

FACTORS AFFECTING OUTCOME OF PEDIATRIC ONCOLOGY PATIENTS  
WITH FEBRILE NUTROPENIA AT JIMMA UNIVERSITY SPECIALIZED  
TEACHING HOSPITAL, JIMMA, ETHIOPIA



A THESIS PROPOSAL TO BE SUBMITTED TO DEPARTMENT OF PEDIATRICS AND  
CHILD HEALTH, SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE FOR  
THE PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE CERTIFICATE IN  
PEDIATRICS AND CHILD HEALTH

BY: TesfahunAdmasu, (MD and Pediatric Resident)

JANUARY, 2022

ADDIS ABABA, ETHIOPIA

FACTORS AFFECTING OUTCOME OF PEDIATRIC ONCOLOGY PATIENTS  
WITH FEBRILE NUTROPENIA AT JIMMA UNIVERSITY SPECIALIZED  
TEACHING,HOSPITAL,JIMMA,ETHIOPIA



A THESIS PROPOSAL TO BE SUBMITTED TO DEPARTMENT OF PEDIATRICS AND  
CHILD HEALTH, SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE FOR  
THE PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE CERTIFICATE IN  
PEDIATRICS AND CHILD HEALTH

BY: Tesfahun Admasu, (MD and Pediatric Resident)

ADVISOR: Dr.Mamude Dinkiye (MD, Assistant professor of pediatrics and child health,  
Pediatric hematologist and oncologist, MPH)

JANUARY, 2022

ADDISABABA,ETHIOPIA

St. Paul's Hospital Millennium Medical College Specialty Thesis Research Paper Submission Form

|                                            |                                                                                                                                                     |
|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of principal investigator             | Dr.Tesfahun Admasu(MD,pediatric resident)                                                                                                           |
| The full title of thesis research proposal | Factors affecting outcome of pediatric oncology patients with febrile neutropenia at JUSTH, Jimma,Ethiopia                                          |
| Duration of research                       | January 1,2020-december 31,2021                                                                                                                     |
| Study area                                 | Jimma university specialized teaching hospital                                                                                                      |
| Total cost of the project                  | 25,875 Birr                                                                                                                                         |
| Source(s)of funding                        | St. Paul Hospital Millennium Medical College                                                                                                        |
| Address of investigator                    | E-mail: admasutesfahun87@gmail.com<br>Phone No: +251984184189                                                                                       |
| Name of advisor                            | Dr.Mamude Dinkiye (MD, Assistant professor of pediatrics and child health, Pediatric hematologist and oncologist, MPH)<br>E-mail:mdinkiye@gmail.com |

## **Abstract**

**Background:** Cancer treatment is associated with variable degrees of myelosuppression. Infection is often a life threatening complication of chemotherapy-induced neutropenia, and it is also considered an oncologic emergency. Febrile neutropenia is a common, costly and potentially fatal complication in oncology.

**Objective:** To assess factors affecting treatment outcome of cancer patients with chemotherapy induced febrile neutropenia.

**Method:** We conducted a review of records of pediatric cancer patients hospitalized and treated for FN from January 1, 2020 to December 31, 2021 who met the selection criteria. Analysis was made on SPSS 26. Chi square statistical analysis was performed to identify the association between independent variables and disease outcomes with P-value of less than 0.05, were used for testing significance.

**Result:** A total of 65 patients (31 males and 34 females) fulfilled the selection criteria. thirteen of them died while in hospital. The mean (SD) age of patients who died was 6.07 ( $\pm 3.44$ ) years and the mean (SD) duration of neutropenia before death was 12.69 days. Eight of 13 patients had temperature  $\geq 39$  degree Celsius. Eleven of 13 patients had prolonged neutropenia. Ten children had hematologic malignancy and three had a solid tumor. Ten of the 13 patients had an absolute neutrophil count of less than 100/mm<sup>3</sup> and eight of 13 patients had febrile neutropenic episodes greater than three. Patients with temperature  $\geq 39^{\circ}\text{C}$  ( $P=0.000$ ), profound neutropenia ( $P=0.000$ ), prolonged neutropenia ( $P=0.018$ ) and those who had febrile neutropenic episodes greater than three ( $P=0.000$ ) were more likely to die.

**Conclusion:** The result of this study showed that temperature  $\geq 39$  degree Celsius, prolonged neutropenia, profound neutropenia and febrile neutropenic episodes greater than 3 were factors affecting outcome of patients with febrile neutropenia. Careful evaluation of these factors and assessing severity of patients' clinical condition at time of admission can be useful for early decision-making in inpatient management and allocation of resources.

**Keywords:** fever, neutropenia, cancer, Absolute neutrophil count, febrile neutropenia, oncologic emergency

## **Acknowledgment**

First and foremost, I would like to thank God for giving me the courage, patience, and determination for the completion of this thesis. Next, I would like to pass my gratitude towards my advisor, for the guidance and support he have given me throughout the completion of this paper. Special thanks also go to the St. Paul Hospital Millennium Medical College staff for inspiring me to pursue this subject. Finally, I would like to thank St. Paul Hospital Millennium Medical College, the Department of pediatrics and child health and Jimma university oncology unit for facilitating conditions.

## **ACRONYMS**

|             |                                                  |
|-------------|--------------------------------------------------|
| FN.....     | febrile neutropenia                              |
| ANC.....    | absolute neutrophil count                        |
| AMC.....    | absolute monocyte count                          |
| ALL.....    | acute lymphoblastic leukaemia                    |
| AML.....    | acute myeloid leukemia                           |
| HL.....     | Hodgkin's lymphoma                               |
| NHL.....    | Non-Hodgkin's lymphoma                           |
| CI.....     | confidence Interval                              |
| ICU.....    | Intensive care unit                              |
| SBI.....    | significant bacterial infection                  |
| LDH.....    | lactate dehydrogenase                            |
| BUN.....    | blood urea nitrogen                              |
| ETB.....    | Ethiopian Birr                                   |
| G.C.....    | Gregorian Calendar                               |
| PI.....     | Principal Investigator                           |
| SPHMMC..... | Saint Paul's Hospital Millennium Medical College |
| SPSS.....   | Statistical Package for Social Sciences          |
| TASTH.....  | Tikur Anbessa Specialized Teaching hospital      |
| JUSTH.....  | Jimma university Specialized Teaching hospital   |

## Table of Contents

|                                                                                         |                                     |
|-----------------------------------------------------------------------------------------|-------------------------------------|
| Abstract.....                                                                           | iv                                  |
| Table of Contents.....                                                                  | vii                                 |
| LIST OF TABLES.....                                                                     | ix                                  |
| 1.Introduction .....                                                                    | 1                                   |
| 1.1 Background.....                                                                     | 1                                   |
| 1.2 Statement of the problem.....                                                       | 3                                   |
| 1.3 Significance of the study.....                                                      | 3                                   |
| 2.Literature review.....                                                                | 4                                   |
| 3. Objectives .....                                                                     | 8                                   |
| 3.1 General Objective .....                                                             | 8                                   |
| 3.2 Specific objectives .....                                                           | 8                                   |
| 4.Methodology.....                                                                      | 9                                   |
| 4.1 Study Area .....                                                                    | 9                                   |
| 4.2 Study Period.....                                                                   | 9                                   |
| 4.3 Study Design.....                                                                   | 9                                   |
| 4.4 Source Population .....                                                             | 9                                   |
| 4.5 Study Population.....                                                               | 9                                   |
| 4.6 Study Unit .....                                                                    | 9                                   |
| 4.7 Sample Size Determination and Sampling Technique.....                               | 9                                   |
| 4.8 Inclusion Criteria .....                                                            | 10                                  |
| 4.9 Exclusion criteria .....                                                            | 10                                  |
| Incomplete or missing charts will be excluded .....                                     | 10                                  |
| Patients who died before reaching hematooncology unit.....                              | <b>Error! Bookmark not defined.</b> |
| 4.10 Dependant and Independent variables .....                                          | 10                                  |
| 4.10.1 Dependant Variables.....                                                         | 10                                  |
| 4.10.2 Independent variables .....                                                      | 10                                  |
| 4.11 Data Collection .....                                                              | 11                                  |
| 4.12 Data processing & analysis.....                                                    | 11                                  |
| 4.13 Data Quality Assurance .....                                                       | 11                                  |
| 4.14 Result Dissemination Plan .....                                                    | 12                                  |
| 4.15 Ethical Consideration.....                                                         | 12                                  |
| 4.16 Operational definition.....                                                        | 13                                  |
| 5. Results .....                                                                        | 14                                  |
| 5.1 Socio-demography and admission characteristic .....                                 | 14                                  |
| 5.2 Baseline laboratory and blood culture finding .....                                 | 16                                  |
| 5.3 The type of malignancy with further stratification and associated co-morbidity..... | 16                                  |
| 5.4 Outcome of the patients with FN .....                                               | 19                                  |

|                                                                                                                                                    |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 5.5 Comparison of Socio- demography,vital-signs ,duration, number of febrile neutropenic episodes, Co morbid illness and laboratory variables..... | 20 |
| 5.6 Factors that predict the mortality of patients with FN .....                                                                                   | 22 |
| 6. Discussion.....                                                                                                                                 | 23 |
| 7. Strengths and Limitations .....                                                                                                                 | 25 |
| 8. Conclusion: .....                                                                                                                               | 26 |
| 9.Recommendation .....                                                                                                                             | 27 |
| 10. References .....                                                                                                                               | 28 |
| 11. Annex I.....                                                                                                                                   | 30 |
| 11.1 Questionnaire .....                                                                                                                           | 30 |
| 11.2 Assurance of Principal Investigator .....                                                                                                     | 32 |

## LIST OF TABLES

|                                                                                                                                     |    |
|-------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 1: Socio-demographic and admission characteristic of the patients with NF admitted at JUSTH, JIMMA, Ethiopia,<br>2020/21..... | 14 |
| Table 2: base line laboratory values and blood culture of the patients with NF admitted at JUSTH, JIMMA, Ethiopia,<br>2020/21.....  | 15 |
| Table 3: types of malignancy and further stratification of the patients with NF admitted at JUSTH, JIMMA, Ethiopia,<br>2020/21..... | 16 |
| Table 4: Identified comorbidities of the patients with NF admitted at JUSTH, JIMMA, Ethiopia, 2021/22<br>.....                      | 18 |
| Table 5: comparison of variables among survivors and non survivors of patients with FN at JUSTH, JIMMA, Ethiopia, 2020/21.....      | 21 |
| Table 6: bivariate and multivariate analysis for risk factors associated with mortality of patients with FN(n=65).....              | 23 |

## List of Figures

|                                                                                                             |    |
|-------------------------------------------------------------------------------------------------------------|----|
| Figure 1: Identified comorbidities among patients with FN admitted at JUSTH, JIMMA, Ethiopia, 2020/21 ..... | 17 |
| Figure 2: outcome among patients with FN admitted at JUSTH, JIMMA, Ethiopia, 2020/21 .....                  | 19 |

## **1.Introduction**

### **1.1 Background**

Fever with neutropenia is one of the most common sequelae among pediatric oncology patients and fever is often the first and only sign of infection (1).

Fever in a neutropenic patient is defined as a single oral temperature of greater than 38.3°C (101°F) or a temperature of 38°C (100.4°F) sustained over 1 hour. Axillary temperatures are discouraged and rectal temperatures are contraindicated in children with chemotherapy induced febrile neutropenia (FN). Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 cells/mm<sup>3</sup> or an ANC of less than 1000 cells/mm<sup>3</sup>, which is expected to decrease to less than 500 cells/mm<sup>3</sup> in the next 48 hours. Profound neutropenia is defined as an ANC of less than 100 cells/mm<sup>3</sup> and prolonged neutropenia is one lasting greater than 7 days (2,3). Fever during neutropenia has always been considered a medical emergency and should always be considered due to infection, unless otherwise proven (4). Clinically or microbiologically proven infections account for 10-40% of children with fever and therapy induced neutropenia. Bacteremia dominates among proven infections with majority of cases in

Febrile neutropenic patients being due to gram-positive organisms. Potential reasons for the unobserved dominance of gram-positive bacteria include the use of indwelling catheters, local environmental conditions, and the administration of prophylactic antibiotic agents. The mainstay of treating FN is an empirical parenteral broad-spectrum antibiotic.(5-7).Fungi, typically *Candida*, occasionally may be a primary pathogen. Empirical antifungal drugs are recommended for children with persistent neutropenia, Fever after 4–7 days of empirical antibiotics (5,8).

The most significant viral etiologies are respiratory viruses, herpes simplex and varicella-zoster virus.(9). Various studies have attempted to identify factors contributing to morbidity and mortality in febrile neutropenia among pediatric oncologic patients. Duration of neutropenia, medical co-morbidities, cancer type and stage, proven infection at time of presentation, the presence or absence of bone marrow recovery, identified pathogens, the severity of vital sign derangements, lab abnormalities at presentation like elevated blood urinary nitrogen (BUN) and serum lactic dehydrogenase (LDH) and age of child have all been related to outcome of febrile neutropenia episodes (10,11). Even though the data is lacking, FN is one of the common causes

of emergency admission of pediatric cancer patients in our setup. FN frequently leads to chemotherapy dose reductions and treatment delays that may compromise long-term clinical outcomes in responsive and potentially curable malignancies. Therefore, the present study primarily intended to assess factors affecting treatment outcome of pediatric cancer patients with FN in JUSTH. The knowledge will help for risk stratification and better management in the future.

## **1.2 Statement of the problem**

Febrile neutropenia (FN) continues to represent a major cause of morbidity, mortality, and cost in patients receiving cancer chemotherapy. Febrile neutropenia continues to have considerable clinical, economic and quality of life impact on affected patients. The risk of mortality associated with FN continues to be relatively high in patients with hematologic malignancies, patients presenting with co morbid illnesses, and patients with bacteremia, pneumonia, or other infection-related complications.

Further study of factors affecting treatment outcome of pediatric patients with febrile neutropenia should help identify patients at greatest risk for mortality and early proper interventions. Factors that are associated with outcome of febrile neutropenia are not clearly known in our set up and that needs an appropriate solution so that the overall quality of care can be improved.

## **1.3 Significance of the study**

The factors that affect treatment outcome of FN patients had negative impact on morbidity, mortality and cost on the patients receiving cancer chemotherapy. Despite this, there is a paucity of data describing factors affecting treatment outcome of FN in patients receiving cancer chemotherapy in Africa, particularly in Ethiopia.

Investigating and analyzing the factors affecting treatment outcome of FN in patients receiving cancer chemotherapy will be helpful for hospital management, especially in determining priorities, improving services and allocating resources appropriately according to the differences in factors they have.

Therefore, this study aimed at assessing factors affecting treatment outcome of FN among patients admitted to hematooncology unit of JUSTH

Therefore, such data would help to design evidence-based problem solving mechanisms and would also help as the base line for future similar large scale researches.

## **2.Literature review**

Fever with neutropenia is one of the most common sequelae among pediatric oncology patients and fever is often the first and only sign of infection (1). Clinically or microbiologically proven infections account for 10-40% of children with fever and therapy induced neutropenia. Bacteremia dominates among proven infections with majority of cases in febrile neutropenic patients being due to gram positive organisms. Potential reasons for the unobserved dominance of gram-positive bacteria include the use of indwelling catheters, local environmental conditions, and the administration of prophylactic antibiotic agents. The mainstay of treating FN is an empirical parenteral broad-spectrum antibiotic.(5-7). Fungi, typically *Candida*, occasionally may be a primary pathogen. Empirical antifungal drugs are recommended for children with persistent neutropenic fever after 4–7 days of empirical antibiotics (5,8). The most significant viral etiologies are respiratory viruses, herpes simplex and varicella-zoster virus. (9) Various studies have attempted to identify factors contributing to morbidity and mortality in febrile neutropenia among pediatric oncologic patients.

Analysis of longitudinal data from university of health system data base from 1995 to 2002 at Antonio,Texas ,USA shows among a total of 12446 patients were identified for study ,the mortality rate was 3% and On bivariate analysis, race, age, cancer type, and associated complications (bacteremia/sepsis, hypotension, pneumonia, and fungal infections) were significantly associated with longer length of stay and death. Race, age group, year of discharge, associated complications, and cancer type were significantly associated with risk of longer length of stay and mortality. These factors may potentially help in identifying high-risk patients who might benefit from targeted antibiotic therapy or prophylactic hematopoietic growth factor support.(12)

A multicenter, retrospective cohort of children with malignant disease and fever with neutropenia was established in three pediatric oncology centers over a 5-year period at Missouri,USA shows among total of 1171 episodes of febrile neutropenia ,11 episodes (0.9%) resulted in ICU admission and 3 of these patients died. All 11 patients had an AMC < 30 cells per mm(3). The lowest frequency of bacteremia (6.1%) occurred in the children with an

admission AMC of  $\geq 155$  cells per mm (3). None of the patients identified as low risk by AMC required an intensive care unit admission or died. Patients with fever and neutropenia and an AMC value of  $\geq 155$  cells per mm(3) have the lowest risk for bacteremia and may be potential candidates for outpatient management.(17)

The records of 161 pediatric patients with neoplastic disease hospitalized for 509 episodes of fever and neutropenia at New York city USA between January 1990 and June 1992 were retrospectively reviewed and the only presenting clinical features that correlated with an increased likelihood of having positive blood cultures were chills, hypotension, the requirement for fluid resuscitation ( $P < 0.001$ ), or a diagnosis of leukemia or lymphoma ( $P < 0.041$ ). Leukemia patients with relapse admitted for fever and neutropenia were no more likely to have positive blood cultures than those patients in remission. There were ten episodes of fever and neutropenia in which patients were transferred to the intensive care unit (ICU), and two sepsis related deaths. Nine episodes involving ICU management and both deaths were in patients who had persistent fever and an absolute neutrophil count (ANC) of less than 100 after 48 hours of hospitalization ( $n = 177$ ). Patients with an ANC of less than 100 after 48 hours were twice as likely to have antibiotic changes, 15 times more likely to receive amphotericin B, and were hospitalized twice as long as patients with an ANC of 100 or higher after 48 hours. Children hospitalized for fever and neutropenia who have persistent fever and an ANC of less than 100 after 48 hours are at high risk for morbidity and are more likely to require antibiotic changes and antifungal therapy.(20)

prospectively derive and validate a clinical prediction rule was done over 1 year period and validated over the following 08 months among 227 episodes of pediatric oncology outpatients presented with fever and neutropenia in Ottawa ,Canada shows found four significant factors were identified with Multivariate analysis : bone marrow disease, general appearance unwell on initial examination, monocyte count less than  $0.1 \times 10^9/L$ , and peak oral or oral equivalent temperature greater than 39 degrees C. Only the monocyte count contributed to determining a low-risk group, excluding SBI with 84% sensitivity (95% confidence interval [CI], 61% to 100%), 42% specificity (95% CI, 38% to 46%), and a negative predictive value of 92% (95% CI, 76% to 100%). If the monocyte count was  $\geq 0.1 \times 10^9/L$  at the time of presentation (low risk), the incidences of SBI(SBI; defined as any blood or urine culture positive for bacteria, interstitial or lobar consolidation on CXR, or unexpected death from infection) and bacteremia were 8%

and 5%, respectively, versus 25% and 17% in the high-risk group. When validated in a new population of 136 episodes of fever and neutropenia, the incidences of SBI and bacteremia in the low-risk group were 12% and 5%, respectively, and 25% and 19% in the high-risk group. Pediatric oncology outpatients with fever and neutropenia who present with an initial monocyte count of  $\geq 0.1 \times 10^9/L$  and do not have comorbidity or an abnormal CXR at the time of presentation are at lower risk for SBI and can be considered for less aggressive initial therapy.(18)

75 cases of IRM(infection-related mortality ) in the United Kingdom Childhood Acute Lymphoblastic Leukemia Randomised Trial 2003 (UKALL 2003) shows 5-year cumulative incidence of IRM was 2.4% (95% confidence interval [CI], 1.9%-3.0%), accounting for 75 (30%) of 249 trial deaths and 75 (64%) of 117 TRM(treatment-related mortality) deaths. Risk for IRM as a proportion of TRM was greater in induction than other phases (77% vs 56%;  $P = .02$ ). Sixty-eight percent of cases were associated with bacterial infection (64% Gram-negative) and 20% with fungal infection Down syndrome was the most significant risk factor for IRM (odds ratio [OR], 12.08; 95% CI, 6.54-22.32;  $P < .0001$ ). Importantly, patients with Down syndrome were at significantly higher risk for IRM during maintenance ( $P = .048$ ). Results confirm Down syndrome as a major risk factor for IRM. Enhanced supportive care and prophylactic antibiotics should be considered in high-risk patient groups and during periods of increased risk.(19)

prospective, multicenter study which was done in Chile among children admitted with high risk FN episodes shows total of 393(70%) Of 561 FN episodes evaluations from June 2004-dec 2005 resulted in an infectious-related death. most dying children were admitted with relapse of acute lymphocytic leukemia (36%), hypotension (71%), and a diagnosis of sepsis (79%), compared with surviving children (16%, 20%, and 5% respectively,  $P < 0.001$ ). Children who died were admitted with lower absolute neutrophil count ( $P < 0.001$ ) and absolute monocytes count levels ( $P = 0.008$ ), higher blood urinary nitrogen ( $P = 0.03$ ) and C-reactive protein values ( $P < 0.001$ ), and had more positive cultures (79% versus 32%,  $P = 0.008$ ). Identified early clinical and laboratory findings significantly associated with death occurring at a later stage. Routine evaluation of these variables may prove to be useful in the early identification of children with a high-risk FN episode at risk for death.(11)

Cross-sectional study which was done at Dr. Sheikh pediatric hospital, Iran from December 2008 to November 2009, shows among 68 patients who were analyzed, 9 (7.5%) died from an

infection and 35 patients (29.1%) had a LTI (life threatening infection). Five variables were identified as RFs (risk factors) for LTI, that is, body temperature  $\geq 39^{\circ}\text{C}$  ( $P=0.000$ ), presence of mucositis ( $P=0.000$ ), abnormal chest x-ray ( $P=0.001$ ), platelet count  $<20,000/\text{mm}$  ( $P=0.000$ ), and absolute neutrophil count  $<100/\text{mm}$  ( $P=0.001$ ). Risk of LTI was increasing according to number of RFs presented at the beginning of admission (from 2.8% in patients without RF to 100% in patients with 5 RF). Data mining analysis showed relationship between RFs with platelet count as the most important variable in the high-risk group for LTI. Evaluation of important RFs and judging the severity of patients' condition by studying the importance and relationship between RF at the time of admission can be a useful method for screening LTI in children with FN.(13)

a retrospective cohort study which was done from May 2001 to April 2008 at Wendy Fitzwilliam Pediatric Hospital (WFPH) in Trinidad and Tobago, west India among 36 patients who received chemotherapy for haematological or solid tumor malignancies, 43.7% accounted for Acute Lymphoblastic Leukaemia (ALL) The mean WBC for the study population was  $0.88 \times 10(9)/\text{L}$  (+/- SD 0.61), with the mean absolute neutrophil count (ANC) at  $0.16 \times 10(9)/\text{L}$  (+/- SD 0.23). Antifungal therapy was used in 6 cases and the incidence of blood culture positive sepsis was 8.5%.The further analysis of the relationships found in this study between the total white blood cell count at presentation and the duration of antimicrobial therapy, the duration of the febrile neutropenic episodes and outcome is needed.(16)

Retrospective review of records of pediatric patients hospitalized and treated for chemotherapy induced febrile neutropenia at Tikur Anbessa Specialized Teaching Hospital (TASH), Addis Ababa, Ethiopia shows among total of 60 patients Twelve (20%) of the patients died while in hospital , Ten of the mortalities had a hematologic malignancy The remaining 2 had a solid tumor. Six of the 10 children (10%) had sepsis. Patients with profound neutropenia, platelet count of less than 50,000 and sepsis were more likely to die ( $P=0.048$ ,  $\text{OR}=7$ ). The result of this study showed that absolute neutrophil count of less than  $100/\text{mm}^3$ , platelet count of

less than  $50,000/\text{mm}^3$  and a diagnosis of sepsis were factors affecting outcome patients with febrile neutropenia. Careful evaluation of these factors and assessing severity of patients' clinical condition at time of admission can be useful for triaging children with febrile neutropenia.(21)

### **3. Objectives**

#### **3.1 General Objective**

To assess factors affecting treatment outcome of pediatric cancer patients with febrile neutropenia at Jimma university specialized teaching hospital, Jimma, Ethiopia.

#### **3.2 Specific objectives**

1. To determine outcome of pediatric cancer patient with febrile neutropenia
2. To identify factors that affect outcome of pediatric cancer patients with febrile neutropenia.

#### **4. Methodology**

##### **4.1 Study Area**

The study was conducted at JUSTH, pediatric oncology department. JUSTH is a referral and teaching hospital in Jimma, south west Ethiopia. This hospital offers diagnosis and treatment for approximately 370000-400000 patients per year. This hospital serve community with specialty and sub specialty service. The collage has more than 1500 clinical and academic staffs. The hospital can accommodate inpatient service by more than 600 beds. The pediatric hematology oncology unit is one of a few centers in the country and has isolated ward with 26 beds in it

##### **4.2 Study Period**

The data was collected retrospectively from Jan 1, 2020-Dec 31, 2021

##### **4.3 Study Design**

A Hospital based cross-sectional study was conducted by using a validated standard questionnaire.

##### **4.4 Source Population**

All pediatric Cancer patients who were admitted to oncology unit in the study period.

##### **4.5 Study Population**

All pediatric Cancer patients who were admitted to oncology unit who develop febrile neutropenia in the study period.

##### **4.6 Study Unit**

JUSTH pediatric oncology ward.

##### **4.7 Sample Size Determination and Sampling Technique**

All pediatric Cancer patients who were admitted to oncology unit during study period, who had developed febrile neutropenia and met the inclusion criteria were included in the study.

#### **4.8 Inclusion Criteria**

Pediatric patients who had ANC  $\leq 500/\text{mm}^3$  and axillary fever record of  $\geq 37.5^\circ\text{C}$  over 1 hour or single measurement of  $\geq 37.8^\circ\text{C}$ .

#### **4.9 Exclusion criteria**

Incomplete or missing charts were excluded

#### **4.10 Dependant and Independent variables**

##### **4.10.1 Dependant Variables**

Treatment outcome

##### **4.10.2 Independent variables**

Age

Gender

Type of malignancy

Degree of neutropenia

Degree of fever

Comorbid condition

Duration of neutropenia

Neutropenic fever episodes

Platelet count

Blood culture

#### **4.11 Data Collection**

Records of patients with febrile neutropenia were retrieved from record office and charts were reviewed using a structured questionnaire/check list by GP who was trained on the questionnaire.

#### **4.12 Data processing & analysis**

After data collection, each questionnaire were checked for completeness based on the code given during data collection. The data was entered in to Epi-Info version 7 and then exported and analyzed using SPSS version 26. Descriptive statistics was used to describe the independent variable. Descriptive statistical method was used to produce percentages and mean and

For categorical variables, chi square statistical analysis was carried out to examine the significance of the observed difference between the outcome variable to be studied.

P-Value < 0.05 were considered statistically significant.

#### **4.13 Data Quality Assurance**

- ✓ The principal investigator provide supportive supervision to the data collector to make sure that, data collection was performed according to the protocol.
- ✓ Each day the collected data was checked for accuracy and completeness
- ✓ The participant's names was not collected and the data was identified after the questionnaire completed.

The collected data was stored in a secure location and only the lead investigator had access to this location.

#### **4.14 Result Dissemination Plan**

After the data was analyzed, the results of the research was presented to SPHMMC's department of pediatrics and child health. The findings will be sent for publication on relevant scientific journals and disseminated online so that they can be of use for other academic researchers and clinical practitioners. The data can also serve as a base line for future studies.

#### **4.15 Ethical Consideration**

Ethical clearance was obtained from the Institutional Review Board (IRB) of St. Paul Hospital Millennium Medical College. The officials at a different level in the study area were communicated through letters from St. Paul Hospital Millennium Medical College, Department of pediatrics and child health. All data collected for this study were stored and confidentiality was maintained.

#### **4.16 Operational definition**

**1.Fever :**is single Axillary temperature of greater than 37.8°C (100°F) or a temperature of 37.5°C (99.5°F) sustained over 1 hour.

**2. Neutropenia:**is absolute neutrophil count (ANC) of less than 500 cells/mm<sup>3</sup> or an ANC of less than 1000 cells/mm<sup>3</sup>, which is expected to decrease to less than 500 cells/mm<sup>3</sup> in the next 48 hours.

**3. Profound neutropenia:**is ANC of less than 100 cells/mm<sup>3</sup>.

**4. Prolonged neutropenia:**is one lasting greater than 7 days.

**5. Comorbidity:** any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease.

## **5. Results**

### **5.1 Socio-demography and admission characteristic**

A total of 65 patients (31 male, 34 female) participated in the study. 57(87.7%) patients were 2–10 years old, 7 (10.8%) were 11–18 years old, and 1 (1.5%) were <1 year old. The mean(SD) age of the patient was 6.15 ( $\pm$  3.44) years.

Regarding the admission vital signs ,the patients had a mean heart rate of 134 ( $\pm$ 14) beats per minutes.27(41.5%) had pulse rate of 121-140 beats per minutes rang. mean (SD) body temperature recordings was 38.61°C ( $\pm$ 0.5) ,fifteen (23.1%) patients had above 39°C at diagnosis. Regarding the number of febrile neutropenic episodes ,majority of the patients had one and two episodes ,accounting 43.1% and 41.5% respectively.55.4% of the patients had duration of neutropenia greater than 7 days which accounts majority of the cases.

Table 1: Socio-demographic and admission characteristic of the patients with NF admitted at JUSTH, JIMMA, Ethiopia, 2020/21

|                              |           | Frequency | Percent |
|------------------------------|-----------|-----------|---------|
| Gender                       | female    | 34        | 52.3    |
|                              | male      | 31        | 47.7    |
|                              | Total     | 65        | 100.0   |
| Age                          | 0-1       | 1         | 1.5     |
|                              | 2-10      | 57        | 87.7    |
|                              | 11-18     | 7         | 10.8    |
|                              | Total     | 65        | 100.0   |
| Pulse rate                   | 100-120   | 17        | 26.2    |
|                              | 121-140   | 27        | 41.5    |
|                              | 141-160   | 18        | 27.7    |
|                              | 161-180   | 3         | 4.6     |
|                              | Total     | 65        | 100.0   |
| Temperature(°C)              | 37.7-38.5 | 30        | 46.2    |
|                              | 38.6-38.9 | 20        | 30.8    |
|                              | 39-39.5   | 10        | 15.4    |
|                              | 39.6-40   | 5         | 7.7     |
|                              | Total     | 65        | 100.0   |
| Febrile neutropenic episodes | 1         | 28        | 43.1    |
|                              | 2         | 27        | 41.5    |
|                              | 3         | 2         | 3.1     |
|                              | 4         | 6         | 9.2     |
|                              | 5         | 2         | 3.1     |
|                              | Total     | 65        | 100.0   |
| Duration of neutropenia      | 1-6       | 29        | 44.6    |
|                              | 7-14      | 24        | 36.9    |
|                              | 15-21     | 9         | 13.8    |
|                              | above 21  | 3         | 4.6     |
|                              | Total     | 65        | 100.0   |

## 5.2 Baseline laboratory and blood culture finding

Regarding the laboratory tests, most 46(70.8%) of the patients had WBC count of between 1000-10000.

The mean (SD) of ANC was 256.78/mm<sup>3</sup> ( $\pm 155$ ) and profound neutropenia was observed in 12 (18.5%) patients. seventeen (26.2%) patients had platelet counts <50,000/mm<sup>3</sup> and a mean (SD) platelet count was 115927/mm<sup>3</sup> ( $\pm 111,249$ ).

Seven children (10.7%) had positive blood culture results. The pathogens isolated were, 3 *Klebsiella* spp, 3 *E. coli* and 1 *Providencia* reffegeri .

Table 2: base line laboratory values and blood culture of the patients with NF admitted at JUSTH, JIMMA, Ethiopia, 2020/21

|                    |               | Frequency | Percent |
|--------------------|---------------|-----------|---------|
| WBC count          | below 1000    | 14        | 21.5    |
|                    | 1000-10000    | 46        | 70.8    |
|                    | 10001-20000   | 2         | 3.1     |
|                    | above 20000   | 3         | 4.6     |
|                    | Total         | 65        | 100.0   |
| ANC                | 0-99          | 12        | 18.5    |
|                    | 100-249       | 21        | 32.3    |
|                    | 250-500       | 32        | 49.2    |
|                    | Total         | 65        | 100.0   |
| Platelet count     | below 50000   | 17        | 26.2    |
|                    | 50001-99999   | 23        | 35.4    |
|                    | 100000-150000 | 10        | 15.4    |
|                    | above 150000  | 15        | 23.1    |
|                    | Total         | 65        | 100.0   |
| Blood culture sent | no            | 48        | 73.8    |
|                    | yes           | 17        | 26.2    |
|                    | Total         | 65        | 100.0   |

## 5.3 The type of malignancy with further stratification and associated co-morbidity

The topographic distribution of malignancy by primary site showed 53 children (81.5%) with hematologic malignancies and 12 children (18.5%) with solid tumors.

Further stratification of hematologic malignancy showed 36 cases of acute lymphoblastic leukemia (ALL), 5 cases of acute myeloid leukemia (AML), 8 cases of non-Hodgkin lymphoma (NHL), and 4 case of Hodgkin lymphoma. Solid tumor distribution showed 3 children with Wilm's tumor, 3 children with hepatoblastoma ,3

children with osteosarcoma 1 child with rhabdomyosarcoma, 1 child with neuroblastoma and 1 child with retinoblastoma. Overall, 43 (66.2%) patients had co-morbidity ,among which 11 (25.5%) SAM,5(11.6%)mucositis 4 (9.3%) sepsis, 3 (6.9%) MAM, 3(6.9%) gastroenteritis. More than one co-morbidity were diagnosed in 9 children (20.9%) .

Table 3: types of malignancy and further stratification of the patients with NF admitted at JUSTH, JIMMA, Ethiopia, 2020/21

| variable           |                  | Frequency | Percent |
|--------------------|------------------|-----------|---------|
| Type of malignancy | hematologic      | 53        | 81.5    |
|                    | solid            | 12        | 18.5    |
|                    | Total            | 65        | 100.0   |
| Hematologic        |                  |           |         |
|                    | ALL              | 36        | 55.4    |
|                    | AML              | 5         | 7.7     |
|                    | HL               | 4         | 6.2     |
|                    | NHL              | 8         | 12.3    |
| solid              |                  |           |         |
|                    | Hepatoblastoma   | 3         | 4.6     |
|                    | neuroblastoma    | 1         | 1.5     |
|                    | osteosarcoma     | 3         | 4.6     |
|                    | retinoblastoma   | 1         | 1.5     |
|                    | rhabdomyosarcoma | 1         | 1.5     |
|                    | wilm's tumor     | 3         | 4.6     |
|                    | Total            | 65        | 100.0   |

Overall, 43 (66.2%) patients had co-morbidity ,among which 11 (25.5 %) SAM,5(11.6%)mucositis 4 (9.3%) sepsis, 3 (6.9%) MAM, 3(6.9%) gastroenteritis. More than one co-morbidity were diagnosed in 9 children (20.9%) .

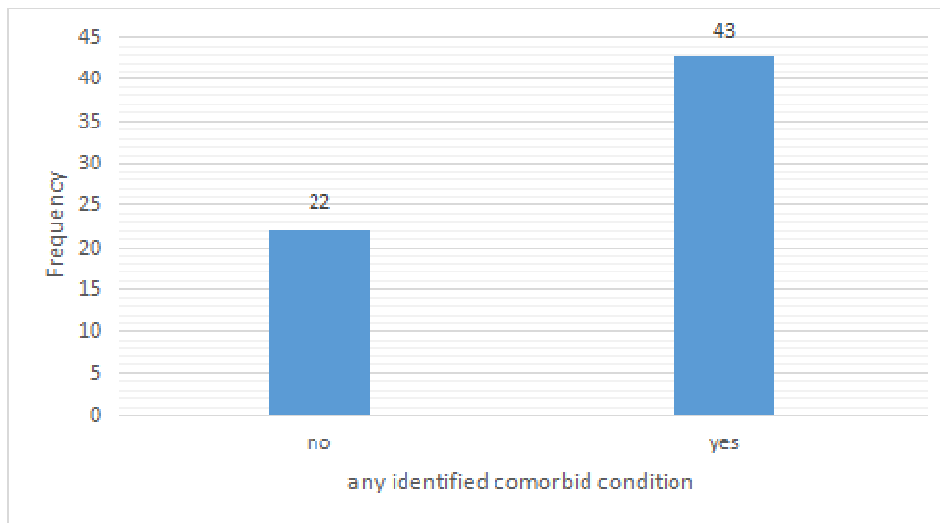


Figure 1: Identified comorbidities among patients with FN admitted at JUSTH, JIMMA, Ethiopia, 2020/21

Table 4: Identified comorbidities of the patients with NF admitted at JUSTH, JIMMA, Ethiopia, 2020/21

| Comorbidity                | Frequency | Percent |
|----------------------------|-----------|---------|
| SAM                        | 11        | 25.5    |
| Mucositis                  | 5         | 11.6    |
| Sepsis                     | 4         | 9.3     |
| MAM                        | 3         | 6.9     |
| More than one co-morbidity | 9         | 20.9    |
| Others                     | 11        | 25.8    |

#### 5.4 Outcome of the patients with FN

Regarding outcome of the patients, 13 (20%) of the patients died and the mean age of the deceased patients was 6.07 ( $\pm 3.44$ ) years. 6 were male and death occurred at a mean(SD) duration of neutropenia of 12.69 days after admission. Mean neutropenic fever episodes were 3.3 and 8 (61.6%) of 13 deceased patients have grater than 3 neutropenia episodes.

Their mean ANC and platelet counts were 110/mm<sup>3</sup> and 56,000/mm<sup>3</sup>, respectively. 10(76.9%) of the 13 patients have profound neutropenia .

Ten of the 13 deaths were hematologic malignancies:8 ALL ,1 AML, and 1 HL. The remaining three had solid tumors(2 hepatoblastoma and 1 retinoblastoma).

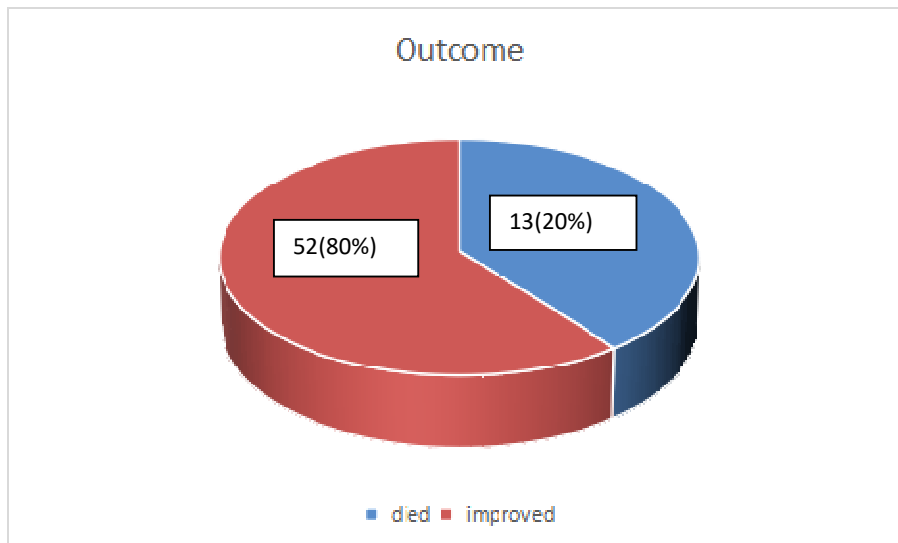


Figure 2: outcome among patients with FN admitted at JUSTH, JIMMA, Ethiopia, 2020/21

**5.5 Comparison of Socio- demography,vital-signs ,duration, number of febrile neutropenic episodes, Co morbid illness and laboratory variables between survivor and non-survivor groups in FN patients.**

Majority of the patients who died were observed among the groups classified by the age of 2-10 (84.6%), grater than 3 febrile neutropenia episodes (61.9%) ,duration of neutropenia  $\geq 7$  days (84.7%) and those who had comorbidities (69.2%). among the vital signs and laboratory markers : pulse rate  $> 120$  beats per minutes (84.6%), temperature  $\geq 39^{\circ}\text{C}$ (61.9%) ,profound neutropenia which was ANC  $< 100$  (76.9%) and platelate  $< 50,000$ (76.9%) were observed among the patient who died.(table 5)

Table 5: comparison of variables among survivors and non survivors of patients with FN at JUSTH, JIMMA, Ethiopia, 2020/21.

| variables               |               | outcome   |               |
|-------------------------|---------------|-----------|---------------|
|                         |               | Died n(%) | Improved n(%) |
| age                     | 0-1           | 0(0)      | 1(1.9)        |
|                         | 2-10          | 11(84.6)  | 46(88.5)      |
|                         | 11-18         | 2(15.4)   | 5(9.6)        |
| gender                  | male          | 6(46.2)   | 27(51.9)      |
|                         | female        | 7(53.8)   | 25(48.1)      |
| Temperature(°C)         | 37.7-38.5     | 4(30.8)   | 26(50)        |
|                         | 38.6-38.9     | 1(7.7)    | 19(36.5)      |
|                         | 39-39.5       | 3(23.1)   | 7(13.5)       |
|                         | 39.6-40       | 5(38.5)   | 0(0)          |
| Pulse rate              | 100-120       | 2(15.4)   | 15(28.8)      |
|                         | 121-140       | 4(30.8)   | 23(44.2)      |
|                         | 141-160       | 7(53.8)   | 11(21.2)      |
|                         | 161-180       | 0(0)      | 3(5.8)        |
| ANC                     | 0-99          | 10(76.9)  | 2(3.8)        |
|                         | 100-249       | 2(15.4)   | 19(36.5)      |
|                         | 250-500       | 1(7.7)    | 31(59.6)      |
| platelet                | ≤50000        | 10(76.9)  | 8(15.4)       |
|                         | 50001-99999   | 1(7.7)    | 21(40.4)      |
|                         | 100000-150000 | 0(0)      | 10(19.2)      |
|                         | >150000       | 2(15.4)   | 13(25)        |
| # of FN episodes        | 1             | 1(7.7)    | 27(51.9)      |
|                         | 2             | 4(30.8)   | 23(44.2)      |
|                         | 3             | 0(0)      | 3(3.8)        |
|                         | 4             | 6(46.2)   | 0(0)          |
|                         | 5             | 2(15.4)   | 0(0)          |
| Duration of neutropenia | 1-6           | 2(15.4)   | 27(51.9)      |
|                         | 7-14          | 6(46.2)   | 18(34.6)      |
|                         | 15-21         | 3(23.1)   | 6(11.5)       |
|                         | >21           | 2(15.4)   | 1(1.9)        |
| Blood culture sent      | yes           | 6(46.2)   | 11(21.2)      |
|                         | no            | 7(53.8)   | 41(78.8)      |
| Type of malignancy      | hematologic   | 10(76.9)  | 43(82.7)      |
|                         | Solid tumor   | 3(23.1)   | 9(17.3)       |
| Co-morbidity            | yes           | 9(69.2)   | 34(65.4)      |
|                         | no            | 4(30.8)   | 18(34.6)      |

## 5.6 Factors that predict the mortality of patients with FN

chi square statistical analysis was carried out to examine the significance of the observed difference between the outcome variable to be studied. Some factors were found significantly associated and predict the outcome (in-hospital death). These factors were: temperature, ANC, number of febrile neutropenic episodes and duration of neutropenia. (Table 6)

Table 6: chi square statistical analysis for risk factors associated with mortality of patients with FN(n=65)

| variable                |             | outcome   |               | Chi square | P-value      |
|-------------------------|-------------|-----------|---------------|------------|--------------|
|                         |             | Died n(%) | Survived n(%) |            |              |
| gender                  | male        | 6(46.2)   | 27(51.9)      | 0.015      | 0.901        |
|                         | female      | 7(53.8)   | 25(48.1)      |            |              |
| age                     | ≤10 years   | 11(84.6)  | 47(90.4)      | 0.000      | 1.000        |
|                         | >10 years   | 2(15.4)   | 5(9.6)        |            |              |
| Temperature(°C)         | <39         | 5(38.5)   | 45(86.5)      | 17.524     | <b>0.000</b> |
|                         | ≥39         | 8(61.6)   | 7(13.5)       |            |              |
| Pulse rate              | ≤140        | 6(46.2)   | 38(73)        | 3.447      | 0.063        |
|                         | >140        | 7(53.8)   | 14(27)        |            |              |
| ANC                     | <100        | 10(76.9)  | 2(3.8)        | 36.895     | <b>0.000</b> |
|                         | ≥100        | 3(23.1)   | 50(96.2)      |            |              |
| platelet                | <150000     | 11(84.6)  | 39(75)        | 1.229      | 0.268        |
|                         | ≥150000     | 2(15.4)   | 13(25)        |            |              |
| # of FN episodes        | ≤3          | 5(38.5)   | 52(100)       | 26.591     | <b>0.000</b> |
|                         | >3          | 8(61.5)   | 0(0)          |            |              |
| Duration of neutropenia | <7 days     | 2(15.4)   | 27(51.9)      | 5.562      | <b>0.018</b> |
|                         | ≥7 days     | 11(84.6)  | 25(48.1)      |            |              |
| Blood culture sent      | yes         | 6(46.2)   | 11(21.2)      | 3.366      | 0.067        |
|                         | no          | 7(53.8)   | 41(78.8)      |            |              |
| Type of malignancy      | hematologic | 10(76.9)  | 43(82.7)      | 0.230      | 0.632        |
|                         | solid       | 3(23.1)   | 9(17.3)       |            |              |
| Co-morbidity identified | yes         | 9(69.2)   | 34(65.4)      | 0.069      | 0.793        |
|                         | no          | 4(30.8)   | 18(34.6)      |            |              |

## 6. Discussion

In the current study, we conducted a retrospective cross-sectional study to evaluate factors affecting treatment outcome of pediatric oncology patients with febrile neutropenia at JUSTH, Jimma, Ethiopia from Jan 1, 2020-Dec 31, 2021.

Despite the widespread approach of treating all febrile neutropenic patients with empiric broad spectrum antibiotics for potential bacteremia, febrile neutropenia in the child with cancer remains associated with a significant mortality rate. In our study, a death rate of 20% was noted. This outnumbers observations from a multi-center study from Chile (3.8%), the US (3%), Iran (7.5%), and Norway (1%) (11-14). This might be due to poor supportive care, inadequate use of antimicrobial or a smaller sample size (65) in the study as compared to 373 (Chile), 12,446 (US), 120 (Iran) and 95 (Norway). This concurs with reports by selamawitassefa (Ethiopia) where death rate documented in 20% (21). Infants and adolescents were found to be at a greater risk of death in the US, which contrasts to the mean age of patients who died in our study (12). Overall, 66.2% of the children enrolled in our study had co-morbid conditions. SAM, Mucositis, sepsis, MAM and gastroenteritis accounted for 25.5%, 11.6%, 9.3%, 6.9%, and 6.9% respectively. Over all they account about 60.2% of co morbid diagnoses in our patients. Patients with sepsis accounted for 9.3% of all children; This concurs with reports by selamawitassefa (Ethiopia) where sepsis documented in 10% (21).

The most common malignancy identified among children with febrile neutropenia episodes in our series was ALL accounting for 55.4% of the cases. This concurs with reports by Badiei et al (Iran), Stabell et al. (Norway) and Timothy et al. and Trinidad & Tobago where ALL was documented in 53.3%, 51.6% and 43.7% of childhood febrile neutropenic episodes, respectively (13,14,16).

Only 7 (10.7%) of the patients had documented bacterial infection as compared to a German and a Swiss studies (21.5%) and a Norwegian report which showed bacterial infection of 16.5% (14,15). The lower proportion of cases with positive culture result in our series can be attributed to the smaller study sample size and a poor culture yield due to prior antibiotic use or laboratory quality. As opposed to the global shift toward a preponderance of gram-positive organisms, this study showed predominance of gram-negative sepsis, which is in agreement with reports by selamawitassefa (Ethiopia) where gram-negative preponderance observed. But our findings contrast to

the results reported by Agyeman et al., which showed preponderance of gram-positive sepsis (15). All of our patients were on prophylactic cotrimoxazole not on ciprofloxacin and non-use of indwelling venous catheter might be the reasons for gram-negative preponderance in our set up.

Correspondingly, febrile neutropenic patients with greater than 3 episodes of febrile neutropenia had significant risk of mortality (chi square=26.59;  $p=0.000$ )

Similarly our study showed, febrile neutropenic patients with prolonged neutropenia had significant risk of mortality (chi square=5.56;  $p=0.018$ ). This is consistent with records of 161 pediatric patients with neoplastic disease hospitalized for neutropenic fever at New York USA which showed neutropenic episodes involving ICU management and deaths were in patients who had persistent fever and ANC <100 (20). Temperature greater than or equal to  $39^{\circ}\text{C}$  is associated with increased risk of in hospital mortality (chi square=17.52;  $p=0.000$ ), this is consistent with study done at Ottawa Canada and Iran where body temperature greater than or equal to  $39^{\circ}\text{C}$  was significantly associated with life threatening infection and mortality with  $p$  value of  $p=0.000$ ,  $p=0.001$  respectively (13,18). Laboratory marker which found to be significant determinant of disease outcome is low ANC at time of admission. Having profound neutropenia which is ANC <100, is associated significant in hospital mortality (chi square=36.89;  $p=0.000$ ). This is consistent with prospective, multicenter study which was done in Chile which showed, children who died were admitted with lower ANC ( $p<0.001$ ) (11). Our finding is also in line with cross sectional study which was done in Dr. Sheikh Pediatric Hospital Iran, where ANC <100 ( $p<0.001$ ) is among the risk factors for increased mortality (13). Similarly our finding is consistent with retrospective cross-sectional study done at TASH, Addis Ababa, where ANC <100 is among the major risk factors which affects the treatment outcome of the patient with FN (21). But this differs from what was detected in Missouri, USA, where AMC less than  $30/\text{mm}^3$  rather than ANC was a significant risk for death (17). AMC of less than  $100/\text{mm}^3$  was found to be the only factor associated with patient outcome in Ottawa, Canada (18).

## **6. Strengths and Limitations**

The results of this study have several clinical implications and strengths. Our data confirms and expands previous results in FN patients and emphasizes the relevance of careful evaluation of these factors and assessing the severity of the patient clinical condition at time of admission. It can be a simple way to determine the poor prognosis of patients with FN, which is conducive to the allocation of medical resources in our limited resource setup.

There are several limitations to the study;

1. We were not able to locate some of patient charts and it is likely that the missed charts could be those of patients who died. This might have resulted in underestimation the number patients who died. Incomplete recording of information in the patient charts could also be a reason for not being able to fully assess some of the study variables.
2. Due to the single center and retrospective nature of the study design, the risk factors might be underestimated or overestimated in predicting poor prognosis. Further prospective multicenter studies that involve different tertiary hospital are needed to ascertain risk stratification and treatment protocols for febrile neutropenia among our pediatric oncology patients. and also needed to validate prospectively in the same center.
3. Since all subjects in our study were hospitalized patients diagnosed with FN, the results of this study might not directly be applied to other ambulatory patients.
4. Unmeasured confounding factors such as the type of medications patient received ,the time of intation of medications ,the duration of treatment are not assessed in this study.

## **8. Conclusion:**

In conclusion, temperature  $\geq 39$  degree Celsius, prolonged neutropenia, profound neutropenia and febrile neutropenic episodes greater than 3 were found to have significant associations with poor clinical outcome in the children in our series. This provides an objective input for early decision-making in the patient's management and allocation of limited resources. Further analysis of data from a larger series of patients preferably with prospective data collection is required in order to devise risk stratification and treatment protocols for febrile neutropenia episodes among our pediatric oncology patients.

## **9.Recommendation**

### **For Health professionals**

The clinician should assess the temperature, degree of ANC, duration of neutropenia and the number of febrile neutropenic episodes and should consider temperature  $\geq 39^{\circ}\text{C}$ , ANC  $< 100$ , Prolonged febrile neutropenia and febrile neutropenic episodes greater than 3 as predictors of mortality and apply to on their patients for early identification and timely treatment modification to reduce in-hospital death.

### **For researchers**

Future studies may be needed to validate our result prospectively on the same center and multicenter study with a larger sample size by including additional confounding factors and dynamic monitoring of risk factors in the course of the disease are recommended.

## 10. References

1. Hakim H, Flynn P, Srivastava DK, Knapp K, Li C, Okuma J et al. (2009); Risk prediction in pediatric cancer patients with fever and neutropenia. *Pediatr Infect Dis J* 2010;29: 53–9
2. Debra LP. The use of antimicrobial agents in children with fever during chemotherapy-induced neutropenia. *Pediatr Infect Dis J* 2011;30: 887–90
3. Sung L, Johnston D. Approach to febrile neutropenia in the general pediatric setting. *Paediatr Child Health* 2007; 12(1): 19-21
4. Mandell GL, Bennett JE, Doolin R, 6theds (2005). Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone, 2005:3442–62.
5. Castagnola E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda F et al..A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. *Clin Infect Dis* 2007; 45(10):1296-304
6. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. *Clin Infect Dis* 2004; 39:25–31
7. Hakim H, Flynn PM, Knapp KM. Etiology and clinical course of febrile neutropenia in children with cancer. *J PediatrHematolOncol* 2009;31(9):623.
8. Gedik H, Yildirmak MT, Simsek F, Aydin D, Demirel N, Yokus O et al. Fungal pathogens and primary antifungal prophylaxis in patients with hematologic malignancies. *African Health Sciences* 2012; 12(3): 390-4
9. Licciardello M, Pegoraro A, Cesaro S. Prophylaxis and therapy of viral infections in pediatric patients treated for malignancy. *Pediatric Reports* 2011; volume 3:e5
10. Koh AY. Prolonged febrile neutropenia in the pediatric patient with cancer. In American Society of Clinical Oncology educational book/ASCO. American Society of Clinical Oncology. Meeting 2011 Dec (pp. 565-9).
11. Santolaya M, Alvarez A, Aviles C, 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;26:794-8
12. Basu SK, Fernandez ID, Fisher S, Asselin B, Lyman G. Length of stay and mortality associated with febrile neutropenia among children with cancer. *J ClinOncol* 2005; 23:7958-66.
13. Badiel Z, Khalesi M, Alami MH, Kianifar HR, Banihashem A, Farhangi H et al, Risk factors associated with life-threatening infections in children with febrile neutropenia. *J PediatrHematolOncol* 2011; 33(1):e9-12.
14. Stabell N, Nordal E, Stensvold E, Gammelsrud KW, Lund B, Taxt A et al. Febrile neutropenia in children with cancer: a retrospective Norwegian multicentre study of clinical and microbiological outcome. *Scand J Infect Dis* 2008;40(4):301-7
15. Agyeman P, Kontny U, Nadal D, Leibundgut K, Niggli F, Simon A. A prospective multi-center study of microbiologically defined infections in pediatric cancer patients with fever and neutropenia. *Pediatr Infect Dis J* 2014;33:e219–e225
16. Timothy M, Bodkyn C. The outcome of febrile neutropenic episodes in pediatric oncology at the Wendy Fitzwilliam pediatric hospital. *West Indian Med J* 2011; 60 (2): 153

17. Baorto EP, Aquino VM, Mullen CA, Buchanan GR, De Baun MR. Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. *Cancer* 2001;92(4):909-13.
18. Klaasen RJ, Goodman TR, Pham B, Doyle JJ. "Low risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J Clinical Oncol* 2000; 18(5):1012-9.
19. O'Connor D, Bate J, Wade R, clack R, Dhir S, Hough R et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths. *Blood* 2014; 124(7): 1056-61
20. Lucas K, Brown A, Armstrong D, Chapman D, Heller G. The identification of febrile, Neutropenic children
21. selamawitassefa, tinsaealemayehu, workeabeba. factors associated with treatment outcome of pediatric cancer patients with FN. *Ethiop Med J*, 2017, vol 55 no 1

## 11. Annex I

### 11.1 Questionnaire

TO ASSES FACTORS AFFECTING OUTCOME OF PEDIATRIC ONCOLOGY PATIENTS WITH FEBRILE NUTROPENIA AT JUSTH, JIMMA ,SOUTH WEST ETHIOPIA

#### 1. Socio demographic characteristics

Age (in years) \_\_\_\_\_

Sex      a. Male ☐      b. Female ☐

#### 2. Disease characteristics

2.1 Vital signs(at time of neutropenia)

a. Temperature (in °C)

b. pulse rate:

2.2 Investigations

a. wbc \_\_\_\_\_

b. neutrophile % \_\_\_\_\_

ANC-----

c.platelet count-----

2.3 blood cultures sent at time of NF? Yes ☐      No ☐

2.4 If yes for question no 2.3, what was the pathogen/s isolated?

Klebsiella specios ☐      E.coli ☐      acintobactor ☐

CONS ☐      staphylococcus aurese ☐      others -----

2.4 Duration of neutropenia (in days) \_\_\_\_\_

2.5 Total number of febrile neutropenic episodes -----

2.6 What was the type of malignancy the patient had?

a. hematologic ☐      b. solid ☐

2.7 If, a , to Q 2.6, which one of the following?

ALL ☐      AML ☐      CML ☐

HL ☐      NHL ☐      others-----

2.8 If, b, to Q2.6, which one of the following?

Wilm's tumore ☐      rhabdomyosarcoma ☐

Neuroblastoma ☐      retinoblastoma ☐      others-----

2.9 What was the status at discharge?

a. Improved ☐

b. died ☐

3.0 If the patient died, were the patient on prophylactic antibiotics?

Yes ☐

No ☐

3.1 If yes for question no 3.0 ,what was it?

a. cotrimozazole ☐

b. ciprofloxacilline ☐

c. Others (specify) \_\_\_\_\_

3.2 Identified comorbid conditions?

Yes ☐

No ☐

3.3 If yes to question no 3.2 what was it?

Mucositis ☐

gastroenteritis ☐

UTI ☐

sepsis ☐

others(specify)-----

### **11.2 Assurance of Principal Investigator**

I the undersigned agreed to accept all responsibilities for the scientific and ethical conduct of the research project. I had provided timely progress report to my advisor and sought the necessary advice and approval from my primary advisors in the course of the research. I had communicated timely to my advisor all stakeholders involved in the study including any source of funding for this research.

Name of the student: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Approval of the Primary Advisor

Name of the primary advisor: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

