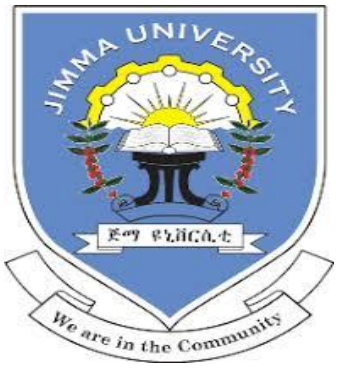

CLINICAL CHARACTERISTICS, ASSOCATED FACTORS, AND TREATMENT OUTCOMES OF PEDIATRIC CANCERS AT PEDIATRIC ONCOLOGY WARD OF JIMMA MEDICAL CENTER, SOUTH WEST ETHIOPIA

BY: FEVEN TESHOME (B. PHARM)

A THESIS TO BE SUBMITTED TO SCHOOL OF PHARMACY, JIMMA FACULTY OF HEALTH SCIENCE, INSTITUTE OF HEALTH JIMMA UNIVERSITY IN PARTIAL FULFILLMENT OF REQUIREMENT FOR MASTERS OF SCIENCE (MSC) DEGREE IN CLINICAL PHARMACY

SEPTEMBER, 2020

JIMMA, ETHIOPIA

JIMMA UNIVERSITY

INSTITUTE OF HEALTH

FACULTY OF HEALTH SCIENCE

SCHOOL OF PHARMACY

CLINICAL CHARACTERISTICS, ASSOCATED FACTORS, AND TREATMENT OUTCOMES OF PEDIATRIC CANCERS AT PEDIATRIC ONCOLOGY WARD OF JIMMA MEDICAL CENTER, SOUTH WEST ETHIOPIA

BY: FEVEN TESHOME (B. PHARM)

ADVISORS:

TEMESGEN MULUGETA (B. PHARM, MSC, CLINICAL PHARMACY)

DIRIBA FUFA (MD, PEDIATRIC HEMATOLOGY/ONCOLOGY SPECIALIST)

SEPTEMBER, 2022

JIMMA, ETHIOPIA

Abstract

Background: Febrile neutropenia (FN) is frequently arises because of bone marrow suppression caused by chemotherapy or radiotherapy. However, information regarding clinical characteristics, associated factors and treatment outcomes of pediatric cancer patients in Ethiopia is scarce.

Objective: To assess clinical characteristics, associated factors and treatment outcomes of pediatric cancers among pediatric cancer patients who received chemotherapy at pediatric hematology/oncology ward, of Jimma Medical Center, Ethiopia.

Methods: A retrospective cohort study design was conducted. All children who received cancer chemotherapy between August 2017 and January 2022 were included. Data was checked and entered into Epi-data version 4.6 and exported to SPSS version 26.0 for statistical analysis. Descriptive statistics was used to describe the findings. Bivariate and multivariate logistic regression was performed to determine the factors associated with endpoints. The effect size was reported using odds ratio along with a 95% confidence interval (CI) and a p-value of 0.05 was used to declare the statistical significance.

Result: Seventy-six (71.7%) of the patients had clinically documented FN associated infections and 92(29.4%) of the patients were died. Hematologic tumors (AOR = 4.16 (95% CI 2.26, 7.65) P< 0.0001), tumor metastasis (AOR = 4.56 (95% CI 2.36, 8.79), P < 0.0001), low baseline neutrophil count (AOR = 1.93 (95% CI 1.01, 3.66), P = 0.046), incomplete vaccination (AOR = 3.11 (95% CI 1.31, 7.35), P = 0.010), and nutritional stunting (AOR = 0.26 (95% CI 0.13, 0.52); P < 0.0001) were significantly associated with FN.For the all-cause mortality, serum creatinine > 1mg/dl (AOR = 3.13 (95% CI 1.13, 8.62), P = 0.028), blood urea nitrogen > 20mg/dl (AOR = 1.69 (95% CI 1.01, 2.84), P = 0.046), low hemoglobin level (AOR = 1.88 (95% CI 1.10, 3.21) P = 0.020), tumor metastasis (AOR = 2.038 (95%CI 1.16, 3.57), P = 0.013) and history of urinary catheterization (AOR = 1.76 (95%CI 1.01, 3.07), P = 0.046) were significantly associated with mortality.

Conclusion: In this study, a significant number of patients had developed FN and died. Several tumor and patient related factors were associated with increased risk for the development of FN and mortality. Therefore, oncologists should improve the evaluation of baseline patient clinical and performance status before initiating cytotoxic chemotherapy.

Key words: Febrile neutropenia, Infection, mortality, pediatric cancers

Acknowledgement

First, I would like to thank Jimma University and School of pharmacy for offering me such an opportunity to conduct this study. I also would like to express my heartfelt gratitude to my advisors Mr. Temesgen Mulugeta (B Pharm, MSc, in clinical pharmacy) and Dr. Diriba Fufa (MD, pediatric senior hematology/oncology), for their meticulous encouragement, guidance, intriguing motivation and their fruitful countless discussions in every detail of the study. Lastly, I would like to thank Wachemo University for its sponsorship.

Table of Contents

List of table

List of figures

List of acronym

ADR - Adverse Drug reaction

ALL- Acute lymphoblastic leukemia

AML— Acute myeloblastic leukemia

ANC- absolute neutrophil count

AST-Alanine amino transferase

ALT-Aspartate transaminase

ALP-Alkaline phosphatase

AOR- Adjusted odds ratio

BSI- Blood Stream Infections

BUN- blood urea nitrogen

CHMC-Children's Hospital and Medical Center

CBC -complete blood count

COR-Crude odds ratio

FN- Febrile neutropenia

ICU-Intensive care unit

IV- Intravenous

IQR-Interquartile range

HTN- Hypertension

Hgb- Hemoglobin

JUMC_ Jimma University Medical center

JMC_ Jimma Medical center

MDI- Microbiologically documented infection

PLT- Platelet

SCr -Serum creatinine

TASH-Tikur Anbesa specialized teaching hospital

USA -United State of America

UTI-urinary tract infection

VGS -Viridans Group Streptococci

WT-Wilms Tumor

WHO-World Health Organization

WBC -White blood cell count

1. Introduction

1.1. Background

Cancer is a group of diseases that start when the cell is divided more than it should or has not died. It may be benign (not cancer) or malignant (cancer). Cancerous tumors can metastasize or spread to other parts of the body and causing the growth of new tumors(1). The incidence and type of malignancy vary with age, with a peak in the first 5 years of life and a lower incidence in those aged 8–10 years (2). The most prevalent forms of childhood cancers are leukemia, brain malignancies, lymphomas, and solid tumors, including neuroblastoma and Wilms tumors. In contrast to adult cancers, the majority of childhood cancers have no known cause (3).

According to the World Health Organization (2020) report, globally, it is estimated that 400,000 children are diagnosed with cancer each year, most of them living in low-and middle-income countries(3). As per the United States of America Cancer Statistics (2021), cancer is the second most common cause of death among children aged 1 to 14 years. It is only surpassed by accidents.

In Ethiopia, estimates show 120,500 new cancer cases per year and 6000 new pediatric cancer cases per year (10). Prevalence of FN was 10.2% (12). As the national data report in 2015 showed, 3,707 cancer cases occurred in the pediatric age group, with leukemia being the commonest cancer (29%), followed by non-Hodgkin's lymphoma, Wilms tumor, and retinoblastoma (11).

Standard therapies for childhood cancer include chemotherapy, surgery, and/or radiotherapy. In addition to standard treatment, palliative care relieves symptoms caused by cancer and improves the quality of life of patients and their families(5).

Chemotherapy is the most commonly used standard treatment, but it can have an impact on both innate and acquired immune responses. It also affects physical immunological defenses such as the gut mucosal barrier. It results in a detrimental effect on the protective immune response (6). Fever and neutropenia are common side effects of myelosuppressive chemotherapy given to pediatric oncology patients, and they are one of the most common reasons for nonselective hospitalization (7).

The mortality rate related to febrile neutropenia in pediatric cancer patients taking chemotherapy in developed countries ranges between 0.7% and 3.9%(8). However, in middle-and low-income countries, mortality rates of FN among pediatric cancer patients taking chemotherapy are considerably higher at 4–13.2% (9). Over 80% of children with cancer in developed countries will be long-term survivors, compared to only about 20% of low-and middle-income countries' children with cancer(4).

1.2. Statement of the problem

Certain malignancies are also inherently associated with immune deficits. A patient with hematologic febrile neutropenia (FN) is a common complication of myelosuppressive drugs used in the treatment of hematological and solid tumor cancers. It is the most commonly encountered complication of childhood cancer treatment(13).

Malignancies may have leukopenia due to infiltration of the marrow with malignant cells (6). Febrile neutropenia (FN) is a common complication in patients with cancer, occurring in 5–10% of patients with solid tumors, 85–95% of patients with acute leukemia, and 20–25% of patients with other hematologic malignancies. Febrile neutropenia has been recognized as a major risk factor for the development of infection in patients with cancer undergoing chemotherapy (14).

Infections are the leading causes of morbidity and mortality in pediatric patients treated for cancer in low and low-middle-income countries (15). At 20–30% of patients with FN have an identifiable site of infection and 10–25% of patients have positive blood culture(16).

Children diagnosed with acute lymphoblastic leukemia (ALL) usually have repeated episodes of febrile neutropenia, conventionally defined as temperature exceeding 38◦C with neutrophil count $\leq 0.5 \times 109/L$, during the course of chemotherapy. Bacteremia is frequent, and life-threatening sepsis or other complications may develop. Febrile episodes cause considerable morbidity, and bacterial infections are the most common cause of treatment-related mortality (17)

In United States of America (USA) between year 2007 and 2014, there were 104, 315 pediatric cancer hospitalizations for pediatric. The number of weighted fever with neutropenia hospitalizations increased from 12.9 (2007) to 18.1 (2014) per 100,000 US population. The comorbidities associated with a higher risk of mortality during fever with neutropenia hospitalizations were sepsis, pneumonia, meningitis, and mycosis (18).

The mortality rate related to febrile neutropenia in pediatric cancer patients taking chemotherapy in developed countries ranges between 0.7% and 3.9% (8). However, in middle-and low-income

countries, mortality rates of FN among pediatric cancer patients taking chemotherapy are considerably higher at 4–13.2% (9).

It causes morbidity, disability, and mortality. Over 80% of children with cancer in developed countries will be long-term survivors, compared to only about 20% of low-and middle-income countries' children with cancer (4).

In Ethiopia the prevalence of FN was 10.2% (12). The most reported types of cancers were acute lymphocytic leukemia was diagnosed in 52.6% of patients. The focus of FN infection was unknown in most (83.7%) of the study participants. Empiric antibiotic therapy with ceftriaxone and gentamycin was given to 71.8% of the patients. Culture and sensitivity tests were done only for 13 (9.6%) of the participants. Seven patients died due to all-cause mortality(19). FN caused 12 to pass away while still in the hospital. Prior to death, patients spent an average of 20.2 (5.26) days in the hospital. Two children had solid tumors, and ten children had hematologic malignancies. Sepsis, low platelet counts, and severe neutropenia in patients were all substantially linked to death (20) .

In Ethiopia, there is a scarcity of studies in the field of oncology, particularly in pediatric oncology. This study area (Jimma Medical Center) was selected, as it is a recently established pediatric hematology/oncology center and a referral for children from all the SW regions of Ethiopia (21). This allows for the detection of several cancer types that are common in children. This study aimed to assess the clinical characteristics, associated factors, and treatment outcomes of pediatric cancers among pediatric cancer patients who received chemotherapy at the pediatric hematology/oncology ward of Jimma Medical Center, Ethiopia.

1.3. Significance of the study

Healthcare experts, Policymakers, and other researchers will benefit from the information provided by this study. It gives health care providers information on the connections between FN and the deaths of children with cancer. This might spread knowledge, lessen the risk of FN, and prevent mortality in pediatric cancer patients who received chemotherapy. This study may increase knowledge of FN-associated infections and aid in the creation of recommendations for the antimicrobial prophylaxis of high-risk pediatric cancer patients in order to prevent FN and its effects.

Policymakers will be better able to treat pediatric cancer patients received chemotherapy with high-quality care by identifying predictors of FN and mortality. As a result, it will assist them in establishing strategies to lessen the incidence of FN and linking related causes of mortality. The findings of this study will also serve as a roadmap for future researchers.

2. Literature Review

Cancer is non-communicable disease that cause morbidity, disability, and mortality .Over 80% of children with cancer in developed country will be long-term survivors, compared to only about 20% of low-and middle-income countries' children with cancer survive(4).

In developed countries, the mortality rate from FN in pediatric cancer patients receiving chemotherapy ranges between 0.7 and 3.9 percent (8) . However, in middle-and low-income countries, mortality rates of FN among pediatric cancer patients taking chemotherapy are considerably higher at 4–13.2% (9).FN is still a major cause of morbidity, mortality, and financial burden in pediatric cancer patients. It can also have an impact on subsequent chemotherapy dosing and scheduling, which affects treatment efficacy and overall prognosis(22).

2.1. Burden or incidence of FN among pediatric cancer patient FN

Retrospective cohort studies on 180 children who received chemotherapy for malignancy in Turkey, Brazil, and Indonesia between 2 and 5 years reported 199–250 FN episodes. Acute lymphoblastic leukemia (ALL) was the most common underlying malignancy (71.1-73.5%), followed by acute meroblastic leukemia (AML)(8,23,24).

A study from South Africa showed within the 2-year study period (2014 to 2016), 100 episodes of FN were reported in 52 pediatric cancer patients [median 2 episodes (range 1–5). The study population included 28 hematological malignancies (54% FN episodes) and 24 solid tumors (46% FN episodes). 24% of the FN episodes were identified in patients with advanced-stage disease (25).

In Ethiopia, one study from Gondar reported the incidence of chemotherapy-related adverse drug reactions (ADRs) among pediatric cancer patients was 41.46%, where neutropenia accounted for 10.2% of the total ADRs (119) among 287 patients. Acute lymphoblastic treatment was diagnosed in a total of 35 (23.8%) patients with ADR(12). In Ethiopia, a one-year retrospective study conducted at TASH on 135 pediatric patients was found to have 85.9% fulfilled the FN diagnostic criteria, and in the remaining 95.9% the diagnosis was made without evidence. 88.9% of patients had an ANC value of less than 500 cells/mm3 (19,20).

2.2. Risk factors for febrile neutropenia

A retrospective cohort study conducted in Germany (2009 and December 2018) reported that among 170 pediatric sarcoma patients who received chemotherapy courses, 58.8% had at least one FN episode occurring in a total of 57 courses. Six neoadjuvant courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) were given at 21-day intervals based on hematological recovery(26).

Within the 2-year study period, among 52 pediatric oncology patients with 100 episodes of FN, patients with advanced-stage disease accounted for 24% of FN episodes, and 18% had at least one underlying comorbidity (25).

In Ethiopia, a cross-sectional study done at Gondar between 2017 and 2019 indicated that among 119 pediatric cancer patients who developed chemotherapy ADRs, 15 (10.2%) were febrile neutropenia. Etoposide, mercaptopurine, and doxorubicin were at higher risk for adverse drug reactions in patients (12). A retrospective study conducted in Ethiopia TASH on 60 pediatric cancer patients treated for chemotherapy and induced FN was followed for 7 months and showed that 10 children (10%) had sepsis. 43.3 percent of the patients had profound neutropenia. Twenty percent of the patients died. Those ten fatalities had a hematologic malignancy: eight had acute lymphoblastic leukemia (ALL) and two lymphomas. The other two were both suffering from solid tumors(20).

2.3. The principle of treatment

A report from 51 pediatric cancer centers in Germany, Austria, and Switzerland showed the first-line management of FN is piperacillin–tazobactam (61%; 30/49), followed by ceftazidime (24%; 12/49), cefepime, and ceftriaxone (4%) (27). A retrospective study in Thailand between 2013 and 2017 on 267 pediatric cancer patients who had 563 febrile episodes found that twenty-three percent of them were multidrug resistant and 18% were carbapenem resistant. Among gram-positive bacterial infections, which accounted for 23.4% of all specimens, the proportion of Methicillin Resistant Staphylococcus aureus (MRSA) was 20%(28).

In Ethiopia, a retrospective study was conducted on 135 FN pediatric cancer patients on chemotherapy from January 1, 2017 to December 31, 2017. Empiric antibiotic therapy was given to all patients, in which ceftriaxone with gentamycin constituted 71.8%, followed by ceftriaxone monotherapy(19).

Retrospective cohort studies on 180 children who received chemotherapy for malignancy in Turkey, Brazil, and Indonesia between 2 and 5 years reported 199–250 FN episodes. Acute lymphoblastic leukemia (ALL) was the most common underlying malignancy (71.1-73.5%), followed by acute myeloblastic leukemia. In Brazil, FN resulted in microbiological infection and 4% in ICU admission. A gram-negative bacterium was the most commonly isolated microorganism in the blood culture of pediatric patients with FN in Turkey, and the most frequently clinically documented foci were mucositis (33.4%) and pneumonia (24.7%). Nine (13.2%) children died of neutropenia septicemic (8,23,24) .

A multicenter prospective, observational cohort study from sub-Saharan Africa reported that during the 3 months following the diagnosis of cancer in children, 104 FN episodes were documented. The maximum number of FN episodes contributed by a single patient was four. The most common cancer was Burkitt's lymphoma (25%). About 72.0% of the patients who received antibiotic prophylaxis received cotrimoxazole (64.0%) and ciprofloxacin (8.0%). In the treatment of FN, ceftriaxone was the most commonly prescribed (34.0%). A total of 11/104 (11.1%) patients died in the FN episodes(29). A study from Egypt reported neutropenia was responsible for treatment discontinuation in 13.3%, dose delay (13.3%) and dose reduction (5.3%) of patients (30). A study from South Africa showed within the 2-year study period (2014 to 2016), 100 episodes of FN were reported in 52 pediatric cancer patients [median 2 episodes (range 1–5)]. The study population included 28 hematological malignancies (54% FN episodes) and 24 solid tumors (46% FN episodes). 24% of the FN episodes were identified in patients with advanced-stage disease (25).

2.4. Treatment outcome

2.4. 1.Pattern of Infection and pathogens

A study from Spain by Pérez-Heras et al. indicated that among 69 chemotherapy-induced FN patients, microbial isolation was found in 44.6% of the episodes, with no infectious source identified in 36% of them (31). A retrospective study done in the USA by Alali et al. reported that among 667 FN episodes in 268 pediatric cancer patients, blood culture was positive for a pathogenic species in 143 episodes (21.5%). The majority of pathogens (95/176, 54%) were gram-positive (GP), whereas 64 of 162 (36%) were gram-negative (GN), 5 were fungal, and 4 were mycobacterial. The most common GP pathogens were Viridian's group streptococci (VGS) (n = 34, 19.3%), coagulase-negative staphylococci (n = 25, 14%), and methicillin-susceptible Staphylococcus aureus (n = 12, 6.8%) (32).

A retrospective study done in Turkey, Thailand, and Brazil on 200–563 febrile episodes revealed that the most common clinically documented infections included mucositis (33.4%), pneumonia (24.7%), and microbiologically documented infections (MDI) (34.1–38.5%). The most common are bacteria (72%), viruses (15%), fungus (12.6%), and Mycobacterium tuberculosis (0.4%). The most common isolated bacteria were gram-negative agents (47.2–50%). The most frequent are Klebsiella pneumonia, Pseudomonas aeruginosa, and E. coli and the most common gram-positive bacteria was Staphylococcus sp. (12.8%). The occurrence of microbiological infection was not associated with the presence of a central venous catheter, gender, ethnicity/skin color, age, or underlying pathology in Turkey (8,23,28).

According to the prospective cohort study done in Egypt, FN was the leading complication of chemotherapy induced neutropenia (73.5%) and was associated with several documented infections, particularly mucositis (54.9%), respiratory (45.1%), gastrointestinal tract (38.9%) and skin (23.9%) infections (30). In South Africa, within the 2-year study period, among 52 pediatric oncology patients with 100 episodes of FN, MDIs included 24 bacteremia, three respiratory tract infections, four urinary tract infections, and two skin infections. The majority (58%) were gram-positive bacteremia [Staphylococcus aureus, Streptococcus species] with 41% gram-negative bacteremia (Klebsiella pneumoniae, Escherichia coli). Polymicrobial bacteremia was detected in four FN episodes (25).

A retrospective study conducted at TASTH showed among 60 pediatric cancer patients with chemotherapy induced FN, 7 children (11.7%) had a positive blood culture result. The pathogens isolated were 3 Klebsiella species, 3 Acinetobacter species, 1 Escherichia coli, and 1 coagulase-negative Staphylococcus (20)

2.4.2. Death

A study by Gupta et al. from El Salvador showed that 13 patients out of 106 FN episodes (12%) resulted in death. Pneumonia was a predictor of death in pediatric FN patients (33). A study from India by Das et al reported that the mortality rate among 264 children with FN was 10.3% (43/414 FN episodes; 8 with invasive fungal disease (IFD), and 35 with bacterial sepsis). The following factors were associated with mortality: 7-day interval since last chemotherapy, clinical focus other than URI, C-reactive protein (CRP) > 90 mg/L, and albumin 2.5 g/Dl (34) . Chaudhur et al from India showed, malnutrition may be a potential predictor of mortality in adverse outcomes in febrile neutropenia associated with hematological malignancies (35).

From 5 sub-Saharan African countries, out of 252 pediatric patients with a new diagnosis of cancer, we did not assess the factors associated with mortality (29) .

A cross-sectional conducted in the pediatric oncology ward of TASTH on 135 FN pediatric cancer patients reported that 7 patients died due to all-cause mortality (19). In the same setting in 2017, another study reported that among 60 patients with chemotherapy-induced febrile neutropenia, 12 (20%) of the patients died in the hospital. The mean (SD) age of patients who died was 4.78 (2.48) years. Among those who died, ten children had hematologic malignancies and two had solid tumors. Ten of the 12 patients had an absolute neutrophil count of less than 100/mm3 and a platelet count of less than 50,000/mm3. Six of the 10 children (10%) had sepsis. Patients with profound neutropenia, a platelet count of less than 50,000, and sepsis were more likely to die(20)

Conceptual Frame work

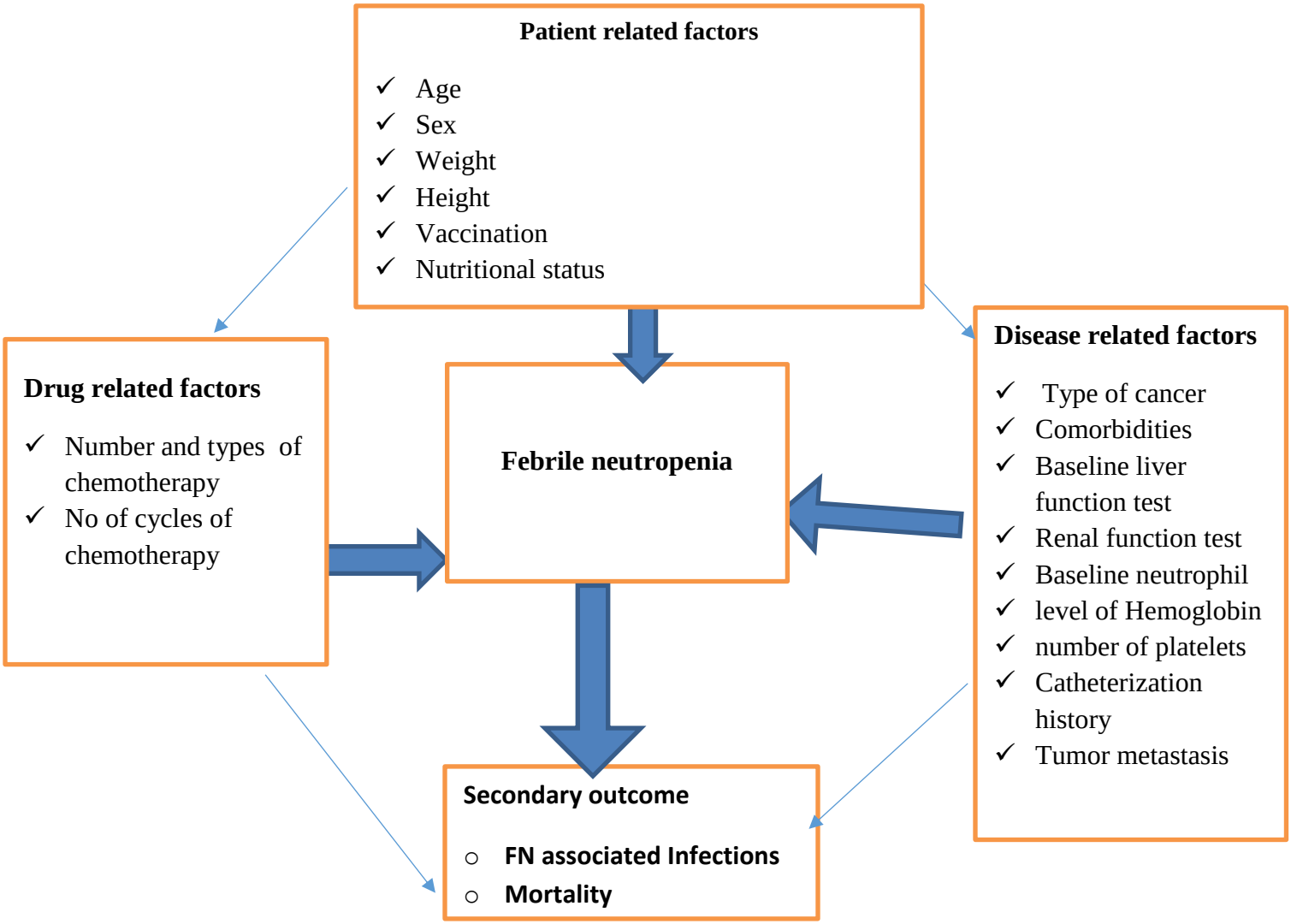

Figure 1: Conceptual framework showing associated factors and treatment outcomes of pediatric cancers among pediatric cancer patients who received chemotherapy(4,8, 20,23,24 , 25, 26, 29, 34 ,35)

3. OBJECTIVES

3.1. Main objective

- To assess clinical characteristics, associated factors and treatment outcomes of pediatric cancers among pediatric cancer patients who received chemotherapy at pediatric hematology/oncology ward, of Jimma Medical Center, Ethiopia

3.2. Specific objectives

- To assess magnitude of FN among pediatric cancer patients who received at least one cycle or phase of chemotherapy
- To assess the patterns of FN associated infections among FN patients.
- To assess predictors of FN among cancer patients who received chemotherapy
- To assess the magnitude and predictors of all-cause mortality among cancer patients.

4. METHODS AND MATERIALS

4.1. Study area and period

Study was conducted at Jimma Medical Center (JMC). It is one of the oldest hospitals in Ethiopia and it is the only teaching and referral hospital in southwest Ethiopia with 800-bed capacity and a catchment population of over 20 million people. It is located in Jimma town, 352 kilometers southwest of Addis Ababa, the capital city (36). JUMC has several specialized treatment units. Pediatric oncology/hematology ward unit is one of the recently implemented (21), which is currently providing oncology services for children. The unit has 22 bed and running with pediatric residents under the supervision of one senior oncologist (21). The data was collected from January 2022 to April 2022.

4.2. Study design

Retrospective cohort study design was used to include pediatric cancer patients who received chemotherapy between August 2017 and January 2022 at JMC.

4.3. Population

4.3.1 Source population

All children who were diagnosed with cancer at pediatric hematology/oncology ward unit of JMC.

4.3.2. Study population

All children who received cancer chemotherapy treatment at pediatric oncology/hematology ward of JMC between August 2017 and January 2022 and fulfilled the inclusion criteria.

Inclusion criteria

- Patients who received at least one cycle or phase of chemotherapy
- Age below 18 years old

Exclusion criteria

- Incomplete data

- Patient referred to other sites

4.4. Sample size

All medical records of children diagnosed with cancer and received/receiving cancer chemotherapy treatment between August 2017 and January 2022 years and full filled inclusion criteria were included.

4.5. Study variables

Dependent variables

- **Primary outcome**: Chemotherapy induced febrile neutropenia (FN)
- **Secondary outcomes**: Mortality, FN associated infections

Independent variables

- Age, gender, weight, nutritional status, vaccination status, comorbidities, history of catheterization, surgery, type of tumor, tumor metastasis, baseline neutropenia, hemoglobin and platelets, number of chemotherapy regimens, phase/cycle of treatment, co-morbid conditions, abnormal organ functions such as liver and kidney function tests .

4.6. Outcome Measurement and Validation

Febrile neutropenia (FN): FN is confirmed when the ANC is below 500 cells/microL and temperature is above 38°C in a patient who received cancer chemotherapy (43).

Infections: In this study, infections developed after FN due to chemotherapy diagnosis were counted as FN associated infections

All-cause Mortality: mortality was confirmed from the clinician death summary notes from the medical chart.

4.7. Data collection, procedures and tool

Data was collected by usingSemi- structured questionnaire from the medical record. Data was collected by two clinical pharmacists and one BSc nurses who were working in the oncology ward under the supervision of the investigators. Before the actual commencement of data collection, two days of training was given to the data collectors by the principal investigator and supervisors.

4.8. Data quality management

Pretest was conducted on five medical records of pediatric cancer patients recently started chemotherapy treatment. Data were collected by two clinical pharmacist and one BSc nurses and supervised by investigators. To ensure data quality, all data collectors were received training and orientation. The accuracy, clarity, and completeness of data were checked daily by the investigators, and feedback and corrections was provided as needed.

4.9. Data processing and analysis

Data was checked, cleaned, and entered into Epi-data version 4.6 and then exported to Statistical Package for Social Science version 26.0 for statistical analysis. Descriptive statistics was performed, and the findings were reported in percentage, frequency, median (interquartile range). Logistic regression model was used to report the identify independent variables associated with FN and mortality. The first episode was taken to assess the risk factors for FN. Univariate analysis was first performed to identify the candidate variables for the multivariate analysis. The variables with a P.Value less than 0.25 were selected for the multivariate analysis. The effect size was reported in odds ratio (OR) along with a 95% confidence interval and a p-value of <0.05 was used to declare the statistical significance.

4.10. Ethical consideration

Ethical clearance & approval (ref.no JUIRB 006/14) was obtained from institutional review board of institute of health, Jimma University and sent to the director of Jimma university medical center and head of oncology/hematology pediatric ward. Then, formal permission letter was obtained from both administrative bodies. Since it is critical card verbal consent was taken

from responsible clinician working in the clinic. All information collected from patient's medical record was keep strictly confidential and names of children weren't included in the data collection format.

4.11. Dissemination plan

The findings of this study will be disseminated through a presentation as a final defense and in scientific seminars or workshops. A copy of the document will be sent to Jimma University's institute of health graduate program coordinating office, pharmacy school, and JUMC of oncology/hematology pediatrics unit. Finally, it will be expected to be published in a reputable international peer-reviewed journal

4.12. Operational definition

Febrile neutropenia: Fever is axillary body temperature measured once above >38.0C sustained over a 1-h period. Neutropenia is described as an absolute neutrophil count (ANC) of 500 cells/mm3 (37).

Neutropenia: Neutropenia is defined as an absolute neutrophil count (ANC) <500 cells/microL (38) .

Fever: An axillary body temperature measured once above 38°C or continuance of the axillary body temperature above 38.2 (37). In Neonates & Infants rectal temperature of ≥38.0°C or greater (39) .

Comorbidity: Disease condition identified before febrile neutropenia.

5. Result

At the study area, the number of pediatric cancer patients registered between August 2017 and January 2022 was 641. For this study, 313 patients were fulfilled the study inclusion criteria and included into the study. The reasons for the exclusion were shown in the figure 2.

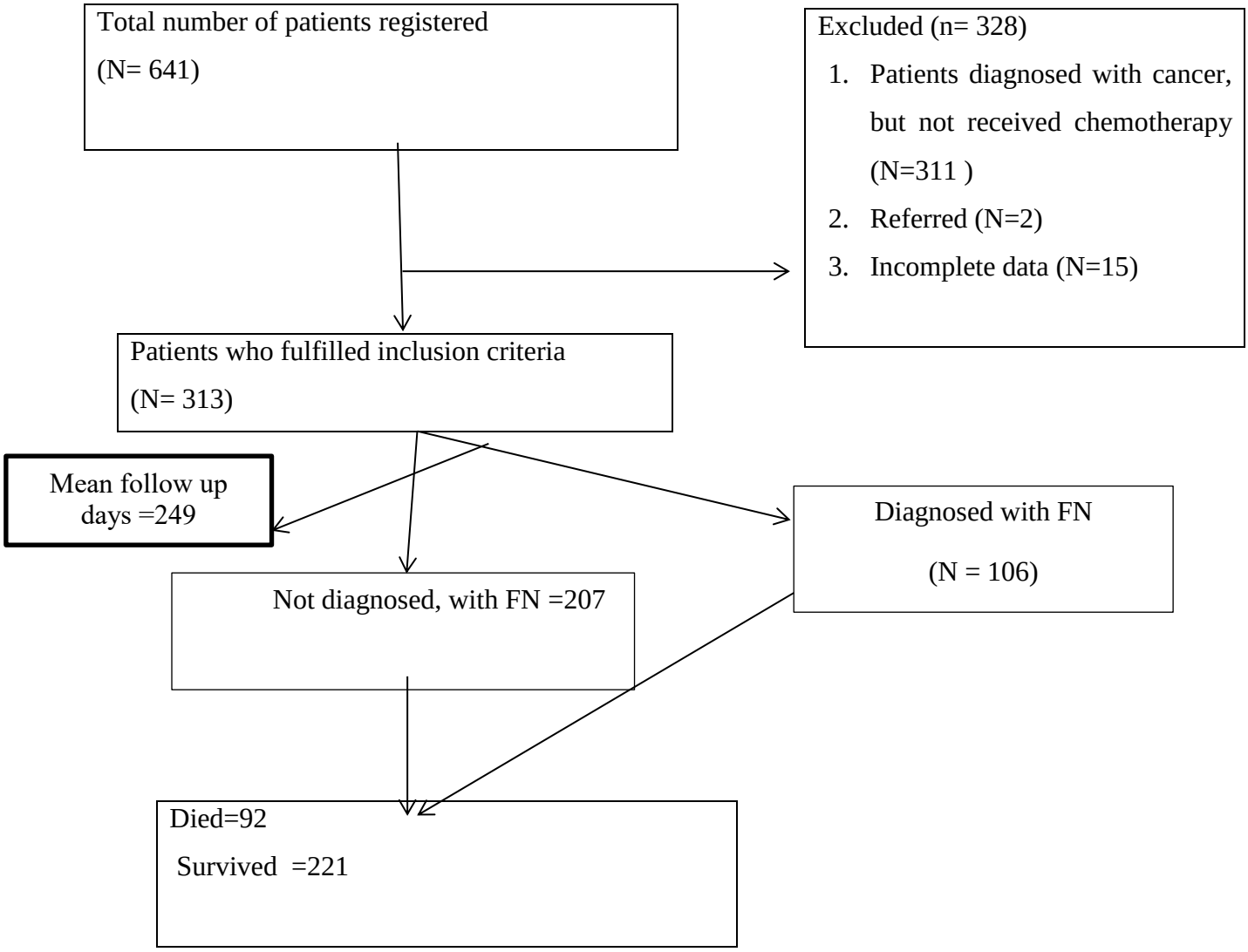

Figure 2: Flowchart of patient recruitment and follow-up, pediatric cancer patients, pediatric oncology, JMC

5.1 Sociodemographic characteristics and anthropometry

From 313 patients included, 52.1% of them were males. The median (interquartile range, IQR) of the patients was 7 (4, 11) years. Most (41.2%) patients were aged less than 5 years. More than half (53.0%) of the patients lived in the rural area. Regarding their nutritional status, 36.7% and 29.1% of the patients were wasted and stunted, respectively. About two-thirds (67.1%) of the patients had a full vaccination history and 2.2% did not vaccinate at all (Table1)

Table 1: Socio-demographic characteristics and anthropometric measurement of pediatric cancer patients at pediatric oncology ward of JMC (N=313):

Characteristics		Frequency	Percent
Age	<5	129	41.2
	5- 10	92	29.4
	10 – 18	90	28.8
Weight	3-10	46	14.7
	10-25	172	55.0
	25-52.2	30.4	28.8
Sex	Male	163	52.1
	Female	150	47.9
Residence	Rural	166	53.0
	Urban	47	47.0
Nutritional status	Wasted	115	36.7
	Stunted	91	29.1
Vaccination status	Fully vaccinated	210	67.1
	Unknown or not	62	19.8
	Partially vaccinated	41	13.1

5.2. Comorbid diseases and other clinical characteristics

Out of the total participants, two-thirds (67.1%) of the patients had comorbid diseases. The most frequent comorbid diseases were malnutrition (47.5%), hospital acquired infection, (23.3%), and pneumonia (13.4 %(Table2).

Table: 2 Types of comorbid disese of pediatric cancer patients at pediatric oncology ward of JMC (N=313)

Types of comorbidity	**Frequency**	**Percent**
Malnutrition	150	47.5
Hospital acquired infection	73	23.3
Pneumonia	42	13.4
Fungal sepsis	22	7
Urinary tract infection	17	5.4
Tinia captitis	12	3.8
Scabies	4	1.3
Malaria	1	0.3

5.3. Baseline laboratory investigations

In this study, the median (IQR) number of white blood cells (WBC) was 7.8 (5.3, 10.4) x 10^3 cells/µL out of which 15.0% of the patients had WBC ≤ 4 x 10^3 cells/ µL. About one-fourth (23.0%) of the patients had absolute neutrophil count (ANC) ≤ 1.5 x 10^3 cells/µL at baseline. The finding also showed that the overall median (IQR) hemoglobin level was 10.0 (7.5, 11.6) gram/dL, where one-third (32.6%) of the patients had ≤ 8.0 gram/dL. One-fourth of the patients had platelet count ≤ 100 x 10^3 cells/µL at baseline. Regarding the organ function tests, the median (IQR) serum creatinine (SCr) and blood urea nitrogen (BUN) were 0.47 (0.3, 0.68) mg/dL and 19.0 (14, 24) mg/dL, respectively. In the same way, the median (IQR) alanine transferase (ALT) and aspartate transferase (AST) enzymes was 18.8 (13.7, 27.9) and 28.0 (21.1, 39) international units per liter (IU/L), respectively. About 8.6% and 2.2% of the patients had AST and ALT values above two times their upper normal limit (UNL), respectively (Table 3).

Table 3: Baseline laboratory investigations of pediatric cancer patients, pediatric oncology ward, JMC, 2022. (N=313)

Investigations	**Median (interquartile range)**
White blood cell counts (10^3 cells/µL)	7.8 (5.3, 10.4)
Absolute neutrophil count (10^3 cells/µL)	3.8 (1.6, 5.9)
Hemoglobin (gram/dL)	10.0 (7.5, 11.6)
Platelets (10^3 cells/µL)	300.0 (100, 434.5)
Serum creatinine (mg/dl)	0.47 (0.3, 0.68)
Blood urea nitrogen (mg/dL)	19.0 (14, 24)
Alanine transferase enzyme (IU/L)	18.8 (13.7, 27.9)
Aspartate transferase enzyme (IU/L)	28.0 (21.1, 39)

5.4 Type of cancers

From all cancers, acute lymphoblastic leukemia (25.2%) and lymphomas (20.4%) were the two most commonly diagnosed cancers. Over all, half (50.2%) of the patients had hematological cancers. From non-hematologic cancers, Retinoblastoma (9.6%), Wilms tumor (8.9%), and osteosarcoma (8.9%) were the most frequent cancers.

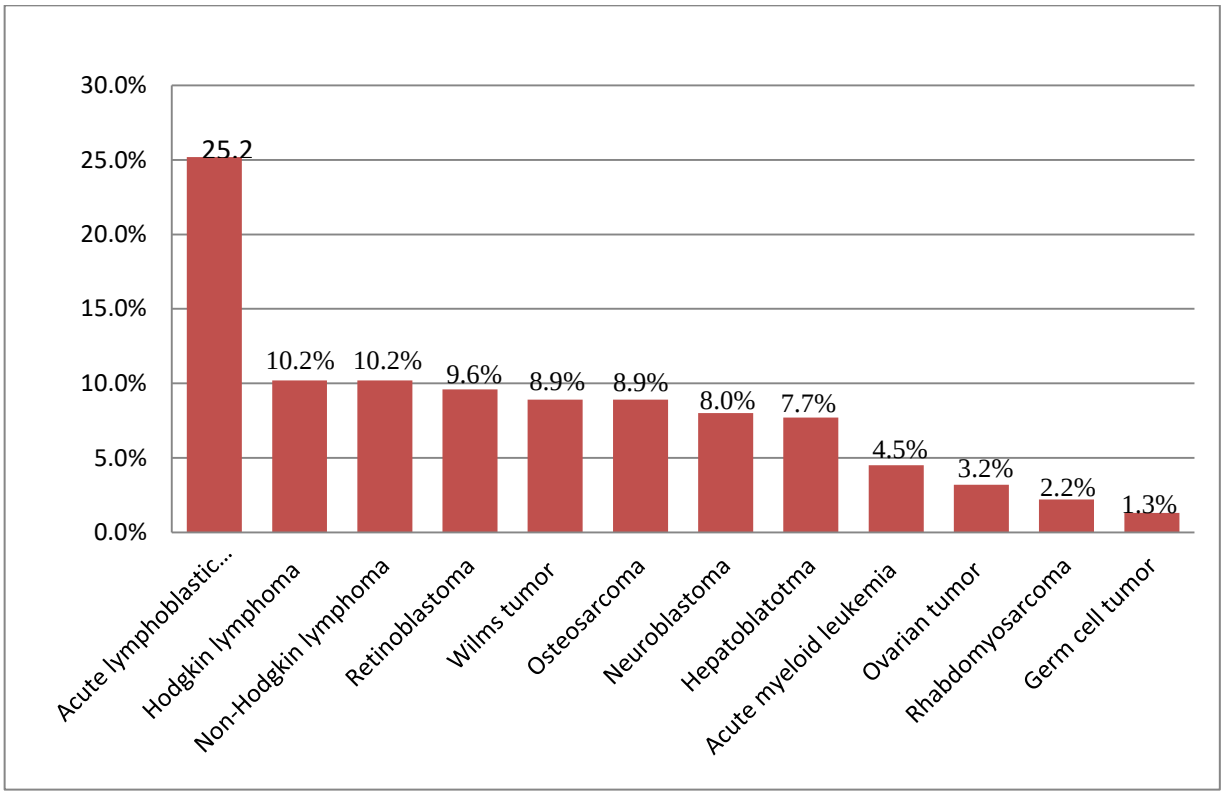

Figure 3: Type of cancers among pediatric cancer patients, at pediatric oncology ward, 2022

In this study about most of the patient was diagnosed after the cancer was metastasize 186(59.4%). Surgical intervention was done for 51 (16.3 %) of case. About 86 (27.5%) of the patient were catheterized. The total number of chemotherapy received were combination of 2-4 drugs in 249 patients (79%) followed by 5-6 in 64 patients (20.4%). Three-quarters (75.8%) of patients with hematologic cancers had a metastasized cancer (Table4).

Table: 4 Pediatric cancer patients who received cancer chemotherapy at pediatric, jimma medical center 2022 (N=313)

Variable		Frequency	Percent
Surgical intervention		51	(16.3 %)
Catheterized		86	27.5
Tumor type	Hematologic tumor	157	50.2
	Non-hematologic	156	49.8
Number of chemotherapy received	2-4	249	79.6
	5-6	64	20.4

5.5. Cycles of Chemotherapy received for solid cancers

In this study, the majority (79.6%) of the patients were received 2 to 4 chemotherapy regimens. And the remaining (20.4%) received 5 to 6 regimens. For solid tumors including lymphomas, the median (IQR) number of chemotherapy cycles received was 4.0 (2, 6). Most (22.3%) of the patients received 4 cycles of chemotherapy. The maximum number of cycle received was 8, in which 13.6% of the patients received it (Table5).

Table: 5 Cycle of chemotherapy received for solid cancers among pediatric cancers, jimma pediatric oncology, 2022 (N=220)

Cycles	**Frequency**	**Percent**
cycle1	39	17.7
cycle2	29	13.2
cycle3	26	11.8
cycle4	49	22.3
cycle5	4	1.8
cycle6	39	17.7
cycle7	4	1.8
cycle8	30	13.6

5.6. Phases of chemotherapy received for liquid cancers

Majority of the acute lymphoblastic leukemia and acute myeloid leukemia patients received the induction phase of chemotherapy (30.1%) and one-fourth (24.7%) received maintenance regimen for that cancer. Moreover, a similar percentage (24.7%) of the patients completed all the phases of treatment for that cancer (Table 6).

Table: 6 Phases of chemotherapy received for liquid cancers among pediatric cancers, Jimma pediatric oncology, 2022 (n = 93)

Phases	Frequency	Percent
Induction	28	30.1
Consolidation	10	10.7
Interim Maintenance	6	6.4
Delayed Intensification	3	3.2
Maintenance	23	24.7
Completed all the phases	23	24.7

5.6.1 Febrile neutropenia

Out of 313 patients who received chemotherapy within the study period, 106 (33.86%) of the patients had FN, with 128 total episodes. Twenty (18.9%) of the patients had 2 to 3 FN episodes (Figure 4). The median (IQR) absolute neutrophil count and temperature at time when the first episode of FN diagnosed was 200 (110, 352) cells/µL and 38.4 (38.2, 38.9) degree Celsius, respectively. Out of all patients with FN, about half (50.9%) of them had acute lymphoblastic leukemia

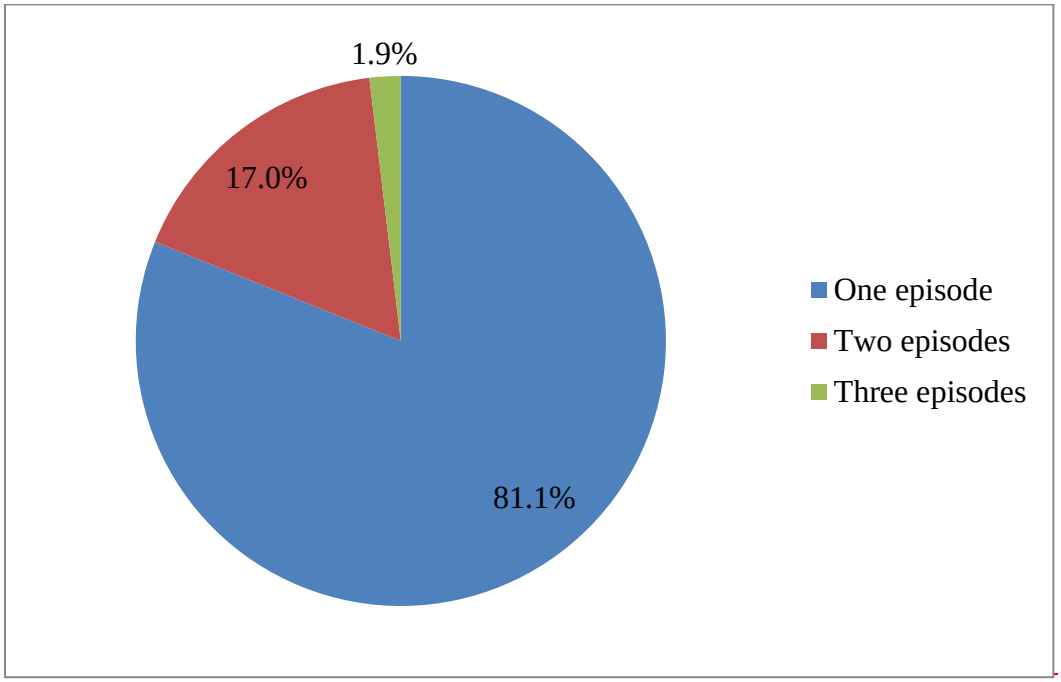

Figure 4: Number of FN episodes among patients with FN at JMC, 2022 (N=106)

5.6.2. Phases /cycles of treatment of cancer chemotherapy at which FN developed

Majority (42.5%) of the patients developed FN during the induction phase treatment for ALL and AML followed by 21.7% during the first cycle of treatment for solid tumors (Table7).

Table: 7 Phase /cycle of treatment of cancer chemotherapy at which FN developed, Jimma Ethiopia, 2022 (N=106)

Cycle or phase of treatment	**Frequency**	**Percent**
Liquid cancers		
Induction	45	42.5
Consolidation	8	7.5
Maintenance	7	6.6
Solid cancers		
Cycle 1	23	21.7
Cycle 2	6	5.7
Cycle 3	5	4.7
Cycle 4	5	4.7
Cycle 6	5	4.7
Cycle 7	1	0.9

5.6.3. Treatment of febrile neutropenia

Nearly all (89.60%) of the FN patients were initially treated with combination of ceftriaxone and gentamycin. And the remaining (10.40%) of patients were treated with combination of ceftazidime and vancomycin. Additionally, cotrimoxazole, ciprofloxacin and fluconazole was prescribed for eight (7.5%), seven (6.6%) and six (5.7%) of FN patients, respectively. After initial treatment with ceftriaxone and gentamycin, the treatment regimen was changed to ceftazidime and vancomycin in 41 (13.1%) patients (Table8).

Table:8Phase /cycle of treatment of cancer chemotherapy at which FN developed, Jimma Ethiopia, 2022 (N=106)

Antimicrobials	**Frequency**	**Percent**
Initial regimens		
Ceftriaxone and gentamycin	95	89.6
Ceftazidime and vancomycin	11	10.4
Second line regimens		
Changed to Ceftazidime and vancomycin	41	13.1%
Fluconazole	14	13.2
Cotrimoxazole	8	7.5
Ciprofloxacin	7	6.6

5.6.4. Pattern of FN associated infections and pathogens

Out of 106 patients with at least one episode FN, 71.7% of the patients had clinical documented FN associated infections. The most common clinically documented infection associated to FN was oral mucosal infection (17.9%) skin and soft tissue infection (14.2%), sepsis (13.2%) and gastroenteritis (9.4%) (Table9).

Table: 9 Infections related to febrile neutropenia treatment of pediatric cancer patient with FN at JMC, Ethiopia Jimma, 2022 (N=106)

Clinically documented infections	Frequency	Percent
Oral mucosal infection	19	17.9
Skin infection	15	14.2
Fungal Sepsis	14	13.2
Urinary tract infection	11	10.4
Gastroenteritis	10	9.4
Meningitis	7	6.6

5.6.5 Microbiology of the FN associated infections

Culture specimens was only collected from 41(38.5) FN patients, out of which the eight patients had positive culture for infections. In remaining 33(31.1) FN patients, there was no growth of bacteria. Coagulase-negative staphylococci, P. aeruginosa, and K-pneumonia were reported in 5(4.7%) patients, 2 (1.8%), and 1 (0.9%), respectively. In five FN patients with Coagulase-negative staphylococci (CoNS), CoNS bacteria were sensitive to clindamycin, ciprofloxacin and cotrimoxazole in two patients. In the other two patients, CoNS were resistant to clindamycin, ciprofloxacin and cotrimoxazole while it was resistant to tetracycline in 1 patient. Both reported Pseudomonas aeruginosa and Klebsiella pneumoniae were sensitive to ciprofloxacin and no resistance was reported for other antimicrobial (Table10).

Table: 10 Culture specimens result related to febrile neutropenia treatment of pediatric cancer patient with FN at JMC, jimma Ethiopia, 2022 (n=106)

Culture done (n = 41)		Frequency	Percent
No growth (n=33)		33	**31.1**
Microorganism growth (n =8)	Coagulase-negative staphylococci	5	4.7
	Pseudomonas aeruginosa	2	1.8
	Klebsiella pneumoniae	1	0.9

5.7 Factors associated with febrile neutropenia among patients who received cancer chemotherapy

In Univariate analysis, rural residency (COR = 1.66 (95% CI 1.03, 2.68), P< 0.001), Nutritionally Stunted (COR = 0.34 (95% CI 0.19, 0.62, P< 0.001)), hematologic tumors (COR = 4.84 (95% CI 2.88, 8.14), P< 0.001)), tumor metastasis (COR = 6.63 (95% CI 1.34, 3.60), P<.002), Number of chemotherapy received 5-6 (COR=3.02 (95%CI 1.72, 5.32) P< 0.001), baseline neutropenia (COR=2.63 (95%CI 1.53, 4.52, P<0.001), hemoglobin≤ 8, (mg/dl) COR=2.20 (95%CI 1.34, 3.60) p= 0.002 and number of chemotherapy received (5 – 6) COR=3.02 (95%CI 1.72, 5.32) P< 0.001 were significantly associated with FN.

Based on univariate analysis the variables that have p-value less than 0.25 were included in multivariate analysis. weight (kg) <10 COR=0.59, 10-25 COR=0.70 , Partial Vaccination COR= 1.616 ,Unknown vaccination COR= 1.541 , Surgical interventions COR =0.62 ,Urinary Catheterization COR=1.51, Baseline platelets cells COR= 1.96 and Baseline BUN(mg/dl) COR =1.43 The variables that have p-value less than 0.25 were included in multivariate analysis

In multivariate analysis, patients who had hematologic tumors (AOR = 4.16 (95% CI 2.26, 7.65) P< 0.001) and tumor metastasized (AOR = 4.56 (AOR = 4.16 (95% confidence interval (CI) 2.26, 7.65) P< 0.0001) and tumor metastasized (AOR = 4.56 (95% CI 2.36, 8.79), P < 0.0001) were more than four times more likely to develop FN after chemotherapy started compared to those with non-hematologic tumors. Patients who had a baseline low neutrophil count (≤ 1.5 x 10^3) had about two times more likely (AOR = 1.93 (95% CI 1.01, 3.66), P = 0.046) to develop FN after treatment with chemotherapy compared to patients who had a normal neutrophil count. Similarly, pediatric patients who were an incomplete vaccination were more than three times more likely (AOR = 3.11 (95% CI 1.31, 7.35), P = 0.010) to develop FN compared to patients who were fully vaccinated. In contrast to other findings, patients who were nutritionally stunted had a lower risk to develop FN (AOR = 0.26 (95% CI 0.13, 0.52) P < 0.0001) [Table11]

Table: 11 Multivariate analysis of factors associated with febrile neutropenia in cancer Variables in the Equation patients who received chemotherapy

Variables	**Category**	**FN**		**COR (95% CI)**	**p.value**	**AOR (95%CI)**	**P.value (AOR)**
		yes	No		(COR)		
Residency	Rural	65	101	1.66 (1.03, 2.68)	.036	1.62 (0.92, 2.87)	0.096
	Urban	41	106	1		1	
Weight (kg)	<10	13	33	0.59 (0.27, 1.26)	.176	.84 (0.32, 2.20)	0.719
	10 – 25	55	117	0.70 (0.42, 1.18)	.189	.768 (0.40, 1.47)	0.428
	>25	38	57	1		1	
Stunted	Yes	17	74	0.34 (0.19, 0.62)	P<0.001	0.26 (0.13, 0.52)	P<0.001*
	No	89	133	1		1	
Vaccination status	Full	64	146	1		1	
	Partial	17	24	1.616(.813, 3.213)	0.17	3.11 (1.31, 7.35)	P<0.010*
	Unknown or not	25	37	1.541 (.86, 2.771)	0.148	1.12 (0.55, 2.26)	0.75
Tumor type	Hematologic	79	78	4.84 (2.88, 8.14)	P<0.001	4.16 (2.26, 7.65)	P<0.001*
	Non-hematologic	27	129	1		1	
Tumor metastasis	Yes	90	95	6.63 (3.65, 12.06)	P<0.001	4.56 (2.36, 8.79)	P<0.001*
	No	16	112	1		1	
Surgical interventions	Yes	13	38	0.62 (0.31, 1.22)	0.170	.879(.375,2.06)	0.767
	No	93	169	1		1	
Catheterization history	Yes	35	51	1.51 (0.90, 2.52)	0.117	1.40(.760,)2.577	.280
	No	71	156	1		1	
Baseline ANC cells	$\leq 1.5 \times 10^3$	37	35	2.63 (1.53, 4.52)	P<0.001	1.93 (1.01, 3.66)	0.046*
	$>1.5 \times 10^3$	69	172	1		1	
Baseline hemoglobin, (mg/dl)	≤ 8	47	55	2.20 (1.34, 3.60)	0.002	1.258(.688,2.299)	0.457
	> 8	59	152	1		1	
Baseline platelets cells	$\leq 100 \times 10^3$	36	43	1.96 (1.16, 3.31)	0.012	1.311(.704,2.441)	0.393
	$> 100 \times 10^3$	70	164	1		1	
Baseline BUN(mg/dl)	≤ 20	53	122	1		1	
	> 20	53	85	1.43 (0.89, 2.30)	0.132	1.284(.732,2.252)	0.383
Number of chemotherapy received	2 – 4	71	178	1		1	
	5 – 6	35	29	3.02 (1.72, 5.32)	P<0.001	1.094(.515,2.327)	0.815

* indicates statistical significance, ANC: absolute neutrophil count, BUN: blood urea nitrogen

5.8 Predictors of mortality among pediatric patients who received cancer chemotherapy

In this study, 29.4% of cancer patients were died after receiving at least one cycle or phase of chemotherapy within the study period. Based on the univariate analysis, tumor metastasis (COR = 2.52 (95% CI 1.47, 4.30) P< 0.001, catheterization history (COR = 1.90 (95% CI 1.13, 3.22) p = 0.016), serum creatinine greater than 1 mg/dl (COR = 3.61 (95% CI 1.40, 9.31) p=0.008), BUN greater than 20 mg/dl (COR = 1.92 (95% CI 1.17, 3.13) p= 0.010), and hemoglobin less than 8 g/dL.

Upon multivariate logistic regression analysis, tumor metastasis, history of urinary catheterization, abnormal renal function at baseline, and low level of hemoglobin were significantly associated with the increased risk of mortality. Patients who had serum creatinine (SCr) (>1mg/dL and blood urea nitrogen (BUN> 20 mg/dL) had three (AOR = 3.13 (95% CI 1.13, 8.62), P = 0.028) and about two (AOR = 1.69 (95% CI 1.01, 2.84), P = 0.046) times more likely to die compared to those patients who had a normal level of SC and BUN at baseline. Patients who had hemoglobin level ≤ 8mg/dl was significantly associated with an increased risk of mortality at a later time (AOR = 1.88 (95% CI 1.10, 3.21) P = 0.020). Similarly, patients who had tumor metastasis and were catheterized had about two times increased risk of mortality compared to their counterparts, respectively (Table12).

Table: 12 Multivariate analysis of factors associated with mortality among pediatric cancer patients who received chemotherapy

Variables	Category	Died		COR (95% CI)	P.value (COR)	AOR (95%CI)	P.value P(AOR)
		yes	No				
Tumor type	Hematologic	51	106	1.35(0.83,2.20)	0.229	.836 (.473,1.478)	0.538
	Non-hematologic	41	115	1		1	
Tumor metastasis	Yes	68	117	2.52 (1.47, 4.30)	0.001	2.038 (1.16, 3.57)	0.013*
	No	24	104	1		1	
Catheterization history	Yes	34	52	1.90 (1.13, 3.22)	0.016	1.76 (1.01, 3.07)	0.046*
	No	58	169	1		1	
Wasted	Yes	39	76	1.4 (0.85, 2.31)	0.182	1.435 (.844, 2.440	0.182
	No	53	145	1		1	
Serum creatinine, mg/dl	≤ 1	81	213	1		1	
	>1	11	8	3.61 (1.40, 9.31)	0.008	3.13 (1.13, 8.62)	0.028*
Blood urea nitrogen, mg/dl	≤ 20	41	134	1		1	
	> 20	51	87	1.92 (1.17, 3.13)	0.010	1.69 (1.01, 2.84)	0.046*
ALT, IU/L	≤ 2 ULN	88	218	1		1	
	>2 ULN	4	3	3.30 (.72, 15.06)	0.123	2.398(.448,12.23)	0.307.
Hemoglobin, mg/dl	≤ 8	42	60	2.25 (1.36, 3.74)	0.002	1.88 (1.10, 3.21)	0.020*
	> 8	52	161	1		1	
Number of chemotherapy received	2 - 4	69	180	1		1	
	5 – 6	23	41	1.46 (0.82, 2.62)	0.199	1.302(.629,2.695)	0.477

*indicates statistical significance, IU/l: international units/liter, ULN: upper limit normal

6. DISCUSSION

In this study Out of 313 study participants 128 episodes of FN were identified (33.86%) of the who received at least one phase or cycle of cancer treatment. It is low compared to one study done in Germany 58.8% of participants experienced at least one episode of FN (26). On the other hand, in a study in Egypt, 73.5% of pediatric cancer patients were diagnosed with chemotherapy induced febrile neutropenia (30). The variation in percentage might be due to sample size and study design. A prospective cohort study in Egypt , a sample size of 170 in Germany and under diagnosis in our setting .

Of the 106 study participants who experienced at least one episode of FN, 76 (71.7%) had clinically verified FN-related infections. Of the FN patients, only 41 (38.5%) had culture specimens taken, and only eight bacteria were grown. The most frequently identified clinical infections linked to febrile neutropenia were oral mucosal infection19 (17.9%), skin infection15 (14.2%), sepsis 14(13.2%), and gastroenteritis 10(9.4%). Similar studies were conducted in Turkey, Thailand, and Brazil on 200–563 febrile episodes, and they found that mucositis (33.4%), pneumonia (24.7%), and microbiologically documented infections (MDI) (34.1–38.5%) were the most often clinically documented infections.(8,23,24). The difference in percentage could be attributed to the number of FN episodes compared to 128 in this finding. Variation in percentage might be due to study design prospective and sample size, Economic status.

In this study, hematologic tumors were more than four times more likely to develop FN after chemotherapy was started compared to those with non-hematologic tumors. According to this study, patients with a low neutrophil count at baseline (1.5 x 103) had a slightly higher chance of developing FN than those with a normal neutrophil level. In a similar study in India, patients with hematologic malignancy had a 4.5 (AOR = 4.6; P = 0.019) times higher risk of developing febrile neutropenia compared with patients with solid tumors. The risk of developing febrile neutropenia was increased by 1.005 (AOR = 1.005; P 0.001) (40). Variation might be study design case87and control94 and sample size .During neutropenia, the neutrophil cells required to fight bacteria are depleted. Thus, it increases the susceptibility to developing febrile neutropenia.

Being stunted was not associated with an increase in risk of FN. This opposite finding might be due to the difference in research methods and nutritional status parameters between these studies. Similarly in Pakistan Hematology increase risk of FN by 1.8 (41). Studies conducted in Thailand (ANC <300/mm3) and France, low absolute neutrophilic counts were risk factors for FN (ANC <1000) (39 ,42) . Variation might be sample size872 and clinical setting

In this study, 29.4% of cancer patients were died after receiving at least one cycle or phase of chemotherapy within the study period. Patients who had a history of catheterization and metastatic malignancies had death risks that were almost twice as high as those compared to non-catheterized and non-metastasized tumors. Similarly study in Thailand catheterization history increases mortality risk by 4.28(43). While metastasized tumors elevated the chance of mortality by 4.8, according to a study done in Pakistan State(44). Metastatic tumor increased the risk of death by twofold compared to our study. This might be due to the low sample size (84 patients) and only one type of cancer being included.

On the one hand, according to this study, people with baseline high (above 20 mg/dl) blood urea nitrogen are roughly twice died. Similarly, studying in Santiago, BUN greater than 18 mg/dL, p 0.001, increased the risk of death by 6.8, which is four times higher than our finding; the difference could be attributed to the smaller sample size (313), as well as different laboratory measurements or clinical setting (2). Patients in this study who had a baseline hemoglobin level less than 8 mg/dl had a significantly higher risk of passing away than patients who had a baseline hemoglobin level greater than 8 mg/dl. This study in line with study done in Denmark , hemoglobin levels of 9.7 g/dL increase mortality risk by 1.3.(45) .Similarly In South America and India, hemoglobin levels less than 7 mg/dl increase the risk of death by 1.51 and 1.46 respectively (32,44). Variation might be due to study design prospective multicenter, sample size 393, Economic statues and clinical setting.

Conclusion

In this study, a significant number of patients developed FN and died. Several tumor and patient-related factors were associated with an increased risk of the development of FN and mortality. FN was linked to hematologic tumors, tumor metastasis, a low baseline neutrophil count, and incomplete vaccination. While tumor metastasis, history of urinary catheterization, abnormal renal function at baseline, and low levels of hemoglobin were significantly associated with the increased risk of mortality.

Recommendation

In light of these findings, the following suggestions will be made: Jimma Medical Center should strive for early diagnosis and treatment to reduce the risk of tumor metastasis. Healthcare providers should improve the evaluation of baseline laboratory tests such as renal function, hemoglobin, and neutrophil count. It would be preferable if policymakers developed alternative strategies, such as vaccination, to reduce the risk of FN. It is also better if researchers conduct multicenter prospective cohort studies to provide evidence for association factors for death and FN with specific drugs regimen used in pediatric cancer treatment and nutritional statues.

Limitations

The study's drawback is that it was conducted in a single center and was retrospective in nature. There were some patient records that couldn't be found, and it's possible that those missed documents were those of patients who passed away. It's possible that this led to an undercount of patients who passed away. The failure to fully evaluate some of the study variables may also be due to incomplete records of data in the patient charts

6. Reference

1. National Comprehensive Cancer Network Inc. NCCN Guidelines for Patients: Adolescents and Young Adults with Cancer. 2019; Available from: https://www.nccn.org/patients/guidelines/content/PDF/aya-patient.pdf

2.Santolaya ME, Alvarez AM, Avilés CL, Becker A, Mosso C, O'Ryan M, et al. Admission clinical and laboratory factors associated with death in children with cancer during a febrile neutropenic episode. Pediatr Infect Dis J. 2007;26(9):794–8.

3. WHO. global Initiative for childhood cancer, An Overview. 2020;

4. Aristizabal P, Winestone LE, Umaretiya P, Bona K. Disparities in Pediatric Oncology: The 21st Century Opportunity to Improve Outcomes for Children and Adolescents With Cancer. Am Soc Clin Oncol Educ B. 2021;(41):e315–26.

5. WHO. Childhood cancer. South east Asia Reg websites. 2021;

6. Lighter-Fisher J, Stanley K, Phillips M, Pham V, Klejmont LM. Preventing infections in children with cancer. Pediatr Rev. 2016;37(6):247–58.

7. Reinecke J, Lowas S, Snowden J, Neemann K. Blood Stream Infections and Antibiotic Utilization in Pediatric Leukemia Patients With Febrile Neutropenia. 2018;00(00):1–5.

8. Kar YD, Özdemir ZC, Bör Ö. Evaluation of febrile neutropenic attacks of pediatric hematology-oncology patients. Turk Pediatr Ars. 2017;52(4):213–20.

9. Anoop P, Patil CN. Management of Febrile Neutropenia in Children: Current Approach and Challenges. Pediatr Infect Dis. 2021;2(4):135–9.

10. Aziza Shad, Julia Challinor MLC. Paediatric oncology in Ethiopia: An INCTR-USA and Georgetown University Hospital twinning initiative with Tikur Anbessa Specialized Hospital.

Cancer Control [Internet]. 2013;108–12. Available from: http://cancercontrol.info/wp-content/uploads/2014/08/cc2013_108-112-Ethiopia-PEDIATRIC-ONCOLOGY-NEW_2012.pdf

11. Memirie ST, Habtemariam MK, Asefa M, Deressa BT, Abayneh G, Tsegaye B, et al. Estimates of cancer incidence in Ethiopia in 2015 using population-based registry data. J Glob Oncol. 2018;2018(4).

12. Workalemahu G, Abdela OA, Yenit MK. Chemotherapy-related adverse drug reaction and associated factors among hospitalized paediatric cancer patients at hospitals in North-West Ethiopia. Drug Healthc Patient Saf. 2020;12:195–205.

13. Davis K, Wilson S. Febrile neutropenia in paediatric oncology. Paediatr Child Heal (United Kingdom) [Internet]. 2020;30(3):93–7. Available from: https://doi.org/10.1016/j.paed.2019.12.002

14. Monedero P, Martin S, Aldecoa C. Prevention and treatment of infections. Anesth Thorac Surg Chang Paradig. 2020;221–43.

15. Melgar M, Reljic T, Barahona G, Camacho K, Chang A, Contreras J, et al. Guidance statement for the management of febrile neutropenia in pediatric patients receiving cancer-directed therapy in Central America and the Caribbean. J Glob Oncol. 2020;6:508–17.

16. Bhardwaj P V., Emmich M, Knee A, Ali F, Walia R, Roychowdhury P, et al. Use of MASCC score in the inpatient management of febrile neutropenia: a single-center retrospective study. Support Care Cancer. 2021;

17. Care S. Prediction of Bacteremia in Children with Febrile. 2013;131–40.

18. Lekshminarayanan A, Bhatt P, Linga VG, Chaudhari R, Billimoria ZC, Bhaskaran S, et al. National Trends in Hospitalization for Fever and Neutropenia in Children with Cancer, 2007-2014. J Pediatr [Internet]. 2018; Available from: https://doi.org/10.1016/j.jpeds.2018.06.056

19. Mohammed HB, Yismaw MB, Fentie AM, Tadesse TA. Febrile neutropenia management in pediatric cancer patients at Ethiopian Tertiary Care Teaching Hospital. BMC Res Notes

[Internet]. 2019;12(1):1–6. Available from: https://doi.org/10.1186/s13104-019-4569-5

20. Assefa S, Alemayehu T T. Taye Factors associated with Treatment outcome of Pediatric Cancer Patient Admitted With Febrile Neutropenia in Tikur Anbessa Specialized Teaching Hospital ,Addis Ababa ,Ethiopia. 2017;55(1):43–7.

21. Hailu D, Adamu H, Fufa D, Karimi D, Alexander T, Habashy C, et al. Training Pediatric Hematologists / Oncologists for Capacity Building in Ethiopia. Blood. 2019;134(Supplement_1):3423–3423.

22. Braga CC, Taplitz RA, Flowers CR. Clinical implications of febrile neutropenia guidelines in the cancer patient population. J Oncol Pract. 2019;15(1):25–6.

23. Peter K, Ortiz C, Valete S, Ricardo A, Esther S. Evaluation of risk stratification strategies in pediatric patients with febrile neutropenia ಔ , ಔಔ. J Pediatr (Rio J) [Internet]. 2020;(xx):1–7. Available from: https://doi.org/10.1016/j.jped.2020.05.002

24. Astria Y, Satari HI, Gunardi H, Sjakti HA. Microbiological profiles and prognostic factors of infection mortality in febrile neutropenic children with malignancy. Paediatr Indones. 2021;61(5):283–90.

25. Green L, Goussard P, Zyl A Van, Kidd M, Kruger M. Predictive Indicators to Identify High-Risk Paediatric Febrile Neutropenia in Paediatric Oncology Patients in a Middle-Income Country. 2018;(November 2017):395–402.

26. Willmer D, Zöllner SK, Schaumburg F, Jürgens H, Lehrnbecher T, Groll AH. Infectious morbidity in pediatric patients receiving neoadjuvant chemotherapy for sarcoma. Cancers (Basel). 2021;13(9):1–13.

27. Scheler M, Lehrnbecher T, Groll AH, Volland R, Laws HJ, Ammann RA, et al. Management of children with fever and neutropenia: results of a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. Infection [Internet]. 2020;48(4):607–18. Available from: https://doi.org/10.1007/s15010-020-01462-z

28. Jungrungrueng T, Anugulruengkitt S, Lauhasurayotin S, Chiengthong K, Poparn H,

Sosothikul D, et al. The Pattern of Microorganisms and Drug Susceptibility in Pediatric Oncologic Patients with Febrile Neutropenia. J Pathog. 2021;2021:1–9.

29. Israels T. Fever and neutropenia outcomes and areas for intervention : A report from SUCCOUR - Supportive Care for Children with Cancer in Africa.

30. Badr M, Hassan T, Sakr H, Karam N, Rahman DA, Shahbah D, et al. Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences. Mol Clin Oncol. 2016;5(3):300–6.

31. Pérez-Heras Í, Raynero-Mellado RC, Díaz-Merchán R, Domínguez-Pinilla N. Post chemoterapy febrile neutropenia. Length of stay and experience in our population. An Pediatr. 2020;92(3):141–6.

32. Alali M, David MZ, Danziger-Isakov LA, Elmuti L, Bhagat PH, Bartlett AH. Pediatric febrile neutropenia: Change in etiology of bacteremia, empiric choice of therapy and clinical outcomes. J Pediatr Hematol Oncol. 2020;42(6):E445–51.

33. Gupta S, Bonilla M, Gamero M, Fuentes SL, Caniza M, Sung L. Microbiology and mortality of pediatric febrile neutropenia in El Salvador. J Pediatr Hematol Oncol. 2011;33(4):276–80.

34. Das A, Trehan A, Bansal D. Risk Factors for Microbiologically-documented Infections, Mortality and Prolonged Hospital Stay in Children with Febrile Neutropenia. Indian Pediatr. 2018;55(10):859–64.

35. Chaudhuri J, Biswas T, Datta J, Sabui TK, Chatterjee S, Ray S, et al. Evaluation of malnutrition as a predictor of adverse outcomes in febrile neutropenia associated with paediatric haematological malignancies. J Paediatr Child Health. 2016;52(7):704–9.

36. Story O. Jimma University Medical Center (JUMC). Luca Incrocci Found [Internet]. 2018; Available from: https://www.lucaincroccifoundation.org/JUMC

37. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer:

2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4).

38. Patel K, West HJ. Febrile Neutropenia. JAMA Oncol. 2017;3(12):1751.

39. Recommendations BL. Fever in Neonatos E Infants. 2018;28–9.

40. Sulviani R, Idjradinata P, Raspati H. The risk factors for febrile neutropenia during chemotherapy in children with malignancy. Paediatr Indones. 2007;47(2):83.

41. M.M. A, S. Q, R. M, Z. F. Prolonged febrile neutropenia: Risk factors and outcome in pediatric oncology patients. Pediatr Blood Cancer [Internet]. 2014;61(April):S386--S387. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71656630%0Ahttp://onlinelibrary.wiley.com/doi/10.1002/pbc.25314/pdf%0Ahttp://dx.doi.org/10.1002/pbc.25314

42. Delebarre M, Tiphaine A, Martinot A, Dubos F. Risk-stratification management of febrile neutropenia in pediatric hematology-oncology patients : Results of a French nationwide survey. 2016;(May):1–6.

43. Predictive Factors of Severe Adverse Events in Pediatric Oncologic Patients with Febrile Neutropenia.

44. Ghafoor T, Bashir F, Ahmed S, Khalil S, Farah T. Predictors of treatment outcome of Wilms Tumour in low-income country; single centre experience from Pakistan. Vol. 16, Journal of Pediatric Urology. 2020. p. 375.e1-375.e7.

45. Aagaard T, Reekie J, Jørgensen M, Roen A, Daugaard G, Specht L, et al. Mortality and admission to intensive care units after febrile neutropenia in patients with cancer. 2020;(June 2019):3033–42.

46. Lee SJ, Kim JH, Han SB, Paik JH, Durey A. Prognostic factors predicting poor outcome in cancer patients with febrile neutropenia in the emergency department: Usefulness of qSOFA. J Oncol. 2018;2018:6–13.

ANNEXES

Annex-: Information sheet

Principal investigator (PI): Feven Teshome (B. Pharm)

Advisors: Mr. Temesgen Mulugeta (B.Pharm, MSc),

Dr. Diriba Fufa (MD, Pediatric Hematology/Oncologist)

Sponsoring organization: Jimma University

Purpose of the study: To assess clinical characteristics, associated factors and treatment outcomes of pediatric cancers among pediatric cancer patients who received chemotherapy at pediatric hematology/oncology ward, of Jimma Medical Center, Ethiopia

PART I: 1. Socio demographic characteristics	
1. Sex:	1. Male 2.Female
2. Age (in years):	_____
3. Height(cm):	_____
4. Residence:	1. Rural 2. Urban
PART I: 2. Anthropometric measurements at admission	1) WFH_____ 2) WFA: ___ 3) Wasted: _____ 4) Stunted: _____

PART II: Disease related variables

1. Date cancer was confirmed: _____
2. Primary cancer diagnosis: _____

3. Did tumor metastasize? 1.Yes 2 .No
4. History of catheterization 1.Yes 2. No
5. Does the patient have other comorbid diseases? 1.Yes 2.No
6. If yes Q5 to _____
7. History of documented infections: _____
8. Was surgical interventions done for solid tumors? 1. Yes 2. No

Part 3: Laboratory and other Investigations

Investigations		**At baseline**
CBC	WBC (3.6-10.2) 10^3/UL	
	neutrophil# (1.7-7.6)10^3/UL	
	RBC	
	Hgb(12.5-16.3)g/dl	
	Plt #(152-348)10^3/UL	
Renal function tests	Scr (0.7-1.2)mg/dl	
	BUN (16.6-48.5) mg/dl)	
Liver function tests	AST (0-40 U/)	
	ALT (0-41 U/L)	
	ALP(40-129 U/L)	

Part 4: Drug related variables

1. Date chemo was initiated _____
2. Cycle or phase receive up to end of study period
3. Number chemotherapy sessions received: _____

<u>If the patient had FN diagnosis due to chemotherapy, part 5, 6 and 7 should be filled, if not go to Part 8</u>

Part 5: Febrile neutropenia related data

1. What was the ANC value? _____
2. What was the temperature value (in degree Celsius): ____
3. Number of FN episode _____
4. Indicate the phases/cycle of the treatment when the 1st episode of FN dx:
5. Initial antibiotic prescribed _____
6. Was the initial antibiotic regimen changed/modified during the course of FN treatment? 1.Yes 2.no
7. If yes to Q6, write the modified antibiotic regimens and time to modification from the initiation:

_____

_____

___

8.If antifungal was prescribed, write the regimen _____

Part 6: FN related Outcomes/Etiology of fever

8. Clinically/chest x-ray documented infections: 1. Yes 2.No
9. If the answer is yes,

1. Oral mucosal infections
2. Otitis media
3. Pneumonia
4. Skin and soft-tissue infection
5. Infectious diarrhea/enteritis
6. Urinary tract infections
7. Bone/joint infection
8. Meningitis
9. Others: _____

10. Was there any microbiologically confirmed infection? **1.** Yes 2.No
11. If yes to Q10, how it was identified?_____
12. *If culture was done, fill the below table*.

Tests	Microorganisms grown	Sensitivity result
Blood culture		

13. If died, what was the suspected cause of death (from what was status of the patient?

1. Alive

2. Disappeared/LAMA and date: _____

3. Transferred/ref

4. Died and date: _____the death summary note): _____