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Original article

Survival in rhino-orbito-cerebral mucormycosis: An international, multicenter ID-IRI study

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ABSTRACT

Background: Mucormycosis is an emerging aggressive mold infection. This study aimed to assess the outcome of hospitalized adults with rhino-orbito-cerebral mucormycosis (ROCM). The secondary objective was to identify prognostic factors in this setting.
Methods: This study was an international, retrospective, multicenter study. Patients' data were collected from 29 referral centers in 6 countries. All qualified as "proven cases" according to the EORTC/MSGERC criteria.
Results: We included 74 consecutive adult patients hospitalized with ROCM. Rhino-orbito-cerebral type infection was the most common presentation (n = 43; 58.1%) followed by rhino-orbital type (n = 31; 41.9%). Twenty (27%) had acquired nosocomial bacterial infections. A total of 59 (79.7%) patients (16 in combination) received appropriate antifungal treatment with high-doses of liposomal amphotericin B. Fifty-six patients (75.7%) underwent curative surgery. Thirty-five (47.3%) required intensive care unit admission (27; 36.5% under mechanical ventilation). Hospital survival was 56.8%, being reduced to 7.4% in patients with invasive mechanical ventilation. A multivariate binary backward logistic regression model identified confusion at admission (OR 11.48), overlapping hospital-acquired infection (OR 10.27), use of antifungal treatment before diagnosis (OR

The members of the ID-IRI Mucormycosis Study Group are listed in the Appendix.

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10.20), no surgical debridement (OR 5.92), and the absence of prior sinusitis (OR 6.32) were independently associated with increased risk for death.
Conclusion: Today, ROCM still has high mortality rate. Improving source control, rational therpy, and preventing nosocomial infections may improve survival in this severe infection.

1. Introduction

Mucormycosis is an aggressive mold infection that mostly attacks patients with certain underlying conditions such as diabetes, hematological malignancies, neutropenia, major solid organ transplantation, or hematopoietic stem cell transplantation [1,2]. Given the increased prevalence of predisposing conditions in the modern era including Coronavirus disease 2019 (COVID-19) [3,4], the incidence of mucormycosis has increased as well [5–8]. Despite the advances in modern medicine, rhino-orbito-cerebral mucormycosis (ROCM) still has excessively high mortality rates. Mortality rates have been reported above 50% in different studies [2,9].

The most common clinical manifestation of mucormycosis is rhino-orbital-cerebral infection [10]. Although adverse outcomes associated with mucormycosis are likely to depend on underlying conditions [5] and the site of involvement [10], understanding risk factors associated with adverse outcomes is of high importance for the treating physician. Published studies on mucormycosis outcomes indicated various poor prognostic indicators such as delays in diagnosis and medical treatment, facial and/or eyelid gangrene, hemiplegia, cerebral invasion, active malignancy and neutropenia at enrollment, and higher baseline serum iron and ferritin concentrations [9,11,12]. On the other hand, timely application of surgical debridement of necrotic tissues, and administration of appropriate antifungal treatment have been reported to be associated with favorable outcomes [7,13,14]. Unfortunately, wide-scale studies analyzing poor outcomes specific to ROCM are either lacking or sparse in the literature.

In this international and multicenter study, the main objective was to assess the outcome among ROCM patients and to identify variables associated with mortality. We hypothesized that some of these variables are modifiable and subject to improve implementation.

2. Materials and methods

2.1. Study design

We conducted a retrospective cohort study. The Ethical Committee of the Istanbul Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey, approved the study with a waiver of informed consent (17073117-050.99).

2.2. Settings and data collection

We collected patient data from 29 referral centers in six countries: Albania, France, Hungary, Italy, Spain, and Turkey. The members of the Infectious Diseases International Research Initiative (ID-IRI), which serves as a network for clinical research on infectious diseases and clinical microbiology (https://infectdisiri.com/) had joined the study to provide the data in their hospitals. Participants screened hospital records of potential subjects for eligibility. We sent a webpage link to participants, and the data were entered and collected via Google Drive.

We included all data of consecutive patients hospitalized with ROCM (including rhino-orbital, rhino-cerebral and rhino-orbito-cerebral) from June 2002 through September 2017. Patient demographics and data on co-morbid conditions such as diabetes mellitus, ketoacidosis, hematological malignancy, hematopoietic stem cell transplantation, solid organ malignancy, solid organ transplantation, chronic renal failure and HIV infection. We also included data on predisposing factors for mucormycosis such as neutropenia, corticosteroids usage, IV drug abuse, trauma, deferoxamin usage, and antifungal treatment prior to diagnosis [10,15]. Other data collected are prior mucormycosis history, sites of infection, clinical, microbiological and histopathological data, antifungal and surgical therapies, follow-up data, and clinical outcomes. Data from all patients were analyzed for the eligibility by two authors (Yasemin Cag and Hakan Erdem) against inclusion criteria.

2.3. Definitions

The patients were classified as proven according to the definitions of opportunistic invasive fungal infections published by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) [16,17]. Only adult patients (>14 years of age) with “proven” ROCM were included in the study. Sterile culture was defined as fungal culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding a paranasal or mastoid sinus cavity specimen [16,17]. Surgical debridement was defined as removing all necrotic tissues, including bones, if necessary [18]. SOFA score was applied to assess severity at admission according to organ failures [19]. Neutropenia was defined as neutrophil count $< 500/mm^3$. Appropriate antifungal treatment was defined as the administration of $\geq$5 mg/kg/day of Liposomal amphotericin B (L-AmB) or AmB lipid complex (ABLC) [20]. Ventilator-associated pneumonia is defined as pneumonia occurring more than 48 h after patients have been intubated and received mechanical ventilation. Hospital-acquired infection (HAI) was defined as an infection neither present nor at incubation period at admission and acquired after hospitalization of more than two days. Infection data were extracted from medical records. The centers were using Centers for Disease Control and Prevention (CDC) definitions for infection types [21].

2.4. Statistical analysis

The primary outcome of interest was in-hospital all-cause mortality. Descriptive statistics for the numerical data were computed as mean, standard deviation and quartiles, and also descriptive values of the categorical variables were computed as frequencies (number and percentages). Relationships between categorical features and mortality and clinical status were examined with Pearson chi-square analysis or Fisher-Freeman-Halton exact test, depending on the expected frequencies. The Shapiro-Wilks test was used to evaluate whether the numerical variables showed a normal distribution. The Mann-Whitney U test was used for comparing deceased and surviving patients in terms of non-normal distributed clinical variables. $P < 0.05$ was accepted as statistical significance level in univariate analyses.

According to univariate analyses, the variables that were significantly associated with the risk of death were included in the multivariate binary logistic regression model and their main effects were examined. The final model was established by using the backward variable selection method, and variables with a p-value less than 0.15 were left in the model. In this model statistical significance was accepted as $p<0.05$. All statistical analysis was done in SPSS statistical software [IBM Corp. Released 2013. IBM SPSS for Windows, Version 22.0 (Armonk, NY:IBM Corp, USA)].

Table 1
Demographic and clinical features of patients with ROCM.

Variables	Number of patients (*n*)	
Underlying conditions		
Male gender, *n* (%)	74	44 (59.5)
Age, median (IQR)	74	55.5 (42.75–66.25)
Diabetes mellitus, *n* (%)	74	42 (56.8)
• Insulin treatment, *n* (%)	74	39 (52.7)
• Ketoacidosis, *n* (%)	74	8 (10.8)
Chronic renal failure, *n* (%)	74	17 (23)
Hematologic malignancy, *n* (%)	74	23 (31.1)
• AML, *n* (%)		9 (39.1)
• Others, *n* (%)		14 (60.9)
• HSCT, *n* (%)		6 (8.1)
Solid organ transplantation, *n* (%)	74	4 (5.4)
Steroid treatment before admission, *n* (%)	74	12 (16.2)
Penetrating trauma, *n* (%)	74	5 (6.8)
Sinusitis history, *n* (%)	74	22 (29.7)
Smoking, *n* (%)	74	10 (13.5)
Antifungal treatment prior to diagnosis, *n* (%)	74	17 (23)
Findings at admission		
Fever (temperature 38 °C), median (IQR)	74	38 (36.95–38.7)
Confusion, *n* (%)	74	16 (21.6)
Convulsion, *n* (%)	74	6 (8.1)
Focal neurological signs, *n* (%)	74	14 (18.9)
Glasgow Coma Scale score, median (IQR)	40	14 (9–15)
SOFA score, median (IQR)	32	10 (5–12.75)
Laboratory findings at admission		
Neutrophil count (cells/uL), median (IQR)	71	6260 (2360–11200)
Lymphocyte count (cells/uL), median (IQR)	71	1260 (300–2300)
CRP (mg/dl), median (IQR)	60	15.55 (6.72–29.58)
Sedimentation (mm/h), median (IQR)	46	72 (56–99.75)
Procalcitonin (ng/ml), median (IQR)	15	0.53 (0.11–1.3)
Serum iron (mg/L), median (IQR)	20	51 (21–105.5)
Ferritin (mg/L), median (IQR)	18	350 (141.75–1240.5)
Treatment		
Initial antifungal treatment *n* (%)	74	74 (100)
• L-AmB, *n* (%)		66 (89.2)
• C-AmB, *n* (%)		4 (5.4)
• ABLC, *n* (%)		1 (1.4)
• Posaconazole oral suspension, *n* (%)		2 (2.7)
• Voriconazole, *n* (%)		1 (1.4)
• L-AmB dose (mg/kg/day), median (IQR)	66	5 (5-5)
Antifungal combination, *n* (%)	74	17 (23)
Elapsed time between onset of symptoms and antifungal (days), median (IQR)	72	5.5 (2–12)
Total treatment time (days), median (IQR)	73	45 (19.5–68.5)
Surgical debridement, *n* (%)	74	56 (75.7)
Elapsed time between diagnosis and surgical debridement (hours), median (IQR)	52	36 (24–66)
Number of surgical debridement, median (IQR)	52	2 (1-2)
Follow-up		
Intensive Care Unit, *n* (%)	74	35 (47.3)
• Mechanical ventilation, *n* (%)	74	27 (36.5)
Hospital acquired infection, *n* (%)	74	20 (27)
Length of hospital stay (days), median (IQR)	74	43.5 (20.75–60)
Mortality, *n* (%)	74	32 (43.2)
Clinical presentation	74	
• Rhino-orbital, *n* (%)		31 (41.9)
• Rhino-orbito-cerebral, *n* (%)		43 (58.1)

3. Results

3.1. Participants and descriptive data

Data from a total of 74 patients were registered. A summary of demographic and clinical features of patients with ROCM is presented in Table-1. The median age of the patients was 55.5 years (range: 42.7–66.2 years), and 44 patients (59.5%) were males. Rhino-orbito-cerebral-type infection was the most common presentation ($n = 43$; 58.1%), and 31 (41.9%) were rhino-orbital. Diabetes mellitus was the most common underlying disease ($n = 42$; 56.8%) followed by hematologic malignancies ($n = 23$; 31.1%), which were acute myeloid leukemia (AML) ($n = 9$), acute lymphocytic leukemia (ALL) ($n = 6$), myelodysplastic syndrome (MDS) ($n = 3$), lymphoma ($n = 2$), chronic lymphocytic leukemia ($n = 2$), and multiple myeloma ($n = 1$). Types of stem cell transplantations were allogeneic ($n = 5$) and autologous ($n = 1$). All 4 transplanted solid organs were kidneys.

Seventeen patients were using systemic antifungals prior to diagnosis (3 AmB, 3 posaconazole, 9 fluconazole, 1 itraconazole and 1 voriconazole).

Abbreviation: IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; CRP, C-reactive protein; SOFA,Sepsis-related Organ Failure Assessment; L-AmB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; C-AmB, conventional amphotericin B.

Of the 52 (52/74, 70.3%) cases for whom a sterile material culture was obtained, 30 (30/52, 57.7%) were fungal culture positive. The participating centers isolated most frequently *Rhizopus spp.* ($n = 15$); followed by *Mucor spp.* ($n = 13$), and *Rhizomucor spp.* ($n = 2$). Identification of the species could be done only in 4 patients and all were identified as *Rhizopus oryzae*. Seventy (94.6%) cases were diagnosed by histopathology, 26 cases (35.1%) were diagnosed by both sterile material culture and histopathology, and 4 cases diagnosed by only sterile material culture.

A total of 59 (79.7%) patients received appropriate antifungal treatment (58 L-AmB ≥5mg/kg/day, 1 ABLC ≥5mg/kg/day) but 15 patients receive suboptimal treatment (8 L-AmB 3 mg/kg, 4 conventional amphotericin-B, 2 posaconazole oral suspension, and 1 voriconazole). A total of 17 patients initially received combination therapy (10 L-AmB + posaconazole oral suspension, mean 53.2 days;4 L-AmB + voriconazole, mean 40.3 days; 2 L-AmB + caspofungin, mean 47.5 days; 1 posaconazole oral suspension + voriconazole, 14 days).

Treatment of one patient who received voriconazole + posaconazole was switched to L-AmB 5 mg/kg on day 14 due to clinical unresponsiveness. Treatment of two patients who received L-AmB and one patient who received conventional amphotericin B (C-AmB) was switched to posaconazole (30th, 50th and 14th days respectively), treatment of one patient who received C-AmB was switched to L-AMB (15th days) due to the nephrotoxicity and resistant hypokalemia side effects of L-AmB and C-AmB.

In 20 (27.0%) patients HAIs developed after diagnosis on mucormycosis. Pneumonia was the most common HAI ($n = 11$, 55%) (9 of whom were ventilator-associated pneumonia), followed by bloodstream infections ($n = 4$, 20%), urinary tract infections ($n = 2$, 10%), central nervous system infection (with extensively drug resistant (XDR) Gram-negative bacteria) ($n = 1$, 5%), intra-abdominal infection ($n = 1$, 5%) and skin and soft tissue infection ($n = 1$, 5%).

3.2. Outcome data

Thirty-five (56.8%) patients required intensive care unit (ICU) admission and 27 (36.5%) underwent mechanical ventilation. The average SOFA score was 10. Forty-two survived and all-cause in-hospital mortality rate was estimated to be 43.2%. Mortality rates increased to 80.0% and 92.6% in ICU and mechanically ventilated patients, respectively. The univariate analysis showed that female gender, underlying hematologic malignancy, hematopoietic stem cell transplantation (HSCT), use of antifungal treatment before diagnosis, presence of confusion at admission, presence of convulsions at admission, requiring mechanical ventilation (invasive or noninvasive) during follow-up, and overlapping nosocomial infection during follow-up were significantly associated with higher mortality. In contrast, underlying diabetes, use of insulin therapy, having extensive surgical debridement, having prior sinusitis history, having <500 neutrophils at admission were associated

Table 2
Comparison of variables among patients with survived and died.

Variables	Survived*N* = 42	Died*N* = 32	*P*
Underlying conditions			
Male gender. *n* (%)	29 (65.9)	15 (34.1)	0.050*
Age, median (IQR)	56.0 (42.25–66.50)	55.0 (42.50–66.50)	0.883**
Diabetes mellitus, *n* (%)	29 (69.0)	13 (31.0)	0.014*
Insulin treatment, *n* (%)	28 (71.8)	11 (28.2)	0.006*
Ketoacidosis, *n* (%)	3 (37.5)	5 (62.5)	0.280*
Chronic renal failure, *n* (%)	13 (76.5)	4 (23.5)	0.094*
Hematologic malignancy, *n* (%)	6 (26.1)	17 (73.9)	0.001*
• AML, *n* (%)	1 (11.1)	8 (88.9)	0.190*
• HSCT, *n* (%)	1 (16.7)	5 (83.3)	0.039*
Solid organ transplantation, *n* (%)	2 (50)	2 (50)	0.998*
Steroid treatment before admission, *n* (%)	8 (66.7)	4 (33.3)	0.536*
Penetrating trauma, *n* (%)	1 (20.0)	4 (80.0)	0.159*
Sinusitis history, *n* (%)	17 (77.3)	5 (22.7)	0.020*
Smoking, *n* (%)	6 (75.0)	4 (25.0)	0.824*
Antifungal treatment prior to diagnosis. *n* (%)	5 (29.4)	12 (70.6)	0.010*
Findings at admission			
Fever (temperature 38 °C)	16(42.1)	22 (57.9)	0.009*
Confusion, *n* (%)	2 (12.5)	14 (87.5)	0.001*
Convulsion, *n* (%)	1 (16.7)	5 (83.3)	0.040*
Focal neurological signs, *n* (%)	6 (42.9)	8 (57.1)	0.040*
Glasgow Coma Scale score, median (IQR)	15.0 (13.0–15.0)	10.50 (8.0–15.0)	0.021**
SOFA score, median (IQR)	6.0 (4.50–9.50)	12.0 (9.0–18.0)	0.007**
Laboratory findings at admission			
Neutrophil count <500, *n* (%)	2 (15.4)	11 (84.6)	0.001*
CRP (mg/dl), median (IQR)	9.39 (4.32–21.40)	23.15 (13.33–32.63)	0.001**
Sedimentation (mm/h), median (IQR)	66.0 (39.50–98.50)	82.00 (66.0–110.00)	0.124**
Procalcitonin (ng/ml), median (IQR)	0.20 (0.09–0.58)	1.24 (0.43–3.65)	0.045**
Serum iron (mg/L), median (IQR)	47.00 (19.50–78.75)	78.00 (27.25–107.50)	0.375**
Ferritin (mg/L), median (IQR)	325.0 (160.0–1500.0)	961.0 (87.0–1154.0)	0.964**
Treatment			
Appropriate antifungal treatment, *n* (%)	32 (54.2)	27 (45.8)	0.386*
Antifungal combination, *n* (%)	11 (64.7)	6 (35.3)	0.451*
Elapsed time between onset of symptoms and antifungal (days), median (IQR)	7.0 (2.0–15.75)	5.0 (1.25–8.0)	0.146**
Surgical debridement, *n* (%)	38 (67.9)	18 (32.1)	0.001*
Elapsed time between diagnosis and surgical debridement (hours), median (IQR)	48.0 (24.0–48.0)	36.0 (24.0–120.0)	0.928**
Follow-up			
Intensive Care Unit, *n* (%)	7 (20.0)	28 (80.0)	0.001*
• Mechanical ventilation, *n* (%)	2 (7.4)	25 (92.6)	0.001*
Hospital acquired infection, *n* (%)	3 (15.0)	17 (85.0)	0.001*
Clinical presentation			0.253*
Rhino-orbital, *n* (%)	20 (64.5)	11 (35.5)	
Rhino-orbito cerebral, *n* (%)	22 (51.2)	21 (48.8)	

Abbreviation: IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; SOFA, Sepsis-related Organ Failure Assessment; CRP, C-reactive protein.
* : Fisher-Freeman-Halton exact test or Pearson Chi-Square test.
** : Mann-Whitney U test.

with lower mortality (Table 2). Mean levels of fever, SOFA score, CRP, and procalcitonin were significantly higher in those who died, whereas, the mean Glasgow Coma Scale score was significantly lower in those who died (Table 2).

Use of steroid treatment prior to diagnosis ($p = 0.042$) and having confusion at admission ($p = 0.028$) were significantly higher in the rhino-orbito-cerebral group.

3.3. Main results

The predictive accuracy of the multivariate logistic regression model (Nagelkerke R-Square) was 76.3%. According to the multivariate logistic regression model, the presence of confusion at admission, use of antifungal treatment prior to diagnosis, and secondary HAIs during follow-up were independently associated with an increased risk of death (Table 3). In contrast, source control and prior sinusitis were independently associated with better survival. According to the multivariate model, 36 of 42 surviving patients and 27 of 32 deceased patients were predicted successfully. In this case, the specificity and sensitivity of the model are 85.7% and 84.4% respectively. These results indicate that the model performance is quite good and successfully predicts patients who died and survived.

4. Discussion

Our study is a multicenter, international collaboration investigating prognostic factors in a large series of ROCM hospitalized in medical wards and in the ICU. In this cohort, diabetes represented 56.8% of the underlying diseases, followed by one-third with hematological malignancies. In addition, this study is the first to analyze the association of HAI with mortality among ROCM patients. In our study, Average SOFA score was 10 and 56.8% of patients survived. We identified three independent factors (confusion, nosocomial infections, and prior antifungal exposure) associated with mortality. In contrast, extensive surgical debridement and prior sinusitis history were independent factors associated with survival. Our findings suggest that more aggressive source control and preventing nosocomial infections were interventions that can improve survival.

Chen et al. reported that “hospital infection” is an important prognostic factor among invasive pulmonary fungal infections [22]. Whereas, our study is the first large-scale study to reveal HAI as a risk factor for poor outcome among ROCM patients. Because of severe underlying conditions, extensive tissue destruction and abundant invasive procedures like surgical debridement and the need for ICU follow-up, mucormycosis patients are vulnerable to HAIs. In critically ill patients with hematological malignancies and all type of mucormycosis, Jestin et al. [30] reported that bacterial infections were not associated with higher mortality. However, our cohort differed with a predominance of diabetes cases in the medical wards, whereas the Jestin’s cohort [30] was constituted by only 26 adults with very high mortality rates (88%) due to the severity of the patient population, restricted to hematological patients in the ICU.

Concomitant surgical and antifungal therapy was associated with significantly lower mortality compared to treatment with amphotericin B alone [11,23]. Surgically maintained source control has already been known to impact prognosis dramatically in ROCM [18]. Prompt institution of effective antifungal treatment, and early and extensive debridement of all necrotic tissues are the mainstays of mucormycosis management. Our study confirmed that surgical debridement was a preventive independent factor for fatal outcomes in ROCM, too.

On the other hand, the timing of medical and surgical treatments are other concerns. In a recent systematic literature review, it was reported that early initiation of medical treatment (within the first 12 days of presentation) was associated with better survival outcomes, but the timing of surgical treatment was not found to be associated [9]. In our study, the elapsed time between the onset of symptoms and antifungals was a median of 5.5 days. Therefore, we did not find the elapsed time between the onset of symptoms and antifungal treatment to be associated with mortality.

Table 3
Final model, including independent predictors of mortality.

	B	S.E.	Wald	df	*P*	OR	95% CI for OR	
							Lower	Upper
Sinusitis history (No / Yes)	1.845	0.959	3.699	1	0.050	6.329	1.000	41.492
Antifungal treatment prior to diagnosis (Yes / No)	2.323	0.944	6.052	1	0.014	10.205	1.604	64.943
Confusion (Yes / No)	2.441	1.076	5.148	1	0.023	11.486	1.394	94.613
Surgical debridement (No / Yes)	1.778	0.956	3.457	1	0.050	5.920	1.000	38.592
Hospital infection (Yes / No)	2.330	0.853	7.451	1	0.006	10.275	1.929	54.732
Neutrophil count (<500 / >500)	1.866	1.169	2.546	1	0.111	6.464	0.653	63.967
Constant	-3.893	1.073	13.160	1	0.000	0.020		

L-AmB or ABLC is recommended as the first-line antifungal agent for the treatment of mucormycosis [20]. A study evaluating diabetic and non-diabetic ROCM patients reported that the mortality rate was 7.4 times higher in diabetic ROCM treated with non-liposomal amphotericin-B [24]. Although point estimates in our study did not reveal any association between receiving appropriate antifungal treatment and favorable outcomes, 80% of patients received appropriate treatment in our study. In a study population where the majority received appropriate antifungal therapy, it would not be surprising to find this feature uniform, in other words, statistically insignificant. Recently published meta-analysis indicated that initial therapy with the combination of antifungals did not result in significantly lower mortality than amphotericin-B mono-therapy [23]. Accordingly, combining antifungals were not found to be related to reduced mortality in our study.

Mignogna et al. reported that all five patients reported a history of chronic sinusitis of unknown etiology in their study [25]. Impairment or loss of immune defense in sinus mucosa due to chronic sinusitis may drive individuals more vulnerable to fungal colonization [25]. In our study, one-third of the patients had a prior history of sinusitis, and prior history of sinusitis was paradoxically a preventive independent factor for fatal outcomes of ROCM.

Breakthrough mucormycosis can occur during exposure to Mucorales-active or other mold-active antifungals [26]. If a patient is on posaconazole prophylaxis has signs of an invasive fungal infection, mucormycosis should be included in the differential diagnosis [27]. Axell-House et al. reported that breakthrough mucormycosis on Mucorales-active antifungals is an independent risk factor for mortality in patients with hematologic cancer [26]. Claustre et al. reported that previous exposure to antifungal drug in the last three months is associated with mortality of mucormycosis in patients with hematological malignancies in ICU [28]. In our study, 17 patients were using systemic antifungals prior to diagnosis. Accordingly, we found that prior antifungal exposure was an independent factor associated to mortality.

Invasive mucormycosis can lead to multi-organ failure which requires ICU management. Jestin et al. showed that severity according to SOFA score was associated with a poorer outcome in critically ill hematological patients with mucormycosis [30]. Accordingly, we found that high SOFA score was found to be associated with mortality in the univariate analysis. However, we did not include SOFA score due to missing data in our final model.

Mucormycosis patients can require ICU management at any stage of the disease due to underlying complex comorbidities, multiple invasive procedures, medical and surgical treatment-associated complications, or severe infections. Despite the technological advances and the improvement of care, the global ICU mortality for mucormycosis remained very high. A multi-center study evaluated the prognosis of mucormycosis patients in ICU revealed that mortality rate was 71.6% and old age, malnutrition, and underlying hematological malignancies are associated with mortality [28]. Similarly, in our study, ICU mortality was 80%.

In our study, only one-third of the patients had hematological malignancies and only 13 patients were neutropenic (<500) at the time of diagnosis. Neutropenia influences not only the onset of the fungal complication in patients with hematological malignancies, but also the outcome. Pagano et al. showed that recovery from neutropenia is statistically correlated with an improvement in the mucormycosis infection in the univariate analyses. However, multivariate analysis has repeatedly shown that the significance was lost [29]. In our study, neutropenia was not an independent factor contributing to mortality of ROCM, but increased risk of death (OR 6.54), suggesting to be a type II statistical error. There are other shortcomings in our study. First, it is a retrospective study, which renders it prone to various types of bias. On the other hand, it is nearly impossible to provide cases prospectively for such a rare disease. However, the inclusion of only proven cases according to the EORTC/MSGERC criteria is an important strength of the current study.

5. Conclusion

This study documented that the acquisition of secondary infections during the management of ROCM is a significant factor associated with hospital mortality. In addition, the presence of prior sinusitis and surgical debridement improved survival chances. Therefore, opportunities exist to improve the survival of this severe disease by implementing aggressive source control and preventing nosocomial infections.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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Appendix

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