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Retrospective Evaluation of Risk Factors for the Development of Invasive Fungal Infections in Immunosuppressed Patients

İmmünsüprese Hastalarda İnvaziv Fungal Enfeksiyon Gelişimindeki Risk Faktörlerinin Retrospektif Değerlendirilmesi

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ABSTRACT

Objective: The incidence of invasive fungal infection (IFI) is increasing in immunosuppressed patients. Thus, this study aimed to compare the types and the distribution of IFI, determine the probable risk factors in its development, and assess the mortality and underlying diseases among patients with hematological malignancies and those with non-hematological immunosuppression.

Methods: This retrospective study included 84 adult patients with IFI diagnosis between January 1, 2012, and April 1, 2014, at our hospital.

Results: The distribution of cases was documented as follows: 58 (69.0%) patients were proven with IFI, 12 (14.3%) with probable IFI, and 14 (16.7%) with possible IFI. Patient distributions with proven IFI were as follows: 91.4% (53/58) with invasive candidiasis (IC), 5.2% (3/58) with invasive pulmonary aspergillosis (IPA), 1.7% (1/58) with nasopharyngeal invasive fungal involvement, and 1.7% (1/58) with invasive fungal involvement in the colon. All cases of probable and possible IFE (26/26, 100%) were determined as IPA. The following is previously known risk factors for IFI development were evaluated for both groups: immunosuppressive drug usage, renal replacement therapy requirement, mechanical ventilation requirement, presence of a central venous catheter, presence of a urinary catheter, presence of gastrointestinal catheter, mucositis/diarrhea/ileus history, malnutrition, blood product transfusion, bacterial infection, antibacterial treatment, length of hospital and intensive care unit stay, and duration of neutropenia. The immunosuppressive drug usage and neutropenia duration were found to be statistically significant between the hematologic malignancy and non-hematologic immunosuppressive groups. No significant difference was found in other parameters ($p<0.05$).

Conclusion: Our findings followed the literature; however, the mortality in the IC group was found high, similar to the IPA group. Additionally, this study revealed that IFI epidemiology may vary based on the region and the patient. IFIs, which are increasing in frequency, need to be evaluated with a good knowledge of risk factors, using newly developed diagnostic methods, with a multidisciplinary approach.

Keywords: Immunosuppression, invasive fungal infection, risk factors

ÖZ

Amaç: İmmünosüpresif hastalarda invazif fungal enfeksiyon (İFE) görülme sıklığı giderek artmaktadır. Çalışmamızın amacı hematolojik maligniteli ve non-hematolojik immünsüpresif hasta gruplarında saptanan İFE tiplerini ve dağılımını karşılaştırmak; İFE gelişiminde olası risk faktörlerini saptamak; mortaliteyi değerlendirmek; altta yatan hastalıkları karşılaştırmaktır.

Yöntemler: Bu retrospektif çalışmaya, hastanemizde 01 Ocak 2012 ve 1 Nisan 2014 tarihleri arasında İFE tanısı almış, 84 erişkin hasta dahil edildi.

Bulgular: Olguların dağılımı; kanıtlanmış İFE (58/84, %69), olası İFE (12/84, %14,2), mümkün İFE (14/84, %16,6) olarak tespit edildi. Kanıtlanmış İFE olgularının %91,3'ü (53/58) invazif kandidiyazis (İK), %5,1'i (3/58) ise invaziv pulmoner aspergillozis (İPA), nazofaringeal invazif fungal tutulum (1/58, %1,7) ve kolonda invazif fungal tutulum (1/58, %1,7) idi. Olası ve mümkün İFE hastalarının hepsi (26/26, %100) İPA olarak saptandı. Bilinen İFE risk faktörleri olan immünsüpresif tedavi kullanımı, renal replasman tedavisi ihtiyacı, mekanik ventilasyon ihtiyacı, santral venöz kateter mevcudiyeti, üriner kateter mevcudiyeti, GİS kateter mevcudiyeti, mukozit/diyare/ileus öyküsü, malnutrisyon, kan ürünü transfüzyonu, bakteriyel enfeksiyon, antibakteriyel tedavi, hastane ve yoğun bakım yatış süreleri, nötropeni süresi tüm hastalarda irdelendi. Hematolojik malignite ve non-hematolojik immünosüpresif

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ÖZ

gruplar arasında, immünosüpresif tedavi kullanımı ve nötropeni süresi istatistiksel olarak anlamlı bulundu. Bunun dışındaki parametreler için iki grup arasında anlamlı fark bulunamadı (p<0,05).

Sonuç: Çalışmamız genel olarak literatürle uyumlu olmakla birlikte; İK hasta grubunda görülen mortalitenin, İPA hasta grubuna benzerlikte yüksek saptanması dikkat çekicidir. Yine İFE epidemiyolojisi açısından bölgesel ve hastaya yönelik farklılıkların olabileceği bu çalışmada gösterilmiştir. Giderek sıklığı artan İFE'lerin, risk faktörlerinin iyi bilinmesi, yeni gelişen tanı yöntemlerinin kullanılması ve multidisipliner yaklaşılması ile değerlendirilmesi gerekmektedir.

Anahtar kelimeler: İmmünsüpresyon, invazif fungal enfeksiyon, risk faktörleri

INTRODUCTION

The epidemiology of fungal infections has changed in recent times. The widespread use of broad-spectrum antibacterial agents and the increasing popularity of fluconazole prophylaxis for controlling Candida albicans infections increased the incidence of filamentous fungal infections (1). Invasive fungal infection (IFI) usually presents as candidemia or invasive aspergillosis, particularly in immunosuppressed patients, such as those with hematological malignancy and solid organ transplant (SOT) recipients (2-4).

Risk factors, such as neutropenia history or corticosteroid or cytotoxic agent consumption, remain important for IFI development (5,6). Today, the risk of IFI in patients without neutropenia is increasing with increasing medical care (7). Therefore, IFI is encountered not only in hematological malignancy, solid cancer, and SOT recipient groups, but also in the immunosuppressed group, such as those with rheumatoid arthritis, chronic renal failure, inflammatory bowel disease, and diabetes mellitus (4,6,8). The presence of predisposing factors, as well as the underlying disorders, is important for IFI developments, which include prolonged hospital or intensive care stay, antibacterial agent administration, serious burn injury, major surgery, malnutrition, and the use of central venous catheter (8).

IFI is a difficult process both in diagnoses and treatments and requires a multidisciplinary approach (9,10). In addition to the comprehensive knowledge of patient risk factors, appropriate and timely usage of microbiological, serological, molecular, and radiological analyses is required for IFI diagnosis. It should be kept in mind that Candida species display different resistance patterns. Therefore, identification at the species level in IFIs is of great importance.

Several studies investigated the development of IFIs in immunosuppressed patients; however, these studies have usually focused on patients with hematological malignancy. Thus, the present study aimed to evaluate the types, distribution, risk factors, and prognosis of IFIs in patients with non-hematological immunodeficiencies, such as solid cancer and SOT recipients, as well as patients with hematological malignancy, and determine the differences between these two groups in terms of risk factors for IFI development.

METHODS

After obtaining approval from the Başkent University Institutional Review Board (decision no: KA14/158, date: 14.05.2014), the present study comprised a total of 84 patients aged ≥18 years, who had been diagnosed with IFI between January 1, 2012, and April 1, 2014, in our hospital. Case identification and classification were performed based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus criteria (5), wherein IFI cases, excluding endemic mycoses, were evaluated in three groups as "proven," "probable," and "possible."

Cases were examined for underlying disorders (hematological malignancy, solid malignancy, and SOT), immunosuppressive therapies (corticosteroid, chemotherapy, T-cell immunosuppressant, etc.), and concomitant systemic diseases. Patients with an absolute neutrophil count of <500/mm^3 in the complete blood count were considered neutropenic. The number of days that patients remained neutropenic, treated as an inpatient, and utilized intensive care service before IFI development was recorded. The presence of mechanical ventilator support, central venous catheter, port, urinary catheter, gastrointestinal catheter, and ostomy (nasogastric catheter, gastrostomy, colostomy, ileostomy, etc.) was also investigated. The history of mucositis, diarrhea, or ileus or blood product transfusions (erythrocyte suspension, thrombocyte suspension, albumin, etc.) before the IFI development was also determined, as well as bacterial infections and antibacterial therapies in the last 3 months before IFI. Patients who require dialysis were considered as patients with renal insufficiency. Malnutrition was assessed based on the serum prealbumin concentration in the last 1 month before the IFI development; those with prealbumin concentration of <14 mg/dL were considered to have malnutrition. The types and agents of IFI were investigated. Thoracic computed tomography was performed for radiological examination of lung involvement in patients with IPA. Galactomannan (GM) antigen was analyzed in all but one IPA patient; the threshold value was predetermined as 0.5. With this, the antifungal treatment of patients was recorded.

Blood culture specimens that were sent to the microbiology laboratory of our hospital were incubated in the BD BACTEC (Becton Dickinson, Sparks, MD, USA) automated blood culture system for 5 days. At the end of this period, the specimens, which grew, were examined under the microscope, and those that formed germ tubes were typed as C. albicans. Those with negative germ tube tests were evaluated by API 20AUX (BioMerieux, Marcyl'Etoile, France) commercial kit. Samples that are taken from

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sterile body fluids or tissues were cultivated in the Sabouraud dextrose agar, Cornmeal agar, and potato dextrose agar for the fungus, which was named according to the growth time, pigment formation, and microscopic appearance on the preparations with lactophenol cotton blue.

Statistical Analysis

All collected data were transferred to the Statistical Package for the Social Sciences (SPSS®) 19 data system. Continuous variables (age) were presented as mean ± standard deviation, whereas categorical variables (gender, IFI types, immunosuppressant therapy, etc.) were presented as numbers and percentages. The Pearson chi-square test, Yates chi-square test, and Fisher Exact test were used to compare categorical variables between the groups. Data without normal distribution (hospital stay, intensive care stay, and neutropenia duration) were analyzed using the Mann-Whitney U test, which is a nonparametric test to compare outcomes between two independent groups. For all analyses, the level of statistical significance was predetermined as p-values of <0.05.

RESULTS

This study included 84 immunosuppressed patients, of whom 47 (55.9%) were females and 37 (44.1%) were males. The mean age of patients was 61.4±1.65 (22-88) years. Adult immunosuppressed patients were divided into two groups as hematological (15/84, 17.9%) and non-hematological (69/84, 82.1%) and then were compared. The distribution of patients among the types of IFI according to the EORTC/MSG consensus criteria determined that 58 (58/84, 69.0%) had proven IFI, 12 (12/84, 14.3%) had probable IFI, and 14 (14/84, 16.7%) had possible IFI. Invasive candidiasis (IC) accounted for 91.4% of proven IFI cases (52 candidemia and 1 candidal mediastinitis), whereas IPA accounted for 5.2% (3/58) of this group. Additionally, one of two cases had invasive fungal involvement of the nasopharynx (1/58, 1.7%) and the other case had invasive fungal involvement of the colon (1/58, 1.7%). Spores stained with periodic acid-Schiff were seen in these two cases; however, the agent could not be identified. All probable and possible IFI cases manifested pulmonary aspergillosis (26/26, 100%). The types of IFI according to hematological and non-hematological groups are shown in Table 1. The underlying disorders are presented in Table 2.

The hematological and non-hematological groups were compared in terms of the risk factors, including immunosuppressive therapy, the need for renal replacement therapy and mechanical ventilation, the presence of a central venous, urinary, and gastrointestinal catheter, and history of mucositis, ileus, diarrhea, malnutrition, and blood transfusion. The group comparison in terms of the rate of immunosuppressive therapy administration before developing IFI revealed it to be statistically significantly higher in the hematological malignancy group (15/15, 100%) compared to the non-hematological group (50/69, 72.5%) (p=0.018). No statistically significant difference was determined between the groups, except for receiving immunosuppressive therapy before developing IFI (p>0.05) (Table 3).

The group comparison in terms of 6-month survival following IFI revealed no statistically significant difference between the two groups (p=0.932), (Table 4). The 6-month follow-up period revealed mortality in 37.9% (11/29) of IPA cases and 32.1% (17/53) of IC cases.

Moreover, 75 (89.3%) patients had a bacterial infection before developing IFI (Table 5).

The causative agent was C. albicans in 59% and non-albicans Candida (C. glabrata in 21%, C. tropicalis in 10%, C. parapsilosis in 8%, and C. kefyr in 2%) in 41% of the 53 patients with candidemia (Figure 1).

Antifungal therapies that are performed in the patients were fluconazole in 36 (42.9%), voriconazole in 22 (26.2%), caspofungin in 19 (22.6%), amphotericin B in 4 (4.8%), and anidulafungin in 3 (%3.6) patients, in order. Of the 84 patients, 30 (35.7%) died in 6 months despite appropriate treatment.

GM antigen testing was performed in 29 patients with pulmonary aspergillosis, wherein GM was positive (>0.5) in the serum samples of 6 of 7 (6/7, 85.7%) patients with hematological malignancy and 5 of 22 (5/22, 22.7%) patients with non-hematological malignancy.

No statistical difference was determined between the groups in terms of the mean hospital stay (p=0.301) and intensive care stay (p=0.069) duration; however, the mean duration of neutropenia was statistically significantly longer in the patient group with hematological malignancy vs. the patient group with non-hematological malignancy (p=0.018) (Table 6).

Table 1. Type of IFI according to hematological and non-hematological groups

	Invasive candidiasis				Pulmonary aspergillosis				Other	Total
	Proven	Probable	Possible	Total (%)	Proven	Probable	Possible	Total (%)	Proven (%)	
Hematological patients	8	-	-	8 (53.3)	-	7	-	7 (46.7)	-	15 (100)
Non-hematological patients	45	-	-	45 (65.2)	3	5	14	22 (31.9)	2 (2.9)	69 (100)
Total	53	-	-	53 (63.1)	3	12	14	29 (34.5)	2 (2.4)	84 (100)

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Table 2. Underlying disorders details in hematological malignancy and non-hematological immunosuppressive patient groups

(n, %)	Underlying disorders (n, %)	n (%)
Hematological malignancy patient groups (15, 17.9%)	AML	5 (5.9%)
	CLL	4 (4.7%)
	CML	3 (3.5%)
	Multiple myeloma	2 (2.3%)
	Lymphoma	1 (1.2%)
Non-hematological immunosuppressive patient groups (69, 82.1%)	Solid cancer (29, 34.5%)	8 (9.5%) over
		5 (5.9%) colon
		3 (3.5%) cervix
		2 (2.3%) endometrioma
		2 (2.3%) peritoneum
		2 (2.3%) breast
		2 (2.3%) pancreas
		1 (1.2%) vagina
		1 (1.2%) prostate
		1 (1.2%) kidney
		1 (1.2%) liver
		1 (1.2%) mesenchymal
	Solid-organ transplantation (20, 23.8%)	9 (10.7%) kidney
		6 (7.1%) heart
		5 (5.9%) liver
	Other (20, 23.8%)	5 (5.9%) CVD
		4 (4.7%) rheumatoid arthritis
		4 (4.7%) kidney failure
		2 (2.3%) heart failure
		1 (1.2%) ulcerative colitis
		1 (1.2%) temporalarteritis
		1 (1.2%) glomerulonephritis
		1 (1.2%) Parkinson's disease
		1 (1.2%) femur fracture operation

AML: acute myeloid leukemia, CLL: chronic lymphocytic leukemia, CML: chronic myeloid leukemia, CVD: cerebrovascular disease

DISCUSSION

The incidence of fungal infections has increased and its epidemiology has changed in the last two decades. Additionally, the incidence of filamentous fungal infections has increased (1). First, infectious disease authorities formed a consensus in 2002 and classified IFIs as proven, probable, and possible (11). Later, they were revised in 2008 and the IFI classification followed the EORTC/MSG consensus criteria. Classification is based on host-related factors, clinical criteria, and mycological criteria. The group that has been repeatedly investigated in IFI studies included patients with hematological malignancies (12-14). SOT recipients and patients with solid cancer are important patient groups for IFI; however, studies with these patient groups are limited. Additionally, studies that compare these two groups are scarce (1,15).

The incidence of candidiasis, with C. albicans as the leading agent, began to decrease in the 1990s, but the incidence of fluconazole-resistant or dose-dependent non-albicans Candida has increased.

The incidence of IFI s, which range from 2% to 49% in patients with hematological malignancy, varies based on the chemotherapy regimen and prophylaxis (13,14,16-19). Many studies revealed that pulmonary aspergillosis was the most common IFI followed by candidemia. A study that evaluated the autopsies of 220 patients with hematological malignancy in the 1990s and 2000s revealed that IPA was the most prevalent with 55-58%. The incidence of Candida infections decreased to 26% in the 2000s from 40% in the 1990s. Contrarily, the incidence of infections caused by Mucorales or Fusarium spp. has slightly increased (12). The present study revealed that 53.3% of the developed IFIs in the hematological group were IC and 46.7% were IPA. Additionally, the finding that primary candidemia accounted for 98% of the IC cases suggests

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Table 3. The comparison of hematological malignancies and non-hematological immunosuppressive groups in terms of risk factors

	Hematological malignancy patient groups	Non-hematological immunosuppressive patient groups	p
Immunosuppressive therapy before IFI (+) (n=65)	15	50	0.018
Immunosuppressive therapy before IFI (-) (n=19)	0	19	
Need for renal replacement therapy before IFI (+) (n=21)	2	19	0.335
Need for renal replacement therapy before IFI (-) (n=63)	13	50	
Mechanical ventilation before IFI (+) (n=29)	2	27	0.074
Mechanical ventilation before IFI (-) (n=55)	13	42	
Central venous catheter before IFI (+) (n=60)	10	50	0.892
Central venous catheter before IFI (-) (n=24)	5	19	
Urinary catheter before IFI (+) (n=56)	11	45	0.763
Urinary catheter before IFI (-) (n=28)	4	24	
Gastrointestinal catheter before IFI (+) (n=19)	2	17	0.502
Gastrointestinal catheter before IFI (-) (n=65)	13	52	
History of mucositis, ileus, diarrhea (+) (n=30)	5	25	0.932
History of mucositis, ileus, diarrhea (-) (n=54)	10	44	
Malnutrition before IFI (+) (n=24)	2	22	0.212
Malnutrition before IFI (-) (n=60)	13	47	
Blood transfusion before IFI (+) (n=40)	6	34	0.713
Blood transfusion before IFI (-) (n=44)	9	35	

IFI: invasive fungal infections

Table 4. Six-month survival after IFI (n= patients)

	6-month survival after IFI		Total (n=84)	p
	Alive (n=21)	Ex (n=63)		
Hematological malignancy patient groups	9	6	15	0.932
Non-hematological immunosuppressive patient groups	45	24	69	
Total	54	30	84	

IFI: invasive fungal infections

that the difference with the other studies occurred from the higher rate of catheter-related infections in Turkey compared to developed countries.

In patients with hematological malignancy, the most frequently identified risk factors for IC are long-term broad-spectrum antibiotic use, immunosuppression, neutropenia, central venous or arterial catheter, urinary catheter, nasogastric catheter, total parenteral nutrition, mechanical ventilation, renal failure, hemodialysis, splenectomy, steroid use, and long-term (>9 days) intensive care stay (20). The most critical risk factor for developing invasive aspergillosis is deep and prolonged neutropenia. Other risk factors include high-dose corticosteroid or other immunosuppressive therapies, mucosal barrier injury due to cytotoxic chemotherapy, and impaired microbial flora due to broad-spectrum antibiotic use (21). The IPA prevalence among the patients with hematological malignancy is associated with underlying disorders and neutropenia duration, which changes based on the type of chemotherapy (12). The present study revealed a statistically significant duration of neutropenia and immunosuppressive therapy administration (p=0.018 and p=0.018, respectively) for the hematological malignancy group compared to the non-hematological group.

The incidence of IFI in SOT recipients, who account for the substantial proportion of the non-hematological immunosuppressed group, changes based on the transplanted organ. A 5-year prospective study conducted by The Transplant Associated Infection Surveillance Network with 23 transplantation centers from the United States of America the following cumulative incidence of IFI according to the transplanted organs: small intestine in 11.6%, lung in 8.6%, liver in 4.7%, heart in 4%, pancreas in 3.4%, and kidney in 1.3%. The most common IFIs in order of decreasing prevalence were IC in 53%, invasive aspergillosis in 19%, and cryptococcosis in 8% (3). Another prospective study revealed that Candida is the most common agent pathogen of the IFIs, excluding lung transplantation, and IPA was the agent most frequently reported after lung transplantation (22). The present

Table 5. Recent bacterial infections before IFI

	Bacteremia	Pneumonia	İntra abdominal	Urinary system	Febrile neutropenia	Complicated soft tissue infection	None
Hematological malignancy patient groups (n=15)	1 (6.7%)	5 (33.3%)	0	4 (26.7%)	5 (33.3%)	0	0
Non-hematological immunosuppressive patient groups (n=69)	14 (20.3%)	30 (43.5%)	6 (8.7%)	6 (8.7)	1 (1.5%)	3 (4.3%)	9 (13.0%)
Total (n=84)	15 (17.9%)	35 (41.7%)	6 (7.1%)	10 (11.9%)	6 (7.1%)	3 (3.6%)	9 (10.7%)

IFI: invasive fungal infections

study revealed that IC dominated the entire non-hematological group, but specific to the SOT recipients, wherein pulmonary aspergillosis accounted for 75% and candidemia accounted for 25% considering 9 renal, 6 heart, and 5 liver transplant recipients. In the literature, IFI was most commonly determined in the form of pulmonary aspergillosis in the heart and liver transplant recipients and the form of IC in the liver and kidney transplant recipients (3,22,23). The present study revealed that pulmonary aspergillosis was determined in five of the six (5/6, 83.3%) heart transplant recipients, which was higher compared to the liver and kidney transplant recipients, consistent with the literature (22).

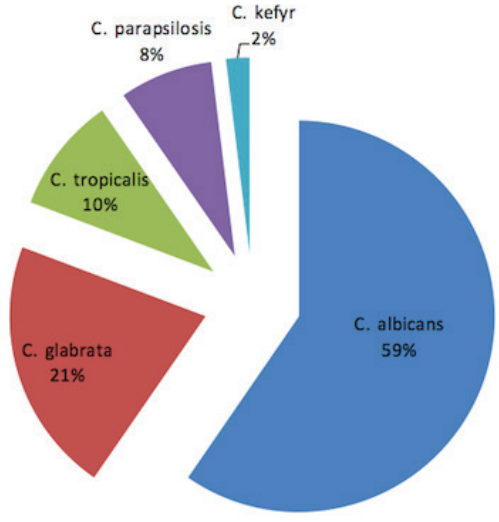


Figure 1. Range of Candida species

Statistically significantly different parameters between the groups include neutropenia duration and immunosuppressive therapy administration, which were determined in the hematological group (1). Other parameters, such as the need for renal replacement therapy, need for mechanical ventilation, and the presence of a central venous catheter, posed similar risks for the hematological and non-hematological groups.

The literature reported a crude mortality rate increasing up to 60% (16-19) after IFI. The present study revealed a 35.7% overall crude mortality rate (for 6 months after IFI). However, the crude mortality rate was 40% for the hematological malignancy group and 34.8% for the non-hematological group, which were similar to the limited number of studies in the literature (1,15). These data suggest that IFIs are very serious and are used to determine the prognosis not only in the hematological group but also in the non-hematological group. The evaluation of the mortality according to the agent pathogens revealed no difference between the IPA and IC. Determining the association of crude mortality rates with fungal infections is impossible; however, a high mortality rate in the patients who develop IC is inconsistent with the literature and is striking (1).

The present study revealed consistent GM antigen testing results with the literature and suggest that serum GM has limited diagnostic value, particularly in the non-hematological group (24).

The multicenter study published in 2009 revealed that fungi account for 19%, and Candida spp. account for 18.5% of the culture-positive circulatory system infections (23). The present study revealed 59% C. albicans and 41% non-albicans Candida of the candidemia, which was determined to be the most common type of IFI. Therefore,

Table 6. Mean hospital stay, mean ICU stay, and mean duration of neutropenia before IFI (days) [mean/median (minimum-maximum)]

	Hematological malignancy patient groups	Non-hematological immunosuppressive patient groups	Overall average	p
Mean hospital stay before IFI (days)	19.7/16.0 (3-64)	37.8/22.0 (0-360)	34.6/18.0 (0-360)	0.301
Mean ICU stay before IFI (days)	2.8/0.0 (0-16)	9.7/4.0 (0-51)	8.4/1.0 (0-51)	0.069
Mean duration of neutropenia before IFI (days)	7.1/0.0 (0-30)	2.5/0.0 (0-30)	3.3/0.0 (0-30)	0.018

IFI: invasive fungal infections, ICU: intensive care unit

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C. albicans remains the leading cause of candidemia with non-albicans Candida having considerable prevalence.

Study Limitations

The limitations of our study are its retrospective nature and the low number of our cases as 84. Multi-center studies on a much larger number of cases will significantly contribute to this issue.

CONCLUSION

Our findings are following the literature, but the high mortality rate in patients with IC drives attention. This study also revealed that the epidemiology of IFI may vary based on the region and the patient. A better understanding of the risk factors of common sensed IFIs is necessary, as well as maintaining the extensive usage of newly developed diagnostic methods and multidisciplinary approaches.

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