




A Study on Enumeration of Factors Prone to the Development of COVID-19-Associated Mucormycosis

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Abstract

Background Patients with pre-existing chronic medical conditions with altered immunity are prone to COVID-19-associated mucormycosis (CAM).

Objective In this study, our objectives were to identify the risk factors that increase the chances of developing CAM and to determine the severity of the risk factors of CAM. Thereby, we can optimize the modifiable risk factors for developing CAM in coronavirus disease 2019 (COVID-19) patients. For instance, better control of blood glucose levels in COVID-19 patients can decrease the risk of developing CAM.

Materials and Methods The data was collected retrospectively from 1000 COVID-19 infected patients, above the age of 18 years during the time period of March 2021 to August 2021, in which 86 patients had confirmed CAM.

Statistical Analysis Binary logistic regression and curve estimation analysis were performed using SPSS software version 29 for identifying the associated risk factors of CAM with the significance of *p*-value less than 0.05.

Results Factors such as severe inflammation (*p* = 0.048), high dose of steroid administration (*p* = 0.005), increasing age (*p* < 0.001), and prolonged hospital stay (*p* < 0.001) were statistically proven to be significant risk factors, associated with CAM.

Conclusion Increasing age, severe inflammation, high dose of steroid administration, and prolonged hospital stay have association with occurrence of CAM.

Keywords

- ▶ CAM
- ▶ hypoxia
- ▶ increasing age
- ▶ hyperglycemia
- ▶ inflammation
- ▶ steroids

Introduction

Coronavirus disease 2019 (COVID-19) outbreak was first witnessed in Wuhan in November 2019, which has later become a global pandemic since 2020.¹ The second wave of pandemic has severely affected several countries around the world and India is one among them. The disease has been related with various symptoms like, cough, fever, fatigue, shortness of breath, and loss of taste and smell.² Patients with known comorbid conditions like uncontrolled diabetes mellitus, hypertension, and coronary artery dis-

ease had severe COVID-19 manifestations. Along with these comorbidities, if the patients have immune compromised conditions, compromised pulmonary function, or on invasive mechanical ventilator support, then they are highly vulnerable for developing secondary infections.³ Mucormycosis, a deadly invasive fungal infection, which is caused by molds called mucormycetes, leads to infarction and necrosis of a variety of end-organ host tissues.^{2,4} COVID-19-associated mucormycosis (CAM) can be fatal if not treated. It affects various parts such as sinuses, eyes, face, and brain. Patients who are immunocompromised, solid organ

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transplant recipients, with diabetes mellitus, on prolonged corticosteroid use, have neutropenia, and hematological malignancies are vulnerable to CAM infection. CAM possesses a major concern pertaining to public health significance owing to high fatality rate. The incidence of CAM reached 8% in leukemia patients, 54 to 76% in diabetic population, and 25% in usage of corticosteroids (prednisolone, methylprednisolone, dexamethasone).^{5,6} Although steroids are found to reduce COVID-19-related inflammation and lung injury,⁷ steroids in high dose prescribed for a longer duration suppress human's immunological system, making them more vulnerable to CAM in addition to hyperglycemia, that is, increased blood glucose levels, a common side effect of steroid, which serves as a classic environment for the growth of Mucorales.^{5,8,9} The spectrum of CAM involves rhino-orbital cerebral, pulmonary, disseminated, cutaneous, gastrointestinal, and disseminated forms.^{9,10} The mortality rate of each type is as follows: cutaneous mucormycosis of 16%, rhinocerebral mucormycosis of 67%, pulmonary mucormycosis of 83%, and 100% of disseminated gastrointestinal mucormycosis.⁵ Mucormycosis is treated with surgery in most of the cases initially followed by antifungal medications. Because of the high mortality rate, early detection and recovery from predisposing factors are in need of the hour. Antifungal drug liposomal amphotericin B, a first-line treatment, is known as the standard gold drug for CAM.¹¹ In this study, we aimed to analyze the concerned risk factors causing CAM.

Materials and Methods

This single-center, retrospective, observational study included patients diagnosed with COVID-19 infection between the months of March 2021 and August 2021 who are above the age of 18 years. The study was performed in accordance with Declaration of Helsinki. The data regarding COVID-19 infection and CAM for the study was collected from our hospital medical record department and hospital information system.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS for Windows version 29 software (IBM Corp., Coimbatore, Tamil Nadu, India). The relation between the occurrence of CAM and the predictors such as increasing age, gender, comorbid conditions (systemic hypertension, diabetes mellitus, coronary artery disease, bronchial asthma, chronic kidney disease), high dose of steroid administration, hypoxia, ventilator support, severe inflammation, prolonged hospital stay, infection rate, and severity of COVID-19 lung injury were analyzed using binary logistic regression. Severity of COVID-19 lung injury was observed by the parameters such as "covid19 reporting and data system (CORADS) score and chest CT severity score (CTSS)." Similarly, the parameter "elevated white blood cell (WBC) count" indicated the infection rate, the parameter "increased level of c-reactive protein (CRP)" indicated severe inflammation, and the parameter "increased hospitalization of above 14 days" indicated prolonged duration of hospital stay. Another statistical method,

curve estimation analysis, was performed to find out the relation between increasing age and occurrence of CAM. The acceptable significance of relation between the predictors and occurrence of CAM is observed with a *p*-value of less than 0.05.

Results

In total 1,000 COVID-19 infected patients were included for descriptive and statistical analysis. The descriptive analysis for baseline characteristics of COVID-19 infected patients was mentioned in ►Table 1. Majority of the population were male. Nearly 65% of the population were patients below 60 years of age. The most common comorbidity among the patients was diabetes mellitus, followed by systemic hypertension. From the steroids administered COVID-19 patients, 98% were given with methylprednisolone.

Eighty-six out of 1,000 COVID-19-infected patients were diagnosed with CAM; that is, the incidence of CAM in our study was only 8.6%. The types of CAM were mentioned in ►Table 2.

CAM was usually treated with both antifungals and surgery. The most common antifungals prescribed were liposomal amphotericin B followed by posaconazole. The surgeries that had been done commonly was endoscopic debridement followed by maxillectomy. The treatment of CAM was mentioned in ►Table 3.

Using various independent variables such as increasing age, gender, comorbid conditions (systemic hypertension, diabetes mellitus, coronary artery disease, bronchial asthma, chronic kidney disease), high dose of steroid administration, hypoxia, ventilator support, severe inflammation, prolonged hospital stay, infection rate, severity of COVID-19 lung injury, and dependent outcome variable, that is, occurrence of CAM, the forward stepwise (likelihood ratio) method of binary logistic regression analysis was performed and the results were shown in ►Table 4.

At the end of binary logistic regression, few independent variables such as increasing age, gender, comorbid conditions, severity of COVID-19 lung injury, and infection rate were excluded since they were insignificant. The other independent variables such as severe inflammation (*p*-value = 0.048), high dose of steroid administration (*p*-value = 0.005), and prolonged hospital stay (*p*-value ≤ 0.001) were proven statistically significant. The significant risk factors were positively correlated.

The predicted probability of occurrence of CAM versus change in deviance of risk factors was graphically represented in ►Fig. 1. Similarly, the predicted probability of occurrence of CAM versus analogue of Cook's influence statistics was graphically represented in ►Fig. 2. Cook's distance is proposed to measure the effect of excluding any specific observation on the parameter estimates. Cook's gives the value of *D*, *D* > 1 resembles predisposing factors are influential in causing CAM.

Also, the predictor variable, increasing age, was separately estimated using curve estimation analysis to determine its significance showed in ►Table 5.

The linear model states that the development of CAM was equal to (−0.034) + (0.002 X age). The quadratic model states

Table 1 Baseline characteristics of COVID-19-infected patients

Parameters	Observation (n = 1,000)
Gender	
Male	645 (64.5%)
Female	355 (35.5%)
Age	
18–39 years	155 (15.5%)
40–59 years	492 (49.2%)
60–74 years	283 (28.3%)
75–84 years	60 (6.0%)
≥85 years	10 (1.0%)
Comorbidities	
Diabetes mellitus	389 (38.9%)
Systemic hypertension	310(31.0%)
Coronary artery disease	59 (5.9%)
Bronchial asthma	41 (4.1%)
Chronic kidney disease	15 (1.5%)
Steroids	
Administered	849 (84.9%)
–Methylprednisolone	837 (83.7%)
–Prednisolone	13 (1.3%)
Dexamethasone	3 (0.3%)
CO-RADS score	4.74 ± 0.83
CTSS	8.90 ± 3.93
CRP	4.67 ± 5.89
WBC count	6.50 ± 2.80

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; WBC, white blood cell.

Table 2 Types of CAM

Parameters	Observation (n = 1,000)
Rhino orbital mucormycosis	73 (84.8%)
Sino nasal mucormycosis	10 (11.6%)
Rhino palatal mucormycosis	1 (1.2%)
Rhino sinus mucormycosis	2 (2.4%)

Abbreviation: CAM, coronavirus disease 2019-associated mucormycosis.

that the development of CAM was equal to $(0.140) + \{[-(0.005) \times \text{age}] - [(6.425 \times 10^{-5}) \times \text{AGE}^2]\}$.

According to the obtained linear and quadratic model B1 and B2 values, curve estimation showed increasing age significantly increases the risk of occurrence of CAM depicted in **Fig. 3**.

The descriptive analysis of the count of the significant risk factors in entire population as well as CAM diagnosed cases

Table 3 Treatment of CAM

Parameters	Observation (n = 1,000)
Antifungals administered	
Liposomal amphotericin B	65 (75.6%)
Posaconazole	42 (48.8%)
Isavuconazole	21 (24.4%)
Conventional amphotericin B	5 (5.8%)
Itraconazole	2 (2.3%)
Voriconazole	2 (2.3%)
Type of surgery done	
Endoscopic debridement	35 (40.7%)
Maxillectomy	30 (34.9%)
Functional endoscopic sinus surgery	29 (33.7%)
Exenteration	6 (7.0%)
Orbital decompression	5 (5.8%)
Sphenoidotomy	4 (4.7%)
Others	9 (10.5%)

Abbreviation: CAM, coronavirus disease 2019-associated mucormycosis.

Table 4 Estimation of predisposing factors by binary logistic regression

Parameters	p-Value
Ventilator support	0.973
Hypoxia	0.973
Severe inflammation	0.048 ^a
High and prolonged dose of steroid administration	0.005 ^a
Prolonged duration of hospital stay	<0.001 ^a

^aSignificant predisposing factors.

was listed in **Table 6**. The severity rate was classified as mild, moderate, and severe based on the scoring out of 12. Increasing age was given the scores of 1, 2, 3, and 4 based on age group of 18 to 59, 60 to 74, 75 to 84, and more than or equal to 85, respectively. Severe inflammation was given the scores of 0, 1, and 2 based on CRP values less than 0.6, 0.6 to 20, and more than 20, respectively. Prolonged hospital stay was given the scores of 1 and 2 based on hospitalization for more than 14 days and less than 14 days, respectively. The total steroid dosage of individual patients was calculated by summing up every prescribed doses cumulatively. Due to patient-specific factors, three different steroids such as methylprednisolone, prednisolone, and dexamethasone were administered in different individuals. Since majority of the population received methylprednisolone, the cumulative dose of methylprednisolone was calculated and in population those who received prednisolone and dexamethasone, its equivalent doses to methylprednisolone were identified and added up. High

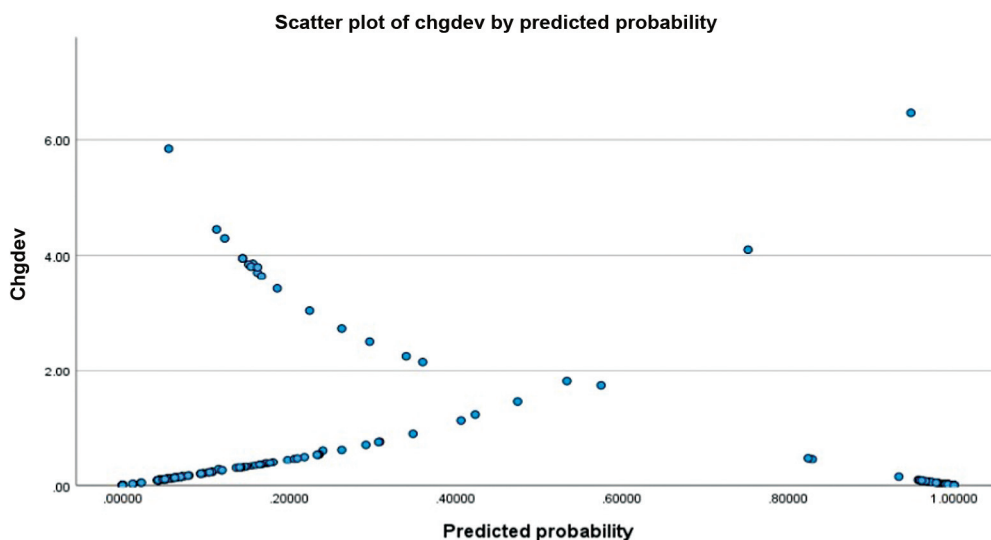


Fig. 1 Predicted probability versus change in deviance.

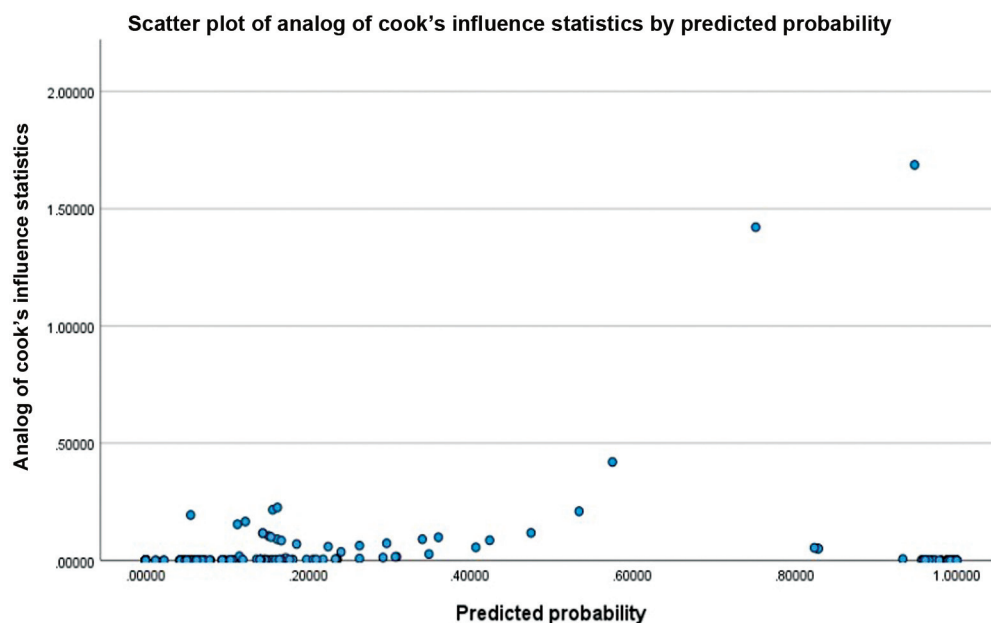


Fig. 2 Predicted probability versus analogue of Cook's influence.

Table 5 Estimation of increasing age by curve estimation

Equation	R square	Sig	Constant	B1	B2
Linear	0.011	<0.001	-0.034	0.002	
Quadratic	0.014	<0.001	0.140	-0.005	6.425×10^{-5}

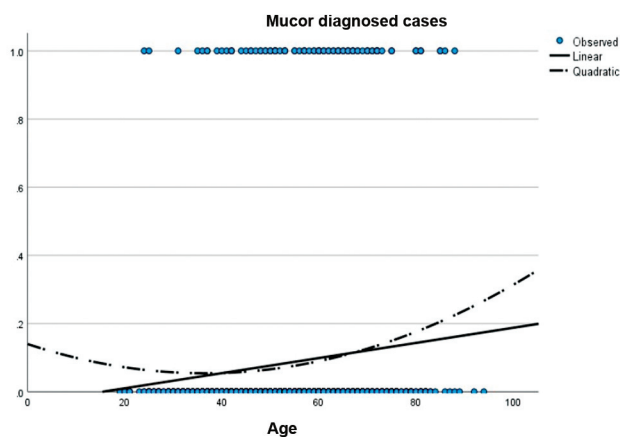


Fig. 3 Curve estimation of increasing age in relation with occurrence of coronavirus disease 2019-associated mucormycosis.

Table 6 Descriptive analysis of significant risk factors

Parameters	Observation (n = 1,000)	Observation (n = 86; CAM diagnosed)
Count		
1 risk factor	35 (3.5%)	0
2 risk factors	109 (10.9%)	1
3 risk factors	106 (10.6%)	6
4 risk factors	750 (75%)	79
Severity rate		
1–4 (mild)	750 (75%)	18
5–8 (moderate)	249 (24.9%)	67
9–12 (severe)	1 (0.1%)	1

Abbreviation: CAM, coronavirus disease 2019-associated mucormycosis.

dose of steroid administration was given the scores of 1, 2, 3, and 4 for less than or equal to 460 mg, 461 to 920 mg, 921 to 1,380 mg, and more than 1380 mg, respectively, based on total steroid dosage prescribed as mentioned above.

Discussion

Older age increases the risk of various factors such as multiple organ dysfunction, prolonged hospitalization, and increased use of medications like corticosteroids.¹ Similarly, we identified increasing age has a significant association with the occurrence of CAM in COVID-19 patients. Though high level of CRP has no association with occurrence of CAM,^{6,7,12} we observed elevated levels of CRP in majority of COVID-19-infected patients have significant association with occurrence of CAM, which is a contradictory finding to previously available literature. A lot of evidences suggest that improper, inappropriate, increased usage of corticosteroids leads to CAM.^{1,2,6,13} Likely, we observed that high and prolonged dose of steroid administration has a significant association with the occurrence of CAM. Older age passes on the in-

creased risk for prolonged hospitalisation.¹ Correspondingly, we noticed that prolonged hospitalization (>14 days) has a statistically significant association with the occurrence of CAM.

During first and second wave of COVID-19, hypoxia was observed in a minor CAM population.¹¹ Similarly, we observed that the risk factors such as hypoxia and need for ventilator support were not having significant correlation with occurrence of CAM. Review of literature for other parameters such as gender, infection rate (elevated WBC counts), and severity of COVID-19 lung injury (CO-RADS score and CTSS) does not show sufficient evidence as the risk factors of developing CAM. Yet we analyzed the above-mentioned parameters and we could not find any significant correlation or association with development of CAM.

A larger part of COVID-19 infected population had at least one comorbid condition like diabetes mellitus, systemic hypertension, coronary artery disease, chronic kidney disease, and bronchial asthma. Among that, uncontrolled diabetes^{2,14} and chronic kidney disease^{7,15} are highly related to the development of CAM, whereas systemic hypertension² and coronary artery disease² are not related to the development of CAM. There is a lack of studies about relation of bronchial asthma with the development of CAM. Yet we noticed that all the comorbid conditions such as diabetes mellitus, systemic hypertension, coronary artery disease, chronic kidney disease, and bronchial asthma have no association with occurrence of CAM.

Conclusion

Increasing age, severe inflammation, prolonged hospital stay, and high dose of steroid administration were the four statistically proven significant risk factors associated with CAM. Other risk factors taken into consideration such as gender, comorbid conditions (systemic hypertension, diabetes mellitus, coronary artery disease, bronchial asthma, chronic kidney disease), hypoxia, ventilator support, infection rate, and severity of COVID-19 lung injury were not statistically significant in our study population. Among 750 patients with all four significant risk factors, 79 developed CAM, which is 91.8% of the CAM diagnosed population. The incidence of CAM was 1 in 1 patient with severe rate of severity, whereas the incidence of CAM was 67 in 249 patients with moderate rate of severity.

Limitation of the Study

The limitation of our study is that we had a smaller number of CAM diagnosed cases (86) in a larger COVID-19 population (1,000). We need further studies with a greater number of CAM cases to extrapolate an accurate conclusion.

Ethics

The study obtained the human ethics permission from the Institutional Human Ethical Committee. The approval date and number are August 16, 2022 and IHEC # 208, respectively. Due to the retrospective study design, waiver of the informed consent was obtained.

Declaration

The study was performed in accordance with Declaration of Helsinki.

Author's Financial Disclosures

None.

Conflict of Interest

None.

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