Received: 31 May 2022 | Revised: 25 July 2022 | Accepted: 1 August 2022

DOI: 10.1002/hsr2.789

NARRATIVE REVIEW

Health Science Reports Open Access WILEY

Comparative risk assessment of COVID-19 associated mucormycosis and aspergillosis: A systematic review

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Abstract

COVID-19 is not only limited to a defined array but also has expanded with several secondary infections. Two uncommon opportunistic fungal infections, COVID-19 associated mucormycosis (CAM) and aspergillosis (CAA), have recently been highly acquainted by many worldwide cases. Two immune response deteriorating factors are considered to be responsible for immunosuppression: comorbidities and medication. Due to unlike infection sites and patterns, CAM and CAA-associated factors deflect a few degrees of proximity, and the present study is for its assessment. The study evaluated 351 CAM cases and 191 CAA cases retrieved from 65 and 53 articles based on inclusion criteria, respectively. Most of the CAM reported from India and CAA were from four South-European and West-European neighbor countries. The mean ages of CAM and CAA were 52.72 ± 13.74 and 64.81 ± 11.14, correspondingly. Mortality of CAA (56.28%) was two times greater than CAM (26.02%). Nevertheless, the count of diabetes cases was very high in CAM compared to CAA. The main comorbidities of CAM were diabetes (nearly 80%) and hypertension (more than 38%). All noticeable complications were higher in CAA except diabetes, and these were diabetes (34.55%), hypertension (45.03%), and obesity (18.32%). Moreover, pre-existing respiratory complications like asthma and chronic obstructive pulmonary disease are visible in CAA. The uses of steroids in CAM and CAA were nearly 70% and 66%, respectively. Almost one-fourth of CAA cases were reported using immunosuppressant monoclonal antibodies, whereas only 7.69% were for CAM. The overall finding highlights diabetes, hypertension, and steroids as the risk factors for CAM, whereas obesity, chronic pulmonary disease, and immunosuppressants for CAA.

KEYWORDS

aspergillosis, comorbidities, diabetes, medication, mucormycosis, risk-factors, SARS-CoV-2, steroids

1 | INTRODUCTION

Severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2) is the causative organism of zoonotic coronavirus disease (COVID-19). It is a highly contagious mRNA virus that spreads from person to person through respiratory droplets. The virus has involvement in diverse pathophysiology and causes multiorgan dysfunction along with death.[1] As the time and cases of COVID-19 emergence are increasing, the tremendous associated problems are uncovering. Multiorgan involvement and pathological reactions of the virus make the human body vulnerable to invasive secondary infection. Mucormycosis and aspergillosis are two mostly reported terrible fungal infections. These infections are also known as opportunistic fungal infections because the fungi take the chance to grow and multiply when body immunity is suppressed, and physiology assists them.[2]

In 1885, Paltauf described a very uncommon and aggressive fungal infection called mucormycosis or zygomycosis.[3] It is caused by mold fungi of the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella, and *Absidia* of Order—Mucorales, Class—*Zygomycetes*.[4] *Rhizopus oryzae* is responsible for around 60% of cases of mucormycosis in humans, and the environmental fungal spores enter the body by inhalation. Most cases of COVID-19 associated mucormycosis (CAM) are diagnosed after COVID-19 treatment. The major sites of the CAM are the sinus, rhino-orbital, rhino-orbito-cerebral region, lung, and bones of the infected regions.[5] Usually, the infection starts in paranasal sinuses and then rapidly extends into the palate and orbit.[6] CAM presents atypical signs and symptoms such as nasal blockage, facial pain, edema, pneumonia, compartment syndrome, crusting, proptosis, ptosis, chemosis, ophthalmoplegia, and even vision loss. Though few existing antifungal drugs are used to treat this infection, debridement and surgical removal of infected tissue are two options for severe necrosis.[7,8]

Aspergillus, a fungal genera ubiquitous in the environment, is responsible for a wide range of infectious fungal diseases called aspergillosis. The few common types of infections are invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), chronic rhinosinusitis, allergic bronchopulmonary aspergillosis (ABPA), fungal asthma, and aspergillus bronchitis.[9,10] As the respiratory system is the primary infection site of both SARS-CoV-2 and *Aspergillus*, COVID-19 associated aspergillosis (CAA) is relatively more common than mucormycosis. Some researchers have reported that nearly 20%–35% of COVID-19 positive cases had CAA, raising the mortality rate.[11–13]

The invasive fungi are highly susceptible to immunocompromised COVID-19 cases with a weak neutrophilic response. Uncontrolled diabetes mellitus (DM), acquired immunodeficiency syndrome (AIDS), hematological malignancies, iatrogenic immunosuppression, and chronic pulmonary diseases are well-documented reasons behind these secondary infections.[3,14] Nevertheless, other associated comorbidities are considered to have a few degrees of impact on the infection accretion.[15] Besides, steroids and other immunosuppressants are assumed to suppress immunity that enhances fungal commotion.[9,11,16] The two fungal genera of CAM and CAA have different infection sites with varying patterns of infection. Therefore, somewhat, the diseases may have dissimilar risk factors. This study targeted to find out the significant risk factors and the extent of similarities in CAM and CAA pathogenesis, tracing points to control and manage these infections.

2 | METHODS

2.1 | Data sources and search

The study focused on two factors: drug usage and comorbidity, associated with the opportunistic fungal infection. Both prospective and retrospective case reports of CAM and aspergillosis were picked up. The searching keywords were “fungal infection” or “opportunistic fungal infection” or “secondary infection” or “co-infection” or “mucormycosis” or “mucor” or “aspergillosis” or “aspergillus” with “COVID-19” or “coronavirus” or “SARS-CoV-2” or “severe acute respiratory syndrome 2.” The comprehensive literature searches of Google Scholar, PubMed, and Web of Science were conducted from June 20, 2021. We collected data from the cases published from January 2020 to July 1, 2022.

2.2 | Selection criteria and validity assessment

The data of case reports were taken if they met the following criteria: (1) the study was published in the peer-review journal enlisted in Scientific Journal Rankings (SJR), (2) the study included hospitalized patients with COVID-19, (3) the case was confirmed COVID-19 positive before the diagnosis of fungal infection, (4) the report comprehensively described the case history, and (5) the diagnosis of mucormycosis and aspergillosis met the case definitions or diagnostic algorithms of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG)[17] and the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria.[18,19] Besides, observational cases mentioned as not proved or uncertain or possible infection and case series were excluded.

2.3 | Data abstraction

The search results were reviewed and assessed based on inclusion and exclusion criteria for final selection. At first, the full-text articles were retrieved for further assessment and analyses after the initial screening with the title and abstract. The following data sets were taken out from each qualified study: author name, study location, patient characteristics, drug usage, comorbidities, and outcomes, and then tabulated into a primarily designed table.

2.4 | Statistical analysis

All analyses were accomplished using Microsoft Excel and SPSS version 25 (IBM Corp.). In the test of significance, $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Study selection and quality assessment

According to the search strategy, 596 articles were retrieved from online databases (Figure 1). Then a preliminary screening of the title and author's name helped to remove duplicates, and then 303 articles were subjected to screening to cancel out further irrelevancy by reading the abstract. After the exclusion of 96 records, 207 articles were selected for final screening. The 121 full-text articles met the inclusion criteria and research adequacy, and the other 86 articles were excluded. Finally, 118 highly focused articles on the case report of CAM or CAA are included in the present study. Among them, 65 articles described a total of 351 cases of CAM (Table 1), and the other 53 articles described 191 cases of CAA (Table 2).

3.2 | Demographic characteristics

Demographic features and the fate of the secondary fungal infections in 542 cases are shown in Table 3. A total of 351 CAM cases were included under the study, and above three-fourths (262) were from India, out of the 19 reported countries. Egypt, Iran, and the United States are also reported with 32, 22, and 9 cases, respectively. On the other hand, 191 cases of CAA are published from 26 countries, where highly noticeable 31, 31, 27, and 22 cases are reported from France, Italy, Netherlands, and Spain, respectively. Other countries had records of equal to or less than 10 cases. The mean ages of CAM and CAA were 52.72 ± 13.74 and 64.81 ± 11.14, respectively. On both infections, the prevalence among males was more remarkable than among females. Males occupied 70.65% of CAM cases and 75.13% of CAA cases. The mortality rate of CAA (almost 26%) was two times that of CAM (above 56%).

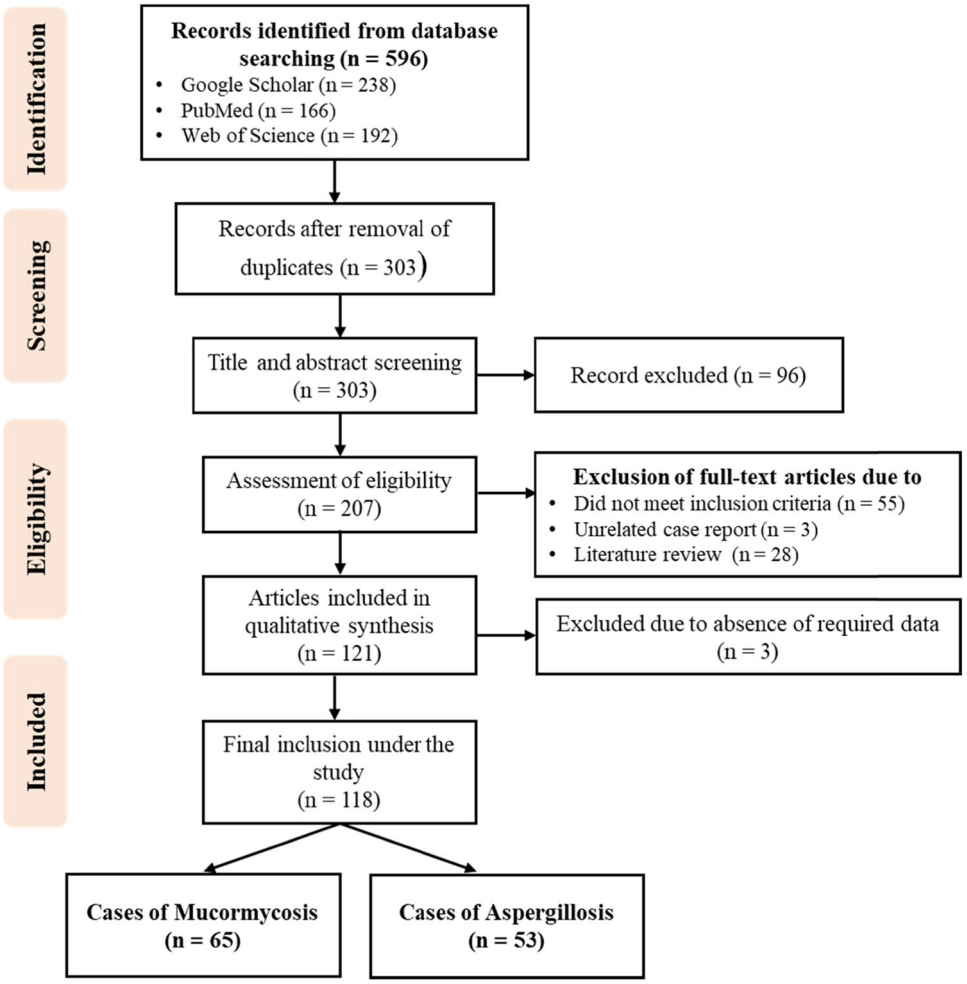

FIGURE 1 A flow diagram of the records selection procedure

TABLE 1 A brief presentation of CAM case reports

Source	Country	No. of cases	Mean age	Female/male	Comorbidities (case number)	Drug uses (case number)	No. of deaths
Waizel-Haiat et al.[20]	Mexico	1	24	1/0	DM, obesity	BSA	0
Moorthy et al.[7]	India	16	54.6	2/14	DM (15)	Steroids (15)	6
Pakdel et al.[21]	Iran	15	52	5/10	DM (13), HTN (7), malignancy (2), cardiac disease (2), HT (1), hepatic cirrhosis (1), tuberculosis (1)	Steroids (7), ISx (7), HCQ (1), chemotherapy (2), IFn (2), AVD (1)	7
Sharma et al.[3]	India	23	-	8/15	DM (21), HTN (14), renal failure (1)	Steroids (23)	NM
Sen et al.[22]	India	5	57.8	0/5	DM (5), HTN (2), CAD (1)	Steroids (4), BSA (1)	0
Kim et al[23]	South Korea	1	32	0/1	DM	Steroids	0
Kanwar et al.[24]	United States	1	56	0/1	CRD	Steroids, ISx	1
Mekonnen et al.[25]	United States	1	60	0/1	DM, HTN, asthma, HLD	No	1
Zurl et al.[26]	Austria	1	53	0/1	Obesity, AML, myeloblastic syndrome	No	1
Garg et al.[27]	India	1	55	0/1	DM, HTN, CKD	Steroids, BSA, remdesivir, anticoagulant	0
Krishna et al.[28]	United Kingdom	1	22	0/1	Obesity, HT	Steroids	1
Buli et al.[29]	Netherlands	4	65.6[a]	0/4	DM (2), obesity (1), CLL	Steroids (4), ISx (3)	3
Placik et al.[30]	United States	1	49	0/1	No	Steroids, BSA, remdesivir, ISx	1
Pasero et al.[31]	Italy	1	66	0/1	HTN	HCQ, AVD	1
Khatri et al.[32]	United States	1	68	0/1	DM, HTN, ICH, OHT, CKD	Plasma therapy	1
Arana et al.[33]	Spain	2	55	0/2	DM (1), HTN (2), IHD (1), HT (1), CKD (2), previous fungal infection (1)	Steroids (2), BSA (2), HCQ (1), ISx (1), AVD (1)	0
Ravani et al.[34]	India	31	56.3	11/20	DM (30), HTN (17), IHD (1), CKD (2)	Steroids (19)	3
Saidha et al.[35]	India	6	47	2/4	DM (4), HTN (1) CKD (1), hypoalbuminemia (1)	Steroids (1), remdesivir (1)	1
Rao et al.[36]	India	1	66	0/1	DM	Steroids	0
Saldanha et al.[37]	India	1	32	1/0	DM	No	0
Alekseyev et al.[38]	United States	1	41	0/1	DM	Steroids, HCQ	0
Veisi et al.[39]	Iran	2	47	1/1	DM (1)	Steroids (2), BSA (2), remdesivir	0
Maini et al.[40]	India	1	38	0/1	No	Steroids, BSA	0
Fouad et al.[41]	Egypt	6	53.7	2/4	DM (6), CKD (2), IHD (1)	Steroids (3), HCQ (6)	3
Jain et al.[42]	India	1	57	1/0	DM	Steroids, BSA	1
Revannavar et al.[43]	India	1	50[b]	1/0	DM	No	0

TABLE 1 (Continued)

Source	Country	No. of cases	Mean age	Female/ male	Comorbidities (case number)	Drug uses (case number)	No. of deaths
Baskar et al.[44]	India	1	28	0/1	No	No	1
Karimi-Galougahi et al.[45]	Iran	1	61	0/1	No	Steroids, remdesivir, IFn	0
Nehara et al.[46]	India	5	62.2	1/4	DM (5), HTN (2)	Steroids (3), BSA (2), remdesivir (2), anticoagulant (1)	0
Awal et al.[47]	India	3	48.7	1/2	DM	Steroids, remdesivir	0
Desai et al.[48]	India	50	23–73	21/29	DM (41), HTN (17), HD (3), CKD (6), liver disease (1), cancer (1)	Steroids (42), ISx (2), remdesivir (27)	12
Werthman-Ehrenreich[49]	United States	1	33	1/0	HTN, Asthma	BSA	1
Crone et al.[50]	Denmark	1	50	0/1	PTLB	ISx, chemotherapy, and radiotherapy	1
Alamin et al.[51]	Qatar	1	59	0/1	DM	Steroids, AVD	0
Mehrabi et al.[52]	Iran	1	51	0/1	-	Steroids, BSA	0
Singh et al.[53]	India	13	43.69	3/10	DM (8), HTN (7), CAD (2), liver disease (1), TB (1), asthma (1), malignancy (3), others (4)	Steroids (11),remdesivir (2), ISx (1)	8
Roy et al.[54]	India	5	49.6	2/3	DM (3), HTN (2), HT (1), nephropathy (1)	Steroids (4)	0
Bhat et al.[55]	India	1	22	1/0	-	BSA	0
Prasad et al.[56]	India	1	65	1/0	DM	-	0
Verma et al.[57]	India	1	61	0/1	DM	Steroids, Remdesivir	1
Ortega et al.[58]	United States	1	68	0/1	DM	-	0
Roushdy and Hamid[59]	Egypt	4	67.75	1/3	DM (4), HTN (3), CKD (1), CD (1), malignancy (1)	Steroids (2), BSA (1),	1
do Monte Junior et al.[60]	Brazil	1	86	0/1	HTN	Steroids, AVD, BSA	1
Palou et al.[61]	Honduras	1	56	0/1	DM	BSA	0
Dilek et al.[62]	Turkey	1	54	0/1	-	Steroids, BSA	1
Alfishawy et al.[63]	Egypt	21	50	7/14	DM (19), HTN (8), IHD (7), obesity (1)	Steroids (21), ISx (5)	7
Singh et al.[64]	India	1	48	0/1	-	Steroids, remdesivir, ISx	0
Sarkar et al.[65]	India	1	63	0/1	DM	-	0
Diwakar et al.[66]	India	2	12	1/1	DM	-	0

(Continues)

TABLE 1 (Continued)

Source	Country	No. of cases	Mean age	Female/ male	Comorbidities (case number)	Drug uses (case number)	No. of deaths
Tambe et al.[67]	India	1	32	0/1	DM	Steroids, remdesivir, BSA	0
Saltini et al.[68]	Italy	1	72	0/1	DM, HTN, malignancy	Steroids, BSA	1
Mitra et al.[69]	India	32	57 ± 13	9/23	DM (20), HTN (6), CKD (1)	Steroids (25)	NM
Selarka et al.[70]	India	47	55 ± 12.8	12/35	DM (36), HTN (27), sinusitis (6)	Steroids (47), AVD (29), BSA (47), ISx (3)	11
Shakir et al.[71]	Pakistan	1	67	0/1	DM, HTN, IHD	-	0
Arjun et al.[72]	India	10	53	2/8	DM (10), HTN (2), CAD (3), HT (1), CKD (1), arthritis (1)	Steroids (8),	1
Ostovan et al.[73]	Iran	1	61	1/0	DM, HTN	-	1
Johnson et al.[74]	United States	1	79	0/1	DM, HTN	Remdesivir, BSA,	0
Leung et al.[75]	Hong Kong	1	51	1/0	DM, hepatitis B, PVD, previous pulmonary mucormycosis	Steroids, ISx	0
Saad and Mobarak[76]	Egypt	1	44	1/0	-	-	1
Tabarsi et al.[77]	Iran	1	50	1/0	DM, HTN	Steroids, remdesivir	0
Deek et al.[78]	United States	1	75	0/1	DM, CAD, atrial fibrillation	Steroid	0
Alian et al.[79]	Iran	1	73	1/0	DM, HTN, CKD, dyslipidemia	Steroid, NSAID, antihypertension drug, insulin	1
Martins et al.[80]	Brazil	6	58,45, 35,50,44,60 (48.7 ± 9.4)	2/4	DM(5), HTN (1), Cancer (1)	-	1
Chaudhary et al.[81]	India	1	21	0/1	DM, asthma	STEROID, ISx	0
Horiguchi et al.[82]	Japan	1	58	0/1	DM, HTN,	STEROID, ISx, remdesivir	1

Abbreviations: AML, acute myeloid leukemia; AVD, antiviral drug; BSA, broad-spectrum antibiotic; CAD, coronary artery disease; CAM, COVID-19-associated mucormycosis; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; CRD, chronic respiratory disease; DM, diabetes mellitus; HCQ, hydroxychloroquine; HLD hyperlipidemia; HT, hypothyroidism; HTN, hypertension; ICH, *Ichthyophthirius multifiliis*; IFn, interferon; IHD, ischemic heart disease; ISx, immunosuppressants; OHT, ocular hypertension; PTLB, post-transplant lymphoproliferative disorder.

[a]Author mentioned mid-60s, late-50s, late-60s, early 70s.

[b]The author mentioned middle age.

TABLE 2 A brief presentation of CAA case reports

Source	Country	No. of cases	Age	Female/ male	Comorbidities (case number)	Drug uses (case number)	No. of deaths
Meijer et al.[83]	Netherlands	1	74	1/0	Polyarthritis	-	1
Santana et al.[84]	Brazil	1	71	0/1	DM, HTN, CKD	BSA, AVD, norepinephrine	1
Sharma et al.[85]	Australia	1	66	1/0	HTN, osteopenia	BSA, anti-HTN drug	0
Benedetti et al.[86]	Argentina	5	52.4	1/4	DM (3), HTN (2), obesity (2), leukemia, bronchiectasis, illicit drug abuse	Steroids (5), BSA (5), ISx (5)	1
Rutsaert et al.[12]	Belgium	7	66.6	0/7	DM (3), HTN (3), obesity (2), HIV, HCL (4), AML, CKD, pemphigus foliaceus	Steroids (1), AVD	4
Nasir et al.[87]	Pakistan	5	69	2/3	DM (4), HTN (4), atrial myxoma, recent stroke	Steroids (4), BSA (4), ISx (3)	3
Meijer et al.[88]	Netherland	13	67.3	3/10	DM (3), HTN (3), Heart disease, Polyarthritis	Steroids (8), HCQ (4), remdesivir (3)	6
Schein et al.[89]	France	1	87	1/0	No	Steroids, BSA (2), HCQ	0
Abdalla et al.[90]	Qatar	2	66	0/2	DM (1), HTN (1), lipidemia, hepatitis B	Steroids (2), HCQ (2), BSA, ISx (1)	2
Hakamifard et al.[91]	Iran	1	35	0/1	No	Steroids, BSA	1
Blaize et al.[92]	France	1	74	0/1	HTN, myelodysplastic syndrome, lymphocytosis, thyroiditis	-	1
Nasir et al.[87]	Iran	1	42	1/0	AML	Steroids, AVD, IFn	1
Lamoth et al.[93]	Switzerland	3	62	0/3	DM (1), HTN (2), obesity (2), asthma, pulmonary fibrosis	ISx (3)	1
Helleberg et al.[94]	Denmark	2	58	2/0	HTN (1), asthma (1)	Steroids (1), BSA	2
Witting et al.[95]	United States	1	72	0/1	No	BSA, remdesivir, ISx	0
Trujillo et al.[96]	Spain	1	55	1/0	HTN, CKD, hepatic hemangiomas	Steroids, BSA, HCQ, ISx, anticoagulant, tacrolimus, mycophenolate	0
Prattes et al.[97]	Austria	1	70	0/1	DM, HTN, obesity, COPD, sleep apnea, retinopathy, polyneuropathy, CKD, thrombosis	Steroids, BSA, HCQ, valsartan, spironolactone, ivabradine, atorvastatin, metformin, liraglutide, insulin glargine, enoxaparin	1
Machado et al.[98]	Spain	8	64.5	2/6	DM (1), HTN (7), obesity (4), asthma, COPD	Steroids (8), ISx (8)	8
Falces-Romero et al.[99]	Spain	10	67.1	2/8	DM (4), obesity (4), COPD (4), CIH (1), CLL (1), HIV (1), myelodysplastic syndrome	Steroids (10), HCQ (10), IFn (1), ISx (4), AVD	7

(Continues)

TABLE 2 (Continued)

Source	Country	No. of cases	Age	Female/ male	Comorbidities (case number)	Drug uses (case number)	No. of deaths
					(1), ankylosing spondylitis (1), HT (1), hemophilia (1)		
Flikweert et al.[100]	Netherland	6	72.3	2/4	DM (1), HTN (1), CKD (1)	Steroids (3)	6
Alanio et al.[101]	France	9	62.8	4/5	DM (3), HTN (7), obesity (3), myeloma (1), IHD (2), asthma (2)	Steroids (6), BSA (4), HCQ (2), AVD (7)	4
Bartoletti et al.[102]	Italy	30	63	6/24	DM (5), HTN (16), obesity (10), heart disease (3), CVD (3), CKD (6), COPD (4), malignancy (2),	Steroids (18), BSA (9), HCQ (28), remdesivir (3), ISx (22), AVD (14)	13
van Someren Gréve et al.[103]	Netherland	1	79	0/1	DM, HTN, paroxysmal atrial fibrillation, CHF	Steroids, BSA	1
Dupont et al.[104]	France	19	69	4/15	DM (7), HTN (7), COPD (4), malignancy (3), asthma (4), tuberculosis (2)	Steroids (7), HCQ (3)	7
Alobaid et al.[105]	Kuwait	2	55	NM	DM (1), HTN (1), IHD	Steroids (2), BSA (1), HCQ (2), ISx (1)	2
Mitaka et al.[106]	United States	4	78.7	0/4	Malignancy (1), cardiac disease (1), COPD (1), cerebrovascular accident (1)	Steroids (4), BSA (4), ISx (1)	4
Ghelfenstein-Ferreira et al.[107]	France	1	56	0/1	DM, HTN, obesity, HLD, COPD	Steroids (nasal), BSA	0
Fernandez et al.[108]	Argentina	1	85	0/1	HTN	Steroids, BSA, HCQ, AVD	1
van Arkel et al.[13]	Netherland	6	62.5	0/6	COPD (2), asthma	Steroids (2)	4
Koehler et al.[109]	Germany	5	62.6	2/3	DM (1), HTN (3), obesity (1), HCL (1), COPD (2), emphysema	Steroids (3), HCQ (1), AVD	3
Mohamed et al.[110]	Ireland	1	66	0/1	DM, HTN, obesity, HLD	HCQ, BSA	1
Patti et al.[111]	United States	1	73	0/1	HTN	Steroids, BSA, remdesivir	0
Wu et al.[112]	United States	1	46	0/1	DM, HTN	Steroids, AVD	0
Imoto et al.[113]	Japan	1	72	0/1	HTN, atrial fibrillation, COPD	Steroids anticoagulants, β2-agonist, muscarinic antagonist, remdesivir, BSA	1
Haglund et al.[114]	Denmark	1	52	0/1	CVD, DM, obesity,	BSA, anticoagulant	0
Trovto et al.[115]	Italy	1	73	0/1	DM, HTN	Steroids, BSA	1
Sánchez Martín et al.[116]	Spain	3	70.33	1/2	DM (1), HTN (2), thalassemia minor (1), dyslipidemia (2)	Steroids (3), ISx (1), AVD (3), HCQ (3), BSA (3)	1

TABLE 2 (Continued)

Source	Country	No. of cases	Age	Female/ male	Comorbidities (case number)	Drug uses (case number)	No. of deaths
Nasrullah et al.[117]	United States	1	68	0/1	DM, HTN	Steroids, remdesivir	1
White et al.[118]	United Kingdom	1	58	0/1	Thrombocythemia	Hydroxycarbamide	1
Abolghasemi et al.[119]	Iran	1	66	1/0	-	Steroids, BSA, IFn	1
Bhopalwala et al.[120]	United States	1	56	1/0	DM, HTN, obesity, GERD, CVD, sleep apnea	-	0
Toc et al.[121]	Romania	1	53	1/0	DM, CKD, obesity, asthma, thyroiditis, IHD, severe pulmonary hypertension, and mitral valve stenosis	Steroids, remdesivir, AVD, BSA, others (5)	0
Tabarsi et al.[122]	Iran	1	50	1/0	DM, HTN	Steroids, remdesivir	0
Iwanaga et al.[123]	Japan	1	79	0/1	DM, polymyalgia rheumatica	Steroids, methotrexate	1
Salehi et al.[124]	Iran	1	70	0/1	-	Steroids, HCQ, IFn	1
Wang et al.[125]	China	8	73	0/8	DM (2), HTN (7), HD (1), COPD (2), CKD (2)	Steroids (6), AVD (8), BSA (6)	NM
Chaurasia et al.[126]	India	1	57	0/1	TB	Steroids, remdesivir, anticoagulant	0
Traver et al.[127]	United States	1	59	0/1	COPD, obesity, liver cirrhosis, CAD, APNEA, DM	Steroids, BSA, beta blocker	1
Hoyek et al.[128]	Lebanon	1	70	0/1	DM	Steroid	1
Swain et al.[129]	India	10	60,64, 43,31, 52,70, 47,55, 40,45, (50.7 ± 11.8)	4/6	DM (7), HTN (2), CAD, cancer	Steroid (10)	4
Nasri et al.[130]	Iran	1	42	1/0	DM, cancer	Chemotherapy, BSA, AVD, antidiabetic therapy	1
Katsiari et al.[131]	Greece	1	70	0/1	DM, HTN	Steroid, BSA, AVD	1
Lim et al.[132]	Malaysia	2	62, 56	2/0	DM (1), dyslipidemia	Steroid (2)	1

Abbreviations: AML, acute myeloid leukemia; AVD, antiviral drug; BSA, broad-spectrum antibiotic; CAA, COVID-19 associated aspergillosis; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HCL, hypercholesterolemia; HCQ, hydroxychloroquine; HLD, hyperlipidemia; HT, hypothyroidism; HTN, hypertension; IFn, interferon; IHD, ischemic heart disease; ISx, immunosuppressants; NM, not mentioned.

TABLE 3 The CAM and CAA case demography

Category	Mucormycosis case	Aspergillosis case
Number of articles	65	53
Total cases	351	191
Reported from (country-wise cases)	Austria (1), Brazil (7), Denmark (1), Egypt (32), Honduras (1), Hong Kong (1), India (262), Iran (22), Italy (2), Japan (1), Turkey (1), Mexico (1), Netherland (4), Pakistan (1), Qatar (1), South Korea (1), Spain (2), United Kingdom (1), United States (9)	Argentina (6), Australia (1), Austria (1), Belgium (7), Brazil (1), China (8), Denmark (3), France (31), Greece (1), Germany (5), India (11), Iran (6), Ireland (1), Italy (31), Japan (2), Kuwait (2), Lebanon (1), Malaysia (2), Netherland (27), Pakistan (5), Qatar (2), Romania (1), Spain (22), Switzerland (3), United Kingdom (1), United States (10)
Mean age	52.72 ± 13.74[a]	64.81 ± 11.14
	(Range: 5–86)	(Range: 23–87)
Female/male	103/348	47/142
	(29.34/70.65%)	(24.87/75.13%)[b]
Death	83 (26.02%)[c]	103 (56.28%)[d]

Abbreviations: CAA, COVID-19 associated aspergillosis; CAM, COVID-19 associated mucormycosis.

[a]Without Sharma et al.[3] (no data), Desai et al.[48] (only age range mentioned), Mitra et al.,[69] and Selarka et al.[70]

[b]Data absence in Alobaid et al.[105]

[c]Without Mitra et al.[69] (no data).

[d]Not included in Wang et al.[125] (no data).

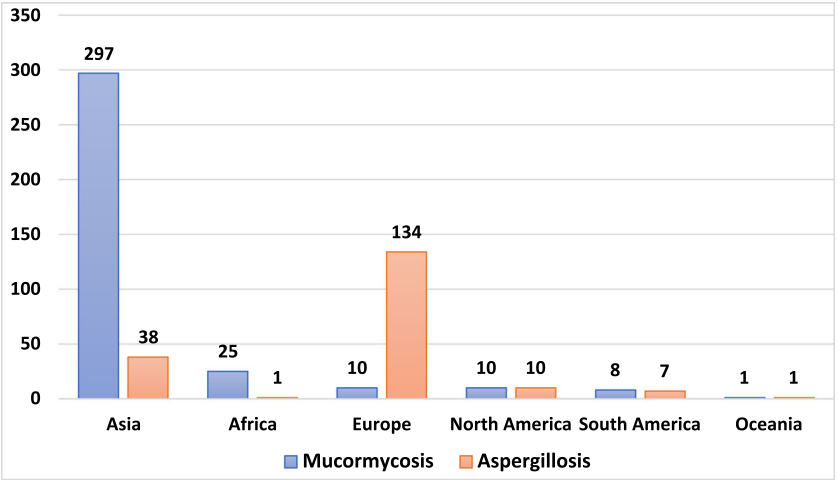

FIGURE 2 The continental accounts of CAM (n = 351) and CAA (n = 191). CAA, COVID-19 associated aspergillosis; CAM, COVID-19 associated mucormycosis.

3.3 | Continental emergence

When the study looked for the continental case distribution, the emergence of opportunistic fungal infections was observed in Asia and Europe (Figure 2). Mucormycosis prevalence in Asia was far greater than aspergillosis, and the infection scenario was vice versa in Europe. CAM in Asia was the highest on the list with 297 cases, and Europe showed its maximum with 134 CAA cases. In Africa, only 25 cases of CAM were observed, and the opposite evidence in South America, where 8 and 7 cases were reported for each infection, respectively. South America and Oceania also presented less emergence of the two infections. Overall, the infection scenario in Asia and Europe was significantly greater than in other continents.

3.4 | Comorbidities and drug use

Table 4 illustrates a comparative measure of comorbidities and medications before diagnosing the two fungal infections. The study categorized all critical existing chronic diseases of patients into 11 categories. The most prominent comorbidity of CAM was diabetes, with 79.20%, and hypertension was reported for 37.32%. Twenty-one cases out of 351 showed kidney disease and cardiovascular disease individually, while the counting for obesity, malignancy, and chronic heart disease was not significant.

On the other hand, CAA disclosed enormous dissimilarities, where 34.55% of 191 cases were diabetic. Hypertension and obesity occupied 45.03% and 18.32%, respectively, which was relatively

TABLE 4 Comorbidities and drug use before CAM and CAA confirmation

Risk factors		Cases of mucormycosis, *n* = 351 (%)	Cases of aspergillosis, *n* = 191 (%)
Comorbidities	Diabetes (type I and II)	278 (79.20)	66 (34.55)
	Hypertension	131 (37.32)	86 (45.03)
	Obesity	5 (1.42)	35 (18.32)
	Kidney disease	21 (5.98)	13 (6.80)
	Cardiovascular disease	21 (5.98)	19 (9.94)
	Asthma	6 (1.71)	11 (5.76)
	Malignancy	12 (3.42)	13 (6.81)
	Hypothyroidism (HT)	4 (1.14)	2 (1.05)
	COPD	0 (0.0)	25 (13.09)
	Hyperlipidemia	2 (0.56)	10 (5.24)
	Others	27 (7.70)	37 (19.37)
	Total chronic complications	507	317
	Mean complications	1.44	1.66
Drugs in COVID-19 treatment	Steroids use	243 (69.23)	126 (65.97)
	Hydroxychloroquine	12 (3.41)	63 (32.98)
	Remdesivir	44 (12.53)	13 (6.81)
	Immunosuppressant	27 (7.69)	45 (23.56)
	Broad-spectrum antibiotics	74 (21.08)	58 (30.37)
	Antiviral drug	37 (10.54)	44 (23.04)
	Anticoagulant	4 (1.14)	5 (6.62)
	Plasma therapy	1 (0.28)	2 (1.05)
	IFn	5 (1.42)	4 (2.09)

Abbreviations: CAA, COVID-19 associated aspergillosis; CAM, COVID-19 associated mucormycosis; COPD, chronic obstructive pulmonary disease; IFn, interferons.

higher than the report of CAM in these categories. Surprisingly, 25 chronic obstructive pulmonary disease (COPD) cases were observed in CAA, whereas no such case was reported in CAM. The comorbidities associated with the excretory and cardiovascular systems were below 10%. Here, two HIV-positive patients were also reported. The mean comorbidity of CAA was a little bit more than CAM, yet both are around 1.5, which means every two patients had at least three chronic complications.

The study extracted the drugs used in COVID-19 treatment and used them before diagnosing CAM and CAA to correlate therapeutic involvement in fungal pathogenesis. The frequency of steroid use had some similarities; 69.23% for CAM and 65.97% for CAA. The uses of hydroxychloroquine, broad-spectrum antibiotics, and antiviral drugs (including remdesivir) in CAM were comparatively higher in CAA (Table 4). Similarly, immunosuppressant drugs had been used before 7.69% of CAM, while one-fourth of CAA patients received the medication. Specifically, 12.53% of CAM and 6.81% of CAA cases were reported as antiviral drug remdesivir used in COVID-19 treatment. Moreover, a few instances of convalescent plasma therapy, anticoagulant, and interferon uses were also retrieved from the articles.

4 | DISCUSSION

Aspergillosis and mucormycosis are rare secondary fungal infections. So, the SARS-CoV-2 virus certainly creates a favorable environment for fungi that might be strange to other pathogens. The patients of COVID-19 do not face the same clinical condition; some severe, some mild, and some asymptomatic. Several studies have amnestied comorbidities for the severity of viral infections. Therefore, do the same factors have the same role in secondary fungal infection? Besides, immunomodulators and steroids are theoretically supposed to be involved here. The present study is an endeavor for the answer relating to mucormycosis and aspergillosis.

At first, the noticeable outcome of this study is the geolocation of the prevalence of the infections. The CAM cases are high in India, whereas the CAA cases are high in a few European neighbor

countries of Western Europe and Sothern Europe. As racial diversity is a reason for infection disparity, genetic variation might influence here.[133,134] Furthermore, environmental factors like humidity, temperature, and light might be considered to influence fungal growth. The SARS-CoV-2 has taken chances of variant change and exhibited deviance in infection pattern and severity.[135] A particular variant may potentially cause a particular secondary infection, but such evidence is not available until now.

A recent study finds a highly significant difference between the two groups of cases. The median age of Asian and European people was 32 and 42.5 years, respectively.[136] So, high infections from the two continents might create this significant age difference. However, very young cases are reported here. Few studies also reported pediatric mucormycosis and aspergillosis in non-CAM and non-CAA cases.[137–139] The male and female sex ratio of COVID-19 infection is 61.8% and 38.2%.[140] Jin et al. found that the severity of COVID-19 greater in males than in females, and mortality is 2.4 times in males.[141] Therefore, it is obvious to find more cases of males than females.

The mortality count showed a spectacular difference. Mortality in CAA is two times greater than in CAM. Spellberg et al. showed 55% 90-day mortality in mucormycosis of non-COVID-19 cases, but the number of patients was only 20.0.[142] Another contemporary study reported 33% lethality in all cases of the infection.[143] The mortality had similarities with the study finding (nearly 30%) on CAM. Around 56% fatality was reported by Lin et al., which matches the result of CAA.[144] The finding of several studies on mucormycosis and aspergillosis had obvious dissimilarities in mortality that hint at multifactorial association with the disease severity.

As understood so far, COVID-19 itself lessens the immunological response due to the induction of significant and persistent lymphopenia.[145] Further, parallel diseases worsen the defensive mechanism that makes the body more susceptible to secondary infections. Diabetes causes a functional immune deficiency that directly reduces immune cell function. That is why it is the prime concern of pathologists. In this study, mucormycosis exhibited nearly 80% of diabetes cases, whereas aspergillosis had below 35%. However, the finding on CAM is more than that of non-CAM reported by Hong et al.[143] Other comorbidities like hypertension, kidney disease, obesity, malignancy, and asthma were comparatively more predominant in CAA than CAM. A highly observable morbidity was COPD. Twenty-five cases were reported as COPD in CAA, yet no such case occurred in CAM. The studies described by Baddley complied with the finding that pulmonary complications might enhance the risk of CAA.[146]

An analysis on 22,753 COVID-19 cases estimated the percentage of pre-existent diseases: diabetes (17.4%), HTN (27.4%), CKD (2.6%), COPD (7.5%), CVD (8.9%), cancer (3.5%), and other (15.5%).[147] Several meta-analyses on the disease severity proved a resilient relation between comorbidity and disease severity. For instance, males and elderly patients are at greater risk of severity, and comorbidities could substantially affect the severity of COVID-19.[148] These studies helped to conclude that diabetes, hypertension, kidney disease, and COPD might be highly provocative to CAM and CAA.

From the very beginning, it was argued whether taking steroids and immunosuppressants is the risk of COVID-19 or whether the immunosuppressive state would be responsible for severe COVID-19 infection.[149] Nevertheless, the use of these drugs is widespread for critical patients with risk-benefit ratio consideration. Dexamethasone in the RECOVERY trial on COVID-19 of RECOVERY Collaborative Group (2021) showed the most significant mortality benefit with a low dose.[150] Despite this, World Health Organization (WHO) recommended systemic corticosteroids to treat critically ill patients with nasal oxygen or ventilation and provided a guideline on September 2, 2020, to meet the pandemic[151] Besides steroids, the immunosuppressant monoclonal antibody is also used for critical patients. Another RECOVERY trial of tocilizumab on hospitalized patients primarily found mortality reduction and improved clinical outcomes.[152]

The study revealed the high use of steroids in CAM (nearly 70%) and CAA (almost 66%). The immunosuppressant uses were comparatively high in CAA. A meta-analysis on 73 studies with 21,350 COVID-19 patients included 21.6% of patients receiving corticosteroids, and the median value was 35.5%.[153] The finding of the present study was very high, which might be a differentiating factor between fungal infections and noninfections. In the two cases of CAM and CAA, some patients also received remdesivir, antiviral drugs: lopinavir-ritonavir, hydroxychloroquine, and broad-spectrum antibiotics. However, the effectiveness of these drugs in COVID-19 is uncertain, and some are disproved.[154] However, these drugs have no available evidence to relate the involvement in secondary fungal infections.

5 | CONCLUSION

COVID-19 is a devastating chapter of human civilization that has amassed multidirectional health issues with robustness. Secondary fungal infections are a threat to COVID-19-infected people. Mucormycosis and aspergillosis are highly fatal fungal infections, and their pathophysiology is not entirely known. Therefore, investigation of the comparative risk factors provides a guide to controlling and mitigating their race. Mucormycosis mainly emerged in Indians, whereas Europeans are highly affected by aspergillosis. Diabetes, hypertension, obesity, and kidney disease are prominent factors of infections. Even a young person can be affected by mucor fungi but should be highly careful if the COVID-19 case is diabetic. Chronic respiratory complications like COPD increase the risk of aspergillosis. The high percentage of steroids used indicates its association with the infection. However, much immunosuppressant use in aspergillosis might be responsible for the infection. Nevertheless, comprehensive studies are required focusing on the extent of immunological involvement of the drugs in COVID-19 patients. It might explore the list of the relative priority of these risk factors.

AUTHOR CONTRIBUTIONS

Conceptualization: Mohammad Safiqul Islam. *Data curation*: Prodip Kumar Baral and Md. Abdul Aziz. *Formal analysis*: Prodip Kumar Baral. *Methodology*: Prodip Kumar Baral, and Md. Abdul

Aziz. *Supervision*: Mohammad Safiqul Islam. *Validation*: Prodip Kumar Baral, Mohammad Safiqul Islam. *Visualization*: Prodip Kumar Baral and Md. Abdul Aziz. *Writing—original draft*: Prodip Kumar Baral and Md. Abdul Aziz. *Writing—review and editing*: Md. Abdul Aziz and Mohammad Safiqul Islam. All authors have read and approved the final version of the manuscript. Mohammad Safiqul Islam had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author (manuscript guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Upon request in the future, the corresponding author confirms that all the pertinent information will be disclosed for further use.

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How to cite this article: Baral PK, Aziz MA, Islam MS. Comparative risk assessment of COVID-19 associated mucormycosis and aspergillosis: a systematic review. *Health Sci Rep*. 2022;5:e789. doi:10.1002/hsr2.789