Aspergillosis and Mucormycosis in COVID-19 Patients: A Systematic Review

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ABSTRACT

Fungal infections have increased in number since the onset of this lethal pandemic. This study aimed to assess risk factors and case fatality in COVID-19 cases with aspergillosis or mucormycosis. A systematic review was done according to PRISMA guidelines. Databases used were Google scholar, Pakmedinet, PUBMED, and MEDLINE. Twenty-one case reports and case series of mucormycosis in COVID-19 patients were identified and the mean age was 56.3 years (36 men and 12 women). The most common comorbidity was diabetes and the site was rhino orbital mucormycosis. Case fatality of 48 combined cases was calculated to be 52%. Nineteen articles of aspergillosis were included. Diabetes was the most common comorbidity in cases. The number of affected men cases was more than women. The incidence of aspergillosis in critically sick COVID-19 patients was calculated to be 9.3%. Case fatality was calculated to be 51.2%. Screening can be a beneficial tool for decreasing morbidity and mortality.

Key Words: *COVID-19, Mucormycosis, Aspergillosis.*

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INTRODUCTION

COVID-19 pandemic started in China and subsequently spread throughout the world at an alarming rate. The disease caused by this virus can involve multiple systems of the body. Recently, researchers and medical care providers have noticed that fungal infections such as Aspergillosis and Mucormycosis are on an increasing trend among patients already infected with this lethal covid virus. These fungal infections spread through spores of these fungi that are spread everywhere in the environment. Normal healthy people continue to breathe in the air without being affected by these spores. Getting infected with these fungi is a rare occurrence but patients who are already immunocompromised and suffering from lung diseases due to COVID-19 are more vulnerable to acquiring these devastating pathogens.

Mucormycosis is also known as black fungus. It can affect the nasal cavity, sinuses, lungs, gastrointestinal tract, and skin. When a pathogen enters the bloodstream, it can cause disseminated mucormycosis. Rhino cerebral is the most common site involved in mucormycosis. This disease does not spread by person--to-person contact. Treatment is done with anti-fungal agents and most cases do require surgical recession of the site involved.[1]

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Aspergillosis is commonly known as mold that also affects those who have a weakened immune system or any lung disease for example asthmatics or chronic obstructive lung disease. The mortality with this disease is high.[2] There is an association between increased frequency of pulmonary aspergillosis and influenza. Influenza was an independent risk factor for aspergillosis. Early diagnosis and prophylactic antifungals improve the prognosis of patients.[3] It is speculated that immune dysregulation associated with acute respiratory distress syndrome (ARDS), disrupted ciliary clearance, and lymphopenia due to severe respiratory viral infection may contribute to the development of invasive pulmonary aspergillosis in critically ill patients with COVID-19.[4]

Aspergillosis and mucormycosis have a high prevalence in the covid-19 positive population. A study done on 184,500,000 people has revealed that 1.78% have been shown to have serious fungal infections.[5] The present study aimed to identify the comorbidities and case fatality of aspergillosis or mucormycosis in COVID-19 cases. This study will also identify the incidence of aspergillosis in critically sick persons that will including both ICU patients and mechanically ventilated cases. Knowledge generated from this systematic review will highlight the importance of preventing and early screening in critically sick persons of COVID-19 as this disease has high morbidity and mortality.

METHODOLOGY

The systematic review was done according to PRISMA guidelines 2020 for an extensive literature search. Articles on

aspergillosis or mucormycosis in COVID-19 patients from 1st January 2020 to 15th June 2021 were searched. Databases used were Google scholar, Pakmedinet, PUBMED and MEDLINE. The date of my search was 15th June 2021. PRISMA flowchart is shown in Figure 1. In each database Boolean operators and keywords used were [(Aspergillosis or Mucormycosis) and COVID-19].

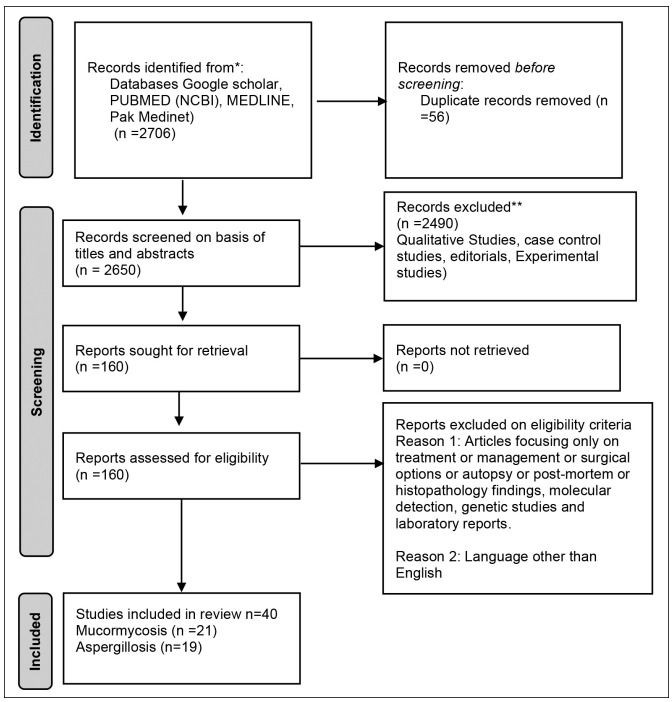

Figure 1: Identification of studies *via* databases and registers.

The participants were hospitalised for COVID-19 cases having fungal infections aspergillosis or mucormycosis. There was no intervention and comparison group. The outcome was noted in terms of case fatality.

The inclusion criteria was articles on mucormycosis and aspergillosis in COVID-19 patients which have mentioned co-morbidities and case fatality. For mucormycosis in COVID-19 cases; case reports and cases series were included in this study. For aspergillosis in COVID-19 cases; original articles and abstracts were included. Case reports and case series were excluded for aspergillosis and COVID-19 patients. Articles focusing on treatment, management, surgical options, autopsy, postmortem, histopathology findings, molecular detection, genetic studies, and laboratory reports were excluded. Articles with languages other than English were also excluded.

For the selection of articles, 2 researchers independently screened the articles on basis of title and abstract during the first phase. The articles meeting the eligibility criteria entered phase 2 of screening in which the full text of the articles was read by both reviewers independently. Articles were included according to standard PRISMA guidelines.

Two reviewers independently extracted data from the included studies. Data were extracted from eligible studies which included authors' name, age, gender, site of disease, co-morbidities, and case fatality. Incidence of aspergillosis in COVID-19 was also extracted. These were entered in Microsoft Excel. For calculating comorbidities and case fatality of mucormycosis in COVID-19; the quality of case reports and case series of mucormycosis for bias assessment was not accessed due to the limited number of case reports and case series.

Articles used for calculating the combined incidence of aspergillosis were published in peer-reviewed journals, and were either prospective or retrospective cohort studies on hospitalized patients of COVID-19 (either mechanically ventilated or not mechanically ventilated). The articles with the confirmed diagnosis on culture, galactomannan, and PCR for aspergillosis were included. For quality assessment of articles used for calculating incidence The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews (Checklist for Cohort Studies) was used.[6] Data was extracted and entered in Microsoft Excel.

RESULTS

As mentioned in Figure 1, databases (Google scholar, PUBMED (NCBI), MEDLINE, Pak Medinet) yielded 2706 articles. Fifty-six duplicates were removed. Screening on basis of titles and abstracts yielded 160 papers. The full text of these 160 papers were read by both reviewers thoroughly. Articles focusing only on treatment or management or surgical options or autopsy or post-mortem or histopathology findings, molecular detection, genetic studies, and laboratory reports. Articles other than English were also excluded. As a result of which 40 articles were included in the study.

Twenty-one case reports and case series of mucormycosis in COVID-19 patients were identified.[7-27] The total number of cases was 48 patients. The mean age was found to be 56.312 years with a standard deviation of 15.55 years. There were 36 men and 12 women. The most common comorbidity was diabetes (35 out of 48 cases). Other risk factors included chronic kidney disease, ischemic heart disease, transplant, decompensated liver disease, and hypertension (Table I). History of steroid use was present in 45.83% of COVID cases developing mucormycosis as shown in Figure 2. The most common site was Rhino orbital mucormycosis. However cutaneous, gastrointestinal, and pulmonary mucormycosis were also reported. Twenty-five cases died and 23 were discharged (Table I). The chi-square test did not show a significant difference in outcome between men and women ($p = 0.133$). The combined case fatality of 48 cases was calculated to be 52%.[7-27]

For Aspergillosis, ninteen articles meeting the inclusion criteria were included. Diabetes was the most common comorbidity in cases. Other risk factors include hypertension, steroid use, hypertension, heart disease, chronic obstructive pulmonary disease, malignancies, and chronic kidney disease. The incidence of aspergillosis in critically sick COVID-19 patients was calculated by including 9 studies as shown in Table II.[28-36] Forest plot shows the incidence of aspergillosis in critically sick COVID-19 patients using a 95% confidence interval (Figure 3).

Table I: Case Reports and Case Series of Mucormycosis.

Study Name	Age in years	Gender	Site of mucormycosis	Comorbidities	Outcome
Fouad YA *et al*. 2021[7]	55	Male	Rhino-orbital Cerebral	Diabetes	Death
	63	Female		Diabetes	Discharged
	54	Male		Diabetes, CKD, IHD	Death
	67	Male		Diabetes, CKD	Death
	41	Female		Diabetes	Discharged
	42	Male		Diabetes	Discharged
	62	Male		Diabetes	Death
Paul SS *et al*. 2021[8]	70	Male	Rhino-orbital Cerebral Sino-nasal	Diabetes	Discharged
	53	Male	Rhino-orbital Cerebral Rhino-Sino Orbital Sino nasal Rhino orbital Cerebral Rhino orbital Cerebral Pulmonary Sino nasal	Diabetes, CKD	Death
	38	Male		Renal transplant, Diabetes DCLD, Diabetes	Discharged
	37	Male		Chronic Granulomatous Disease	Discharged
	32	Male		Diabetes	Discharged
	48	Male		Diabetes, Tuberculosis	Discharged
	60	Male		End Stage Kidney Disease	Death
	34	Female		-	Death
Tabarsi P, *et al* 2021[9]	50	Female	Sino nasal	Diabetes, Hypertension	Discharged
Bayram N, *et al*. 2021[10]	Mean age 73.1	Male	Rhino orbital	CKD	Death
		Male		CKD, Diabetes	Death
		Male		CKD, Diabetes	Death
		Male		AKF, Diabetes	Death
		Male		AKF	Death
		Male		Myelodysplastic Syndrome	Death
		Male		Diabetes Diabetes	Death
		Male		Diabetes	Discharged
		Male		Diabetes	Discharged
		Female		Diabetes	Discharged
		Female		-	Discharged
Shah D, *et al*. 2021[11]	45	Male	Rhino orbital	Diabetes	Discharged
	50	Male	Orbital	-	Discharged
	60	Female	Sinuses	Diabetes	Discharged
	65	Male	Sinuses	-	Discharged

Waizel-Haiat S, *et al.* 2021[12]	24	Female	Sino Orbital	-	Discharged
Alekseyev K, *et al*. 2021[13]	41	Male	Cutaneous	Diabetes	Death
Khatri A, *et al.* 2021[14]	68	Male	Naso orbital	Heart transplantation, CHD, Diabetes, Hypertension	Discharged
Maini A, *et al*. 2021[15]	38	Male	Gastrointestinal	-	Died
do Monte Junior ES, *et al*. 2020[16]	86	Male	Rhino Orbital	Hypertension	Death
Mehta S, *et al*. 2020[17]	60	Male	Pulmonary	Diabetes	Died
Khan N, *et al*. 2020[18]	44	Female	Rhino Orbital Cerebral	Diabetes	Discharged
Revannavar SM, *et al*. 2021[19]	50	Female	Rhino Cerebral	Diabetes	Died
Farid HA, *et al*. 2021[20]	53	Male	Sino Orbital	Diabetes, hypertension	Discharged
Meshram HS, *et al*. 2021[21]	47	Male	Rhino orbital	Hypertension, Diabetes, Kidney Transplant	Died
	25	Male	Pulmonary	Hypertension, Diabetes, Kidney Transplant	Died
Mekonnen ZK, *et al*. 2021[22]	60	Male	Rhino orbital	Hypertension, Diabetes, Asthma, Hyperlipidemia	Died
Johnson AK, *et al*. 2021[23]	79	Male	Pulmonary	Diabetes, Hypertension	Discharged
Chowdhary S, *et al*. 2021[24]	45	Female	Rhino orbital	Diabetes	Death
Saldanha M, *et al*. 2021[25]	32	Female	Paranasal	Diabetes	Discharged
Pasero D, *et al*. 2021[26]	66	Male	Pulmonary	Hypertension	Death
Garg D, *et al*. 2021[27]	55	Male	Pulmonary	Diabetes, Hypertension, IHD, End Stage Kidney Disease	Discharged

The combined incidence was 9.3% with a confidence interval of 3.93% to 14.67%. Case fatality was calculated to be 51.2% as shown in Table III.[37-44] The number of male cases was more than females.[33, 37]

DISCUSSION

This study aimed to assess the risk factors and case fatality of aspergillosis and mucormycosis in COVID-19 patients. Incidence of aspergillosis in critically sick patients that included both intensive care unit patients and mechanically ventilated patients of COVID-19 has also been calculated. This study highlighted the importance of prevention and early screening of fungal infections in severe cases of COVID-19 as this lethal disease has high morbidity and mortality. Repeated surgical interventions are required to remove infected tissue which causes disfigurement and mental trauma.

The mean age of cases with mucormycosis was 56 years. This result is similar to other studies.[45] The number of males is more than females. This finding is consistent with previous studies but the exact cause of this gender disparity is unknown.[46,47]A retrospective study in Mexico has shown more male patients with mucormycosis. There are more males in this study as severe COVID-19 and mucormycosis are generally more common in males.[48]

Diabetes was the most common risk factor found in other systematic reviews of mucormycosis.[47-49] Diabetes is an immunocompromised state and its prevalence is high across the globe.

Table II: Incidence of aspergillosis in critically sick patients of COVID-19.

Study Name	Study design	Sample size (n)	Incidence (n) %
Dellière S, *et al*. 2021[28]	Retrospective Cohort	366	21 (5.7%)
Versyck M, *et al*. 2021[29]	Cohort	54	2 (3.7%)
Gouzien L, *et al*. 2021[30]	Retrospective Cohort	53	1 (1.8%)
Bedini A, *et al*. 2021[31]	Retrospective Cohort	53	5 (9.4%)
Lahmer T, *et al*. 2021[32]	Cohort	32	11 (34%)
Pintado MV, *et al*. 2021[33]	Cohort	83	16 (19.2%)
van Arkel A , *et al*. 2021[34]	Cohort	31	8 (25.8%)
Bartoletti M, *et al*. 2020[35]	Cohort	185	30 (16.2%)
Machado M, *et al*. 2021[36]	Prospective Study	239	8 (3.3%)
Total		1096	102 (9.3%)

Table III: Number of cases who died due to aspergillosis in COVID-19.

Study	Total number of cases n	Number of cases who died n (%)
Nasir N, *et al.* 2021[37]	9	4 (44.4%)
Lai CC, *et al.* 2021[38]	34	22 (64.7%)

Kariyawasam RM, *et al.* 2021[39]	182	91 (50%)
Chong WH, *et al*. *202140*	192	94 (48.9%)
Pintado MV, *et al*. 2021[33]	16	5 (31.2%)
Apostolopoulou A, *et al.* 2021[41]	85	46 (54.1%)
Salmanton-Garcia J, *et al*. 2021[42]	186	97 (52.1%)
Abdalla S, *et al*. 2021[43]	2	2 (100%)
Alobaid K, *et al*. 2021[44]	2	2 (100%)
Total	708	363 (51.2%)

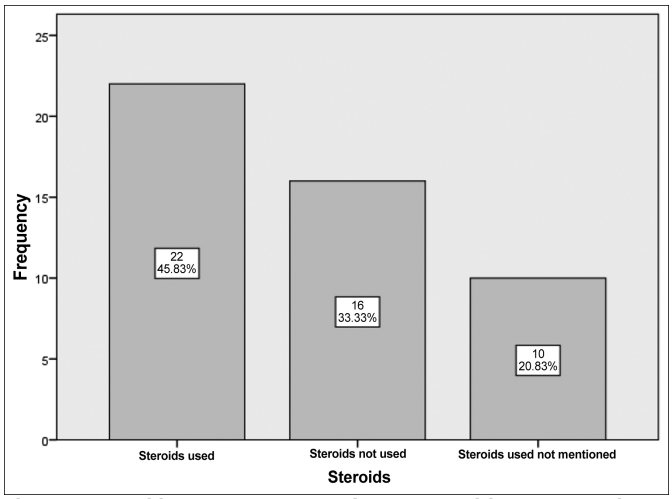

Figure 2: Steroid use among cases of COVID-19 with mucomycosis.

History of steroid use was fairly common among respondents of this study. Glucocorticoid-induced immunosuppression may be responsible for increased fungal infections.[50] Rhino orbital mucormycosis was the most common site in cases.[51] The combined case fatality in this study was found to be 52%. The mortality of pulmonary mucormycosis is slightly higher. A study done has demonstrated mortality of 57%. Another systematic review on mucormycosis has shown 67% survival with antifungal medications and surgery.[40] This study has reported higher mortality (52%). This may be because cases of mucormycosis have COVID-19 infection as well which has resulted in higher case fatality.

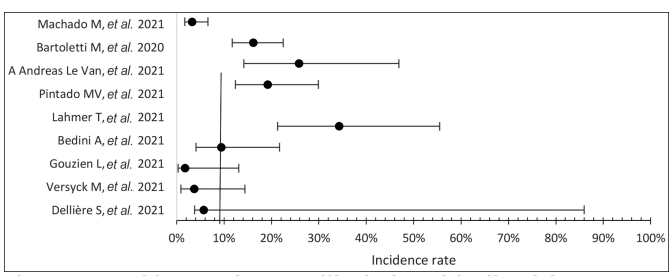

Figure 3: Incidence of aspergillosis in critically sick COVID-19 Patients.

Aspergillosis has a higher incidence in critically sick COVID-19 patients. That demands early screening. The combined incidence was found to be 9.3% with a range of 1.88% to 25%.

In another systematic review, the incidence was found to be 13.5%.[40] This may be because in this study both mechanically ventilated and not mechanically ventilated Intensive Care Unit (ICU) patients were included. The average case fatality was found to be 51.2%. Another systematic review has calculated the case fatality of aspergillosis to be 58%.[52] The risk factors of aspergillosis were diabetes, hypertension, steroid use, hypertension, heart disease, chronic obstructive pulmonary disease, malignancies, and chronic kidney disease.

The limitations of this study are that it has covered comorbidities and case fatalities. Treatment, management, and diagnosis options were beyond the scope of this article. Quality assessment of articles (case reports and case series) on mucormycosis in COVD-19 cases was not accessed due to their limited number. The strengths of this study are that it is a systematic review with a thorough data search. It has covered two lethal fungal infections which have shown increased prevalence since the COVID pandemic. The most common risk factor was diabetes. Health education and lifestyle modifications should be promoted to halt the rise in diabetes.

CONCLUSION

Case fatality from aspergillosis and mucormycosis in Covid-19 cases is quite high. Diabetes is the most common comorbidity in the cases of COVID-19 developing mucormycosis or aspergillosis. The incidence of aspergillosis in critically sick COVID cases is around 9.3%. Early screening and prophylactic antifungals can improve the prognosis of this disease.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SA: Carried out the conception and design of the research, Screening of articles and data extraction, analysis, and interpretation.

MN: drafted the manuscript and screening of articles was done with data extraction and analysis.

All authors approved the final version of the manuscript to be published.

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