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Trends in Hospitalizations Related to Aspergillosis and Mucormycosis in the United States, 2016 - 2021

By

Robert Rhee

Master of Public Health
Executive MPH, Applied Epidemiology

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Alex Edwards, Ph.D.
Thesis Committee Chair

_____

Kaitlin Benedict, MPH
Thesis Committee Advisor

_____

Jeremy Gold, MD, MS
Thesis Committee Advisor

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By

Robert Rhee

B.A., University of California – Berkeley, 2007

Thesis Committee Chair: Alex Edwards, Ph.D.

An abstract submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Applied Epidemiology

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TITLE: Trends in Hospitalizations Related to Aspergillosis and Mucormycosis in the United States, 2016-2021

By Robert Rhee

Background: Aspergillosis-related hospitalizations (A-RH) and mucormycosis-related hospitalizations (M-RH) pose significant clinical challenges due to their aggressive progression, high mortality, frequent readmissions, and substantial financial burden. While these infections can affect immunocompetent individuals, immunocompromised patients face particularly high hospitalization costs and mortality rates. The COVID-19 pandemic exacerbated this burden, as corticosteroid use increased the risk of COVID-19-associated aspergillosis (CAA) and COVID-19-associated mucormycosis (CAM), driving up hospitalization rates and in-hospital mortality.

Methods: We analyzed 2016–2021 National Inpatient Sample (NIS) discharge data using ICD-10 codes to estimate A-RH and M-RH rates, clinical subtypes, and associated comorbidities. Annual percentage changes (APC) were calculated using weighted least-squares regression on log-transformed rates. U.S. Census population estimates allowed calculation of rates with trend assessments and 95% confidence intervals.

Results: Between 2016 and 2021, an estimated 86,570 A-RHs and 8,565 M-RHs occurred. A-RH rates rose from 42.3 to 51.5 per million persons (APC = +2.4%; p = 0.2904), and M-RH rates rose from 3.8 to 5.8 (APC = +3.2%; p = 0.2033). In-hospital mortality increased significantly in 2021 for A-RH (26.8%; APC = +20.0%; p = 0.0363) and M-RH (24.7%; APC = +16.5%; p = 0.0162). Invasive aspergillosis and pulmonary mucormycosis showed significant increases (APC = +7.2%; p = 0.0005 and APC = +9.6%; p = 0.0111, respectively).

Underlying conditions associated with A-RH included COPD (33.1%), diabetes (27.9%), and HM (20.7%), while M-RH was associated with COPD (11.1%), diabetes (45.7%), and HM (31.2%). Among CAA-RH and CAM-RH cases during 2020–2021, diabetes was a major comorbidity, present in 42.2% and 63.1% of cases, respectively. COPD followed with 21% in CAA-RH and 14.3% in CAM-RH. In-hospital mortality during this period rose to 55.7% for CAA-RH and 52.4% for CAM-RH.

Conclusion: Rates of A-RH and M-RH continue to rise, along with in-hospital mortality and clinical subtypes. The COVID-19 pandemic has amplified these trends, extending risk to populations beyond traditionally recognized immunocompromised groups. These findings underscore the need for broader clinical awareness and preventive strategies.

Keywords: Invasive Mold Infections (IMI), Aspergillosis, Mucormycosis, COVID-19-associated fungal infections, hospitalization trends, immunocompromised population

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BACKGROUND

Invasive fungal infections, characterized by their opportunistic nature, exploit and exacerbate health challenges faced by those with immunocompromising conditions or critical illness. Among patients hospitalized in 2019, approximately 451,000 fungal infections were diagnosed with an estimated 60,000 (~10%) categorized as invasive fungal infections.[1]

For immunocompromised persons, invasive fungal infections can lead to severe illness with increased morbidity and mortality. For health systems, invasive fungal infections can impose substantial financial burdens on healthcare systems, prolong hospital stays, draw limited resources, and escalate healthcare expenses. In the US, hospitalization costs attributed to fungal infections amounted to $6.7 billion in 2018. [2]

Among invasive mold infections (IMI), aspergillosis and mucormycosis are most common.[3], [4] Invasive aspergillosis (IA) can progress quickly into a severe infection of the lower respiratory tract with a mortality rate ranging from 30-85% dependent on the underlying condition.[5] Mucormycosis has been noted to have a high mortality rate, while being difficult to diagnose due to a lack of distinguishable biomarkers. Among patients with hematologic malignancy (HM), hematopoietic stem cell transplant (HSCT), and solid organ transplant (SOT), it most commonly presents as a pulmonary infection, with potential to disseminate to other anatomical loci[6].

With the advent of the COVID-19 pandemic, patients began to develop serious complications attributed to fungal infections. In a study by Gold et. al., 13.4% of fungal hospitalizations were associated with an underlying COVID-19 diagnosis. ICU admission rates were approximately twice as high, and in-hospital mortality rates were nearly four times greater for COVID-19-associated fungal hospitalizations compared to those not linked with COVID-19 during 2020-2021.[7] As the condition of certain COVID-19 patients deteriorated in hospital settings, the use of corticosteroids to suppress the immune system became increasingly common, particularly in cases of acute respiratory distress syndrome (ARDS). However, this immunosuppression may have inadvertently created conditions conducive to the development of COVID-19-

associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM), leading to potentially severe lung complications.

In addition to underlying and concomitant conditions listed above, IA and mucormycosis disproportionately affect individuals with preexisting conditions such as COPD, diabetes, and cirrhosis. Moreover, heightened incidence rates of these infections have been observed in populations with underlying conditions for asthma, autoimmune disorders, and respiratory infections including influenza and tuberculosis. Previous research has linked disparities in health outcomes related to sex, race, ethnicity, and socioeconomic factors with invasive fungal infections.

ASPERGILLOSIS

Aspergillosis, primarily caused by the fungus *Aspergillus*, is a significant opportunistic infection that can lead to severe morbidity and mortality, particularly in immunocompromised individuals. The most common species involved in human infections is *Aspergillus fumigatus*, which is ubiquitous in the environment, particularly in decaying organic matter and soil. Aspergillosis can manifest in various clinical subtypes, including allergic bronchopulmonary, chronic pulmonary aspergillosis, and invasive aspergillosis (IA), the latter being the most severe and life-threatening subtype [8], [9].

Invasive aspergillosis is characterized by the invasion of the fungus into lung tissue and can disseminate to other organs, particularly in patients with weakened immune systems, such as those undergoing chemotherapy, organ transplantation, or those with chronic lung diseases [2], [10]. The clinical presentation of IA often includes fever, cough, chest pain, and hemoptysis, and it is associated with high mortality rates, ranging from 30% to 60% depending on the patient's underlying conditions and the timeliness of diagnosis and treatment [11], [12].

The impact of aspergillosis on populations is profound, particularly among high-risk groups. For instance, patients with hematological malignancies, solid organ transplant recipients, and those with chronic obstructive pulmonary disease (COPD) are particularly susceptible[13], [14]. The emergence of COVID-19 has further complicated the landscape, with reports indicating a rise in cases of COVID-19-associated pulmonary aspergillosis (CAPA), particularly in critically ill patients requiring mechanical ventilation [15], [16]. This co-infection has been linked to increased mortality rates, highlighting the need for vigilant screening and management strategies in this population.

Furthermore, the rising incidence of antifungal resistance, particularly to triazole antifungals, poses an additional challenge in managing aspergillosis, necessitating ongoing research and development of new therapeutic strategies [17], [18].

EPIDEMIOLOGY

The estimates for incidence and prevalence of aspergillosis in the United States has shown an increasing trend during 2000-2013. Invasive aspergillosis-related hospitalizations (IA-RH) rose from 9252 in 2000 to 14,560 in 2013, with a hospitalization rate of 32.7per million persons in 2000 to 45.7 per million persons in 2013[19]. During 2004 to 2013, Zilberberg et al. reported a 74.2% increase in annual IA-RH, from 29,774 in 2004 to 51,870 in 2013 [20]. Zilberberg et al. noted a 4.4% per annum increase in age-adjusted annual IA-RH from 2004 to 2013. Age-stratified analysis revealed that the highest volume of cases, sustained across the study period, was observed in individuals aged 65–84 years, followed by those in the 45–64-year age group[20]. Male patients were observed to be 1.6 times more at risk to experience IA-RH than females[1]. Of the 21 of 23 studies investigated, Egger et al. found the majority of IA cases to be composed of males ranging from 51% to 87% [21]. In terms of race and ethnic groups, Non-Hispanic Whites compared to other racial/ethnic groups were more at risk for IA[1]. During 2004-2013, the South U.S. census region contributed the most cases (40%)[20]. Although the length of hospital stay decreased from 13.3 days in 2004 to 11.5 days in 2013, mean hospital charges increased from $71,164 to $123,005 during this period, highlighting the growing economic burden of IA in the US[20].

Concurrently, during 2000 to 2013, Vallabhaneni et al. reported that in-hospital deaths due to IA occurred in 16% of IA-RH[19]. During 2009 to 2013, IA was associated with significantly higher adjusted mortality rates compared to non-IA hospitalizations, 14.1% vs 10.3% with 1.43 greater odds of in-hospital death. In addition, relative to no IA, IA was attributed to an excess LOS of 6.0 days and increased hospitalization costs by $15,542 [22].

In specific patient populations, the impact of IA on outcomes varied between immunocompromised and immunocompetent populations. Among kidney transplant recipients, IA was linked with a 5.02 times greater risk of one-year mortality, with an all-cause mortality rate of 31.5% post-diagnosis, compared to 5.2% in matched controls [23]. Similarly, hematopoietic stem cell transplant (HSCT) recipients with IA had an in-hospital mortality rate of 18.3% compared to mortality rate of 4.2% of recipients without IA [24]. In patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease (AECOPD), IA was strongly

associated with 4.47 increased odds of death, as well as longer LOS, more ICU admissions, and higher healthcare costs, compared to AECOPD patients without IA[25]. The prognosis is even more severe for COVID-19-associated pulmonary aspergillosis (CAPA). White et al. found that CAPA carried a mortality rate of 57.9%, with outcomes varying by treatment adequacy: mortality was 46.7% in patients receiving appropriate antifungal therapy (AFT) but reached 100% in those who did not receive AFT[26].

RISK FACTORS

Invasive aspergillosis is a significant cause of morbidity and mortality, with an expanding risk profile beyond traditionally immunocompromised patients. Traditionally, classic risk factors included hematologic malignancy (HM), hematopoietic stem cell transplant (HSCT), solid organ transplant (SOT), prolonged neutropenia, and corticosteroid use [27] [3]. In a predictive model for HM patients, which integrated genetic markers, clinical risk factors, and biomarkers, the average probability of developing IA was found to be 56.7% [24]. In a separate study, the one-year incidence of invasive fungal diseases among HSCT recipients ranged from 8% to 10.3%, with IA identified as the most prevalent infection within this group [25]. For SOT recipients, IA is linked with high mortality rates, with non-liver SOT recipients showing 3-month mortality rates between 15–25%, while liver SOT recipients experienced mortality rates reaching as high as 80–90% within the same period [26]. Corticosteroids are prescribed to manage a range of inflammatory conditions and autoimmune disorders by suppressing the immune response and reducing inflammation. Delsuc et al. found that the use of corticosteroids for longer than 3 months before ICU admission significantly increased the risk of IPA[28].

Extending beyond the traditional immunocompromised patients, IA has emerged as a significant complication in immunocompetent patients with exposure to high fungal loads, like environmental or occupational exposure, or with those experiencing severe viral infections. Workplaces with high fungal contamination, and consequently elevated mycotoxin exposure, include industries involved in processing or storing organic material. Key sectors include the feed and food industries, animal husbandry, waste management, and slaughterhouses. Specific environments such as coffee and grain processing facilities, mushroom farms, and animal feed plants exhibit particularly high fungal loads. Handling large quantities of

contaminated materials, even if they contain low mycotoxin concentrations, can elevate airborne mycotoxin levels, posing risks to workers [29].

Workers exposed to organic materials—such as farmers, sawmill workers, and waste collectors—are particularly vulnerable, with airborne fungal particle concentrations reported as high as 10^8 colony-forming units per cubic meter [29]. Waste sorting plants are identified as critical sites for fungal contamination, often surpassing the WHO guideline of 150 cfu/m³, with higher fungal loads indoors compared to outdoors[30]. This discrepancy suggests the potential presence of indoor fungal growth foci and attachment of fungal elements to dust particles, further exacerbating exposure risks.

In addition, for patients suffering from a respiratory viral infection, some develop acute respiratory distress syndrome (ARDS), resulting damage to the lung structures. It has been documented in cases involving influenza, cytomegalovirus and SARS-CoV-2, where high mortality rates have been observed [31]. For viral infections, the diagnosis of IA is challenging as the clinical manifestations of IA (fever, dsypnea, and cough) closely resembles those seen in severe influenza and COVID-19 [31]. For influenza-associated pulmonary aspergillosis, reported incidence varies globally, ranging from 5% to 31%, excluding U.S.-based studies[32].

Severe influenza can damage the respiratory epithelium, creating an entry point for *Aspergillus* infections. A review revealed that 28% of 128 cases of post-influenza IA occurred in individuals without preexisting health conditions [33]. Similarly, some patients with IA are at heightened risk for co-infections with cytomegalovirus (CMV), which can negatively impact both patient and graft survival. CMV and IA share overlapping risk factors, and CMV's immunomodulatory effects—such as inducing leukopenia—further increase susceptibility to fungal infections. Studies have identified CMV infection as an independent risk factor for IA, reporting a pooled odds ratio of 3.31 for the association between CMV and IA in solid organ transplant recipients [23].

COVID-19 IMPACT

The COVID-19 pandemic has led to an increase in aspergillosis, in the US. While reports of COVID-19-associated pulmonary aspergillosis (CAPA) have varied, studies report hospitalizations occurring between 1% to 35%, significantly increasing mortality, hospital stays, and costs[8], [16], [34], [35]. Zhang et al. attributed some low US incidence rates of CAPA to limitations in diagnostic procedures, which obfuscate accurate identification: (1) hesitancy to perform bronchoalveolar lavage (BAL) coupled with low rate of BAL galactomannan (GM) testing, (2) rare use of fungal diagnostic protocols, (3) the poor sensitivity of serum GM, and (4) the absence of alternative diagnostic tools like lateral flow assays [35].

During 2020 to 2021, the annual rates of hospitalization for aspergillosis grew significantly from 7.9 to 18.9 per 10,000 COVID-19 hospitalizations, reflecting a 58.2% change[7]. Along the same period, the incidence of fungal deaths rose from 1.2 per 100,000 in 2019 to 1.8 per 100,000 in 2021, with 21.9% of fungal deaths in 2020-2021 being COVID-19-associated and 57.6% of hospitalized deaths resulting in aspergillosis [7], [36].

The development of COVID-19-associated pulmonary aspergillosis (CAPA) has been linked to multiple risk factors, including corticosteroid use, other immunosuppressive therapies, comorbidities such as chronic obstructive pulmonary disease (COPD) and liver failure, invasive mechanical ventilation, and advanced age [37], [38]. These risk factors collectively contribute to immune dysregulation caused by SARS-CoV-2 infection, which includes functional exhaustion of natural killer (NK) and T cells, along with impaired neutrophil fungicidal activity [19]. SARS-CoV-2 infections can also cause extensive structural damage to the respiratory system, including the airway epithelium, alveolar endothelium, and cilia, creating favorable conditions for opportunistic fungal infections like aspergillosis [18, 20].

During 2020–2021, Gold et al. reported that Aspergillus was among the most frequently documented fungal pathogens, contributing to 16.4% of all fungal-related deaths. COVID-19–associated fungal deaths involved Aspergillus more often (23.3%) compared to non–COVID-19 fungal deaths (14.5%). Most fungal deaths occurred in individuals aged ≥65 years (54.1%) and males (59.7%). Disparities in age-adjusted death

rates per 100,000 population were evident across racial and ethnic groups. Rates were highest among American Indian/Alaska Native (AI/AN) individuals (1.3 for COVID-19-associated deaths, 3.0 for non-COVID-19 deaths). Hispanic and Black populations also exhibited higher rates than White or Asian populations. Residents of nonmetropolitan areas faced higher crude fungal death rates (2.4) than those in metropolitan areas (1.9), a trend consistent across both COVID-19 and non-COVID-19 fungal deaths [36].

Although commonly used to manage COVID-19, corticosteroids significantly increase the risk of invasive aspergillosis (IA), especially in individuals with preexisting conditions [39]. The dysregulated immune response seen in COVID-19 not only hampers effective viral clearance but also enhances susceptibility to secondary fungal infections [40]. Additional contributors to fungal infections in COVID-19 patients include the prolonged use of mechanical ventilation, broad-spectrum antibiotics, and monoclonal antibody therapies [41]. A better understanding of these mechanisms is essential for optimizing clinical management strategies to reduce the risk of invasive fungal diseases during COVID-19 and in future pandemics.

CLINICAL PRESENTATIONS

Aspergillosis presents a spectrum of clinical manifestations, primarily affecting the lungs. Clinically common manifestations include invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), and allergic bronchopulmonary aspergillosis (ABPA) [27]. IPA typically affects severely immunocompromised patients, while CPA and ABPA affects those with underlying lung conditions [4].

Categorization of these clinical manifestations is best understood based on the patient's condition. In adapting a prior study, Sabino et al. categorizes pulmonary diseases caused by *Aspergillus spp.* into three subgroups based on host status: (1) invasive immunosuppressed host (e.g. angioinvasive aspergillosis, acute bronchopneumonia, pseudomembraneous necrotizing tracheobochitis, invasive pleural disease), (2) saprophytic structurally damaged host (e.g. aspergilloma, chronic necrotizing aspergillosis, aspergillus bronchitis, and obstructing bronchial aspergillosis), and (3) allergic immunocompetent host (e.g. asthma, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, bronchocentric granulomatosis, and eosinophilic pneumonia) [29]. Symptoms and diagnostic challenges vary between immunocompetent and

immunocompromised hosts. In immunocompromised patients, early IPA presentation is often silent and non-specific, requiring a high index of suspicion [27].

Diagnosis relies on clinical, radiological, and microbiological criteria, with serum and bronchoalveolar lavage (BAL) galactomannan (GM) assays recommended for IPA [5]. Obtaining clinical specimen to establish a diagnosis range from more to less intrusive, with biopsy, BAL, tracheal aspirate, blood, and sputum. Many of these clinical specimens are then used in a myriad of diagnostic testing from GM testing to histology and culture, PCR, lateral flow assay, and (1-3)-beta-D-glucan (BDG) testing.

The sensitivity of culture-based tests from lower respiratory tract specimens for diagnosing IA is limited, with reported sensitivity rates of 65% or lower. In contrast, bronchoalveolar lavage fluid (BALF) GM testing offers significantly higher sensitivity and specificity, both nearing 90% [42]. GM testing, now considered the gold standard for IA diagnosis, detects galactomannan, a polysaccharide released by Aspergillus hyphae and spores. While GM can appear in the serum of immunocompromised patients with angio-invasive disease, it is more reliably detected in BALF for non-neutropenic patients with airway-invasive growth.

To establish a positive GM test, an optical density (OD) index should be ≥0.5 for serum and >1.0 for BALF. However, false-positive results can occur, particularly in patients treated with antibiotics such as amoxicillin-clavulanate, piperacillin-tazobactam, cefepime, and carbapenems. Conversely, false-negative GM results are more likely in individuals receiving mold-active antifungal prophylaxis or when diagnostic delays occur, complicating early IA detection [42], [43].

TREATMENT + MANAGEMENT

Antifungal therapies are classified into azoles, polyenes, and echinocandins, each targeting key fungal structures. The azoles and polyenes disrupt the fungal cellular membrane by targeting ergosterol, while echinocandins inhibit beta-1,3 glucan synthesis, compromising the fungal cell wall. Based on these therapies, treatment strategies vary depending on the host's immune status, with immunocompromised patients requiring more intensive interventions [44]. Immunocompetent patients suffering from ABPA are managed

with corticosteroids to suppress inflammatory immunopathology induced by *Aspergillus spp.* infection while complementing with triazoles[44], [45]. For immunocompetent patients suffering from CPA, oral itraconazole and intravenous deoxycholate amphotericin B (d-AMB) are administered over an extended duration, with relapses occurring months outside of discontinuation, sometimes years[44], [45]. For immunocompromised patients suffering from IA, a combination of antifungal therapies, surgeries, and immunomodulating agents may be used to improve outcomes for patient: triazoles are recommended as primary treatments, while liposomal amphotericin B serves as secondary, despite its toxicity [44], [45]. Despite the necessity for antifungal therapies, these current treatments have limitations, including toxicity and emerging resistance.

Azole resistance, particularly in *A. fumigatus*, is a growing global concern. Cases of resistance to triazoles, such as voriconazole, have been documented even in patients with no prior azole exposure, posing challenges for management. During 2010 to 2017, *A. fumigatus* isolates were identified across three states, with four samples obtained from patients without prior triazole exposure. Notably, triazole-resistant infections emerged even in individuals of whom had no documented history of triazole use [46]. While resistance to voriconazole in *A. fumigatus* ranged from 3.05% to 4.07% between 2015 and 2020, with minor fluctuations from year to year, the emergence of multidrug-resistant strains poses a significant challenge, necessitating ongoing surveillance and research to inform treatment protocols[45].

Prophylactic strategies, particularly in high-risk populations like immunocompromised patients, have been recommended to mitigate the risk of developing invasive aspergillosis. Primary antifungal prophylaxis for those at high risk for IA are posaconazole or voriconazole[47]. Echinocandins serve as alternatives for patients with health complications or drug interactions. For instance, with HSCT recipients, if a mold-active agent resolves IA before transplant, it should be continued during and after transplantation to prevent relapse. Effective post-transplant monitoring is critical to detect IA reemergence[47]. Guidelines from the Infectious Diseases Society of America (IDSA) emphasize tailoring treatments based on individual risk profiles and infection severity to mitigate the risks associated with multidrug-resistant fungal strains and improve patient outcomes [48].

MUCORMYCOSIS

Mucormycosis, a severe and often fatal fungal infection, is primarily caused by fungi belonging to the Mucorales order, which includes genera such as Rhizopus, Mucor, and Lichtheimia [5]. Traditionally, this opportunistic infection predominantly affects immunocompromised individuals, including those with diabetes mellitus, hematological malignancies, and solid organ transplant recipients. The global incidence of mucormycosis has been rising, particularly within the context of the COVID-19 pandemic, where it has emerged as a significant complication among patients with severe disease, especially those with uncontrolled diabetes or receiving immunosuppressive therapies [37], [49], [50], [51].

The pathogenesis of mucormycosis is closely linked to the host's immune status. In healthy individuals, the innate immune system is generally effective in preventing infections by Mucorales. However, in immunocompromised patients, the risk of infection increases dramatically due to factors such as neutropenia, prolonged corticosteroid use, and uncontrolled diabetes, particularly in cases of diabetic ketoacidosis [52], [53], [54]. In developing countries, diabetes is the most common underlying condition associated with mucormycosis, while in developed nations, hematological malignancies and organ transplants are more prevalent risk factors [37], [49], [50].

Clinically, mucormycosis can manifest in several forms, with the most common being rhino-orbital-cerebral mucormycosis (ROCM), pulmonary mucormycosis, and cutaneous mucormycosis. ROCM typically presents with sinusitis, facial swelling, and neurological symptoms, often leading to significant morbidity and mortality if not treated promptly [54], [55]. Pulmonary mucormycosis, characterized by respiratory symptoms, is particularly concerning in patients with underlying lung disease or those who are mechanically ventilated [56], [57]. Cutaneous mucormycosis can occur following trauma or in burn patients, where the infection can spread rapidly and lead to severe complications[58], [59].

The emergence of COVID-19-associated mucormycosis (CAM) has highlighted the intersection of viral and fungal infections, particularly in patients with severe COVID-19 who are treated with corticosteroids or other immunosuppressive agents [37], [50], [51], [60].

EPIDEMIOLOGY

The overall rate of mucormycosis-related hospitalizations (M-RHs) in the United States doubled from 1.7 per million in 2000 to 3.4 per million in 2013, with an estimated 1,080 M-RHs in 2013, serving as a proxy for the disease burden [19]. The prevalence of mucormycosis during hospital discharges was estimated at 0.12 per 10,000 discharges [61]. Globally, the disease occurs at a rate ranging from 0.005 to 1.7 per million people [54].

Mucormycosis disproportionately affects older adults and certain racial or ethnic groups. The average age of patients with M-RHs is 51.7 years, with 29% aged 65 or older, 63% male, and 61% white [61]. Hispanic ethnicity (OR=1.45), Black race (OR=1.74), and age over 65 years (OR=1.64) have been associated with higher odds of developing the disease[62].

The disease has significant morbidity and mortality. Approximately 41% of patients with M-RHs required ICU admission, and the in-hospital mortality rate was 23%[61]. Mortality rates vary by underlying conditions and infection sites, with overall rates ranging from 40% to 80% [54]. Disseminated mucormycosis has the highest mortality (68%), while cutaneous mucormycosis has the lowest (31%) [63]. Prognosis is poorest for patients with hematological malignancies, hematopoietic stem cell transplants, or extensive burns, especially if the infection disseminates to the central nervous system, where mortality exceeds 80% [54]. Conversely, localized sinus or skin infections have better outcomes, particularly with early diagnosis and aggressive surgical debridement [54].

The incidence of mucormycosis increased from 1990 to 2000, peaking at 17.6 per 100,000 person-years, and has since demonstrated variability. Risk factors include tacrolimus use, cadaveric organ transplantation, and environmental or demographic factors[62]. Despite advances in diagnosis and treatment, survival rates remain poor, underscoring the need for timely, multidisciplinary management [54].

RISK FACTORS

Mucormycosis predominantly impacts individuals with compromised immunity, with underlying health conditions being a significant determinant of vulnerability. Diabetes mellitus is recognized as the

leading risk factor globally, particularly in regions with a high prevalence of poorly managed diabetes. Approximately 52% of mucormycosis cases are linked to diabetes, while 40% are associated with hematological malignancies, although the incidence rate is slightly higher in the latter group (23% vs. 19%) [61], [64]. Diabetic ketoacidosis exacerbates this risk by creating metabolic conditions conducive to fungal growth, such as elevated free iron levels and impaired neutrophil function [49], [50].

According to Gulli et al.'s explanation of fungal infiltration and mechanism, in type 2 diabetes, high blood sugar levels cause stress and low oxygen conditions in cells, leading to the release of harmful molecules like free radicals, fatty acids, and inflammatory proteins. This creates a pro-inflammatory environment that weakens immune cells, alters proteins to make iron more available for fungal growth, and attracts immune cells like M1 macrophages that fail to kill mucormycosis spores [55].

In diabetic ketoacidosis (DKA), the acidic blood environment supports the growth of Rhizopus arrhizus, a common mucormycosis-causing fungus, by enabling it to use ketones. This environment affects both the host and the fungus. In the host, a protein called GRP78 moves to the surface of nasal cells, while the fungus increases production of specific proteins (cotH3 and cotH7) that help it attach to and invade these cells. The spores bind to structural proteins (laminin and collagen IV) in the nasal passages or sinuses, triggering growth and infection [55].

Once inside, the fungus produces a toxin called mucoricin, which damages tissues, increases blood vessel permeability, and enables the infection to spread through the bloodstream. Although immune cells like neutrophils respond and kill fungal hyphae, they also release mucoricin, worsening tissue damage and inflammation. This vicious cycle makes it harder for additional immune cells and antifungal treatments to reach the infection site [55].

Hematologic malignancies and solid organ transplants represent the less predominant predisposing factors. Neutropenia induced by chemotherapy, hematopoietic stem cell transplantation, and immunosuppressive therapies weaken immune defenses, making patients particularly susceptible to invasive fungal infections. Chronic kidney disease, hemochromatosis, and iron overload conditions also elevate risk, as

excess iron is a critical nutrient for *Mucorales* proliferation [19], [54]. Furthermore, the pathogen's ability to utilize free iron in hyper-ferritinemic states, such as diabetic ketoacidosis, iron-chelation therapy, or severe COVID-19, significantly contributes to its virulence [64]. Other chronic illnesses, such as HIV/AIDS and autoimmune disorders requiring immunosuppressive treatments, further compound susceptibility to mucormycosis [50].

Environmental exposure to Mucorales spores plays a crucial role in mucormycosis pathogenesis, particularly in regions and seasons with high spore density, such as tropical climates and the summer.[5]. Frequent exposure to soil, decomposing organic material, and dust from adjacent construction sites increases the risk of spore inhalation, particularly for immunocompromised individuals [54].

Furthermore, environmental exposures have manifested in natural disasters increasingly linked to fungal infections, including mucormycosis outbreaks [65]. Mucormycosis can occur following natural disasters due to traumatic injuries contaminated with organic matter[66]. Specifically, outbreaks have been associated with events like the 1985 volcanic eruption in Armero, the 2004 Indian Ocean tsunami, and the 2011 Joplin tornado, [65].

Within healthcare environments, outbreaks have been traced to contaminated linens, water systems, and ventilation units, underscoring the need for stringent infection control measures [67]. In Sunderman et al.'s study, nearly half (47%) of the transplant and cancer hospitals received healthcare linens (HCLs) contaminated with *Mucorales*, and 20% of these facilities failed to meet hygienic standards for these fungi. At individual hospitals, up to 24% of HCLs tested positive for *Mucorales*. Visibly dirty HCLs or carts were noted at 6 out of 15 of hospitals and were strongly associated with fungal contamination. This is particularly alarming given that several outbreaks of healthcare-associated mucormycosis have been traced back to contaminated HCLs [67].

CLINICAL PRESENTATIONS

Much like aspergillosis, clinical presentations of mucormycosis presentations vary depending on the host's immune status, immunocompetent vs immunocompromised, as well as loci of interest. The spectrum

of clinical presentations includes rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated forms, each with distinct pathophysiological mechanisms, symptomatology, and diagnostic challenges. Understanding these varied presentations is critical for early recognition, timely diagnosis, and effective management to improve patient outcomes.

Rhino-orbito-cerebral mucormycosis (ROCM) is a predominant manifestation of mucormycosis, particularly in patients with diabetes and less frequently in hematologic malignancy patients. Patients typically acquire the infection through inhalation of fungal spores, presenting with acute onset facial swelling, numbness, tingling, bulging of the eyes, headache, nasal congestion, and, in some cases, a black necrotic eschar in the palate or nasal cavity. Although this necrotic eschar is a critical diagnostic feature, it is present in only half of the cases [55]. This necrotic eschar may progress with bone destruction and subsequent invasion into the orbit, eye, and brain. According to Jeong et al., ROCM accounts for 34% of mucormycosis cases globally [63], with uncontrolled diabetes and diabetic ketoacidosis being the most common risk factors [68]. These presentations are distinct from pulmonary mucormycosis, which primarily affects immunocompromised individuals, such as those with neutropenia or graft-versus-host disease [5].

Pulmonary mucormycosis, the second most common form, typically arises in more severely immunocompromised patients with blood cancers, organ or stem cell transplants, or those undergoing steroid therapy [5]. The condition follows the inhalation of fungal spores and presents with nonspecific symptoms, including fever, cough, and sometimes hemoptysis, resembling rapidly progressive bacterial pneumonia. Patients with solid organ transplants face the highest odds for developing pulmonary mucormycosis, which can spread to other organs [63]. While hematological malignancies and prolonged neutropenia are primary predisposing factors, the disease's clinical progression often complicates early diagnosis.

Cutaneous mucormycosis, in contrast, results from direct infection of fungal spores into the skin, independent of dissemination from other infection sites. In immunocompetent individuals, cutaneous and soft tissue mucormycosis is the most common form, often arising after traumatic injuries, surgery, or burns. A significant portion of cutaneous mucormycosis cases, nearly 40%, occur in patients without underlying risk

factors [55]. It typically presents acutely and may rapidly progress to necrosis, gangrene, or hematogenous dissemination. The infection is characterized by black eschar or necrotizing lesions. Dissemination to deeper organs occurs in approximately 20% of cases, underscoring the potential severity of this condition [69].

DIAGNOSTICS

Diagnosing mucormycosis is challenging due to its varied clinical presentations and the lack of specific biomarkers. Accurate diagnosis requires a multifaceted approach, integrating imaging, histopathology, culture, microscopy, and molecular methods.

In immunocompromised patients, pulmonary CT scans are crucial for identifying key indicators such as the "reversed halo sign" or vessel occlusion via CT pulmonary angiography [54]. For diabetic patients with facial pain, sinusitis, or vision-related symptoms, cranial CT or MRI can detect sinusitis and assess orbital or cerebral involvement, with MRI preferred for its sensitivity. Suspected mucormycosis should prompt biopsy collection, and for confirmed cases, imaging of cranial, thoracic, and abdominal regions is recommended to assess disease extent. Weekly CT scans are advised for unstable patients due to the disease's rapid progression.

Mucormycosis is often identified through direct microscopy, which reveals non-pigmented, ribbon-like hyphae 6–25μm wide, typically non-septate or sparsely septate. However, artifacts during tissue processing can mimic septation, making hyphal width and irregularity more reliable diagnostic features [54]. Misidentification with Aspergillus species is common, necessitating additional techniques like immunohistochemistry or PCR for confirmation, although these methods are not widely available [63].

Culture remains essential for species identification and antifungal susceptibility testing, with direct microscopy strongly recommended to confirm hyphal morphology [55]. Molecular diagnostics using fresh tissue specimens are promising but limited by variability and the lack of standardized protocols for detecting fungal DNA in serum and body fluids [63].

COVID-19 IMPACT

COVID-19–associated mucormycosis (CAM) has emerged as a significant global health challenge during the pandemic, particularly due to a combination of environmental, medical, and host-related factors. The high incidence of CAM is associated with environmental exposure to fungal spores and predisposing conditions such as poorly controlled diabetes mellitus, often exacerbated by systemic corticosteroid use and severe COVID-19 treatment protocols [37].

In high-income countries, the predominant clinical manifestations are pulmonary or disseminated infections, which have mortality rates exceeding 80% [37]. However, the true burden may be underestimated due to diagnostic challenges like misclassification or insufficient testing methods [37]. In contrast, low- and middle-income countries, particularly India, have reported a disproportionately higher burden of CAM, where rhino-orbital mucormycosis is the most prevalent form, contributing to comparatively lower mortality rates[55]. India's elevated CAM incidence is attributed to the high prevalence of diabetes, widespread corticosteroid overuse, and environmental factors that facilitate exposure to Mucorales fungi [70].

Underlying conditions like diabetic ketoacidosis (DKA) and hyperglycemia create an ideal metabolic environment for fungal proliferation, fueled by hyperferritinemia and metabolic acidosis [64], [70]. These factors, combined with systemic effects of severe COVID-19, such as immune dysregulation, endothelialitis, and iron overload, further increase susceptibility to CAM [64], [70]. Notably, glucocorticoid therapy, while beneficial in mitigating severe COVID-19 outcomes, has been a critical driver of secondary fungal infections like mucormycosis due to its immunosuppressive effects and exacerbation of hyperglycemia [7], [37].

The demographic profile of CAM patients has shifted, many cases were linked to new-onset diabetes or undiagnosed diabetes revealed by SARS-CoV-2–induced pancreatic islet damage, suggesting a possible "diabetogenic" effect of COVID-19 [49], [70]. CAM-associated mortality is influenced by the clinical form of the disease, with rhino-orbital-cerebral cases demonstrating better outcomes compared to gastrointestinal or pulmonary forms, which remain highly fatal [37], [55].

The pandemic has also highlighted changes in the microbiological profile of mucormycosis. For instance, Rhizopus microsporus, previously less prevalent, has shown an increased incidence in CAM cases, with worrying implications due to its lower susceptibility to standard treatments like amphotericin B [70]. Diagnostic delays, often due to overlapping clinical features with COVID-19 or insufficient awareness among clinicians, have further exacerbated the disease burden and associated mortality [71].

TREATMENT + MANAGEMENT

Mucormycosis presents significant challenges in treatment and management due to its high mortality rate, particularly in immunocompromised individuals. The cornerstone of management involves a multimodal approach: emphasizing early diagnosis coupled with prophylaxis, surgical debridement of necrotic tissue, and systemic antifungal therapy. Prophylactic measures, such as using posaconazole in neutropenic or immunosuppressed patients, can reduce the risk of infection. For immunocompromised individuals previously diagnosed with mucormycosis, continuation of effective antifungal therapy and surgical intervention is crucial for secondary prophylaxis. Treatment initiation should not be delayed in immunocompromised patients with suspected mucormycosis, even as diagnostic efforts continue.

Pharmacologically, liposomal amphotericin B remains the first-line drug of choice due to its efficacy in treating mucormycosis across various organ systems, including cases with central nervous system involvement. Dosages typically range from 5–10 mg/kg per day, with reduced doses considered in cases of renal toxicity [54], [55], [72]. Early initiation of liposomal amphotericin B is critical, as delays are associated with worse outcomes. Isavuconazole and posaconazole are viable alternatives, particularly in patients with renal dysfunction, though lipid formulations of amphotericin B remain the first-line treatment due to their broad-spectrum efficacy against Mucorales [37], [55], [64]. While these agents show activity against Mucorales, challenges such as breakthrough infections, resistance, and absorption variability, particularly with posaconazole, necessitate therapeutic drug monitoring (TDM) [72].

Adjunctive strategies are equally vital, including controlling underlying risk factors such as diabetes and immunosuppression. Correcting metabolic abnormalities, such as diabetic ketoacidosis, and reducing

corticosteroid use are pivotal steps to mitigate the progression of the disease.[37], [55] Surgical debridement is crucial in managing invasive infections, particularly rhino-orbital disease, although robust guidelines for precise surgical techniques are still lacking. Studies emphasize that surgery should not be delayed in favor of antifungal therapy alone, as combined treatment significantly improves outcomes.

The emergence of new antifungal drugs like isavuconazole, which offers advantages such as fewer drug interactions and excellent oral bioavailability, and advanced formulations of posaconazole, including delayed-release tablets and intravenous options, has broadened the therapeutic arsenal [55]. However, therapeutic drug monitoring is recommended to ensure efficacy and minimize toxicity, especially in complex cases [72]. Experimental antifungals, such as rezafungin and olorofim, show promise but require further evaluation [55].

In the context of the COVID-19 pandemic, mucormycosis has been particularly devastating among patients treated with corticosteroids and those with pre-existing diabetes. These individuals exhibit higher susceptibility to invasive fungal infections, often with poor prognoses [37], [64]. The pandemic has underscored the need for heightened vigilance, early intervention, and tailored therapeutic strategies to manage this life-threatening condition effectively.

The duration of therapy is highly individualized, often lasting weeks to months, and is contingent on resolving the underlying immune deficits, achieving infection clearance on imaging, and ensuring substantial clinical improvement [37], [64].

Methods

Data Source

The analysis used data from the 2016–2021 Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) (https://hcup-us.ahrq.gov/nisoverview.jsp), the largest publicly available all-payer inpatient healthcare database in the United States. The NIS represents a 20% stratified sample of discharges from U.S. community hospitals, excluding rehabilitation and long-term acute care facilities. Discharge-level weights are based on hospital characteristics, including U.S. census division, ownership, urban or rural location, teaching status, and bed size, ensuring the representativeness of the data. Each year, the unweighted NIS dataset includes approximately 7 million inpatient stays. When weighted, the NIS represents nearly 35 million hospitalizations nationwide. Of note, the NIS hospitalization dataset lacks unique patient identifiers, preventing the differentiation of multiple hospitalizations for the same patient.

Medical Coding and Data Collection

The NIS has up to 40 International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes listed per discharge record in 2020, with fewer diagnosis codes for earlier years of data. For this study, aspergillosis-related hospitalizations (A-RH) were defined as those with any of the following ICD-10-CM codes listed anywhere on the discharge record: B44.0 (invasive pulmonary), B44.1 (other pulmonary), B44.2 (tonsillar), B44.7 (disseminated), B44.81 (allergic bronchopulmonary), B44.89 (other forms), and B44.9 (unspecified). After subtype analysis was conducted, a secondary analysis consolidated invasive aspergillosis and disseminated aspergillosis into a singular "invasives" category. Mucormycosis-related hospitalizations (M-RH) were defined as those with any of the following ICD-10-CM codes listed on the discharge record: B46.0 (pulmonary), B46.1 (rhinocerebral), B46.2 (gastrointestinal), B46.3 (cutaneous), B46.4 (disseminated), B46.5 (unspecified), B46.8 (other zygomycoses), and B46.9 (zygomycosis, unspecified). Much like A-RH, ICD-10-CM coding scheme enabled classification of clinical forms of M-RH.

Based on previous studies, underlying conditions of clinical significance associated with aspergillosis and mucormycosis were identified and included in the analysis if listed on the discharge record[2], [5], [37],

[71]. The conditions included: asthma, cirrhosis, chronic obstructive pulmonary disease (COPD), COVID-19, diabetes, end stage renal disease (ESRD), hematologic malignancy, hematopoietic stem cell transplant, HIV, immune-mediated inflammatory diseases, influenza, solid organ transplants, and solid malignancy.

International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) for conditions of interest for aspergillosis- and mucormycosis-related Hospitalizations, 2016—2021	
Conditions	**ICD-10 Codes**
Asthma	J45
Aspergillosis	B44.0, B44.1, B44.2, B44.7, B44.81, B44.89, B44.9
Cirrhosis	K74
Chronic Obstructive Pulmonary Disease	J43, J44
COVID-19	U071
Diabetes	E08, E09, E10, E11, E13
End Stage Renal Disease	D17, N18.6
Hematologic Malignancy	C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96
Hematopoietic Stem Cell Transplant	Z94.84, Z948.1
HIV	B20, Z21
Immune-mediated inflammatory Diseases	G35, G70, K50, K51, L40, L93, M023, M05, M06, M08, M33, M352, M45
Influenza	J09, J10, J11
Mucormycosis	B46.0, B46.1, B46.2, B46.3, B46.4, B46.5, B46.8, B46.9
Solid Organ Transplant	Z94.0, Z94.1, Z94.3, Z94.4, Z94.5, Z94.6, Z94.81, Z94.82, Z94.83, Z94.84, Z94.89, Z94.9
Solid Organ Malignancy	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C7A, C7B, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80

Data Analysis

National estimates of the number of A-RHs and M-RHs were derived using HCUP-provided discharge weights, which adjusted for the stratified sampling design and allowed for the extrapolation of results to represent the U.S. population. Trend in hospitalization rates were analyzed across various

demographic and clinical variables, including age group, sex, census region (https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf, accessed on August 4, 2024), payor, clinical manifestation, and presence of specific concurrent conditions. Trends in in-hospital mortality and the prevalence of concurrent medical conditions among A-RH and M-RH were systematically assessed.

Annual hospitalization rates were calculated overall and stratified by age, sex, and U.S. census region; population estimates from the U.S. Census Bureau (https://www.census.gov/data/tables/time-series/demo/popest/2020s-national-detail.html)were used to obtain denominators. We examined annual changes in the percentage of A-RH and M-RH involving selected concurrent conditions, different payor types, and in hospital-mortality. For 2020—2021 data, COVID-19-associated and non-COVID-19 associated hospitalizations were compared, examining differences in demographic characteristics, underlying conditions, and in-hospital mortality.

Categorical variables were analyzed using Rao–Scott chi-square goodness-of-fit tests, which accounts for the complex survey design. Linear regressions were applied to compare continuous variables.

To estimate the average annual percentage change (APC), weighted least-squares regressions were applied to log-transformed rates, using the delta method to approximate the variances, which served as weights. To assess significant temporal changes in the prevalence of underlying conditions among A-RH and M-RH, logistic regression analyses were conducted using survey data techniques. A significance level (α) of 0.05 was established as the threshold for all statistical tests. The total number of cases across the study period was aggregated to ascertain the cumulative proportion of each underlying condition.

Data analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC, USA) survey procedures, which accounted for the complex survey design. This study was reviewed by the Emory University Institutional Review Board (IRB) and determined this research qualifies as exempt from the requirements of the Federal Policy for the Protection of Human subjects given the secondary analytical nature of this research. All patient data were fully de-identified prior to study acquisition. However, to access and utilize the database, the HCUP

Data Use Agreement Training Tool was completed, and the corresponding Data Use Agreement was thoroughly reviewed and signed.

The protocol was reviewed by the Centers for Disease Control and Prevention (CDC) and Emory University, in compliance with applicable federal laws and CDC policies, including but not limited to 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; and 44 U.S.C. §3501 et seq."

RESULTS

Aspergillosis-Related Hospitalizations

Overall

During 2016–2021, an estimated 86,570 A-RHs (95% Confidence Interval [CI]: 83,770–89,370) occurred (**Table 1a**.). The hospitalization rate per million population (pmp) rose from 42.3 pmp(95% CI: 28.7–46.1) in 2016 to 51.5 pmp (95% CI: 47.0–56.0) in 2021 (**Figure 1**).

Mortality

Overall, in-hospital mortality occurred among an estimated 14,460 (95% CI: 13,795–15,125) hospitalizations, translating to 16.7% among all A-RHs during 2016 to 2021. For A-RHs, the percentage of in-hospital mortality increased significantly from 13.4% in 2016 to 26.8% in 2021 (APC= +20.0%, p= 0.0363) (**Table 1a.; Figure 2**).

Subtype Analysis

Within this period, the rate of hospitalization for invasive aspergillosis, other pulmonary, and unspecified aspergillosis were most notable. An estimated 12,435 (95% CI: 11,537–13,333) invasive aspergillosis-related hospitalizations (IA-RHs) occurred, with annual hospitalizations rising from 1,770 persons (95% CI: 1,476–2,064) in 2016 to 2,530 (95% CI: 2,127–2,933) in 2021. Likewise, the IA-RH rate increased from 5.5 pmp (95% CI: 4.6–6.4) in 2016 to 7.6 pmp (95% CI: 6.4–8.8) in 2021.

Among the categorical subtypes of A-RHs, "other pulmonary" and "unspecified" aspergillosis demonstrated the highest rates of hospitalization. The rate for "other pulmonary" aspergillosis increased from 18.7 pmp (95% CI: 17.1–20.2) in 2016 to 24.1 pmp (95% CI: 22.1–26.2) in 2021. "Unspecified" aspergillosis hospitalizations rose from 15.5 pmp (95% CI: 14.2–16.9) in 2016 to 17.7 pmp (95% CI: 16.2–19.1) in 2021(**Table 1a.; Figure 3**). “Other pulmonary” and “Unspecified” accounted for 66.8% of all A-RHs from 2016-2021. Among trends in aspergillosis subtypes, invasive aspergillosis-related hospitalizations (IA-RH) increased from 5.5 pmp (95% CI: 4.6–6.4) in 2016 to 7.6 pmp (95% CI: 6.4–8.8) in 2021 (APC= +7.2%, p= 0.0005) (**Table 1a.; Figure 4**).

Demographic

Overall, A-RH rates were highest for hospitalizations involving persons aged ≥65 years, with rates declining from 119.9 pmp (95% CI: 110.1–129.7) in 2016 to 113.0 pmp (95% CI: 103.2–122.8) in 2020 and peaking at 138.0 pmp (95% CI: 127.5–148.5) in 2021(**Table 1a.; Figure 5**). A-RH rates involving males were higher (vs. females), with rates declining from 37.5 pmp (95% CI: 34.3–40.7) in 2016 to 32.3 pmp (95% CI: 29.1–35.4) in 2020 and increasing to in 42.1 pmp (95% CI: 38.7–45.5) in 2021. A-RH rates were highest in the West U.S. census region, where rates escalated from 47.9 pmp (95% CI: 40.1–55.6) in 2016 to 51.2 pmp (95% CI: 43.2–59.2) in 2018 before dropping to 46.7 pmp (95% CI: 37.7–55.7) in 2020.*

From 2016–2021, rates were higher for hospitalizations involving persons classified as non-Hispanic Other and non-Hispanic Black: non-Hispanic Other from 41.6 pmp (95% CI: 23.3–59.9) in 2016 to 54.0 pmp (95% CI: 39.1–68.8) in 2021; non-Hispanic Black from 38.2 pmp (95% CI: 33.3–43.1) in 2016 to 50.8 pmp (95% CI: 44.5–57.1) in 2021(**Table 1a.; Figure 5**).

Comorbidities and Concurrent Conditions

Across the period, the most common underlying conditions for A-RH were chronic obstructive pulmonary disease (COPD) (33.1%) followed by diabetes (27.9%), hematologic malignancies (HM) (20.7%), and solid organ malignancies (SOM) (10.1%). The percentage of A-RHs involving diabetes, COVID-19, and SOM increased, while the percentage involving COPD and HM decreased(**Table 1a.; Figure 6**).

For those conditions experiencing an increase during 2016–2021, the percentage of A-RH with underlying diabetes increased from 26.0% in 2016 to 31.6% in 2021 (APC= +6.7%, p= 0.07). Similarly, the percentage of A-RH with underlying COVID-19 increased from 10.9% in 2020 to 26.8% in 2021. In addition, the percentage of A-RH with underlying SOM increased from 9.7% in 2016 to 11.1% in 2020 then declined to 9.7% in 2021, still noting the significant increase in the annual percent change (APC= +3.7%, p=0.03).

For the declining underlying conditions, the percentage of A-RH with underlying COPD decreased from 36.4% in 2016 to 28.2% in 2021 (APC= -2.2%, p=0.3435). Similarly, the percentage of A-RH with

underlying HM decreased from 21.3% in 2016 to 16.6 % in 2021 (APC= -1.4%, p= 0.1898). The percentage of A-RH with underlying asthma decreased from 11.8% in 2016 to 7.8% in 2021 (APC= -7.0%, p= 0.0546).

COVID-19 vs. Non-COVID

During 2020–2021, an estimated 6025 (19.9%) of A-RHs were associated with COVID-19, whereas 24,285 (80.1%) of A-RHs were not associated with COVID-19 (**Table 2a.**). The in-hospital mortality for COVID-19 co-infected A-RHs was 55.7% (p<0.0001) contrasted with 15.5% (p<0.0001) for non-COVID-19 associated A-RHs(**Table 2a.; Figure 9**).

Among COVID-19-associated aspergillosis-related hospitalization (CAA-RH), 5,460 (90.6%, p<0.0001) hospitalizations involved persons aged ≥45 years (**Table 2a.**). In comparison, 20,190 (83.1%, p<0.0001) hospitalizations of persons with non-COVID-19-associated A-RHs (non-CAA-RH) were ≥45 years of age.

Compared with hospitalizations of persons with non–CAA-RHs, hospitalizations of persons with CAA-RHs more frequently involved those who were male (N=3660, 60.8%, p= <0.0001) rather than female (N=2365, 39.2%, p = <0.0001). There was no distinct regional difference between COVID-19 and non-COVID-19 associations (**Table 2a.**).*

For CAA-RHs, the percentages were highest for non-Hispanic Whites (52.8%, p<0.0001) and Hispanic populations (24.2%, p<0.0001). In contrast, for non-CAA-RHs, non-Hispanic Whites (66.1%, p<0.0001) accounted for a higher percentage, followed by non-Hispanic Blacks (13.6%, p<0.0001) (**Table 2a.**).

For underlying conditions, diabetes was reported in 42.2% (p<0.0001) of CAA-RHs compared to 27.2% (p<0.0001) in non-CAA-RHs. COPD was present in 21.0% (p<0.0001) of CAA-RHs, while it comprised 31.4% (p<0.0001) of non-CAA-RHs. HM was observed in 6.2% (p<0.0001) of CAA-RHs, while in 22.4% (p<0.0001) of non-CAA-RHs(**Table 2a.; Figure 8**).

Mucormycosis-Related Hospitalizations

Overall Trends

During 2016–2021, approximately 8,565 M-RHs (95% CI: 8,009–9,121) were recorded. The number of M-RHs increased from 1,240 M-RHs (95% CI: 1,024–1,456) in 2016 to 1,920 M-RHs (95% CI: 1,622–2,218) in 2021. The overall rate of hospitalization of M-RHs rose during this period from 3.8 per million persons (pmp) (95% CI: 3.2–4.5) in 2016 to 5.8 pmp (95% CI: 4.9–6.7) in 2021 (**Table 1b.; Figure 10**).

Mortality

In total, M-RH consisted of 1720 (95% CI: 1519–1921) in-hospital mortalities or 20.1% of M-RHs during 2016 to 2021. For M-RHs, the percentage of in-hospital mortality increased significantly from 16.5% in 2016 to 24.7% in 2021 (APC= +16.5% , p= 0.0162) (**Table 1b.; Figure 11**).

Subtype Analysis

During the study period, the rate of hospitalizations for M-RHs were most common for "unspecified" (39.9%), pulmonary (25.3%), rhinocerebral (11.4%), and cutaneous (10.6%) mucormycosis subtypes. The hospitalization rate of "unspecified" mucormycosis increased significantly, rising from 1.5 pmp (95% CI: 1.1–1.8) in 2016 to 2.5 pmp (95% CI: 2.1–3.0) in 2021 (APC= +11.8%, p=0.0044) (**Figure 12**). Similarly, pulmonary mucormycosis saw an increase from 0.9 pmp (95% CI: 0.6–1.2) to 1.5 pmp (95% CI: 1.2–1.9) over the same period (APC= +9.6%, p=0.0005) (**Figure 13**). Rhinocerebral mucormycosis saw an increase from 0.5 pmp (95% CI: 0.3–0.6) to 0.7 pmp (95% CI: 0.5–0.9). Cutaneous mucormycosis saw an increase from 0.5 pmp (95% CI: 0.3–0.7) to 0.6 pmp (95% CI: 0.4–0.8). The “unspecified” and pulmonary codified subtypes accounted for approximately 65.1% of all M-RHs from 2016 to 2021.

Demographic

The rate of hospitalization for M-RHs exhibited varying trends across age groups during 2016–2021 (**Table 1b.; Figure 14**). Notably, the "45 to 64 years" and "18 to 44 years" age cohorts saw increases in M-RH rates, whereas the rates for those aged "<18 years" and "≥65 years" remained relatively stable. Among individuals aged 45 to 64, the incidence of M-RHs rose from 5.5 pmp (95% CI: 4.2–6.8) in 2016 to 6.8 pmp

(95% CI: 5.4–8.3) in 2020, with a pronounced rise to 10.7 pmp (95% CI: 8.7–12.7) by 2021. Similarly, for those aged 18 to 44, the incidence increased from 2.3 pmp (95% CI: 1.6–3.0) in 2016 to 4.0 pmp (95% CI: 3.1–4.9) in 2021. Despite a consistently higher rate in the "≥65 years" group, the hospitalization rate remained stable, from 7.5 pmp (95% CI: 5.6–9.5) in 2016 to 7.2 pmp (95% CI: 5.5–8.9) in 2021.

M-RHs rose across both sexes, with males consistently exhibiting higher rates. For males, the hospitalization rate increased from 5.3 pmp (95% CI: 4.3–6.3) in 2016 to 7.4 pmp (95% CI: 6.2–8.7) in 2021. Geographically, the West region displayed the highest rates of hospitalization compared to other U.S. census regions, rising from 5.5 pmp (95% CI: 3.8–7.2) in 2016 to 7.4 pmp (95% CI: 5.4–9.4) in 2020.[1]

Racial and ethnic disparities were also observed in M-RH trends. Most racial/ethnic groups experienced moderate increases in M-RH incidence from 2020 to 2021, with notable exceptions. The American Indian/Alaska Native (AIAN) group saw a substantial rise increase in rate, from 1.2 pmp (95% CI: 0–3.5) in 2019 to 11.9 pmp (95% CI: 2.8–18.2) in 2020, reflecting a more than tenfold increase. Conversely, the "Other" race/ethnic group experienced a decline in M-RH rates from 6.3 pmp (95% CI: 2.8–9.9) in 2020 to 5.6 pmp (95% CI: 1.3–9.9) in 2021(**Table 1b.; Figure 14**).

Comorbidities and Concurrent Conditions

For M-RHs, the most common underlying conditions were diabetes (45.7%), followed by hematologic malignancy (31.2%), chronic obstructive pulmonary disease (11.1%), and solid organ transplant (10.3%) (**Figure 15**). The percentage of M-RHs involving COPD increased, while the percentages involving diabetes, hematologic malignancy, solid organ transplant and end stage renal disease decreased during the period.

[1] * NIS hospital region data associated with U.S. census region was only available for 2016-2020. At the time of this study, hospital region data for 2021 was unavailable.

During 2016–2021, the percentage of M-RH with underlying diabetes rose significantly from 44.0% in 2016 to 49.2% in 2021, escalating from 545 (95% CI: 542-848) hospitalizations in 2016 to 945 (in 2021 (APC= +10.2%, p= 0.0315). Conversely, the percentage of M-RHs with underlying COPD initially declined from 11.7% in 2016 to 8.4% in 2018 but grew to a noticeable, but nonsignificant, increase of 12.2% in 2021 (APC= +11.6%, p= 0.0589).

In terms of declining trends in annual percent changes, the percentage of M-RH with underlying HM declined from 37.1% in 2016 to 25.8% in 2021 (APC= -0.8%, p=0.8408). In addition, the percentage of M-RH with underlying SOT decreased from 11.3% in 2016 to 7.0% in 2021 (APC= -0.8%, p=0.8239). Although not one of the common conditions, the percentage of M-RHs with underlying SOM rose from 3.2% in 2016 to 4.4% in 2021 (APC= 13.6%, p= 0.0242).

COVID-19 vs. Non-COVID

During 2020–2021, COVID-19-associated mucormycosis-related hospitalizations (CAM-RH) comprised 420 (12.6%), whereas 2,920 (87.4%) hospitalizations were non-COVID-19-associated mucormycosis-related hospitalizations (CAM-RH) (**Table 2b**). The in-hospital mortality amounted to an estimated 220 CAM-RH in-hospital mortalities, 52.4% (p<0.0001) contrasted with 18.0% (p<0.0001) for non-CAM-RHs (**Table 2b.; Figure 17**).

Among the CAM-RH, 160 (38.1%, p<0.0001) hospitalizations involved persons aged 45 to 64; 155 (36.9%, p<0.0001) hospitalizations included persons ages 18 to 44 years of age. In comparison, 1295 (4

4.4%, p<0.0001) hospitalizations with non-CAM-RH persons were 45 to 64 years of age; 715 (24.5%, p<0.0001) hospitalizations with non-CAM-RHs persons were 18 to 44 years of age.

Compared with hospitalizations of persons with non–CAM-RHs, hospitalizations of persons with CAM-RHs more frequently involved those who were male (N=310, 73.8%, p= <0.0001) rather than female (N=110, 26.2%, p = <0.0001).

For CAM-RH in 2020, the West region reported 65 (43.3%, p= 0.0041) hospitalizations compared to 515 (40.6%, p<0.0001) hospitalizations of non-CAM-RHs.* The South region reported 45 (30.0% , p= 0.0041) CAM-RHs compared to 430 (33.9%, p<0.0001) non-CAM-RHs.

During 2020–2021, CAM-RHs percentages were highest for non-Hispanic Whites (46.3%, p= 0.0271), Hispanic (25.0%, p= 0.0271), and non-Hispanic Black (21.3%, p= 0.0271) groups. In contrast, for non-CAM-RHs, non-Hispanic Whites (52.8%, p<0.0001) accounted for a higher percentage, followed by Hispanic (22.3%, p<0.0001), and non-Hispanic Black (14.6%, p<0.0001) populations.

For underlying conditions, diabetes was reported in 63.1% (p<0.0001) of COVID-19-associated M-RHs compared to 45.9% (p<0.0001) in non-COVID-19-associated M-RHs. COPD was present in 14.3% (p= 0.8338) of COVID-19-associated A-RHs, while it comprised 11.6% (p= 0.555) of non-COVID-19-associated M-RHs. Hematologic malignancy (HM) was observed in 7.1% (p<0.0001) of COVID-19-associated M-RHs, while in 28.3% (p<0.0001) of non-COVID-19-associated M-RHs (**Table 2b; Figure 17**).

DISCUSSION

OVERALL

This analysis updates trends in hospitalization for aspergillosis and mucormycosis in the United States, leveraging HCUP National Inpatient Sample (NIS) data from 2016 to 2021. Our results confirm that hospitalizations related to these invasive mold infections are rising, nationally. The observed increases in hospitalization rates, number of hospitalizations, and in-hospital mortality rates for A-RH and M-RH and their clinical subtypes highlight an intensifying burden of invasive mold infections. Hospitalization rates grew from 42.3 per million persons in 2016 to 51.5 per million persons in 2021 for A-RH. Despite an overall decline in A-RH from 2018 to 2020, hospitalizations and rates peaked in 2021 with an estimated 17,110 hospitalizations (95% CI: 15,610-18,610). Closer examination of clinical subtypes revealed that the combined annual percentage change for invasive and disseminated aspergillosis showed an increase of +7.2% annually (p=0.0005), growing from 5.5 (95% CI: 4.6-6.4) per million persons in 2016 to 7.6 (95%CI: 6.4-8.8) per million persons in 2021.

Correspondingly, M-RH hospitalization rates steadily rose from 3.8 per million persons in 2016 to a peak of 5.8 per million persons by 2021. Hospitalization estimates rose to their highest in 2021 with an estimated 1920 (95% CI: 1622-2218). Further, pulmonary mucormycosis rose significantly with an annual percentage change of +9.6% annually (p=0.0111) with a drastic uptick from 2020-2021. This trend highlights exacerbating respiratory implications for aspergillosis and mucormycosis infections within the context of the COVID-19 pandemic, particularly for immunocompromised patients [73].

The study further found a significant rise in in-hospital mortality. During the study period, there was an estimated 14,460 (16.7%; 95% CI: 13,795-15,125) in-hospital mortalities associated with A-RH and an estimated 1,720 (20.1%; 95% CI: 1519-1921) in-hospital moralities associated with M-RH. As annual in-hospital mortality rates increased for A-RH (APC= +20.0%, p=0.0363) and M-RH (APC=+16.5%, p=0.0162), in-hospital mortality peaked in 2021 for both A-RH (26.8%) and M-RH (24.7%). During 2020–2021, in-hospital mortality for COVID-19-associated aspergillosis-related hospitalizations (CAA-RHs) and

mucormycosis-related hospitalizations (CAM-RHs) reached a staggering 55.7% ($p<0.0001$) and 52.4% ($p<0.0001$), respectively. These figures underscore the severe and compounding impact of SARS-CoV-2 co-infection on invasive mold infections, highlighting an urgent need for focused clinical and public health interventions to mitigate these life-threatening outcomes.

As aspergillosis and mucormycosis typically necessitate hospitalization, the estimated hospitalization rates likely reflect the current burden of these infections in the United States. The rising trends in overall hospitalization rates and in-hospital mortality for both A-RH and M-RH may be attributable to several factors. Key factors among these are the increased use of immunosuppressive treatments, especially corticosteroids, in critically ill COVID-19 patients, alongside a growing prevalence of diabetes, chronic obstructive pulmonary disease (COPD), and immunocompromised conditions, including cancer and organ transplantation.

Demographics

Overall, A-RH and M-RH rates have increased across various age groups, sexes, racial/ethnic groups, and regions. Hospitalization rates for A-RH were notably higher among individuals $\geq$ 65 years old, findings consistent with previous studies [19], [20], [21]. Among individuals aged 18 to 64 years, the hospitalization rates of M-RH increased. In contrast, hospitalization rates for <18 and $\geq$65 age groups remained relatively stable. However, the $\geq$65 cohort consistently exhibited the highest rate, except in 2021, when hospitalization rates among the 45 to 64 age group surpassed them. Rates of A-RH and M-RH also increased across both sexes, with males consistently exhibiting higher rates than females during the study period, a trend consistent with prior studies [21].

Within the context of racial/ethnic groups, racial disparities were pronounced. Hospitalization rates for A-RH were disproportionately elevated among non-Hispanic Black and non-Hispanic Other populations compared to other ethnic groups. Similarly, for M-RH, disproportionately higher rates were observed among non-Hispanic Black, non-Hispanic Other, and Hispanic populations.

This observation is consistent with prior research demonstrating that specific racial and ethnic groups, particularly Black/African American, Hispanic, and other minority populations, experienced elevated rates of invasive fungal infections [1], [74]. Rayens et al. found a high frequency of mucormycosis diagnoses in AA/PI and Hispanic patients when compared to non-Hispanic White patients. In contrast in the same study, Rayens et al. found a higher frequency of aspergillosis diagnoses among non-Hispanic White and Asian American/Pacific Islander (AA/PI) patients. This finding was attributed to higher income in these ethnic and racial groups in 2019—specifically, greater likelihood of receiving transplants and improved access to healthcare associated with the comorbidities discussed in this study—this aspergillosis trend was not reflected in our analysis of the NIS dataset during 2016-2021[1].

Alternatively, our findings align with existing evidence that both COVID-19 and fungal infections disproportionately impact these populations [36], [74]. Disproportionate effects of COVID-19 have been frequently attributed to inequities in social determinants of health— from increased occupational exposure to limited access to quality healthcare [74], [75]. Furthermore, underlying conditions, like diabetes and COPD, may be more pronounced among certain racial and ethnic groups, compounding the observed disparities in A-RH and M-RH burden [74]. Notably, from our study, the American Indian/Alaska Native (AIAN) group saw a dramatic increase, rising from 2019 to 2020, representing a more than tenfold jump. Due to weighted estimate of a potentially small sample, this finding requires further investigation. Conversely, the "Other" racial/ethnic group saw a decline from 2020 to 2021.

In terms of regional variation, our findings are consistent with a recent study that highlights the rates in the West U.S. census region during 2020-2021. Our study found that the West U.S. census region consistently exhibited the highest rates compared to all other regions from 2016 to 2020 [36]. These findings seem to extend the previously documented start of the regional trend. In their 2017 study, Vallabhaneni et al. found no significant difference in the highest A-RH and M-RH rates between the Midwest and the West U.S. in 2013 [19].

Predominantly for A-RH and minimally for M-RH, age, sex, and regional trends experienced a slight but noticeable decline from 2018 to 2020 among individuals aged over 65, males, and across the West census region, with most rates reaching their lowest point in 2020. The 2020 inflection point, marked by a dip in A-RH and M-RH, likely reflects underreporting or undetected cases rather than genuine reductions in IMI hospitalizations. Two factors likely contributed to underreporting: (1) pulmonary subtypes of A-RH and M-RH mimic COVID-19 symptoms, complicating diagnosis, and (2) diagnostic limitations during the pandemic, including reluctance and reduced use of bronchoalveolar lavage (BAL) and related assays. The reduced use of BAL for assays came as both a recommendation by the American Association for Bronchology and International Pulmonology and due to a potential hesitancy to exacerbate conditions for patients during the COVID-19 pandemic [76], [77]. While serum GM tests are available, BALF-related GM assays and subsequent cultures and histopathology remain the most accurate diagnostic tools.

In concordance with this trend, a prior study by Gold et al. attributed the lack of a noticeable rise in fungal-related mortality in 2020 due to limited detection and reporting of COVID-19–associated fungal infections during this period rather than a true decrease in cases[36]. The observed peak in 2021 might indicate improved clinician awareness and increased testing for these infections, potentially influenced by the heightened use of corticosteroids and tocilizumab—both recognized risk factors for invasive fungal infections, including mold infections—administered in treating severe COVID-19 cases [36]. In 2021, a noticeable increase to its highest rates reflects the substantial impact of COVID-19, introducing a new cohort of vulnerable patients affected by the pandemic.

Comorbidities + Concurrent Conditions

ASPERGILLOSIS

In our analysis, comorbidities and concurrent conditions accounted for a substantial portion of hospitalizations related to A-RH and M-RH. Especially with the rise in multi-comorbidities, patients may possess more than one concurrent comorbidity, as reflected in the crude proportions of IMIs with underlying conditions.

During the period from 2016 to 2021, the leading comorbidities for A-RH were COPD (33.1%), diabetes (27.9%), HM (20.7%), and SOM (10.1%). The A-RH trends in underlying COPD declined, not significantly, by -2.2% (p=0.3435), composing 28.2% of all A-RH in 2021. With COPD being globally underdiagnosed, A-RH rates may not be capturing the exact toll of COPD as an underlying condition, but rather, underestimating its prevalence, as COPD is most likely higher than previously estimated [78]. A study on the National Readmissions Database (NRD) illustrates similar declining yearly rates with aspergillosis related COPD, from 2013 to 2018 [25]. Nonetheless, COPD remains an independent predictor of mortality in A-RH, as documented by many who observed significantly higher mortality rates among patients with aspergillosis than without [25], [79], [80].

In contrast to declining yet substantial trends in COPD, diabetes among A-RH cases exhibited an average annual increase of +6.7% (p=0.0714), though this trend did not reach statistical significance. Our findings may correlate with the growing proportion of adult hospitalizations with diabetes, which climbed from 17.1% to 27.3% during 2000-2018 [81]. As diabetes-related hospitalizations continue to grow, infection-related hospitalizations remain a major burden for people with diabetes, with rates up to 15.7 times higher than those without diabetes in 2015 [82]. This finding is consistent with previous research highlighting diabetes as a leading clinical risk factor for aspergillosis-related hospitalizations, particularly among kidney transplant recipients, as reported in the US Renal Data System [83]. These trends highlight the need for improved diabetes management and infection prevention strategies, particularly among the growing diabetes populations.

Our findings show a non-significant decline in the association of HM with A-RH. In the past, aspergillus species have become one of the primary causes of infectious mortality in severely immunocompromised individuals, with mortality rates ranging from 40% to 50% in patients with acute leukemia and those undergoing HSCT [44]. In the mid-2000s, several epidemiological studies documented a notable decrease in the incidence and mortality rates of IPA in patients receiving allogeneic HSCT and SOT [44]. This reduction was linked to changes in HSCT procedures for HM patients, such as shortened periods of neutropenia before engraftment, along with advancements in the diagnosis, prevention with prophylaxis,

and treatment of fungal infections [44]. These advancements in treatment and patient care likely played a substantial role in the observed decline reported in this study.

Lastly, the final comorbidity composing more than 10% of the total A-RHs during 2016-2021 was SOM. In our study, we observed a statistically significant annual increase of +3.6% ($p=0.0286$) in the hospitalization rate for A-RH associated with SOM. In a study, researchers found a notably higher risk of mortality in SOM patients with aspergillosis infections [80]. Additionally, among the various solid organ malignancies linked to A-RH, lung cancer was identified as the most common, accounting for $\geq$ 51% of cases [80], [84]. Chen et al. suggested that the increased incidence of aspergillosis could be attributed to the improvements in cancer survival rates and the advancements in diagnostic capabilities, which suggests not an actual increase in hospitalization but rather better awareness and reporting.

MUCORMYCOSIS

We identified significant comorbidities contributing to M-RH between 2016 and 2021. The largest contributing conditions were diabetes (45.7%), HM (31.2%), COPD (11.1%), and SOT (10.3%). Of particular note, diabetes showed a significant annual increase of +10.2% ($p=0.0315$) in M-RH over the study period. This aligns with findings from Kontoyiannis et al. (2016), who reported diabetes as the most common underlying condition from 2005 to 2014 [61]. Individuals with diabetes were shown to have a 3.5-fold increased risk of mortality associated with mucormycosis-related hospitalizations [50]. This observed association can be attributed to a combination of factors, including the impact of uncontrolled diabetes mellitus and diabetic ketoacidosis, the overuse of steroids, and the complications of SARS-CoV-2 infection, all of which significantly contribute to the rising incidence of mucormycosis[50], [64], [71]. Elevated blood sugar levels induce cellular stress and hypoxia, triggering the release of free radicals, fatty acids, and inflammatory proteins. This pro-inflammatory environment impairs immune cell function, alters proteins to increase iron availability for fungal growth, and attracts ineffective immune cells, such as M1 macrophages, incapable of eliminating mucormycosis spores [55]. These findings further emphasize the critical need for vigilant monitoring and intervention strategies for individuals with diabetes, especially in the context of immunosuppressive treatments and viral infections like COVID-19.

Previously, Vallabhaneni et al.'s study reported a significant annual increase of 7% in mucormycosis cases among HM-related hospitalizations in 2013 [19]. Extending to our study period of 2016—2021, our study found a modest nonsignificant change of -0.76%, which may be attributable to new treatments and therapies. However, breakthrough infections continue to be a concern, particularly among high-risk patients with leukemia. Rausch et al. (2018) highlighted the persistence of such infections even in patients receiving single-agent isavuconazole, emphasizing the challenges in managing mucormycosis in this vulnerable population[85].

For chronic obstructive pulmonary disease (COPD), our study identified an increasing APC of +11.6% in M-RH over the period of 2016–2021, albeit statistically insignificant. In 2021, an estimated 235 M-RHs had COPD, comprising 12.2% of the overall M-RHs. Historically, COPD is recognized as a risk factor for pulmonary mucormycosis, particularly in patients receiving low-dose corticosteroids [73]. However, there remains a limited body of research on the specific trends of mucormycosis in COPD populations. Some correlate the lack of evidence to difficulties in diagnosing pulmonary mucormycosis, given the damage from COPD. There could be a lack of clinical suspicion in pulmonary mucormycosis due to associating symptoms with COPD rather than mucormycosis and vice-versa. Additionally in 2020, there were challenges with diagnostically identifying mucormycosis, especially for fear of spreading SARS-CoV-2 virus, and the lack of highly specific biomarkers [86]. These associations warrant further investigation to better understand the current state of this relationship.

Among solid organ transplant (SOT) recipients, we observed a peak in M-RH in 2018, followed by a subsequent decline in the United States. This trend may reflect the clinical remediation and evolving practices in the management of mucormycosis among SOT recipients, building upon findings from Vallabhaneni et al. (2017), who documented a rising incidence of M-RH over 2000-2013 [19]. International data corroborates the ongoing threat of mucormycosis in SOT populations. A systematic review by Palomba et al. (2024) found that kidney transplant recipients represented half of all SOT-related mucormycosis cases, with striking mortality rates of 36.3% at 90 days and 63.4% at one year[87]. Liver transplant recipients faced the highest mortality rates and the shortest time to infection onset compared to other SOT types [88]. Numerous studies

have identified key risk factors for mucormycosis in SOT recipients, including advanced age (≥65 years), deceased donor transplants, and the use of tacrolimus [62], further underscoring the importance of tailored care and preventive measures in SOT high-risk population.

Despite prior studies highlighting the increasing trends in the populations of those with cirrhosis, ESRD, HSCT, and influenza, this study found these concurrent conditions and comorbidities to compose less than 10% of total hospitalizations per year and across the study period.

COVID-19 Impact

This study examines the critical issue of co-infections involving SARS-CoV-2 viral infections and invasive mold infections, highlighting their severe clinical and potentially fatal implications. Due to limitations in the data preventing distinctions between primary and secondary infections, the findings present two perspectives on the overall estimates. First, COVID-19-associated aspergillosis-related hospitalizations (CAA-RH) constituted 19.9% of all A-RHs during 2020–2021, suggesting a secondary role for COVID-19. Conversely, CAA-RH accounted for 0.15% of approximately 4.1 million COVID-19 hospitalizations during the same period. These dual estimates aim to contextualize the findings within the scope of prior research, which reports incidence rates ranging from 0.1% to 35% [8], [15], [16], [34], [89]. While distinguishing primary and secondary infections is important for tailoring treatments for at-risk populations, the distinction should not diminish the grave effects on elevated in-hospital mortality rates for this co-infected population.

Mortality for CAA-RH was significantly higher than for non-CAA-RH, almost four-fold greater, corroborating findings from prior studies [8], [16], [26], [90]. While it is unclear if CAA-RH directly contributes to mortality or disproportionately affects the most critically ill, its presence likely signifies a heightened risk of death. Variability in mortality rates across studies likely reflects differences in patient numbers and antifungal treatment strategies [8]. An international multicenter study found that variability in CAA-RH mortality was inherently fatal between those who received appropriate antifungal treatment against those who did not, with the latter group reaching 100% mortality when not provided with appropriate antifungal treatments [26]. Chong et al.'s systematic review highlights that, despite comparable lengths of

hospital stay and durations of invasive mechanical ventilation, critically ill CAA-RH patients experience higher mortality rates than their non-CAA-RH counterparts [16].

Among CAA-RHs, 46.1% of hospitalizations were composed of individuals aged 45 to 64, compared to 36.3% of non-COVID-19-associated aspergillosis hospitalizations (non-CAA-RH). Age-related differences were more pronounced in CAA-RH than non-CAA-RH. Sex distribution showed no difference between CAA-RH and non-CAA-RH. Compared with non-Hispanic white populations, racial and ethnic disparities between CAA-RH and non-CAA-RH were mostly notable for the Hispanic racial/ethnic group: Hispanics made up 24.2% of CAA-RH compared to just 10.9% of non-CAA-RH. Based on other studies, Hispanic patients experience a disproportionately higher rate of COVID-19 hospitalization overall [36], [75], [91]. With social determinants of health contributing to many factors, as previously stated in this study, more research is necessary to determine exact causative agents responsible for these findings. Regional differences were also observed in 2020, with CAA-RHs more prevalent in the West, whereas non-CAA-RHs were concentrated in the South.

Underlying conditions showed a strong link to CAA-RH, with diabetes (42.2%) and COPD (21.0%) as the most common comorbidities above 10%, compared to non-CAA-RH where COPD (31.4%), diabetes (27.2%), and hematologic malignancies (HM) (22.4%) were prominent. According to Kluge et al.'s recent global study, many ICU patients with invasive aspergillosis lacked traditional risk factors, such as neutropenia, malignancies, or a history of stem cell or solid organ transplantation. Key risk factors in critically ill ICU patients include corticosteroid use, antibiotic treatment, exacerbated COPD, decompensated liver disease, severe viral pneumonias like influenza and COVID-19, and possibly sepsis [39]. This is not to overlook a smaller proportion of patients presented with asthma, malignancies, ESRD, IMID, and SOT, but to rather highlight the still and ever-present vulnerability of immunocompromised individuals to these infections.

Because COVID-19 can lead to hyperinflammatory cytokine responses that left uncheck can create irreversible damage, immune suppression and impairment by corticosteroids can prevent severe outcomes like acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) through neutrophil, macrophage,

and T cell impairment. Although beneficial for COVID-19, immune impairment has led to the proliferation of aspergillosis, contributing not only to CAA-RH but in-hospital mortality [37].

During 2020–2021, COVID-19-associated mucormycosis hospitalizations (CAM-RH) represented 12.6% of all mucormycosis-related hospitalizations (M-RHs), indicating a potential secondary relationship with COVID-19. In contrast, CAM-RH accounted for just 0.01% of approximately 4.1 million COVID-19 hospitalizations during this timeframe, reflecting its relatively rare occurrence among the broader population hospitalized with COVID-19.

Demographically, among CAM-RH, 36.9% were in patients aged 18 to 44, compared to 24.5% of non-COVID-19-associated mucormycosis hospitalizations (non-CAM-RH) in the same age range. Although the 45 to 64 age group had the highest proportion of CAM-RH (38.1%), the proportion was lower than for non-CAM-RH (44.3%). Males had a higher percentage of CAM-RH (60.3%), though this difference was less pronounced with non-CAM-RH (39.7%). Aligned with Gold et al.'s 2023 study, regional patterns revealed a concentration of mucormycosis-related hospitalizations (M-RH) in the West, while racial disparities indicated a larger impact of CAM-RH on the Black/African American population (21.3%) compared to non-CAM-RH (14.6%) [36].

For CAM-RH, diabetes (63.1%) and COPD (14.3%) were the predominant underlying conditions. Among non-CAM-RH, the distribution spanned diabetes (45.9%), HM (28.3%), and COPD (11.6%). Diabetes, specifically poor glycemic control or uncontrolled, was found not only to be a risk factor for CAM, but to hasten the development of Mucorales infection than compared to well-controlled diabetes [37]. This has shifted the demographic profile of patients with CAM, with many cases emerging in individuals with newly diagnosed or previously unrecognized diabetes. This trend may be attributable to pancreatic islet damage induced by SARS-CoV-2, indicating a potential "diabetogenic" effect of COVID-19 [49], [70]. Even worse, corticosteroid use in severe COVID-19 was a well-documented risk factor that exacerbated the progression of CAM in diabetic patients [70], [92].

In-hospital mortality was significantly higher in CAM-RH than non-CAM-RH, aligning with previous studies [37], [49], [50], [71]. Despite CAM-RH's relatively rare occurrence in overall estimates, the high mortality associated with CAM varies depending on the clinical presentation. ROCM cases are associated with comparatively better outcomes, while gastrointestinal and pulmonary forms exhibit substantially higher fatality rates, underscoring the severity of these manifestations [37], [55]. In their systematic review, Ozbek et al. found in-hospital mortality to be lower in India, potentially due to the higher incidence of rhino-orbital mucormycosis, a clinical subtype that is associated with better outcomes and characterized by a unique clinical presentation that is seldom overlooked, when compared with pulmonary [71]. Unfortunately, with the higher rates of pulmonary M-RH than ROCM-RH from 2020-2021 in the United States, higher mortality rates were documented: in-hospital mortality was 52.4% for CAM-RH patients compared to 18.0% for non-CAM-RH patients.

Limitations

As a retrospective observational study, our analysis is inherently limited by the data structure and time frame, restricting causal inference. Furthermore, selection bias may be present, as the analysis focuses exclusively on hospitalized patients, excluding outpatient or milder cases that could provide a more comprehensive view of fungal infection prevalence and outcomes across various care settings.

The NIS datasets, which relies on ICD-10 coding, poses challenges related to the accuracy of diagnostic coding. In the prior Vallabhaneni study, one ICD-9 coding was used to identify the totality of aspergillosis (117.3) and the whole of mucormycosis (117.7). The limiting coding prevented previous studies to stratify these infections into subtypes, potentially skewing the effects of the data. This would explain some of the discrepancies we observed in our current study.

Coding errors, including underreporting, misclassification, and redundant hospitalization counts, may lead to overestimation of hospitalizations and obscure differences in mortality rates. The lack of detailed clinical information in the dataset allows only for a broad understanding. Key variables such as medication and prophylactic use, as well as surgical procedures, are not recorded, limiting the depth of analyses.

Additionally, the data do not clearly differentiate between pre-existing comorbidities and complications that developed during hospitalization, complicating our ability to assess the severity and impact of fungal infections in the context of other health conditions.

Diagnosing mucormycosis and aspergillosis presents inherent difficulties. Invasive mold infections are particularly challenging to detect accurately due to their non-specific symptoms and low sensitivity in standard diagnostic methods. This was evident in our study with both A-RH and M-RH. "Unspecified" mucormycosis, (ICD-10: B46.5), had the highest rates. Specifying clinical subtypes can evade most practitioners, evidenced by 66.8% of all A-RHs being labeled as either "Other Pulmonary" or "Unspecified." Even worse, pulmonary-related aspergillosis and mucormycosis can present similarly to COVID-19, further complicating differentiation. Conventional diagnostic tests, including galactomannan (GM) testing, histopathological cultures, and imaging, often have suboptimal sensitivity and specificity, with added uncertainty about invasive infection or colonization. Furthermore, this complicates reliable case confirmation and potentially leads to underreporting or misclassification of fungal infections.

A major assumption in this study is that fungal infections in COVID-19 patients are secondary infections. This assumption may not hold universally, especially given the possibility of primary invasive mold infections. Invasive mold infections were likely underreported during the pandemic, as COVID-19 patients may present with similar symptoms and sites of infection, which can complicate diagnostic clarity. Additionally, diagnostic procedures with higher sensitivity and specificity, such as bronchoalveolar lavage fluid galactomannan (BALF-GM) tests, were often deprioritized or unavailable due to resource constraints and reluctance to perform them during COVID-19 surges.

CONCLUSION

Rates of A-RH and M-RH continue to increase, accompanied by a notable rise in specific clinical subtypes and in-hospital mortality. Unlike earlier studies that focused primarily on immunocompromised patients, our findings reveal that a wider population with underlying conditions, including those not

traditionally classified as severely immunocompromised, are now at elevated risk. This echoes concerns from other studies. The COVID-19 pandemic has further intensified the burden of disease, amplifying the severity of underlying conditions and escalating mortality rates. This underscores the need for a broadened clinical awareness and preventive focus, extending beyond the traditionally recognized high-risk populations.

APPENDIX

Table 1a. Rates of Aspergillosis-Related Hospitalizations during 2016-2021 in the United States

		2016			2017			2018			2019			2020			2021		
Characteristic		**n**	**col %**	**rate**	**n**	**col %**	**rate**	**n**	**col %**	**rate**	**n**	**col %**	**rate**	**n**	**col %**	**rate**	**n**	**col %**	**rate**
OVERALL	ASPERGILLOSIS	13655		42.3	14010		43.1	14550		44.5	14045		42.8	13200		40.1	17110		51.5
Mean age, years		58			58			59			59			61			60		
Age group, years																			
	<18	690	5.1%	9.4	865	6.2%	11.7	685	4.7%	9.3	550	3.9%	7.5	365	2.8%	5.0	570	3.3%	7.8
	18 to 44	1855	13.6%	16.0	1860	13.3%	15.9	1965	13.5%	16.8	2010	14.3%	17.0	1600	12.1%	13.5	2125	12.4%	17.7
	45 to 64	5210	38.2%	62.0	5165	36.9%	61.4	5575	38.3%	66.5	5125	36.5%	61.5	4945	37.5%	59.7	6655	38.9%	80.0
	≥65	5900	43.2%	119.9	6120	43.7%	120.6	6325	43.5%	120.8	6360	45.3%	117.7	6290	47.7%	113.0	7760	45.4%	138.0
Sex																			
	Male	7675	56.2%	48.2	7765	55.4%	48.5	8075	55.5%	50.2	8150	58.0%	50.4	7965	60.3%	49.1	10175	59.5%	61.8
	Female	5965	43.7%	36.4	6245	44.6%	37.8	6475	44.5%	39.0	5895	42.0%	35.4	5235	39.7%	31.3	6935	40.5%	41.5
Hospital Region*																			
1	Northeast	2385	17.5%	42.5	2570	18.3%	45.8	2520	17.3%	44.9	2380	16.9%	42.5	2085	15.8%	37.3	.		
2	Midwest	2930	21.5%	43.1	2885	20.6%	42.3	3090	21.2%	45.3	2915	20.8%	42.7	2940	22.3%	43.0	.		
3	South	4675	34.2%	38.2	4770	34.0%	38.6	4955	34.1%	39.8	5060	36.0%	40.3	4500	34.1%	35.5	.		
4	West	3665	26.8%	47.9	3785	27.0%	49.0	3985	27.4%	51.2	3690	26.3%	47.1	3675	27.8%	46.7	.		
Race/Ethnicity																			
	White	9055	69.6%	36.5	9090	67.0%	36.5	9745	68.6%	39.0	9160	66.5%	36.6	8195	63.7%	33.2	10570	63.4%	42.0
	Black	1645	12.6%	38.2	1965	14.5%	45.2	1900	13.4%	43.3	1910	13.9%	43.2	1760	13.7%	39.5	2290	13.7%	50.8
	Hispanic	1345	10.3%	23.5	1465	10.8%	25.1	1495	10.5%	25.1	1605	11.6%	26.6	1710	13.3%	27.9	2275	13.6%	36.3
	Asian or Pacific Islander	560	4.3%	29.1	570	4.2%	28.9	555	3.9%	27.5	640	4.6%	31.2	740	5.8%	35.5	915	5.5%	42.9
	Native American	55	0.4%	13.5	75	0.6%	18.1	105	0.7%	25.0	90	0.7%	21.2	55	0.4%	12.8	100	0.6%	23.1
	Other race/ethnicity	355	2.7%	41.6	405	3.0%	46.1	410	2.9%	45.4	375	2.7%	40.5	400	3.1%	42.1	530	3.2%	54.0
Payor																			
	Medicaid	2295	16.8%		2270	16.2%		2465	17.0%		2370	16.9%		2165	16.4%		2835	16.6%	
	Medicare	6975	51.1%		7140	51.0%		7455	51.3%		7445	53.1%		6955	52.7%		8525	49.9%	

	Private	3940	28.9%	4235	30.3 %	4340	29.9 %	3875	27.6 %	3760	28.5 %	5140	30.1 %
	Other	430	3.2%	355	2.5%	275	1.9%	340	2.4%	305	2.3%	600	3.5%
Comorbidities and complications													
	Asthma	1615	11.8%	1605	11.5 %	1510	10.4 %	1325	9.4%	1025	7.8%	1335	7.8%
	Cirrhosis	225	1.6%	280	2.0%	300	2.1%	255	1.8%	225	1.7%	285	1.7%
	COPD	4975	36.4%	4660	33.3 %	5210	35.8 %	4930	35.1 %	4065	30.8 %	4820	28.2 %
	COVID-19	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1445	10.9 %	4580	26.8 %
	Diabetes	3555	26.0%	3630	25.9 %	3850	26.5 %	3950	28.1 %	3720	28.2 %	5415	31.6 %
	End Stage Renal Disease	605	4.4%	610	4.4%	650	4.5%	615	4.4%	730	5.5%	890	5.2%
	Hematologic Malignancy	2910	21.3%	3155	22.5 %	2995	20.6 %	3020	21.5 %	2975	22.5 %	2840	16.6 %
	Hematopoietic Stem Cell Transplant	340	2.5%	510	3.6%	500	3.4%	440	3.1%	480	3.6%	490	2.9%
	HIV	230	1.7%	300	2.1%	380	2.6%	310	2.2%	325	2.5%	255	1.5%
	Immune-mediated Inflammatory Diseases	845	6.2%	910	6.5%	945	6.5%	895	6.4%	870	6.6%	1130	6.6%
	Influenza	365	2.7%	300	2.1%	515	3.5%	370	2.6%	460	3.5%	50	0.3%
	Solid Organ Transplant	775	5.7%	895	6.4%	945	6.5%	935	6.7%	865	6.6%	1005	5.9%
	Solid Organ Malignancy	1320	9.7%	1390	9.9%	1360	9.3%	1565	11.1 %	1470	11.1 %	1655	9.7%
In-hospital Death		1830	13.4%	1870	13.3 %	1790	12.3 %	1850	13.2 %	2540	19.2 %	4580	26.8 %
Mean Length of Stay		16		15		15		15		17		20	

FIGURE 1. OVERALL ASPERGILLOSIS-RELATED HOSPITALIZATION RATES PER 1,000,000 POPULATION, 2016-2021

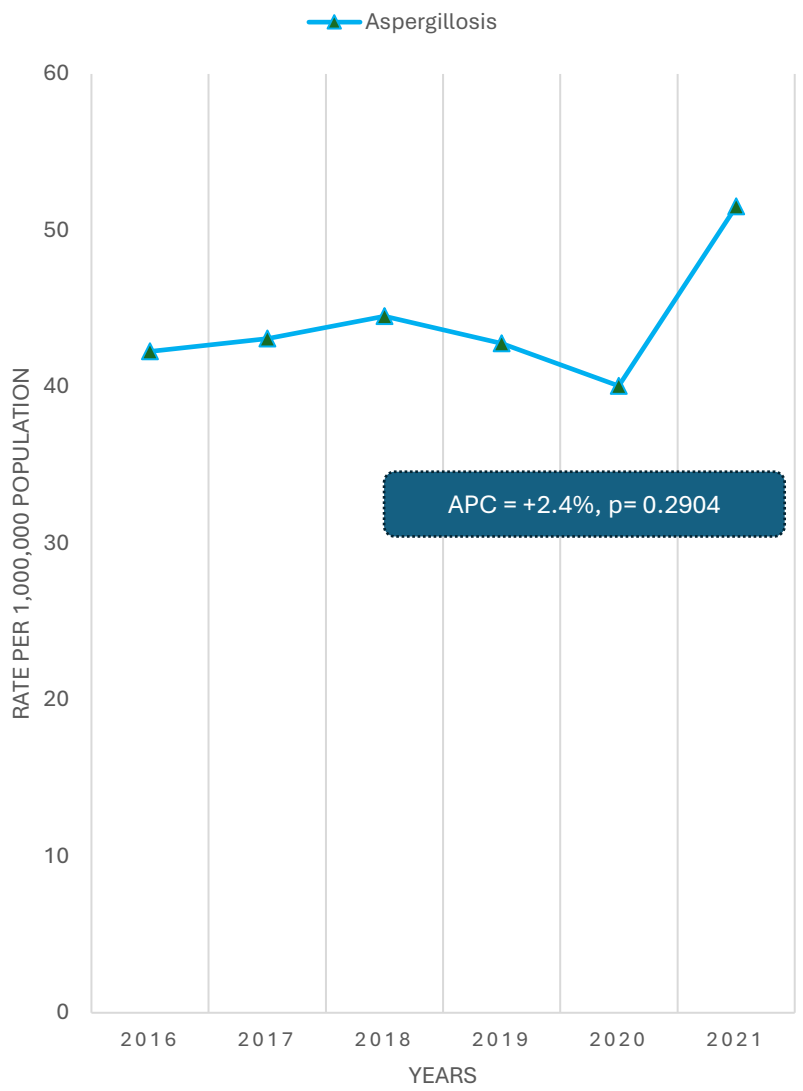


FIGURE 2. IN-HOSPITAL MORTALITY ASSOCIATED WITH ASPERGILLOSIS-RELATED HOSPITALIZATIONS

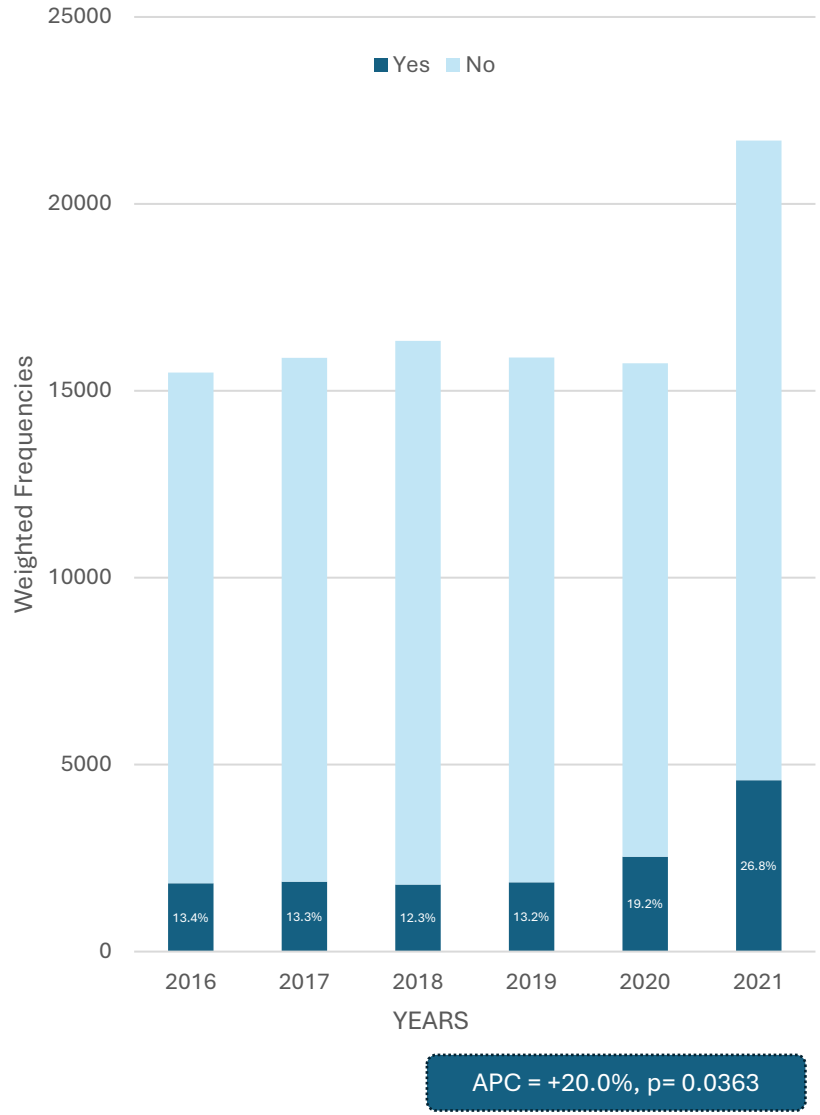


FIGURE 3. ASPERGILLOSIS SUBTYPE-RELATED HOSPITALIZATION RATES PER 1,000,000 POPULATION, 2016-2021

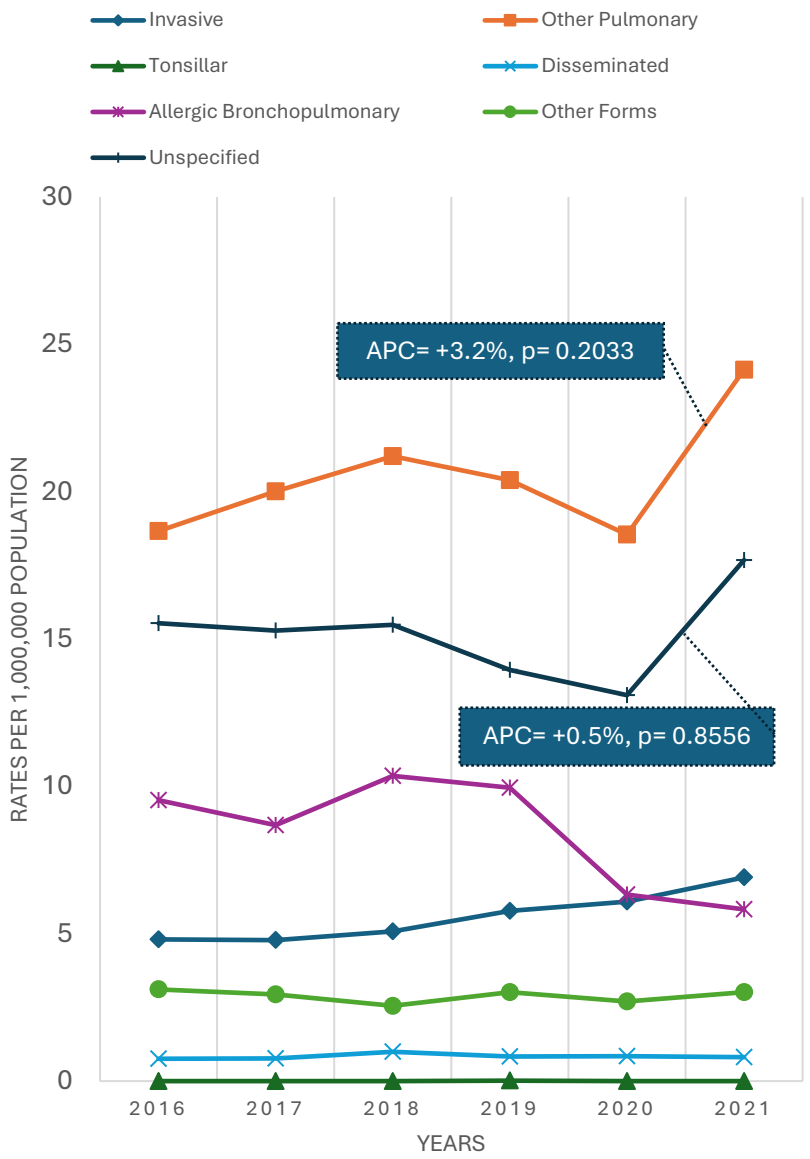


FIGURE 4. INVASIVE VS. OTHER ASPERGILLOSIS-RELATED HOSPITALIZATION RATES PER 1,000,000 POPULATION, 2016-2021

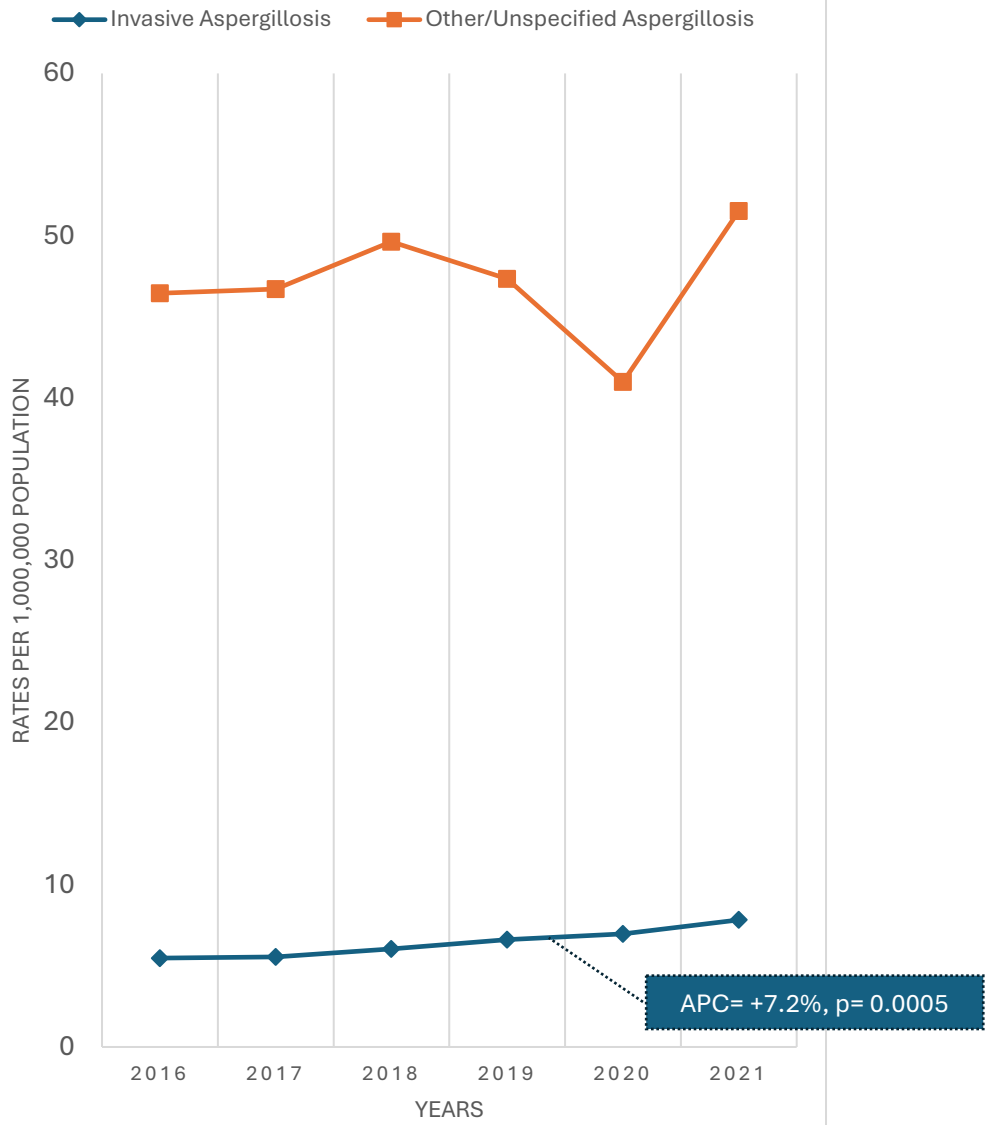
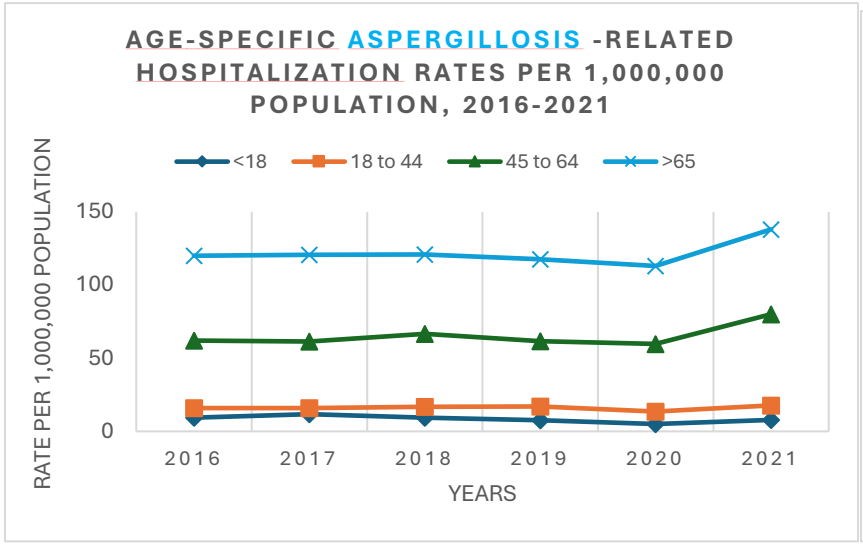
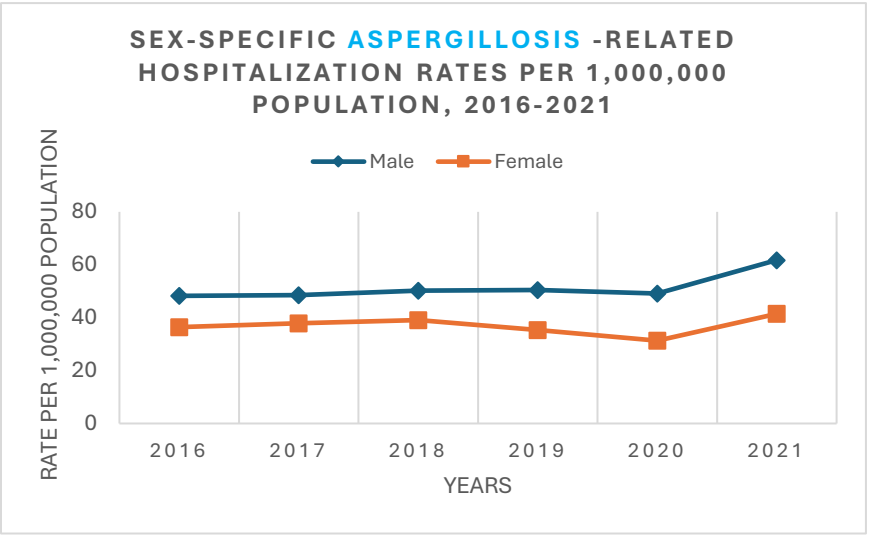
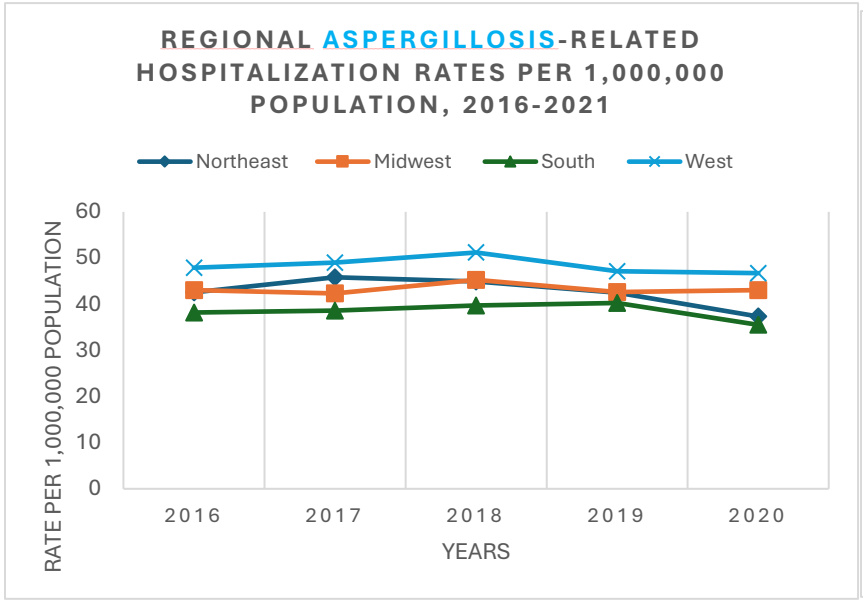


FIGURE 5. RATES OF ASPERGILLOSIS-RELATED HOSPITALIZATIONS BASED ON DEMOGRAPHIC CHARACTERISTIC







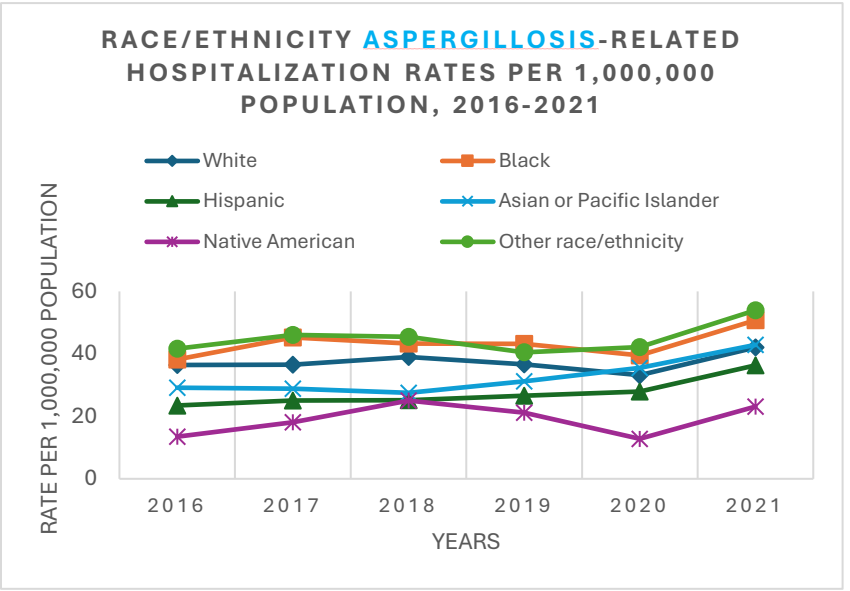
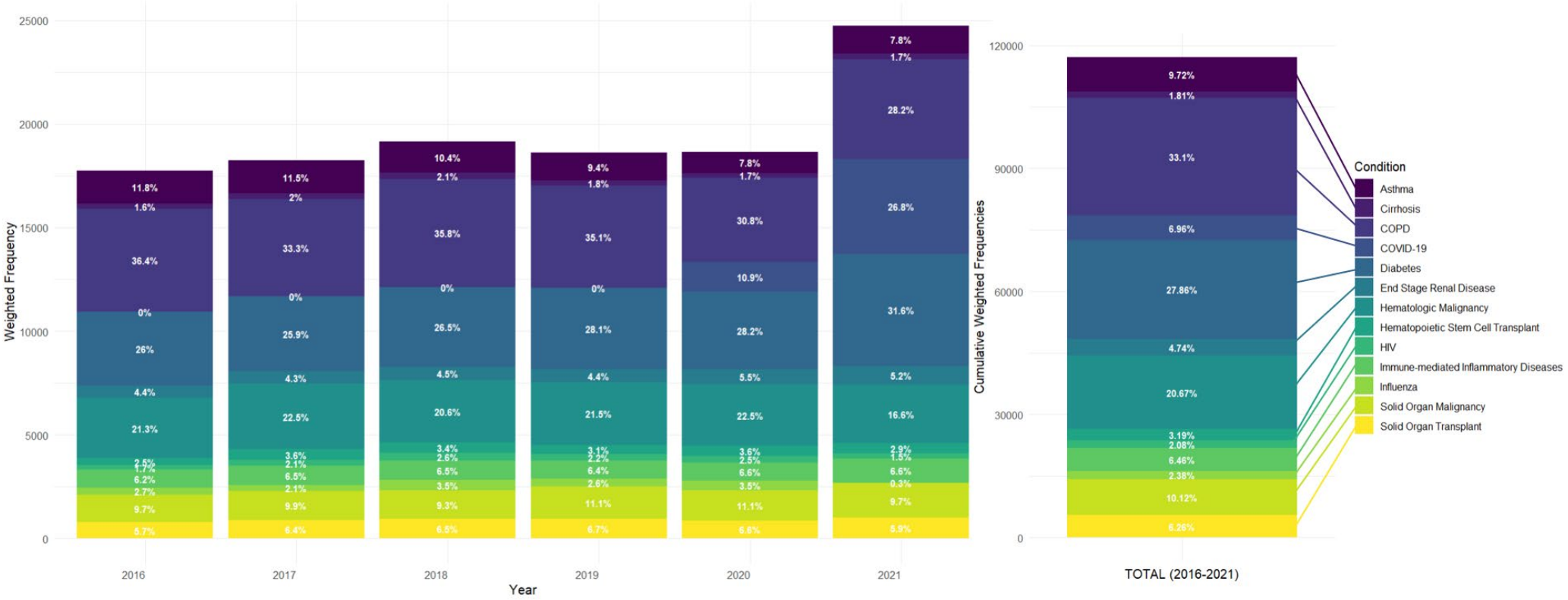


FIGURE 6. CRUDE PROPORTIONS OF COMORBIDITIES + CONCURRENT CONDITIONS COMPOSING ASPERGILLOSIS-RELATED HOSPITALIZATIONS*



*PATIENTS CAN HAVE MORE THAN ONE CONCURRENT COMORBIDITY

FIGURE 7. HEAT MAP OF COMORBIDITIES + CONCURRENT CONDITIONS COMPOSING ASPERGILLOSIS-RELATED HOSPITALIZATIONS WITH CUMULATIVE TOTAL

	2016	2017	2018	2019	2020	2021	TOTAL
Asthma	11.82%	11.46%	10.38%	9.43%	7.77%	7.80%	9.72%
Cirrhosis	1.65%	2.00%	2.06%	1.82%	1.70%	1.67%	1.81%
COPD	36.41%	33.26%	35.81%	35.10%	30.80%	28.17%	33.10%
COVID-19	0.00%	0.00%	0.00%	0.00%	10.95%	26.77%	6.96%
Diabetes	26.02%	25.91%	26.46%	28.12%	28.18%	31.65%	27.86%
End Stage Renal Disease	4.43%	4.35%	4.47%	4.38%	5.53%	5.20%	4.74%
Hematologic Malignancy	21.30%	22.52%	20.58%	21.50%	22.54%	16.60%	20.67%
Hematopoietic Stem Cell Transplant	2.49%	3.64%	3.44%	3.13%	3.64%	2.86%	3.19%
HIV	1.68%	2.14%	2.61%	2.21%	2.46%	1.49%	2.08%
Immune-mediated Inflammatory Diseases	6.18%	6.50%	6.49%	6.37%	6.59%	6.60%	6.46%
Influenza	2.67%	2.14%	3.54%	2.63%	3.48%	0.29%	2.38%
Solid Organ Transplant	5.67%	6.39%	6.49%	6.66%	6.55%	5.87%	6.26%
Solid Organ Malignancy	9.66%	9.92%	9.35%	11.14%	11.14%	9.67%	10.12%

TABLE 2A. COVID-19 STATUS FOR ASPERGILLOSIS-RELATED HOSPITALIZATIONS, 2020-2021

	COVID-19 associated			Non-COVID-19 associated		
Characteristic	**n**	**col %**	**p-value**	**n**	**col %**	**p-value**
OVERALL	**6025**	**19.9%**		**24,285**	**80.1%**	
Mean age, years (std err)	**62 (0.4096)**			**59 (0.2047)**		
Age group, years			**<.0001**			<.0001
<18	45	0.7%		890	3.7%	
18 to 44	520	8.6%		3205	13.2%	
45 to 64	2780	46.1%		8820	36.3%	
≥65	2680	44.5%		11370	46.8%	
Sex			**<.0001**			**<.0001**
Male	3660	60.7%		14480	59.6%	
Female	2365	39.3%		9805	40.4%	
Hospital region			**<.0001**			**0.0003**
Northeast	180	12.5%		1905	16.2%	
Midwest	365	25.3%		2575	21.9%	
South	435	30.1%		4065	34.6%	
West	465	32.2%		3210	27.3%	
Race/ethnicity			**<.0001**			**<.0001**
White	3050	52.8%		15715	66.1%	
Black	815	14.1%		3235	13.6%	
Hispanic	1400	24.2%		2585	10.9%	
Asian Pacific Islander	270	4.7%		1385	5.8%	
Native American/American Indian/Indigenous	45	0.8%		110	0.5%	
Other	195	3.4%		735	3.1%	
Payer			**0.0011**			**<.0001**
Medicare	2880	47.9%		12600	51.9%	
Medicaid	1155	19.2%		3845	15.8%	
Private	1760	29.3%		7140	29.4%	
Other	215	3.6%		690	2.8%	
Comorbidities						
Asthma	465	7.7%	0.7436	**1895**	7.8%	**<.0001**
Cirrhosis	80	1.3%	0.2903	430	1.8%	**0.0441**
COPD	1265	21.0%	<.0001	7620	31.4%	**<.0001**
Diabetes	2540	42.2%	<0.0001	6595	27.2%	**<.0001**

End Stage Renal Disease	375	6.2%	<0.0001	1245	5.1%	**<.0001**
Hematologic Malignancy	375	6.2%	<0.0001	5440	22.4%	**<.0001**
Hematopoietic Stem Cell Transplant	60	1.0%	<.0001	910	3.7%	**<.0001**
HIV	50	0.8%	0.1684	530	2.2%	**<.0001**
Immune-mediated Inflammatory Diseases	350	5.8%	0.0002	1650	6.8%	**<.0001**
Influenza	25	0.4%	0.2959	485	2.0%	**<.0001**
Solid Organ Transplant	225	3.7%	<.0001	1645	6.8%	**<.0001**
Solid Organ Malignancy	280	4.6%	0.0001	2845	11.7%	**<.0001**
Mean length of stay, days (std err)	**30.24 (0.7624)**			**15.56 (0.2178)**		
Income quartile for patient's ZIP code			**0.2903**			**0.0441**
0-25th percentile	1855	31.4%		5960	25.1%	
26th to 50th percentile	1550	26.2%		5910	24.9%	
51st to 75th percentile	1420	24.0%		6085	25.7%	
76th to 100th percentile	1085	18.4%		5765	24.3%	
In-hospital Mortality			<.0001			<.0001
Yes	3355	55.7%		3765	15.5%	
No	2670	44.3%		20505	84.5%	

FIGURE 8. CRUDE PROPORTIONS OF COMORBIDITIES + CONCURRENT CONDITIONS COMPOSING COVID-19-ASSOCIATED ASPERGILLOSIS-RELATED HOSPITALIZATIONS (CAA-RH), 2020-2021

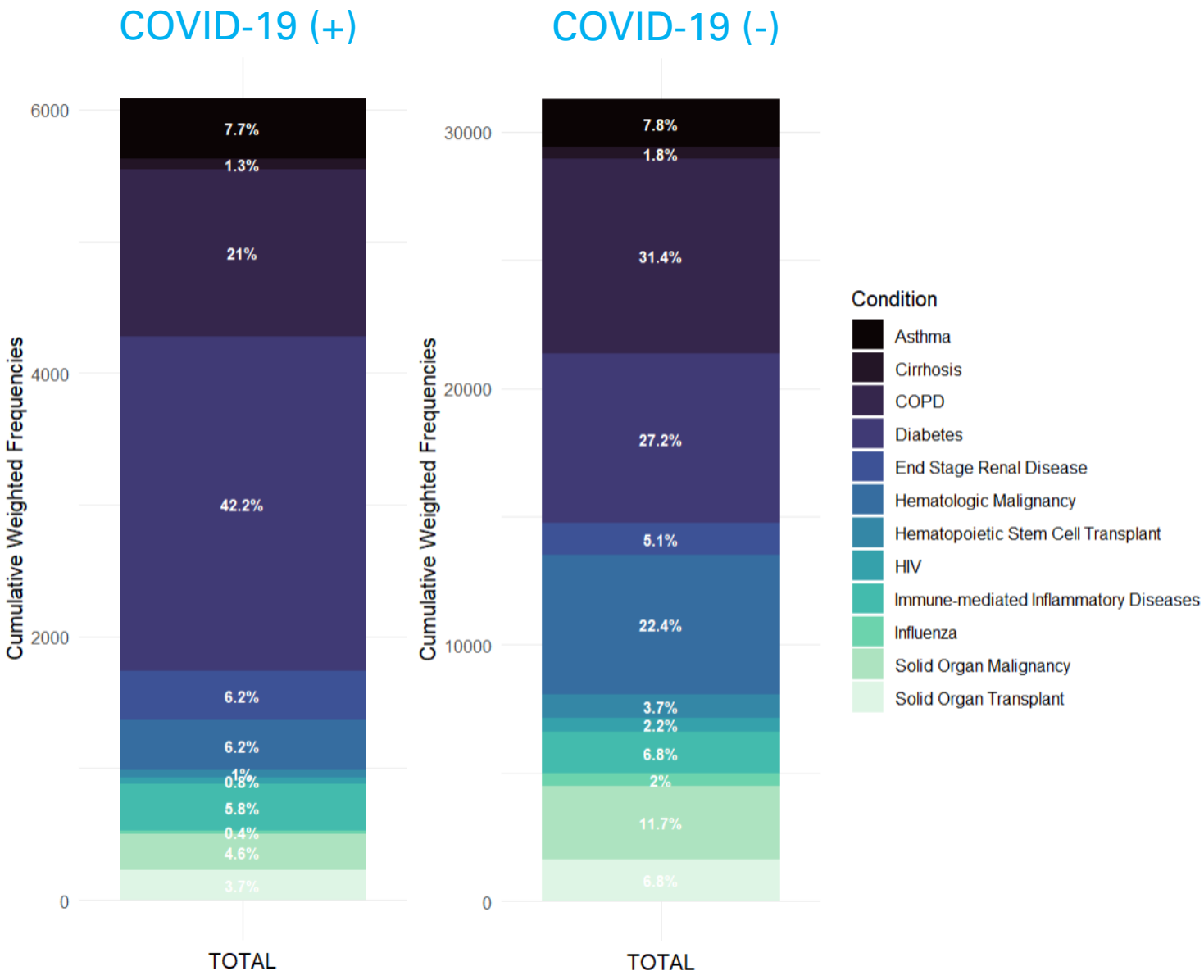


FIGURE 9. IN-HOSPITAL MORTALITY FOR COVID-19-ASSOCIATED ASPERGILLOSIS-RELATED HOSPITALIZATIONS (CAA-RH), 2020-2021

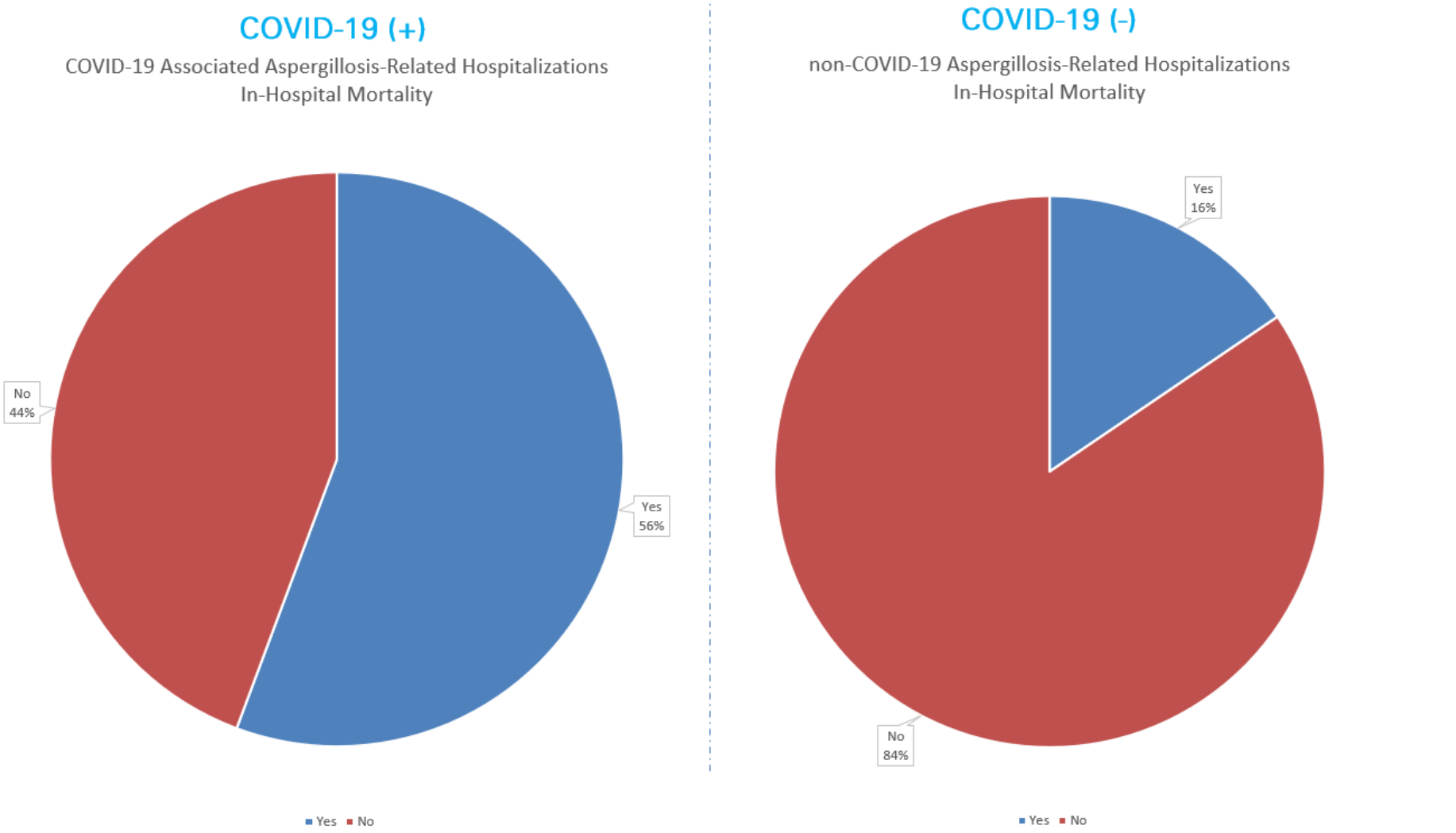


TABLE 1B. RATES OF MUCORMYCOSIS-RELATED HOSPITALIZATIONS IN THE U.S., DURING 2016-2021

Characteristic		2016			2017			2018			2019			2020			2021		
		n	col %	rate	n	col %	rate	n	col %	rate	n	col %	rate	n	col %	rate	n	col %	rate
OVERALL		1240		3.8	1220		3.8	1370		4.2	1395		4.2	1420		4.3	1920		5.8
Mean age, years		50			51			50			52			51			50		
Age group, years																			
	<18	145	11.7%	2.0	140	11.5%	1.9	160	11.7%	2.2	100	7.2%	1.4	100	7.0%	1.4	145	7.6%	2.0
	18 to 44	265	21.4%	2.3	220	18.0%	1.9	280	20.4%	2.4	255	18.3%	2.2	390	27.5%	3.3	480	25.0%	4.0
	45 to 64	460	37.1%	5.5	490	40.2%	5.8	575	42.0%	6.9	635	45.5%	7.6	565	39.8%	6.8	890	46.4%	10.7
	≥65	370	29.8%	7.5	370	30.3%	7.3	355	25.9%	6.8	405	29.0%	7.5	365	25.7%	6.6	405	21.1%	7.2
Sex																			
	Male	845	68.1%	5.3	715	58.6%	4.5	795	58.0%	4.9	785	56.3%	4.9	845	59.5%	5.2	1225	63.8%	7.4
	Female	395	31.9%	2.4	505	41.4%	3.1	575	42.0%	3.5	610	43.7%	3.7	575	40.5%	3.4	695	36.2%	4.2
Hospital Region																			
1	Northeast	215	17.3%	3.8	135	11.1%	2.4	165	12.0%	2.9	165	11.8%	2.9	175	12.3%	3.1	.		
2	Midwest	235	19.0%	3.5	235	19.3%	3.4	230	16.8%	3.4	255	18.3%	3.7	190	13.4%	2.8	.		
3	South	370	29.8%	3.0	380	31.1%	3.1	465	33.9%	3.7	490	35.1%	3.9	475	33.5%	3.8	.		
4	West	420	33.9%	5.5	470	38.5%	6.1	510	37.2%	6.6	485	34.8%	6.2	580	40.8%	7.4	.		
Race/Ethnicity																			
	White	615	53.2%	2.5	615	54.2%	2.5	700	53.2%	2.8	755	56.1%	3.0	680	49.8%	2.8	985	53.5%	3.9
	Black	115	10.0%	2.7	140	12.3%	3.2	195	14.8%	4.4	195	14.5%	4.4	230	16.8%	5.2	265	14.4%	5.9
	Hispanic	285	24.7%	5.0	295	26.0%	5.1	335	25.5%	5.6	265	19.7%	4.4	300	22.0%	4.9	425	23.1%	6.8
	Asian or Pacific Islander	75	6.5%	3.9	25	2.2%	1.3	35	2.7%	1.7	70	5.2%	3.4	50	3.7%	2.4	90	4.9%	4.2
	Native American	15	1.3%	3.7	0	0.0%	0.0	10	0.8%	2.4	5	0.4%	1.2	45	3.3%	10.5	20	1.1%	4.6
	Other race/ethnicity	50	4.3%	5.9	60	5.3%	6.8	40	3.0%	4.4	55	4.1%	5.9	60	4.4%	6.3	55	3.0%	5.6
Payor																			
	Medicaid	315	25.4%		255	21.0%		400	29.2%		330	23.7%		345	24.3%		625	32.6%	
	Medicare	530	42.7%		515	42.4%		450	32.8%		515	36.9%		465	32.7%		510	26.6%	

	Private	35	2.8%	30	2.5%	50	3.6%	60	4.3%	60	4.2%	90	4.7%
	Other	360	29.0%	415	34.2%	470	34.3%	490	35.1%	550	38.7%	695	36.2%
Comorbidities and complications													
	Asthma	80	6.5%	80	6.6%	120	8.8%	105	7.5%	65	4.6%	70	3.6%
	Cirrhosis	30	2.4%	25	2.0%	15	1.1%	50	3.6%	30	2.1%	25	1.3%
	COPD	145	11.7%	125	10.2%	115	8.4%	165	11.8%	165	11.6%	235	12.2%
	COVID-19	0	0.0%	0	0.0%	0	0.0%	0	0.0%	150	10.6%	270	14.1%
	Diabetes	545	44.0%	530	43.4%	635	46.4%	595	42.7%	660	46.5%	945	49.2%
	End Stage Renal Disease	140	11.3%	110	9.0%	90	6.6%	155	11.1%	130	9.2%	105	5.5%
	Hematologic Malignancy	460	37.1%	425	34.8%	480	35.0%	455	32.6%	360	25.4%	495	25.8%
	Hematopoietic Stem Cell Transplant	85	6.9%	60	4.9%	115	8.4%	75	5.4%	85	6.0%	75	3.9%
	HIV	20	1.6%	20	1.6%	25	1.8%	35	2.5%	25	1.8%	5	0.3%
	Immune-mediated Inflammatory Diseases	50	4.0%	35	2.9%	40	2.9%	55	3.9%	60	4.2%	60	3.1%
	Influenza	20	1.6%	20	1.6%	10	0.7%	10	0.7%	30	2.1%	0	0.0%
	Solid Organ Transplant	140	11.3%	130	10.7%	185	13.5%	150	10.8%	145	10.2%	135	7.0%
	Solid Organ Malignancy	40	3.2%	60	4.9%	50	3.6%	80	5.7%	75	5.3%	85	4.4%
In-hospital Death		205	16.5%	225	18.4%	255	18.6%	290	20.8%	270	19.0%	475	24.7%
Mean Length of Stay		20		20		18		23		25		22	

FIGURE 10. OVERALL MUCORMYCOSIS-RELATED HOSPITALIZATION RATES PER 1,000,000 POPULATION, 2016-2021

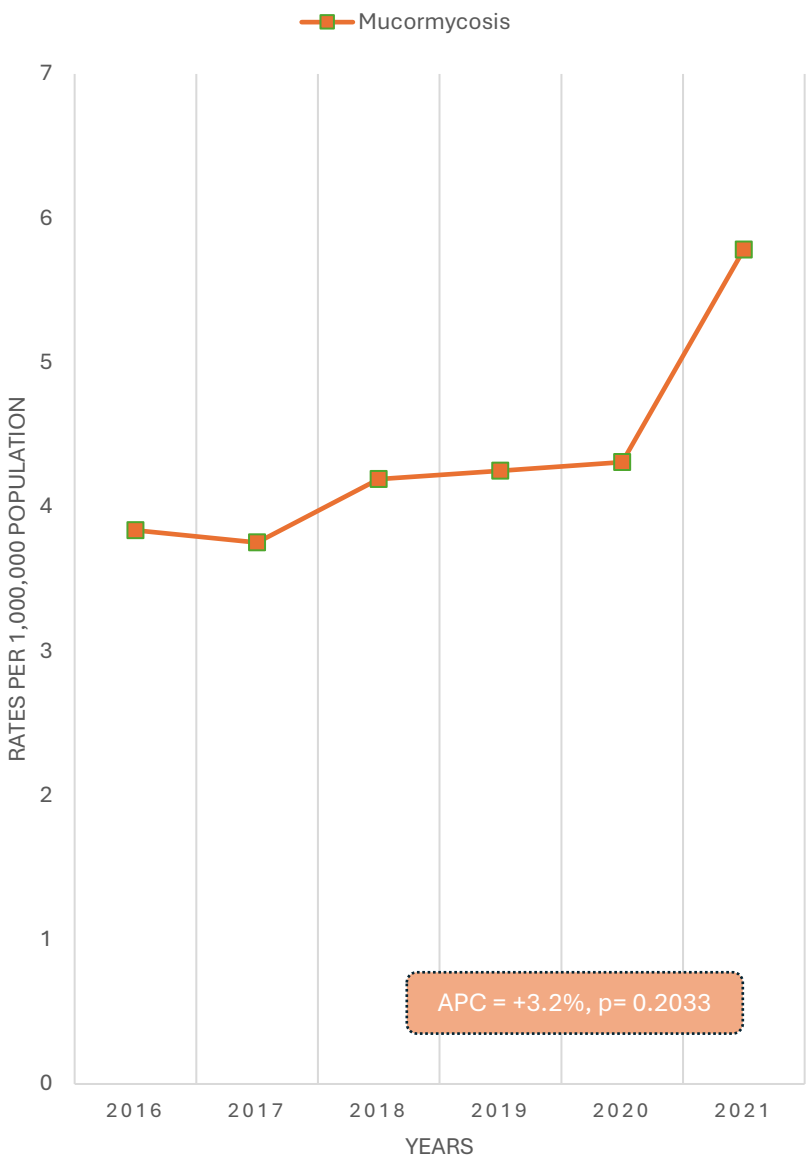


FIGURE 11. IN-HOSPITAL MORTALITY ASSOCIATED WITH MUCORMYCOSIS-RELATED HOSPITALIZATIONS

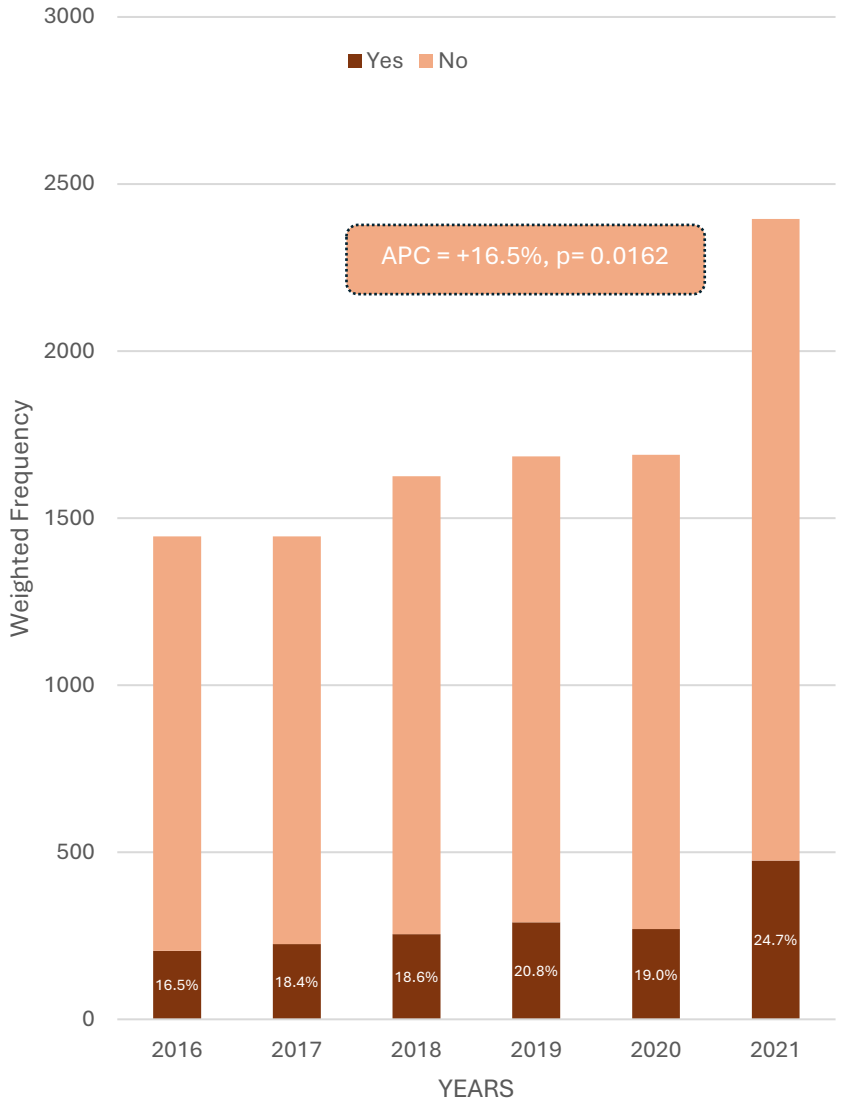


FIGURE 12. MUCORMYCOSIS SUBTYPE-RELATED HOSPITALIZATION RATES PER 1,000,000 POPULATION, 2016-2021

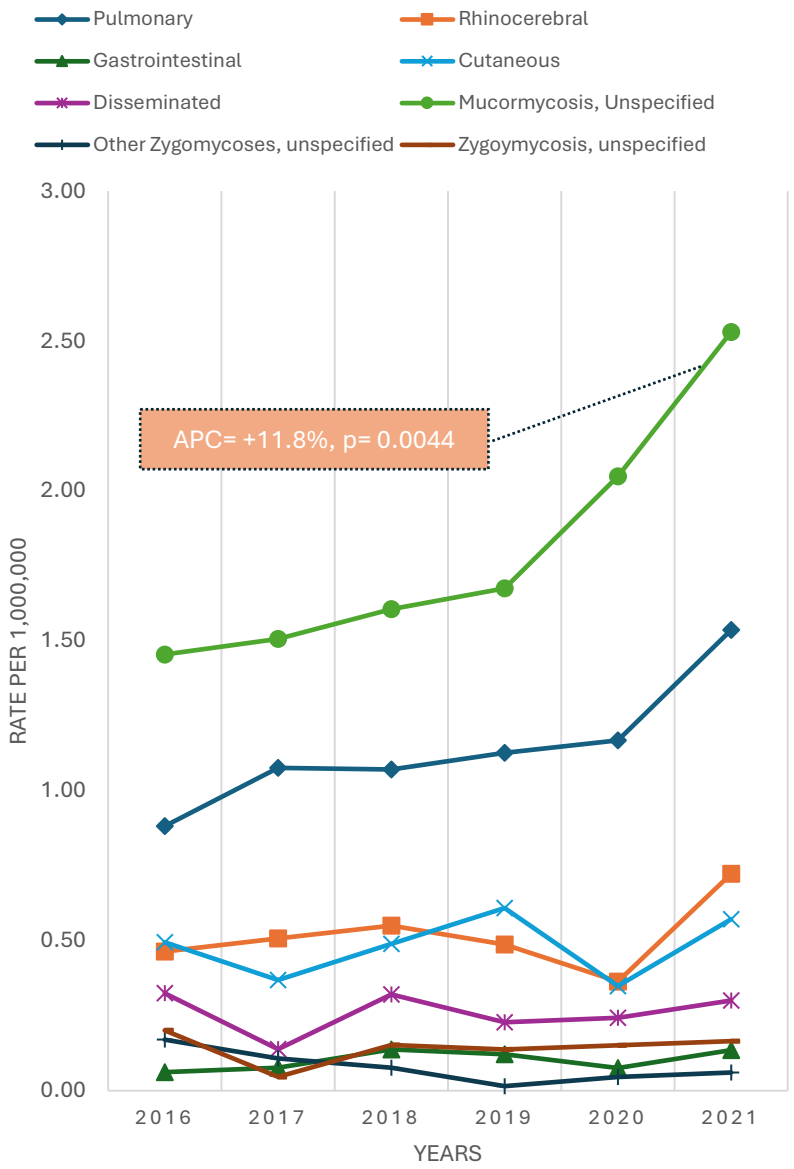


FIGURE 13. MUCORMYCOSIS SUBTYPE-RELATED HOSPITALIZATION RATES PER 1,000,000 POPULATION, 2016-2021

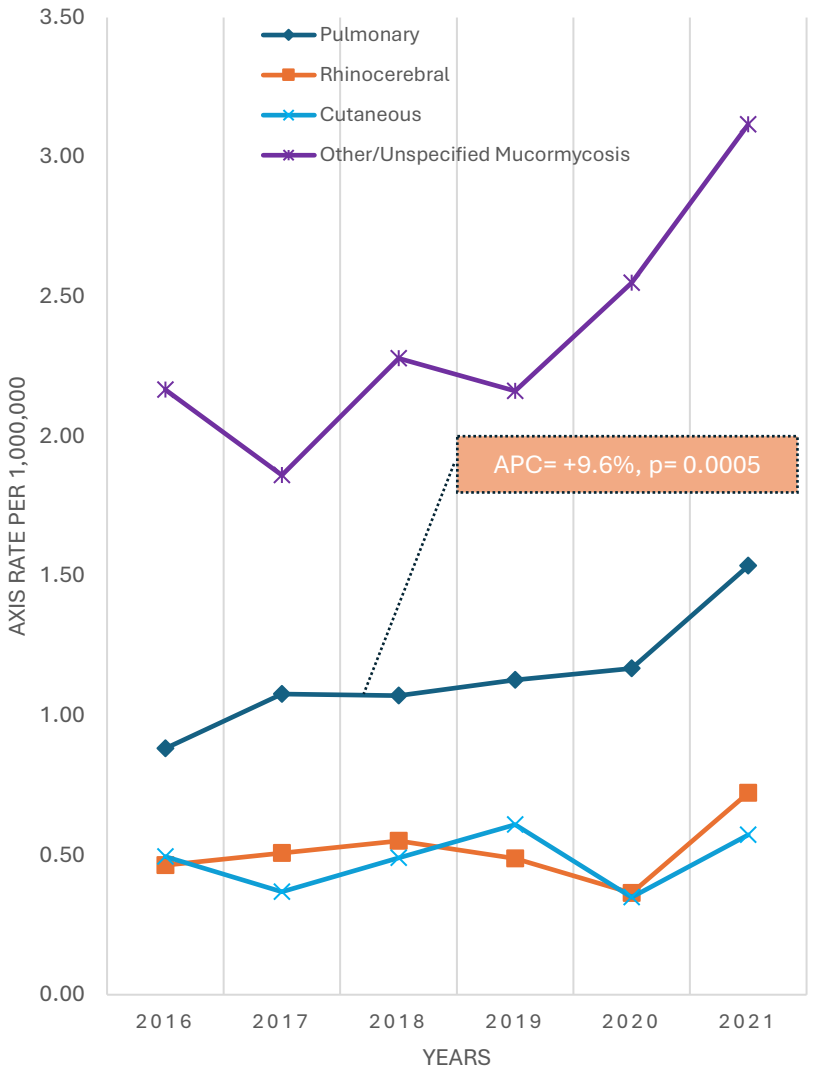
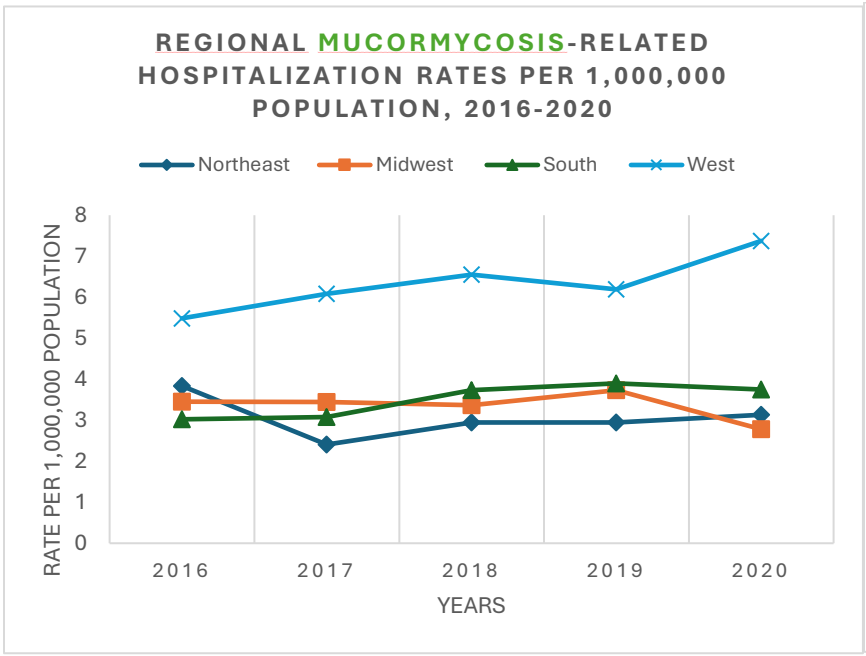
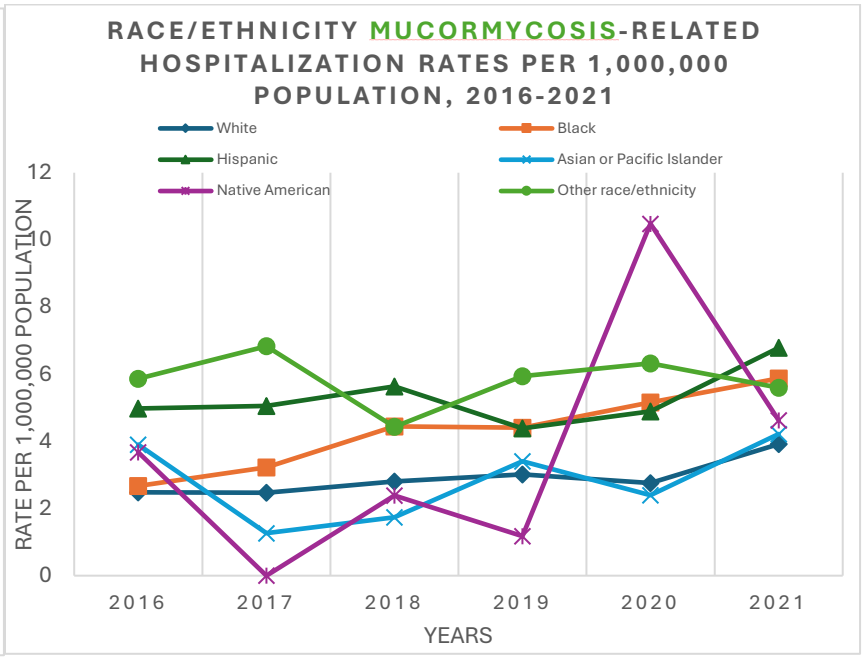
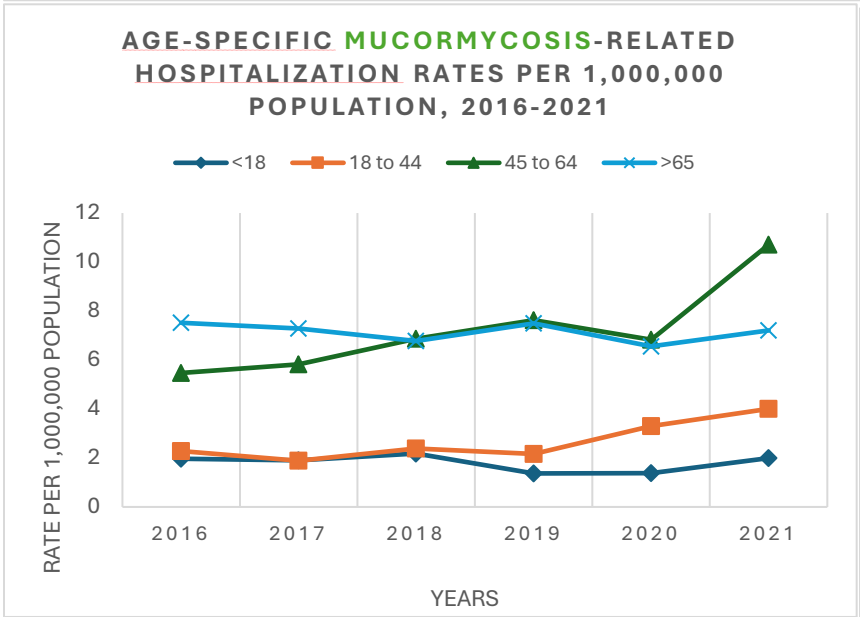


FIGURE 14. RATES OF MUCORMYCOSIS -RELATED HOSPITALIZATIONS BASED ON DEMOGRAPHIC CHARACTERISTIC







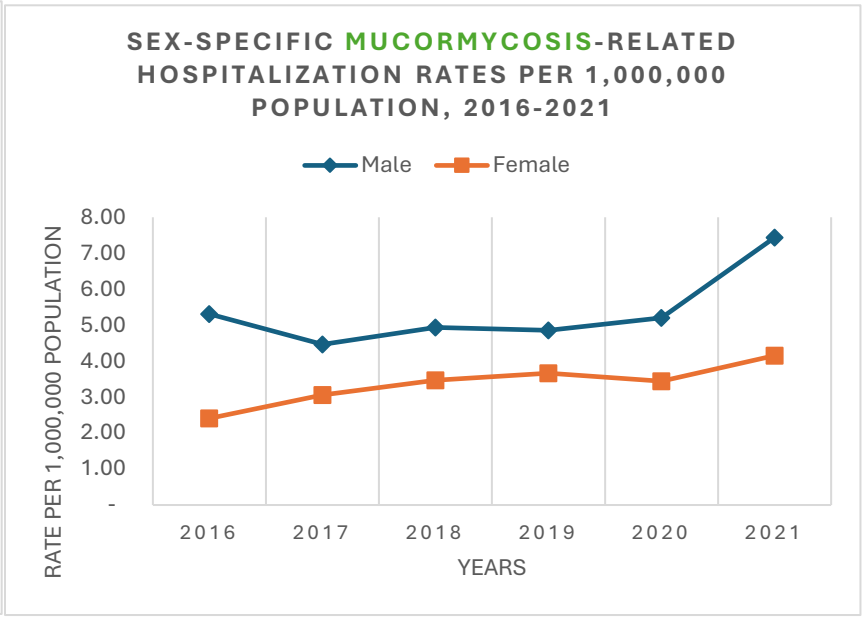
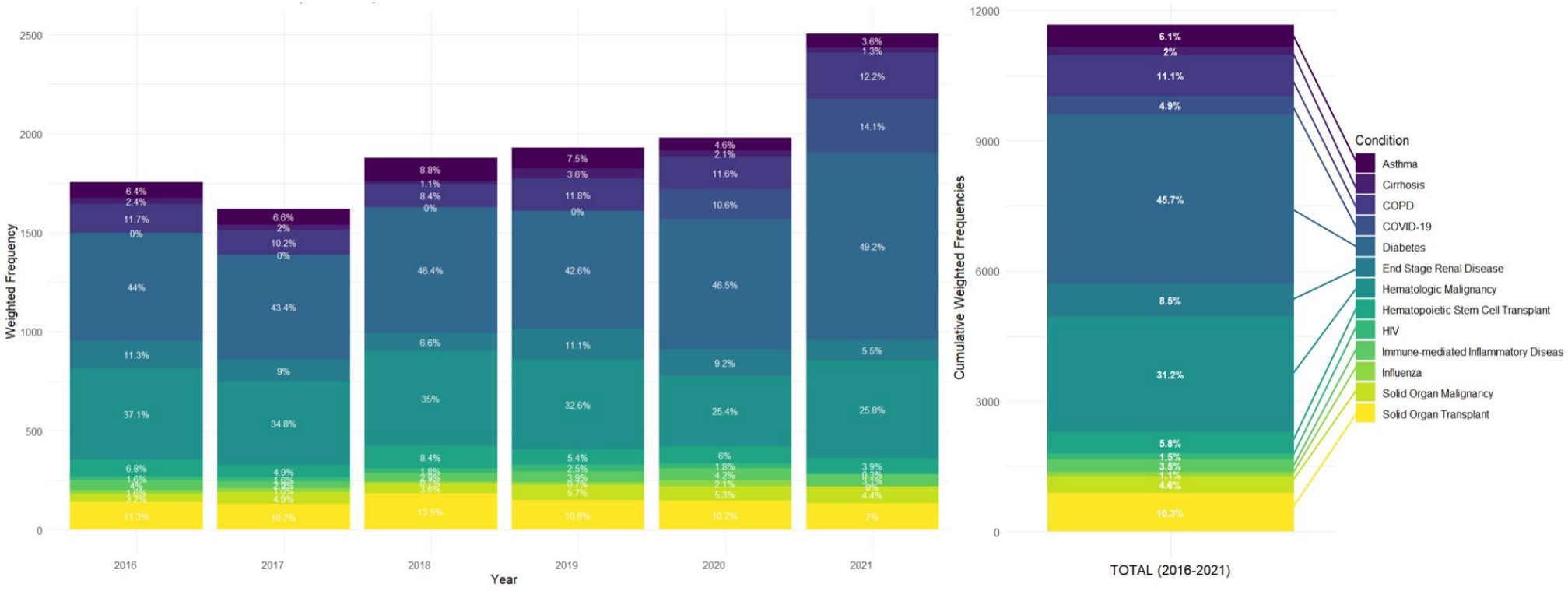


FIGURE 15. CRUDE PROPORTIONS OF COMORBIDITIES + CONCURRENT CONDITIONS COMPOSING MUCORMYCOSIS-RELATED HOSPITALIZATIONS



*PATIENTS CAN HAVE MORE THAN ONE CONCURRENT COMORBIDITY

	2016	2017	2018	2019	2020	2021	Total
Asthma	6.5%	6.6%	8.8%	7.5%	4.6%	3.6%	6.1%
Cirrhosis	2.4%	2.0%	1.1%	3.6%	2.1%	1.3%	2.0%
COPD	11.7%	10.2%	8.4%	11.8%	11.6%	12.2%	11.1%
COVID-19	0.0%	0.0%	0.0%	0.0%	10.6%	14.1%	4.9%
Diabetes	37.10%	40.16%	41.97%	45.52%	39.79%	46.35%	45.7%
End Stage Renal Disease	11.3%	9.0%	6.6%	11.1%	9.2%	5.5%	8.5%
Hematologic Malignancy	37.1%	34.8%	35.0%	32.6%	25.4%	25.8%	31.2%
Hematopoietic Stem Cell Transplant	6.9%	4.9%	8.4%	5.4%	6.0%	3.9%	5.8%
HIV	1.6%	1.6%	1.8%	2.5%	1.8%	0.3%	1.5%
Immune-mediated Inflammatory Diseases	4.0%	2.9%	2.9%	3.9%	4.2%	3.1%	3.5%
Influenza	1.6%	1.6%	0.7%	0.7%	2.1%	0.0%	1.1%
Solid Organ Transplant	11.3%	10.7%	13.5%	10.8%	10.2%	7.0%	10.3%
Solid Organ Malignancy	3.2%	4.9%	3.6%	5.7%	5.3%	4.4%	4.6%

FIGURE 16. HEAT MAP OF COMORBIDITIES + CONCURRENT CONDITIONS COMPOSING MUCORMYCOSIS -RELATED HOSPITALIZATIONS WITH CUMULATIVE TOTAL

TABLE 2B. COVID-19 STATUS FOR MUCORMYCOSIS -RELATED HOSPITALIZATIONS, 2020-2021

	COVID-19 associated			Non-COVID-19 associated		
Characteristic	**n**	**col %**	**p-value**	**n**	**col %**	**p-value**
OVERALL	**420**	**12.6%**		**2920**	**87.4%**	
Mean age, years (std err)	**50.9 (1.7066)**			**50.5 (0.5936)**		
Age group, years			**<.0001**			<.0001
<18	5	1.2%		240	8.2%	
18 to 44	155	36.9%		715	24.5%	
45 to 64	160	38.1%		1295	44.3%	
≥65	100	23.8%		670	22.9%	
Sex			**<.0001**			**<.0001**
Male	310	73.8%		1760	60.3%	
Female	110	26.2%		1160	39.7%	
Hospital region			**0.0041**			**<.0001**
Northeast	25	16.7%		150	11.8%	
Midwest	15	10.0%		175	13.8%	
South	45	30.0%		430	33.9%	
West	65	43.3%		515	40.6%	
Race/ethnicity			**0.0271**			**<.0001**
White	185	46.2%		1480	52.8%	
Black	85	21.3%		410	14.6%	
Hispanic	100	25.0%		625	22.3%	
Asian Pacific Islander	5	1.2%		135	4.8%	
Native American/American Indian/Indigenous	15	3.7%		50	1.8%	
Other	10	2.5%		105	3.7%	
Payer			**0.0018**			**<.0001**
Medicare	120	28.6%		855	29.3%	
Medicaid	120	28.6%		850	29.1%	
Private	165	39.3%		1080	37.0%	
Other	15	3.6%		135	4.6%	
Comorbidities						
Asthma	25	6.0%	0.4935	110	3.8%	0.0121
Cirrhosis	0	0.0%	-	55	1.9%	0.3374
COPD	60	14.3%	0.8338	340	11.6%	0.555
Diabetes	265	63.1%	<.0001	1340	45.9%	<.0001

End Stage Renal Disease	20	4.8%	0.5745	215	7.4%	<.0001
Hematologic Malignancy	30	7.1%	<.0001	825	28.3%	<.0001
Hematopoietic Stem Cell Transplant	10	2.4%	<.0001	150	5.1%	<.0001
HIV	10	2.4%	0.0201	20	0.7%	0.7687
Immune-mediated Inflammatory Diseases	10	2.4%	0.5078	110	3.8%	0.9389
Influenza	0	0.0%	-	30	1.0%	0.0193
Solid Organ Transplant	25	6.0%	<.0001	255	8.7%	<.0001
Solid Organ Malignancy	0	0.0%	-	160	5.5%	0.2587
Mean length of stay, days (std err)	**19.48 (1.6125)**			**21.52 (0.6822)**		
Income quartile for pt's ZIP code			**0.9772**			**0.7664**
0-25th percentile	140	35.4%		840	29.6%	
26th to 50th percentile	105	26.6%		690	24.3%	
51st to 75th percentile	90	22.8%		685	24.2%	
76th to 100th percentile	60	15.2%		620	21.9%	
In-hospital Mortality			<.0001			<.0001
Yes	220	52.4%		525	18.0%	
No	200	47.6%		2395	82.0%	

FIGURE 17. CRUDE PROPORTIONS OF COMORBIDITIES + CONCURRENT CONDITIONS COMPOSING COVID-19-ASSOCIATED MUCORMYCOSIS -RELATED HOSPITALIZATIONS (CAM-RH), 2020-2021

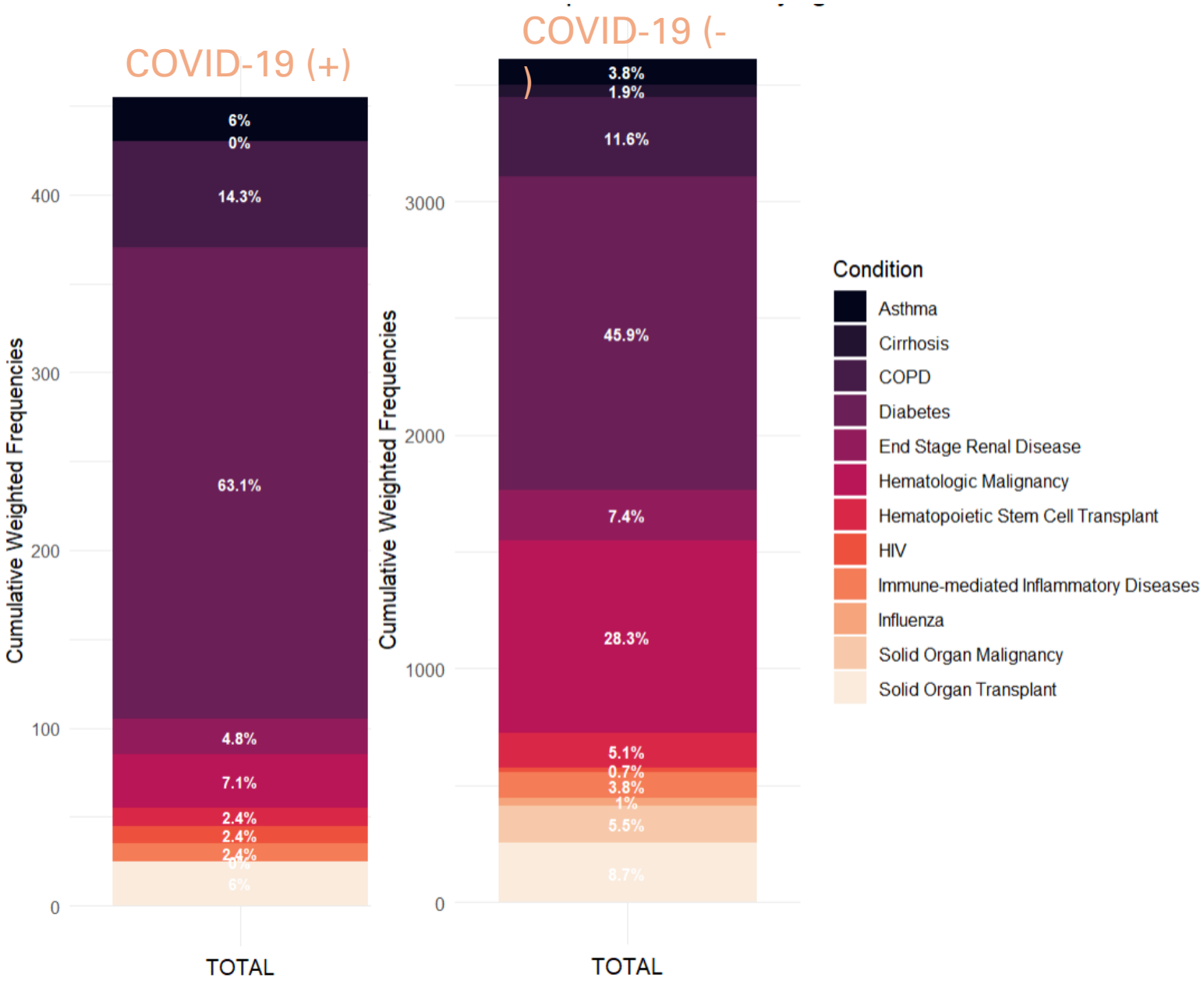


FIGURE 18. IN-HOSPITAL MORTALITY FOR COVID-19-ASSOCIATED MUCORMYCOSIS -RELATED HOSPITALIZATIONS (CAA-RH), 2020-2021

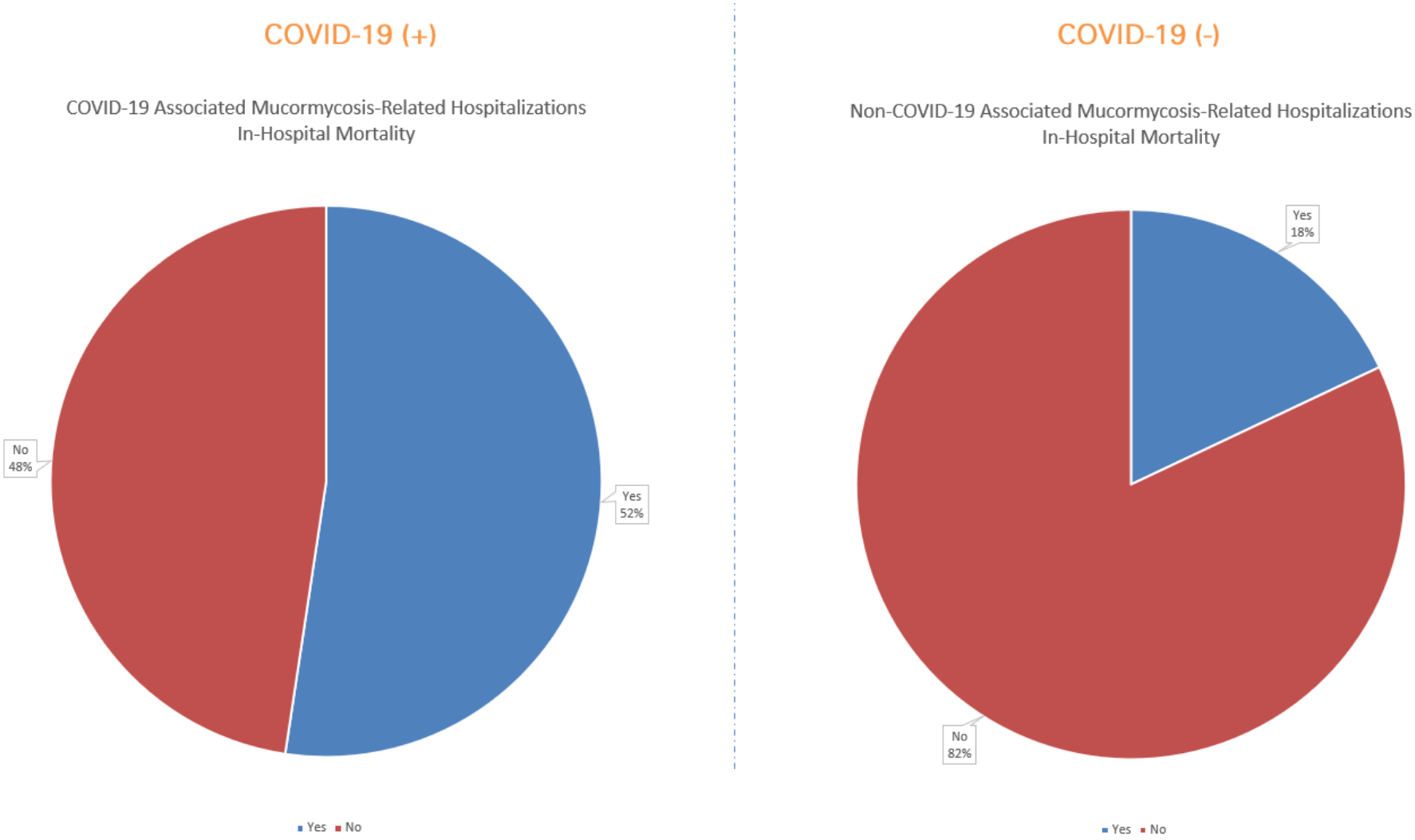


Table 3. Annual Percentage Change for Hospitalization Rates from 2016-2021				
	Aspergillosis		Mucormycosis	
	APC	p-value	APC	p-value
Overall	2.4	0.2904	3.2	0.2033
In-Hospital mortality	20.0	0.0363	16.5	0.0162
Asthma	-7.0	0.0546	-4.2	0.5534
COPD	-2.2	0.3435	11.6	0.0589
Diabetes	6.7	0.0714	10.2	0.0315
ESRD	7.0	0.0365	-1.9	0.7199
HM	-1.4	0.1898	-0.8	0.8048
HSCT	4.6	0.2631	-1.9	0.7470
SOM	3.6	0.0286	13.6	0.0242
SOT	3.0	0.1475	-0.8	0.8239
Cutaneous MUCOR	-	-	3.1	0.6322
Invasive sub-type	7.2	0.0005	-	-
Pulmonary	3.2	0.2033	9.6	0.0111
Rhinocerebral MUCOR	-	-	5.8	0.3429
Unspecified/Other sub-type	-0.1	0.9537	11.8	0.0044

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