MAGNITUDE AND ASSOCIATED FACTORS OF POSSIBLE FUNGAL INFECTION AMONG HEMATO-ONCOLOGY PATIENTS WITH NEUTROPENIA AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

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A RESEARCH THESIS TO BE SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES; PEDIATRICS AND CHILD HEALTH DEPARTMENT IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE SPECIALTY CERTIFICATE PROGRAM IN PEDIATRICS AND CHILD HEALTH

OCTOBER, 2021ADDISABABA, ETHIOPIA

APPROVAL SHEET

ADDIS ABABA UNIVERSTY COLLEGE OF HEALTH SCIENCE SCHOOL OF MEDICINE DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

I, the undersigned Pediatrics and Child health resident, declare that I have submitted My original thesis on a title Magnitude And Associated Risk Factors Of Possible Fungal Infection In Hemato-Oncology Patients With Neutropenia At Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia , 2021, in partial fulfillment of the specialty program.

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Magnitude and Associated Risk Factors Of Possible Fungal Infection Among Hemato-Oncology Patients With Neutropenia at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

RESEARCH THESIS

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ACKNOWLEDGEMENTS

I would like to express my gratitude to the TASH Department of Pediatrics and Child Health for giving me this opportunity to research an issue I am inquisitive about. I would also like to express my heartfelt gratitude to my advisers, Dr. Workeabeba Abebe and Dr. Daniel Hailu, for their continuous support and constructive advice.

Last but not list I gratefully thank Addis Ababa University for sponsoring the thesis and the Pediatric and Child health department for giving me this opportunity to work on this topic.

Abstract

Background A fungal infection represents a growing problem in children with hematologic malignancies during chemotherapy-induced neutropenia.

Objectives: This study aimed to evaluate the magnitude of possible fungal infection among hemato-oncologic children admitted to the hospital between 2017 and 2021 in TASH, Ethiopia.

Methods: Institution-based retrospective cross-sectional study reviewed the charts of 256 neutropenic patients at TikurAnbessa specialized hospital. Required data were collected using a questionnaire. The data were entered into a computer using Excel and exported to Statistical Package for Social Sciences Version 25 for analysis. Binary logistic regression analysis assessed predicting factors associated with a fungal infection, and p-value <0.05 was considered statistically significant.

Results: Among 256, 152 were males, and most of the patients were in the age range of 5-10 years. In this study, the magnitude of fungal infection among haemato-oncology neutropenic patients was 31%. Among those patients diagnosed with a possible fungal infection, 56 (72%) ALL patients, 6 (7.7%) AML patients and 15 (19%) of NHL patients. Age, duration, and severity of neutropenia and prolonged use of steroids are significantly associated factors.

Conclusion: Our finding suggests a high rate of fungal infections in neutropenic ALL and AML patients. These results help improve the management of these patients. However, further studies are needed.

Keywords: *Neutropenia, Invasive fungal infection, hemato-oncology, pediatrics*

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ACRONYMS

AAU	Addis Ababa University
AL	Acute Leukemia
ALL	Acute Lymphoblastic Leukemia
AML	Acute Mylogenous Leukemia
BMA	Bone Marrow Aspiration
CBC	Complete Blood Count
CHS	College Of Health Science
CT	Computed tomography
GC	Gregorian Calendar
EORTC	European Organization for Research and Treatment of Cancer
HR	High Risk
HSCT	Hematopoietic Stem Cell Transplantation
IA	Invasive Aspergilosis
IFD	Invasive fungal disease
IFI	Invasive Fungal Infections
IFIG	Invasive Fungal Infections Group
MSG	Mycoses Study Group
NIAID	National Institute for Allergy and Infectious Diseases
PI	Principal Investigator
SPSS	Statistical Package For Social Sciences
TASH	TikurAnbesa Specialized Hospital
USA United	States of America

1.INTRODUCTION

1.1Background

Fungal infections represent an important complication among patients with cancer in general and those with leukemia in particular (1). Clinical and epidemiologic data are generally derived from a series of studies on adults(1). Data available in the literature on fungal infections among patients with cancer are sometimes discordant, and the possible reason for this is the lack of a common language for their definition. The European Organization for Research and Treatment of Cancer (EORTC)–Invasive Fungal Infections Group (IFIG) and the National Institute for Allergy and Infectious Diseases (NIAID)–Mycoses Study Group (MSG) had therefore published a consensus statement for the definitions of fungal infections in immune-compromised patients to be used in clinical trials, epidemiologic studies and in studies of health economics (1,12).

Invasive fungal infections (IFIs) are among the most important causes of morbidity and mortality in patients with hematological malignancies. Factors such as neutropenia, damaged mucosa, patients receiving high-dose chemotherapy, undergoing invasive medical procedures, and using broad-spectrum antibacterial drugs, constitute the risk factors for IFIs. Clinical symptoms and radiological patterns are not specific, and late diagnosis may lead to delayed therapy, which is associated with a poor outcome. Examination commonly includes a direct smear with potassium hydroxide, culturing, and histopathological analysis; however, in some cases, this can be challenging since sampling requires invasive procedures, which are not possible in critically ill patients. Hence, using a non-invasive method, such as real-time polymerase chain reaction (PCR), to detect fungal infections in clinical samples could be a suitable approach in aiding early diagnosis in high-risk infected patients (3,10).

Timely diagnosis and initiation of appropriate antifungal therapy are imperative for improving outcomes. Fortunately, there have been significant recent advances in the ability to more rapidly identify invasive fungal infections, accompanied by an evolution in the number of available antifungal agents for treatment.

1.2. Statement of the problem

Current studies show a high survival rate of hemato-oncology patients in the pediatrics age group. The inappropriate, delayed, and difficulty of managing complications not related to the malignancy perse is not giving us the expected survival rate, especially in our setup. One of the commonly mentioned complications is a severe fungal infection.

Invasive fungal infection is causing significant mortality and morbidity in hemato-oncologic patients with neutropenia in Ethiopia. The burden of the problem is increasing due to the contribution of different factors. Lack of availability of adequate Intensive Care Unit service is also making the disease prognosis worse. Therefore, this study addressed how common problem mentioned above, associated factors to its occurrence, and its impact on the overall outcome of patients who get service at the pediatrics hemato-oncology unit in TASH.

1.3. Significance of the study

This is the first study in TASH and will help us understand the burden of the disease and suggest which patient categories require close surveillance. Second, it will provide recommendations for evaluation and follow-up of the patients and suggest interventions to improve outcomes. Third, the finding of this study can serve as baseline data and help other investigators as references for future studies. Additionally, it will be an input for the scientific community, and it will be a base for further research based on the gaps that will be identified. Furthermore, it will guide policymakers and government bodies in planning and providing services for children with malignancy in Ethiopia.

2. LITERATURE REVIEW

2.1 Prevalence and causes of invasive fungal infection

The incidence of IFDs in the pediatric population with cancer and/or undergoing allogeneic HSCT is highly influenced by the use of prophylactic systemic antifungal agents, the availability of tests and procedures for earlier diagnoses, the adopted IFD definitions, population denominators, and local epidemiology(10,12). The pediatric patients at greatest risk for developing IFD are children undergoing allogeneic HSCT, those with acute myeloid leukemia (AML) and cases of relapsed acute lymphoblastic leukemia (ALL). Children with acute leukemia are continuously exposed to multiple risk factors for IFD and up to one third of them may develop IFD in the absence of antifungal prophylaxis(10).

In one observational prospective study done over 13 month period on 86 patients ,the rates of IFIs among pediatric patients with hematological disorders were found to be 16.3%(1).

In another prospective study, authors looked for the prevalence of IFI as per the revised definition of the EORTC /MSG group along with predictors of IFI and common etiological fungal species. IFI's were seen in 17 episodes out of 74 enrolled episodes. Prevalence of IFI's in index study was 22.97% [95% CI(13.99–34.21%)]. Most common fungal isolates in the index study was Aspergillus species followed by Candida species. The most common sites for isolation were respiratory tract followed by blood (8,12).

There are Variables that may modulate the risk of IFDs in cancer patients ,these includes age, intensity and duration of neutropenia, use of broad spectrum antibiotics, type of chemotherapy used and use of preventive precautions(10).

Age is an independent risk factor for IFDs in children being treated for AML or undergoing HSCT (10,24).Younger children may have less effective phagocytic activity and T-lymphocyte recovery after being exposed to intensive chemotherapy. The differences are more significant when comparing immune responses in extreme pediatric ages. Children with AML tend to be older, and it may also contribute to their incidence of IFDs. In addition, older children and adolescents are more susceptible to mucous membrane injury due to chemotherapy exposure, and mucositis may also increase the risk of IFDs.

The risk of IFDs is directly related to the intensity and duration of the neutropenia. Chemotherapy further impairs neutrophil, macrophage, B and T-lymphocyte function, also

decreasing immunoglobulin production and opsonization(17,18,10).A neutrophil count lower than 500/mm3 for longer than10 days is an important risk factor for IFDs, but the risk is highest with counts below 100/mm3 in patients with malignant neoplasms, on corticosteroids and chemotherapy, AML induction, and early post HSCT. A low lymphocyte counts of less than 100/mm3further increases the incidence of IFDs in neutropenic febrile children after chemotherapy. The use of some new immune suppressors, as infliximab, may be, by itself, a risk factor for invasive aspergillosis(10).

Children with AML, relapsed or refractory acute leukemias (both lymphoid and myeloid), and undergoing HSCT have the highest risk of developing IFDs. Once these high-risk patients are identified, they should be maintained under protective environment, including rooms with HEPA filter, clean water and diet free of food-borne fungal contamination. In addition, they should be submitted to an intensive workup to actively screen for IFDs, and different regimens of antifungal prophylaxis should be also considered. In ALL patients, steroids used during induction therapy amplify the negative impact of neutropenia by impairing phagocytosis, neutrophil migration and humoral immune response. The use of an equivalent prednisone dose of2 mg/kg/day is associated with a high risk of IFDs. High-dose antimetabolites, anthracyclines and intensive asparaginese regimens lead to rupture of the mucosal barriers in the gastrointestinal tract, further increasing the occurrence of IFDs. In patients undergoing allogeneic HSCT, the use of high-dose steroids for over 10 days and its prolonged use to treat GvHD are additional risk factors for IFD. Even minimizing invasive procedures during treatment, such as bone marrow aspirates, cerebrospinal fluid collections, peripheral venipunctures and insertion of central venous catheters, children continue susceptible to bloodstream invasion by translocation of endogenous microbiota. All efforts should be taken to warrant that health workers working with hematologic patients will be committed with best practices for controlling infections related to health assistance.

The overuse of broad-spectrum antibiotics for empirical treatment of febrile neutropenia changes the endogenous microbiota, favoring colonization by fungal pathogens. Indeed, the use of antibiotics for more than seven days is associated with an increased risk of IFDs.

The prolonged use of prophylactic fluconazole often indicated in high-risk patients, substantially decreases the incidence of candidemia, usually to less than 1%, but it may contribute to a selection of fluconazole-resistant fungal pathogens such as C. glabrataand C. krusei.

Hand washing is an important part of preventing fungal dis-eases. *Candida parapsilosis* infections have been associated with the exposure of patients to central venous catheterization and the use of parenteral nutrition. In this scenario, the transmission of this agent can occur through the hands of healthcare providers, since these organisms are frequently present in their hands. It is very important to minimize exposure to airborne fungal propagules throughout hospitalization, not only during the period of neutropenia. A high efficiency particulate air (HEPA)filter, providing an air filtration rate of more than 12 exchanges per hour, is highly recommended in hospital facilities assisting allogeneic HSCT recipients and AML patients in order to decrease their risk for developing infections due to air borne filamentous fungi(10,1,24).

2.2 Etiology of invasive fungal infections in pediatric cancer patients and their clinical impact

Candida spp continues to be responsible for the majority of IFDs among onco-hematologic pediatric patients. However, in the past decades, the number of patients infected by filamentous fungi has increased, including Aspergillus spp, Mucorales, and Fusariumspp(16,9,10,13).This new epidemiological scenario is probably related to the widespread use of prophylaxis with fluconazole, the intensity of immunosuppression secondary to new chemotherapy regimens and the development of better diagnostic tools for fungal infections. The clinical presentation of candidemia is usually fever or sepsis refractory to broad spectrum antibiotics. C. albicans, C.parapsilosisand C. tropicalisare the most frequent isolates (6,7).Dis-seminated candidemia is reported in 10–20% of the pediatric patients; severe sepsis and septic shock occurs in 30%. Mortality rates vary between 10% and 25% and can be up to 50%in patients admitted to an intensive care unit.10,6 In the HSCT setting, Candida spp infections are usually identified within the first month after transplantation, especially in patients with severe mucositis, during neutropenia or immediately after neutrophil recovery. Other IFDs can also occur in this period, but they are usually due to airway colonization and immunosuppression prior to the transplant. Epidemiological studies of invasive Aspergillosis (IA)in pediatrics are usually represented by single center reports (10).

2.3 Outcome

Mortality due to IFDs varies from 20% to 70%, depending on the intensity of the immunosuppression, presence of comorbidities, the availability of tools for early diagnosis, the site and severity of the infection, as well as the time to initiate therapy and antifungal regimens used. Lower survival rate is usually seen in patients with disseminated fungal disease, central nervous system (CNS) involvement, underlying disease refractory to the first regimen of chemotherapy and persistent neutropenia. During periods of deeper immuno-suppression, use of antifungal prophylaxis may mitigate the risk of acquiring IFD, reducing morbidity and high mortality rates of these infections (1,10).

3. OBJECTIVES

3.1. General objective

- To determine the magnitude of possible fungal infection and describe associated factors and outcome of fungal infection among hemato- oncology neutropenic patients.

3.2. Specific objectives

- To determine the magnitude of possible fungal infection in hemato-oncology neutropenic patients in Tikur Anbesa Specialized Hospital.
- To identify factors associated with possible fungal infection in hemato-oncology neutropenia patients in Tikur Anbesa Specialized Hospital.
- To determine the treatment outcome of possible fungal infection in hemato-oncology neutropenic patients in Tikur Anbesa Specialized Hospital.

4. METHODS

4.1Study area and period

TASH is the largest governmental hospital in the country. The hospital offers comprehensive health care service for around half a million patients per year through specialty clinics and inpatient service departments. It has over 700 beds and about 1,700 professional and support staffs in-patient, outpatient and emergency units.

Besides this, it is the first governmental hospital in which both hematologic and oncology service was started. The Pediatrics hemato-oncology unit has 26 beds in the TASH oncology ward and 16 beds in the cancer center. The activity is currently run by three pediatric hemato-oncologists, 10 residents (six first years, five-second year, two third-year residents) assigned every month. The cancer center has 16 beds and provides outpatient service every day for more than 600 patients every month, accepting 500-700new patients every year for both hematology and oncology service.

TASH is chosen for this study because it is widely involved in delivering services for hemato-oncology patients coming from all over the country. The hospital serves as the referral center for cases referred from various facilities in the country. This study was conducted from June2021-August 2021since the data were collected during this period.

4.2 Study design

The study was retrospective with cross-sectional data collection techniques that determined hospital proportion of possible fungal infection in hemato-oncology neutropenic patients using a review of patient records.

4.3 Selection of study population

4.3.1 Source population

The source population includes pediatrics hematology, neutropenic oncology patients, at TASH.

4.3.2. Study population

The study population was a representative number of neutropenic hemato-oncology patients sampled from the source population as registered in the sampling frame.

4.3.3 Inclusion and Exclusion criteria

4.3.3.1Inclusion criteria

All hemato-oncology patients who fulfill both the clinical and radiological criteria for the diagnosis of hemato-oncologic neutropenia

4.3.3.2 Exclusion Criteria

- All incomplete patient charts.

4.4. Sample size and sampling technique

The final sample size is calculated using 50% as prevalence of overall possible fungal infection among all neutropenic patients and because we could not find the previous study done in the same area. 95 % level of certainty and a maximum discrepancy of 5% was considered. For incompleteness, 20% of the calculated sample size was considered, and the following single population proportion formula is used to calculate the sample size.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n= sample size

Z= Standard proportion population at 95% confidence interval (1.96)

P= Estimated proportion of possible fungal infection (50%)

d= Margin of error (5%)

Sample size, n = Give as 384 We deducted the sample size by finite population correction formula because our source of the population was less than 10,000 patients diagnosed with acute leukemia, and the calculated sample size was larger than 5% of the source population.

$$n = \frac{n_0}{\left(1 + \frac{n_0}{N}\right)}$$

Where n0 = 384

The sample from finite population N = 7500, source population

Considering 20% incompleteness (missing data, since secondary data may have significant incomplete variables), the final sample size is 286 patients.

4.4.1Sampling method

We employed a simple random sampling technique to identify study participants for our study. A simple lottery method was used to complete the sampling procedure.

4.4.2 Sampling frame

A list of patients with neutropenia who were registered during the five years period from august 2017-august 2021at the pediatrics hematology-oncology unit for treatment was our sampling frame.

4.6. Data collection procedure

4.6.1. Data collection instrument

Data were retrieved using a structured questionnaire adapted from previously published studies with some modifications to ensure applicability to our current study. The questionnaire consists of questions on socio-demographic factors, Major clinical presenting signs and symptoms, primary diagnosis, and outcome.

4.6.2. Data collection Method

Trained data collectors collected data under the supervision of the Investigator from patients' charts and logbooks. Data collectors were selected from among the hospital hematology-oncology unit nursing staff. Personnel assisting in chart retrieval and management was recruited among the staff of TASH working in the patient records storage and retrieval office. Data collectors took one-day training on extracting the required information from patients' charts.

4.7. Study Variables

7.1.Dependent Variables

- Presence of possible fungal infection

4.7.2.Independent variable

- Socio-demographic factors (Age, Sex, Address)
- Vaccination status
- Nutritional status
- Type of the malignancy
- History of chronic illness
- Involvement of other systems
- CBC profile at diagnosis of infection
- Degree of neutropenia
- Site of fungal infection

- Duration of antibiotics treatment
- Time of initiation of antifungal
- Imaging finding
- Microbiological diagnosis

4.8. Operational Definitions

Possible invasive fungal disease is defined based on host factors, use of antibiotics for more than five-seven days, and clinical features.

Host factor has been defined as a characteristic of individuals predisposed to, and not simply at risk of, an IFD

Host factors

- Recent history of neutropenia (<0.5 × 109 neutrophils/L [<500 neutrophils/mm3] for >10 days) temporally related to the onset of invasive fungal disease
- Hematologic malignancy
- Receipt of an allogeneic stem cell transplant
- Receipt of a solid organ transplant
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
- Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogs during the past 90 days
- Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, e.g., imatinib
- Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)
- Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

Clinical features

- Pulmonary aspergillosis

The presence of 1 of the following four patterns on CT:

- Dense, well-circumscribed lesions(s) with or without a halo sign
- Air crescent sign
- Cavity
- Wedge-shaped and segmental or lobar consolidation

- Other pulmonary mold diseases

As for pulmonary aspergillosis, but also includes a reverse halo sign

- Tracheobronchitis

-Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis

- Sino-nasal diseases

-Acute localized pain (including pain radiating to the eye)

-Nasal ulcer with black eschar

-Extension from the paranasal sinus across bony barriers, including into orbit

- Central nervous system infection

One of the following two signs:

-Focal lesions on imaging

-Meningeal enhancement on magnetic resonance imaging or CT

- Candidemia

At least 1 of the following two entities after an episode of candidemia within the previous two weeks:

-Small, target-like abscesses in liver or spleen (bull's-eye lesions) or in the brain, or, meningeal enhancement

-Progressive retinal exudates or vitreal opacities on ophthalmologic examination

Prolonged use of antibiotics: considered if antibiotics are taken for more than 7 days

4.9. Data quality control

The Investigator examined the appropriateness of the methodologies followed. The questionnaire was reviewed for completeness. Data collectors were trained, and data were collected by the

trained nurses and supervised by the Investigator. Filled questionnaires were checked for completeness and consistency of information by the data collector and the Investigator once weekly during data collection. Any ambiguity & other problems of data collection were addressed.

4.10. Data analysis techniques

The data were entered using SPSS version 25 for analysis. Data cleaning and screening were conducted exclusively by the Principal Investigator. Any error in the data was cleaned. Descriptive summary measures were presented using Tables and Figures. Frequency distributions were used to organize the data and present the responses obtained. Measures of central tendency were calculated and utilized for appropriate variables to describe the data. The data were categorized and summarized with descriptive statistics and inferential statistics.

All variables with $p<0.25$ in the univariable binary logistic regression analysis were included in the multivariable binary logistic regression. The statistical significance was declared at $P<0.05$. The odds ratio was computed to determine the strength of statistical association between the dependent and independent variables.

4.11. Ethical clearance

Proposal approval and waiver of consent were obtained before the beginning of data collection from the Department Research and Publication Committee (DRPC) of the Department of Pediatrics and Child Health (DPCH), College of Health Sciences (CHS), TASH. All information in the charts was kept confidential, and the information collected was used solely for the intended research purpose. Personal Identifier Information (PII), including names of patients, was not included in the questionnaire. Codes were used instead, and completed questionnaires were stored safely by the Investigator

5. RESULTS

5.1 Socio-demographic characteristics

In this study, 256 patients' charts were reviewed, and 52.3% were in the age group of 5-11 years, and 59.4% were male, as shown in the table below.

Table 6. The socio-demographic characteristics of neutropenic hemato-oncology patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2021

Variable	Frequency	Percent
Age		
≤5	88	34.4
5-11	134	52.3
>11	34	13.3
Sex		
Male	152	59.4
Female	104	40.6
Residence		
Urban	103	40.2
Rural	153	59.8

5.3 Clinically presenting symptoms and signs of the study participants

In this study, 55.9% of the study participants had a fever, followed by 23%, 22.7%, 18.4%, 14.8% cough, dysphagia, abdominal pain, and odynophagia, respectively.

Table7.Clinically presenting symptoms and signs among Hemato-Oncologic pediatric patients in TASH, 2021

Variable		Frequency	Percent
Fever	Yes	143	55.9
	No	113	44.1
Cough	Yes	59	23.0
	No	197	77.0
Dysphagia	Yes	58	22.7
	No	198	77.3
Odynophagia	Yes	38	14.8
	No	218	85.2
Retrosternal /epigastric pain	Yes	22	8.6
	No	234	91.4
Abdominal pain	Yes	47	18.4
	No	209	81.6
Whitish vaginal discharge	Yes	4	1.6
	No	252	98.4
Whitish oral lesion	Yes	12	4.7
	No	244	95.3
Chest pain	Yes	14	5.5
	No	242	94.5
Sputum production	Yes	6	2.3
	No	250	97.7
Shortness of breath	Yes	15	5.9
	No	241	94.1
Fast breathing	Yes	19	7.4
	No	237	92.6
Grunting	Yes	16	6.3
	No	240	93.8
Tachypnea	Yes	17	6.6
	No	239	93.4

Crepitation	Yes	9	3.5
	No	247	96.5
Saturation of oxygen with atmospheric oxygen	Yes	2	.8
	No	254	99.2
Involvement of other system	Yes	3	1.2
	No	253	98.8
Haemoptysis	No	256	100.0

5.4 Host factors characteristics of study participants

From all the study participants, 35.9% of them had prolonged use of corticosteroid, 33.2% had Immunosuppressive nucleoside analogues during the past 90 days

Table 8. Host factors characteristics of study participants among Hemato-Oncologic pediatric patients in TASH, 2021

Variable		**Frequency**	**Percent**
Prolonged use of corticosteroids	Yes	92	35.9
	No	164	64.1
Receipt of a transplant	Yes	1	0.3
	No	255	99.7
Immunosuppressive chemotherapy	Yes	85	33.2
	No	171	66.8

5.6 Primary diagnosis of study participants

The primary diagnosis of a study participant in TASH Hemato-Oncology was 53.9% had ALL followed by 21.1% of WT, 16% of NHL, and AML of 5.1%(Figure 1).

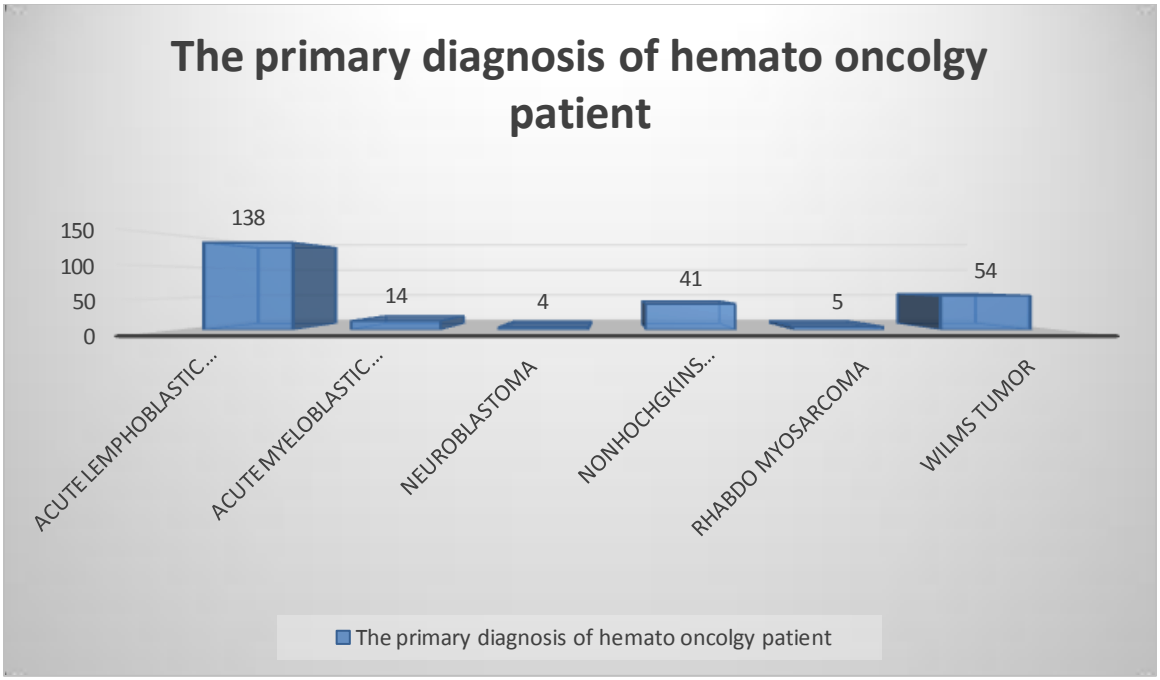

Figure 6. Primary diagnosis among Hemato-Oncologic pediatric patients in TASH,2021

5.7.The relation between grading of neutropenia and duration of neutropenia

The finding demonstrates that 42.9 % of patients were neutropenic for more than 10 days,26.1% were for five to ten days, and 28.1 % were for less than 5 days, as shown in the figure below.

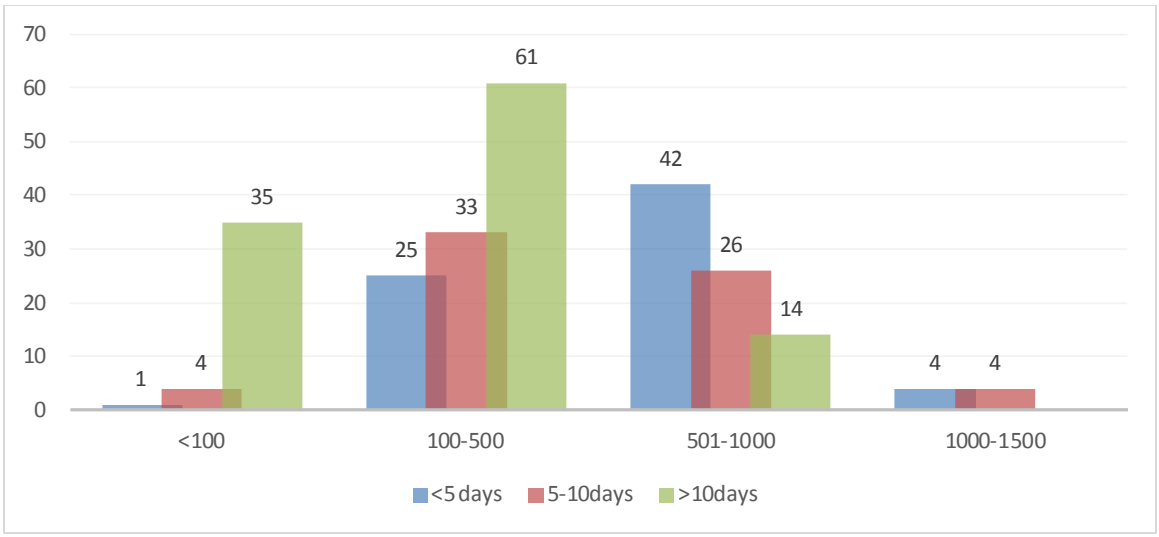

Figure 7. The figure showed that the relation between grading of neutropenia and duration of neutropenia

5.9 CBC Profile at diagnosis of pulmonary complication

The study finding showed that One hundred eleven (37.9 %) of the children had a platelet count of <150 k and 34.4% of the children had a total WBC count of < 4000, and 189 children's had recorded hemoglobin less than 10.5 and 130(50.8%) had neutrophil count ranging between101-500.(Table 6).

Table 4. CBC findings *among Hemato-Oncologic pediatric patients, in TASH,2021*

		frequency	Percent
CBC profile	WBC		
	<4000	88	34.4
	4000-12000	18	7.0
	>12000	150	58.6
	ANC		
	<100	53	20.7
	101-500	130	50.8
	501-1000	62	24.2
	1000-1500	9	3.5
	>1500	2	.8
	Hemoglobin		

	<10.5	187	73.0
	10.5-16.1	67	26.2
	>16.1	2	.8
	Platelet		
	<150k	97	37.9
	150k-400k	48	18.8
	>400k	111	43.4

5.10 Magnitude of fungal infection

In this study, the magnitude of fungal infection among childhood hemato oncology patients was 31% as shown in the figure 3.

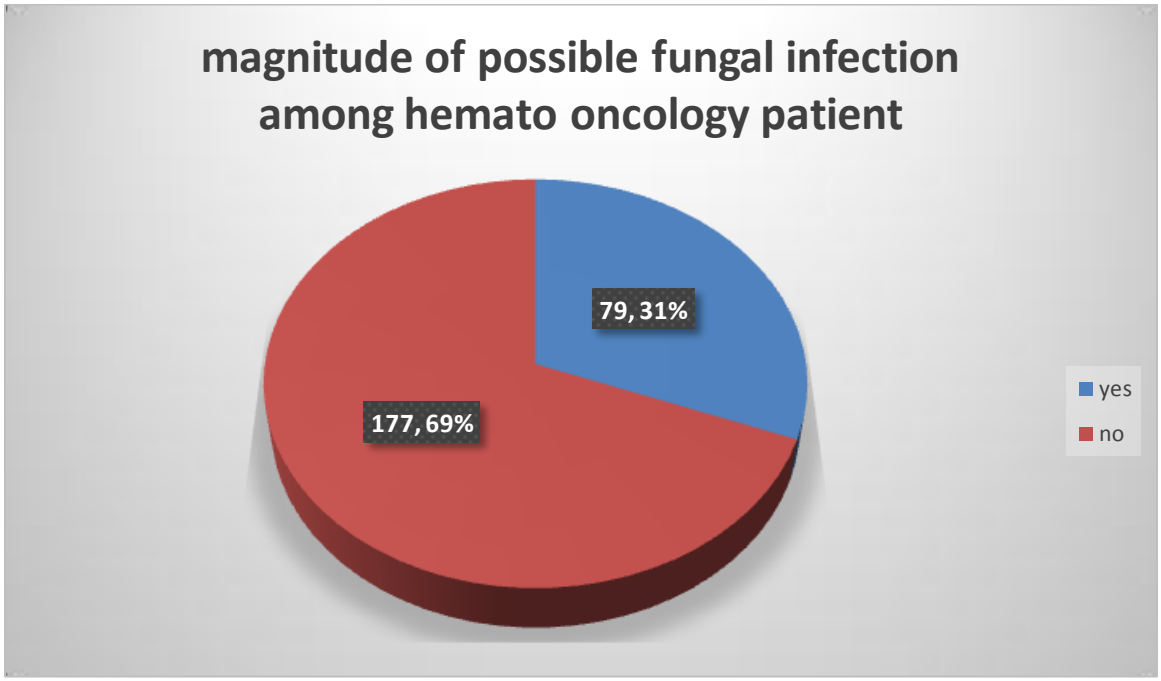

Figure 8.the magnitude of suspected fungal infection among hemato oncology pediatric patients ,TASH 2021

5.11 The relation of primary diagnosis and possible fungal infection among hemato

Oncology pediatric patients,TASH 2021

The study result showed that, 56 (72%) ALL patients, 6 (7.7%) AML patients and 15(19%) of NHL patients, were diagnosed possible fungal infection, figure 3.

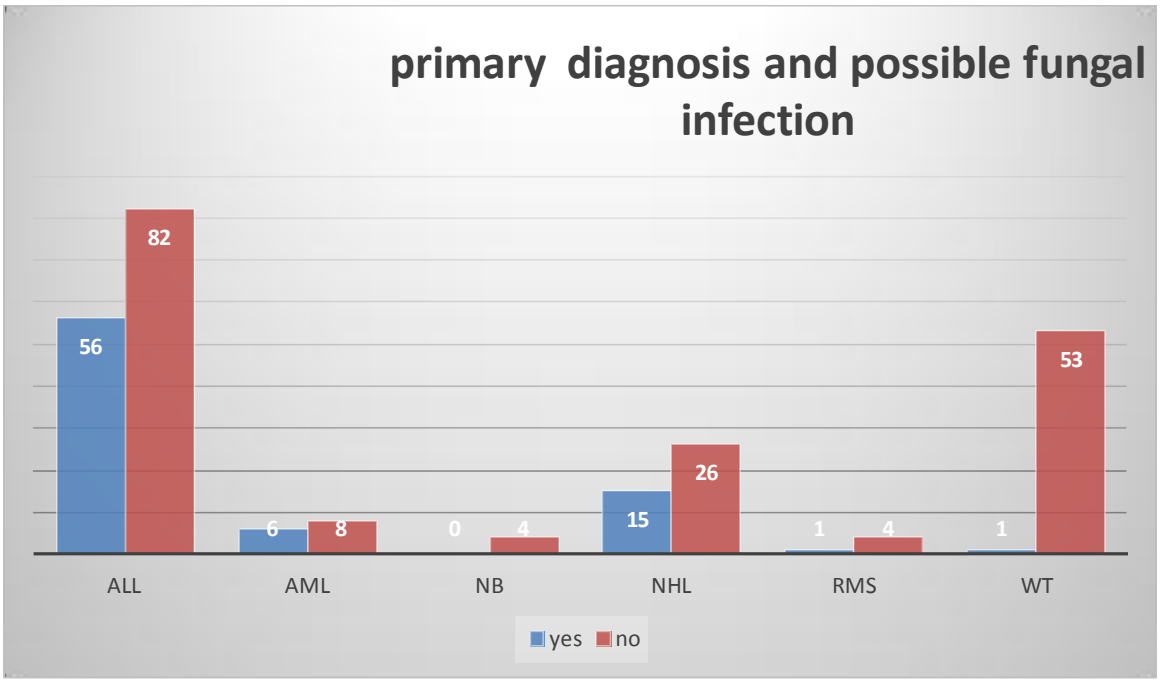

Figure 4,the relation ofprimary diagnosis and possible fungal infectionamong hematooncology pediatric patient,TASH 2021

5.11 Outcome of the treatment of the study participants

Concerning the outcome of the treatment of the study participants, 93% were improved and discharged where as 7% were died as shown in the figure 5

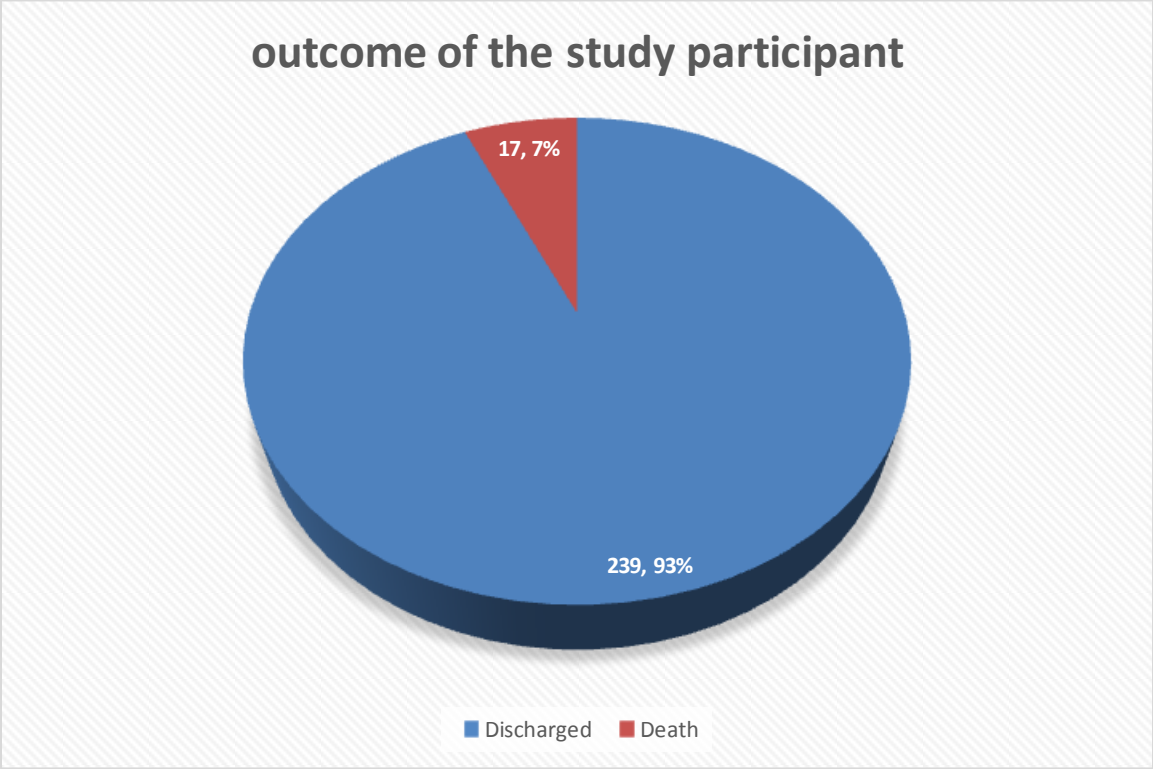

Figure 9. The outcome of the study infectionamong hemato oncology pediatric patient,TASH 2021

5.13 The determinant of fungal infections of hemato-oncology patient

Univariate binary logistic regression analyses were done among the nine variables to select candidate variables for the multivariable binary logistic regression analyses. Six variables having p-value <0.25 in the univariate binary logistic regression analysis were taken into the multivariable binary logistic regression analyses to determine potential factors associated with possible fungal infection. Finally, six of them with a p-value <0.05 in the multivariable analysis were found to have a significant association with fungal infection.

As a result, this study has revealed that children with the age range of < 5 years were 1.9 fold increased odds of developing possible fungal infection (AOR=1.9, 95%CI=1.46, 4.22). Also, those with the WBC count < 4000 cells/mm3 had 2.1 times increased odds of developing a possible fungal infection compared with the higher values(AOR=2.1, 95% CI=1.98, 4.42). Those patients with ANC grading of profound, severe, and moderate has also significant odds ratio and the duration of neutropenia more than ten days had 14.9 folds increased odds of having possible fungal infection compared with the duration of neutropenia <5 days (AOR=14.9, 26 95%CI=10.66, 23.19). Patients who took steroids for prolonged duration had 1.2 folds increased odds ratio than those who did not take it for a long duration (AOR=1.2, 95%CI=1.01, 2.12).

Table5. The association of dependent and independent variables using binary logistic regression on hemato-oncology patient of fungal infection in TASH, Addis Ababa, Ethiopia 2021

Variable	Possible fungal infection		p-value	COR(95%CI)	P-value	AOR (95%CI)
	Yes	no				
Age of the patient						
<5	47	41	0.019	2.7(1.18, 6.43)	0.049	**1.9(1.46, 4.22)**
5-11	22	112	0.089	0.47(0.19, 6.43)	0.073	0.38(0.13, 1.09)
>11	10	24	1		1	
Sex of the children						
Male	53	99	1		1	
female	26	78	0.094	0.62(0.36, 1.08)	0.478	0.75(0.34, 1.67)
Residence						
Urban	34	69	1		1	

Rural	45	108	0.541	0.85(0.49, 1.45)	0.723	0.88(0.42, 1.83)
Cough						
Yes	36	23	0.000	3.6(3.01, 10.45)	0.008	**4.1(1.44, 11.24)**
No	43	154	1		1	
Fever						
Yes	71	72	0.000	12.9(5.87, 28.52)	**0.023**	**2.7(1.15, 6.41)**
No	8	105	1		1	
Dysphagia						
Yes	42	16	0.000	11.4(5.8(22.49)	0.005	**3.8(1.48, 9.65)**
No	37	161	1		1	
Odynophagia						
Yes	32	6	0.000	19.4(7.66, 49.17)	0.011	**4.2(1.39, 12.69)**
No	47	171	1		1	
Retrosternal/ epigastric pain						
Yes	19	3	0.000	18.4(5.25, 64.27)	0.316	2.2(0.18, 9.81)
No	60	174	1		1	
WBC						
<4000	31	57	0.537	1.2(0.68, 2.01)	0.005	**2.1(1.98, 4.42)**
4000-12000	1	17	0.050	0.13(0.017, 0.99)	0.180	0.02, 1.62)
>12000	47	103	1		1	
ANC						
<100	32	21	1		1	
101-500	45	85	0.002	0.35(0.18, 0.67)	0.010	**0.38(0.18, 0.79)**
501-1000	2	60	0.000	0.02(0.005, 0.099)	0.000	**0.02(0.004, 0.09)**
1000-1500	0	9	**		**	
>1500	0	2	**		**	
Hemoglobin						
<10.5	62	125	1		1	
10.5-16.1	16	51	0.160	0.63(0.33, 1.19)	0.549	1.3(0.58, 2.78)
>16.1	1	1	0.622	2.1(0.12, 32.77)	0.549	2.4(0.14, 41.52)

Prolonged use of corticosteroid						
Yes	40	52	0.001	2.5(1.43,04.26)	**0.002**	**1.2(1.01, 2.12)**
No	39	125	1			
Immunosuppressive chemotherapy						
Yes	42	53	0.000	2.6(1.54, 4.58)	**0.046**	**2.2(1.37, 12.84)**
No	37	124	1		1	
Duration of neutropenia						
<5days	2	74	1		1	
5-10 days	11	62	0.017	6.6(1.4, 30.74)	**0.012**	**7.6(1.57, 36.84)**
>10days	66	41	0.000	15.9(13, 25.58)	**0.000**	**14.9(10.66, 23.19)**
Took antifungal prophylaxis						
Given	32	120	1		1	
Not given	47	57	0.000	3.1(1.78, 8.35)	0.281	1.5(0.73, 2.98)
Took antibiotic						
Yes	33	106	0.008	2.1(1.21, 3.57)	0.331	1.4(0.69, 3.02)
No	46	71	1		1	

6. Discussion

This retrospective cross sectional study confirmed a higher magnitude of possible fungal infection in neutropenic patients. We found that patients with fever, cough, odynophagia or dysphagia, neutropenia < 500 and duration of neutropenia lasting >10 days, use of prolonged corticosteroid therapy and imunusuppresive chemotherapy were significant independent variables associated with possible Fungal infection in this study on multivariate analysis. Patients with hematologic malignancies ALL and AML and from solid tumor, NHL were at higher risk of developing fungal infection when compared with others.

In the present study the magnitude of possible fungal infection is 79(31%), this proportion is made among the hematologic malignancy and solid tumors. We have used the revised EORTC/MSG definition of possible fungal infection to look for the prevalence. A previous prospective study were done in Amir Hospital in Iran over 13 month period on 86 patients revealed the rates of IFIs among pediatric patients with hematological disorders were found to be 16.3%(1). An other prospective, observational study conducted from January 2013 through June 2014 in a tertiary care centre in New Delhi, conducted among children between 1 and 12 y of pediatric neutropenic patients. As we see from this study the prevalence of IFI was 22.97% (13.99–34.21). Positive cases were further classified into proven 3(17.6%), probable 11(64.8%) and possible 3(17.6%) according to EORTC/MSG criteria.

When we compare our study result with the Iran and New Delhi, it is estimated higher. The reason for this could be due to lack of laboratory investigations the proven and probable diagnosis may be merged. The other reason is probably the way we diagnose fungal infection; it is based on the clinical features and risk factors and the other is the source population, the type of study and the hospital set up are also different from both Iran and New Delhi study. There fore this reasons could have inflated our findings.

The pediatric patients are at greatest risk for developing IFD, children undergoing allogeneic HSCT, those with acute myeloid leukemia (AML), and cases of relapsed acute lymphoblastic leukemia (ALL). Children with acute leukemias are continuously exposed to multiple risk factors for IFD, and up to one-third of them may develop IFD in the absence of antifungal prophylaxis.

Younger children may have less effective phagocytic activity and prolonged T-lymphocyte recovery after being exposed to intensive chemotherapy(10,24). Our study showed that 56 (72%) ALL patients, 6 (7.7%) AML patients and 15(19%) of NHL patients, were diagnosed with possible fungal infection, and children with an age range of < 5 years were 1.9 fold increased odds of developing possible fungal infection (AOR=1.9, 95%CI=1.46, 4.22).

The risk of IFDs is directly related to the intensity and duration of the neutropenia. When we look for the severity of neutropenia, our study determined a significant odds ratio for the patients with the duration of neutropenia of more than ten days had 14.9 folds increased odds of having possible fungal infection when compared with the duration of neutropenia <5 days (AOR=14.9, 95%CI=10.66, 23.19). Chemotherapy further impairs neutrophil, macrophage, B, and T-lymphocyte function, decreasing immunoglobulin production and opsonization(17,18,10). A neutrophil count lower than 500/mm3 for longer than10 days is an important risk factor for IFDs, but the risk is highest with counts below 100/mm3 in patients with malignant neoplasms, on corticosteroids and chemotherapy, AML induction, and early post HSCT. A low lymphocyte count of less than 100/mm3further increases the incidence of IFDs in neutropenic febrile children after chemotherapy. The use of some new immune suppressors, like infliximab, maybe, by itself, be a risk factor for invasive aspergillosis(10).

In ALL patients, steroids used during induction therapy amplify the negative impact of neutropenia by impairing phagocytosis, neutrophil migration, and humoral immune response(18,10). In this study, patients who took steroids for prolonged duration had 1.2 folds increased odds ratio than those who did not take it for a long duration (AOR=1.2, 95%CI=1.01, 2.12).

Using an equivalent prednisone dose of 2 mg/kg/day is associated with a high risk of IFDs. High-dose antimetabolites, anthracyclines, and intensive asparaginase regimens lead to rupture of the mucosal barriers in the gastrointestinal tract, further increasing the occurrence of IFDs. In patients undergoing allogeneic HSCT, high-dose steroids for over ten days and prolonged use to treat GvHD are additional risk factors for IFD. Even minimizing invasive procedures during the treatment, such as bone marrow aspirates, cerebrospinal fluid collections, peripheral venipunctures, and insertion of central venous catheters, children continue susceptible to bloodstream invasion by translocation of endogenous microbiota. All efforts should be taken to

warrant that health workers working with hematologic patients will be committed to best practices for controlling infections related to health assistance.

The overuse of broad-spectrum antibiotics for empirical treatment of febrile neutropenia changes the endogenous microbiota, favoring colonization by fungal pathogens. Indeed, antibiotics for more than seven days is associated with an increased risk of IFDs.

7. Limitations

In our setting, patients' records were generally poorly kept. The overall flow of clinical notes was not streamlined, and the bulkiness of the records made it difficult to locate pertinent information. A substantial number of patient cards were missing, especially cards registered as a death in the logbook. This may have potentially biased the measurement of independent factors and the outcome. There was a challenge with the retrieval of patients' records. Some of them were lost or mislabeled, which might have contributed to underestimation in frequency of observation of some of the study variables.

Conclusion

Our finding suggests that there is a high rate of possible fungal infections in neutropenic ALL and AML patients.

Recommendations

More studies are required to determine the extent and influence of the course and outcome of possible fungal infection.

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ANNEX: QUESTIONNAIRE

Magnitude And Outcome Of Possible Fungal Infection In Hemato-Oncology Patients With Neutropenia At TikurAnbessa Specialized Hospital, Addis Ababa, Ethiopia

PART 1: Socio-demographic characteristic

	Variables	**Response**	**Remarks**
1.1	Code number		
1.2	Date (dd/mm/year)		
1.3	Age of the patient (year)		
1.4	Sex	Male	
		Female	
1.5	Address	Addis Ababa	
		Outside Addis Ababa	
1.6	Vaccination history	BCG	
		PCV	
		Pentavalent	
		Measles	
1.7	Family size	<5	
		5-10	
		>10	
1.8	Literacy of the Mother	Unable to read and write	
		Primary school	
		Secondary school	
		Diploma and above	
	Literacy of the Father	Unable to read and write	
		Primary school	
		Secondary school	
		Diploma and above	
1.9	Occupation of the Mother	Housewife	
		Government employee	
		Private business	
		Student	
		Farmer	
	Occupation of the Father	Government employee	
		Private business	
		Student	
		Farmer	
1.10	Residency	Urban	
		Rural	
1.11	Anthropometry	Wt.	

		Ht		
		Body mass index		

PART 2. Major clinical presenting symptoms and signs

	Symptom and signs	**Yes**	**No**	**Remark**
2.1	Fever			
2.2	Cough			
2.	Dysphagia			
3.	Odynophagia			
4.	Rerosternal /epigastric pain			
5.	Abdominal pain			
6.	Whitish vaginal discharge			
7.	Whitish oral lesion			
2.9	Chest pain			
2.10	Sputum production			
2.11	Shortness of breath			
2.12	Fast breathing			
2.13	Grunting			
2.14	Tachypnea			
2.15	Crepitation			
2.16	Saturation of oxygen with atmospheric oxygen			
2.17	Involvement of other system			
2.18	Haemoptysis			
2.19	Others (specify)_____			

3. Host factors

	Yes	No	Remark
Prolonged use of corticosteroids			
Receipt of a transplant			
Immunosuppressive nucleoside analogues during the past 90 days			

4.Co morbid condition

		YES	NO	REMARK
4.Comorbid condition	HIV			
	ASTHMA			
	CARDIAC ILLNESs			
	RENAL ILLNESS			
	Malnutrition			
	OTHER			

5.Primary diagnosis

	Primary disease	YES	NO	REMARK
5.1	ALL			
5.2	AML			
5.3	NHL			
5.4	RMS			
5.5	NEUROBLASTOMA			
5.6	WILMS TUMOR			
5.7	Others			

6, CBC Profile at diagnosis of pulmonary complication

		PERCENTAGE	REMARK
6.1 CBC profile with differential	- Total WBC		
	-Lymphocyte %		
	-Neutrophil %		
	-ANC		
	-Basophil %		
	-Monocyte %		
	-Hemoglobin		
	-Platelet		

6.2 Grading of neutropenia	Duration of neutropenia			remark
	<5 days	5-10 days	>10 days	
- 1500-1000				
- 1000-500				
- <500				
- <100				

7. Chest X-ray

		Yes	No	REMARK
7.1 Chest X-ray finding	Consolidations			
	Interstitial process			
	Pleural fluid collection			
	Ground glass attenuations			
	Cavitations			
	Nodules			
	Other (specify)			

8. Chest CT

		Yes	NO	REMARK
8.1 Chest CT finding	Consolidations			
	Interstitial process			
	Pleural fluid collection			
	Ground glass attenuations			
	Cavitation			
	Nodules			
	Nodules with ground glass halo			
	Lymphadenopathy			
	Other (specify)			

		YES	NO	Remark
8.3 Imaging diagnosis	Pneumonia			
	Tuberculosis			
	Aspergillosis			
	Pulmonary hemorrhage			
	Pulmonary edema			
	Malignant infiltrations			
	Diagnosis not made			

9. Blood Culture

		YES	NO	Remark
9.1 Blood Culture result	Candidia			
	Aspergillus			
	Bacteria			
	Other			

10. Time of antifungal initiation in relation to duration of antibiotic treatment

		YES	NO	REMARK
10.1	With in 5 days			
10.2	With in 5-10 days			
10.3	After 10 days			

11. Final Diagnosis of IFD

	YES	NO	REMARK
Possible			
Probable			
Proven			

12. Duration of therapy _____ (months)
13. Antfungal prophylaxis A) Given B) not given

14. If yes to Q13 Route of delivery of therapy

	ROUTE OF MEDICATION	YES	NO	REMARK
14.1	PER OS			
14.2	INTRAVASCULAR			

15 Broad spectrum antibiotics a) given b) not given

16. Outcome of the patient

	Variables	Yes	No	Remark
15.1	Improved and discharged			
15.2	Discharge deteriorated			
15.3	Abandonment			
15.4	Death			