Prevalence, Risk Factors and Predictors of Adverse Outcomes of Febrile Neutropenia in Oncology Patients on Chemotherapy at the Red Cross War Memorial Children's Hospital: A Three Year Retrospective Study.

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DECLARATION

I, Motunrayo Oluwabukola ADEKUNLE hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATION

To every child who has succumbed to cancer in Nigeria, you all are the motivation for this training and research.

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LIST OF ABBREVIATIONS

ALCL: Anaplastic large cell lymphoma

ALL: Acute lymphoblastic leukaemia

AML: Acute myeloid leukaemia

ANC: Absolute neutrophil count

APC: Absolute phagocyte count

ATRT: Atypical rhabdoid tumour

CIN: Chemotherapy induced neutropenia

CML: Chronic myeloid leukaemia

CVAD: Central venous access device

FN: Febrile neutropenia

G-CSF: Granulocyte colony stimulating factor

HIV; Human immunodeficiency virus

HL: Hodgkin lymphoma

ICD: International classification of diseases

ICU: Intensive care unit

IQR: Interquantile range

MDI: Microbiologically defined infection

NHL: Non Hodgkin lymphoma

PCR: Polymerase chain reaction

PICU: Paediatric intensive care unit

RCWMCH: Red Cross War Memorial Children's Hospital

SCT: Stem cell transplant

SPOG: Swiss Paediatric Oncology Group

WHO: World Health Organisation

ABSTRACT

Background: Febrile neutropenia (FN) is the commonest fatal acute complication of cancer treatment in children. The need for regional clinical decision rules allowing for home-based care in those at low risk for adverse outcomes has been identified.

Aims: To evaluate the prevalence and potential risk factors for FN, identify adverse outcomes and validate a tool to identify risk for adverse outcomes in a cohort of children treated for cancer at the Red Cross War Memorial Children's Hospital, Cape-Town, South Africa.

Methodology: A retrospective cohort study from 1st January 2017 to 31st December 2019.

Results: In all, 179 patients had chemotherapy and 267 FN episodes occurred. Independent predictors of FN were AML (p = 0.039), ALL (p = 0.020) and intensive chemotherapy (p = < 0.001). Mucositis (p = 0.001), CVAD (p = 0.004, haematologic malignancies (p = 0.040), blood transfusion during FN episode (p = <0.001) and severe neutropenia (white cell counts < 0.3 x 10^9cells/L) (p = <0.001) were risk factors for adverse outcomes. The mortality rate from FN was 3.57%. Independent predictors of adverse outcomes were AML (p = 0.001), CVAD in-situ (p = 0.019) and severe neutropenia (p = 0.005). Validation of risk stratification for adverse outcomes using the Swiss Paediatric Oncology Group (SPOG) index with a cut-off value of nine demonstrated a sensitivity and specificity of 52.3% and 62.0%, respectively. Positive and negative predictive values were 56.3% and 58.2%, respectively, with an overall accuracy of 57.4%. In our cohort, coordinates of the curve are best able to predict adverse outcomes with a cut-off value of 7.5.

Conclusion: Adverse outcomes from treatment are likely in children with AML, severe neutropenia and those with CVADs in-situ. A lower cut-off of 7.5 using the SPOG FN risk index best predicted adverse outcomes in our cohort.

CHAPTER ONE

INTRODUCTION

Febrile neutropenia (FN) is a major cause of morbidity and the commonest fatal acute complication of cancer treatment in children[1,2]. It is the second commonest cause of hospital admission and a leading cause of prolonged admissions among children with malignancies, as well as a chemotherapy dose reduction and/or delay which increases the risk of treatment failure[3]. Due to the need for several admissions, FN significantly affects the quality of life of children living with cancer and their caregivers[4].

There are various definitions of FN with different cut-off values for temperature and leucocyte count or absolute neutrophil count (ANC). These include a single oral temperature of at least 38.0^0 C or > 37.5^0 C as a single axillary temperature with an ANC < 0.5 or < 1.0 (x 10^9/L) in patients with a predictably deteriorating clinical condition; fever above 38.3^0C with ANC < 0.5 x10^9/L ; > 38.5^0C as an oral temperature or two consecutive readings of > 38.0^0 C two hours apart with ANC < 0.5 x10^9/L or predicted decline to < 0.5 x10^9/L; or ≥ 38.3^0 C as an oral temperature or ≥ 38.0^0 C over 1 hour and ANC < 0.5 x10^9/L or < 1.0 x10^9/L with predicted decline to ≤ 0.5 x10^9/L over the ensuing 48 hours[5–8]. Variations in definitions of FN have resulted in differences in the classification as well as the management of individuals with this complication in various centres[9].

Approximately 50% of children on chemotherapy will develop at least one episode of FN in the course of their treatment[10]. The incidence of FN has been reported to be as high as 50% and 80% in solid tumours and haematologic malignancies, respectively[11,12].

Reported risk factors for FN are broadly classified based on patients' demographics, chemotherapy agents, disease type and genetic factors. Increased myelosuppression and FN have been reported to be more common in older patients compared to those in younger age groups[13]. Chemotherapy regimens containing anthracycline and alkylating agents are common causes of myelosuppression[14]. With modification and increased intensity of treatment protocols, a commensurate increased incidence in FN has been observed due to more severe myelosuppression[15] Some adult studies have shown a genetic predisposition such as the H/H promoter genotype which is linked to low mannose binding lectin levels (a protein required in innate immunity) and the expression of rs351855 in fibroblast growth factor receptor 4[16,17]. Currently, mortality from FN is on the decline due to the availability and judicious use of broad spectrum antibiotics but FN still remains a significant cause of morbidity and mortality[18–20].

Febrile neutropenia may be classified as high or low risk. This helps to distinguish patients requiring hospital admission and inpatient care from those who could be treated as out-patients. Managing patients on an out-patient basis with low risk FN helps to reduce hospital admissions, the cost of treatment, reduces nosocomial infection and ultimately improves their quality of life[4,21].

Previous studies have identified risk factors for adverse events in children with FN[12,22–24]. There has been variability in the studied risk factors as well as the outcomes. This disparity is accounted for by differences in risk factors evaluation and the management guidelines adopted as a result, which are institutionally determined. Clinical decision rules for risk prediction of adverse outcomes focused mainly on bacteraemia despite several adverse events that occurred from FN[25–27]. Green *et al*[28] at a tertiary institution in Cape Town, South Africa

validated a reported tool by Ammann *et al*[24] as a predictor of high risk disease in 52 children with cancer reporting a sensitivity and specificity of 51% and 68% respectively.

Despite reports from previous studies on risk stratification of FN in children with cancer, it is difficult to adopt their findings due to inconsistencies between studies. More so, concerns related to the adaptation of results obtained in developed countries and their application in low-and-middle income countries (LMIC) has been raised[29]. There are discrepancies between health care systems, patients' nutritional status and varying patterns of microbiological pathogens between countries[29]. These differences led to a proposal for more studies in LMIC to identify risk stratifiers for FN that would contribute to the development of guidelines tailored to the particular needs of children with cancer in this setting[29]. The International Febrile Neutropenia Guideline with input from oncology experts from various countries, made recommendations regarding the validation and application of risk stratification for various centres, but this is yet to be adopted at the paediatric oncology unit of Red Cross War Memorial Children's Hospital (RCWMCH) [30]. In addition, there is paucity of data reported on the length of hospital admission as an adverse outcome in FN despite it being a major contributor to the quality of life of children with cancer, which is a further prompt for more interrogation of setting appropriate guidelines[19].

This study aimed to evaluate the prevalence and potential risk factors for FN and to evaluate its impact on outcomes in a cohort of children with cancer diagnoses treated at RCWMCH over a three-year period from January 2017 to December 2019. Also, we validated the Swiss Paediatric Oncology Group FN index which is a tool for risk stratification. These findings, we hoped, would aid in the identification of patients at risk and help to better define those requiring hospital admission versus those needing only out-patient care. By proxy, this may also impact subsequent morbidity and mortality.

AIM

To determine the prevalence and risk factors for FN and predictors of outcome in paediatric oncology patients on intensive chemotherapy at RCWMCH treated from January 2017 to December 2019.

Specific objectives:

To determine:

1. The prevalence of FN among children with malignancies.
2. The risk factors associated with FN in study subjects (e.g. age, disease type, stage of disease, chemotherapy regimen, presence of central venous access devices (CVADs), absolute neutrophil count, absolute phagocyte count, identification of a focus of infection, and bone marrow involvement).
3. The predictors of outcomes (e.g. intensive care unit admission, length of hospital stay, radiologically confirmed pneumonia, microbiologically confirmed infection) in the study subjects.
4. The validation of risk stratification for adverse outcome of FN using SPOG FN index (sensitivity, specificity, positive predictive and negative predictive value).

Secondary Objective:

1. To compare the prevalence of FN in subjects with solid tumours and haematologic malignancies.

RESEARCH QUESTIONS

1. What is the prevalence of FN in the study subjects?
2. What are the risk factors associated with FN in the study subjects?
3. What are the predictors of adverse outcomes in children with FN?
4. To what extent does the SPOG FN risk index predict adverse outcomes in patients in our study?

HYPOTHESIS

Null Hypotheses:

1. There will be no statistically significant difference in the prevalence and adverse outcome of febrile neutropenia between subjects with solid tumours and blood cancers.

2. There will be at least 90% sensitivity, specificity prediction of adverse outcomes using SPOG FN risk in our study population.

Alternate hypotheses:

1. There will be a statistically significant difference in the prevalence and adverse outcomes of febrile neutropenia between subjects with solid tumours and haematological malignancies.

2. The sensitivity and specificity prediction of adverse outcomes in subjects using SPOG FN risk in our study will be below 90%.

CHAPTER TWO

LITERATURE REVIEW:

DEFINITIONS OF FEBRILE NEUTROPENIA AND EFFECTS OF ITS VARIATION

Febrile neutropenia is defined as the presence of a fever above 38° C with an absolute neutrophil count (ANC) of $<1.0\times10^9/L$[10,12,31]. Some authors have adopted as high as $< 1.5 \times10^9/L$ ANC[32]. There are however, various definitions of temperature thresholds in neutropenic patients and their applications vary from centre to centre. Temperature thresholds have ranged from 37.5^0 C to 39^0 C whilst the definitions for neutropenia have remained fairly constant at $< 0.5 \times10^9/L$ or $< 1\times10^9/L$ in a count that is expected to fall. In the oncology unit at RCWMCH, FN is defined as a documented axillary temperature measured with a standard mercury thermometer of $\geq 38^0$C at a single time point or $\geq 37.5^0$ C on two occasions measured 20 minutes apart without administering anti-pyretics in the interval between temperature measurements, in a patient with an absolute neutrophil count (ANC) of $0.5\text{-}1\times10^9/L$ or $\geq37.5^0$ C at a single time point in a child with an ANC $< 0.5\times10^9/L$. In some centres, there has been modification of the definition of fever over the years and this has resulted in different rates of diagnoses of FN[33].

Wagner *et al* reported the influence in variation of FN at diagnosis and post-chemotherapy in children[9]. A tympanic temperature of at least 39^0 C was the standard definition for fever in neutropenic patients. This standard cut-off corresponds to 39.1^0C and 38.4^0C core and axillary temperatures, respectively. This standard temperature was compared to the intervention of lowering the temperature-limit-defining-fever (TLDF) and its effects on FN-related measures were simulated in silicon using software, thereby avoiding disruption in the diagnosis and management of the studied subjects. In all, 45 cases of FN were diagnosed: all had blood cultures at diagnosis and an additional blood culture was done with

Various definitions of febrile neutropenia[5].

Source	Fever	Neutropaenia
Japan Febrile Neutropenia Study (2005)	≥ 38.0^0C single oral or ear probe temperature or > 37.5^0C single axillary temperature	ANC < 0.5 x 10^9/L or < 1.0 x 10^9/L in subjects with predictably deteriorating clinical condition.
British Columbia Cancer Agency (2008)	> 38.3^0C	ANC < 0.5×10^9/L.
European Society of Medical Oncology (2010)	>38.5^0C oral temperature or 2 consecutive readings of > 38.0^0C for 2 hours	ANC < 0.5 x 10^9/L or predicted decline to < 0.5×10^9/L.
National Comprehensive Cancer Network (2011)	≥ 38.3^0C oral temperature. or ≥ 38.0^0C over 1 hour	ANC < 0.5 or < 1.0×10^9/L with predicted decline to ≤ 0.5 ×10^9/L over next 48 hours.
Infectious Diseases Society of America (2011)	≥ 38.3^0C oral temperature, or ≥ 38.0^0C over 1 hour	ANC <0.5×10^9/L or predicted decline to < 0.5 ×10^9/L over next 48 hours
Bugs & Drugs (2012)	≥ 38.3^0C oral temperature or ≥ 38.0^0C over 1 hour	ANC < 0.5 x 10^9/L.
National Cancer Institute (CTCAE) (2017)	a single temperature of >38.3^0C or a sustained temperature of 38^0C for >1 hour	ANC of < 1×10^9/L.

CTCAE = Common Terminology Criteria for Adverse Events, ANC = Absolute neutrophil count

temperature spikes. A total of 43 additional blood cultures was done in 22 episodes of fever above 39^0 C, which corresponded to 68 cultures in 29 fever episodes at a fever limit of 38.5^0 C. When the fever limit was 38^0 C and 37.5^0 C, a total of 103 in 33 fever episodes and 148 blood cultures in 38 fever episodes would have been done, respectively. This finding also reflected escalation of antibiotics to a broader spectrum in patients with persistent fever based on the fever threshold.

In contrast, Binz *et al*[33] demonstrated no significant differences in the outcomes with variation in fever definitions in neutropenic paediatric oncology cases in Switzerland. A retrospective review of data in all children and adolescents aged below 18 years with cancer treated with chemotherapy between January 1, 2004 and June 30, 2011 was analysed. During the study period, three definitions for fever in neutropenic patients were used. In univariate but not multivariate analysis, the rate of FN significantly increased with a decrease in temperature threshold adopted for the definition of FN at certain periods. The FN rate was 0.10/month with the highest definition 0.13 and 0.15/month for the intermediate and lowest temperatures used in defining fever in neutropenic patients.

PATHOPHYSIOLOGY OF FEBRILE NEUTROPENIA

Neutrophils are the largest in number of white blood cells as they account for 50 –70% of all leucocytes[34]. They are the first line of defence against microorganisms. The lifespan of the neutrophil is altered in cancer, with prolongation of its maturation time. Cancer cells also cause humoral and cellular immune dysfunction[34].

Direct bone marrow invasion by cancer cells leads to an alteration in the primary function of haematopoietic stem cells production. Cancer cells also induce defective chemotactic and phagocytic function of neutrophils, mostly in haematologic malignancies[34].

Chemotherapeutic agents target the rapidly dividing cancer cells but in the process also destroy normal blood cells. The direct effect of these drugs on the bone marrow leads to abnormal haematopoiesis with a marked effect on white blood cells[35].

Similarly, radiotherapy can also cause a decline in the production of haematopoietic stem cells. This reduction in haematopoietic progenitors can also be accompanied by elevated numbers of adipocytes in the marrow cavity, which inhibit haematopoiesis and the recovery of the bone marrow microenvironment[36]. The end result of these therapeutic agents is a higher risk of infection due to deficient neutrophils.

Mucous membranes that line the body tracts serve as barrier to microorganisms in the body. Chemotherapeutic agents kill the rapidly dividing cells in the mucous membranes leading to mucositis allowing easy access of microorganisms into the body.

During infection there is release of exogenous pyrogens (microbes or their bi-products) into the body[37]. These result in release of bone-marrow-derived cytokines from phagocytes such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), IL-6, which are all endogenous pyrogens that circulates to the thermoregulatory center of the brain, the hypothalamus. These endogenous pyrogens then cause an elevation in the "set-point" for normal body temperature in the hypothalamus[37,38].

PREVALENCE/INCIDENCE OF FEBRILE NEUTROPENIA IN PAEDIATRIC ONCOLOGY

FN is the commonest complication in paediatric oncology patients treated with chemotherapy and is the commonest reason for hospital admission, affecting at least half of these patients[1,10].

The prevalence of FN in children on chemotherapy was reported as 12% by Sulviani *et al*[23] in a 15-year retrospective record review of children less than 15 years old treated at Hasan

Sadikin Hospital, Indonesia. In this study, FN was defined as an absolute neutrophil count of less than 1000/mm^3 and fever with temperatures more than 38º C. Comparatively, in a ten-year retrospective of paediatric oncology patients from Berne, Switzerland, Zermattan *et al* reported a higher proportion of patients with FN[10]. Two hundred and ninety one (50%) out of 583 patients, aged below 17 years, reported at least one episode of FN while on chemotherapy. The median and maximum numbers of episodes of FN were two and nine, respectively. There was a change in fever definitions over the study period but the two definitions were comparable[31]. Castagnola *et al*[12] in a prospective study from Italy, reported a high occurrence of FN in children below 15 years with central nervous system tumours. A total of 72 febrile episodes was observed in 62 neutropenic episodes. In all 10%, 30% and 48% of patients on gentle chemotherapy (vincristine and carboplatin), standard chemotherapy and those undergoing peripheral blood stem transplantation had FN. Despite the lower threshold of 38^0 C for fever definition in the study by Castagnola *et al*[12] compared to 38.5^0 C by Zermattan *et al*,[10] recruitment of patients with solid tumours, who are less likely to have intensive chemotherapy and therefore a reduced risk of FN, could account for the lower number of FN episodes compared to the reported findings by Zermattan *et al*[10]. Similarly, a high number of chemotherapy-induced episodes of FN as observed by Zermattan *et al*[10] was reported in Egypt by Badr *et al*[22] in a one year report (June 2013 to June 2014). In all, 113 episodes of FN were reported in 50 children. A large majority of patients (73.5%) receiving chemotherapy had at least one episode of FN.

RISK FACTORS FOR FEBRILE NEUTROPENIA/ADVERSE OUTCOME IN PAEDIATRIC ONCOLOGY

Several clinical and laboratory parameters have been identified as risk factors for FN in paediatric oncology patients[12,22,23,39–43]. In some studies further stratification into high and low risk categories for severe infection with poorer outcomes has been documented[13,39].

CLINICAL FACTORS AS PREDICTORS FOR RISK FOR FEBRILE NEUTROPENIA

Age: Age is an inconsistently reported risk factor for FN[12,22,23,39–41]. In a retrospective study of 283 children with different oncology diagnoses recruited between January 2000 and December 2003 at Hospital do Cancer A. C. Camargo, São Paulo, Brazil, severe infective complications were found in 44 (37.9%) of 116 children under 5 years which was significantly higher than 49 (23.9%) of 167 children over 5 years[39]. A likely hypothesis to explain the poorer outcome in the younger age group could be the low inherent immunity in children under-5 years. Similar effects of age on FN in children with cancer were reported by other researchers[40,41]. In comparison, Sulviani *et al*[23] found age not to be a risk factor for FN citing a higher mean age in their patient cohort.

In a large multicentre study that involved 115 member academic institutions in the United States between 1995 and 2002, Basu *et al*[19] reported that infants and adolescents over 12 years of age with FN were at higher risk for increased hospital stays and mortality. The mean length of hospital stay for infants and adolescents was 12 days which was significantly longer than the reported duration of 9 days in subjects between one and twelve years. Poor immune system functioning in infants was cited as an explanation for the higher risk of prolonged infections in that age group. In addition, they postulated that genetic predisposition, poor health-seeking behaviour or differences in treatment administered may have accounted for the differences seen. By contrast, Badr *et al*[22] and Castagnola *et al*[12] also reported no relationship between age and FN.

Sex: As with age, the reporting of sex as a risk factor for FN is similarly inconsistent. A few studies have shown no relationship between sex and the risk for FN[12,14] and a study in adults identified a marginally increased risk in females[44]. Rondinelli *et al*[39] reported an increased risk of severe infection in girls with FN compared to boys. In their study, severe infection

occurred in 55/133 (41.4%) girls with FN which, significantly higher than 38/150 (25.3%) FN observed in boys (p = 0.001). No plausible explanation was offered other than the probable role of oestrogen in strengthening the immune system[45].

Disease type: Patients with cancer can be broadly divided into those with haematologic malignancies and those with solid tumours (which may or may not include brain tumours). Studies have shown that patients with haematologic malignancies are at higher risk for FN compared to those with solid tumours. This may be explained by the greater intensity of chemotherapy administered to those patients in the former group. Importantly, acute leukaemia accounts for highest proportion of cancers in children and this could account for the increase in FN.

Sulviani *et al* similarly identified a higher risk of FN in patients with haematologic malignancies compared to those with solid tumours. A total of 65/87 (75%) patients with FN had haematological malignancies. Again, significantly higher than 22/87 (25%) of the subjects with FN diagnosed with solid tumours (p = < 0.001)[23].

In a prospective study from two French centres in children under 18 years of age by Delebarre *et al*[46], haematological malignancy was a risk factor for FN. A total of 225 (28.4%) leukaemia subjects had FN compared to 42 (10.4%) with solid tumours. Severe infection was commoner in subjects with haematological malignancies with the highest proportion in patients with acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) (38% and 27% respectively) while patients with rhabdomyosarcoma and brain tumours had the lowest rate of 5% and 6% respectively (p = < 10^{-5}). All deaths (n = 5, 2.2%) in patients with FN occurred in those with haematological malignancies. Intensive care unit admission following a FN was higher in patients with haematological malignancies than those with solid tumours (n = 21, 9.3%) vs (n= 2, 4.8%) respectively.

In patients with haematological malignancies, children with AML are more prone to severe FN[19,47], explained again by chemotherapy intensity. In a retrospective study of oncology patients with FN admitted at Boston Children's Hospital, Alexander *et al*[47] reported that the duration of neutropenia was significantly longer in patients classified as high risk (AML, relapse solid malignancies with bone marrow involvement and ALL induction) than those in the low risk group. The duration of fever was similar between the two groups but patients in the high risk category were more likely to have a new fever after the settling of the initial temperature. Similar findings were reported by Basu *et al*[19] in the United States where the researchers documented longer hospital stay (> 5 days) and increased deaths (6.3%) in patients with AML compared to those with other cancers diagnoses.

Children with relapsed ALL and AML, and those following stem cell transplantation have been reported to have a higher risk of FN compared to those with primary disease. In a prospective multi-centre study from Santiago, Chile, Santolaya *et al*[27] reported that patients with relapsed leukaemia were amongst those with the five independent risk factors for invasive bacterial infection (RR 1.8, 95% Cl 1.7 to 2.3). These independent risk factors were hypotension, elevated C-reactive protein of at least 90mg/L, patients with relapse cancers, thrombocytopaenia with platelet count of $\leq$ 50,000/mm^3 and recent recipient of chemotherapy.

Prolonged neutropenia has also been reported in relapse ALL and AML, and stem cell transplant patients by Badr *et al*[22] and Castagnola *et al*[12]. In the latter, the median number of days of neutropenia was 13.5 in patients who have undergone peripheral stem cell transplant, significantly higher than ten and eight days in patients that had gentle (vincristine and carboplatin alone) and standard chemotherapy treatment respectively (48% vs 30% and 11%,

p = < 0.0001). “Gentle” chemotherapy was defined by authors as low intensity chemotherapy that was given to patients with low grade glioma.

Malnutrition: Whilst there have been reports of an increased risk for FN in malnourished children[48,49], results have been conflicting[14,22,23]. In a prospective Indian study of 34 children aged one to fifteen years with ALL and non-Hodgkin lymphoma, Linga *et al*[48] showed that episodes of FN were significantly higher in the malnourished groups compared to those with normal nutritional status (p =.0.001). A total of 28 FN episodes occurred in the nine subjects with severe malnutrition. In all, five and eight of the subjects with mild and moderate malnutrition had 11 and 22 episodes of FN, respectively, compared to 20 episodes in 12 well-nourished patients. The study was limited by the small sample size and the number of subjects in each nutritional class but exclusion of subjects with previous therapy which could have had an effect on the findings is a potential strength. In a retrospective study in India by Ramamoorthy *et al*[49], malnourished patients with ALL had a higher risk of recurrent fever from FN compared to their counterparts with normal nutritional status. In all, 38 recurrent febrile episodes were reported in 113 patients (14.8%). Severely underweight (< -3 z score) was an independent predictor of recurrence of FN. Differences in the states of malnutrition (acute vs. chronic), the variable use of WHO measurements and absence of methods for assessing nutrition are amongst the reasons which make comparison between studies difficult.

Mucositis: Mucositis complicated by neutropenia has been identified as a risk factor for FN but not an independent predictor of outcome by Badr *et al*[22]. The mean neutrophil count of subjects with mucositis was significantly lower than those without mucositis (201.2 vs 262.3; p = 0.01). Also, the mean duration of FN was longer in subjects with mucositis compared with their counterparts (12.3 vs 9.8 days; p = 0.07). Rondinelli *et al*[39] reported similar findings. A total of 36/68 (52.9%) with mucositis had severe infection compared to 57/215

(26.5%) with no mucositis. Castelan-Martinez *et al*[14] also reported mucositis as a risk factor for FN in children with solid tumours receiving cisplatin-based chemotherapy.

Central Venous Access Devices (CVAD): CVADs are commonly used in the paediatric oncology setting. It reduces the pain associated with frequent peripheral venous cannulation for investigations and administration of treatment. It also reduces the risk of chemotherapy extravasation from peripheral lines. It contributes to improved quality of life of paediatric oncology patients. Conversely though, CVADs are a potential source of infection due to direct access to the blood stream and potentially frequent accessing of the device. They have been reported as a major contributor to infection in cancer. Studies have identified CVADs as a risk factor for FN and for bacterial infection in children with cancer[12,39,50,51].

In a prospective study by Castagnola *et al*[12] in Italy, the presence of CVADs was identified as a risk factor for FN. The rate of FN per thousand neutropenic days was significantly higher in subjects with CVADs compared to those without (22.7 vs 4.92; p = 0.0039). Rondinelli *et al*[39] also identified CVADs as an independent risk factor for severe infectious complications. A total of 73 (43.2%) patients with CVADs had severe infections, significantly higher than the 20 (17.5%) subjects without central lines who also had severe infection (p = 0.001). In a prospective study done at the three largest paediatric haematology/oncology centres in Israel, blood stream infection was identified as a common complication of CVADs. Over a 25 month period, 423 CVADs were inserted in 262 children with cancer. At least one episode of blood stream infection occurred in 152 patients with an incidence of 1.95 per 1000 patient days and at least one blood stream infection was recorded in 187 CVADs with an incidence of 2.84 per 1000 catheter days[52].

Ethnicity: We recognise that race as a predictor of risk for any clinical complication is problematic by its very nature, but we report previous findings for the sake of completeness.

There is paucity of data concerning ethnicity as a risk factor for FN in cancer. Basu et al[19] reviewed the University Health System Consortium Database for 7 years (1995-2002). Children below 21 years with code of neoplasm and FN information were recruited. Most of the patients were Caucasian (n = 8349, 67%) while African-Americans and Hispanic patients accounted for 10% each of the study population (1262 and 1259, respectively). Other categories included Asians and an unclassified group (10%). The length of hospital stay over 5 days was significantly higher in blacks patients compared to white patients (OR 1.46 vs 1.00) and as well as (OR 1.00 vs 1.95; p = < 0.0001). The finding could not be adequately explained. The likely link of non-Caucasian ethnic group to lower socioeconomic class with a consequently higher risk of infection was considered, however, authors did not review the social classes of the participants. Also, the possibility of a genetic susceptibility was suggested by the authors but in the absence of rigorous genetic interrogation, this is merely cause for speculation.

Shorter time to diagnosis: In a retrospective single centre review of children and adolescents less than 17 years of age with FN, Wicki *et al*[50] reported a significant decline in the risk for FN and FN associated bacteraemia with increase in time (in years) since diagnosis of cancer. The group showed that the relative risk of FN increased linearly with an increase in the number of years to diagnosis and patients diagnosed between the year 2002 and 2004 were 1.7 times more at risk of FN compared to those in which diagnosis was made between 1993 and 1995. (p = < 0.001). Similarly, the result of the risk for associated bacterial infection followed the same trend (RR 0.07 (0.04 - 0.15; p = < 0.001). Intensity of chemotherapy, which reduces with duration of treatment was corrected for, and hence could not account for this finding.

Prior febrile neutropenia: In the study by Wicki *et al*[50] prior occurrence of FN was found to be an independent risk factor for FN and bacterial infection. The relative risk for FN in these patients was 2.10 (1.68-2.62), (p = < 0.001). Similar findings were documented in a study involving adults with cancer[53]. Reports on several episodes of FN in the same patients in some studies could also point to a higher number of episodes of FN in those cases but this was not a focus[24,54]. In contrast, Limvorapitak *et al*[55] reported an increased risk of FN in individuals on their first chemotherapy regimen compared to those on subsequent chemotherapy regimens. The study involved subjects with haematologic malignancies seen at Thammasat University Hospital, Thailand over a 5 year period.

Bone Marrow Involvement: There is paucity of data on solid tumour with bone marrow involvement as a risk factor for FN in children with cancer[50]. Wicki *et al*[50] identified bone marrow involvement as an independent risk factor for FN [rate ratio 2.02 (95% Cl = 1.57–2.59) p = < 0.001]. Haematopoietic stem cells produced in the bone marrow plays an essential role in immunity. Infiltration of the bone marrow by cancer cells that leads to either reduced production or the production of immature blood cells results in defective immune system functioning and an increased risk of infection in individuals with metastatic cancers to the bone marrow.

TREATMENT FACTORS AS PREDICTORS OF RISK FOR FEBRILE NEUTROPENIA

Chemotherapy regimen: Chemotherapeutic agents are myelosuppressive to varying degrees. This can be broadly classified based on expected duration of severe neutropenia as minimally suppressive, briefly suppressive, strongly suppressive and myeloablative[56]. Severe myelosuppression is not expected following minimally suppressive chemotherapy regimens. At most, either ten days and more than ten days of severe neutropenia is expected with briefly and strongly suppressive drugs, respectively, while haematopoietic stem cell recovery is

required for myeloablative rgimens[56]. Studies have shown that higher intensity chemotherapy regimens are associated with a greater risk of FN in children[14,23,50,57]. Wicki *et al*[50] identified a higher number of episodes of FN and FN associated with bacterial infections to be secondary to increased chemotherapy intensity. Chemotherapy intensity was classified from I to IV as reported by Kern et al[56] and as stated above. In the same institution as Wicki *et al*[50] and with an overlapping of study period, Schlapbach *et al*[57] studied 94 children below seventeen years of age with newly diagnosed cancer or relapsed disease. Using the same classification for chemotherapy intensity by Kern *et al*[56], the authors also reported a significantly increased risk of FN episodes with an increase in intensity of chemotherapy. The risk ratio for FN increased linearly with an increase chemotherapy intensity (briefly, strongly and myeloablative with minimally intense chemotherapy regimen as the reference). (3.76 vs 11.56 vs 14.06, p = < 0.001). However, some studies have not shown a relationship between intensive chemotherapy and the occurrence of FN. In a retrospective study by Sulviani *et al*[23], 15/87 (17%) and 72/87 (83%) patients with FN had high dose and conventional chemotherapy, respectively, and no significant difference between the two groups could be demonstrated (p = 0.129). One possible explanation for the disparity in the finding when compared to studies done in Switzerland could be the large proportion (25%) of missing data in the later study, rather than differences in the classification of chemotherapy intensity.

Radiotherapy: Radiotherapy-induced neutropenia is a common complication with increased risk of infection and FN. Castelan-Martinez *et al* [14] identified radiotherapy as an independent risk factor for FN. A total of 12/87 (13.8%) patients who had FN were exposed to radiotherapy. This was higher than 3/52 (5.8%) of patients who had the same cisplatin based chemotherapy but without FN. Multivariate analysis, showed that the odds ratio was 6.67 (Cl = 1.24-35.94) in the group which received radiotherapy. In contrast, Wicki *et al*[50] did not find radiotherapy to be a risk factor for FN. A total of 29.6% of the patients in this study received

radiotherapy concurrently with chemotherapy. None of the studies reported the radiation dose and no immediate explanation could be provided for the disparity in results.

Haematopoietic growth factors: Granulocyte Colony Stimulation Factor (G-CSF) or Granulocyte Macrophage Colony stimulating factor (GM-CSF) are glycoproteins that primarily regulate granulocyte differentiation and function.[58] They are used in oncology patients to prevent or reduce the duration of neutropenia[59,60]. Inconsistent findings of the benefit of prophylactic GCSF have been reported[12,24,61,62]. Castagnola *et al*[12] reported that G-CSF does not prevent or reduce the risk of FN in children on treatment for cancer. A total of four subjects had G-CSF and 14 were not given the glycoprotein. No significant difference in the rate of FN per 1000 days of risk was observed between subjects that had G-CSF and those without (38.09 vs 27.18; p = 0.143). Castelan-Martinez *et al*[14] identified the administration of G-CSF as a risk factor for FN. A total of 47/66 (54.0%) patients who had G-CSF developed FN which was higher than 40/73 (46%) patients with no prophylactic G-CSF administered that had FN (OR 1.3, 95% Cl = 1.0-1.7). Calderwood *et al*[62] also reported that GM-CSF did not prevent FN in children on the intensification phase of chemotherapy given at a dose of 5.5 microgram/kilogram (μg/kg) subcutaneously. This was a randomised control study involving 20 cases and 20 controls. The beneficial effect of G-CSF was however, documented by Clarke *et al*[61]. In a randomised clinical trial that involved 17 children with ALL and T-cell non-Hodgkin lymphoma, G-CSF was given during the intensification phase of chemotherapy at a dose of 5μg/kg subcutaneously daily. A significant reduction in the number of FN episodes, duration of neutropenia and days in hospital was observed in the cases compared to the controls. A systematic meta-analysis by Wittman *et al*[63] showed the beneficial effect of G-CSF in children receiving chemotherapy. The incidence of FN was significantly higher in controls (68/400 controls vs 59/404 cases, p = 0.01). There was a significant mean decline of 3.5 days in the duration of neutropenia in the cases and the rate of

documented infection was also lower in the cases, however, this was not significant (20% vs. 25%, p = 0.12). Other factors that could have affected the results of the effect of G-CSF on occurrence of FN was the sample size, with few subjects receiving G-CSF. The review was not able to demonstrate the impact of prophylaxis, given that G-CSF was administered in various studies at different stages of treatment using different doses, making meaningful comparison between studies difficult.

LABORATORY INDICATORS AS PREDICTORS OF RISK FOR FEBRILE NEUTROPENIA

Several studies have been undertaken which identified haematological and biochemical risk factors for FN in children with cancer[12,13,39,43,64]. Some of the investigations include baseline white cell count before chemotherapy commencement, depth of neutropenia during chemotherapy, serum haemoglobin level and platelet count.

Peripheral Blood Cells: Low baseline and a rapid decline in white cell counts have been documented as risk factors for FN mostly in adults[13,43,65]. Castagnola *et al*[12] identified low baseline granulocyte as a risk factor for FN in children with central nervous system tumours. The rate of FN per a thousand neutropenic days was highest in severely neutropenic patients ($\leq 100/mm^3$) and intermediate and lowest in subjects with neutrophil counts of 500-101/mm3 and $501/mm^3$ and above [11.07 (7.42-16.52) vs. 24.60 (16.35-37.02 vs. 42.99 (27.42-67.40), p = < 0.0001], respectively. Low leucocyte and granulocyte counts are also risk factors for severe infection in FN. Rondinelli *et al*[39] identified leucocyte and granulocyte counts < 0.5 x 10^9/L as significant risk factors for severe infection. In patients with leucocyte counts ≥ 0.5 x 10^9/L, 47/166 (28.3%) had severe infection compared to 46/117 (39.3%) with a leucocyte count of 0.5 x 10^9/L and below (p = 0.021). Similar findings were observed with granulocytes < 0.5 x 10^9/L. Perez-Heras *et al*[66] reported that patients with a lymphocyte count of ≤ 0.5 x 10^9/L were admitted for a significantly higher number of days (above ten).

Low baseline haemoglobin and platelet count were also reported as risk factors for FN in the same study. In children, Perez-Heraz *et al*[66] also reported longer duration of admission above ten days in patients with baseline haemoglobin level < 9 g/dl. Also, subjects with a baseline platelet count < 50 x 10^9/L had significantly higher hospital stays compared to those with higher platelet counts.

RISK STRATIFICATION AND OUTCOMES OF FEBRILE NEUTROPENIA

The stratification of patients with FN as being at low or high risk for adverse outcomes has yielded varying results. This is due to different parameters for adverse outcome being used by different authors. Risk stratification helps to identify individuals that can be treated as out-patients or with few doses of intravenous antibiotics compared to those at risk of higher morbidity or mortality. Scoring parameters to identify individuals at risk for adverse outcome of FN have been reported. Non-uniformity in scoring assessments is mostly due to differing procedures and protocols adopted in the various study centres. Clinical and laboratory parameters that predict adverse outcomes in previous studies have included: absolute monocyte count, blood culture proven bacterial infection, admission to intensive care units, severe sepsis/septic shock, prolonged hospital admission for FN and FN related death.

In Canada, Klaassen *et al*[67] did a prospective validation study that predicted the risk category of adverse outcome in children with FN. Significant bacterial infection, (defined as a blood or urine culture positive for bacteria), a chest radiograph with interstitial or lobar consolidation and unexpected death from infection, were classified as adverse outcomes. Independent predictors of those at higher risk of adverse outcomes included bone marrow disease, general appearance of an unwell child, a peak oral temperature of more than 39^0 C (or its equivalent) and a monocyte count below 0.1 x 10^9/L. Rackoff *et al*[26] also reported a low absolute monocyte count and high grade fever as predictors of adverse outcome in paediatric oncology

FN cases. This prospective study was conducted in Indianapolis in 72 patients. An absolute monocyte count of ≥ 100 cells/L was defined as a low risk for bacteraemia. In all, 17% of the patients classified as low risk did not have bacteraemia as compared to 19% of the intermediate risk patients (defined as absolute monocyte count of < 100 cells/L and temperature < 39.0^0 C) and 48% of the high risk patients (absolute monocyte count of < 100 cells/L and temperature of ≥ 39.0^0 C) in individuals with proven bacterial infection. Besides bacteraemia, absolute monocyte count was also identified as a risk factor for ICU admission and death by Baorto *et al*[25]. Patients admitted to the ICU and those who died had an absolute monocyte count < 30 cells/mm^3. This finding was limited by the low number of patients that required ICU care (n =11, 0.9%) and those who died (n = 3, 0.3%).

Alexander *et al*[47] reported on risk prediction of FN in children with cancer. Risk stratification was based on disease type, the presence of comorbidities and the presence of focal infection. AML, Burkitt-lymphoma, subjects with ALL on induction chemotherapy and patients with progressive or relapsed disease were classified as high risk based on an anticipated neutropenia of more than seven days. Adverse outcomes studied included duration of neutropenia, bacteraemia, length of hospital stay and death. The duration of neutropenia was significantly higher in high risk subjects than those at lower risk of an adverse outcome (7 vs. 4.7 days, p = < 0.001). Subjects classified as high risk for adverse outcomes had significantly more events compared to those categorised as lower risk (41% vs 4%, p = < 0.001). Also all disease mortality (23%) occurred in the high risk group but only one death was related to FN. In a prospective multi-centre study, Ammann *et al*[68] developed a score to predict the adverse effect of FN in children with cancer. Unlike previously reviewed articles, white cell count and not its differential, such as absolute monocyte count, was one of the predictive parameters. Other predictors for adverse outcomes were preceding chemotherapy more intense than ALL maintenance which was scored four, a haemoglobin of at least 9g/dL with

the highest score of five, while a platelet count < 50g/dL and leucocyte count < 0.3g/dL were allocated a score of three each. A score (sum of weights) of more than or equal to nine predicted future adverse events. Adverse outcomes studied included serious medical complications such as death, ICU admission, potentially life threatening complications as judged by the physicians, microbiologically defined infection and radiologically confirmed pneumonia. Adverse outcomes were seen in 122 (28.8 %) episodes of FN. On multivariate analysis, a diagnosis of AML, preceding chemotherapy more intensive than ALL maintenance, a haemoglobin level ≥ 9 g/dL, a leucocyte count < 0.3g/L, an absolute phagocyte count < 0.1 g/L (neutrophils and monocytes not included) and a platelet count < 50 g/L predicted risk of an adverse outcome. Late predictors of adverse outcomes within 24 hours of admission and not just at presentation were also assessed by the authors. Late assessment was shown to be a better predictor of adverse outcomes than assessment done at admission. A score of more than nine predicted future adverse events (AEs) in 47/ 57 (82.4%) episodes with AEs. Low risk of adverse outcome was classified based on a score of less than nine in 35% of the episodes with 92% sensitivity, 45% specificity, 93% negative predictive value, and 40% positive predictive value. In order to further identify the effect of a haemoglobin > 9g/dL as a risk factor for AEs, the authors evaluated the likely pathophysiology and reported that dehydration in subjects that did not received blood transfusion had a direct relationship with AEs which was not observed in patients who received recent blood transfusion. Therefore, the high haemoglobin in patients that had adverse outcomes was as a result of haemoconcentration[69]. Evaluation of adverse outcomes at point of admission and extending into 24 hours of admission is a strength of this study compared to previously reviewed studies[26,47,67] which helped to focus on evolving clinical features in affected patients.

In an observational study, Bothra *et al*[70] reported on predictors of adverse outcomes defined as the presence of at least one of the following: death, invasive infection haemodynamic instability defined as hypotension or hypoxia with chest retractions. Adverse outcomes occurred in 53/155 (34.2%) patients. Predictors of adverse outcomes included history of more than two episodes of FN, prior commencement of oral antibiotics and a chest radiograph abnormality.

In a prospective study by Das *et al*[71] in India, undernutrition was included in the parameters tested as a predictor of adverse outcome in FN. An indigenous model used in this study addressed the major issue of malnutrition common in LMIC. A total of 264 recruited subjects had 414 FN episodes. Undernutrition was scored two points, time since last chemotherapy less than or equal to seven days (two points), presence of a clinically obvious, non-upper respiratory focus of infection (two points), CRP level > 60 mg/L (five points), and an ANC ≤ 100/μL at admission (two points). Subjects with a score below seven points were classified as low risk. Almost equal proportions of subjects were at low and high risk of an adverse event (50.2% vs. 49.8%). The adverse outcomes evaluated were mortality, microbiologically defined infection (MDI), ICU admission, metabolic and non-metabolic severe complications. A low serum albumin < 2.5 g/dL was identified as an independent predictor for an adverse outcome. Other predictors identified were an elevated CRP and non-upper respiratory tract infection. Patients with a non-upper respiratory focus of infection had a higher odds ratio of developing complications, and these complications were associated with higher odds of death [OR 2.80 (95% Cl = 1.59-4.93, p = < 0.05].

A hospital stay of over 5 days has been reported as an adverse event in children with FN. This parameter was not included by other previous studies except one. There is an increased risk of invasive fungal infection in FN lasting more than five days[34]. In a large prospective

US-based study, Basu *et al*[19] reported that AML or multiple cancers defined as having more than one type of cancer which authors did not specify were associated with an increased risk of death as compared with other cancer types. A diagnosis of bacteraemia/sepsis significantly increased the risk of death (9% bacterial infection vs. 2% in non-bacterial infection). Similarly, hypotension, pneumonia, and fungal infections were significantly associated with an increased risk of death. Similar parameters also predicted an increased risk of prolonged hospital admission. One of the factors that affected outcome generally in children with FN was prolonged hospital stay (admission beyond five days). Its evaluation as an outcome is a strength that points to a clinically evaluable parameter that cuts across different countries.

The Swiss Paediatric Oncology Group (SPOG) clinical decision rule for classification of FN in children involves children admitted to hospital with fever ($\geq 38.0^0$C) and neutropenia with an absolute neutrophil count < 1.0 x 10^9 cells/L. Children with scores less than nine are classified as low risk for an adverse outcome based on the following parameters: admission haemoglobin ≥ 9g/dL (score, five), preceding chemotherapy more intensive than ALL maintenance (score, four), an admission total white cell count < 0.3 x10^9/L (score, three) and an admission platelet < 50 x10^9/L (score, three)[72].

At Tygerberg Hospital in Cape-Town, South Africa, Green *et al*[28] set out to validate the predictor parameters previously published by Ammann *et al*[68]. A total of 52 children aged < 16 years had 100 episodes of FN for a period of two years (22 January 2014 to 22 January 2016). Adverse outcomes occurred as previously assessed by Ammann *et al*[68] in 40 (40%) of the FN episodes. Out of 55 subjects classified as low risk (score < nine), adverse outcomes occurred in 18 (45%) patients and 21/42 (55%) high-risk episodes had adverse outcomes (score ≥ nine) This yielded a sensitivity of 60%, specificity 65%, positive predictive value 53%, negative predictive value 71% which was lower than the predefined sensitivity of ≥

90%. Differences in the study population as well as those who had adverse outcomes were some of the reasons proffered by the authors for the low sensitivity and poor validation of the studied parameters.

In the Multinational Association for Supportive Care in Cancer (MASCC) study, a risk-index score ≥ 21 was used to identify low-risk adult patients. This scoring system is widely used in assessing risk in adults with FN and in some paediatric cases. In 756 patients, predictive factors for low risk FN were the absence of symptoms or mild symptoms (weight, five), absence of hypotension (weight, five), absence of chronic obstructive pulmonary disease (weight, four), the presence of a solid tumour or the absence of a previous fungal infection in patients with haematologic malignancies (weight, four),), moderate symptoms (weight, three), out-patient status (weight, three), the absence of dehydration (weight, three), and age < 60 years (weight, two). The positive predictive value was 91% with a specificity and sensitivity of 68 and 71% respectively[73].

MANANGEMENT OF FEBRILE NEUTROPENIA

Proper evaluation of the febrile and neutropenic child is important. The child's general appearance as well as the identification of a focus of infection is key. This is a critical step in assignment of risk infection in affected individuals.

Investigations required include a full blood count with a differential count, a blood culture from a peripheral line as well a CVADs (if present). Urine, sputum, stool and radiographic imaging are done based on clinical presentation and local guidelines.

FN is conventionally treated with broad spectrum antibiotics.[74] For those at low-risk of an adverse event, a starting dose of intravenous antibiotics and subsequent switch to oral antibiotics has been advocated[34]. The choice of antimicrobial agent should depend on the

clinical presentation of patients, the microbial sensitivity (once known), the cost of locally available treatments and local epidemiological bacterial isolates.[75] The duration of treatment with antibiotics depends on the culture result, the time of resolution of fever and the well-being of the child.

The International Paediatric Fever and Neutropenia Guideline Panel recommend monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem as empirical therapy in paediatric high-risk FN. The addition of a gram negative agent or glycopeptide is recommended for unstable patients and in centres with high rates of antimicrobial resistance[30]. SPOG recommends intravenous piperacillin-tazobactam in children that are not allergic to beta lactam antibiotics. Oral amoxicillin-clavulanic acid and ciprofloxacin should be considered in subjects at low risk for adverse outcomes that can be managed as out-patient.[72]

Haeusler *et al*,[76] employed home-based care for subjects identified as low risk for FN in children ≤ 18 years with cancer. The authors identified low risk of adverse outcome using the SPOG risk index with a score below nine as the threshold for those at low risk for an adverse outcome. Patients at low risk for FN were managed as out-patients and were reviewed daily in the hospital or at home by a nurse who administered parenteral antibiotics. Over an 18 month period, 292 episodes of FN were seen and 132 (45%) were classified as low risk for FN but only 44 (33%) were assigned to home based care. In all, 36 patients required an in-hospital medical review for 32 FN episodes, for conditions such as severe thrombocytopaenia requiring platelet transfusion, a positive bacterial culture and CVAD complications. Hospital readmission occurred in eight (13%) subjects and there were no deaths. The programme positively recorded a significant reduction in long hospital stays for both low and high risk subjects with FN and 291.2 in-hospital beds were saved. Risk stratification and home

treatment of subjects at low risk for adverse outcomes resulted in reduction of hospital stays in affected individuals.

Antifungal therapy is recommended in patients at high risk of invasive fungal disease (IFD) such as AML, high-risk or relapsed ALL, children undergoing allogeneic haematopoietic stem cell transplant, patients with prolonged neutropenia and children on high-dose corticosteroids[30].

CHAPTER THREE

SUBJECTS AND METHODS

Study Site:

The study was carried out at the oncology unit of Red Cross War Memorial Children's Hospital (RCWMCH), Cape-Town, South Africa. RCWMCH is the largest children's hospital in sub-Saharan Africa. The oncology unit serves as a major referral centre and manages all types of childhood cancer. Approximately ninety to one hundred new oncology cases are seen per year. The unit has a 17 bed capacity which includes three high care beds, a negative and two positive pressure ventilation rooms for highly infectious diseases and post-transplant patients, respectively. The unit accommodates three consultants, two to four fellows in training and trained oncology nurses. The duty shift operates with a consultant-on-call and a senior nurse after hours and on the weekends, while the full cadre of staff works during office hours. The unit has access to the ICU of the hospital and patients are admitted there as required.

Study Design:

This study was a retrospective cohort study.

Study Duration:

Data review was done from 1st January 2017 to 31st December 2019.

Study Population:

The study population comprised of children newly confirmed with diagnosis of cancer on chemotherapy within the study period. Each episode of FN was evaluated.

Sample Size Determination:

The study involved all children with diagnosis of cancer admitted for FN during the study period.

Approval for the study was obtained from the Health Research Ethics Committee of University of Cape Town, South Africa as well as the Departmental Research Committee, RCWMCH (HREC 351/2020, approved 2nd July 2020). Data was stored in the University of Cape Town computer available in the unit. This was password protected and only the investigator and supervisors had access to the information to ensure confidentiality. All subjects were also anonymised.

This is a retrospective study with no direct involvement of patients and eliminating the need for consent. This proposed study fulfils the requirement for non-maleficence since no harm came to any patient. Also, confidentiality was strictly adhered to, to prevent harm associated with information disclosure.

The benefit from the study was in the identification of a risk stratification for FN that would serve as a basis for the development of a protocol to guide the management of FN on an in-patient or out-patient basis. This will result in reduction of hospital admissions; reduce risk of nosocomial infections and ultimate increase in quality of life of patients and their families.

Recruitment of Subjects:

Data of children with biopsy-proven solid and haematologic malignancies on chemotherapy was extracted. Episodes of FN in each subject that occurred over the study period were

evaluated. All patients with FN were assessed at most within 12 hours of admission by an oncologist.

Inclusion Criteria:

1. Confirmed haematologic malignancies, biopsy proven solid tumors and radiologically and/or histologically confirmed brain tumours diagnosed within the study period who received chemotherapy.
2. Children below eighteen years with confirmed diagnosis of malignancy

Exclusion Criteria:

1. Data of children with FN with missing data.
2. Children with FN with diagnosis of cancer prior the study period.
3. Children with non-conclusive diagnosis of malignancy.
4. Data with insufficient information such as last date of chemotherapy prior to FN and adverse outcomes

Data Collection Method:

The International Classification of Diseases (ICD) 10 code is currently in use at RCWMCH. Data of all new admissions are entered into a hospital based registry and information is updated regularly by dedicated staff. Information of admissions and daily management are entered in hospital folders as well as in separate oncology folders which are kept in the unit as record document of treatment. The data of children with confirmed diagnoses of cancer during the study period was retrieved by folder review. Each folder was examined for clinical and laboratory information to ascertain risk of FN which included age at cancer diagnosis,

sex, type of cancer, presence of bone marrow involvement in solid tumors, presence of CVADs, concurrent radiotherapy, intensity of chemotherapy, presence of mucositis and use of prophylactic granulocyte colony stimulating factor (G-CSF).

The intensity of chemotherapy was classified during the period of FN: (i). Minimally suppressive with unlikely risk of FN as for those patients on maintenance chemotherapy (ii) briefly myelosuppressive chemotherapy (expected duration of severe neutropenia less than ten days) such as those receiving induction and consolidation therapy for precursor-B ALL and chemotherapy for solid tumors except those with relapsed disease who had more intensive chemotherapy, (iii) strongly myelosuppressive chemotherapy, (more than ten days) such as therapy for acute myeloid leukemia (AML) and intensive chemotherapy for haematolymphoid malignancies; and (iv) myeloablative chemotherapy requiring haematopoietic stem cell transplantation (HSCT)[56]. Chemotherapy exposure was defined as the cumulative duration of chemotherapy of a specified intensity. The cumulative duration of neutropenia was defined as the sum of weeks with at least one documented severe neutropenia[57].

All FN episodes from time of diagnosis were extracted. Furthermore, the numbers of episodes of FN on each cycle of chemotherapy course during the study period were obtained. In patients with FN, information such as occurrence of FN during admission or on presentation as an out-patient, appearance at diagnosis/time of FN and focus of infection were obtained. Radiological confirmation of pneumonia and positive bacterial or fungal infection were extracted for each subject. Other laboratory parameters such as haemoglobin, absolute neutrophil count and platelet count recorded at each FN admission were captured. Duration of hospital stay on account of FN was ascertained. Prolonged hospital admission was defined as

a hospital admission of more than five days[19]. All extracted information was stored electronically in a *Microsoft-Access*™ spread sheet.

Definitions:

***Febrile neutropenia*:** FN was defined as axillary temperature (≥ 38.0^0C) and neutropenia (ANC < 1.0 x 10^9 cells/L).[10]

Hypotension: Systolic blood pressure below the 5th centile for age and sex[77].

***Severity of neutropenia*:** Very severe = ANC < 0.1 x 10^9 cells/L; severe = ANC 0.1 to < 0.5 x 10^9 cells/L; moderate neutropenia 0.5 x 10^9 cells/L to < 1.0 10^9 cells/L, and no neutropenia is ANC ≥ 1.0 10^9 cells/L[78].

***Absolute phagocyte count (APC)*:** Was defined as the sum of segmented neutrophils, bands, and monocytes[79].

***Significant clinical focus of infection*:** Presence of apparent localising signs/symptoms likely to be causing fever either at the first presentation, or during the course of FN[29].

***Adverse Outcome*:** An adverse event in the current proposed study was defined as serious medical complication such as death, a complication requiring ICU admission and a potentially life-threatening complication as judged by the treating physician as a result of infection, a microbiologically defined infection (positive bacterial or fungal culture from a normally sterile site and detection of a viral antigen by PCR) or radiologically confirmed pneumonia[68]. In addition, prolonged hospital admission for FN more than five days was documented as adverse outcome.

***Prolonged length of admission*:** Defined as hospital admission for more than five days primarily for FN[19].

The validation of Risk for Adverse Outcomes

The Swiss Paediatric Oncology Group (SPOG)[68] FN Risk Index was used as a predictor of adverse outcome. Individuals with a score below nine were classified as low risk for an adverse event and subjects with score of at least nine were classified as high risk for an adverse event. The scoring parameters are shown below:

Parameters	**Yes**	**No**
Preceding chemotherapy more intensive than ALL maintenance	4 ☐	0 ☐
Admission haemoglobin ≥ 9 g/Dl	5 ☐	0 ☐
Admission total white cell count < 0.3 x10^9/L	3 ☐	0 ☐
Admission platelet < 50 x10^9/L	3 ☐	0 ☐
Total Score		

DATA ANALYSIS

All data was anonymised and stored in an electronic format in a secure location with restricted access which was password protected. Data was stored in a *Microsoft Access*™ spreadsheet and analysed using *Statistical Package for Social Sciences* (SPSS) version 20.0. The test of normality for continuous variables was assessed using graphical visualisation and the Kolmogorov-Smirnov test. Patients' demographics were summarised as frequencies and percentages. Continuous variables were summarised using mean and standard deviation if normally distributed while median and interquartile range was computed for skewed data.

Comparison among normally distributed continuous data was carried out using the Independent student t-test and analysis of variance (ANOVA) test while comparison of non-parametric data was done using appropriate non-parametric equivalents, Mann-Whitney test or Kruskal-Wallis test. Comparisons between categorical data were made using the Chi square or Fischer exact test when appropriate.

To determine risk factors for FN, risk ratios (RR) with 95% CI was estimated using the ratio between the probability to develop FN in subjects with proposed risk factors and the probability to develop FN in subjects without the proposed risk for FN. A multiple logistic regression was conducted to estimate the independent risk factors for developing FN and adverse outcome**.** Diagnostic parameters including sensitivity, specificity, positive predictive value and negative predictive value and accuracy was calculated for the SPOG risk index assessment in predicting adverse outcome. Receiver operating characteristics was used in predicting area under curve (ROC) and optimal cut in predicting adverse outcome. Probability value less than 5% (0.05) was considered to be statistically significant using 95% confidence interval. Charts including bar, pie, box and whisker plots were used for data presentation where appropriate.

CHAPTER FOUR

RESULTS

Demographics of all cancer subjects

A total number of 256 oncology diagnoses were made over the study period. Analysis was performed on 254 (99.2%) patients in this current study as shown in Figure 1.

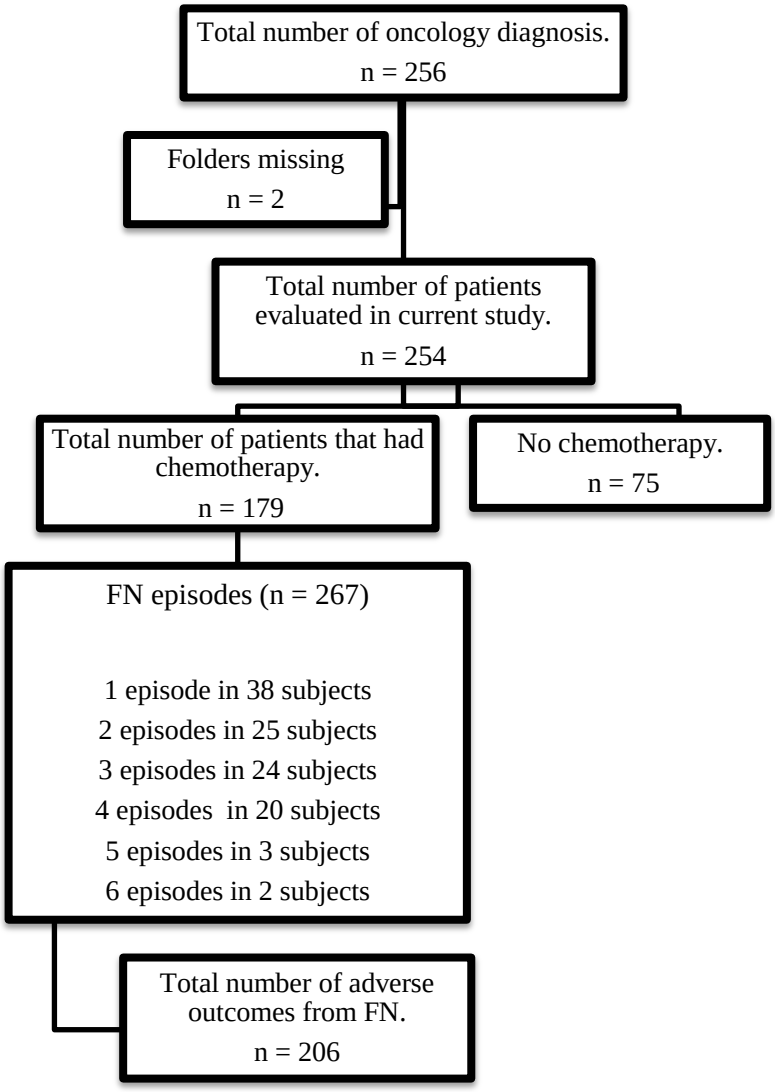

Figure 1: Flow sheet of study subjects

Demographic Characteristics of Patients who did not received chemotherapy (n = 75)

In table I, the patient group who did not receive chemotherapy were mainly comprised of those with brain tumours. Subjects with retinoblastoma were all Stage 1, (N_1,C_0,S_0) and required no chemotherapy. A patient with stage IV Wilms tumour with metastases to the brain and lungs was palliated upfront and another with stage V disease was subsequently transferred to another unit. Patients with anaplastic medulloblastoma, rhabdoid tumour of kidney and alveolar rhabdomyosarcoma were also palliated. A patient with adrenal ganglioneuroblastoma (low risk stage I) who had a complete excision had no chemotherapy and a patient with meningioma (WHO grade 1) had a surgical resection and subsequent radiotherapy only. The last patient with stage 1 neuroblastoma did not require any chemotherapy.

Table I: Characteristics of subjects who received no chemotherapy (n = 75)

Age at diagnosis (IQR)	6 (3-10 years)
Male: Female	1.1:1

Type of cancer	**No of subjects**	**Percentages**
Brain Tumours		
Astrocytoma	17	22.7
Hypothalamic glioma	10	13.3
Ependymoma	7	9.3
ATRT	6	8.0
Midline glioma	4	5.3
Choroid plexus carcinoma	3	4.0
Pineoblastoma	2	2.6
Meningioma	1	1.3
Craniopharyngioma	1	1.3
Medulloblastoma	1	1.3
Solid tumours		
Retinoblastoma	8	10.6
Chondrosarcoma	4	5.3
Hepatocellular carcinoma	2	2.6
Wilms tumor	2	2.6
Juvenile granulosa cell tumour	2	2.6
Mature teratoma	2	2.6
Rhabdomyosarcoma	1	1.3
Neuroblastoma	1	1.3
Rhabdoid tumour of the kidneys	1	1.3

ATRT = Atypical teratoid/rhabdoid tumour of the brain.

Demographic Characteristics of Patients that received Chemotherapy (n = 179)

A higher proportion of subjects were males (57.1%) with a male to female ratio of 1.3:1. The minimum and maximum age at diagnosis was three weeks and 16 years respectively. The median age at diagnosis was five years (IQR 2 to 8 years). The median age at diagnosis for females was 6 (IQR 2.7 - 8.5 years). Males had a median age at diagnosis of five years (IQR 2 - 8.5 years). There was no significant difference of age at diagnosis in either males or females (χ^2 = 16.712, p = 0.938). Most subjects who had received chemotherapy were less than six years old (Figure 2).

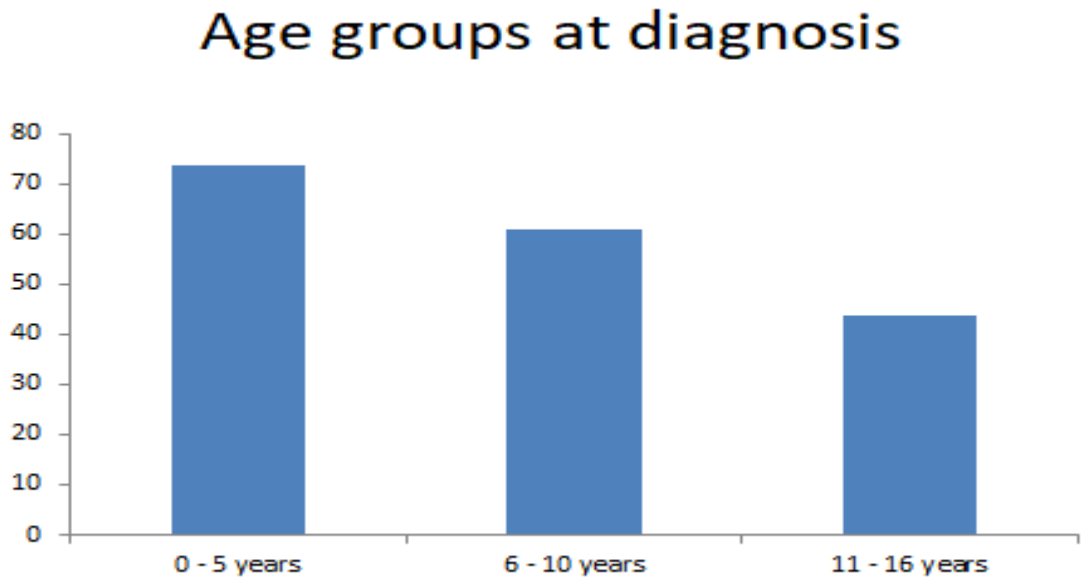

Figure 2: Proportion of subjects according to age at diagnosis.

Patterns of Disease in Patients who received Chemotherapy (n=179)

A. Patients with Haematolymphoid Malignancies (n = 94)

Sixty- four patients with haematolymphoid malignancies had leukaemia (ALL, AML and CML). In all, 30 patients had lymphomas (25 NHL and five classical HL) and eight patients underwent stem cell transplantation (5 AML, 2 ALL and 1 CML blast crisis). These are shown in Table II.

Table II: Haematolymphoid malignancies in study subjects (n = 94)

Disease types/statuses	**Number of subjects**	**Percentages**
Haematolymphoid malignancies		
A. Leukaemia	64	
ALL	*46*	***71.9***
i. Standard risk	15	32.6
ii. High risk	31	67.4
AML	17	***26.6***
CML	1	***1.5***
B. Lymphoma		
NHL	*25*	
a. Burkitt leukaemia	1	***4.0***
b. Burkitt lymphoma	24	***96.0***
i. Group A	1	4.2
ii. Group B	6	25
iii. Group C	10	41.7
c. Lymphoblastic T cell	5	20.8
d. Lymphoblastic B cell	1	4.2
e. ALCL	1	4.2
HL	*5*	
a. Mixed cellularity	3	***60.0***
b. Nodular sclerosis	2	***40.0***
Allogeneic SCT	**n = 179**	
No	171	96.8
Yes	8	3.1

ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; CML = chronic myeloid leukaemia; NHL = non Hodgkin lymphoma; HL = Hodgkin lymphoma; ALCL = Anaplastic large cell lymphoma; SCT = stem cell transplant

B. Patients with Solid Tumours (n = 70)

The disease profile of patients with solid tumours is represented in table III with neuroblastoma (14) and rhabdomyosarcoma (13) and Wilms tumour (12) being most commonly encountered. Stages for the neuroblastoma, rhabdomyosarcoma and Wilms tumour are shown. The group designated as *"other"* were comprised of one tumour in each of the following categories: malignant rhabdoid tumour of the kidney, malignant peripheral nerve sheath tumour, sarcoma (not-otherwise specified), adrenocortical carcinoma, Ewing's sarcoma, synovial sarcoma, chondrosarcoma, hepatocellular carcinoma and embryonal sarcoma of the liver.

Table III: **Classification of non-haematolymphoid Solid Tumours (n = 70)**

Disease type	**n = 70**	**Percentages**
Neuroblastoma	14	***20.0'***
Stage 3	2	14.3
Stage 4	12	85.7
Rhabdomyosarcoma	13	***18.6'***
Stage 1	3	23.0
Stage 2	1	7.7
Stage 3	4	30.8
Stage 4	5	38.5
Wilms tumour	12	***17.1'***
Stage 1	1	8.3
Stage 2	1	8.3
Stage 3	8	66.7
Stage 4	2	16.7
Osteosarcoma	8	***11.4'***
Localized	2	25.0
Metastasized	6	75.0
Retinoblastoma	5	***7.1'***
Stage 1 (N_1,C_2,S_0)	4	80.0
Stage 2	1	20.0
Hepatoblastoma	3	***4.3'***
Extracranial GCT	3	***4.3'***
Disseminated Kaposi sarcoma	2	***2.8'***
CCSK	2	***2.8'***
Others	8	***11.4'***

N_1 = prelaminar invasion of tumour; C_0 = choroid negative; S_0 = no scleral involvement; C_2 = massive choroid invasion; GCT = germ cell tumour; CCSK = clear cell sarcoma of kidney. ' = Percentages in total number of subjects with solid tumour with total of 70.

C. Patients with Brain Tumours (n = 15)

Fifteen patients with brain tumour had chemotherapy. Astrocytoma and pinealoblastoma were most commonly encountered during the study period as shown in table IV.

Table IV: Classification of subjects with brain tumour that received chemotherapy:

Brain tumour	**n = 15**	**Percentages**
Astrocytoma (WHO grade 1)	5	**33.3**
Pineoblastoma (High risk)	5	**33.3**
Medulloblastoma	2	**13.3**
Desmoplastic	1	50.0
Anaplastic	1	50.0
Optic pathway glioma (Grade 1)	2	**13.3**
Ependymoma (Grade III)	1	**6.7**

WHO = World Health Organisation

Patients with Advanced Disease (n = 70)

Amongst the total number of patients who received chemotherapy (n = 179), 23 patients with non haematologic diseases had bone marrow involvement and 70/179 (39%) had progressive or relapse disease. Table V gives more details about the specific diagnoses of the latter group. Eight patients designated as others had a single diagnosis of the following tumours: ependymoma, sarcoma (not-otherwise specified), retinoblastoma, germ cell tumour, optic pathway glioma, rhabdoid tumour of the kidney, malignant peripheral nerve sheath tumour and Hodgkin lymphoma.

Table V: Classification of Patients' with Advanced Disease (n = 70)

Disease Relapse/Progression	**n = 179**	
No	109	60.9
Yes	70	39.1
Specific diseases with relapse/progression	**n = 70**	
ALL	10	14.3
Neuroblastoma	9	12.8
AML	8	11.4
Osteosarcoma	4	5.7
NHL	4	5.7
ATRT	4	5.7
Midline glioma	4	5.7
Hypothalamic glioma	3	4.3
Astrocytoma	3	4.3
Pineoblastoma	3	4.3
Choroid plexus tumour	3	4.3
Wilms tumour	3	4.3
Medulloblastoma	2	2.8
Rhabdomyosarcoma	2	2.8
Others	8	11.4
Bone Marrow Involvement in non-haematologic malignancies	***n = 84***	
No	61	72.6
Yes	23	27.6

ALL = Acute lymphoblastic leukaemia; AML = acute myeloid leukaemia, NHL = Non Hodgkin lymphoma; ATRT= Atypical teratoid/rhabdoid tumour

Episodes of Chemotherapy Induced Febrile Neutropenia (n = 179)

In the 179 patients who received chemotherapy, at least one episode of FN was recorded in 112 (62.6%) subjects. The highest number of episodes of FN was six which were seen in two subjects (1.8%). Most patients had a single episode of FN (n = 38; 33.9%). In 25 (22.3%) and 24 (21.4%) subjects, two and three episodes of chemotherapy induced FN were recorded. A total of 20 (17.8%) subjects had four episodes of FN while a further three patients (2.7%) had five episodes each. In all, 267 FN episodes were documented. Only 67 (37.4%) patients that received chemotherapy did not have FN. The vast majority of FN episodes (249; 93.2%) occurred in patients following intensive chemotherapy whilst the remaining 18 (6.7%) occurred in subjects on maintenance chemotherapy.

Chemotherapy reduction following FN occurred in 18 (16.1%) out of 112 subjects with FN while 37.5% (n = 42/112) patients had delay in chemotherapy due to FN.

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Chemotherapy Status in Study Subjects:

The duration in days preceding the onset of fever in a neutropenic patient ranged from 5 to 25 days (median ten days (IQR 8 -14 days). One (0.5%) subject was transferred to another centre to complete chemotherapy treatment. Three patients were lost to follow up while on intensive chemotherapy, of which two had an episode of FN each that was treated at the study centre. The majority of patients (n = 112; 62.6%) had completed chemotherapy during the study period as shown in Figure 3:

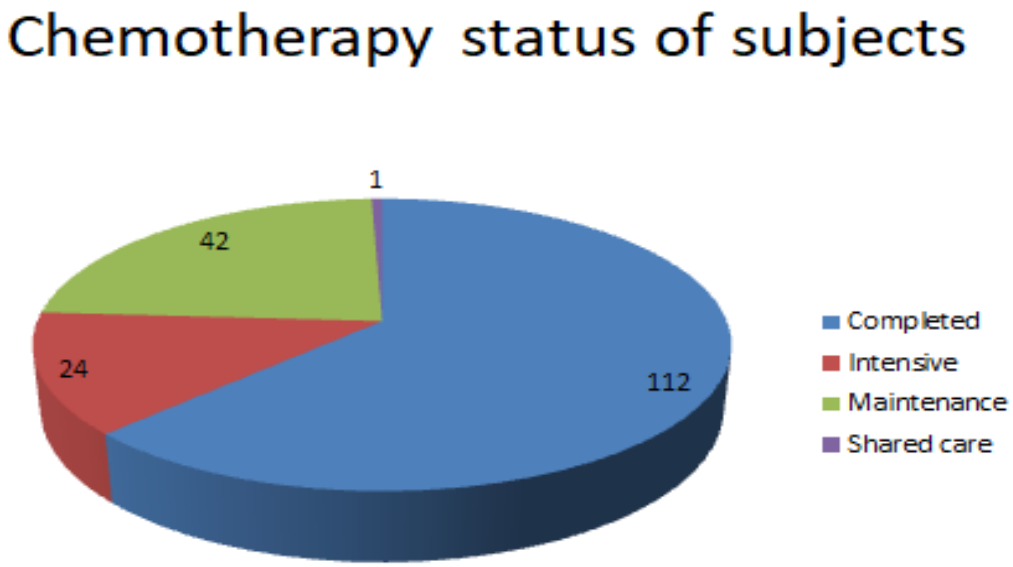


Figure 3: Chemotherapy status of subjects

Clinical and Laboratory Profiles of Patients with Episodes of Febrile Neutropenia (n = 267)

Of the 179 patients that received chemotherapy, only 12 (6.7%) were identified as having co-morbidities (shown in table VI). A specific focus of infection was identified in 38 out of 267 FN episodes (14.2%) with the chest (16), and gut (14) being the commonest sites.

Table VI: Clinical and haematologic characteristics of study subjects based on febrile neutropenia episodes

Variables	Number	Percentage
**Co-morbidities*	n = 12	
Human immunodeficiency virus infection	6	50
Trisomy 21	4	33.3
Attention deficit hyperactivity disorder	1	8.3
Neurofibromatosis 1	1	8.3
Haemoglobin		
Mean (g/dL)	8.31 ± 1.87	
< 9 (g/dL)	167	62.5
≥ 9 (g/dL)	97	36.3
Missing	3	1.1
Neutrophils		
Absolute neutrophil count cells/mm^3 (IQR)	300 (98-138)	
Very severe neutropenia (< 100 cells/mm^3)	193	72.3
Severe neutropenia (100 – 499 cells/mm^3)	55	20.6
Moderate neutropenia (500 – 999 cells/mm^3)	19	7.1
Platelets		
Platelet x10^9/L (IQR)	72 (31-145)	
< 50 x10^9/L	96	35.9
≥ 50 x x10^9/L	169	63.3
Missing	2	0.7
Monocyte		
Absolute monocyte count cells/mm^3 (IQR)	5 (0-17)	
< 50 cells/mm^3	244	91.4
≥ 50 cells/mm^3	18	6.7
Missing	5	1.9
Phagocyte		
Absolute phagocyte count cells/mm^3 (IQR)	24 (5-51)	
< 50 cells/mm^3	194	72.6
≥ 50 cells/mm^3	68	25.5
Missing	5	1.9
Blood transfusion		
Yes	145	54.3
No	119	44.6
Missing	3	1.1
Source of infection identified		
Yes	38	14.2
No	227	85.0
Missing	2	0.7
Focus of infection		
Respiratory	16	36.8
GIT	14	36.8
Renal	7	18.4
Multiple	1	2.6

*Data in total number of subjects (n = 179). IQR = Interquartile range

Patterns of Disease in Patients with Episodes of Febrile Neutropenia

The median age at diagnosis for males with at least one episode of FN with fever was five years (IQR 3 years-9 years) whilst for girls it was at six years (IQR 2.25 -11 years). There was no difference in the age at diagnosis based on sex in patients with FN (χ^2 = 17.763, p = 0.603). In all, 33 out of 46 patients with ALL had FN (71.7%). Amongst this group, patients who were risk stratified as high risk had a higher number of episodes of FN compared to those with standard risk disease [n = 25; (80.6%) vs n = 8 (53.3%), χ^2 = 4.281, p = 0.118], although the difference did not reach the threshold for statistical significance. Table VII shows the relative proportions of patients with FN relative to their diagnoses. It is notable that all patients with AML who received myeloablative chemotherapy developed FN. No significant relationship between the number of FN episodes and the number of chemotherapy courses could be demonstrated.

Table VII: Proportion of subjects with febrile neutropenia according to disease type and treatment intensity

	Presence of FN			
Variables	**Yes (%) 112(%)**	**No (%) 67 (%)**	**Total (%)**	
Type of cancer (n = 179)				χ^2 = 18.410,
Solid	36 (52.1)	33 (47.8)	69 (100.0)	**p = 0.002**
ALL	33 (71.7)	13 (28.3)	46 (100)	
Lymphoma/HD	19 (63.3)	11 (36.4)	30 (100)	
AML	17 (100)	0 (0)	17 (100)	
Brain	6 (40.0)	9 (60.0)	15 (100)	
Others	1 (50.0)	1 (50.0)	2 (100)	
Grouping of no chemotherapy courses (n = 179)				
≤ 5	30 (60.0)	20 (40.0)	50 (100)	χ^2 = 1.833,
6 – 10	48 (68.6)	22 (31.4)	70 (100)	p = 0.400
≥ 11	34 (57.6)	25 (42.4)	59 (100)	
***Chemotherapy Intensity (n = 334)**	**Yes**	**No**	**Total**	
Minimally	13 (43.3)	17 (56.6)	30 (100)	χ^2 = 64.853
Briefly	90 (67.7)	43 (32.3)	133 (100)	p = < **0.001**
Strongly	154 (95.6)	7 (4.3)	161 (100)	
Myeloablative	10 (100)	0 (0)	10 (100)	

ALL= acute lymphoblastic leukemia; AML = acute myeloid leukaemia, HD = Hodgkin lymphoma.
*Chemotherapy intensity in total chemotherapy courses.

Risk Factors for Febrile Neutropenia

Seventy-four of 112 patients had more than 1 episode of FN out of 112.There was a significant risk of another episode of FN after the first (66.1%, n = 74; χ^2 183.00, p = 0.001. All patients with AML had FN. Haematolymphoid malignancies (p < 0.001), intensive chemotherapy (p= < 0.001), stem cell transplant (p = 0.021) and presence of CVAD (p = 0.018) were found to be significant risk factors for development of FN (table VIII).

Table VIII: Risk factors for febrile neutropenia in study subjects (n = 179)

Variables	**Yes (%)**	**No (%)**	**Total (%)**	**RR**	**95% Cl**	**p = value**
Age						
≤ 5 years	42 (56.7)	32 (43.2)	74 (100)	1.297	.669-1.083	0.851
>5 years	70 (66.6)	35 (33.3)	105 (100)			
Sex						
Male	67 (63.8)	38 (36.2)	105 (100)	1.049	.831-1.324	0.400
Female	45 (60.8)	29 (39.2)	74 (100)			
Cancer type						
Haematologic	50 (79.4)	13 (20.6)	63 (100)	2.256	1.431-4.154	**< 0.001***
Non-haematologic	62 (53.4)	54 (46.5)	116 (100)			
Comorbidity						
Yes	8 (66.7)	4 (33.3)	12 (100)	1.132	0.239-2.853	0.511
No	104 (62.3)	63 (37.7)	167 (100)			
BM Involvement for solid tumours						
Yes	14 (63.6)	8 (36.4)	22 (100)	1.322	0.221-1.720	0.252
No	27 (51.9)	25 (48.1)	52 (100)			
Disease progress/relapse						
Yes	31 (65.9)	16 (34.0)	47 (100)	1.135	0.408-1.647	0.353
No	81 (61.4)	51 (38.6)	132 (100)			
****Type of chemotherapy***						
Intensive	249 (83.8)	48 (16.2)	297 (100)	5.476	1.233-2.409	**< 0.001***
Maintenance	18 (48.6)	19 (51.3)	37 (100)			
SCT						
Yes	8 (100)	0 (0)	8 (100)	1.796	1.152-1.943	**0.021***
No	104 (60.8)	67 (39.2)	171 (100)			
Concurrent radiotherapy						
Yes	21 (61.8)	13 (38.2)	34 (100)	1.016	0.483-1.91	0.531
No	91 (62.7)	54 (37.2)	145 (100)			
****Central line***						
Yes	131 (75.3)	43 (24.7)	174 (100)	1.648	1.050-2.586	**0.018***
No	136 (85.0)	24 (15.0)	160 (100)			
****GCSF***						
Yes	232 (79.2)	61 (20.8)	293 (100)	1.423	0.807-1.607	0.241
No	35 (85.4)	6 (14.6)	41 (100)			

CI = Confidence interval; BM = Bone marrow; SCT = Stem cell transplant; GCSF = Granulocyte colony stimulating factor; RR = relative risk. *In number of febrile neutropenia episodes (n = 267), others in number of subjects

Independent Predictors of Febrile Neutropenia

Multivariate analysis revealed that intensive as opposed to maintenance chemotherapy (RR 14.294; $p < 0.001$), a diagnosis of AML (RR 4.019; p=0.039) or ALL (RR7.698; p=0.02) and stem cell transplantation (RR 11.662; $p < 0.001$) emerged as independent risk factors for FN. The presence of a CVAD increased the relative risk (RR 2.685) of FN but narrowly failed to meet the threshold for statistical significance ($p = 0.051$) (Table IX).

Table IX: Logistic regression showing independent predictor of febrile neutropenia

Variables	Relative risk	95% CI	P value
Chemotherapy intensity			
Maintenance	1		
Intensive	14.294	37.206-544.200	**<0.001***
Central line			
No	1		
Yes	2.685	0.998-7.226	0.051
Type of cancer			
Brain	1		
HD/Lymphoma	2.104	0.391-6.091	0.291
Solid	2.019	0.354-8.093	0.301
AML	4.019	1.104-10.304	**0.039***
ALL	7.698	1.374-43.113	**0.020***
Others	1.292	0.695-1.930	0.503
SCT			
No	1		
Yes	11.662	3.093-36.013	**<0.001***

SCT = stem cell transplant, HD = Hodgkin's lymphoma, AML = acute myeloid leukaemia, ALL = acute lymphoblastic leukemia; RR = relative risk

Patients with Adverse Outcomes as a Result of Febrile Neutropenia (n = 206)

There were 206 adverse events in all episodes of FN (n = 267; 77.1%). Adverse events included prolonged hospital stay (hospital admission for febrile neutropenia for more than five days), bacteraemia, positive radiological findings, ICU admission, life threatening events (septic shock) and death. The median number of days for hospital admission for FN was five days (IQR 3; 7 days). One hundred and thirty seven patients (51.3%) had at least one adverse event following FN. Multiple adverse outcomes were observed across 62 episodes of FN. A prolonged hospital admission due to FN was the most common adverse outcome and four patients out of 112 studied (3.57%) died as a result of FN which accounted for 1.94% of the adverse outcomes. Cause of death in a patient was due to multiple organ failure with disseminated intravascular coagulopathy while the rest died of septic shock.

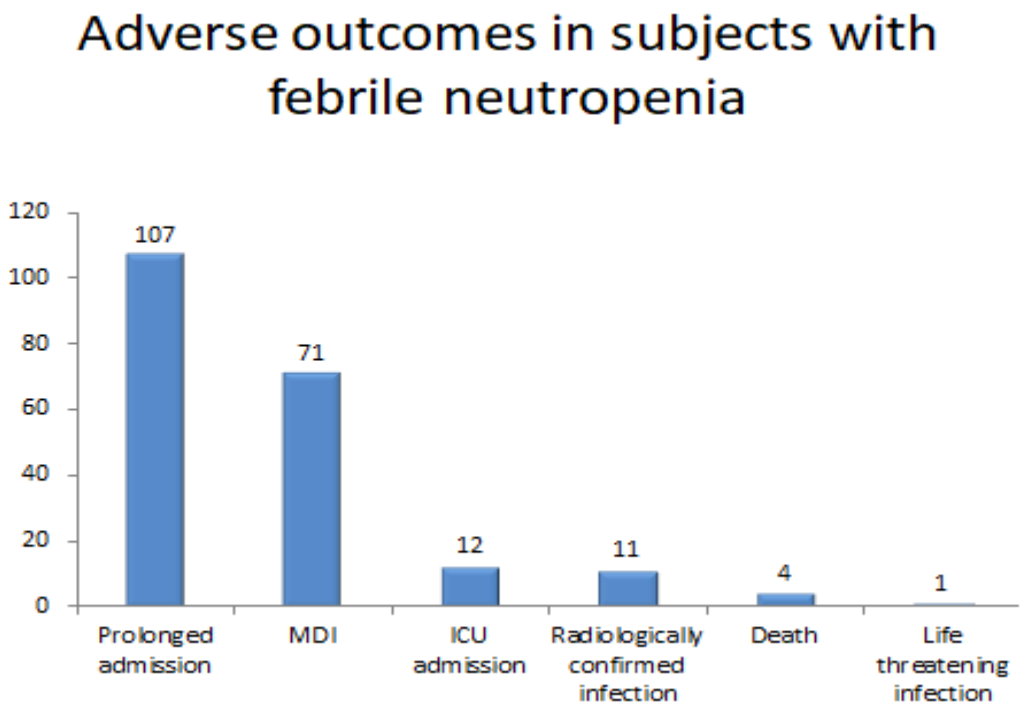


Figure 4: Adverse outcomes in subjects with febrile neutropenia.

ICU = Intensive care unit.

MDI = microbiologically determined infection.

Risk Factors for Prolonged Hospital Admission for Febrile Neutropenia (n = 107)

There was no relationship between the two age strata of five years and below and the older age group and risk for prolonged admission for neutropenia (χ^2 = 0.064, p = 0.478). Also, adolescents above ten years were not more likely to be admitted for more than five days than the younger age groups (χ^2 = 0.010, p = 0.549). Sex was not a risk factor for prolonged hospital admission (χ^2 = 1.022, p = 0.208). Patients with AML were more likely to have prolonged admission (n = 16, 94.1%) compared with ALL (n = 5, 17.8%), HD/lymphoma (n = 8, 72.7%), other solid tumour (n = 10, 38.5%) and brain cancer (n = 2, 05%). χ^2 = 32.837, p = 0.001). Patients with microbiologically defined infection (n = 71) were more at risk for prolonged hospital admission compared to those with no defined infection. Of the 71 patients with MDI, all three (4.22%), with fungal sepsis had prolonged admission. The median duration of admission for MDI was seven days which was significantly higher than four days seen in non-microbiologically confirmed FN cases (Mann-Whitney U-value -7.599, p = 0.0001). Of the four who died, three had prolonged admission (n = 3, 75%). Patients with AML were more than 70 times at risk for prolonged admission as shown in table X below.

Table X: Independent Predictors of Prolonged Admission

	Relative risk	95% C I	p-value
Present of MDI			
No	1		
Yes	3.487	1.075-11.313	**0.037**
Disease type			
ALL	1		
AML	74.696	7.789-716.304	**<0.001**
HD/Lymphoma	3.206	0.812-12.661	0.096
Solid tumor	2.601	0.746-9.069	0.134
Brain Tumor	3.825	0.522-28.052	0.187
Others	1.039	0.291-8.092	0.891

MDI = microbiologically defined infection; ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; HD = Hodgkin lymphoma

Clinical Risk Factors for Adverse Outcomes (n = 206)

A higher proportion of patients with AML (n = 16; 94.1%) had adverse outcomes compared to those with ALL (n = 11; 23.9%), solid tumours (n = 20; 20%) and brain cancers (n = 3; 20%) (χ^2 23.256, p = < 0.001). Adolescents (age above ten years) were not more likely to have adverse outcomes compared to the younger age groups (χ^2 = 1.595, p = 0.207). Haematologic malignancies, the presence of mucositis, the placement of CVADs and blood transfusion at admission emerged as significant risk factors for adverse outcomes as shown in table XI.

Table XI: Clinical Risk Factors for Adverse Outcome in Study Subjects

	Presence of adverse outcome					
Variables	**Yes**	**No**	**Total**	**RR**	**95% Cl**	**p-value**
***Age**						
<5	20 (27.0)	54 (72.9)	74 (100.0)	1.022	0.850-1.228	0.477
>5	30(28.6)	75 (71.4)	105 (100.0)			
***Sex**						
Male	28(26.7)	77 (73.3)	105(100.0)	1.163	0.601-2.251	0.388
Female	22(29.7)	52 (70.3)	74 (100.0)			
Intensity of chemo						
Intense	124(49.8)	125(50.0)	249(100.0)	1.494	0.768-2.905	0.177
Maintenance	6(33.3)	12(66.7)	18(100.0)			
***Type of cancer**						
Haematologic	27(42.8)	36 (57.1)	63 (100.0)	3.033	1.542-5.964	**0.040**
Non-haematologic	23(19.8)	93 (80.1)	116 (100.0)			
GCSF episode						
Yes	20(57.1)	15(42.9)	35(100.0)	1.2052	0.8781.655	0.283
No	110(47.4)	122(52.6)	232(100.0)			
Mucositis						
Yes	52(63.4)	30(36.6)	82(100.0)	1.5041	1.188-1.903	**0.001**
No	78(42.2)	107(57.8)	185(100.0)			
Central line						
Yes	78(57.4)	58(42.6)	136(100.0)	1.754	1.344-2.288	**0.004**
No	52(39.7)	79(60.3)	131(100.0)			
***BM involvement in solid tumour**						
Yes	5(22.7)	17 (77.3)	22 (100.0)	1.120	0.528-1.665	0.264
No	7(13.5)	45 (86.1)	52 (100.0)			
Blood transfusion						
No	42(35.3)	77(64.7)	119(100.0)			
Yes	85(58.6)	60(41.4)	145(100.0)	1.661	1.257-2.196	< **0.001**

RR= relative risk; BM = bone marrow; GCSF = granulocyte colony stimulating factor;
Cl = confidence interval. * Total number of subjects with FN and not febrile neutropenia episodes.

Laboratory Risk Factors for Adverse Outcomes

A white cell counts below 0.3 x 10^9/L was found to be a risk factor for an adverse outcome as shown in table XII. Subjects with episodes of very severe neutropenia (n = 106; 54.9%) were more likely to have adverse outcome compared with those with severe (n = 18; n = 32.7%) and moderate neutropenia (n = 6; (31.6%) (χ^2 = 10.837, p = 0.004).

Table XII: Laboratory Risk Factors for Adverse Outcomes

	Yes (%)	**No (%)**	**Total (%)**	**RR**	**Cl**	**p = value**
APC (cells/mm^3)						
<50,000	101(52.1)	93(47.9)	194(100.0)	1.311	0.950-1.810	0.079
>50,000	27(39.7)	41(69.3)	68(100.0)			
Haemoglobin (g/dL)						
< 9	79(45.5)	91(54.5)	167(100.0)	1.131	0.883-1.451	0.268
≥ 9	51(52.6)	46(47.4)	97(100.0)			
WBC (X 10^9/L)						
<0.3	67(65.0)	36(35.0)	103(100.0)	1.728	1.354-2.204	**<0.001**
>0.3	61(37.7)	101(62.3)	162(100.0)			
Platelet x10^9/L						
<50,000	49(51.0)	47(49.0)	96(100.0)	1.092	0.847-1.407	0.501
>50,000	79(46.7)	90(53.3)	169(100.0)			

WBC= white blood cell; g/dL = gram per decilitre; APC= absolute phagocyte count; mm^3 = cubic millilitre; RR = relative risk; Cl = confidence interval

Independent Predictors of Adverse Outcomes

On multivariate analysis, AML, severe neutropenia and presence of CVAD were shown to be an independent predictor of adverse outcome as shown in table XIII.

Table XIII: Logistic regression showing independent predictor of adverse outcomes

	Adjusted risk ratio	**95% CI**	**P value**
Type of cancer			
Brain	1		
HD/Lymphoma	3.894	0.222-6.041	0.693
Solid	2.091	0.201-6.864	0.759
AML	64.000	5.901-694.096	**0.001***
ALL	1.257	0.299-5.280	0.755
Others	0.985	0.594-4.301	0.749
ICU admission			
Yes	1		
No	2.301	0.909-6.091	0.093
Mucositis			
No	1		
Yes	1.726	0.944-3.154	0.076
Central line			
No	1		
Yes	1.938	1.114-3.370	**0.019***
ANC Strata			
Moderate	1		
Severe	1.052	0.298-3.720	0.937
Very severe	1.170	0.346-3.960	0.801
WBC Strata			
>0.3	1		
<0.3	2.451	1.318-4.558	**0.005***
Blood transfusion			
No	1		
Yes	1.742	0.983-3.086	0.057

AML = acute myeloid leukemia; ALL = acute lymphoblastic leukaemia, WBC= white blood cell; ANC = absolute neutrophil count; ICU = intensive care unit; HD = Hodgkin lymphoma

Validation of Risk Stratification for Adverse Outcomes (n = 206)

Using the SPOG FN Risk Index clinical decision rule for classification of adverse events in FN children with cancer which defines cut-off for adverse outcome as score of nine and above, a median score of seven was obtained in our cohort with the lowest and highest score of zero and fifteen respectively as shown in Figure 5.

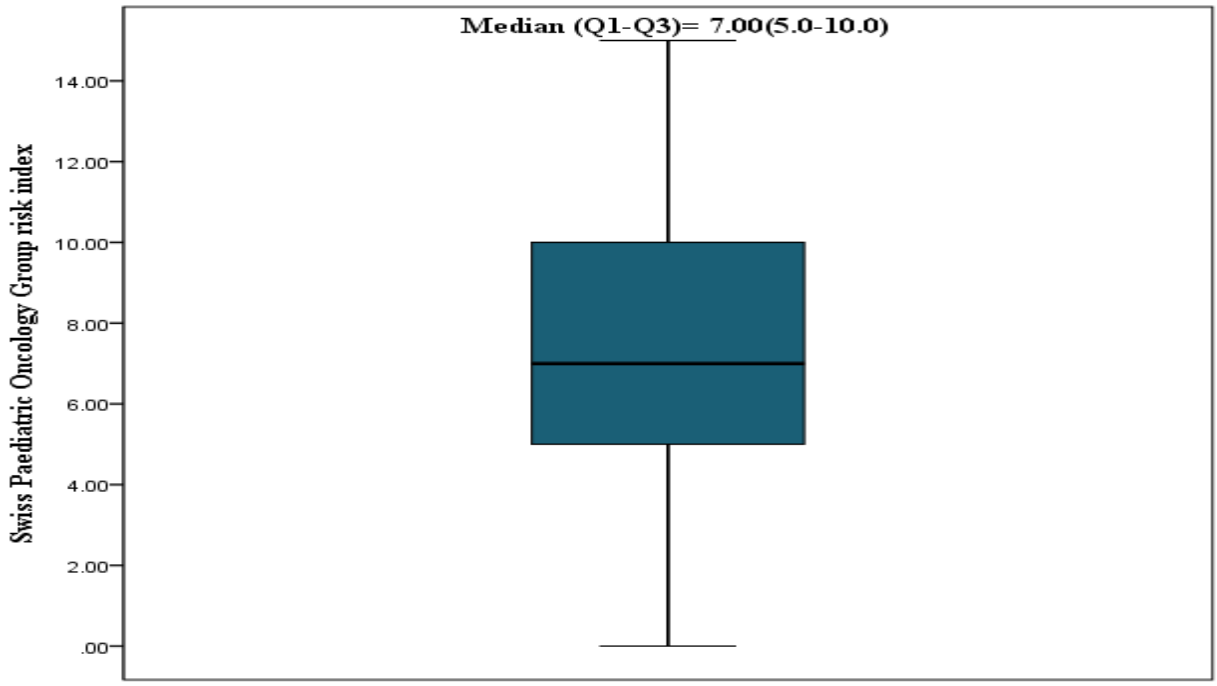


Figure 5: Diagrammatic representation of median score in study subjects

Risk Stratification of Patients with Febrile Neutropaenia (n = 267)

Using the SPOG clinical decision tool for FN, the majority of patients in our cohort study were found to be low risk for adverse outcomes with score below nine (55%) as shown in Figure 6. Excluding patients with prolonged neutropenia as having adverse outcomes in comparison with the validating tool, the percentage of patients with adverse outcomes was 31.1%.

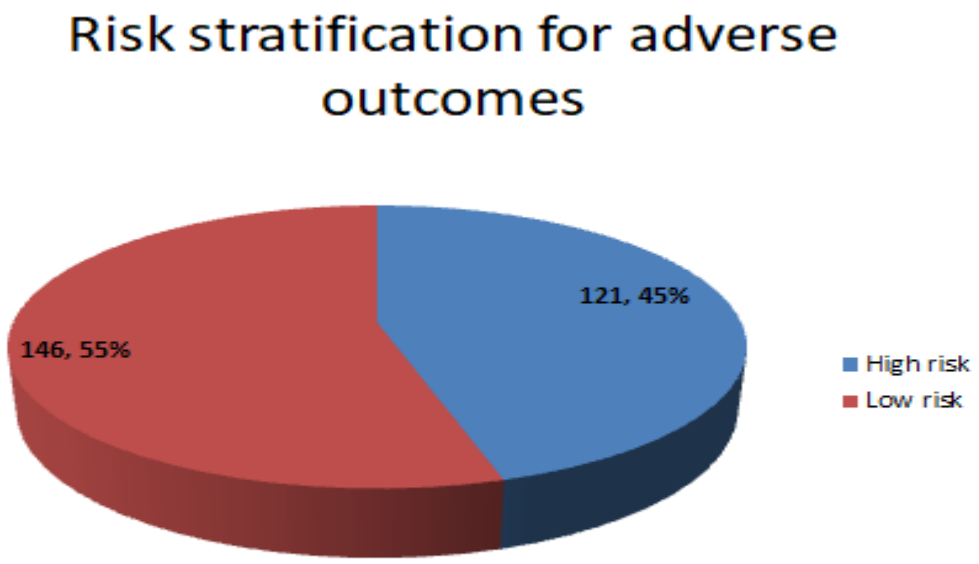


Figure 6: Risk stratification for adverse outcomes in study subjects.

The Relationship of Adverse Outcomes to Risk Stratification (n = 267)

In our cohort, the SPOG clinical decision stratification was applied to determine the relationship of the stratification to adverse outcomes occurrence in our patient cohort. As shown in table XIV, a significantly higher proportion of patients that had adverse outcomes in the current study also had scores above nine (p = 0.013) and would have been classified as high risk for adverse outcome using the SPOG stratification.

Table XIV: Comparison of Risk Stratification and Adverse Outcomes

Risk Strata	**Adverse outcomes (%)**	**No adverse outcome (%)**	**Total (%)**	**RR**	**95% Cl**	**p = value**
High risk	77 (63.6)	44(36.4)	121(100.0)	1.365	1.067-1.746	**0.010**
Low risk	70 (47.9)	76 (52.0)	146 (100.0)			

RR = relative risk; Cl = confidence interval

Validation of Risk Stratification

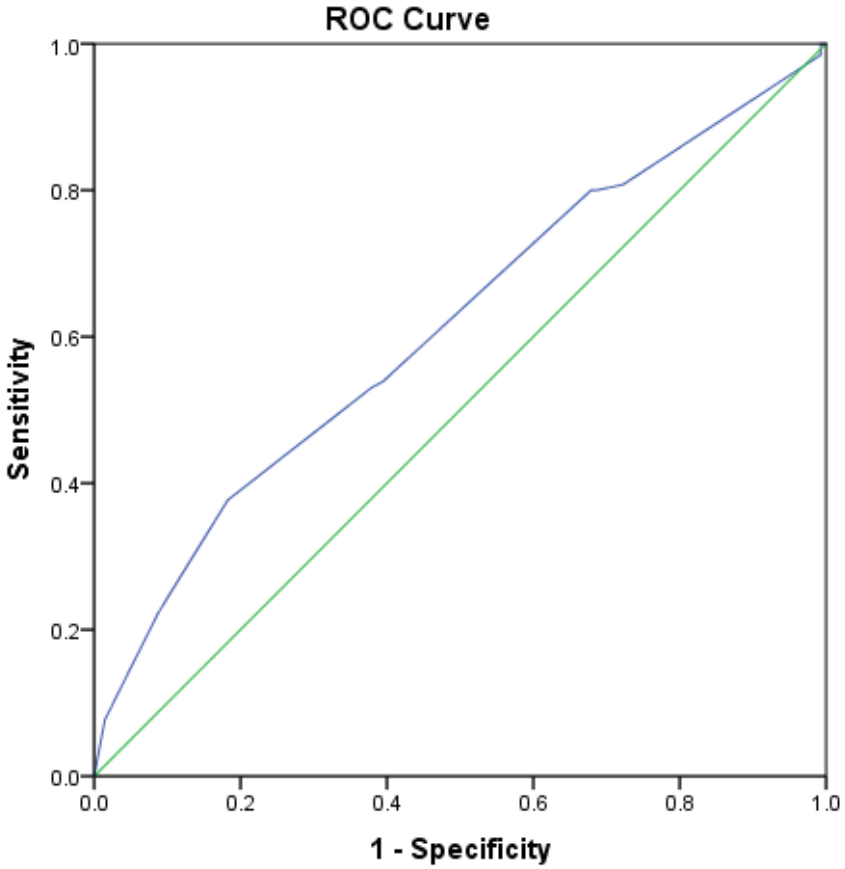
In table XV, the validation of the SPOG clinical decision for adverse outcome was carried out in our cohort. We observed a relatively low sensitivity and specificity of the tool to predict the occurrence of adverse outcomes following febrile neutropenia.

Table XV: Validation of Swiss Paediatric Oncology Group (SPOG) Clinical Decision for Febrile Neutropenia in Study Subjects:

Parameters	**Diagnostic accuracy**
Sensitivity	52.3
Specificity	62.0
Positive predictive value	56.3
Negative predictive value	58.2
Overall accuracy	57.4

Accuracy of Adopted Tool

To predict the best cut-off for adverse outcomes using the SPOG clinical decision rule in our patients, a receiver operating characteristic (ROC) curve was developed. The area under the curve was 0.612 which translates to 61.2% accuracy with a p-value of 0.002 (Figure 7).



Area Under the Curve

Test Result Variable(s): score1

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.612	.034	.002	.545	.680

Coordinates of the Point on the Curve

In table XVI, coordinates of the curve were generated. This was done to assess the different sensitivity and specificity that best determines the risk of adverse outcome. Considering the inverse relationship in the values of sensitivity and specificity, the best coordinate of the curve is the point with the highest sensitivity and specificity. In our cohort, this fell between 7.5 and 8.5. The most specific sensitivity value using Youden's index (sensitivity + specificity) – 1 is 0.531

Table XVI: Coordinates of a Curve in Study Subjects

Coordinates of the Curve

Test Result Variable(s): score1

Positive if Greater Than or Equal To[a]	**Sensitivity**	**1– Specificity**
1.0000	1.000	1.000
1.5000	1.000	.993
3.5000	.985	.993
4.5000	.808	.723
5.5000	.800	.686
6.5000	.800	.679
7.5000	**.538**	**.384**
8.5000	**.531**	**.380**
9.5000	.377	.182
11.0000	.223	.088
13.5000	.077	.015
16.0000	.000	.000

Patients' that had prolonged admission from FN were further excluded from adverse outcome because it was not a parameter explored in SPOG FN risk index. As shown below, the sensitivity and specificity in our report were 50.6% and 57.1% respectively.

Table XVII: Validation of SPOG Clinical Decision for Febrile Neutropenia in Study Subjects (excluding prolonged neutropenia as outcome):

Parameters	Diagnostic accuracy
Sensitivity	50.6
Specificity	57.1
Positive predictive value	34.7
Negative predictive value	71.9
Overall accuracy	55.1

With the exclusion of prolonged hospital admission as an adverse outcome of FN, the most predictive score for adverse outcome using SPOG clinical decision rule is 7.5 as shown in table XVIII.

Table XVIII: Coordinates of a Curve in Study Subjects (Excluding prolonged admission)

Positive if Greater Than or Equal To[a]	Sensitivity	1 – Specificity
-1.0000	1.000	1.000
1.5000	1.000	.995
3.5000	.976	.995
4.5000	.783	.755
5.5000	.771	.728
6.5000	.771	.723
7.5000	**.506**	**.446**
8.5000	.506	.429
9.5000	.373	.234
11.0000	.229	.120
13.5000	.072	.033
16.0000	.000	.000

The test variable has at least one tie between the positive actual state group and negative actual state group. The smallest cut-off value minus 1, and the largest cut-off value plus 1. All the other cut-off values are averages of two consecutive ordered observed test values.

CHAPTER FIVE

DISCUSSION:

Over a three-year period, 263 newly diagnosed children with cancer were enrolled for care at RCWMCH, Cape-Town.

A slightly higher proportion of male adolescents aged above ten years were enrolled compared to female counterparts but no sex differences were observed in the younger children. This is consistent with findings reported by Badr *et al*[22] in Egypt and Gurlinka *et al*[54] in India. In a large population data base involving UN regions on childhood cancer, male preponderance for cancer has also been reported but the explanation for the higher incidence in boys has not been established[80].

The median age at diagnosis in this study was five years whilst the proportion of subjects diagnosed decreased with an increase in age. Similar median ages at diagnosis were observed in the studies by Badr *et al*[22] and Mogensen *et al*[81], whilst others like Mostert *et al*[82] in Kenya reported higher median ages at diagnosis. Differences in ages at cancer diagnosis in children are likely to be multifactorial and poor knowledge of cancer and delayed presentations are likely to be significant contributors to late diagnosis in LMIC.

In this study, solid tumours accounted for the highest number of cases whilst, ALL was the commonest haematologic malignancy seen. In Africa, prevalence of solid tumours is high compared to other developed parts of the world. The high endemicity of *Plasmodium falciparum* in Africa (which has been linked to endemic Burkitt lymphoma) is a major reason for the higher occurrence of solid tumours in LMIC[83]. In addition, the high prevalence of HIV infection in sub-Saharan Africa with associated with an increased occurrence of HIV related malignancies contributes to the predominance of solid tumours in these regions[84]. Earlier studies have consistently shown that ALL is the commonest haematologic malignancy

with boys being at higher risk for ALL than girls[22,54,85]. Given the common nature of ALL and the propensity for boys to be more at risk may in part account for the higher prevalence amongst boys compared to girls.

At least one episode of chemotherapy-induced FN occurred in well over half of our study population. This finding supports the experience that FN is a common treatment-related complication in children with malignancies. The high occurrence of chemotherapy-induced FN has consistently been reported in previous studies in children[10,22,28,86]. Given that one episode of FN is a known risk factor for subsequent episodes of FN, it is hardly surprising that almost two-thirds of our patients presented with multiple episodes. This phenomenon has been previously documented by Wicki *et al* in Bern, Switzerland.[50] .

A median interval of ten days before occurrence of FN was observed in the present study. This is not unexpected considering that the nadir of the neutrophil count and subsequent increase in the risk of infection occurs between seven and 12 days post-chemotherapy[87]. Chemotherapeutics cause bone marrow suppression and rapidly reduce dividing haematopoietic stem cells with a more significant impact on neutrophils that have the shortest half-life of 6 to 12 hours thereby increasing susceptibility to infection post-chemotherapy[88,89].

At RCWMCH, all subjects that present with FN have a pre-admission complete blood count. In the present cohort, the majority had anaemia at presentation and over half required blood transfusion during their FN episodes. Comparison with other studies is complicated by the disparity in cut-off values for anaemia and threshold for transfusions[24,54]. Chemotherapy induced anaemia is a common clinical phenomenon occurring in conjunction with FN. Risk factors for anaemia and the requirement for blood transfusion include the baseline haemoglobin level, chemotherapy type, haematologic malignancies and bone marrow infiltration by non-haematologic malignancies[90]. Similarly, almost two-third of our cohort

with FN had severe neutropenia. This is in contrast with 36.5% reported by Gurlinka *et al* in India[54]. Whilst our cohort was larger than the Indian study (n = 40), factors such as chemotherapy intensity and baseline neutrophil count pre-chemotherapy (that are risk for severe neutropenia), could account for the disparity in the findings in the two studies. Monocytes and neutrophils originate from same myeloid progenitor granulocyte–macrophage (GM) colony forming cells and similar response to chemotherapy occurs. Also, monocytes play a significant role in neutrophil proliferation and survival[91,92]. This is a probable explanation for the high proportion of subjects with FN that had severe monocytopenia and severe neutropenia in our cohort. In contrast to the trend in neutrophil and monocyte counts, most subjects did not have severe thrombocytopenia. The explanation for this is the differences in myeloid progenitor cells. Whilst myeloblast gives rise to neutrophils and monocytes, platelets do not arise directly from that same progenitor cells but from megakaryocytes. This explains why the neutrophil and monocyte nadir is not related to platelet nadir[93]. The absolute phagocyte count (APC) is a reflection of the segmented neutrophils, bands and monocyte count[79], Therefore, the higher proportion of subjects with low APC that reflects the trend of neutrophil and monocyte count in our cohort is not surprising.

No focus of infection could be identified in the majority of our patients, again, a phenomenon reported by others[2,86]. This perhaps is due to reduced inflammatory response to infective agents from defective immune system[94]. In our cohort, microbiologically confirmed infection was seen in only 26.6% of FN episodes. Low occurrence of bacteraemia or fungal infection has been previously documented, 21.6% and 26.9% respectively[86,95]. Low yields (below 25%) from widely adopted conventional methods of mycobacterial identification has been raised as a possible explanation and the need for more specific tool like rapid testing polymerase chain reaction (RT-PCR) testing has been suggested[96], although adoption of this

methodology would be limited by its potential cost for low-and middle-income settings. In addition, microbial yield has been shown to be inversely proportional to the specimen volume[97].

Risk factors for FN and adverse outcomes were reviewed for each FN episode. This is because events (clinical and non- clinical) associated with FN are more often related to chemotherapy regimen than patients factors. In our study, age was not a risk factor for FN. This finding is similar to previously reported studies[12,22,50]. An increased risk of FN has been widely reported in advanced age above 65 years due to factors such as impaired immunity with age, but this finding has not been consistently demonstrated in the very young with similar undeveloped immunity. Similarly, sex was not identified as a risk factor for FN and again, this is consistent with previous studies[12,14]. Although, immunological responses (innate and adaptive immunity) to micro-organisms is sex related, this has not been shown to predict risk for chemotherapy complicated FN in children[98].

Patients with haematologic malignancies had a higher propensity for CIN compared to their counterparts with solid tumours which has been previously reported[23,46,50]. Replacement of haematopoietic cells with blast cells predisposes individuals with haematologic malignancies to intense bone marrow suppression and an increased risk of FN. Also, the increased intensity of chemotherapy regimen used to treat haematolymphoid malignancies further elevates the risk for FN[99]. This can also be elaborated to patients undergoing stem cell transplantation (SCT). Interestingly though, the number of courses of chemotherapy did not prove to be a risk factor for FN in our study cohort. In contrast to haematological treatment regimens which are continuous, solid tumour chemotherapy by and large is given in a cyclical fashion allowing for count recovery between courses and reducing the effect of CIN which may be associated with subsequent episodes of FN.

Similarly, solid tumour patients with bone marrow disease are also at risk for FN like those with haematologic malignancies[100]. Although, a higher proportion of our patients with solid tumours with bone marrow involvement experienced FN, it did not meet the threshold for statistical significance.

Diverse comorbidities such as liver, renal, bone and thyroid diseases in cancer patients increase risk of FN in adults[101,102]. In our cohort, two-third of the HIV infected children had chemotherapy induced FN although the overall numbers were small. HIV impairs haematopoiesis and thereby predisposes infected individuals to a higher risk of FN with chemotherapy administration[103].

Concurrent radiotherapy with chemotherapy increases the risk of FN[14]. This however was not proven in our cohort. Radiation (particularly total body irradiation) destroys haematopoietic cells and causes bone marrow suppression. However, the increase risk of FN when combined with chemotherapy depends on the dose, radiation field and treatment volume; parameters which were not evaluated in our study and which may have impacted our findings[104].

Prior history of FN was identified as a risk factor for another episode in our study, again, previously reported[50]. Genetic predisposition to FN has been proposed as the likely reason for this finding[16,17]..

Haematopoietic cells growth factors reduce the risk of FN by stimulating the production of myeloblasts[105]. Its administration as a preventive measure for FN or as a mechanism to reduce the risk and severity of infection is recommended. However, there have been conflicting reports on its beneficial effect in haematologic malignancies. Whilst, some studies documented recovery in absolute neutrophil count and reduction in days of neutropenia, there was unanimous finding of no significant clinical significant impact on hospitalisation and the incidence of severe infection[106,107]. In the current study, G-CSF administration had no

significant impact on FN risk reduction consistent with findings by *Ammann et al*[24]. More so, its use is limited in our institution making the finding of a significant impact unlikely.

The placement of CVADs was identified as a risk factor for FN in our cohort. Again, this is consistent with findings in other studies[12,50,108]. Biofilms which are aggregates of microbial organisms have an affinity for catheters and colonises these surfaces. Characteristically, these biofilms form a self-produced, protective, extracellular matrix that hinders their destruction by host immune systems or systemic antibiotics[109].

Individuals with AML, ALL and those receiving myeloablative chemotherapy for SCT are independently at risk for FN. This is directly related to the chemotherapy intensity. AML as an independent risk for FN, prolonged hospital stay and mortality and this has been previously reported[19,47,55]. Likewise, the intensity of chemotherapeutics in ALL excluding maintenance phase is high and this increases the occurrence of FN in affected children. Additionally, ALL is the most commonly occurring malignancy in children and this also impacts on the high prevalence of FN. Some studies have excluded subjects who have had myeloablative therapy for SCT, as these patients are independently at risk for FN due to intensity of chemotherapy and total body irradiation as part of myeloablative pre-transplant conditioning[71,86].

Adverse outcomes were observed in almost three-quarters of the FN episodes in our cohort. This result is higher than previously reported by investigators in India and the Netherlands[71,110]. The inclusion of prolonged admissions as an adverse outcome in our cohort could account for the higher proportion of patients with adverse outcomes. Whilst the same tool excluding prolonged FN was used by Miedema *et al*[110] in Netherlands, Das *et al*[71] included other parameters such as nutritional status which limits direct comparison. A study by Green *et al*[28] in South Africa also reported a high incidence of adverse events (45%) using

a similar tool to Miedema *et al*[110] in Netherlands . This perhaps reflects a high occurrence of adverse events in middle-income countries like South Africa compared to high income countries.

Closer attention is being paid to the health related quality of life of children with cancer and prolonged hospital admission is a major factor impacting psychosocial health[19,47,111]. It has been shown that fungal infections, bacteraemia and life-threatening complications increase after five days of admission for FN[19,34]. Consequently, we included prolonged hospital admission as a measure of adverse outcome in our study. At RCWMCH, children with FN and severe neutropenia (ANC below 1000/mm^3) are admitted for a minimum of three days for intravenous antibiotics dependent on blood culture results and the decrudescence of fever. Prolonged admission may occur if fever continues beyond 72 hours, if a blood culture is reported as positive or if an additional complication arises. This makes the adoption of five days as the definition for prolonged admission acceptable compared to longer durations defined by other authors. For example, in adults, a longer duration of hospital stays (seven to ten days) was associated with adverse outcomes (AEs) such as bacteraemia and hypotension[18,112].

Microbiologically confirmed infection accounted for the second commonest of the adverse outcomes in our patient cohort. Some studies have identified bacteraemia alone as an adverse outcome and it has been reported as the commonest cause of adverse outcome in other studies[2,24,27,50,110,113]. The rate of bacterial isolation using conventional blood culture sampling in children with FN is low and this has resulted in the interrogation of research other than microbiologically determined infection such as molecular testing using RT-PCR that can help in identifying individuals at risk of adverse outcomes from FN such as prolonged admission[41].

Intensive care unit admissions accounted for third commonest adverse outcome (5.8%) in our cohort. A similar finding was reported by Ammann *et al*[68] and Das *et al*[71]. In the study by Ammann *et al*[68], ICU admission for FN was reported as the fourth commonest adverse outcome (4.3%). The authors, however, did not include patients that had prolonged hospital admission from FN. Despite Das *et al*[71] having used a different tool to classify adverse outcome, ICU admission was still a common occurrence (6.7%). In comparison, a lower ICU admission was reported by Green *et al*[28] in South Africa. In both cases, small sample sizes may have impacted their findings as well as more stringent criteria for ICU admission considering the pressure for ICU care and access to beds.

Mortality from FN was relatively high (3.57%) in our cohort. Mortality rate from FN varies from country to country. In Germany, Ammann *et al*[68] reported a mortality rate of 0.7%., compared to 10% in India and 21.3% in Pakistan. This is almost certainly related to access to health care in particular, the availability of paediatric PICU facilities and staff. In Pakistan, the high mortality rate was related to the selection of subjects with poor prognostic factors for acute leukaemia.

Acute lymphoblastic leukaemia (ALL) was found to be a risk factor for AE but was not independently predictive of outcome in our cohort. The intensity of chemotherapeutic regimens in haematologic malignancies has increased in an attempt to achieve higher rates of cure. This treatment intensity predisposes affected individuals to profound neutropenia and prolonged hospital admission. Acute myeloid leukaemia (AML) was an independent predictor of adverse outcome in our study. Similarly, AML was identified as an independent risk factor for adverse outcomes by Alam *et al*,[114] Basu *et al*[19] and Das et al[115]. Intensity of chemotherapy in AML is a primary cause for adverse outcome resulting from severe neutropenia. In this context, neutropenia tends to be severe and prolonged, predisposing

affected children to invasive fungal infection[116]. The administration of prophylactic G-CSF leads to the peripheral proliferation of myeloid leukaemic cells[117] and as such is not used in patients with AML before remission is achieved at our institution.

Mucosal barrier injury is a common clinical manifestation of patients on chemotherapy. Its identification as a non-independent risk factor for adverse outcome was observed in our cohort. There is paucity of reporting on its impact on risk for adverse outcome in FN. However, mucositis was not identified as a cause of prolonged FN by Alali *et al*[118]. The increased risk of micro-organism invasion from the breached mucosa is a likely mechanism[119].

CVAD placement was identified as an independent risk factor for adverse outcome in the present study. This has also been reported by Suttitossatam *et al*[120]. Its risk for prolonged hospital admission has also been reported[121]. Central line associated blood stream infection is a common occurrence in patients and this by proxy increases of FN related adverse outcomes[122].

Severe neutropenia was found to be an independent risk factor for adverse outcome in our patients, again, a finding similar to those reported by other authors[54,114,120]. Severe neutropenia increases the risk of severe infection, which may lead to the need for intensive care, invasive fungal infections and/or prolonged hospital stays[112,123].

As observed with the risk of FN, G-CSF administration had no effect on FN outcomes in our cohort. This finding was also reported by Prasad *et al*[29], however, Suttitussatam *et al*[120] reported lower risk of adverse effect following G-CSF administration. Moreover, its use had no effect on other adverse outcomes evaluated here. In non-haematologic diseases, bone marrow involvement in patients had no relationship with disease outcome in our cohort. This is possibly due to lower chemotherapy intensity used in patients with solid tumours compared

to patients with haematologic malignancies. Also, treatment modalities for patients with stage IV disease, specifically those with bone marrow involvement, differ, and some patients received less intense chemotherapy with palliative intent, but this discrimination was outside the scope of this analysis.

In our study, haematologic parameters (Hb, platelet count and APC) did not impact outcome. Findings from other studies are inconsistent. Whilst Bothra *et al*[70] observed that both haemoglobin and platelet count had no effect on disease outcome, Gurlinka *et al*[54] documented similar finding with only low haemoglobin count. Meanwhile, some authors reported an increase risk of adverse outcome with either or both low platelets and haemoglobin[27,55,114]. The different cut-off values for haemoglobin that ranged from 7g/dL to 10g/dL used by these authors limits comparison of results. Conversely, despite similar cut-off value for platelet count as a likely risk factor for adverse outcome, differences in the adverse outcome reporting between studies hinders any likely explanation for the differences observed. Thrombocytopaenia in FN occurs as a result of bone marrow suppression and platelet consumption[124]. It has been identified as a prognostic marker for sepsis and no immediate explanation can be offered for its non-significant increase in patients that had adverse outcomes. A high haemoglobin concentration was classified as risk for adverse outcome by Ammann *et al*[68]. This was subsequently identified to be as a result of haemoconcentration in patients with dehydration[69].

Using the SPOG classification, almost half (45%) of our patients were found to be high risk for AEs. This reduced to less than one-third (31.1%) with exclusion of prolonged hospital admission for neutropenia. In comparison to studies that used the same tool, a slightly higher value was obtained in our cohort compared to reported value of 29% by Ammann *et al*[68] while this was lower than 45% reported by Green *et al*[28]. Whilst the current study assessed

patients at admission for FN with ANC defined as < 1.0 x 10^9/L, the previous studies inclusion criteria was a much lower ANC of 0.5 x 10^9/L. Additionally, Ammann *et al*[68] did a reassessment study at least 8 hours after admission and not at admission. At RCMWCH, CIN in children is defined as an ANC below 1.0 x 10^9/L. The disparity in the inclusion criteria may account for the differences between studies.

A significantly higher proportion of patients who had AEs in our cohort fell in the high risk category according to the SPOG criteria. However, this significance was lost when patients with prolonged admission from FN were excluded. This may indicate that other reasons may have influenced clinical decision making in patients with prolonged admission, not only the ANC. For example, sometimes social factors influence the length of hospital stays in children who may be vulnerable for other reasons like those with poor parental supervision, food insecurity or lack of transport. When validating the SPOG clinical decision criteria, a low sensitivity and positive predictive value was obtained in our cohort. This is contrary to a sensitivity of 82% reported by Miedema *et al*[110] in the Netherlands. However, a low sensitivity and positive predictive value was obtained by Green *et al*[28] in South Africa despite the adoption of similar inclusion criteria of patients with ANC of < 0.5 x 10^9/L. The differences in results seen may be explained by differences in inclusion criteria and treatment regimens. Using the SPOG tool, subjects with score of 7-7.5 were more likely to have adverse outcomes with or without inclusion of prolonged admission. In our cohort, patients were more likely to have had adverse outcomes at a lower score compared to what has been predicted by Ammann *et* al[68]. In the present study, the decision to use the tool by Ammann *et al*[68] was based on the fact that criteria used in the previous study are in place at RCWMCH. Some studies have used laboratory parameters like C-reactive protein to predict adverse outcome which is not routinely done in patients with FN at RCWMCH[27,71].

The drawbacks in our study include retrospective data collection but the effect of missing data was not significant due to over 99% data recruitment. Also, some investigation results such as platelet count were not available in some folders and were considered missing data, however, this accounted for less than 2% of the results. The small sample size and a single institutional based study site were also identified limitations in our study. We could not evaluate death as an outcome for prolonged admission due to low mortality in our cohort. Some patients diagnosed prior the commencement of the study 2017 who had FN during the study period, may have excluded because their date of diagnosis precluded the starting date of inclusion of patients into the study. If these patients had been included it would have prolonged the study duration by at least three years (duration for treatment of ALL) and thereby increased the study population.

CONCLUSIONS

Based on the findings of the study, we can conclude that (i) febrile neutropenia is a common complication in children with cancer treated with chemotherapy: (ii) patients receiving intensive chemotherapy and those with haematologic malignancies are at higher risk of FN (iii) adverse outcomes from treatment are likely in children with AML, severe neutropenia and those with CVADs in-situ (iv) patients with scores above 7.5 using clinical decision rule by SPOG were shown to be at a higher risk of adverse outcomes (v) the need for institutional and perhaps regional development of risk stratification for adverse outcomes cannot be over-emphasised.

RECOMMENDATIONS:

Based on these conclusions, the following recommendations can be made: (i) prolonged admission more than five days following febrile neutropenia should be considered and evaluated as an adverse outcome in subsequent studies, (ii) adoption of risk stratification protocol should be developed and implemented using the clinical decision rule by SPOG such that patients, with a score of > 7.5 are considered to be at risk of adverse outcomes and should be managed as inpatients preferentially for the administration of parenteral antibiotics, (iii) conversely, outpatient management with oral antibiotics is feasible in patients with risk stratification score of < 7.5 and this treatment plan can be adopted, (iv) in future evaluations, particularly if done prospectively, it would be instructive to include factors of social vulnerability which influence clinical decision making impacting prolonged hospital stay to evaluate the role that these may potentially play in the development of adverse outcomes in and out of hospital.

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PROFORMA

Biodata:

Serial Number: ……

Name:…….

Age: ……

Gender: ……

Disease Classification

ICD 10 Code…….

Date of Birth (dd/mm/yyyy) ……/……./……..

Date of diagnosis:……..

Age at diagnosis:…….

Type of cancer:……

Stage:……

Is there bone marrow involvement at diagnosis: Yes □ / No □

Any previous relapse? Yes □ / No □

Treatment information:

No of chemotherapy courses since diagnosis

Number of chemotherapy before study period…….

Current chemotherapy course:

Classification of chemotherapy: Intensive □, Maintenance □, Myeloablative □

Information on First episode of FN:

Age:……..

Chemotherapy course at first FN:……..

Date of 1st episode of FN…….

No of days from commencement of first chemotherapy:……..

No of days on admission for first FN:……

Outcome of 1st episode of FN:…….

Risk factor for FN:

Central venous access in situ? Yes □ / No □

Mucositis at time of diagnosis of FN? Yes □ / No □

Prophylactic GCSF: Yes □ / No □

Concurrent radiotherapy?: Yes □ / No □

Absolute neutrophil count:……

Monocyte count:…….

Haemoglobin:……..

Platelet count:……

Adverse events at first FN:

Focus of infection identified? Yes □ / No □

Radiologic features of pneumonia? Yes □ / No □

Any positive stool or urine culture? Yes □ / No □

Microbiological confirmation of infection? Yes □ / No □

Admission in ICU? Yes □ / No □

Death from FN? Yes □ / No □

Information on subsequent FN:

Episodes of FN since chemotherapy (intensive chemotherapy)

Course of chemotherapy FN occurred?.....

Any above listed risk factors for FN? Yes □ / No □

What were the risk factors for FN if identified?.....

Any above listed adverse event in subsequent FN?

What is/are the adverse events?.....

What course of chemotherapy did the adverse event occur?.....

UNIVERSITY OF CAPE TOWN
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Human Research Ethics Committee

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02 July 2020

HREC REF:351/2020

Dr M Hendricks
Department of Paediatrics
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Dear Dr Hendricks

PROJECT TITLE: PREVALENCE, RISK FACTORS AND PREDICTORS OF ADVERSE OUTCOMES OF FEBRILE NEUTROPENIA IN ONCOLOGY PATIENTS ON CHEMOTHERAPY AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A THREE-YEAR RETROSPECTIVE STUDY-MPHIL CANDIDATE: DR MOTUNRAYO ADEKUNLE

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherance to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 July 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Motunrayo Adekunle will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval, where necessary, before the research may occur.

Please quote the HREC reference number in all your correspondence.