cases of co-infection primarily involve *Cryptococcus neoformans* affecting the central nervous system, while tuberculosis predominantly impacts the lungs [127]. Cryptococcal osteomyelitis in TB patients is exceedingly rare. Given the high misdiagnosis rate as bone TB in this review, future diagnostic algorithms should consider concurrent testing for both pathogens, especially in high-risk populations.

Diabetes mellitus (DM) is another frequently observed predisposing condition for cryptococcal osteomyelitis in individuals who are HIV-negative, contributing to 10–20% of cases [128,129]. DM is the third most prevalent risk factor (12.71%) observed in the present study. DM weakens cell-mediated immunity, impairs neutrophil chemotaxis, disrupts phagocytosis, reduces lymphocyte blast transformation, and causes defects in opsonization. Additionally, elevated blood glucose levels can compromise the antimicrobial activity of macrophages. These immune system dysfunctions create a favourable environment for opportunistic infections which is believed to explain the link between DM and cryptococcal infection [130,131]. This has important implications for clinicians, as routine screening for fungal pathogens in diabetic patients with persis-

tent bone lesions may aid in timely diagnosis and management. Moreover, malignancy was noted in 9.32% of the included patients (11 patients); the majority of these patients (7 out of 11) were diagnosed with haematological malignancies, and five were receiving hemotherapy. Chronic low-dose chemotherapy regimens, as well as steroid use in patients with haematological disorders, have been linked to an increased risk of bone cryptococcal infection [36]. Of note, a case series conducted at MD Anderson Cancer Centre between 1989 and 1999 examined 31 cancer patients with cryptococcal disease, including 20 with haematological malignancies. The study found that 61% of patients had lymphopenia, and over half (52%) had received steroid treatment, suggesting that lymphopenia may be a key underlying risk factor for cryptococcal disease in general, as well as for osteomyelitis, in patients with haematological malignancies [132]. Sarcoidosis, noted in 6.78% of the included patients, is a multisystem inflammatory disease marked by the development of non-caseating epithelioid granulomas in various organs, with the lungs and lymphatic system being the most commonly affected [133]. Cryptococcal osteomyelitis has been linked to sarcoidosis, with impaired cell-mediated immunity and prolonged corticosteroid use proposed as possible explanations for this association. However, this relationship remains controversial and the exact underlying pathophysiological mechanisms are not yet fully understood [134]. Several other predisposing factors have been recognized to induce the development of cryptococcal disease, including severe trauma, organ transplantation, and autoimmune diseases. Despite numerous case reports, the literature remains fragmented, as no prior comprehensive review has thoroughly summarized the spectrum of predisposing conditions in cryptococcal osteomyelitis; this review seeks to consolidate that knowledge and identify relevant predisposing factors.

Cryptococcal osteomyelitis lacks specific clinical characteristics that clearly distinguish it from other bone infections. In the majority of cases, it is typically marked by localized pain and swelling, mild constitutional symptoms, fever, and elevated inflammatory markers [58,69]. More severe clinical complications include abscess formation, which was, in particular, the most common complication observed in the present review (34.75%), as well as bone fracture or ulceration [14]. Symptoms may persist for 2 years before a diagnosis is established [77]. The majority of cryptococcal osteomyelitis cases are confined to a single site, with the thoracic bones, vertebra, and upper extremities bones being the most frequently affected. However, several cases of multifocal osteomyelitis have also been described; in the present systematic review, 16.1% of the included patients exhibited multifocal osteomyelitis. The misdiagnosis rate is quite high; given the disease's non-specific clinical presentation, cryptococcal osteomyelitis may resemble a bone tumor or an abscess presenting as a pathological rib fracture accompanied by a soft-tissue mass [44]. This is in accordance with the results of the present systematic review, where 36.44% of the included patients were initially misdiagnosed; more precisely, 34% of these patients were diagnosed with bone tumors, whereas 20.9% were diagnosed with bone tuberculosis.

The radiological appearance of cryptococcal osteomyelitis is non-specific, with lesions generally presenting as lytic, well-demarcated areas, and may or may not show periosteal reactions [69,70]. These imaging characteristics can also resemble those of neoplastic lesions, as well as infections caused by *Staphylococcus aureus* or *Mycobacteria* spp. [69]. The diagnosis is ultimately confirmed through the identification of the organism within the bone lesion. This can be achieved by sampling from draining sinuses, aspiration, incision and drainage, or open biopsy [64,70]. Traditional diagnostic methods for Cryptococcal osteomyelitis include fungal culture, India ink staining, the Cryptococcal capsular polysaccharide antigen (CrAg) test, and histopathology. However, fungal culture is often slow and has limited sensitivity. While India ink staining is a cost-effective and rapid technique, its sensitivity is low and highly dependent on the examiner's skill. The CrAg test is currently the most sensitive and specific diagnostic tool, with both metrics exceeding 96%. However, it has limitations, as it cannot confirm active infection, detect antigen-deficient strains, or differentiate between specific *Cryptococcus* species [17]. In the latest years, metagenomic next-generation sequencing (mNGS), a genomics-based microbial detection method, has seen expanding use in diagnosing infectious diseases. This technology has been proven particularly beneficial in complex and critical cases where traditional diagnostic methods struggle to identify the causative pathogen. By enabling the detection of a broad range of infections with high precision, mNGS has become an invaluable tool in clinical microbiology [135,136]. While mNGS has slightly lower sensitivity and concordance rates than CrAg tests (97.4%), it outperforms India ink (63.0%) and culture (76.7%). mNGS also demonstrates 100% sensitivity compared to culture and can identify *Cryptococcus* at species level. As a new diagnostic tool, mNGS provides valuable support in diagnosing cryptococcal osteomyelitis and differentiating *Cryptococcus gattii* from *Cryptococcus neoformans*, which aids clinical decision-making [136]. Our findings support the incorporation of molecular techniques, such as mNGS and MALDI-TOF, in diagnostic workflows, especially in cases with atypical presentations or where initial cultures are inconclusive. As these methods become more accessible, a reduction in diagnostic delay and more tailored therapies may be observed.

To date, due to the rarity of cryptococcal osteomyelitis, there is a shortage of evidence-based research on its treatment. Although a standardized treatment protocol for cryptococcal osteomyelitis has not yet been established, most experts emphasize the importance of a combined med-

ical and surgical approach [21]. Surgical debridement aids in reducing the infectious load and offers the chance to collect specimens for histological and microbiological analysis. Subsequently, medical management with antifungal therapy is advised [53]. The Infectious Diseases Society of America provides treatment guidelines for non-meningeal, non-pulmonary cryptococcosis in HIV-negative patients. For cases with disseminated disease, the recommended initial induction treatment is amphotericin B (0.7–1 mg/kg/day) combined with flucytosine for 2 weeks, followed by fluconazole (12 mg/kg/day or 800 mg daily) for 8 weeks. Afterward, the fluconazole dose should be reduced to 3 mg/kg/day (or 200 mg daily) for 6–12 months [137]. Amphotericin B is a key treatment for disseminated fungal infections, but given its serious side effects, such as liver dysfunction, haematological abnormalities, and acute kidney failure, its use should be limited to severe fungal infections where the therapeutic benefits justify the potential risks [55]. In general, bone involvement necessitates high doses of antifungal agents due to its limited blood supply [107]. Fluconazole, amphotericin B, and flucytosine were the three most widely used antifungal agents in the present review. However, given that antifungal susceptibility testing was performed in only 16.1% of cases, resistance patterns remain largely understudied and should be interpreted with caution. This represents a significant knowledge gap that future research should address to guide therapeutic decisions. Ongoing monitoring, including radiological follow-up, is essential as the infection may relapse and develop into a chronic condition [69]. In the majority of the included cases, a favourable clinical outcome was observed, with a survival rate of 92.37%. Despite the absence of standardized treatment protocols, the high rate of clinical improvement and survival (92.37%) observed in this review emphasizes the potential efficacy of combination therapy and highlights the importance of individualized management based on disease severity, comorbidities, and anatomical site. The mortality rate was relatively low (7.63%) and mainly occurred in patients with severe comorbidities. This low mortality rate, despite the severity of cryptococcal osteomyelitis, supports recent studies indicating improved outcomes with early antifungal intervention and surgical management. It also underscores the importance of multidisciplinary approaches, especially in complex or disseminated infections.

This study has several limitations. The literature search may not have captured all relevant research on epidemiology and mortality, as some studies could have been overlooked due to the search methodology. Future research should consider using broader databases to minimize publication bias. The present analysis was limited to case reports and case series, which rely on accurate documentation for validity. Prospective cohort studies or registry-based data could provide more robust and general insights. Moreover, several studies provided incomplete data, which restricted the statistical analysis to the available information. Due to incomplete data of included case reports along with scarcity of this rare entity, the overall data volume was too small. As a result, it was possible to present findings only from studies with complete data. Standardized reporting guidelines for case reports and series would help improve the quality and consistency of future analyses. Due to limitations in reporting, treatment outcomes were not consistently stratified by specific antifungal regimens; future studies should aim to analyze outcomes in relation to specific drug combinations to better inform clinical decision-making. Lastly, studies published in languages other than English were excluded. Future reviews should consider including non-English literature to enhance comprehensiveness.

Conclusions

This systematic review provides key insights into the epidemiology, symptoms, microbiology, treatment, and outcomes of *Cryptococcus* osteomyelitis, emphasizing its potential to cause serious disease. The review aims to collect scattered cases' data, improve diagnosis and guide treatment for this rare and severe condition. *Cryptococcus neoformans* was the most common species found, with thoracic bones were most often affected. Although no official treatment guidelines have been established, the most common approach included antifungal agents like fluconazole, amphotericin B and flucytosine. Patients' immune status significantly affects clinical outcome, while prompt treatment initiation remains critical. Due to its unusual clinical manifestation the infection can easily be missed; thus, greater awareness among healthcare and laboratory professionals is required for proper diagnosis. Despite the reported limitations, this review highlights the need for more long-term studies to further understand this disease, assess potential risk and develop standard treatments. Future priorities should include standardizing mNGS testing for unclear cases as well as creating a global registry to track rare strains and resistance trends, helping to improve research and ameliorate patient care.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, PI, GS; methodology, AZ; AG; IG, PI, and GS; software, AZ; validation, IG, AG, and PI; formal analysis, AZ, and PI; investigation, AZ, AG, and IG; resources, AT, and PI; data curation, GS; writing—original draft preparation, AZ, AG, IG; writing—review and editing, AT, GS, and PI; visualization, AT; supervision, PI; project administration, PI, GS. All authors have read and agreed to the published version of the manuscript. All authors agreed to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Fig. 1 was created using the canva website. The authors have no financial or personal relationship with the canva website, and the use of this tool does not imply any endorsement.

Supplementary Material

Supplementary material associated with this article can be found in the online version, at https://doi.org/10.24976/Discov.Med.202537199.147.

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