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Cryptococcosis among hospitalised patients with COVID-19: A multicentre research network study

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Abstract

It is unclear if there is an association between COVID-19 and cryptococcosis. Therefore, this study aimed to describe the clinical features, risk factors, and outcomes associated with cryptococcosis in hospitalised patients with COVID-19. The objectives of this study were to determine the incidence of and examine factors associated with cryptococcosis after a diagnosis of COVID-19. We used TriNetX to identify and sort patients 18 years and older hospitalised with COVID-19 into two cohorts based on the presence or absence of a diagnosis of cryptococcosis following diagnosis of COVID-19. Outcomes of interest included the incidence of cryptococcosis following the diagnosis of COVID-19 as well as the proportion of patients in each group who had underlying comorbidities, received immunomodulatory therapy, required ICU admission or mechanical ventilation (MV), or died. Propensity score matching was used to adjust for confounding. Among 212,479 hospitalised patients with COVID-19, 65 developed cryptococcosis. The incidence of cryptococcosis following COVID-19 was 0.022%. Patients with cryptococcosis were more likely to be male and have underlying comorbidities. Among cases, 32% were people with HIV. Patients with cryptococcosis were more likely to have received tocilizumab ($p < .0001$) or baricitinib ($p < .0001$), but not dexamethasone ($p = .0840$). ICU admission (38% vs 29%), MV (23% vs 11%), and mortality (36% vs 14%) were significantly higher among patients with cryptococcosis. Mortality remained elevated after adjusted propensity score matching. Cryptococcosis occurred most often in hospitalised patients with COVID-19 who had traditional risk factors, comparable to findings in patients without COVID-19. Cryptococcosis was associated with increased ICU admission, MV, and mortality.

KEYWORDS
COVID-19, cryptococcus, cytokine release syndrome, immunotherapy, SARS-CoV-2

1 | INTRODUCTION

The dysregulated immune response in patients with COVID-19 is multifactorial due to comorbidities, cytokine dysregulation, impaired cell-mediated immunity, and receipt of immunomodulatory therapies.[1–3] As a result, there is an increased risk for reactivation of previously latent diseases or development of secondary opportunistic infections. Invasive fungal infections (IFIs) have been reported in

patients with COVID-19, especially those with neutropenia, lymphopenia, comorbidities, as well as treatment with antibacterial or immunomodulatory therapies, such as corticosteroids, interleukin (IL)-1 and IL-6 inhibitors, or Janus kinase (JAK) inhibitors.[4–8]

Invasive pulmonary aspergillosis has been extensively reported in patients with COVID-19. The incidence of coronavirus disease-associated pulmonary aspergillosis (CAPA) ranges from 2% in one post-mortem study[9] to 30% in patients on mechanical ventilation (MV) or in the intensive care unit (ICU).[10,11] A recent meta-analysis found a pooled prevalence of 10% in ICU patients.[12] Risk factors for CAPA include advanced age, chronic pulmonary disease, ICU admission, MV, and treatment with antibacterial therapy, corticosteroids, or IL-6 inhibitors.[5,6,13] However, differences in study designs and challenges in diagnosing and defining CAPA, especially in early case reports and series, limit these findings.

Cases of COVID-19 associated mucormycosis (CAM) have also been reported,[4] but to a lesser extent than CAPA. Though the highest number of cases have emerged in literature from India,[14,15] CAM has been reported in patients across the world.[4,15–17] Candidiasis[18,19] and pneumocystosis[20] in patients with COVID-19 have also been documented, and are often identified in patients with other established risk factors.

Despite the ubiquitous presence of *Cryptococcus* spp. coupled with the immunomodulatory therapies used for COVID-19 and impaired immunologic response (lymphopenia and a paucity of peripheral T cells) associated with SARS-CoV-2,[2,3] few cases of cryptococcosis in patients with COVID-19 have been reported compared to the above IFIs.[8,21] However, it is unclear if cryptococcosis represents a superinfection in these cases and if there is an association between COVID-19 and cryptococcosis. The epidemiology, natural history, and characteristics of patients who develop cryptococcosis following COVID-19 remain unknown and likely underrecognised. Therefore, the purpose of this study was to describe the clinical features, risk factors, and outcomes associated with cryptococcosis in patients hospitalised with COVID-19.

2 | METHODS

The objectives were to determine the incidence of and examine factors associated with cryptococcosis after a diagnosis of COVID-19.

2.1 | Study design and population

We used TriNetX a global federated research network that captures anonymous data from electronic medical records (EMRs) of 57 healthcare organisations (Appendix S1). Available data include demographic characteristics, diagnoses, procedures, medications, and measurements (e.g., laboratory test results).

Patients 18 years and older hospitalised with COVID-19 were identified from TriNetX between February 19, 2020, and April 17, 2022. Diagnosis of COVID-19 was defined by logical observation identifiers names and codes (LOINCs) for SARS-CoV-2 or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes of "COVID-19" or "pneumonia due to COVID-19" (Appendix S1), whereas Current Procedural Terminology (CPT) codes were used to determine hospitalisation (Table S1).

The patient population was divided into two cohorts based on the presence or absence of a diagnosis of cryptococcosis following diagnosis of COVID-19. Patients diagnosed with cryptococcosis within 3 months of the most recent COVID-19 diagnosis (cases) were identified by ICD-10-CM diagnosis code for cryptococcosis, pulmonary cryptococcosis, cerebral cryptococcosis, cutaneous cryptococcosis, osseous cryptococcosis, disseminated cryptococcosis, other forms of cryptococcosis, or unspecified cryptococcosis (Table S2).[22,23] The earliest encounter for cryptococcosis was identified as the index encounter in patients with multiple encounters. Cases were also stratified by HIV status. Controls were defined as patients diagnosed and hospitalised with COVID-19 but without a diagnosis of cryptococcosis (Appendix S1).

Demographics, underlying comorbidities, medications, laboratory data, and outcomes were examined. Demographic information included age at index event (years), sex, race, and ethnicity, as entered into TriNetX from EMRs. ICD-10-CM diagnosis codes were used to identify underlying comorbidities during the 30 days prior to COVID-19 diagnosis and included HIV infection, immunodeficiency with predominantly antibody defects, combined immunodeficiencies, common variable immunodeficiency, other immunodeficiencies, malnutrition, type 2 diabetes mellitus (DM2), heart failure, hepatic fibrosis and cirrhosis, sarcoidosis, systemic connective tissue disorders, rheumatoid arthritis, non-infective enteritis and colitis, chronic kidney disease (CKD), neoplasms, and transplanted organs or tissues (Table S3). Laboratory data, defined as the most recent labs between the index event and 30 days before, included leukocytes, lymphocytes, CD4 cell counts, haemoglobin A1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, serum creatinine, ferritin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) (Table S4). Types of cryptococcosis were based on ICD-10-CM diagnosis codes and included pulmonary cryptococcosis, cutaneous cryptococcosis, cerebral cryptococcosis, osseous cryptococcosis, disseminated cryptococcosis, other forms of cryptococcosis, and unspecified cryptococcosis (Table S1). Medication use was characterised by receipt of immunomodulatory therapies as part of the management of COVID-19, including dexamethasone, tocilizumab, and baricitinib (Table S5). Outcomes determined by CPT codes included ICU admission, receipt of MV, and death (Table S1).

2.2 | Outcome measures

The primary outcome was the incidence of cryptococcosis following the diagnosis of COVID-19 among hospitalised patients. The secondary outcomes included the proportion of patients in each group

who had underlying comorbidities, received immunomodulatory therapy, required ICU admission or MV, or died.

2.3 | Statistical analysis

Statistical analyses were completed on the TriNetX platform. Descriptive statistics were presented as means and standard deviations for continuous variables, and as frequency and proportions for categorical variables. Continuous data were compared using independent t-tests, whereas categorical data were compared using χ^2 or Fisher's exact test, as appropriate. Outcome analysis was reported before and after propensity score matching. Propensity score matching was performed to control for differences between groups based on age, male sex, Hispanic or Latino ethnicity, HIV, transplant, or neoplasm using a 1:1 Greedy nearest-neighbour algorithm. These variables were selected because they are established risk factors for cryptococcosis and associated with increased *Cryptococcus* spp.-related mortality. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for receipt of immunomodulatory therapies, ICU admission, MV, and mortality, with $p < .05$ as the cut off for statistical significance.

The incidence and prevalence of cryptococcosis among all hospitalised patients with COVID-19 and those requiring ICU admission was analysed for the timeframe between February 19, 2020, and April 17, 2022.

2.4 | Ethics statement

Research utilising TriNetX does not require ethical approval because patient-identifiable information is not accessible to users. The authors have adhered to that the ethical policies of the journal, as noted on the journal's author guidelines page.

3 | RESULTS

3.1 | Clinical features of hospitalised patients with COVID-19 complicated with cryptococcosis

A total of 212,479 hospitalised patients with COVID-19 were included of which 65 patients were diagnosed with cryptococcosis. Of those with cryptococcosis, 88% ($n = 57$), 40% ($n = 26$), 28% ($n = 18$), and 23% ($n = 15$) had ICD-10-CM diagnosis codes for cryptococcosis, cerebral cryptococcosis, pulmonary cryptococcosis, and disseminated cryptococcosis, respectively. Fifteen percent ($n = 10$) had cutaneous cryptococcosis, whereas 42% ($n = 27$) and 15% ($n = 10$) had unspecified and other forms cryptococcosis, respectively, based on ICD-10-CM diagnosis codes.

Demographic characteristics were similar between groups, but patients with cryptococcosis were more likely to be male than those without cryptococcosis (Table 1). More patients with cryptococcosis had underlying comorbidities than those without. Immunodeficiencies, such as HIV and transplanted organs or tissues, were more frequent in patients with cryptococcosis (Figure 1). Additionally, a higher proportion of patients with cryptococcosis had autoimmune diseases, DM2, heart failure, hepatic fibrosis and cirrhosis, CKD, and malnutrition.

Mean leukocyte and lymphocyte counts were similar between groups. However, patients with cryptococcosis had significantly lower CD4 cell counts. Patients with cryptococcosis also had higher ALT, alkaline phosphatase, ferritin, and LDH, but lower albumin.

A similar proportion of patients from each group received dexamethasone ($p = .0848$), whereas tocilizumab ($p < .0001$) and baricitinib ($p < .0001$) were administered to more patients with cryptococcosis (Figure 2). Compared to patients without cryptococcosis, those with cryptococcosis were significantly more likely to have received tocilizumab (OR 18.6, 95% CI 9.5–36.3, $p < .0001$) or baricitinib (OR 12.4, 95% CI 6.4–24.1, $p < .0001$), but not dexamethasone (OR 0.7, 95% CI 0.4–1.2, $p = .222$).

3.2 | Clinical features of people with HIV hospitalised with COVID-19 complicated with cryptococcosis

Hospitalised people with HIV (PWH) who developed cryptococcosis were more likely to be male (88% vs 48%, $p < .0001$) and Black or African American (42% vs 21%, $p = .0154$) compared to hospitalised PWH without cryptococcosis. Additionally, cases with HIV were less likely to be White (42% vs 71%, $p = .0154$) and non-Hispanic (71% vs 91%, $p = .0008$). Systemic connective tissue disorders (42% vs 14%, $p = .0001$) and hepatic fibrosis and cirrhosis (42% vs 7%, $p < .0001$) were more common in cases with HIV, while neoplasms (42% vs 64%, $p = .0235$) were less common. Leukocyte and lymphocyte counts were similar (7.02 ± 4.24 cells/μl vs 9.46 ± 21.8 cells/μl, $p = .6255$ and 3.09 ± 5.99 cells/μl vs 5.97 ± 12.6 cells/μl, $p = .3591$, respectively), though CD4 cell counts (73 ± 68.9 cells/μl vs 295 ± 296 cells/μl, $p = .0188$) were significantly lower among those who developed cryptococcosis. Cerebral cryptococcosis was the most common reported form (63%) among cases. Significantly more hospitalised PWH with COVID-19 who developed cryptococcosis received dexamethasone (42% vs 18%, $p = .0027$), while use of tocilizumab and baricitinib were infrequent among both groups (0% vs 1%, $p = .5605$ and 0% vs <1%, $p = .8233$, respectively). Hospitalised PWH with COVID-19 who developed cryptococcosis were significantly more likely to be admitted to the ICU (50% vs 19%, $p < .0001$), require MV (42% vs 6%, $p < .0001$), and die (42% vs 18%, $p = .0030$) compared to those with HIV who did not develop cryptococcosis.

3.3 | Outcome analysis

Unmatched analysis showed a significantly higher proportion of patients who developed cryptococcosis following COVID-19

TABLE 1 Comparison of baseline characteristics between hospitalised patients diagnosed with cryptococcosis within 3 months of the most recent COVID-19 diagnosis and hospitalised patients without a diagnosis of cryptococcosis within 3 months of COVID-19 diagnosis

Variable	Cryptococcosis following COVID-19 ($n = 65$)	COVID-19 without cryptococcosis ($n = 212,414$)	p value
Age at index event (years), mean (SD)	56.8 (14.5)	56 (22.4)	.7692
Male sex	52 (80)	108,802 (51)	<.0001
BMI (kg/m^2), mean (SD)	26.8 (6.93)	29.3 (7.69)	1036
Race			
White	41 (63)	144,234 (68)	.4047
Black or African American	17 (26)	41,868 (20)	.1917
Asian	0 (0)	410,916 (2)	.2571
Unknown race	10 (15)	20,982 (10)	.1368
Ethnicity			
Hispanic or Latino	14 (22)	29,260 (14)	.0694
Non-Hispanic	48 (74)	161,555 (76)	.6763
Underlying comorbidities			
HIV	21 (32)	3461 (2)	<.0001
Transplanted organs or tissues	18 (28)	5659 (3)	<.0001
Neoplasm	17 (26)	46,629 (22)	.4132
Immunodeficiency with predominantly antibody defects	10 (15)	589 (<1)	<.0001
Combined immunodeficiencies	0 (0)	67 (<1)	.8861
Common variable immunodeficiency	0 (0)	137 (<1)	.8377
Other immunodeficiencies	21 (32)	5592 (3)	<.0001
Sarcoidosis	10 (15)	981 (<1)	<.0001
Systemic connective tissue disorders	10 (15)	8378 (4)	<.0001
Rheumatoid arthritis	10 (15)	596 (<1)	<.0001
Non-infective enteritis and colitis	10 (15)	10,007 (5)	<.0001
Hepatic fibrosis and cirrhosis	10 (15)	5351 (3)	<.0001
Type 2 diabetes mellitus	27 (42)	64,126 (30)	.0463
Heart failure	18 (28)	36,674 (17)	.0262
Malnutrition	17 (26)	11,436 (5)	<.0001
Chronic kidney disease	26 (40)	51,074 (24)	.0026
Laboratory values			
Leukocytes (K/μl), mean (SD)	9.18 (6.9)	9.11 (21.8)	.9818
Lymphocytes (K/μl), mean (SD)	1.97 (4.31)	3.68 (10.5)	.3472
CD4 cells (cells/μl), mean (SD)	73 (68.9)	299 (316)	.0242
AST (units/L), mean (SD)	80.3 (235)	58.2 (256)	.5582
ALT (units/L), mean (SD)	85.1 (393)	45.4 (157)	.0769
Alkaline phosphatase (units/L), mean (SD)	139 (141)	101 (101)	.0097
Serum creatinine (mg/dl)	1.61 (1.37)	1.36 (1.79)	.2923
Albumin (mg/dl), mean (SD)	3.02 (0.767)	3.46 (0.665)	<.0001
Haemoglobin A1C (%), mean (SD)	7.34 (2.46)	7.29 (2.36)	0.9404
Ferritin (ng/ml), mean (SD)	5253 (17950)	941 (2344)	<.0001
C-reactive protein (mg/dl), mean (SD)	81.7 (84.3)	79.4 (82.6)	.8972
Lactate dehydrogenase (units/L)	1006 (1798)	433 (501)	<.0001

Note: Data are presented as *n* (%) unless otherwise noted.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; SD, standard deviation.

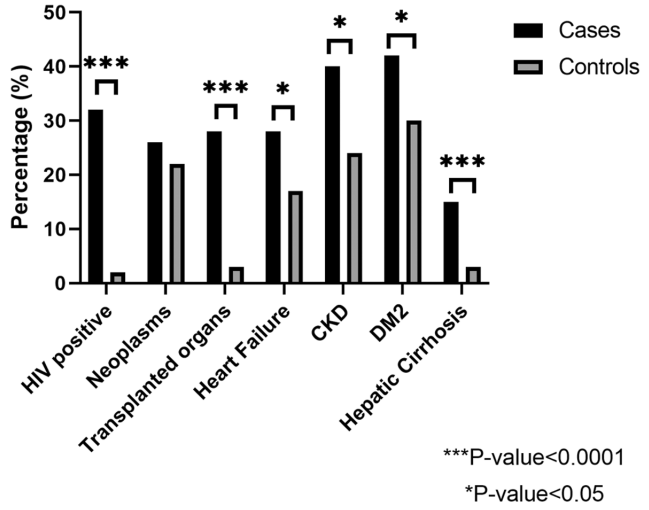

FIGURE 1 Distribution of underlying comorbidities among hospitalised patients with COVID-19 stratified based on a diagnosis of cryptococcosis. The figure compares the percentage of HIV infection, neoplasms, transplanted organs or tissues, heart failure, chronic kidney disease (CKD), type 2 diabetes mellitus (DM2), and hepatic fibrosis and cirrhosis among hospitalised patients based on the presence (cases) or absence (control) of a diagnosis of cryptococcosis following diagnosis of COVID-19. The asterisks denotes a statistically significant difference between groups

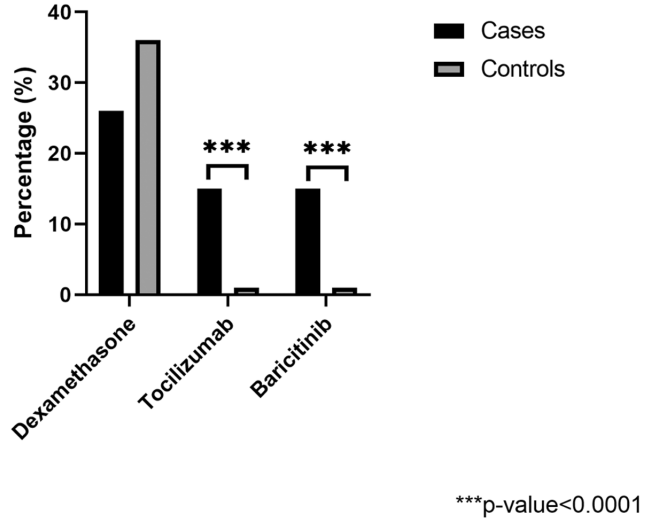

FIGURE 2 Percentage of hospitalised patients with COVID-19 who received immunomodulatory therapies stratified based on a diagnosis of cryptococcosis. The figure compares the percentage of hospitalised patients with COVID-19 with cryptococcosis (cases) to those without cryptococcosis (controls) who received dexamethasone, tocilizumab, or baricitinib. The asterisks denotes a statistically significant difference between groups

required MV than patients without cryptococcosis (Table 2). In addition, mortality was significantly higher in patients with cryptococcosis (Figure 3). In the propensity score matching analysis adjusted by age, male sex, Hispanic or Latino ethnicity, HIV status, transplant, and neoplasm; patients with cryptococcosis remained at significantly higher odds of death compared to patients without cryptococcosis.

3.4 | Frequency analysis

Of 212,479 hospitalised patients with COVID-19 available in the TriNetX system, the incidence of cryptococcosis was 0.022%, while the prevalence was 0.059%. Most episodes of cryptococcosis occurred within 10 days after COVID-19 diagnosis (Figure 4). The incidence and prevalence were higher among males (0.034% and 0.087%, respectively). Hispanic or Latino patients had a higher incidence (0.029%) and prevalence (0.063%) compared to non-Hispanic patients (0.022% and 0.061%, respectively). Risk of cryptococcosis remained higher among Hispanic or Latino patients than non-Hispanic patients after adjusting for age, gender, and HIV status.

Similarly, the prevalence was 0.043% among patients 60–64 years and 0.035% among those 70–74 years. The risk of cryptococcosis was 0.06% among 64,607 patients with COVID-19 requiring ICU admission, with a prevalence of 0.123%. In addition, the risk of cryptococcosis increased to 0.618% among COVID-19 patients requiring ICU admission who were 30–34 years and to 0.16% among Hispanic or Latino patients with COVID-19 requiring ICU admission.

4 | DISCUSSION

We evaluated the epidemiology and characteristics of hospitalised patients diagnosed with cryptococcosis within 3 months of the most recent COVID-19 diagnosis from a multicentre research network. The overall incidence of cryptococcosis was 0.022% among 212,479 hospitalised patients with COVID-19. Notably, the distribution of cryptococcosis cases in our study was similar to that reported in patients without COVID-19 with a higher prevalence of immunodeficiencies in patients diagnosed with cryptococcosis. Multiple IFIs, including CAPA, CAM, and candidiasis, are becoming increasingly recognised as complications in patients with COVID-19.[4,9–11,14–19] While an association between COVID-19 and cryptococcosis is unclear, the low incidence of cryptococcosis in patients with COVID-19 may reflect lack of recognition and underdiagnosis in this population.

In our study, cryptococcosis occurred significantly more often in males with underlying comorbidities or immunodeficiencies, of which 32% had HIV, and 28% were transplant recipients. These findings support broader literature suggesting non-HIV non transplant patients are an emerging group at risk for cryptococcosis and increasing recognition of DM2, CKD, neoplasms, autoimmune diseases, and other immunodeficiencies as risk factors for cryptococcosis.[23,24] Among previous cases of cryptococcosis in patients with COVID-19 summarised in a recent case report and literature review,[21] chronic comorbidities, such as hypertension and DM2, were common. One patient was receiving prednisone for autoimmune haemolytic anaemia,[25] one patient with a renal transplant was taking tacrolimus with prednisone,[26] while one patient was newly diagnosed with HIV.[27]

TABLE 2 Differences in outcomes between hospitalised patients diagnosed with cryptococcosis within 3 months of the most recent COVID-19 diagnosis and hospitalised patients without a diagnosis of cryptococcosis within 3 months of COVID-19 diagnosis

Variable	Before matching				After matching			
	Cryptococcosis following COVID-19 ($n = 64$)[a]	COVID-19 without cryptococcosis ($n = 212,414$)	OR (95% CI)	*p* value	Cryptococcosis following COVID-19 ($n = 63$)	COVID-19 without cryptococcosis ($n = 63$)	OR (95% CI)	*p* value
ICU admission	24 (38)	60,645 (29)	1.5 (0.9–2.5)	.1129	24 (38)	24 (38)	1 (0.5–2.1)	1
Mechanical ventilation	15 (23)	23,888 (11)	2.4 (1.4–4.3)	.0020	15 (24)	12 (19)	1.3 (0.6–3.1)	.5148
Deceased	23 (36)	29,747 (14)	3.4 (2.1–5.7)	<.0001	23 (37)	10 (16)	3.0 (1.3–7.1)	.0084

Note: Data are presented as n (%) unless otherwise noted.

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

[a]Outcome data of interest were unavailable for one patient.

However, traditional risk factors associated with cryptococcosis were not detected in 56% of patients in those previous reports. We found higher rates of cryptococcosis in patients with COVID-19 who had heart failure, DM2, and CKD. CD4 cell counts were significantly lower among patients with COVID-19 who developed cryptococcosis, suggesting impaired cell-mediated immunity may contribute to the pathogenesis of this opportunistic IFI.

Receipt of immunomodulatory therapies, many of which are used routinely in the medical management of COVID-19,[1] could also increase susceptibility to cryptococcosis. Following initial infection, *Cryptococcus* spp. may persist as a pulmonary granuloma without causing overt clinical symptoms.[28,29] Administration of corticosteroids impairs the binding and phagocytic function of alveolar macrophages against *Cryptococcus* spp.,[30] in addition to increasing fungal burden and promoting extrapulmonary dissemination.[28,29] Increased *Cryptococcus* spp. cell proliferation has also been observed following exposure to either dexamethasone or methylprednisolone.[31] Surprisingly, dexamethasone administration in our study was similar among patients with COVID-19 who developed cryptococcosis and those without cryptococcosis. These findings differ from an analysis of nine previous reports whereby eight patients with COVID-19 received corticosteroids prior to diagnosis of cryptococcosis.[21]

IL-6 inhibitors have been administered to patients with COVID-19 to modulate IL-6 concentrations associated with the dysregulated host immune response[1] despite the potential increased risk of bacterial, fungal, and non-SARS-CoV-2 viral infections. Previous data suggest IL-6-deficient mice are more susceptible to *Cryptococcus* spp. infection, suggesting a potential role for IL-6 in the host defence against cryptococcosis.[32] Higher IL-6 concentrations restrict the growth of *Cryptococcus* spp., while suppression of IL-6 with IL-6 inhibitors may allow *Cryptococcus* spp.to subvert host immune response.[1,33] In our study, patients with cryptococcosis were almost 19 times more likely to have received tocilizumab versus those without cryptococcosis, which is consistent with previous reports.[21]

Recently, JAK inhibitors have emerged as a potential treatment option in patients with COVID-19 to inhibit cytokine signalling, thus limiting immune activation and inflammation.[1] However, interferon (INF)-γ may function in a protective role against cryptococcosis, by way of lymphocyte infiltration and macrophage activation.[34] Post-influenza cryptococcosis, while uncommon, is associated with lower concentrations of INF-γ.[35] Cases of pulmonary cryptococcosis have occurred in patients treated with baricitinib,[36] but none had been reported in patients with COVID-19, until now. In our study, patients with COVID-19 who developed cryptococcosis were 12 times more likely to have received baricitinib compared to those without cryptococcosis.

Dexamethasone, tocilizumab, and baricitinib have been recommended in select patients with COVID-19,[1] but widespread, indiscriminate use may lead to impaired host immunity and increased risk of opportunistic infections. Though the mechanism of cryptococcosis in patients infected with SARS-CoV-2 remains to be studied further, it has been proposed to be the result of reactivation of latent *Cryptococcus* spp.infection[28,29,37] due to (1) SARS-CoV-2 associated

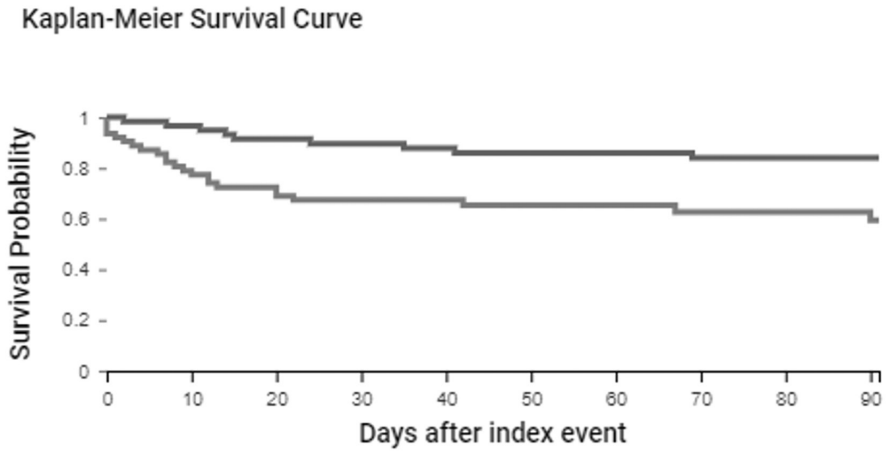

FIGURE 3 Kaplan–Meier survival analysis of hospitalised patients with COVID-19 stratified based on a diagnosis of cryptococcosisThe figure displays the survival probability of hospitalised patients diagnosed with cryptococcosis within 3 months of the most recent COVID-19 diagnosis (light grey line) and hospitalised patients without a diagnosis of cryptococcosis within 3 months of COVID-19 diagnosis (dark grey line)

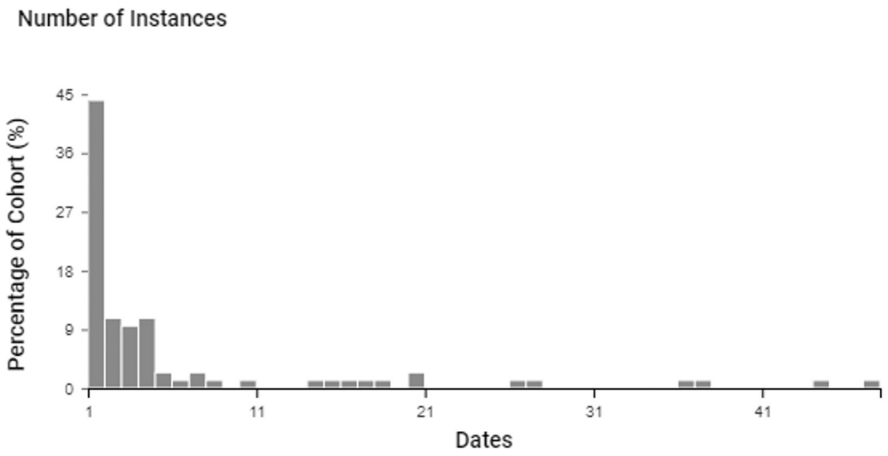

FIGURE 4 Instances of cryptococcosis following COVID-19 among hospitalised patients. The figure displays the number of instances of cryptococcosis among hospitalised patients with COVID-19 represented as a percentage of the cohort stratified by the number of days (dates) from COVID-19 diagnosis to diagnosis of cryptococcosis

lymphopenia,[2,3] (2) vomocytosis of *Cryptococcus* spp. from macrophages following SARS-CoV-2 infection,[38] or (3) receipt of immunomodulatory therapy.[28] Cryptococcosis following COVID-19 is likely multifactorial. The presence of epidemiologic risk factors increasing *Cryptococcus* spp. latency and T-cell immunity defects—from COVID-19 severity associated immunodeficiency to use of immunomodulatory agents—likely play a central role.

However, most cases of cryptococcosis occurred within 10 days after the index hospitalisation with COVID-19 (Figure 4), which may represent unrecognised cryptococcosis before hospitalisation or receipt of immunomodulatory therapy for COVID-19. While early-onset reactivation of cryptococcosis is rare, a previous report of a cluster of *C. neoformans* pulmonary and bloodstream infections found an association between receipt of short-term corticosteroids in the ICU and increased risk of cryptococcosis.[39] It is unknown whether patients in our study who developed cryptococcosis represent reactivation of latent *Cryptococcus* spp. infection following receipt of immunomodulatory therapy or acute infection.

Data describing outcomes among patients with COVID-19 who developed cryptococcosis are limited. Higher rates of ICU admission, MV, and death were observed in patients with cryptococcosis in our study. The significantly increased rate of death among persons with cryptococcosis persisted after propensity score matching variables, which are established risk factors for cryptococcosis and *Cryptococcus* spp.-related mortality. Upon review of previous reports, three of nine patients with COVID-19 died prior to the identification of cryptococcosis.[21] Early suspicion leading to prompt identification and treatment of cryptococcosis is critical. Serum cryptococcal antigen (CrAg) screening could improve detection of asymptomatic infections or early disease in patients with COVID-19, especially those with risk factors for cryptococcosis or those who clinically deteriorate after receipt of immunomodulatory therapy. However, the sensitivity of serum CrAg is unknown in this population.

Although we described the epidemiology and characteristics of a large number of hospitalised patients with COVID-19 and cryptococcosis, our study was retrospective and utilised a multicentre research network. In some cases, COVID-19 may have represented an incidental diagnosis where other well-established risk factors for cryptococcosis were present. Though all patients in our study were hospitalised, the reason for hospitalisation is unknown (manifestations of COVID-19 or cryptococcosis). Our data are based on EMR data aggregation, which may be limited by data entry or coding errors. Collection of ICD-10-CM diagnosis codes, CPT codes, and LOINCs may be subjected to data inaccuracies due to unrecorded, under coding and/or misclassification of diseases. Additionally, granular details, such as medication dosage, duration, and timeframe

prior to diagnosis of cryptococcosis, as well as microbiologic data, could not be assessed. Lastly, laboratory tests were not obtained for all patients due to differences in institutional practices, reflected by the fact that CD4 cell counts were obtained in only 15% of patients who developed cryptococcosis and less than 1% of those without cryptococcosis.

This study is the first to report factors associated with hospitalised patients who developed cryptococcosis following COVID-19. Cryptococcosis occurred most often in patients with COVID-19 who also had traditional risk factors, comparable to findings observed in patients without COVID-19. Clinicians must be aware of traditional and lesser known or recognised risk factors for cryptococcosis among patients with COVID-19 and have a low threshold to screen for cryptococcosis.

AUTHOR CONTRIBUTIONS

D.B.C. involved in conceptualization, data curation, formal analysis, methodology, visualisation, writing—original draft, writing—review and editing. V.M.K. involved in conceptualization, formal analysis, methodology, visualisation, writing—original draft, writing—review and editing. S.G., B.T.J., L.V.B. and G.R.T. involved in writing—review and editing. C.F.P. involved in conceptualization, writing—review and editing. A.F.H.M. involved in conceptualization, data curation, formal analysis, methodology, visualisation, writing—original draft, writing—review and editing.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from TriNetX. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from TriNetX through a third-party agreement option.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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