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Invasive Fungal Infections Among Patients with Hematological Malignancies: A Two-Year Multicentric Study from Tehran, Iran

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Abstract

Background: Invasive fungal infection (IFI) is a life-threatening condition, particularly in individuals with compromised immune systems.

Objectives: Our study aims to evaluate IFI in hospitalized patients with hematological malignancies.

Methods: In this retrospective cross-sectional study, we evaluated patients with hematological malignancies admitted to two university hospitals in Tehran, Iran, from 2020 to 2021 for IFI. We selected only those patients who had been hospitalized for at least four days for antimicrobial treatment. Data analysis was conducted using SPSS-26 software, employing Mann-Whitney U, chi-square, and Fisher exact tests.

Results: During the study period, 60 out of 213 patients with hematological malignancies were admitted for antimicrobial treatment. The average age of the patients was 57.1 years, with fever being the most common symptom, reported in 63.3% of cases. We identified 24 cases of IFI, including three proven cases (*Candida* spp.) and 21 probable cases. Statistical analysis showed a lower mean neutrophil count in the IFI group compared to the non-IFI group (3862 versus 12881, P = 0.001) and a higher mortality rate (58.3% versus 27.8%, P = 0.031).

Conclusions: Our study revealed that severe neutropenia is a significant risk factor for IFI, and the mortality rate associated with IFI remains high despite advances in the treatment of hematological malignancies.

Keywords: Invasive Fungal Disease, Hematological Malignancy, Neutropenia, *Aspergillus*,*Candida*

1. Background

Hematological malignancies are among the common cancers in Iran. A 2014 study using pathology and cytology data from 60 medical universities across the country found that leukemia was the sixth most common cancer among men and fifth among women (1). The Global Cancer Observatory estimates that by 2020, Iran will see over 131,000 new cancer cases, with more than 12,000 due to the three common hematological malignancies: Leukemia, lymphoma, and multiple myeloma. These malignancies rank third in incidence after breast and gastric cancers and are the third leading cause of cancer-related death, with a mortality rate of 8,000 per year following gastric and lung cancers (2).

Invasive fungal infection (IFI) is prevalent among immunocompromised individuals, particularly those with hematological malignancies, and carries a high mortality rate. A population-based study in France from 2001 to 2010 identified about 36,000 IFI cases, estimating an incidence rate of 5.9 per 100,000 in the general population and 4% among patients with hematological malignancies. The mortality rate was 27.6%, with the most common fungi being *Candida* spp. (43%), *Pneumocystis jirovecii* (26%), and *Aspergillus* spp.

(24%) (3). In Italy, a study of approximately 12,000 patients with hematological malignancies showed that 4.6% developed IFI, with a mortality rate of 39%.

The most affected group was patients with acute myeloid leukemia (AML), primarily challenged by *Aspergillus* and *Candida* spp. (4). A meta-analysis of about 17,000 patients revealed a 6.3% incidence of invasive Aspergillosis (IA) (5). Additionally, a 20-year autopsy study in the United States from 1998 to 2008 indicated a decrease in the incidence rate of IA from 0.12 to 0.07 in patients with hematological malignancies. Although the prevalence of IFI in these patients has decreased, the incidence of visceral candidiasis has increased (6).

2. Objectives

Considering the prevalence of hematological malignancies in Iran and the limited data on fungal infections in these patients, our study aims to investigate the frequency, risk factors, and mortality rate of IFI in hospitalized patients with hematological malignancies.

3. Methods

3.1. Study Design

We conducted a retrospective cross-sectional study using medical registry data from April 2020 to September 2021 at two university hospitals, Imam Reza and Khanevadeh, in Tehran, Iran.

3.2. Patient Selection and Study Protocol

All registries of hospitalized patients with hematological malignancies were reviewed and selected those who had received antimicrobial treatment for more than four days, with blood, sputum, and urine cultures revealing no bacteria responsible for the infection. Patients admitted for chemotherapy, blood product transfusion, infectious diseases lasting three days or less, or those admitted to non-hematological wards were excluded. Demographic characteristics, history of diabetes, corticosteroid use, type of hematological malignancy, and the number of chemotherapy treatment courses were collected.

The IFI defined as either a proven or probable diagnosis, according to the criteria of the European Organization for Research and Treatment of Cancer and the Mycoses study group Education and Research Consortium (EORTC/MSGERC) (7). Proven cases required a positive blood culture or PCR for fungi and the presence of yeast cells in histopathologic or direct microscopic examination. Probable cases were defined by a positive bronchoalveolar lavage (BAL) culture or PCR for fungi, recent history of neutropenia, presence of at least one typical finding on pulmonary computed tomography (CT), such as dense well-circumscribed lesions, air crescent sign, cavity, and consolidation, and mycological evidence including any mold recovered by sputum or BAL culture and galactomannan antigen.

3.3. Microbiological Method

All patients underwent mycological assays using blood, urine, and sputum cultures on blood agar media. In both hospitals, 5 mL of peripheral blood was inoculated into a bottle and incubated in the BACTEC system. The first report was available after 72 hours, and the second report after 15 days of incubation. Additionally, serum galactomannan levels and PCR for mycosis from sputum or BAL were conducted on patients exhibiting pulmonary symptoms or signs on CT scans.

3.4. Statistical Analysis

SPSS-26 software was employed by IBM Corporation to analyze the data. The Kolmogorov-Smirnov test assessed the normality of the data. Furthermore, the Mann-Whitney U test was used to compare quantitative data, while chi-square and Fisher exact tests were utilized for qualitative data, with significance set at the 95% level.

4. Results

The registries of 213 patients with 573 hospitalization episodes were reviewed and selected 60 patients hospitalized for at least four days for antimicrobial treatment (Figure 1). The mean age was 57.1 ± 17, with an age range of 20 - 86, and a male-to-female ratio of 38/22. None of the patients received antifungal prophylaxis. The most common hematological malignancy was AML, found in 21 patients (35%), and the most prevalent symptom upon admission was fever, noted in 38 patients (63.3%). Table 1 shows the demographic characteristics and primary symptoms of the patients with hematological malignancies and IFI. Table 2 compares these variables in the patients with hematological malignancies, with and without IFI. We identified 24 out of 60 patients (40%) diagnosed with IFI, which represents 11.3% of total patients—these included three proven (5%) and 21 probable (35%) cases. The proven diagnoses comprised three cases of *Candida* spp. in blood cultures. Probable cases included three

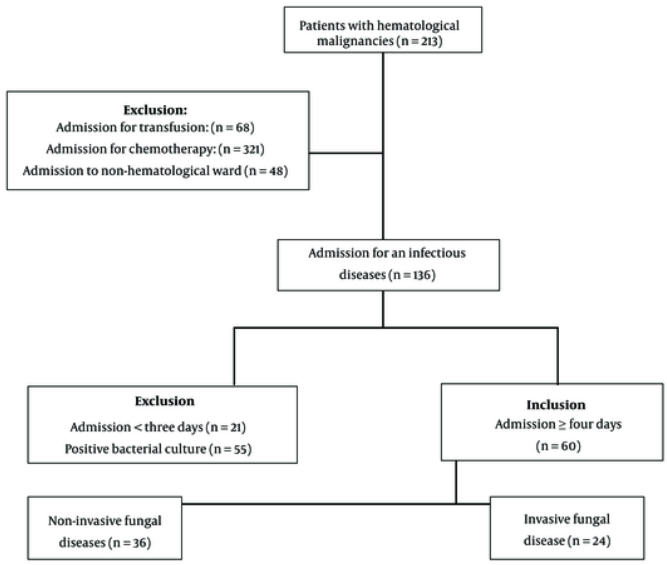

Figure 1. Flow diagram of the study population

Aspergillus spp. in BAL cultures, one PCR-confirmed *Aspergillus* spp. in a BAL sample, nine cases with multiple pulmonary nodules, four with positive serum galactomannan, two with air crescent signs, and two with necrotic skin lesions of the palate and nose compatible with *Mucoral* spp. (Figure 2). Table 3 shows the frequency of IFI in the patients with hematological malignancy.

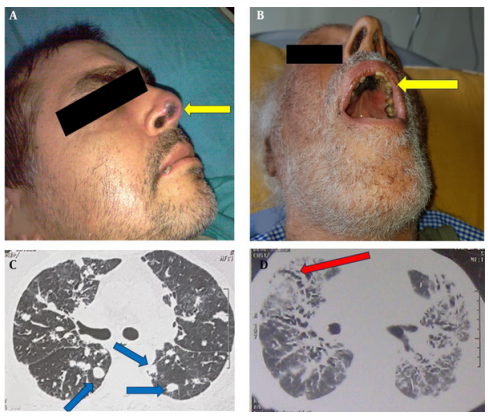

Figure 2. Necrotic skin lesion in the nose (A, yellow arrow) and hard palate (B, yellow arrow). Computed tomography showed pulmonary nodules (C, blue arrow) and air crescent sign (D, red arrow).

The Kolmogorov-Smirnov test showed that variables such as age, neutrophil count, and number of chemotherapy courses did not distribute normally. The Mann-Whitney U test revealed that the mean neutrophil count was significantly lower in the IFI group compared to the non-IFI group (P = 0.001). Fisher's exact test indicated that severe neutropenia (below 500/mL) was more common in the IFI group (P = 0.002) (Table 4). The three-month mortality rate was significantly higher in the IFI group at 58.3% (14 out of 24 patients) compared to 27.8% (10 out of 36 patients) in the non-IFI group (P = 0.031). However, Fischer's exact test showed that mortality rate did not correlate with the etiology of IFI (P = 0.763) (Table 5).

5. Discussion

Invasive fungal infection is a relatively common and life-threatening infection in patients with hematological malignancies. Our study found an 11.3% frequency of IFI among hospitalized patients with these conditions. The mean age of patients with IFI was 57 years, with the most common malignancy being AML. The mortality rate for our IFI patients was 58.3%. The most frequently identified fungi were *Aspergillus*, followed by Candida and *Mucoral* spp. Severe neutropenia, indicated by a neutrophil count below 500/mL, was the only identified risk factor for IFI in our study.

Table 1. Demographic Characteristics, Clinical Symptoms, and Paraclinical Findings of the Patients with Invasive Fungal Infection

No.	Age	Sex	PMH	Clinical Findings	Chemotherapy Course	Neutrophil (mL)	Hb (mg/dL)	Platelet (in mL)	ESR	IFI Sign	Diagnosis Confirmation	Outcome
1	59	Male	ALL	Fever, dyspnea, cough, pharyngitis	4	50	8.2	20000	70	None	*Aspergillus* spp. in BAL	Death
2	70	Male	CLL, DM	Fever, lethargy, abdominal pain, malaise	3	210	7.8	74000	75	Serum GM	None	Death
3	30	Male	AML	Fever, pharyngitis	2	8400	9.5	41000	54	Chest nodule on CT	None	Recovery
4	60	Female	AML	Fever, bone pain, weight loss	7	120	9.8	16000	43	Necrotic lesion	None	Death
5	67	Male	DM, AML	Fever, weight loss, cough, dyspnea, cellulitis	3	4300	10.4	97000	100	None	*Candida* spp. in blood culture	Recovery
6	70	Male	AML	Fever, malaise, lethargy, bleeding	4	670	7.2	6000	89	Necrotic lesion	None	Death
7	59	Male	DM, CLL	Malaise, dyspnea, abdominal pain	1	7600	10.4	84000	17	Chest nodule on CT	None	Recovery
8	29	Male	ALL	Fever, weight loss, cough, cellulitis	2	16000	8.4	648000	45	Chest nodule on CT	None	Recovery
9	48	Male	AML	Fever, dyspnea, cough, abdominal pain	2	340	8.8	3000	50	None	*Candida* spp. in blood culture	Death
10	44	Female	AML	Fever, malaise	3	5600	8.8	141000	56	None	*Candida* spp. in blood culture	Recovery
11	86	Male	MDS	Fever, cough, pharyngitis, dyspnea, lethargy	2	1800	8.5	50000	88	Serum GM	*Aspergillus* spp. in BAL	Death
12	75	Male	MDS	Fever, cough, dyspnea, bleeding	3	23000	9.2	7000	115	Air crescent sign	None	Death
13	55	Male	DM, HD	Fever, bone pain, dyspnea	3	180	11.4	187000	98	Chest nodule on CT	None	Recovery
14	78	Female	MM	Bone pain, dyspnea, lethargy	3	4300	9.8	325	117	None	*Aspergillus* spp. in BAL	Death
15	20	Female	ALL	Fever	5	180	8.6	9000	32	Chest nodule on CT	None	Death
16	52	Male	DM, NHL	Malaise, cough, dyspnea	4	160	9.7	44000	143	Chest nodule on CT	None	Death
17	20	Female	HD	Malaise, cough, abdominal pain, seizure, weight loss	4	1870	11.5	154000	54	Serum GM	None	Recovery
18	20	Male	ALL	Fever, bone pain, malaise, weight loss, lethargy	3	2100	7.2	313000	70	Chest nodule on CT	None	Recovery
19	79	Female	DM, AML	Dyspnea, lethargy, cellulitis	3	13800	8	60000	40	Serum GM	None	Death
20	50	Male	DM, AML	Malaise, pharyngitis, lethargy	7	30	9.9	10000	117	Air crescent sign	None	Death
21	62	Male	AML	Fever, bone pain, malaise, cough, dyspnea	4	1400	11.2	110000	40	Chest nodule on CT	None	Recovery
22	69	Male	DM, ALL	Fever, bone pain, malaise, weight loss, lethargy	6	350	8.8	179000	65	None	*Aspergillus* spp. in BAL	Death
23	71	Male	DM, NHL	Bone pain, weight loss, cough, dyspnea, cellulitis	6	190	10.8	127000	98	Chest nodule on CT	None	Recovery
24	70	Female	DM, AML	Fever, bone pain, malaise, cough, dyspnea, lethargy, cellulitis	5	50	11.2	9000	110	Chest nodule on CT	None	Death

Abbreviations: ALL, acute lymphoid leukemia; CLL, chronic lymphocytic leukemia; acute, myeloid leukemia; DM, diabetes mellitus; HD, hodgkin's disease; NHL, non-hodgkin lymphoma; MDS, myelo dysplastic syndrome; MM, multiple myeloma.

According to various studies in Iran, IFI is most commonly caused by *Candida* and *Aspergillus* spp. A three-year study involving 490 patients with IFI admitted to the ICU reported that 68.8% had *Candida*

Table 2. The Demographic Characteristics and Primary Symptoms of the Patients (n = 60)

Group	IFI (n = 24)	Non-IFI (n = 36)	P-Value
Age (mean ± SD)	55.9 ± 19.8	57.9 ± 15.2	0.675
Male/female	17.07	21.15	0.416
Fever	17	21	0.416
Cough	11	10	0.176
Dyspnea	13	9	0.030 [a]
Malaise	11	12	0.419
Bone pain	8	7	0.362
Weigh loss	7	12	0.784
Bleeding	2	3	1.000
Abdominal pain	4	8	0.787
Lethargy	9	12	0.702
Pharyngitis	4	4	0.702
Cellulitis	5	3	0.247
Seizure	1	1	1.000
Diabetes mellitus	10	13	0.788
Corticosteroid treatment	13	12	0.109

[a] Significant level at 95%.

Table 3. Frequency of Invasive Fungal Infection (IFI) in Patients with Hematological Malignancies

Group	IFI (n = 24)		Non-IFI (n = 36)	P-Value
Primary hematological malignancy	**Proven**	**Probable**		
Acute myeloid leukemia	3	7	11	0.384
Acute lymphoid leukemia	0	5	4	
Myelo dysplastic syndrome	0	2	6	
Chronic lymphocytic leukemia	0	2	5	
Multiple myeloma	0	1	5	
Non-hodgkin lymphoma	0	2	2	
Chronic myelogenous leukemia	0	0	3	
Hodgkin's disease	0	2	0	

spp., 22.1% had *Aspergillus* spp., and 4.3% had *Zygomycetes*, based on molecular diagnosis (8). Another single-center, five-year study involving 617 patients with leukemia in Tehran identified 87 cases of IFI using culture, biopsy, and serum galactomannan levels, finding *Candida* spp. in 74.7%, *Aspergillus* spp. in 17.2%, and *Zygomycetes* in 11.5% (9).

The incidence and mortality rates of IFI vary by region. A ten-year study in Japan found a cumulative IFI incidence of 10.5% among patients with hematological malignancies and a mortality rate of 61.2% (10). In China, a study involving 323 patients with hematological malignancies reported an IFI development rate of 3.5%, consisting primarily of *Candida* and *Aspergillus* spp. (11). Another Japanese study on 2821 patients showed that 1.3% developed IFI, with 40% mortality during the study period (12). A study from Spain (2004-2015) involving 285 patients noted an IFI frequency of 10% (13).

Our study reported higher frequency and mortality rates compared to these studies but found similar fungal etiologies, with *Aspergillus*, *Candida*, and *Mucoral* spp. being the most common causes of IFI. Other studies also reported IFI frequencies ranging from 5% to 45%. Most patients acquiring IFI were middle-aged, with other studies reporting mean ages from 44 to 61 years. Like our findings, AML was frequently the most common hematological malignancy associated with IFI in these studies (10, 14-17).

As demonstrated in Table 4, severe neutropenia, defined as a neutrophil count less than 500 cells/mL, was identified as the most significant risk factor for IFI in our study. This condition commonly results from

Table 4. Mann-Whitney U Test for Comparing Quantitative Data in Invasive Fungal Infection (IFI) and Non-IFI Groups (n = 60)

Variables	Mean		P-Value
	IFD	Non-IFD	
Age	55.9	57.9	0.910
Mean neutrophil count	3862	12881	0.001 [a]
Mean number of chemotherapy courses	3.7	2.9	0.101
Age group			0.938
20 - 39	5	6	
40 - 59	7	10	
> 60	12	20	
Neutrophil count (mL)			0.002 [a]
< 500	11	3	
500 - 1500	2	3	
> 1500	11	30	

[a] Significant level at 95%.

Table 5. Mortality Rate Associated with Invasive Fungal Infection (IFI) Etiology (n = 24)

Etiology of IFI	*Aspergillus* spp.	*Candida* spp.	*Mucoral* spp.	P-Value
Total cases	19	3	2	0.763
Mortality	11	1	2	

chemotherapy, and many studies have confirmed its critical role as a risk factor for IFI. Additionally, various other risk factors for IFI have been identified (18-20). A study involving 102 patients with hematological malignancies in Iran found that being over 60 years old, having diabetes mellitus, a previous history of IFI, receiving more than three types of antibiotics, and undergoing more than eight chemotherapy courses were significant risk factors for IFI (19). Another study from Spain identified corticosteroid treatment and recent viral infection as risk factors in patients with hematological malignancies, with only 12% of these patients being neutropenic (20).

In our patient cohort, the most common causes of IFI were *Aspergillus* spp., followed by *Candida* and *Mucoral* spp. However, the mortality rate among our patients did not correlate with the etiology of the IFI. Previous research has shown varying incidence and mortality rates of IFI in patients with hematological malignancies depending on the fungal etiology. In one study from India, a 10% incidence of candidemia was reported among 150 patients with hematological malignancies associated with acute lymphoblastic leukemia (ALL), leukopenia, long-term intravenous catheter use, and corticosteroid treatment (21). A multicentric study in Greece between 2009 and 2012 reported a candidemia incidence rate of 0.014% among patients admitted with hematological malignancies (22). In Italy, 215 episodes of IFI were recorded among patients with hematological malignancies, with *Candida* spp. being the predominant cause and associated with a 39% mortality rate (23). A German study conducted from 2003 to 2009 found an annual rate of 1.1 per thousand hospitalizations for candidemia, accompanied by a 67% three-month mortality rate (24).

Several studies have documented an increased frequency of pulmonary aspergillosis in patients with hematological malignancies. For instance, an Italian study reported 61 cases of invasive pulmonary *Aspergillus* (IPA) among patients with hematological malignancies, where the incidence rate was 7.1% and the three-month mortality rate was 27%. The most common underlying malignancy in these cases was AML (25). Similarly, a 20-year study in France from 1998 to 2017 identified 217 patients with IPA, again with AML as the most frequent underlying disease and a three-month mortality rate of 75% (26).

Other studies have also noted an increased rate of various invasive fungi in this patient population. A five-year study involving 2083 patients with hematological malignancies in China found that 11.3% had IFI, caused by *Aspergillus* spp., *Cryptococcus*, and *Mucor*, respectively.

AML was the most common underlying malignancy here as well, with a three-month mortality rate from IFI at 5.9% (27). In our study, dyspnea was more prevalent among patients with IFI than those without, potentially due to the higher incidence of IPA in the IFI group.

Our findings indicate a three-month mortality rate of 58.3% for IFI, aligning with other studies showing mortality rates ranging from 5% to 75% (3, 4, 10, 16, 17, 22, 26-28), influenced by factors such as underlying malignancies, chemotherapy regimens, comorbidities, surgical interventions, and history of antifungal prophylaxis. Uniquely, our study identified two cases (8.3%) of facial and oral necrotic lesions likely due to *Mucoral* spp., both of which were fatal. A study in Egypt on children with cancer associated invasive fungal sinusitis with a 35% three-month mortality rate (29).

We recommend that future studies further investigate IFI with respect to types of hematological malignancy, chemotherapy regimens, and antimicrobial prophylaxis strategies. There is also a need for enhanced laboratory capabilities to facilitate the diagnosis of fungal infections, including fungal sub-typing and antifungal susceptibility testing, in all tertiary hospitals or treatment centers for these patients.

5.1. Conclusions

Our study identified a frequency of 11.3% of IFI and a three-month mortality rate of 58.3% among patients with hematological malignancies. *Aspergillus* and *Candida* spp. were the most frequently identified fungi, consistent with previous studies, and AML was the most common underlying malignancy. We recommend that all medical centers with hematology departments implement advanced laboratory systems for the diagnosis and identification of invasive fungal subspecies and antifungal drug sensitivity testing. However, our study faced several limitations:

- Absence of histopathological and microscopical confirmation of fungal infections.

- Lack of fungus sub-typing and antifungal susceptibility tests.

- Unavailability of data on antimicrobial prophylaxis, such as cotrimoxazole, which could prevent *Pneumocystis jirovsi*, preventing a comprehensive analysis of the relationship between antimicrobial prophylaxis and IFI.

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Footnotes

Authors' Contribution: Davod Sheikh-Hoseini contributed to collecting data, reviewing the literature, and writing the primary draft. Saeed Soleiman-Meigooni contributed to the study design, reviewing the literature, analyzing the data, and writing the primary and final draft. Jalil Rajabi, Hasan Jalaeikhoo, Taher Azimi Sarikhanbagloo, and Ali Asgari contributed to reviewing the literature and writing the primary draft. Mohammad Hasan Kazemi-Galougahi contributed to the study design and analysis of the data.

Conflict of Interests Statement: The authors declared that they did not have any conflict of interest in this study.

Data Availabity: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: This study was approved by the Ethics Committee of Aja University of Medical Sciences, Tehran, Iran, with the ethical code IR.AJAUMS.REC.1398.082 .

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