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Identifying Independent Predictors of Mortality in COVID-19 Patients with Mucormycosis

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Coronavirus disease 2019 (COVID-19) may lead to immunosuppression, leaving patients vulnerable to secondary invasive fungal infection like mucormycosis. The present study aimed to determine whether there are any risk factors associated with mortality in mucormycosis among COVID-19 patients. Patients with COVID-19 diagnosed with mucormycosis who received treatment at University Hospitals were included in the study. Complete blood count (CBC), glycated hemoglobin (HBA1c), C-reactive protein (CRP), serum albumin level, creatinine, ferritin levels, lactate dehydrogenase (LDH), D-dimer and histopathological observations were performed for all participants' specimens. The number (N) of patients included in the study was 46. About 85 % (39/46) of patients had post-COVID-19 syndrome and the other 7 cases were in the active phase of the disease. CRP, serum ferritin, D-dimer, CRP/albumin ratio and CRP/absolute lymphocyte counts were statistically significant (P<0.05) within non-survivors as compared to survivors. After analysis of multivariate analysis that patients had oxygen support, while elevated CRP/albumin ratios were independent predictors of mortality in COVID-19 patients associated with mucormycosis. Mucormycosis can be caused by immunosuppression conditions associated with COVID-19 infection. Oxygen levels and C-reactive protein/albumin are independent predictors of mortality and morbidity in post COVID-19 patients.

Keywords: Mucormycosis; Outcome predictors; Prognostic markers; SARS-CoV-2.

The new form of the coronavirus called SARS-CoV-2 has been accused of causing COVID-19, which the World Health Organization declared a global pandemic in March 2020[1,2]. While the majority of COVID-19 patients develop a mild to moderate respiratory illness who recover without requiring specific medications, the severe variant of COVID-19 is likely to have serious impacts both in the elderly as well as in people with comorbidities[3]. In these individuals, the infection proceeds rapidly,

causing respiratory impairment and the possibility of acute respiratory distress syndrome (ARDS)[4].

COVID-19 patients with ARDS who require mechanical ventilation and are treated with high doses of corticosteroids, immunomodulators, interleukin antagonists, and broad-spectrum antibiotics are at a greater risk to developing fungal infections *i.e.,* aspergillosis, mucormycosis, mucosal candidiasis, candidemia, and pneumocystis jiroveci pneumonia (PJP)[5].

Mucormycosis is an acute angioinvasive illness caused by Mucor including Rhizopus, Absidia, Rhizomucor, and Cunninghamella fungi that belonging the Mucorales order[6,7]. Mucor is a saprophytic fungus that may be found in soil decomposing organic debris[7]. The airborne hyphae are inhaled and then settle in the upper or lower respiratory tract. However, mucormycosis is more common amongst people with impaired immune system[8].

This study aimed to predict mucormycosis associated with COVID-19 infection in hospitalized patients.

PATIENTS AND METHODS

In this retrospective cohort study, COVID-19 patients diagnosed with mucormycosis were included. The study was including both active and recovered COVID-19 patients from the period of May 2021 to December 2021. All patients were **e"** 18 years and received treatment in the Departments of Intensive Care Unit (ICU) of Internal Medicine and Otorhinolaryngology and Isolation at Zagazig University Hospitals, Egypt.

Eligible COVID-19 patients who were tested positive for mucormycosis underwent a full examination including previous medical history and chronic diseases such as diabetes mellitus (DM), hypertension (HTN) and chronic obstructive pulmonary disease (COPD), renal insufficiency, chronic liver disease and malignancy in addition to clinical examination along with blood pressure and oxygen saturation. The following laboratory tests were performed: CBC, HbA1c, CRP, serum creatinine, serum albumin level, serum ferritin, LDH and de-dimer.

The diagnosis of mucormycosis was based on Magnetic Resonance Imaging (MRI); T1 MRI with post gadolinium enhancement to evaluate inferior turbinate and T2 with fat suppression to evaluate orbits, intracranial extension and pterygopalatine fossa; preoperative endoscopy for evaluation of the vascularity of the nose and paranasal sinuses and histopathological illustration of fungal spores and non-septate hyphae surrounded by areas of necrosis and aggregates of inflammatory cells. Infection sites were classified as rhinosinusitis, nasopalatine, naso-orbital, rhinocerebral and rhino-orbito-cerebral mucormycosis. Histopathological specimens were stained with hematoxylin and eosin (H&E) and Periodic acid-Schiff (PAS) to detect fungal spores and non-septate hyphae surrounded by areas of necrosis and aggregates of inflammatory cells. The degree of necrosis, inflammation (as percentage of total area of tissue sampled and graded as mild and moderate to severe) and vascular invasion (present/absent) were assessed[9].

Treatment Regimen

Medical treatment

All patients received amphotericin derivatives; liposomal form (AmBisome) at a dose of 5 mg/kg or B-deoxycholate at a dose of 1:1.5mg/kg[10,11]. This was concurrent with other important considerations in medical management including strict blood glucose control in patients with diabetes and weaning off glucocorticoids.

Surgical intervention

Surgical debridement was performed under general anesthesia after good topical nasal preparation for 80.4% patients (N=37). Endoscopic debridement was performed for necrotic tissues of the nose and paranasal sinuses including inferior turbinate, medial maxillectomy and pterygopalatine fossa. Gel foam pledgets impregnated with amphotericin B solution were then applied to the nasal cavity after completion of the procedure and achievement of haemostasias. The patients (N=33) had orbital affection so they subjected to endoscopic orbital decompression; and of these, patients (N=5) underwent orbital exenteration. The patients (N=8) were also developed palatal affection and underwent resection of the palate. Patients were clinically evaluated after surgery and endoscopy.

Outcome Assessment

Clinical progression of all patients with any sign or symptom, severity of previous symptoms, and exacerbation of symptoms, needed

mechanical ventilation and development of shock, sepsis or disseminated intravascular coagulation (DIC) were assessed. Clinical improvement was demonstrated through resolution as well as a general regression in severity of previously reported signs or symptoms. Global response to the main efficacy endpoint was rated as success when the patient was alive and improving according to clinical and radiographic assessment or failing if the patient was dead or progressing according to clinical and radiographic assessment.

Statistical analysis

The collected data were analyzed using the SPSS (Statistical Package for Social Science) version 20 and NCSS 12, LLC, United States. The Shapiro Walk test was used to determine data distribution. Frequencies and relative percentages were used to describe qualitative data. The difference between qualitative variables was calculated using the Chi square test (÷2) and Fisher exact. The median and range were used to express quantitative data. For non-normally distributed data, the Mann Whitney test was employed to quantify the difference between quantitative variables in two groups. The receiver operating characteristic (ROC) curve was created to allow for the selection of test result threshold values as well as the comparison of various testing methods. Univariate and multivariate logistic regression analysis models were done. All statistical comparisons were two-tailed (software version), with a *P*: d" 0.05 reflecting a significant difference[12].

Ethical approval

Official permission was obtained from the Institutional Review Board (IRB) of the Zagazig Faculty of Medicine (Letter N: ZU-IRB #7055/25-7-2021); and a written informed consent was obtained from all enrolled patients after describing the aim of the study and ensuring privacy and confidentiality. The research was carried out in accordance to the World Medical Association's Code of Ethics for Human Studies (Declaration of Helsinki).

RESULTS

Patients (N=46) were included in the study with mean age of 60 years (range: 45-73); and 19 patients (41.3%) were male. Past medical history showed that 27 cases (58.7%) were known with DM, 30.4% recently discovered DM, one case (2.2%) with COPD, 5 (10.9%) with cerebrovascular disease, 3 cases (6.5%) with renal insufficiency and two cases (4.3%) with chronic hepatic disease. No patient had a past history of mucormycosis prior to infection with SARS-CoV-2. Meanwhile, 39 cases of the total 46 of patients (84.8%) had post-COVID-19 syndrome; and the other 7 patients were in the active phase of the disease. Not all of the seven patients in the active phase survived (Table 1).

Comparison between survivors and non-survivors with respect to clinical features as well as pre-existing conditions for patients revealed that several clinical manifestations (Figure 1) including the following: Disturbed consciousness, nasal congestion, black lesions on nose or mouth, dyspnea and cutaneous ulcers or blisters appeared in higher percentage in non-survivors with statistically significant differences (*P*: 0.001, 0.023, 0.013, <0.001, and 0.005, respectively). Renal impairment was also significantly higher in non-survivors (*P*: 0.033). Patients who were shocked upon admission to hospital and who required oxygen support were more likely to die (*P*: 0.033 and 0.001, respectively). Regarding the patients' COVID-19 status at the time of mucormycosis diagnosis, cases with active COVID-19 infection were more likely to have a poor outcome compared to those who recovered (Table 1).

The most common site of infection was the rhino-orbital form followed by the nasal and then the orbital types with no significant difference between the groups. On the other hand, a significant difference between survivors and non-survivors regarding treatment received for mucormycosis with the best outcome was found in patients who underwent surgical debridement in addition to treatment with amphotericin B rather than receiving amphotericin B alone (*P*: 0.001). The most commonly recognized organism was mucor species. Moreover, necrosis, inflammation and vascular invasion were significantly more abundant in non-survivors than in survivors with *P* value of 0.001, <0.001 and <0.001, respectively (Table 2; Figures 2,3).

With respect to laboratory investigations, the ratios of CRP, serum ferritin, D-dimer, CRP-to-albumin (CRP/Alb) and CRP to absolute

Table 1. Comparison of clinical characteristics between patients with invasive mucormycosis according to their clinical outcome after diagnosis

		Outcome							
		SurvivorsN=27		Non-SurvivorsN=19		Total N=46			
		N	%	N	%	N	%	P-value	
Age, years		56 (45-71)		62 (54-73)		60 (45-73)		0.072	
Sex	Male	14	51.9%	5	26.3%	19	41.3%	0.083	
	Female	13	48.1%	14	73.7%	27	58.7%		
Known Diabetic		17	63.0%	10	52.6%	27	58.7%	0.483	
Recently discovered		6	22.2%	8	42.1%	14	30.4%	0.149	
DM	Known Diabetic	17	63.0%	10	52.6%	27	58.7%	0.274	
	Recently discovered	6	22.2%	8	42.1%	14	30.4%		
	No DM	4	14.8%	1	5.3%	5	10.9%		
COPD		0	0.0%	1	5.3%	1	2.2%	0.228	
Cerebrovascular disease			2	7.4%	3	15.8%	5	10.9%	0.368
Renal insufficiency		0	0.0%	3	15.8%	3	6.5%	0.033	
Chronic hepatic disease			1	3.7%	1	5.3%	2	4.3%	0.798
COVID	Active	0	0.0%	7	36.8%	7	15.2%	0.001	
	Recovered	27	100.0%	12	63.2%	39	84.8%		
Fever		0	0.0%	2	10.5%	2	4.3%	0.085	
Headache		21	77.8%	17	89.5%	38	82.6%	0.303	
Confusion or coma		0	0.0%	7	36.8%	7	15.2%	0.001	
Unilateral facial swelling			19	70.4%	16	84.2%	35	76.1%	0.279
Nasal or sinus congestion			18	66.7%	18	94.7%	36	78.3%	0.023
Black lesion on nose or mouth			0	0.0%	4	21.1%	4	8.7%	0.013
Cough		0	0.0%	2	10.5%	2	4.3%	0.085	
Dyspnea		1	3.7%	9	47.4%	10	21.7%	<0.001	
Chest pain		0	0.0%	1	5.3%	1	2.2%	0.228	
GI symptoms		0	0.0%	0	0.0%	0	0.0%		
Cutaneous ulcers or blisters			0	0.0%	5	26.3%	5	10.9%	0.005
Shock at hospital admission			0	0.0%	3	15.8%	3	6.5%	0.033
O2 Sat% RA	Not Needed	26	96.3%	9	47.4%	35	76.1%	0.001	
	Nasal Canula/Mask	1	3.7%	4	21.1%	5	10.9%		
	biBAP/MV	0	0.0%	6	31.6%	6	13.0%		
Use Of Steroid		27	100.0%	18	94.7%	45	97.8%	0.228	
Use Of Actemra (Tocilizumab)			0	0.0%	0	0.0%	0	0.0%	
Use Of Ivermectin		27	100.0%	18	94.7%	45	97.8%	0.228	

Quantitative data were expressed as Median (range) and compared using Mann Whitney test, while qualitative data were expressed as numbers and percentages and compared using Chi-square X2 test.

Table 2: Comparison of invasive mucormycosis data according to patient outcome after diagnosis

		Outcome						
		Survivors N=27		Non-Survivors N=19		Total N=46		
		N	%	N	%	N	%	*P*-value
Location of Mucor mycosis	Nasal/sinus	7	25.9%	2	10.5%	9	19.6%	0.155
	Nasal/sinus, Orbit	9	33.3%	8	42.1%	17	37.0%	
	Nasal/sinus, Orbit, Cerebral	0	0.0%	1	5.3%	1	2.2%	
	Nasal/sinus, Orbit, Cerebral, Cutaneous	0	0.0%	4	21.1%	4	8.7%	
	Nasal/sinus, Orbit, Plate	1	3.7%	0	0.0%	1	2.2%	
	Nasal/sinus, Orbit, Cutaneous	0	0.0%	1	5.3%	1	2.2%	
	Nasal/sinus, Plate	2	7.4%	1	5.3%	3	6.5%	
	Orbit	5	18.5%	1	5.3%	6	13.0%	
	Orbit, Plate	2	7.4%	1	5.3%	3	6.5%	
	Plate	1	3.7%	0	0.0%	1	2.2%	
Treatment received for mucormycosis Isolatedorganism	Amphotericin B	1	3.7%	8	42.1%	9	19.6%	0.001
	Surgical debridement with Amphotericin B	26	96.3%	11	57.9%	37	80.4%	
	N/A	13	48.1%	15	78.9%	28	60.9%	0.081
	Mucormycosis	7	25.9%	2	10.5%	9	19.6%	
	Rhizopus	2	7.4%	2	10.5%	4	8.7%	
	Others	5	18.5%	0	0.0%	5	10.9%	
Necrosis	Mild	20	74.1%	4	21.1%	24	52.2%	0.001
	Moderate	1	3.7%	5	26.3%	6	13%	
	Severe	6	22.2%	10	52.6%	16	34.8%	
Inflammatory cells	Mild	20	74.1%	1	5.3%	21	45.7%	< 0.001
	Moderate	2	7.40%	8	42.1%|	10	21.7%	
	Severe	5	18.50%	10	52.6%	15	32.6%	
Angioinvasion	Present	4	14.8%	12	63.2%	16	34.78%	< 0.001
	Absent	23	85.2%	7	36.8%	30	65.22%	

Qualitative data were expressed as numbers and percentages and compared using Chi-square X^2 test.

lymphocyte count (CRP/ALC) were significantly higher in non-survivors than in survivors with *P*: value: 0.012, 0.013, 0.012, 0.015 and 0.007, respectively (Table 3; Figures 4,5).

ROC curve analysis revealed that CRP/ALC and CRP yielded the best accuracy for the prediction of mortality (cutoff >129.1 had an AUC of 0.735, cutoff >139 had an AUC of 0.72 respectively) with a sensitivity of 63.16, 73.68 respectively and a specificity of (85.19, 70.37 respectively), *P*: 0.002, 0.005, respectively. On the other hand, serum ferritin, CRP/Alb, ALC and PLR had lower AUC (0.717, 0.712, 0.577 and 0.565, respectively (Table 4; Figure 6).

The univariate analysis of predictors for outcome in COVID-19 patients infected

Table 3. Comparison of baseline laboratory values between patients with invasive mucormycosis according to their clinical outcome after diagnosis

	Outcome			
	SurvivorsN=27 Median (Range)	Non-SurvivorsN=19 Median (Range)	TotalN=46 Median (Range)	*P*-value
WBCs count	12.0 (4.4-30.0)	16.6 (3.2-28.7)	13.0 (3.2-30)	0.237
Lymphocytes	1.7 (0.2-3.4)	1.6 (0.1-3.0)	1.6 (0.1-3.4)	0.377
Hemoglobin	10.9 (8.0-15.4)	11.2 (6.6-14.4)	11.2 (6.6-15.4)	0.489
Platelet count	250 (108-430)	218 (57-646)	243 (57-646)	0.409
Creatinine	1.20 (0.30-3.20)	1.10 (0.50-5.70)	1.15 (0.30-5.7)	0.592
Albumin	3.10 (2.10-4.00)	3.03 (2.08-3.80)	3.07 (2.08-4)	0.695
CRP	118 (5-294)	181 (38-438)	138 (5-438)	0.012
Ferritin	600 (380-1107)	786 (27-1637)	655 (27-1637)	0.013
D-dimer	0.6 (0.5-0.6)	0.8 (0.7-1.5)	0.8 (0.5-1.5)	0.012
CK	39.05 (6-124)	85.75 (9.5-162)	39.05 (6-162)	0.667
ESR	58 (22-105)	88 (29-127)	70 (22-127)	0.055
PLR	147.7 (53.3-540)	167.5 (69.5-2010)	156.8 (53.3-2010)	0.455
CRP/Alb	38.60 (1.50-110.4)	71.6 (10.9-166.3)	43.85 (1.5-166.3)	0.015
CRP/ALC	72 (1.9-1115)	176.7 (12.7-930)	94.55 (1.9-1115)	0.007
HbA1C	10 (7-13)	9 (7-14)	10 (7-14)	0.961

Quantitative data were expressed as Median (range) and compared using Mann Whitney test

Table 4. The validity of baseline markers with area under the ROC curve (AUC) as a marker for poor outcome in patients with invasive mucormycosis

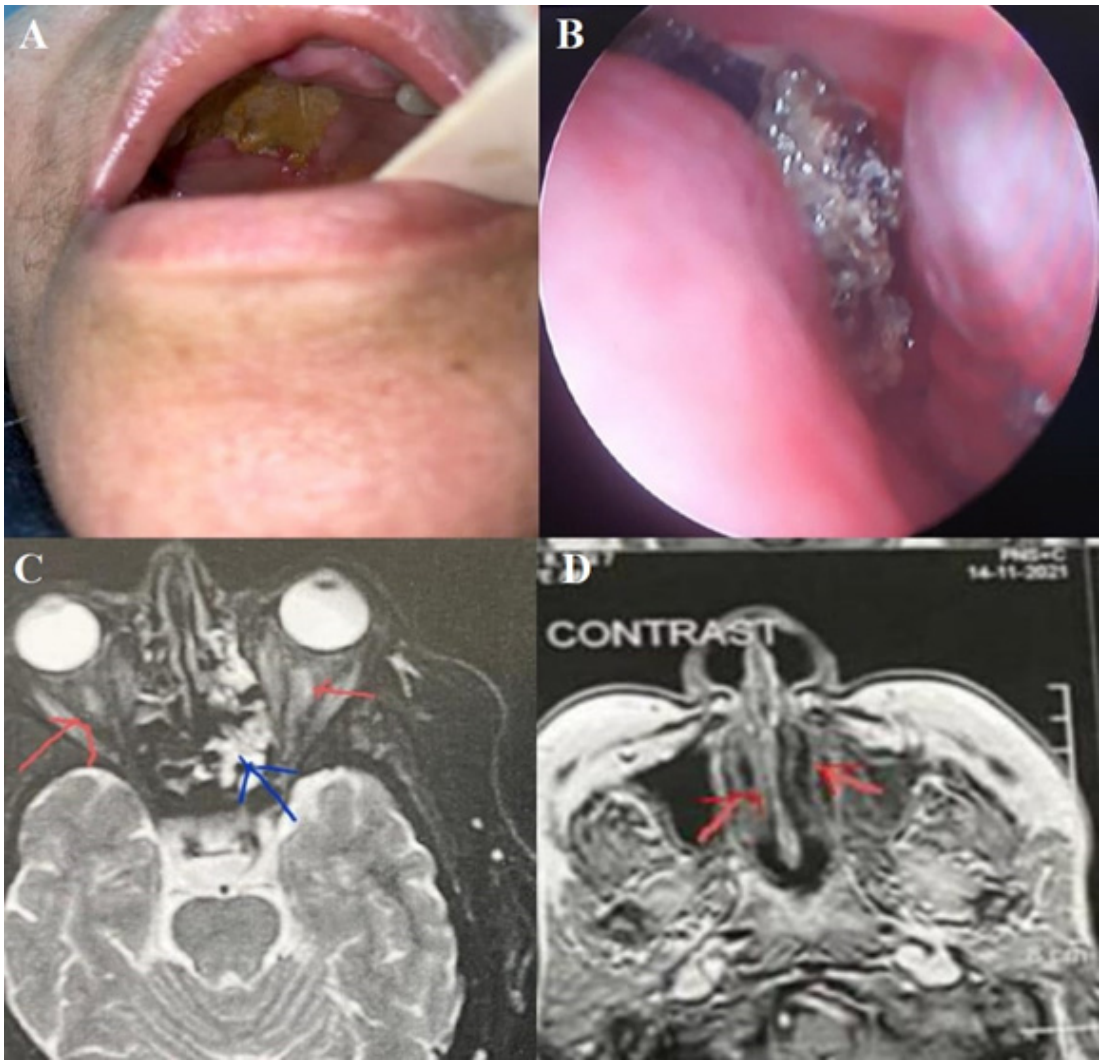
Marker	Criterion	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	AUC 95% CI	*P* Value
Ferritin	>778	68.42	92.59	86.7	80.6	0.717	0.021
		43.4 - 87.4	75.7 - 99.1	62.3 - 96.2	68.1 - 89.1	0.565 to 0.840	
CRP	>139	73.68	70.37	63.6	79.2	0.72	0.005
		48.8 - 90.9	49.8 - 86.2	48.0 - 76.9	63.3 - 89.3	0.568 to 0.842	
ALC	≤2.2	84.21	33.33	47.1	75	0.577	0.37
		60.4 - 96.6	16.5 - 54.0	39.0 - 55.3	48.3 - 90.6	0.423 to 0.721	
CRP/Alb	>44.2	73.68	70.37	63.6	79.2	0.712	0.008
		48.8 - 90.9	49.8 - 86.2	48.0 - 76.9	63.3 - 89.3	0.559 to 0.835	
CRP/ALC	>129.1	63.16	85.19	75	76.7	0.735	0.002
		38.4 - 83.7	66.3 - 95.8	53.3 - 88.8	64.1 - 85.8	0.584 to 0.854	
PLR	>156.7	63.16	59.26	52.2	69.6	0.565	0.465
		38.4 - 83.7	38.8 - 77.6	38.2 - 65.9	54.0 - 81.7	0.411 to 0.711	

The 95%CI: 95% confidence interval, Positive predictive value (PPV) and negative predictive value (NPV), Area under the ROC curve (AUC).

with mucormycosis showed that the significant predictors were the need for oxygen support, treatment received for mucormycosis and CRP/Alb while age, sex and serum ferritin were marginally statistically insignificant. In multivariate regression analysis, the need for oxygen support along with CRP/Alb was spotted as independent risk factor for poor outcome in our patients (Table 5).

DISCUSSION

Mucormycosis, initially identified by Paltauf in 1885, is a rare and fatal fungal infection that severely affects people with weakened immune systems [13]. Despite its low incidence ranging from 0.005 to 1.7 per million people, many cases have been reported recently during the coronavirus pandemic[14]. COVID-19 infection causes severe



(A) A female patient 48 years old with invasive fungal sinusitis with palatal necrosis.
(B) Endoscopic view of a female patient with necrosed left middle turbinate.
(C) T2 MRI axial cut showing hyperintensity in the left ethmoidal and sphenoidal sinuses denoting inflammatory mucosal reaction (blue arrow) with free orbital fat (red arrows).
(D) T1 MRI axial cut with postgadolinium enhancement of a female patient with invasive fungal sinusitis with black turbinate sign (red arrows) on both sides (lost enhancement due to necrosed inferior turbinate).

Fig. 1. Photomicrographs of some gross features of mucormycosis-patients with COVID-19 infections

lymphocytopenia in 85 percent of patients; since lymphocytes play an essential role in immune homeostasis, this leaves patients vulnerable to opportunistic co-infections, such as fungal infections[15]. Identification of factors associated with survival in patients with mucormycosis is essential in clinical practice and development of protocols for the upcoming management of patients with such diseases[16]**.**

84.8 percent (39/46) of patients in this study had post-COVID-19 syndrome. Similarly, Mishra et al[17] evaluated COVID-19 associated mucormycosis (CAM) in a tertiary medical institution in India and found that 65.6 percent of CAM patients had post-COVID-19 syndrome after they completely recovered from COVID-19 in terms of clinical assessment. The rhino-orbital variant of mucormycosis was the most prevalent in this study. This could be attributed to getting mucormycosis through contact with fungal spores in the environment e.g., inhalation of the spore from air. Furthermore, it was noted during surgical intervention that pterygopalatine fossa containing orbital vascular supply was the focus of infection. The rhino-orbital-cerebral type is the most prevalent in India, followed by the pulmonary and cutaneous variants[18]. However, in developed nations, the pulmonary type is the most common presentation[19].

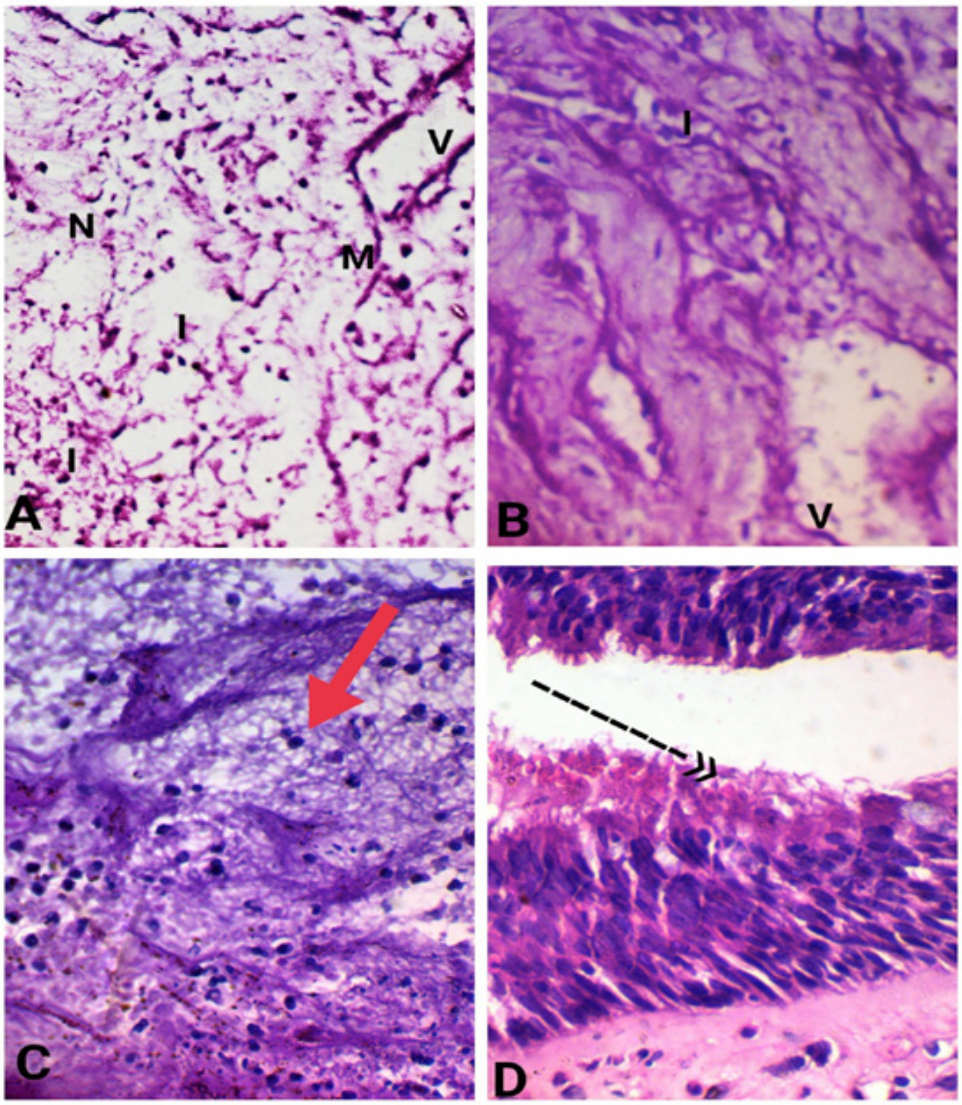
As Egypt ranked the tenth globally in the number of type 2 diabetic patients by the International Diabetes Federation (IDF) in 2021,

Table 5. Univariate and multivariate logistic regression of potential predictors of poor outcome (mortality) in patients with invasive mucormycosis

Covariates	Univariate		Multivariate	
	Sig.	RR (95% CI)	Sig.	RR (95% CI)
O2 sat% indicating support	0.003	5.37 (1.89-16.07)	0.046	8.1 (2.25-29.12)
CRP/Alb	0.019	1.02 (1.00-1.05)	0.045	1.1 (1.11-1.23)
Treatment received for mucormycosis	0.009	0.23 (0.08-0.69)	0.755	
Age	0.057	1.10 (1.00-1.20)	0.090	
Sex	0.088	0.33 (0.09-1.18)	0.072	
Ferritin	0.074	1.00 (1.00-1.00)	0.381	
Recently discovered DM	0.154			
Known Diabetic	0.484			
COPD	>0.999			
Cerebrovascular disease	0.379			
Renal insufficiency	0.999			
Chronic hepatic disease	0.799			
COVID-	0.999			
Fever	0.999			
Shock at admission	0.999			
Use of steroid	>0.999			
Use of ivermectin	>0.999			
Location of mucormycosis	0.95			
Histopathology	0.647			
WBCs count	0.218			
Lymphocytes	0.213			
Hemoglobin	0.432			
Platelet count	0.97			
Creatinine	0.407			
Albumin	0.831			
PLR	0.352			
CRP/ALC	0.165			

All variable with *P*-value <0.1 in univariate analysis were entered in multivariate regression model
O2 sat% indicating support and CRP/Alb were found to be independent risk factor for poor outcome in patients with invasive mucormycosis.

and suspected to be the ninth by 2045[20], it has been shown to be the most common co-morbidity in CAM, appearing in 89.1% in this study. The infection rate was 73.5% of cases in India[21] and 17% in Western nations[19]; also, in other literature review it was the most common risk factor for infection of mucormycosis[22]. In the study by Mishra et al[17], it was shown that 28 out of 32 patients (87.5%) who were infected with CAM had diabetes with poor glycemic control, as measured by a mean HbA1c of 9.06 percent upon admission. However, HbA1c was not as a dependent factor for estimation of glycemic control in this study, as most of patients were anemic and HbA1c was not documented in all of them.

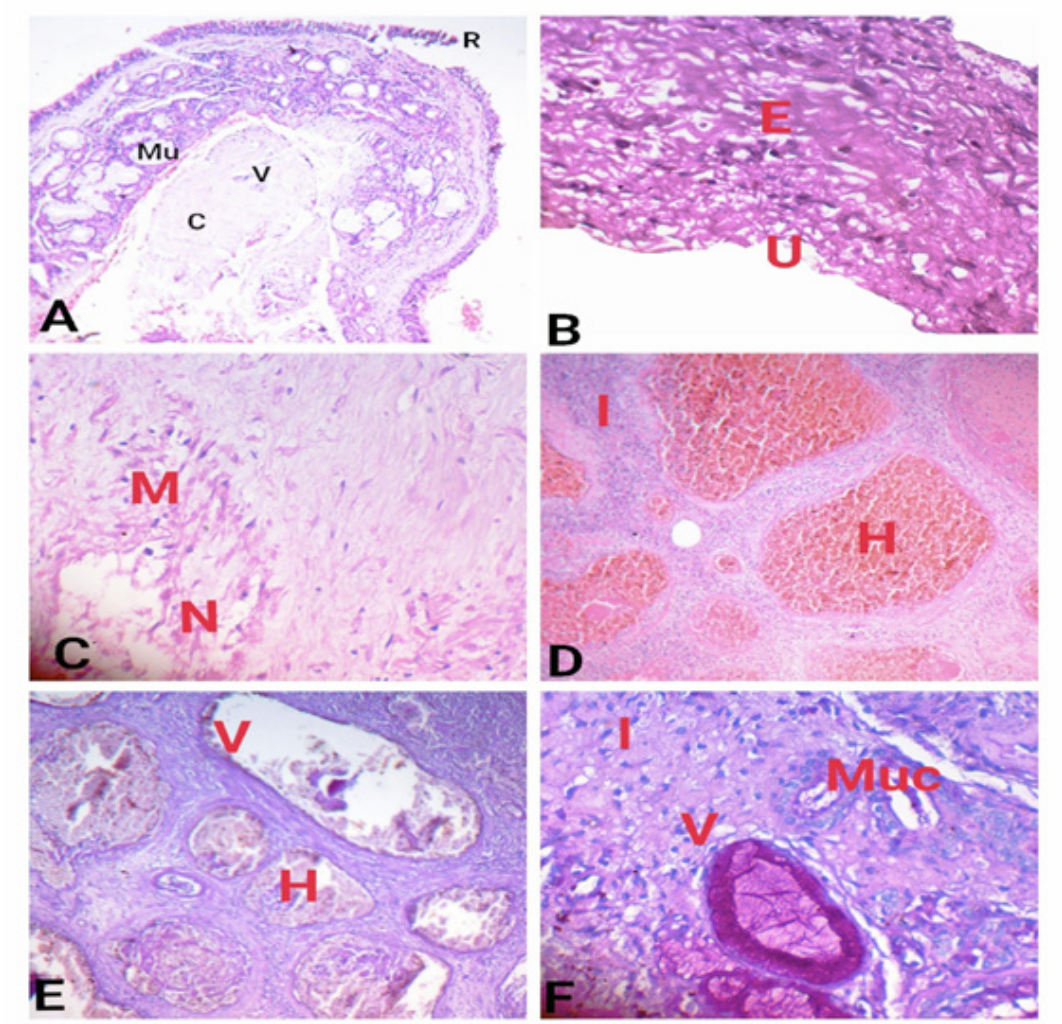


(A) Several fragments of fungal molds (M), angio-invasion (V) and necrosis (N) (×100/H&E).
(B) The sinus showing angio-invasion (V)& inflammatory infiltrate (I) (× 400/PAS).
(C) Severe eosinophilia (thick arrow) was distributed throughout the whole sinus mucosa (×400/PAS).
(D)The surface mucosal epithelium was relatively well preserved with Some attached fungal hyphae were observed on the surface mucosal epithelium (thin arrow) and the underlying connective tissue was heavily infiltrated with inflammatory cells (×400/H&E)

Fig. 2. Photomicrographs of mucormycosis-induced maxillary and ethmoid sinusitis

COVID-19 is usually linked with lymphopenia, which may be related to its severity[23]. In this study, 19.6% of the patients developed lymphopenia; also, Roushdy and Hamid[24] reported four cases with mucormycosis post-COVID-19 with relative lymphopenia. However, the relationship between lymphopenia and CAM needed further investigation.

Non-survivors had considerably higher serum ferritin levels than survivors. This is similar with results of Spellberg et al.,[16] who reported that greater serum ferritin levels were accompanied with significantly higher death rates. Kell et al.,[25] added that ferritin arises from damaged cells and can be raised significantly in response to inflammation and or variety of disease which may



(A): A case of nasal polyp showing ulcerative respiratory epithelium (R), with proliferating mucus glands (Mu), connective core (C) & vessels (V) (×100/H&E)
(B) Sinusitis with ulceration mucosa (U) & underlying inflammatory infiltration mainly eosinophils (E) & fungal hyphe (×400/PAS)
(C): Sinusitis showing fungal hyphe (M), necrosis (N), admixed with inflammatory cells (×100/H&E)
(D) Large vascular spaces filled with hemorrhage (H), necrosis & Inflammatory cells (I) (×100/H&E)
(E) Large vascular (V) spaces filled with hemorrhage (H) and fungal hyphe, necrosis & Inflammatory cells (×100/PAS)
(F) Vascular (V) spaces filled with hemorrhage and fungal hyphe, denotes angioinvasion (V), hyperplastic mucous glands (Mu) necrosis & Inflammatory cells(I) (×400/PAS).

Fig. 3. A case of mucormycosis -induced sinusitis showing

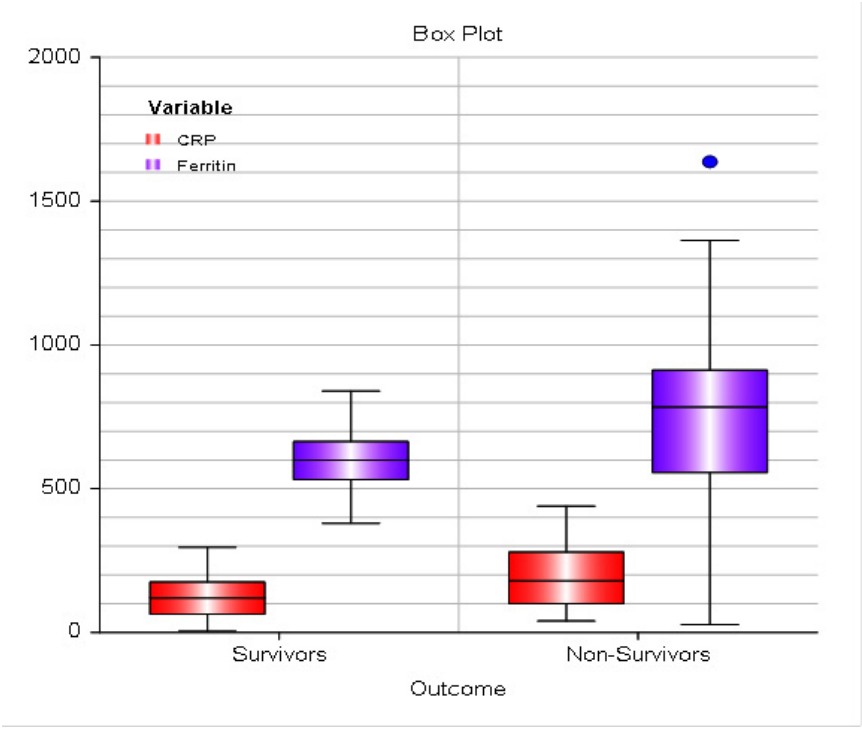


Fig. 4. Box-plot diagram represents the range of baseline inflamatory CRP and ferritin in the studied groups; the upper & lower line in each box represents the 75th & 25th percentile respectively while the line through each box indicates the median. Whiskers represent the range between the minimum and maximum values

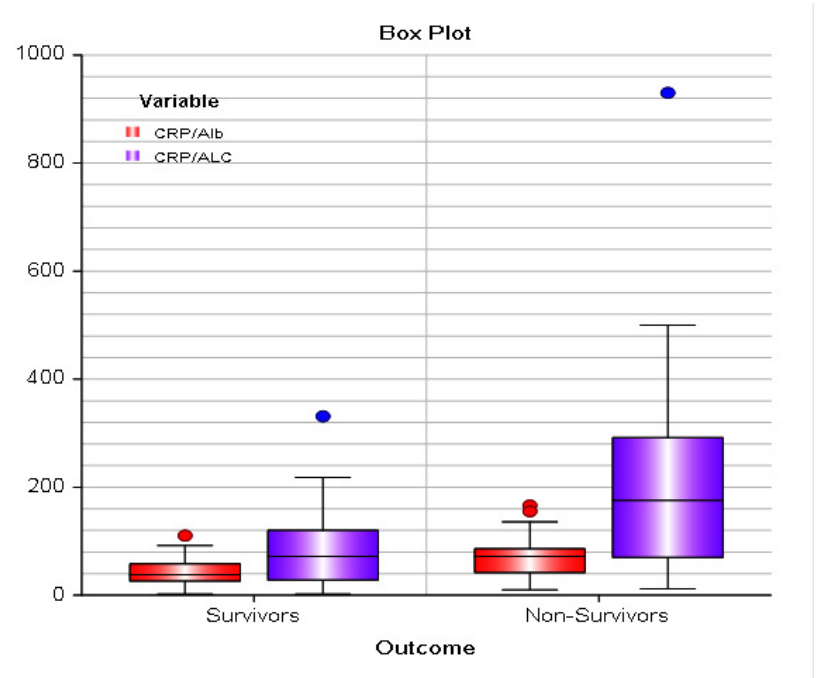


Fig. 5. Box-plot diagram represents the range of baseline inflamatory CRP/Alb and CRP/ALC in the studied groups; the upper & lower line in each box represents the 75th & 25th percentile respectively while the line through each box indicates the median. Whiskers represent the range between the minimum and maximum values

explain correlation of mortality to high serum ferritin level in this study. The mortality rate for patients with mucormycosis varies according to the site of infection, the cause, and the age at diagnosis of the disease[26]. The authors added that overall mortality rate is higher in malignancies and at old ages. It ranges from 35% in cases with no underlying pathology to 66% in diabetic patients and 66% in malignant tumors. The overall mortality in the current study was 19 out of 46 cases (41.3%).

Regarding histopathology results, Goel et al.,[9] and Luo et al.,[27] agreed with the results that angioinvasion was higher in immunocompromised patient. However, Castillo et al.,[28] disagreed with this and stated that patients presented with florid inflammation had a better prognosis.

Previous studies showed that rhino-orbital cases had a 24% death rate and rhino-cerebral cases had a 62% mortality rate[29]. The mortality rate in pulmonary mucormycosis was reported to be 80% by Tedder et al[30] and to be 29% by Lin et al[31].

In our study, patients undergoing combined medical-surgical therapy had a better prognosis when compared to those received medical therapy alone. Piromchai and Thanaviratananich emphasized the necessity of surgical debridement. They added that the appropriate time for treatment to achieve better results in these patients is within two weeks of the onset of symptoms[32]. In comparison to AmBisome monotherapy, Prakash and Chakrabarti [(33)], who studied the epidemiology of mucormycosis in India, also found that patients treated with a combination of AmBisome with surgical debridement of diseased tissue had a lower death rate. These results are consistent with worldwide statistics[34]. Muthu et al.,[35] found that combination medical-surgical treatment was associated with a substantially decreased risk of death in a meta-analysis of 79 trials that included 1544 participants with pulmonary and disseminated mucormycosis.

Lin et al[31] observed no statistically significant association between mortality and age, sex, DM, CKD, or WBCs of pulmonary mucormycosis. This discovery is in line with the findings of this study. Spellberg et al.,[16] also

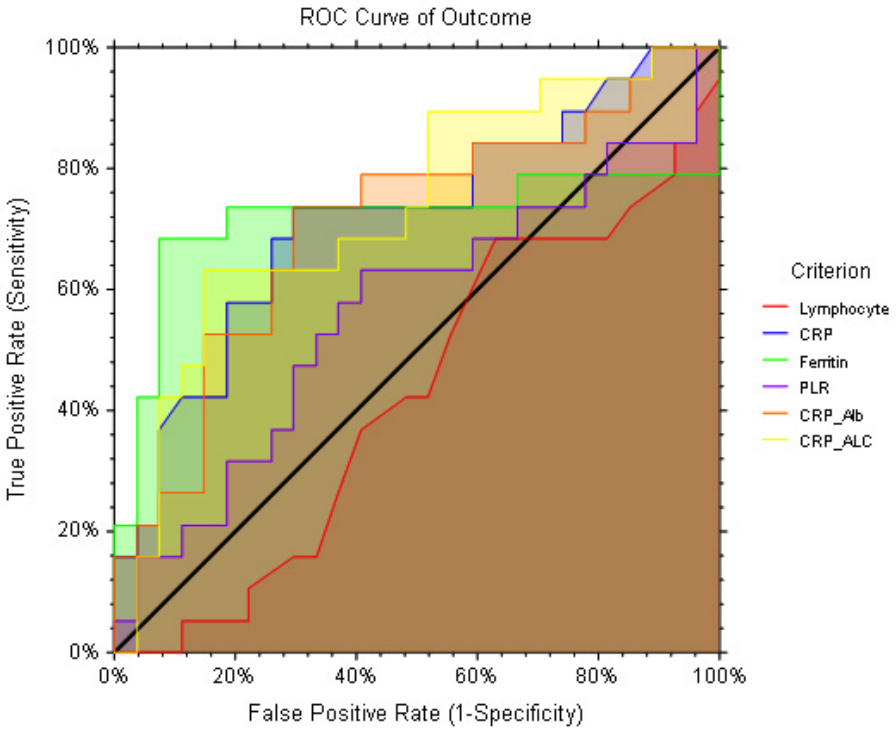


Fig. 6. The validity of baseline markers with area under the ROC curve (AUC) as a marker for poor outcome (mortality) in patients with invasive mucormycosis

reported that age and DM were not associated with mortality; however, neutropenia at enrollment was associated with increased mortality and DM was not associated with a greater mortality risk, which supports these previous findings that DM is not a predictor of outcome in mucormycosis.

In this study, multivariate analysis revealed that only the requirement for O2 support and CRP/Alb were the two independent predictors of death in CAM; however, Lin et al.,[31] found no link between mortality and the need for mechanical ventilation in 35 patients with pulmonary mucormycosis. This discrepancy may be attributed to the difference in sample size, timing of diagnosis, risk factors and site of mucormycosis. CRP/Alb has been used as an indicator of prognosis in various diseases. A study conducted by Karakoyun et al.,[36] CRP/Alb was a useful prognostic marker of hospital stay and mortality in hospitalized patients infected with COVID-19. Also, CRP/Alb was an independent risk factor for 30-day mortality rate in patients with COVID-19 in a study conducted by El-Shabrawy et al[37].

CONCLUSIONS

Present study showed that need of oxygen and CRP/Albumin ratios were independent prognostic factors of survival in COVID-19 patients infected with mucormycosis. Therefore, it is convenient to use these parameters, *i.e.,* oxygen and CRP/Albumin ratio in clinical practice to predict the outcome of patients.

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Contributions

Mohamed G Hamed, Ahmed Embaby, Shimaa Abdelmoneem, Alhoussein Alsayed AbdelAal, Amany Abd Al Badea, Mohammad Walaa, Ali Awad & Mai Ahmed Gobran: Conceptualization, methodology, statistical analysis, interpreting the results, designed the figures, investigation, performed patients' clinical assessment and follow-up as well as drafted this manuscript with help from Mohamad Walaa, Omnia Awwad, Doaa AbdElmonem & Abdelmonem A Hegazy. Mohamed G Hamed, Ahmed Embaby, Shimaa Abdelmoneem & Abdelmonem A Hegazy: Writing, Review & Editing, Nahla A Zaitoun, Mona Ahmed Abdelmaksoud & Alhoussein Alsayed AbdelAal were involved in planning, organization, supervision and reviewing of the work, and the final manuscript. Mai Ahmed Gobran, & Doaa AbdElmonem Data Curation, Measurements, Lab. and histopathologic analysis like CBC, blood smears, biopsy. All authors have reviewed and approved the manuscript.

Declaration of Interest

The authors declare that they have no competing interests.

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