Factors Associated with Mortality in Coronavirus-Associated Mucormycosis: Results from Mycotic Infections in COVID-19 (MUNCO) Online Registry

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Introduction

COVID-19-associated mucormycosis (CAM) is associated with high morbidity and mortality. Preliminary data from the Mycotic Infections in COVID-19 (MUNCO) online registry yielded 728 cases from May to September 2021 in four South Asian countries and the United States. A majority of the cases (694; 97.6%) consisted of a mucormycosis infection. The dataset allowed for the analysis of the risk factors for adverse outcomes from CAM.

Methods

Data Collection

- This was collected through a REDCap database[1] at http://covidmucor.com, as described below[2].
- Cases:
  - from **July 2021 to June 2022**
  - entered at discretion of the reporting physician.
- Case definition: histopathologically confirmed infection.
- Defined outcomes:
  - a full recovery or death at the 6-month time point.

Statistical analysis

- Calculated:
  - mean with standard deviation (SD)
  - median with an inter-quartile range (IQR)
  - frequencies (*n*, %).
- Association testing
  - Categorical: Chi-square or Fisher's exact test
  - Continuous: two-sample *t*-test or Wilcoxon test
- Probability of death: a multivariable logistic regression model was used

Background

- **CAM** emerged as a **significant** healthcare challenge, with more than **41,000 cases** reported as of September 2021 in India alone[3].
- We established an **online registry** (Mycotic Infections in COVID-19; **MUNCO**) to collect clinic–epidemiologic data on CAM online.

Purpose of the study: We sought to **evaluate the association of various factors associated with mortality in CAM.**

Results

- Included 341 patients total (>70% from India)
  - 258 completed treatment and survived
  - 83 patients died

(a) Baseline variables between group with recovery and deceased

Baseline Characteristic	Overall N = 341	Recovery N = 258	Death N = 83	*p* -Value #
Age in years	51.72 (13.02)	50.07 (12.70)	56.88 (12.72)	<0.001
Vaccinated	46 (15.3%)	34 (73.9%)	12 (26.1%)	0.71
Female	269 (79.4%)	204 (75.8%)	65 (24.2%)	0.79
Male	70 (20.6%)	52 (74.3%)	18 (25.7%)	
BMI kg/m^2	24.76 (4.11)	25.04 (4.19)	23.87 (3.73)	0.03
BMI Category:				
Underweight (<18.8)	15 (4.5%)	5 (33.3%)	10 (66.7%)	0.001
Normal (18.5 ≤ BMI < 25)	187 (56%)	144 (77%)	43 (23%)	
Overweight (25 ≤ BMI < 30)	105 (31.4%)	83 (79%)	22 (21%)	
Obese (≥30)	27 (8.1%)	22 (81.5%)	5 (18.5%)	
Comorbidities:				
Hypertension	72 (21.1%)	50 (69.4%)	22 (30.6%)	0.17
DM	286 (83.9%)	208 (72.7%)	78 (27.3%)	0.004
DM with ketoacidosis	11 (3.2%)	3 (27.3%)	8 (72.7%)	0.001
Cancer	1 (0.3%)	0 (0%)	1 (100%)	0.08
Organ Transplant	7 (2.1%)	5 (71.4%)	2 (28.6%)	0.79
IDU	4 (1.2%)	1 (25%)	3 (75%)	0.05
HIV+	1 (0.3%)	1 (100%)	0 (0%)	0.57
Asthma	3 (0.9%)	2 (66.7%)	1 (33.3%)	0.72
Laboratory values:				
CRP mg/L	54.3 (22.6–98.5)	40.2 (18.0–69.6)	85.1 (47.0–118.7)	<0.001
Ferritin ug/L	509 (306–931)	359.5 (234–578)	763 (372.9–1174)	<0.001
A1c%	8.8 (7.4–10.9)	8.0 (6.9–10.0)	9.6 (8.3–11.8)	<0.001
Days from COVID-19 diagnosis to mucor	20 (14–30)	21 (15–30)	17 (11–27)	0.01
Corticosteroid Treatment	292 (85.6%)	219 (75%)	73 (25%)	0.49
Dose, prednisone equivalent	50 (40–53.3)	50 (40–53.3)	53.3 (50–100)	<0.001
Type: Dexamethasone	132 (56.2%)	101 (76.5%)	31 (23.5%)	0.43
Methylrednisone	81 (34.5%)	56 (69.1%)	25 (30.9%)	
Prednisone	22 (9.4%)	15 (68.2%)	7 (31.8%)	
Treatment duration 10+ days	124 (52.1%)	98 (79%)	26 (21%)	0.03

Figure 1a: Baseline Characteristics

	Estimated Odds Ratio	*p*-Value
Patient age, years	1.04 (1.02, 1.07)	0.001
Azithromycin treatment	0.99 (0.49, 2.03)	0.76
Zinc treatment	0.76 (0.37, 1.57)	0.46
History of DM	3.47 (1.01, 11.93)	0.02
BMI, kg/m^2	0.90 (0.82, 0.98)	0.03
Steroid treatment *Ref: no steroid treatment*	1.67 (0.68, 4.12)	0.22
Known ICU stay *Ref: no known ICU stay*	1.50 (0.70, 3.25)	0.16
Days to mucor *(continuous)*	0.98 (0.96, 1.00)	0.15
Location of mucor: Sinus *Ref: not sinus*	0.23 (0.09, 0.57)	0.001
Ophthalmic *Ref: not ophthalmic*	0.87 (0.45, 1.69)	0.61
Cerebral *Ref: not cerebral*	10.96 (4.93, 24.36)	<0.0001

DM: diabetes mellitus; BMI: body mass index; ICU: intensive care unit.

Figure 2: Logistic Regression results for the probability of death

Outcomes

- 83 patients died due to CAM (24.3%)
  - Age of non-survivors was 6.8 years higher
  - non-survivors had a lower BMI (-1.14)
  - Non-survivors were treated with a higher median daily dose of prednisone (+3mg)

Conclusion

- Significant association with **increased risk** of death:
  - Diabetes (mucormycosis)
  - Lower BMI
  - Cerebral disease had much higher odds for death.
    - CNS extension in 21–50% of CAM cases
- **No association** with poor survival:
  - Corticosteroid treatment dose or duration
  - Use of zinc
- Possible confounding factors
  - Time to a CAM diagnosis was shorter in non-survivors as compared to survivors

Limitations

- potential selection bias
  - differing locations have differing access to care
- lack of comparable registry data for an external validation
- lack of a separate verification for the integrity of data at the entry point
- lack of complete follow-up information.

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