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Secondary infection by *Cryptococcus* spp. in HIV-negative patients in the context of Covid-19

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ABSTRACT

Cryptococcosis is an infectious disease with worldwide distribution caused by fungi of the genus *Cryptococcus*, especially by the species C. neoformans and C. gattii. *Cryptococcus* infections begin with the inhalation of fungal particles that reach the lungs and can spread through hematogenous, especially in hosts with deficiencies in the cellular immune system. The acute respiratory syndrome in COVID-19 promotes a decrease in the efficiency of the immune system, either due to exhaustion resulting from the exacerbated response or due to immunosuppression in treatment with corticosteroids to contain the cytokine cascade in COVID-19, facilitating the appearance of opportunistic fungal infections in patients who develop severe cases of the virus due to SARS-CoV-2. The objective of this research is to conduct a review of clinical cases of cryptococcosis in co-infection with SARS-CoV-2 or the appearance of this mycosis in the post-COVID-19 convalescence period in HIV-uninfected individuals, analyzing the risk factors and circumstances associated with the relationship between cryptococcosis and COVID-19. Although cryptococcosis is a relatively rare infection among patients with COVID-19 and in the convalescence period of the disease, this opportunistic mycosis may be responsible for a mortality rate that is considered high (greater than 55%). Susceptibility to *Cryptococcus* spp. infection in the context of COVID-19 disease and treatment is strongly associated with corticosteroid use and pre-existing multiple comorbidities. It is not possible to determine the degree to which cryptococcosis is responsible for mortality in co-infection or infection during the COVID-19 convalescence period. The development of secondary infection by *Cryptococcus* spp. is indicative of a poor prognosis for the patient.

Keywords: *Cryptococcus* spp., SARS-CoV-2, COVID-19, Secondary infection.

1 INTRODUCTION

Cryptococcosis is an infectious disease with worldwide distribution caused by fungi of the genus Cryptococcus, especially by the species C. *neoformans* and *C. gattii. Cryptococcus* spp. are basidiomycete, capsulated yeast fungi with wide distribution in the environment and found in tree bark, soil, fruits, and other organic materials, mainly in poultry feces (KWON-CHUNG et al., 2014; GODINHO et al., 2017; ABRAHAM, 2020. TORRE et al., 2022).

The first description of fungi of the genus *Cryptococcus* was made in 1894 by physicians Otto Busse and Abraham Buschke, who isolated from a patient's bone infection a fungus whose appearance was similar to Saccharomyces*, being named* Saccharomycosis hominis. Also in 1894, researcher Francesco Sanfelice, in Italy, discovered a fungus similar to the one described by the German researchers. This fungus, isolated from a fermented peach juice, was named *Saccharomyces neoformans*, because of the peculiar shape of the colonies. In the first year of the twentieth century, the French researcher Jean-Paul Vuillemin studied the characteristics of both fungi and, due to several physiological differences in relation to the genus *Saccharomyces*, renamed the species to Cryptococcus *hominis and Cryptococcus neoformans*. Studies carried out from the late 1960s onwards by molecular techniques determined that some variants of *C. neoformans* were sufficiently distinct to be characterized as a new species, designated *C. gattii* (DINIZ-LIMA et al., 2022). The genus *Cryptococcus* currently has at least 70 species considered valid (FONSECA et al., 2011).

Cryptococcus *infections* begin by inhaling fungal particles that reach the lungs. (KWON-CHUNG et al., 2014; GODINHO et al., 2017; ABRAHAM, 2020). After aspiration of the fungus, *Cryptococcus* spp. begins to colonize the lung tissue. The immune response of the immunocompetent host is usually able to eradicate *Cryptococcus* spp. infection. However, depending on the amount of fungal particles aspirated, the immune status of the host, or the virulence of the strain, the infection may progress to acute disease or become latent and asymptomatic. From the pulmonary focus, the pathogen can spread through the hematogenous route, especially in hosts with deficiencies in the cellular immune system, such as individuals with HIV, organ transplant recipients, sarcoidosis, lupus erythematosus, leukemia, and patients undergoing immunosuppressive therapies. *Cryptococcus* can remain inside macrophages in thoracic lymph nodes without being destroyed, remaining viable for a long time. In the event of a drop in immunity, the fungus begins to multiply and spreads beyond the lymphatic complex, initiating the disease. This reactivation is more common in *C infection. neoformans*, as *C. gattii* is mainly responsible for acute infections in immunocompetent individuals (KWON-CHUNG et al., 2014; GODINHO et al., 2017; ZAVALA & BADDLEY, 2021; TORRE et al., 2022). After hematogenous dissemination, *Cryptococcus* spp. can cross the blood-brain barrier and implant in the Central Nervous System, causing meningoencephalitis (KWON-CHUNG et al., 2014; GODINHO et al., 2017, TORRE et al., 2022). The symptoms of pulmonary cryptococcosis can range

from a nonspecific cough to more significant symptoms such as chest pain, hemoptysis, dyspnea, weight loss, malaise, and anorexia. Pleural effusions are rare, and progressive lung disease, Severe Acute Respiratory Syndrome, and respiratory failure may occur, especially in immunocompromised patients (HSIAO et al., 2022). Cryptococcal meningoencephalitis is more common in immunocompromised patients, and presents the most frequent symptoms: headache, neck stiffness, photophobia, fever, memory loss, lethargy, and changes in the state of consciousness. Depending on the state of the infected individual's immune system, central nervous system infection can become chronic or lead to death within a few days (GODINHO et al., 2017, ZAVALA & BADDLEY, 2021; TORRE et al., 2022). Cryptococcal meningitis can be caused by either *C. gattii* as per *C. Neoformans*. The characteristic conditions of cryptococcosis most commonly affect the lungs and central nervous system, but atypical clinical presentations can manifest in the skin, prostate, eyes, urinary tract, bones, and other organs, especially in association with AIDS (KWON-CHUNG et al., 2014; GODINHO et al., 2017; GUERY et al., 2019). Symptomatic infections by *Cryptococcus* spp. are potentially fatal when early treatment is not performed, as the necrosis of the tissue adjacent to the foci of infection does not allow the perfusion of antifungals in the affected region (FERNANDES et al., 2016).

According to Godinho et al. (2017), at the beginning of the twentieth century the occurrence of cryptococcosis was sporadic and less than 300 cases were reported before the 50s. Since the 1970s, the number of cases has increased in association with a greater number of organ transplants, immunosuppressive therapies and therapies to support diseases with greater malignancy, becoming a major global public health problem with the emergence of HIV. The emergence of *Cryptococcus* spp. as an emerging pathogen was strongly associated with the AIDS epidemic in the 1980s. Although the incidence of meningitis caused by this fungus has been decreasing among HIV-positive patients in recent years due to early diagnosis and effective treatment with antifungals, cryptococcosis is still the most fatal mycosis among AIDS patients (PARK et al., 2009; GODINHO et al., 2017; ABRAHAM, 2020). The number of estimated cases of cryptococcosis in the world for the year 2014 was 223,100, with 181,000 deaths from this disease (RAJASINGHAM et al., 2017). Globally, cryptococcosis accounts for about 19% of AIDS-related deaths (RAJASINGHAM et al., 2022). The global mortality rate is around 20% in developed countries and can be as high as 70% in developing countries (GUERY et al., 2019).

Acute respiratory syndrome in COVID-19 is associated with increased pro-inflammatory cytokines, interleukins, and an uncontrolled cellular immune response (MANGIAVACCHI et al., 2020). The decrease in the efficiency of the immune system, either due to exhaustion due to the exacerbated response or immunosuppression in treatment with corticosteroids to contain the cytokine cascade in COVID-19, is a factor associated with the appearance of opportunistic fungal infections in patients who develop severe SARS-CoV-2 virus (NORBERG et al., 2021a; NORBERG et al., 2021b,

NORBERG et al., 2022; AKHTAR et al., 2022). The use of corticosteroids is one of the most important risk factors for triggering *Cryptococcus* spp. infections, and this association was recognized even before the COVID-19 pandemic (GOLDSTEIN & RAMBO, 1962; BENNINGTON et al., 1964; KUMARI et al., 2005; MACDOUGALL et al., 2011; KWON-CHUNG et al., 2014).

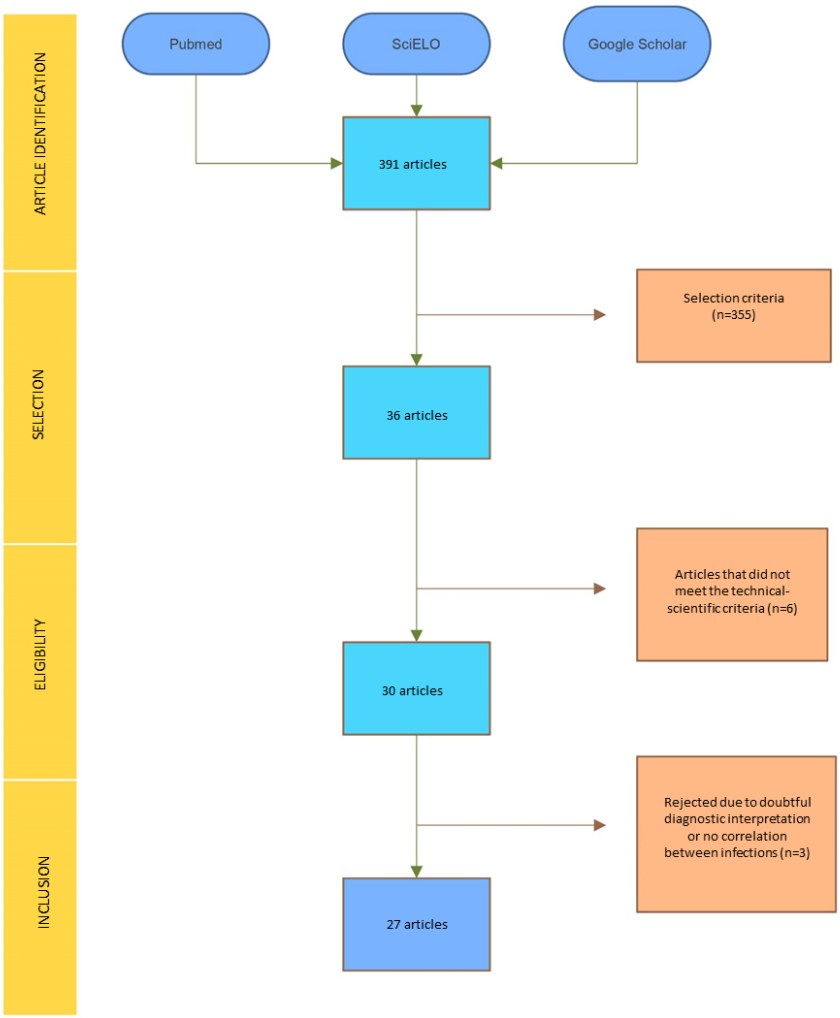
The objective of this research is to conduct a review of clinical cases of cryptococcosis in co-infection with SARS-CoV-2, as well as the appearance of this mycosis in the post-COVID-19 convalescence period in HIV-uninfected individuals, analyzing the risk factors and circumstances associated with the relationship between cryptococcosis and COVID-19.

2 METHOD

The guiding question of the line of investigation was: "what circumstances of COVID-19 can favor opportunistic infection by *Cryptococcus* spp. in non-HIV-infected individuals?". The systematic review, based on this questioning, was based on the methodological model of Moher et al. (2009) in "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA model). The limitations and restrictions for the inclusion of research sources were technical-scientific criteria for determining simultaneous infection by both pathogens investigated and the context of development of co-infection or fungal infection subsequent to COVID-19. In addition to the nexus in SARS-CoV-2 and *Cryptococcus* spp., comorbidities and clinical history that could directly impact susceptibility to fungal infection, as well as the patient's prognosis.

The search was carried out in the PubMed, SciELO and Google Scholar databases for the search of clinical cases. The search strategy used the following descriptors, in various combinations: "SARS-CoV-2", "COVID-19"; "*Cryptococcus*", "cryptococcosis". Articles published in English, Portuguese and Spanish were selected, with a time frame of publication between 2019 and September 2022. After reading each article and case report, the material that presented consistency with the researched theme was selected and organized for data extraction through the collaborative analysis of all authors. The exclusion criterion was applied to review articles, opinion articles, articles with incomplete data or whose diagnostic interpretation was doubtful or the association between SARS-CoV-2 and *Cryptococcus* spp. infections was not possible . After the consensual screening of the collected material, the most important aspects were written for analysis purposes. The flow of the research source sourcing and selection strategy is described in figure 1. The presentation of the results provides a brief report of each clinical case, summarized schematically according to the most relevant clinical variables in Chart 1, which are then discussed analytically.

Figure 1: Flowchart of the publication screening process



Source: the authors

3 RESULTS AND DISCUSSION

Researchers Traver and Sánchez (2022) described the case of a 59-year-old man with a history of Chronic Obstructive Pulmonary Disease treated with corticosteroids, coronary heart disease with the application of three stents, use of a pacemaker, type 2 diabetes mellitus, obesity, nocturnal apnea, cirrhosis caused by the hepatitis C virus. Six months before hospitalization for COVID-19, the patient was hospitalized with pneumonia caused by *Klebsiella pneumoniae* associated with mechanical ventilation. On the first day of hospitalization for COVID-19, the patient was medicated with Vancomycin and Cefepime for suspected bacterial co-infection. In the following 38 days, treatment with methylprednisolone and the use of mechanical ventilation with the use of a mask were required, followed using a nasal cannula and culminating in endotracheal intubation. On the eighteenth day, the individual was extubated. On the twenty-sixth day, the medical team considered it necessary to undergo antibiotic therapy with piperacillin-tazobactam and on the following day with cyclophosphamide due to suspicion of bacterial co-infection. During these two days, there was a worsening of the pneumonia condition, and imaging tests showed bilateral opacities in the lungs. Antibiotic therapy was expanded

with the use of vancomycin and bronchoalveolar lavage material was sent for culture. On the thirty-third day of hospitalization, the culture result was positive for *Aspergillus fumigatus*, in addition to the associated growth of *Cryptococcus neoformans*. Antifungal therapy was performed with amphotericin B and flucytosine. On the thirty-ninth day, the patient's general condition worsened, with severe hypoxia and septic shock. Methylpredinisolone and hydrocortisone were administered as life-sustaining measures in septic shock and *Enterobacter cloacae* pneumonia was diagnosed. The patient refused to continue with respiratory and renal support treatment and died on the forty-fifth day.

Darfaoui et al. (2022) reported on the case of a 64-year-old patient, a smoker with type 2 diabetes, admitted to an Intensive Care Unit with fever, dyspnea, and low blood oxygen saturation. COVID-19 was confirmed by PCR. The patient was treated with methylprednisolone, showing improvement in the stability of respiratory function. Two days later, the patient presented with fever, hemodynamic and respiratory instabilities, and increased leukocytosis and C-reactive protein. The bronchoalveolar lavage material was sent for microorganism culture, and empiric antibiotic therapy with amoxicillin and clavulanic acid was initiated. A few days later, the culture showed growth of *Cryptococcus neofornams*. The CSF infection by *Cryptococcus* was confirmed by direct observation by the India ink method and the species *C. neoformans* identified by biochemical tests. Serology was positive for *C. neoformans.* It was not possible to perform other clinical examinations because on the first day of treatment with antifungal drugs, the patient died.

Co-infection with *Cryptococcus* spp. in COVID-19 was considered by Abohelwa et al. (2021) as a condition that decisively impacts the patient's prognosis. These authors reported the case of a 78-year-old woman with a clinical history of hypertension and diabetes mellitus who was hospitalized with shortness of breath after being diagnosed with COVID-19. The patient was transferred to the Intensive Care Unit after a drop in hemoglobin levels, Respiratory Stress Syndrome and melena, and underwent endotracheal intubation. The tracheal aspirate sent for culture was positive for *Cryptococcus neoformans*, even though the serology was negative for this fungus. The treatment with antifungals was done with Fluconazole, but the patient died after a few days. The authors attribute the risk of cryptococcosis in association with COVID-19 to the use of corticosteroids, as the patient was immunocompetent.

Štingl et al. (2022) reported a case of *Cryptococcus neoformans* pneumonia in COVID-19 superinfection. A 60-year-old man with a history of hypertension, myocardial infarction, and not vaccinated against COVID-19 presented typical symptoms of this virus: cough, dyspnea, chest pain, and fever. Four days after the onset of symptoms, he was hospitalized and the PCR was positive for SARS-CoV-2. X-ray examination showed diffuse infiltrates, mainly in the right upper lobe. Despite therapy with Remdesivir, methylprednisolone, and low molecular weight heparin, respiratory distress increased by the fifth day of treatment. The medical team decided on oxygen supplementation and

antibiotic therapy with clarithromycin and ceftriaxone. On the eleventh day, the patient was transferred to the Intensive Care Unit because the oxygen saturation in the blood was below 60%. Therapy with the corticosteroid methylprednisolone was replaced by dexamethasone. On the twelfth day, the patient was intubated with aggressive oxygenation parameters. Bronchialveolar lavage examination demonstrated a high SARS-CoV-2 viral load but no evidence of fungal infection. On the thirteenth day, ventilator-associated pneumonia was diagnosed with beta-lactamase-producing *Klebsiella pneumoniae*, which was treated with vancomycin. On the nineteenth day, blood culture was negative for *Klebsiella*, but bronchoalveolar lavage revealed an even higher viral load of SARS-CoV-2 and 1200 units of *Cryptococcus neoformans* per milliliter. On the twenty-first day, serology for *C. neoformans* was positive. Antifungal therapy was initiated with Amphotericin B and Fluconazole. Blood and cerebrospinal fluid cultures were negative for fungal and bacterial elements. On the twenty-fourth day, the patient suffered a cardiac arrest and died. The death was attributed to multiple organ dysfunctions and cryptococcal pneumonia. Post-mortem histopathological examination showed severe diffuse alveolar damage, with the presence of an inflammatory reaction and numerous foci of *C. neoformans.*

Torrez-Serrano et al. (2021) presented a clinical case of *Cryptococcus neoformans* co-infection during COVID-19 in a kidney transplant patient. The 45-year-old had received a kidney transplant 20 years before the COVID-19 pneumonia. This patient was using the immunosuppressants Mycophenolate sodium and sirolimus. The patient was admitted after four days of progressive dry cough, asthenia, hypoxia and malaise. One day after admission, there were periods of fever of up to 39°C and self-limited diarrhea. The oxygen saturation index recorded was 83%, but there were no signs of respiratory distress. SARS-CoV-2 infection was confirmed by PCR, and imaging tests were consistent with the patterns observed in COVID-19 pneumonia. During hospitalization, antibiotic therapy was performed with aminopenicillin, beta-lactamase inhibitor and macrolides, in addition to the use of dexamethasone. Tests for the detection of opportunistic infections revealed positivity for *Cryptococcus neoformans*. The patient was treated with amphotericin B and meningeal involvement was ruled out due to the absence of *Cryptococcus* spp. in the cerebrospinal fluid. The patient's clinical condition progressively deteriorated, requiring intubation and transfer to the Intensive Care Unit. After 12 days of hospitalization, the patient worsened in the Acute Respiratory Syndrome and died due to cardiac arrest.

Cryptococcus neoformans *fungemia* in a liver transplant recipient patient with severe COVID-19 was reported by Guimarães et al. (2022). The 70-year-old patient received liver transplantation in March 2020 and had a good postoperative evolution, with maintenance immunosuppressive therapy with Mycophenolate and Methylprednisolone. On the fifth day after surgery, the patient presented respiratory failure, requiring mechanical ventilation and a diagnosis of infection by *multidrug-*

resistant Acinetobacter baumannii. Treatment with Meropenem and Polymyxin B was effective in controlling this bacterium. At the end of the first month of hospitalization, the patient presented fever, hypoxia, leukopenia, and the PCR test was positive for SARS-CoV-2. There was a degradation of hemodynamic and ventilatory status, as well as hepatic dysfunction, which progressed to death. The results of blood cultures collected two days after the diagnosis of COVID-19 were positive for *Cryptococcus neoformans*.

Gil et al. (2021) reported the case of a 59-year-old man with a clinical history of hypertension, diabetes mellitus, and obesity, who was hospitalized with fever, shortness of breath, vomiting, and abdominal pain starting within 24 hours before admission. Chest X-ray revealed the existence of bilateral pulmonary infiltrates, without the presence of nodules, cavitations, or other abnormalities. The serological test was positive for SARS-CoV-2. After five days of hospitalization, the patient required oxygen supplementation through a nasal cannula. Blood culture was negative for microorganisms. Drug therapy was performed with Remdesivir, Azithromycin and Ceftriaxone for four days, and Dexamethasone for 21 days. One week after admission, there was respiratory failure, with cardiopulmonary arrest successfully reversed. After this event, the patient required endotracheal intubation. On the tenth day, a new episode of fever occurred and it was decided to use antibiotic therapy with Meropenem while awaiting the results of the culture of the organic materials. Blood culture was positive for *Cryptococcus neoformans*, although serology was still negative. There were no signs of meningeal infection with neurological involvement on the results of imaging tests and computed tomography of the head and lungs, nor did they reveal evidence of cryptococcosis. The patient was treated with Amphotericin B and Fluconazole and in six weeks, with clinical improvement, a new blood culture was performed, which did not reveal the presence of *C. neoformans.* The authors stated that long-term use of dexamethasone may be responsible for the patient's susceptibility to *Cryptococcus infection*.

Filhao et al. (2022) reported the clinical case of a 54-year-old woman with hypertension, heart disease, obesity, type 2 diabetes, hospitalized with cough and dyspnea, who progressed to respiratory failure. The PCR test was positive for SARS-CoV-2. After four days of hospitalization in the Intensive Care Unit, the patient presented worsening of renal function, hypertension and hemodynamic instability that was difficult to control. Empiric antibiotic therapy with Pipetazobactam was started while awaiting the results of the blood culture. After ten days, the fungal growth of *Cryptococcus laurentii* was identified by genetic sequencing evidence. Treatment with amphotericin B and fluconazole was initiated. As the blood culture results were negative after two weeks, only Fluconazole was prescribed for 84 days. After 107 days of hospitalization, the patient was discharged with oxygen supplementation via tracheostomy.

A clinical case of cryptococcemia concurrent with severe COVID-19 pneumonia was presented by Thyagaranjan et al. (2021). A 75-year-old man with a history of diabetes mellitus, high blood pressure, obesity, osteoarthritis was admitted after four days of fever and difficulty breathing. COVID-19 was confirmed by PCR test. The oxygen saturation level was 50%, requiring immediate intubation. The HIV test was negative. The patient was treated with Remdesivir, convalescent plasma, and dexamethasone. On the eleventh day of hospitalization, the fever persisted and the oxygenation level was even more critical. Sputum culture was positive for methicillin-resistant *Staphylococcus* on days 11, 17 and 22 of admission. The patient received antibiotic therapy with vancomycin, later replaced by linezolid. The clinical picture worsened with kidney damage and cerebral infarction. Because of persistent fever and eosinophilia, treatment with prednisolone was treated. Due to the worsening of the general condition and the difficulty in maintaining support measures, the patient began to receive palliative care. On the twenty-seventh day of hospitalization, the individual died. Four days after death, the blood culture result was positive for *Cryptococcus neoformans*.

Grush et al. (2022) described a clinical case of a 77-year-old patient with several comorbidities such as heart failure, renal failure, and diabetes mellitus. This individual was hospitalized with hypoxia due to COVID-19 and treated with Dexamethasone and Remdesivir. On the fourth day of hospitalization, there was a worsening of the clinical signs and the use of mechanical ventilation and the administration of Tocilizumab were necessary. The medical team suspected co-infection and empirical antibiotic therapy began on the ninth day of hospitalization. Blood cultures performed on the ninth and tenth day of hospitalization were positive for yeast fungi. On the thirteenth day, the yeast was identified as *Cryptococcus neoformans*. Antibiotic therapy was replaced by amphotericin B and flucisosin, but the patient died on the same day.

Khatib et al. (2021) described the clinical picture of a 60-year-old male patient with a history of hypertension, diabetes mellitus, and cardiac ischemia. The patient was admitted to an Intensive Care Unit with confirmed SARS-CoV-2 infection, and required mechanical ventilation from the first day of admission. Three doses of Tocilizumab were applied to contain the cytokine cascade, in addition to several doses of Methylprednisolone and Hydrocortisone. After a few days, bronchoalveolar lavage culture was positive for *Candida glabrata*, and this fungal infection was treated with Anidulafungin for seven days. After 28 days of hospitalization, the development of acute kidney disease was observed, with consequent need for hemodialysis. As the inflammatory markers remained high, a blood culture was performed, which revealed candidemia due to *Candida parapsilosis* on the thirtieth day of hospitalization. Anidulafungin therapy was resumed for a further seven days. The candidemia remained for another two weeks and the treatment with Anidulafungin was prolonged for another 14 days. Ophthalmologic examination revealed fungal ophthalmitis. After 18 days of treatment with Anidulafungin, blood culture was positive for *Cryptococcus neoformans* and antifungal therapy was

reinforced with Amphotericin B and Flucytosine. Despite all efforts, the patient died of crytococcemia ten days after the detection of *C. neoformans.*

Torres et al. (2022) presented the clinical case of a 71-year-old man with a history of hypertension, kidney disease, hepatitis C, and liver cirrhosis, who was hospitalized with fever, dry cough, and dyspnea. Testing for SARS-CoV-2 infection was positive. Chest X-ray revealed the presence of diffuse bilateral infiltrates. Treatment with enoxaparin and dexamethasone was initiated, in addition to oxygen supplementation by nasal cannula. The patient's general condition deteriorated, requiring intubation. After 30 days of hospitalization, leukocytosis was observed and the suspicion of pneumonia advised the initiation of medication with Vancomycin, Cefetime and Fluconazole. The patient died as a result of cardiac arrest. The result of the blood culture was revealed one week after death and showed the growth of *Cryptococcus neoformans*.

Ghanem and Sivasubramanian (2021) described a case of a 73-year-old woman with hydrocephalus and a history of other comorbidities, who presented with fever and hypoxia after orthopedic surgery, requiring supplemental oxygen therapy. X-ray image demonstrated heterogeneous bilateral infiltrates. COVID-19 was confirmed by PCR test. The patient received treatment of Azithromycin for five days and Dexamethasone for ten days. One week after the end of treatment, neurological signs and symptoms such as unsteady gait, constant falls, and aphasia appeared. The patient was intubated and imaging tests showed worsening of hydrocephalus. HIV serology was negative. The analysis of the cerebrospinal fluid revealed positive serology for *Cryptococcus* spp. and in the culture of this organic material there was growth of *C. neoformans.* The diagnostic determination guided drug therapy with Amphotericin B and Flucytosine. Subsequently, the patient developed ventilator-associated pneumonia caused by *Escherichia coli*, which was treated with Meropenem. The treatments were efficient and the patient was taken to recovery in a primary care ward. The authors consider that corticosteroid therapy may have contributed to the dysfunction of T lymphocytes in the patient, in addition to the possibility that immunocellular dysregulation may be linked to the pathophysiological consequences of SARS-CoV-2 infection.

A case of disseminated cryptococcosis as a complicating factor of a severe case of COVID-19 was described by Lupia et al. (2022). The 64-year-old patient had a history of obesity, alcoholism, toxic cirrhosis, decompensated insulin-dependent diabetes mellitus, atrial fibrillation, and chronic kidney disease. The subject was hospitalized with Acute Respiratory Syndrome and SARS-CoV-2 infection confirmed by laboratory tests. On the first day, the use of non-invasive ventilation and therapy with Dexamethasone, Amoxicillin and Clavulate was required. Multiple comorbidities contraindicated the use of Tocilizumab and Remdesivir. After a brief recovery from clinical conditions, there was a degradation of renal and hepatic functions, generalized edema, and encephalopathy due to hepatic dysfunction. At the same time, the rate of blood oxygen saturation decreased and more intensive

respiratory support was required. The suspicion of pneumonia of nosocomial origin led to a change in the antibiotic plan to the use of piperacillin-tazobactam and tigecycline. The use of corticosteroids was also intensified. The deterioration of the patient's clinical condition was responsible for the transfer to the Intensive Care Unit. On the twentieth day of admission, blood culture was positive for *Cryptococcus neoformans*. Antifungal therapy was based on the use of amphotericin B and isafluconazole. The diagnosis of disseminated cryptococcosis without neurological involvement was confirmed by serology by the latex agglutination system and biochemical tests by the BioMerrieux-Vitek system. As a consequence of the patient's critical state of health and the rapid evolution of the disease, the patient died five days after the isolation of *Cryptococcus neoformans* in the blood culture.

Researchers Karnik et al. (2022) described a case of disseminated cryptococcosis with meningoencephalitis in a patient hospitalized for COVID-19. The 57-year-old man with a clinical history of high blood pressure, was admitted with fever, chills, shortness of breath, malaise, loss of appetite for nine days before attending the hospital. Clinical examination revealed a blood oxygen saturation rate of 64% and crackles in both lungs. PCR was positive for SARS-CoV-2 and serology detected antigens for *Legionella* and *Streptococcus*. X-ray revealed bilateral heterogeneous opacities and interstitial opacities consistent with imaging patterns observed in COVID-19. Drug therapy consisted of the administration of Dexamethasone, Remdesivir, Azithromycin and Ceftriaxone. The patient's clinical condition worsened, imaging tests showed an advance of the infiltrates, and the patient was intubated. Antibiotic therapy with vancomycin and meropenem was initiated. Dexamethasone was replaced by methylprednisolone. After 33 days of the beginning of hospitalization, the patient presented diarrhea diagnosed as colitis caused by *Candida* spp., which was treated with Nystatin. On the thirty-sixth day, the patient presented hypoxia and hypotension, and methylprednisolone was replaced by hydrocortisone. Blood culture revealed the presence of fungi, and Micafungin was administered due to presumption of candidemia. The fungal growth in the culture was later identified as *Cryptococcus neoformans*. The fresh test of the cerebrospinal fluid with India ink suggested positivity for *C. neoformans*, which was later confirmed by culture of this organic material. Serology for *Cryptococcus* in the cerebrospinal fluid was positive with a titer of 1:256. The suspicion of HIV infection was ruled out by PCR test. Treatment with Micafungin was discontinued and replaced with Amphotericin B and Flucytosine. On the fortieth day of hospitalization, in addition to the complication of the neurological condition, there was the appearance of cutaneous nodules with characteristics of disseminated cryptococcosis. Two days later, the patient died.

Deepa et al. (2022) reported a case of endophthalmia caused by *Cryptococcus laurentii* in a patient convalescent from COVID-19. A 50-year-old patient with a history of diabetes was hospitalized for COVID-19 and received treatment with Dexamethasone and Prednisolone for three weeks. After medical discharge, the individual noticed a progressive decrease in vision, the diagnosis of which was

presumed to be diabetic retinopathy. Fundus examination of the right eye revealed microaneurysm and hemorrhage, a result compatible with diabetic retinopathy. Examination of the left eye showed opacity and a densely yellowish area occupying half the diameter of the disc. As the patient had septicemia caused by *Klebsiella* spp. at the beginning of the COVID-19 convalescence period, it was suspected that this was the etiologic agent of ophthalmitis. The sample collected from the vitreous humor was submitted to culture, showing growth of *Cryptococcus laurentii*. Antifungigram testing revealed susceptibility to Fluconazole, Micafungin, Amphotericin B and Voriconazole. Two days after starting treatment with Voriconazole, the patient showed a remarkable improvement in vision. After two months of treatment, the granuloma disc and vitreous opacity disappeared. Fundus examination revealed a diffuse epiretinal membrane and cystoid macular edema, characteristic of healing of the injured tissue.

A rare case of pulmonary cryptococcosis after recovery from COVID-19 in an immunocompetent patient was investigated by Choi (2020). A 46-year-old man was seen at a hospital with a clinical complaint of cough, without any other signs or symptoms. The clinical history of COVID-19 three months prior to admission did not indicate the use of corticosteroids, anti-inflammatory drugs, antibiotics, cytokine blockers, or antiviral agents. After 14 days of quarantine, the patient has fully recovered from COVID-19. HIV tests were negative. A computed tomography scan of the chest showed small infiltrated nodules in the upper lobe of the left lung, suggestive of bronchiolitis or tuberculosis. Direct investigation of bronchoalveolar lavage revealed the presence of yeast cells indicative of *Cryptococcus* spp. The second sample of bronchoalveolar lavage was sent for culture, and *Cryptococcus neoformans* was isolated. Serology for *Cryptococcus* spp. was also positive. Histopathological analysis revealed granulomatous inflammation with rounded yeasts, encapsulated by macrophages and multinucleated giant cells. Blood and cerebrospinal fluid cultures were negative for *Cryptococcus* spp., ruling out the possibility of disseminated infection. After six months of treatment with Fluconazole, imaging tests showed the complete disappearance of the Cryptococcus foci in the lung.

A case of *Cryptococcus* pneumonia subsequent to COVID-19 was described by Gullapalli et al. (2021). A 55-year-old man with a history of latent tuberculosis presented with progressive cough and dyspnea. PCR for SARS-CoV-2 was positive. There were no signs of hypoxia, which advised against prescribing Remdesivir or Dexamethasone. Since the patient had been hospitalized for community-acquired pneumonia two months earlier, broad-spectrum antibiotic therapy was initiated. Three weeks later, the patient returned with progressive dyspnea, nausea and vomiting. The PCR test at that time was negative for SARS-CoV-2. Bronchoalveolar lavage cultures and lung biopsy showed fungal elements suggestive of Cryptococcus spp . *Lumbar puncture revealed elevated intracranial pressure, and microscopic examination of the cerebrospinal fluid identified the presence of*

Cryptococcus spp. The serological test for this fungus showed high titer. HIV serology was negative. Due to cryptococcal meningitis, the patient began to present seizures with hypertonia and altered mental status. Antifungal therapy used the drugs Amphotericin B and Flucytosine to control the infection. Biopsy cultures of several tissues showed fungal growth of *Cryptococcus gattii*. The patient's clinical condition improved slowly until mechanical respiration was withdrawn.

Researchers Isaac et al. (2021) presented the clinical case of a 62-year-old man with no comorbidities who was hospitalized with COVID-19. The patient required oxygen therapy and developed pulmonary embolism. In the process of recovery from the acute virus, the formation of pulmonary fibrosis was observed. A month later, the patient was again hospitalized with cough, shortness of breath, tachycardia, and low blood oxygen saturation. The PCR test for SARS-CoV-2 was still positive. Pulmonary auscultation showed bilateral crepitus. The CT scan was consistent with multifocal pneumonia. The drug plan included the administration of Remdesivir, Linezolid, Meropenem, and Dexamethasone. As respiratory failure progressed, Ceftazidime and methylprednisolone were added to the list of drugs. The patient's clinical condition worsened with the onset of myopathy and atrial fibrillation. The serological test was positive for *Cryptococcus antigens* and after 18 days of treatment with Fluconazole, the multifocal infiltrates in the lungs were reduced. The authors attribute the high levels of steroids in the treatment of COVID-19 to the immunosuppression that allowed opportunistic infection with *Cryptococcus* spp.

A case of pulmonary cryptococcosis subsequent to COVID-19 was presented by Sharma et al. (2022). The patient, a 60-year-old man, had a clinical history of hypertension, poorly controlled diabetes mellitus, and hypothyroidism. During his hospitalization for COVID-19, he required oxygen therapy for 11 days and was treated with Remdesivir, blood thinners, and high doses of corticosteroids. Two months after recovery, he was hospitalized with fever, uncontrollable dry cough, headache, and dyspnea, which worsened in the last five days before admission. Computed tomography showed the existence of consolidated spaces in the upper lobe of the right lung with focal lesions. Biopsy of one of these lesions by histopathology revealed the presence of granulomas with rounded, capsulated yeasts, suggestive of *Cryptococcus lesions*. Imaging of the brain, eye sockets, and paranasal sinuses, as well as blood and urine cultures, showed no evidence of disseminated Cryptococcus mycosis. A few days after culture of the biopsy material, the fungal growth was identified as *Cryptococcus neoformans* sensitive to Amphotericin B and Fluconazole. The patient was treated with amphotericin B for 14 days and imaging tests showed resolution of the C. *neoformans foci* in the lung. The subject was discharged from the hospital and continued antifungal therapy with fluconazole was recommended.

Jacob and Jani (2021) reported the clinical case of a 47-year-old woman with hypothyroidism and recent COVID-19 who sought care at a hospital with a complaint of weight loss and presenting with shortness of breath and lymphadenopathy. Imaging showed a right-sided pleural effusion with

pleural thickening. Analysis of fluid drained from the lungs and biopsy of the lymph nodes did not reveal the possible etiologic agent. Biopsy of the material taken from the lower portion of the right lung revealed multiple white deposits, and the cultured material obtained the growth of *C. neoformans.* The patient had no comorbidities or immunosuppressive factors, conditions usually associated with *C. neoformans infections*, and infection with this fungus can be considered as a result of immune depletion caused by COVID-19. The authors did not report the outcome of the clinical picture.

Roesch et al. (2022) reported a clinical picture of a 46-year-old female patient with a history of chronic kidney disease, altered heart rhythm, use of mitral valve prosthesis, and recent SARS-CoV-2 pneumonia three months prior to admission. During hospitalization for COVID-19, the patient received treatment with Remdesivir, Dexamethasone, Tocilizumab, Anakinra, and immunoglobulin. Steroid treatment was continued after medical discharge and terminated one month before admission due to new pneumonia. In this second hospitalization, X-ray examination showed basal collapse in both lungs and several areas of clouding in the lower lobes. The PCR test for SARS-CoV-2 at that time was negative. Blood and sputum cultures were negative for fungi and bacteria. Serology for *Cryptococcus* spp. was positive with a titer of 1:128. A biopsy of the lower lobe material of the right lung revealed the presence of macrophages, neutrophils, and areas of necrosis. Microscopic examination with staining that evidences the presence of fungal elements allowed the identification of *Cryptococcus* spp. encapsulated by immune system cells. The authors did not provide information on the treatment adopted and the resolution of the clinical picture.

Cafardi et al. (2021) reported on a clinical case of a 78-year-old man with a history of hypertension and Chronic Obstructive Pulmonary Disease who was hospitalized after five days of high fever, headache, dyspnea, and diarrhea. The PCR test for SARS-CoV-2 was positive. The patient had a low level of oxygen saturation in the blood, and was admitted to the Intensive Care Unit and submitted to mechanical ventilation. The subject was treated with Remdesivir and Methylprednisolone. After ten days of intensive care, the need for oxygen therapy decreased, and the patient was transferred to a ward. After four days of hospitalization in the ward, there was a recrudescence of signs and symptoms, with fever and respiratory failure, with new intubation. Bronchoalveolar lavage culture performed 36 hours after readmission to the Intensive Care Unit revealed the growth of *Cryptococcus neoformans*, even though serology for *Cryptococcus* antigens had been negative. The suspicion of HIV infection was ruled out by serological test. Treatment with amphotericin B was initiated, which was replaced after six days by isavoriconazole due to severe renal damage. The patient's clinical condition continued to deteriorate with the onset of ventilator-associated pneumonia caused by *multidrug-resistant Enterobacter cloacae* and *Alcaligenes* spp. Due to the severity of the clinical case, the family members decided to interrupt the treatment and the patient died on the thirty-ninth day of hospitalization.

Alegre-González et al. (2021) published a case report of disseminated *Cryptococcus neoformans infection* associated with COVID-19. A 78-year-old man with a history of type 2 diabetes, hypertension, and chronic kidney disease was hospitalized with fever, dyspnea, and asthenia. The PCR test was positive for SARS-CoV-2. On the second day of hospitalization, the individual was transferred to an Intensive Care Unit and required mechanical ventilation and therapy with high doses of Dexamethasone. On the thirtieth day, the improvement of the clinical status allowed the use of non-invasive mechanical ventilation. After 58 days of hospitalization, imaging studies revealed the persistence of bilateral pulmonary infiltrates. Treatment with methylprednisolone for three days resulted in a favorable outcome, and 62 days after the beginning of hospitalization, the patient was discharged with a prescription for home treatment with prednisone. Three days later, he returned to the hospital with fever and crepitus audible on auscultation of both lungs. The leukogram revealed marked neutrophilia. The CT scan showed bilateral infiltrates and a new area of consolidation in the left lung. On the tenth day of the new hospitalization, the blood culture was positive for *Cryptococcus neoformans*. HIV infection was suspected, but PCR was negative for this virus. CSF serology was positive for cryptococcal antigen, with a titer of 1:1024, and blood serology was 1:512. Treatment with amphotericin B and flucytosine was initiated. After 10 days, antifungal therapy was replaced with Fluconazole due to increased creatinine levels. The clinical evolution was favorable and the patient was discharged. After 15 days, he was again hospitalized with pneumonia. Blood culture was negative for Cryptococcus *spp. and positive for* methicillin-resistant Staphylococcus aureus . The patient's health condition worsened, with death progressing on the fortieth day of the last hospitalization.

Ramezanzadeh and Nikfarjan (2021) reported the clinical picture of a kidney transplant patient who was admitted to a hospital in Iran. This patient developed C. *neoformans meningitis* three months after recovering from COVID-19. The individual, a 58-year-old diabetic man, presented with headache, fever, nausea and vomiting. Examination of the cerebrospinal fluid showed evidence of fungal infection, whose etiologic agent was later identified as *C. neoformans.* Treatment was performed with Amphotericin B and Flucytosine. After appropriate therapy, the patient's clinical condition improved and he was discharged from the hospital.

A case of cryptococcal meningoencephalitis in the convalescence period of COVID-19 was described by Thota et al. (2022). A 76-year-old woman was admitted after three days with diarrhoea, weakness and mental confusion. The patient's medical history was hypertension, osteoarthritis and gastric reflux. The PCR test was positive for SARS-CoV-2. The patient was treated with Cefepime, Vancomycin and Ampicillin. On the second day, he developed a fever and the X-ray revealed infiltrates in the lungs. On the third day, the patient required intubation and started treatment with methylprednisolone, tocilizumab, remdesivir and convalescent plasma. On the fourteenth day, sputum culture was positive for *Candida albicans*, treated with Micafungin. On the eighteenth day, the test

was negative for SARS-CoV-2, and on the following day mechanical ventilation was withdrawn, and on the thirtieth day he was discharged from COVID-19. Two weeks later, the patient was again hospitalized with fever and encephalopathy. The PCR test was negative for SARS-CoV-2. Serological analysis in blood and cerebrospinal fluid was positive for *Cryptococcus* spp.com titers greater than 1:2560. The culture of these materials showed growth of *C. neoformans.* Treatment with amphotericin B and flucytosine was started for three weeks, replaced by fluconazole after a negative culture for fungi. Despite the containment of sepsis, the patient did not present any evolution in her general health condition and remained in a coma and on supportive therapy in a long-term care unit. The authors did not reveal the patient's clinical outcome.

Silva et al. (2022) described the clinical picture of a 42-year-old patient admitted to a hospital in Manaus, Brazil. At the time of admission, the patient had headache, fever, vomiting, convulsions, neck stiffness, petechiae and bruises on the skin, hearing loss and arthralgia. Two months prior to admission, the patient had been hospitalized with COVID-19 and developed pneumonia after COVID-19 whose etiologic agent was not identified. During hospitalization with signs of meningitis, the cerebrospinal fluid examination showed a cloudy appearance and the microscopic examination revealed the presence of *Cryptococcus* spp.. The patient died of septic shock and cerebral cryptococcosis six days after admission. The researchers visited the patient's place of residence and reported a large amount of pigeon droppings in the backyard. Family members reported that the patient cleaned the site daily without the use of protective equipment. The researchers concluded that this was the likely site of *Cryptococcus contamination*.

The schematization of the most relevant clinical variables in COVID-19 cases associated with cryptococcosis is organized in Chart 1.

Table 1 – Relevant clinical aspects in cases of cryptococcosis concomitant with SARS-CoV-2 infection or in the development of mycosis in the post-COVID-19 period

Reference	**Time of *Cryptococcus infection* in relation to COVID-19**	**Steroid Use in COVID-19 Treatment or Transplant Maintenance**	**Diabetes**	**Other risk factors, comorbidities, and relevant medical histories**	**Etiological agent of cryptococcosis**	**Clinical form of cryptococcosis**	**Clinical outcome**
Traver and Sánchez (2022)	Concomitant	Methylprednisolone and Hydrocortisone	Yes	Chronic Obstructive Pulmonary Disease, coronary heart disease, stents and pacemakers, obesity, nocturnal apnea, cirrhosis due to hepatitis C virus. Secondary infections by *Aspergillus fumigatus,* and *Enterobacter cloacae*	*Cryptococcus neoformans*	Cryptococcal pneumonia	Death
Darfaoui et al. (2022)	Concomitant	Methylprednisolone	Yes	Diabetes	*Cryptococcus neoformans*	Cryptococcal pneumonia	Death
Abohelwa et al.	Concomitant	Use of steroids, but	Yes	Hypertension	*Cryptococcus*	Cryptococcal	Death

(2021)		no information about the substances used			*neoformans*	pneumonia	
Štingl et al. (2022)	Concomitant	Methylprednisolone and Dexamethasone	No	High blood pressure, myocardial infarction, unvaccinated for COVID-19	*Cryptococcus neoformans*	Cryptococcal pneumonia and cryptococcemia	Death
Torrez-Serrano et al. (2021)	Concomitant	Mycophenolate Sodium, Syrolim and Dexamethasone	No	Kidney transplantation	*Cryptococcus neoformans*	Cryptococcal pneumonia	Death
Guimarães et al. (2022).	Concomitant	Mycophenolate and Methylprednisolone	No	Liver transplantation. *Multidrug-resistant* Acinetobacter baumannii infection.	*Cryptococcus neoformans*	Cryptococcemia and possible cryptcoccal pneumonia	Death
Gil et al. (2021)	Concomitant	Dexamethasone	Yes	Hypertension and obesity	*Cryptococcus neoformans*	Cryptococcemia	Medical discharge
Filhao et al. (2022)	Concomitant	Use of steroids, but no information about the substances used	No	Hypertension, heart disease and obesity	*Cryptococcus laurentii*	Cryptococcemia	Medical discharge
Thyagaranjan et al. (2021)	Concomitant	Dexamethasone and Prednisolone	Yes	High blood pressure, obesity, osteoarthritis. *Methicillin-resistant* Staphylococcus aureus secondary infection	*Cryptococcus neoformans*	Cryptococcemia	Death
Grush et al. (2022)	Concomitant	Dexamethasone	Yes	Heart and kidney failure	*Cryptococcus neoformans*	Cryptococcemia	Death
Khatib et al. (2021)	Concomitant	Methylprednisolone and Hydrocortisone	Yes	Arterial hypertension, and cardiac ischemia. Secondary infection with *Candida glabrata* and *Candida parapsilosis*	*Cryptococcus neoformans*	Cryptococcal Ophthalmitis and Cryptococcemia	Death
Torres et al. (2022)	Concomitant	Dexamethasone	No	High blood pressure, kidney disease, hepatitis C, and cirrhosis of the liver	*Cryptococcus neoformans*	Cryptococcemia	Death
Ghanem e Sivasubramanian (2021)	Concomitant	Dexamethasone	No	Hydrocephalus. Recent orthopedic surgery. Secondary *Escherichia coli infection*	*Cryptococcus neoformans*	Cryptococcal meningitis	Medical discharge
Lupia et al. (2022)	Concomitant	Dexamethasone	Yes	Obesity, alcoholism, toxic cirrhosis, decompensated insulin-dependent diabetes mellitus, atrial fibrillation, and chronic kidney disease	*Cryptococcus neoformans*	Disseminated cryptococcosis without neurologic involvement	Death
Karnik et al. (2022)	Concomitant	Methylprednisolone. Dexamethasone and Hydrocortisone	No	Hypertension. Secondary infections with *Legionella,* Streptococcus, and *Candida* spp.	*Cryptococcus neoformans*	Disseminated cryptococcosis with neurologic involvement	Death
Deepa et al. (2022)	Post-COVID-19	Dexamethasone and Prednisolone	Yes	Post-COVID-19 *Klebsiella* spp. septicemia	*Cryptococcus laurentii*	Cryptococcal ophthalmite	Medical discharge
Choi (2020)	Post-COVID-19	No steroid use	No	No comorbidities	*Cryptococcus neoformans*	Asymptomatic cryptococcal	Medical discharge

						pneumonia	
Gullapalli et al. (2021)	Post-COVID-19	No use of corticosteroids	No	Latent tuberculosis, Recent undiagnosed community-acquired pneumonia.	*Cryptococcus gattii*	Cryptococcal pneumonia	Medical discharge
Isaac et al. (2021)	Post-COVID-19	Methylprednisolone and Dexamethasone	No	No comorbidities	*Cryptococcus* spp.	Cryptococcal pneumonia	Medical discharge
Jacob & Jani (2021)	Post-COVID-19	No use of corticosteroids	No	Hypothyroidism	*Cryptococcus neoformans*	Cryptococcal pneumonia	Not informed
Sharma et al. (2022)	Post-COVID-19	Use of steroids in high doses, but no information about the substances used	Yes	High blood pressure, poorly controlled diabetes mellitus, and hypothyroidism	*Cryptococcus neoformans*	Cryptococcal pneumonia	Medical discharge
Roesch et al. (2022)	Post-COVID-19	Dexametason the	No	Chronic kidney disease, change in heart rhythm, use of mitral valve prosthesis	*Cryptococcus* spp.	Cryptococcal pneumonia	Not informed
Cafardi et al. (2021)	Post-COVID-19	Methylpredinisolone	No	Hypertension and Chronic Obstructive Pulmonary Disease. Secondary infection with *Enterobacter cloacae* and *Alcaligenes* spp.	*Cryptococcus neoformans*	Cryptococcal pneumonia	Death
Alegre-González et al. (2021)	Post-COVID-19	Dexamethasone, Methylprednisolone, and Prednisone	Yes	High Blood Pressure and Chronic Kidney Disease	*Cryptococcus neoformans*	Cryptococcal pneumonia	Death
Ramezanzadeh e Nikfarjan (2021)	Post-COVID-19	Not informed. Presumably a user of corticosteroids for kidney transplant maintenance	Yes	Kidney transplantation	*Cryptococcus neoformans*	Cryptococcal meningitis	Medical discharge
Thota et al. (2022)	Post-COVID-19	Methylprednisolone	No	High blood pressure, osteoarthritis and gastric reflux. Secondary *Candida albicans infection*	*Cryptococcus neoformans*	Disseminated cryptococcosis	Improvement of signs and symptoms, but no information on the clinical outcome.
Silva et al. (2022)	Post-COVID-19	Not informed. The authors state that the patient was immunosuppressed by drug therapy in the treatment of COVID-19	No	Post-COVID-19 pneumonia with unidentified etiology	*Cryptococcus* spp.	Disseminated cryptococcosis with neurologic involvement	Death

Source: the authors

Cryptococcus *infections* have high rates of morbidity and mortality, particularly in the context of immune suppression and when the central nervous system is compromised (GODINHO et al., 2017; AKAIHE & NWEZE, 2021; TORRE et al., 2022; RATHORE et al., 2022). At the same time, Motoa et al. (2021) state that the proportion of HIV-uninfected patients who develop cryptococcosis has increased in recent years and propose that non-compliance with conditions such as severe comorbidities, advanced age, drug immunosuppression, and clinical inexperience may contribute to

the delay in the diagnosis and treatment of cryptococcosis. According to Torre et al. (2022), there is a scarcity of studies on comorbidities or treatments of comorbidities that would cause greater susceptibility to cryptococcal infection. These authors list among the main conditions associated with an increased possibility of cryptococcal disease: HIV infection, history of pulmonary disease treated with corticosteroids, sarcoidosis, Crohn's disease, diabetes, connective tissue diseases, and systemic lupus erythematosus. All of these comorbidities are involved in processes that decrease the efficiency of the immune system. The context of COVID-19 is part of this pattern, as both the effects of the acute form of the disease and treatment with corticosteroids have a direct impact on the body's ability to respond to *Cryptococcus* spp. infection. Among the cases evaluated in this systematic review, the mortality rate was higher than 55%, considering that some reports did not describe the clinical outcome.

The most common comorbidities seen in SARS-CoV-2 co-infection and *Cryptococcus* spp. or post-COVID-19 infection by *Cryptococcus* These are high blood pressure, heart, lung and kidney diseases, diabetes and obesity. These comorbidities are the most commonly identified as risk factors for the worsening of COVID-19 (EJAZ et al., 2020; CALLENDER et al., 2020; GAO et al., 2021). Severe forms of COVID-19 result in deterioration of immune status due to deterioration of clinical status or immunosuppression in control therapies. Cryptococcosis is thus part of the group of opportunistic pathogens with the capacity to infect in the context of the drop in immunity in COVID-19 and in the immediate post-COVID-19 period.

In general, cryptococcosis was associated with COVID-19 in patients with multiple comorbidities. The three case reports of patients immunosuppressed by organ transplants resulted in the death of the patients, and the impact of COVID-19 on patients with a history of low immunity may have been decisive for susceptibility to secondary infection by *Cryptococcus* spp.

Diabetes is a comorbidity common to other mycoses and often associated with cases of fungal infection in the context of COVID-19, present in 80% of individuals who develop mucormycosis (SINGH et al., 2021), 71.4% of those who have coccidioidomycosis (NORBERG et al., 2022), and 48.8% of patients who develop candidiasis (OMRANI et al., 2021). The use of corticosteroids can be a complicating factor in the control of diabetes during COVID-19 by inducing hyperglycemia (FETTERS et al., 2022), with amplified consequences as a risk factor for secondary infection by fungi, including *Cryptococcus* spp. Among the 27 case reports of cryptococcosis in the COVID-19 context analyzed, 12 (44.4%) had this comorbidity.

A survey of 212,479 patients hospitalized for COVID-19 in the United States of America in several health centers involving *cryptococcus* spp. among patients hospitalized for the virus caused by SARS-COV-2 is 0.022% (CHASTAIN et al., 2022). The analysis carried out by these researchers indicated that patients who develop cryptococcosis are predominantly men who already had

comorbidities, such as HIV infection, organ transplantation, neoplasms, innate immunodeficiencies, sarcoidosis, cirrhosis, diabetes, heart failure, and chronic kidney disease. About one-third of cryptococcosis cases in COVID-19 patients were HIV-positive individuals. The researchers did not find an association between the use of dexamethasone in the control of COVID-19 as a susceptibility factor for *Cryptococcus* infection. Individuals who had co-infection with SARS-CoV-2 *and Cryptococcus* spp. had worse prognoses when compared to the group of people with only the viral infection, with a higher rate of admission to Intensive Care Units (38% versus 29%), need for mechanical ventilation (23% versus 11%), and mortality (36% versus 14%). Rathore et al. (2022) indicate that COVID-19 patients rarely become co-infected with *Cryptococcus* spp., and the 0.022% co-infection rate found by Chastain et al. (2022) confirms this claim.

Results obtained by compiling case reports cannot be compared to studies with comprehensive methodologies under penalty of bias and distortion. Case reports tend to be described according to rarity, peculiarity, circumstance or particularities of medical conduct, which makes it impossible to compare data between studies with different methodological profiles (NIESSEN & WYNN, 2014; MURAD et al., 2018; ROUKIS, 2021). Case reports, however, have the merit of detecting novelties and recognizing changes in patterns in the context of specific situations, in addition to generating hypotheses in comparison with the knowledge consolidated by previous studies when other research designs are not feasible (NIESSEN & WYNN, 2014). Thus, although it is not possible to infer conclusions from the comparison of the results obtained by Chastain et al. (2022) with those compiled in our research, it is possible to formulate hypotheses based on the differences found. The research by Chastain et al. (2022) is the only comprehensive study on cryptococcosis among COVID-19 patients that was found in our research and can portray, in the same way, a local situation with its peculiarities in the aspects of epidemiology and health situation of the population evaluated.

The results indicate that, in the context of COVID-19, infection patterns differ from those historically observed, where *Cryptococcus neoformans* is the main agent of infection by reactivation and mainly affects immunocompromised individuals, especially by HIV infection, and *C. gattii* is the etiologic agent of acute pneumonia in individuals or not (KWON-CHUNG et al., 2014; GODINHO et al., 2017; ZAVALA & BADDLEY, 2021; TORRE et al., 2022). Among the case reports that had *the Cryptococcus species identified through biochemical, cultural or genetic sequencing tests*, Cryptococcus neoformans *showed a strong prevalence, with 20* cases, while C. laurentii was *identified in two cases, and* C. gattii in only one case in which there was no use of corticosteroids in the treatment of COVID-19. The predominance *of C. neoformans* may be associated with disturbances in the immune response resulting from COVID-19 or the use of immunomodulatory medication to control the uncontrolled immune response in acute virus. Thus, the COVID-19 situation becomes an important risk factor for susceptibility to *Cryptococcus neoformans*, whose predisposition has been associated

until now mainly with HIV infection. Chastain et al. (2021) indicate that one-third of cryptococcosis cases in COVID-19 patients were HIV-positive individuals. In a review on the epidemiology of *Cruptococcus* spp., Baddley et al. (2021) pointed out that HIV infection and the use of corticosteroids were risk factors that presented the same proportion among the evaluated cases of cryptococcosis caused by *C. neoformans*, present in 38.5% of patients. It is possible that the need for corticosteroid use in a large number of patients due to the COVID-19 pandemic is the main cause of the prevalence of *C. neoformans* among individuals who developed COVID-19 despite not being infected with HIV.

Chastain et al. (2021) did not find a statistical relationship between the use of Dexamethasone and susceptibility to cryptococcosis in patients infected with SARS-CoV-2. Except for the methodological considerations proposed by Niessen and Wynn (2014), Murad et al. (2018), and Roukis (2021), the results compiled in our research suggest that corticosteroids in general are associated with susceptibility to the development of cryptococcosis in the context of COVID-19, including Dexamethasone. The small number of reported cases does not allow for an accurate statistical approach, but among the 18 case reports evaluated in our study that described the immunosuppressive substances used, 11 were from individuals treated with Prednisolone or Prednisone and 12 from individuals treated with Dexamethasone. These data indicate that there may be a relationship between the use of Dexamethasone and susceptibility to cryptococcosis in patients with COVID-19, contrary to what Chastain et al. (2021) maintain, and further studies should be conducted in order to elucidate this possibility. The results of Chastain et al. (2021), although conducted in more than one hospital unit, were conducted in only one geographic region, and may reflect regional epidemiological patterns. These patterns may differ according to the genetic susceptibility of each human population, exposure to *Cryptococcus* spp., virulence and adaptive genetic patterns of each variety of the fungus, and treatment protocols (FANG et al., 2015), and the influence of the COVID-19 pandemic and aspects related to infection dynamics may have an as yet unknown impact on these factors. The lack of medical repertoire and the non-performance of tests for *Cryptococcus* spp. infection in non-HIV-infected patients may be responsible for the underestimation of the disease in immunocompetent patients (HENAO-MARTÍNEZ et al., 2018), and perhaps in a higher proportion among patients with immune system dysfunction in the context of COVID-19.

There are still many aspects in the correlation between COVID-19 and cryptococcosis that have not been well elucidated by science. An interacting factor between COVID-19 and *Cryptococcus* spp. infection to be investigated is the possibility of developing Immune Reconstitution Inflammatory Syndrome or Post-Infectious Inflammatory Response Syndrome (MURTHY et al., 2015. WILLIAMSON, 2015; KULKARNI et al. 2019; ROMANI et al., 2021). These syndromes are the result of an exacerbated but delayed immune reaction, in which individuals develop meningitis caused by *C. gattii* and *C. neoformans*, with the paradoxical worsening of the previous condition of the patient

recovering from the fungal disease. Even after appropriate treatment, there is a sudden-onset deterioration with worsening of meningitis symptoms and progression or development of new neurological symptoms. The general mechanism for the development of the syndrome is increased inflammation, as the immune system, recovering from some interfering factor in the mechanisms of response to infections, recognizes the antigens of the fungus as immunosuppression is reversed. Alterations in immune status, such as cytokine storm reactions and predominant interferon-gamma response of helper T cells, are common to both Immune Reconstitution Inflammatory Syndrome due to cryptococcosis and in the acute phase of COVID-19, and coinfection can have potentiating effects on the imbalance of the immune response both during co-infection and in recovery and convalescence. The recovery of the immune system of patients with COVID-19 who required corticosteroids in the treatment of acute virus can be a triggering factor for these syndromes, as immunosuppressants can delay the recognition of the fungus by the immune system and trigger an intense and uncontrolled reaction at the end of treatment. Although Immune Reconstitution Inflammatory Syndrome is more common in patients with HIV and cryptococcosis, further research on immune dysregulation in the co-infection of SARS-CoV-2 and *Cryptococcus* spp. should be conducted to elucidate the possibility of interaction or activation of inflammatory and immune hyperactivation mechanisms common to the pathophysiology of both diseases, in addition to the conjuncture of the use of corticosteroids in the treatment of COVID-19. The use of corticosteroids in the control of the marked immune and inflammatory response and *the trade-offs* in the consideration of therapies to control both infections may be a complicating factor in the choice of the most appropriate clinical management, because while immunomodulation may be necessary for patient support measures, it may also become a risk for the resurgence or worsening of cryptococcosis. Another condition of interaction between SARS-CoV-2 and *Cryptococcus* spp. is the possible role of proteases produced by the fungus as facilitating agents of viral infection through the activation of the SARS-CoV-2 spike protein (MJOKANE et al., 2021; MJOKANE et al., 2022). Although this evidence is only proven in vitro experiments, the worsening of the general condition of patients with long-term COVID-19 in co-infection by the two pathogens may be related to this physiochemical process.

4 CONCLUSIONS

Although cryptococcosis is a relatively rare infection among patients with COVID-19 and in the convalescence period of the disease, this opportunistic mycosis may be responsible for a mortality rate that is considered high (greater than 51%). Susceptibility to *Cryptococcus* spp. infection in the context of COVID-19 disease and treatment is strongly associated with corticosteroid use and pre-existing multiple comorbidities. It is not possible to determine the degree to which cryptococcosis is responsible for mortality in co-infection or infection during the COVID-19 convalescence period, but

the development of secondary infection with Cryptococcus spp. is indicative of a poor prognosis for the patient.

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