RESEARCH ARTICLE

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Incidence and Risk Factors for Invasive Fungal Infection in Patients with Hematological Malignancies at a Tertiary Hospital in Malaysia

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Abstract

Objective: This study aims to describe the incidence and risk factors of invasive fungal infection (IFI) among patients with haematological malignancies (HM) in a tertiary hospital from Malaysia. **Methods:** This was a cross-sectional study in a teaching hospital involving HM patients, admitted for chemotherapy or haematopoietic stem cell transplantation (HSCT). Each admission for either chemotherapy or HSCT was considered as a separate event. Patients were followed up for development of IFI from the time of each admission to time of discharge or time of death. Outcomes of patients with IFI upon discharge were recorded. Clinical and mycological data during each admission were collected and analysed. **Results:** Eighty-three patients with mean age of 58.8±15.5 years were recruited. Acute myeloid leukemia (AML) was the most common diagnosis (45.8%). A total of 132 admissions were analysed from these 83 patients. Antifungal prophylaxes were prescribed in 94.7% of admissions with fluconazole being the most common agent used (88.6%). The incidence of proven and probable IFI was 7.6%. *Candida tropicalis* was the most common fungi isolated from these patients (22.7%), followed by *Candida krusei* (13.6%). The mortality rate due to IFI was 17.6%. Patients with AML and those with concomitant bacteraemia were associated with higher risk of IFI (odds ratio [OR] 3.69, 95% confidence interval [CI] 1.16–11.71, p=0.029 and OR 4.17, 95% CI 1.37–12.66, p=0.009, respectively), while the use of antifungal prophylaxis was associated with lower IFI risk (OR 0.17, 95% CI 0.03–0.83, p=0.045). After multivariate analysis, the use of antifungal prophylaxis remains significantly associated with lower risk of IFI (OR 0.54, 95% CI 0.01–0.62, p=0.019). **Conclusion:** IFI remains one of serious complications of HM patients undergoing chemotherapy and HSCT, most commonly due to non-*albicans Candida* spp. Appropriate antifungal prophylaxis is therefore crucial in the prevention of breakthrough IFI.

Keywords: Invasive fungal infection- haematological malignancy- candidaemia- Candida spp.

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Introduction

Invasive fungal infection (IFI) is one of the causes of mortality among patients with haematological malignancies (HM), particularly those with acute leukemia and those undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [1]. The development of IFI does not just complicate the treatment process of the underlying HM, but also incurs higher healthcare cost.

The epidemiology of IFI in patients with HMs varies over time and differs according to geographical regions. Medically important yeast, particularly Candida spp., have been historically identified as the most common causative organisms in IFI. In the recent years, the incidence of invasive Candida infections has become relatively less common in patients with HMs due to the use of effective antifungal prophylaxis [2]. Instead, the predominant pathogens responsible for IFI in this cohort of patients are now Aspergillus spp., which often lead to higher risk of mortality [3]. The geographical difference in the incidence of IFI among patients with HM is reported to range from 9.6% to 13.0% in the Western countries, and between 7.0% to 7.7% in Asia [4-7].

Risk factors contributing to the development of IFI include disease related factors such as acute leukemia, refractory or relapse disease; host-related factors such as patients' performance status, presence of comorbidities including organ dysfunction, and older age [8]. Other

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factors such as prolonged duration of neutropenia, severe mucositis, and prior history of IFI also played an important role in the development of IFI [9].

The development of IFI in these vulnerable HM patients often leads to grave outcomes. Even though fungal-infection related mortality has decreased with the practice of prophylactic strategies and introduction of new antifungal therapies, the mortality rate is still relatively high, ranging from 26.2% to as high as 62.9%, especially in low to middle income countries [6, 10]. Moreover, the economic burden of IFI is not to be underestimated due to prolonged hospitalization and the relative high cost of the newer agents [11-14]. A study shines a light on the challenges faced by clinicians in the Asia Pacific regions whereby 74% of them reported limited access to non-culture diagnostic tests such as galactomannan while an even higher proportion (80%) could not use the preferred antifungal therapy due to financial constraints [15]. Therefore, to achieve cost effectiveness in the diagnosis and management of IFI, keeping abreast of updated local mycological data is recommended as it will guide clinicians on the most appropriate therapeutic decisions. However, epidemiology data of IFI among patients with HM in Southeast Asian (SEA) countries is scarce [16].

To the best of our knowledge, there has not been any published report on the epidemiology of IFI among patients with HM in Malaysia. This information is vital to ensure a better antifungal stewardship and appropriate antifungal treatment are administered in the future to prevent worse health outcomes. Hence, we aimed to determine the incidence of IFI among HM patients in Malaysia and the risk factors associated with the development of IFI in these patients.

Materials and Methods

This was a cross-sectional study conducted in a tertiary center in Kuala Lumpur, Malaysia from March 2020 until June 2022. The research was approved by the institutional Medical Research Ethics Committee (MREC-2019514-7415) and was conducted in accordance with principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Only patients aged 18 years-old and above with HM, admitted for in-patient intensive chemotherapy or HSCT were included in this study. All patients under the age of 18 years-old, who were not planned for chemotherapy or HSCT were excluded. The clinical and socio-demographic information were obtained from patient's electronic medical record. Information collected included underlying disease, duration of neutropenia, presence of central venous catheter, types of antifungal prophylaxis, results of bacterial and fungal culture, antimicrobial and antifungal used for the treatment of febrile neutropenia and IFI. Febrile neutropenia was defined as per Infectious Disease Society of America guideline published in 2011 [17]. The classification of proven and probable fungal infections in the study followed the criteria proposed by EORTC/MSGERC in 2020 [18].

Each admission for either chemotherapy or HSCT was considered as a separate event. Patients were followed up for development of IFI from the time of each admission to time of discharge or time of death. Outcomes of patients with IFI upon discharge were recorded.

As part of our routine clinical practice, blood cultures from peripheral veins and central venous catheter were performed using automated BACTEC instruments in the Diagnostic Microbiology Laboratory whenever patients developed febrile neutropenia. Additional fungal blood cultures were collected if patients had more than 7 days of neutropenia. The recovery of invasive fungal pathogens was performed using automated BACTEC instruments in the Mycology Laboratory. Other clinical samples (including sputum, urine or stool) and radiological examination were cultured using routine mycology diagnostic procedures, if clinically indicated. Galactomannan test and polymerase chain reaction (PCR) assay were not performed as they are not offered as a routine laboratory service at our centre. Imaging study such as computed tomography would be arranged if the diagnosis of IFI is suspected, and tissue biopsy or bronchoalveolar lavage (BAL) were performed if there was no contraindication. The choice of empirical antifungal therapy in our centre is micafungin. The diagnostic flow chart for IFI is illustrated in Chart 1.

All statistical analysis was conducted using SPSS version 26.0 (IBM, USA). Descriptive statistics were used for categorical variables. Results were presented as frequencies and percentages for categorical variables. Numerical variables that were normally distributed were presented as mean and standard deviation, while median and interquartile ranges were used to present numerical variables which were not normally distributed. Fisher's exact test and Chi Square test were used to compare categorical variables. Nominal regression was used to estimate odd's ratio for categorical variables. The number of admissions were set as control, whereas number of proven and probable IFI episodes were set as the case. P value of <0.05 was considered statistically significant.

Results

A total of 132 admissions involving 83 patients were recruited. The mean age of the patients was 48.8±15.5 years (Table 1). Majority were males (55.4%), and most of the patients were of Chinese ethnicity (47.0%). Of the 132 admissions, 56 patients were admitted once, 13 patients were admitted twice, while 18 patients had three or more admissions. Acute myeloid leukemia (AML) was the most common underlying diagnosis (45.8%), followed by multiple myeloma (MM) (16.9%) and acute lymphoblastic leukemia (ALL) (15.7%).

Elective admission for HSCT accounted for 34.8% of the cohort studied (Table 2). Majority of the HSCTs were autologous HSCT (60.9%). Peripherally inserted central catheter (PICC) was the most common (84.8%) mean of venous access during admissions. Antifungal prophylaxes were prescribed in 94.7% of the admissions, with fluconazole being the most common antifungal drug used (93.6%), followed by voriconazole (4.8%) and micafungin (1.6%).

The incidence of proven and probable IFI in this study was 7.6%. Patients with AML was associated with

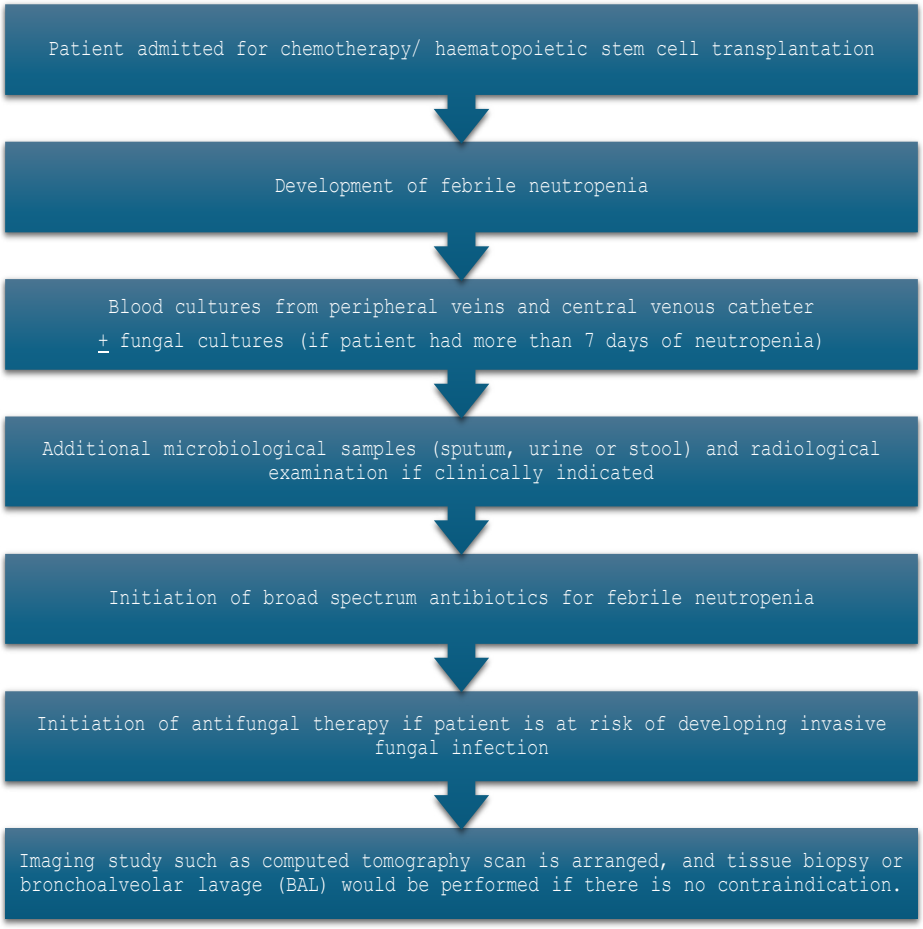

Chart 1. Diagnostic Flow for Invasive Fungal Infection

higher risk of developing IFI (odds ratio [OR] 3.69, 95% confidence interval [95% CI] 1.16–11.71, p=0.029) (Table 1). In patients who had IFI, the mean duration of neutropenia was significantly longer compared to those who did not (21.94 days versus 11.61 days, 95% CI 4.60–16.07, p=0.001). The use of antifungal prophylaxis was associated with lower IFI risk from univariate analysis (OR 0.17, 95% CI 0.03–0.83, p=0.045), whereas concomitant bacteraemia was associated with a greater risk of IFI (OR 4.17, 95% CI 1.37–12.66, p=0.009). (Table 2). After multivariate analysis, the use of antifungal prophylaxis remains significantly associated with lower risk of IFI (OR 0.54, 95% CI 0.01–0.62, p=0.019). Of the 17 admissions which were complicated with IFI, 9 were proven, 1 was probable and the remaining 7 were possible IFIs. Majority (90.0%) of the fungi cultured were obtained from blood. The most common fungi isolated were *Candida tropicalis* (29.4%), *Candida krusei* (17.6%) followed by *Trichosporan asahii* (5.9%). Micafungin was the most common antifungal therapy prescribed for treatment (52.9% of admissions). The mortality rate attributed to IFI was 17.6% (Table 3).

Discussion

IFI is a significant cause of morbidity and mortality among HM patients undergoing intensive chemotherapy and HSCT [10]. The incidence of proven and probable IFI among our patients (7.6%) is comparable to Thailand (7.0%) but lower than Taiwan (20.0%) [6, 19]. These discrepancies could be attributed to the different policy in the use of antifungal prophylaxis whereby antifungal agents are routinely offered as primary prophylaxis in our centre and Thailand. However, it is noteworthy that the study in Taiwan was published more than 5 years ago, and the practice may have changed. Other plausible explanation for the relatively low prevalence of IFI reported in our hospital is the likelihood of under-diagnosis of IFI due to the lack of accessibility of novel biomarker tests such as galactomannan and PCR assays.

Consistent with other studies, patients with AML had significantly higher risk for IFI [6, 20]. This could be due to the usage of more intense chemotherapy that results in prolonged neutropenia, coupled with the suppression of immune systems by the disease itself [21]. Other risk factors associated with increased risk of IFI include advanced age, severity and duration of neutropenia, relapsed or refractory disease, use of immunosuppressive agents and mismatched donor in HSCT cohorts [22].

In concordance to this, our results demonstrated that prolonged neutropenia is associated with increased risk of IFI. Neutrophil is critical in the host defence against invasive candidiasis and aspergillosis by their rapid deployment to the site of fungal invasion and via their effector mechanism mediating fungal destruction [23]. The prolonged deficiency of neutrophils following

Table 1. Baseline Characteristics of Participating Patients and Univariate Analysis of Factors associated with Invasive Fungal Infection during Admissions for Intensive Chemotherapy and Hematopoietic Stem Cell Transplant

		IFI		Univariate analysis		
	Total n=83 (%)	Yes n=17 (%)	No n=66 (%)	Odds ratio	95% CI	p value
Gender						
Male	46 (55.4)	9 (19.6)	37 (80.4)	0.88	0.30 – 2.57	1
Female	37 (44.6)	8 (21.6)	29 (78.4)			
Age Group						
< 65	71 (85.5)	15 (21.1)	56 (78.9)	1.34	0.27 – 6.78	1
> 65	12 (14.5)	2 (16.7)	10 (83.3)			
Ethnicity						
Malay	31 (37.3)	4 (16.0)	21 (84.0)	1.66	0.57 – 4.89	0.406
Chinese	39 (47.0)	5 (12.8)	34 (87.2)	0.39	0.12 – 1.24	0.172
Indian	12 (14.5)	4 (33.3)	8 (66.7)	2.23	0.58 – 8.54	0.255
Others	1 (1.2)	0 (0.0)	1 (100.0)	-	-	1
Diagnosis						
AML	38(45.8)	12 (31.6)	26 (68.4)	3.69	1.16 – 11.71	0.029*
ALL	13 (15.7)	3 (23.1)	10 (79.6)	1.2	0.29 – 4.95	0.724
HL	7 (8.4)	0 (0.0)	7 (100.0)	-	-	0.335
NHL	7 (8.4)	1 (14.3)	6 (85.7)	0.63	0.07 – 5.57	1
MM	14 (16.9)	0 (0.0)	14 (100.0)	-	-	0.063
Others	4 (4.8)	1 (25.0)	3 (75.0)	1.31	1.13 – 13.47	1
Co-morbid						
Yes	35 (42.2)	9 (25.7)	26 (74.3)	1.37	0.59 – 5.06	0.41
No	48 (57.8)	8 (16.7)	40 (83.3)			

Abbreviations: IFI, invasive fungal infection; CI, confidence interval; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; * P <0.05 is statistically significant

Table 2. Characteristics of Patients and Univariate Analysis of Factors Associated with Invasive Fungal Infection during Admissions for Intensive Chemotherapy and Hematopoietic Stem Cell Transplant

		IFI		Univariate analysis		
	Total n=132 (%)	Yes n=17 (%)	No n=115 (%)	Odds ratio	95% CI	p value
HSCT						
Yes	46 (34.8)	3 (6.5)	43 (93.5)	0.36	0.01 – 1.32	0.111
No	86 (65.2)	14 (16.3)	72 (83.7)			
Types of HSCT (n=46)						
Allogeneic/	18 (39.1)	2 (11.1)	16 (88.9)	3.38	0.28 – 40.25	0.552
Haploidentical						
Autologous	28 (60.9)	1 (3.6)	27 (96.4)			
PICC						
Yes	112 (84.8)	17 (15.2)	95 (84.8)	0.85	0.78 – 0.92	0.074
No	20 (15.2)	0 (0.0)	20 (100.0)			
Antifungal prophylaxis						
Yes	125 (94.7)	14 (11.2)	111 (88.8)	0.17	0.03 – 0.83	0.045*
No	7 (5.3)	3 (42.9)	4 (57.1)			
Neutropenia >7 days						
Yes	88 (66.7)	17 (19.3)	71 (80.7)	-	-	0.002
No	44 (33.3)	0 (0.0)	44 (100.0)			
Bacterial infection						
Yes	54 (40.9)	12 (22.2)	42 (77.8)	4.17	1.37 – 12.66	0.009*
No	78 (59.1)	5 (6.4)	73 (93.6)			

Abbreviations: IFI, invasive fungal infection; CI, confidence internal; HSCT, haematopoietic stem cell transplantation; PICC, peripherally inserted central catheter * P <0.05 is statistically significant

Table 3. Characteristics of Patients with Invasive Fungal Infection

	n=17 (%)
IFI category	
Possible	7 (41.2)
Probable	1 (5.9)
Proven	9 (52.9)
Fungal infection	
No positive culture	7 (41.2)
Candida tropicalis	5 (29.4)
Candida krusei	3 (17.6)
Aspergillus fumigatus	1 (5.9)
Trichosporan asahii	1 (5.9)
Source of positive fungal culture (n=10)	
Blood	9 (90.0)
Palate	1 (10.0)
Agents used for treatment	
Voriconazole	8 (47.1)
Micafungin	9 (52.9)
Outcome	
Alive	14 (82.4)
Dead	3 (17.6)

Abbreviations: IFI, invasive fungal infection

chemotherapy or during HSCT significantly increases the risk of patients developing IFI. Similarly, our HM patients who had concomitant bacteraemia were associated with increased risk of developing IFI, consistent with other studies [24, 25]. It is postulated that bacteraemia can lead to systemic immune response, mediated by T cells and B cells. The hyperinflammatory state due to sepsis often leads to neutrophil activation and may leads to organ dysfunction. As a result of the imbalance in cytokine response from systemic infection, compensatory immune paresis predisposes patients to opportunistic infections including IFI [26]. Therefore, it may be important to suspect IFI in patients who have septicaemia and unresponsive to antibiotics.

Antifungal prophylaxis is often recommended in patients who are at high risk of IFI, such as AML or myelodysplastic syndrome (MDS) who are undergoing induction chemotherapy or HSCT. Currently, posaconazole is the recommended antifungal prophylaxis for these patients, as studies have demonstrated a 6% absolute reduction in the incidence of proven and probable IFI [27, 28]. Other antifungal therapies, usually of the triazole group such as isavuconazole and voriconazole have also been shown to reduce the incidence of IFI [29]. Alternatively, micafungin has been used as prophylaxis in HSCT patient and has shown to be an effective alternative [30].

In this study, majority of the patients received fluconazole as primary antifungal prophylaxis. The rationale of using fluconazole is mainly due to the limited resources in our setting. In a small group of patients however, voriconazole was used as antifungal prophylaxis. Voriconazole was administered among these patients instead of fluconazole as they have developed possible IFI during the previous courses of chemotherapy. Nevertheless, we found that usage of antifungal prophylaxis in general, significantly reduced the risk of IFI among patients undergoing treatment for HM. However, it is noteworthy that 11.2% of our patients have experienced breakthrough IFI while on fluconazole prophylaxis. This incidence is higher when compared with other studies which used mainly posaconazole or voriconazole as their choice of prophylaxis [31]. This illustrates that appropriate antifungal agents ought to be chosen if primary prophylaxis is recommended and should be in accordance with the international guidelines to minimise the risk of breakthrough IFI.

Among patients who developed IFI, *Candida tropicalis* and *Candida krusei* were the main fungi isolated from the blood cultures, in contrast to other studies where invasive aspergillosis was the major cause of IFI among patients with HM, identified from BAL or tissue biopsy samples. This is most likely attributed to the lack of availability of galactomannan assay and difficulty in culturing Aspergillus from blood samples, in addition to the difficulties of obtaining tissue biopsy due to cytopenia, leading to underreporting of invasive aspergillosis (IA). In the past, Candida infection was the most common cause of IFI especially in the HSCT population but with the revolution in antifungal prophylaxis over the past 10 years, this has changed with a marked increase in the incidence of IA amongst HSCT recipients [32]. Similarly, there has been a shift from *Candida albicans* to non-*albicans Candida* infection over the years among patients with HM, and this is thought to be driven by the widespread use of antifungal prophylaxis particularly fluconazole, leading to the emergence of non-*albicans Candida* species that are inherently resistant to fluconazole [33].

There are several limitations in this study. Firstly, the small sample size from a study conducted at a single institution might not be truly reflective of the entire population of HM patients. In addition, the unavailable biomarker tests such as galactomannan for aspergillosis or (1,3)-β-D-glucan (BDG) assay for Candidiasis and molecular assays as routine service coupled with the lack of crucial diagnostic procedures such as BAL or biopsy among our patients might have contributed to underdiagnoses of IFI. This highlights the challenges that is faced by majority of the treating haematologists in SEA where resources are limited.

Nevertheless, this is the first study which reported the incidence of IFI among patients with HM and the associated risk factors in a major academic centre in Malaysia where such epidemiological data is lacking. As the susceptibility may differ between continents, the availability of local data is crucial for development of local practice guidelines and policy to improve the outcomes of these patients.

In conclusion, IFI remains an important cause for mortality and morbidity among HM patients who are undergoing intensive chemotherapy and HSCT. Candidaemia secondary to non-*albicans Candida* spp. was the most common IFI among these patients. Therefore, our data highlight the importance to review our clinical

practice regarding the appropriate administration of antifungal prophylaxis, with the aim of minimizing the occurrence of breakthrough infections as much as possible.

Author Contribution Statement

CSC was involved in data collection, analysis of data and manuscript writing. CCL and NH were involved in data collection and review of the manuscript. IT, STT, CS, RV, PCB, EFMC, SK, and YZ were involved in review of the manuscript. GGG has developed the concept, revised and supervised the work. All authors read and approved the final manuscript.

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Approval

The study was not approved by any scientific body nor as part of student thesis.

Ethical Declaration

The study was approved by Universiti Malaya Medical Center-Medical Research Ethics Committee (UMMC-MREC). The reference number for approval was 2019514-7415.

Conflict of Interest

The authors have no conflict of interest to declare.

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