SA Journal of Oncology
ISSN: (Online) 2523-0646, (Print) 2518-8704

Risk factors and predictors of adverse outcomes in paediatric febrile neutropenia

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Dates:
Received: 25 Feb. 2022
Accepted: 29 Aug. 2022
Published: 14 Mar. 2023

How to cite this article:
Adekunle MO, Davidson A, Hendricks M. Risk factors and predictors of adverse outcomes in paediatric febrile neutropenia. S. Afr. j. oncol. 2023;7(0), a232. https://doi.org/10.4102/sajo.v7i0.232

Background: Febrile neutropenia (FN) is the commonest acute complication of cancer treatment in children. The identification of patients at risk for FN as well as adverse outcomes has been described.

Aim: To evaluate the prevalence and potential risk factors for FN and describe adverse outcomes in a cohort of children treated for cancer.

Setting: The study was carried out in a paediatric oncology unit in a children's hospital, Cape Town, South Africa.

Methods: A retrospective study from 01 January 2017 to 31 December 2019 on children with cancer at Red Cross War Memorial Children's Hospital, Cape Town, South Africa.

Results: Two hundred and sixty-seven episodes of FN occurred in 179 patients. Independent predictors of FN were acute myeloid leukaemia (AML) ($p = 0.039$), acute lymphocytic leukaemia (ALL) ($p = 0.020$) and intensive chemotherapy ($p \leq 0.001$). Mucositis ($p = 0.001$), central venous access device (CVAD) placement ($p = 0.004$), haematologic malignancies ($p = 0.040$), blood transfusion during FN episode ($p < 0.001$) and severe neutropenia (white cell counts $< 0.3 \times 10^9$ cells/L) ($p \leq 0.001$) were risk factors for adverse outcomes. The mortality rate from FN was 3.57%. Independent predictors of adverse outcomes in those with FN were AML ($p = 0.001$), CVAD placement ($p = 0.019$) and severe neutropenia ($p = 0.005$).

Conclusion: Treatment related adverse outcomes following chemotherapy-induced FN are likely in children with AML, severe neutropenia and with CVAD placement.

Contribution: Adverse outcomes from paediatric febrile neutropenia is high. There is need for clinical decision making aimed at prevention and early identification of individuals at risk.

Keywords: febrile neutropenia; cancer; chemotherapy; children; risk factors; adverse outcomes.

Introduction

Febrile neutropenia (FN) is a major cause of morbidity and the commonest acute complication of cancer treatment in children, with reported mortality rates of 0.7% – 21.3%.[1,2,3,4,5] Because of the need for multiple admissions, FN significantly affects the quality of life of children with cancer.[6] Approximately 50% of children on chemotherapy will develop at least one episode of FN during the course of their treatment. Previous studies have identified risk factors for adverse events in children with FN.[7,8,9,10] The variability in the studied risk factors and outcomes is accounted for by differences in risk factor evaluation and the management guidelines applied, which are predominantly institutionally determined. There is a paucity of data collected on the length of hospital stay as an adverse outcome in FN, despite its major contribution to patients' quality of life. This study aimed to evaluate the prevalence and potential risk factors for FN and to determine its impact on outcomes in a cohort of children with a range of cancer diagnoses treated at Red Cross War Memorial Children's Hospital (RCWMCH) over a defined period.

Methods

The authors undertook a retrospective folder review of children aged 16 years and below with biopsy-proven haematological malignancies and solid tumours diagnosed at RCWMCH between 01 January 2017 and 31 December 2019. Clinical and laboratory

information of patients with FN was recorded with particular attention to the timing and number of episodes. This included proven foci of infections, with or without radiological confirmation, for example, chest radiographs documenting pneumonia and/or confirmed bacterial or fungal blood stream infections (BSI) or other positive culture samples like urine or stool. The duration of hospital stay as a result of the FN episode was also documented. Patients with incomplete records were excluded.

Febrile neutropenia was defined as an axillary temperature (≥ 38.0 °C) and neutropenia (absolute neutrophil count [ANC] < 1.0×10^9 cells/L). The severity of neutropenia was defined: very severe neutropenia was ANC below 0.1×10^9 cells/L in the presence of a fever; severe, ANC $0.1–0.5 \times 10^9$ cells/L; and moderate neutropenia was 0.5×10^9 cells/L to ≤ 1.0×10^9 cells/L. No neutropenia was defined as an ANC ≥ 1.0×10^9 cells/L.[7,11]

The intensity of chemotherapy was classified during the period of FN: (1) minimally suppressive, with an unlikely risk of FN, as for patients on low-intensity maintenance chemotherapy; (2) briefly myelosuppressive chemotherapy (expected duration of severe neutropenia ≤ 10 days), as in those receiving induction and consolidation therapy for precursor-B acute lymphoblastic leukaemia (ALL) and chemotherapy for most solid tumours; (3) strongly myelosuppressive chemotherapy (> 10 days) like therapy for acute myeloid leukaemia (AML) and non-Hodgkin lymphoma; and (4) myeloablative chemotherapy like that administered as conditioning therapy prior to haematopoietic stem cell transplantation (HSCT).[12] Prolonged neutropenia was defined as the total duration of severe neutropenia episodes.[13] Hypotension was defined as a systolic blood pressure below the 5th centile for age and gender.[14] The absolute phagocyte count (APC) was defined as the sum of segmented neutrophils, bands and monocytes.[15] A significant clinical focus of infection was considered to be the presence of apparent localising signs or symptoms likely to be causing fever either at the first presentation or during the course of FN. A prolonged admission was defined as that beyond five days, as it has been shown to be associated with an increased risk of fungal infection and mortality and has been identified as an adverse outcome from FN in a previous studies.[16,17] Adverse events included prolonged hospital stay (hospital admission for FN of more than five days), bacteraemia, positive radiological findings, intensive care unit (ICU) admission, life-threatening events such as septic shock or disseminated intravascular coagulopathy and death. For evaluation of factors that were associated with increased risk of FN, children who experienced FN were compared to those who never experienced an FN episode during the study period.

Data were stored in a Microsoft Access (Microsoft Corporation, Redmond, Washington, United States) spreadsheet and analysed using the Statistical Package for Social Sciences (SPSS) (IBM Corporation, Armonk, New York, United States) version 20.0. Patients' demographics were summarised as frequencies and percentages. Continuous variables were summarised using mean and standard deviation (s.d.) if normally distributed, whilst median and interquartile ranges (IQR) were computed for skewed data. Comparison between categorical data was carried out using the chi square or Fisher's exact test where appropriate. Odds ratios (OR) with 95% confidence interval (CI) were estimated to measure the relationship between risk factors and outcomes (FN or adverse outcomes). A multiple logistical regression was conducted to estimate the independent risk factors for developing FN and adverse outcomes. A probability value less than 5% (0.05) was considered to be statistically significant using a 95% CI.

Ethical considerations

Approval for the study was obtained from the Health Research Ethics Committee of the University of Cape Town, South Africa (ref. no. HREC 351/2020) on 2 July 2020.

Results

In the 179 patients who received chemotherapy, at least one episode of FN was recorded in 112 (62.6%) patients. The highest number of episodes of FN (six episodes) was seen in two subjects (1.8% of those that experienced FN). Most patients had a single episode of FN (n = 38; 33.9%) (Table 1). In all, 267 FN episodes were documented. Most of the episodes of FN (249; 93.2%) occurred in patients following intensive chemotherapy, with the remaining 18 (6.7%) occurring in subjects on maintenance chemotherapy. Chemotherapy dose reduction following FN occurred in 18 (16.1%) out of 112 subjects with FN, whilst 37.5% (n = 42/112) of patients experienced chemotherapy delays as a result of FN.

Clinical and laboratory profiles of patients with episodes of febrile neutropenia (n = 267)

Two hundred and fifty-six oncology diagnoses were made over the study period, and 254 (99.2%) were included in the analysis. Of the 179 patients who received chemotherapy, 11 (6.1%) were identified as having comorbidities (Table 1).

The impact of diagnosis on patients with episodes of febrile neutropenia

The median age at diagnosis for male patients with at least one episode of FN was five years (IQR: 3–9 years) and six years (IQR: 2.25–11 years) for girls (p = 0.603). In all, 33/46 (71.7%) patients with ALL had FN. Amongst this group, patients with high-risk disease had a higher number of FN episodes 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 meet the threshold for statistical significance. Table 2

TABLE 1: Clinical and haematologic characteristics of study subjects based on febrile neutropenia episodes.

Variables	Number	Percentage	Mean ± s.d.	IQR
Number of FN episodes	112	-	-	-
1	38	33.9	-	-
2	25	22.3	-	-
3	24	21.4	-	-
4	20	17.9	-	-
5	3	2.7	-	-
6	2	1.8	-	-
Comorbidities†	11	-	-	-
Human immunodeficiency virus infection	6	54.5	-	-
Trisomy 21	4	36.3	-	-
Neurofibromatosis 1	1	9.0	-	-
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‡	-	-	-	98, 138
Very severe neutropenia (< 100 cells/mm^3)	193	72.3	-	-
Severe neutropenia (100 cells/mm^3 – 499 cells/mm^3)	55	20.6	-	-
Moderate neutropenia (500 cells/mm^3 – 999 cells/mm^3)	19	7.1	-	-
Platelets	-	-	-	-
Platelet × 10^9/L	72	-	-	31, 145
< 50 × 10^9/L	96	35.9	-	-
≥ 50 × 10^9/L	169	63.3	-	-
Missing	2	0.7	-	-
Phagocyte	-	-	-	-
Absolute phagocyte count cells/mm^3	24	-	-	5, 51
< 50 cells/mm^3	194	72.6	-	-
≥ 50 cells/mm^3	68	25.5	-	-
Missing	5	1.0	-	-
Blood transfusion	-	-	-	-
Yes	145	54.3	-	-
No	119	44.6	-	-
Missing	3	1.1	-	-
Focus of infection	-	-	-	-
Bloodstream	71	65.1	-	-
Respiratory	16	14.7	-	-
GIT	14	12.8	-	-
Renal	7	6.4	-	-
Multiple	1	0.9	-	-

GIT, gastrointestinal tract; IQR, interquartile range; FN, febrile neutropenia.
†, Data in total number of subjects (n = 179); ‡, Median = 300.

shows the proportions of patients with FN relative to their diagnoses.

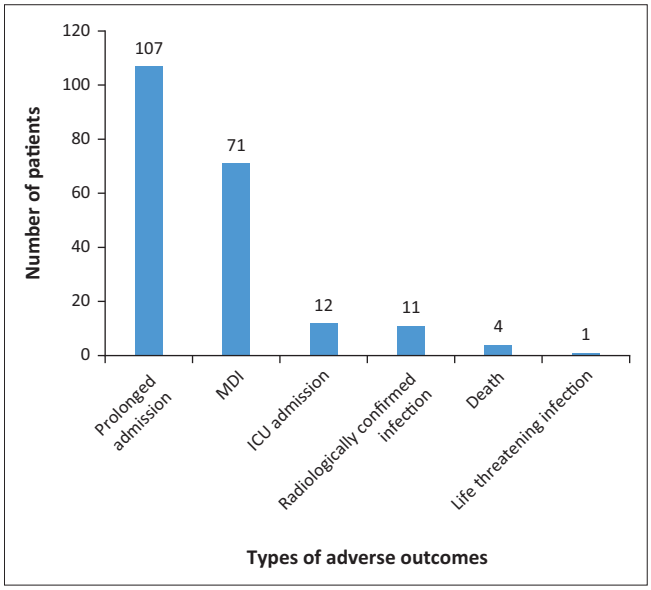
Risk factors for febrile neutropenia

A total number of 74 subjects had more than one 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, $p \leq 0.001$). Haematolymphoid malignancies ($p < 0.001$), intensive chemotherapy ($p \leq 0.001$), stem cell transplantation ($p = 0.021$) and the presence of central venous access devices (CVADs) ($p = 0.018$) were significantly associated with FN (Table 3).

TABLE 2: Proportion of patients with febrile neutropenia according to disease type and treatment intensity.

Variables	Presence of FN						χ^2	p
	Yes (n = 112)		No (n = 67)		Total			
	n	%	n	%	n	%		
Type of cancer (n = 179)							18.410	0.002
Solid	36	52.1	33	47.8	69	100.0		
ALL	33	71.7	13	28.3	46	100.0		
Lymphoma or HD	19	63.3	11	36.4	30	100.0		
AML	17	100.0	0	0.0	17	100.0		
Brain	6	40.0	9	60.0	15	100.0		
Others	1	50.0	1	50.0	2	100.0		
Chemotherapy myelosuppression intensity							64.853	< 0.001
Minimally	13	43.3	17	56.6	30	100.0		
Briefly	90	67.7	43	32.3	133	100.0		
Strongly	154	95.6	7	4.3	161	100.0		
Myeloablative	10	100.0	0	0.0	10	100.0		

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; HD, Hodgkin lymphoma; FN, febrile neutropenia.



ICU, intensive care unit; MDI, microbiologically determined infection.

FIGURE 1: Adverse outcomes in subjects with febrile neutropenia.

Independent predictors of febrile neutropenia

Multivariate analysis revealed that intensive as opposed to maintenance chemotherapy (odds ratio [OR]: 14.294; $p < 0.001$), a diagnosis of AML (OR: 4.019; $p = 0.039$) or ALL (RR: 7.698; $p = 0.02$) and SCT (OR: 11.662; $p < 0.001$) emerged as independent risk factors for FN. The presence of CVADs increased the odds ratio (OR: 2.685) of FN but narrowly failed to meet the threshold for statistical significance ($p = 0.051$) (Table 4).

Patients with adverse outcomes as a result of febrile neutropenia (n = 206)

There were 206 adverse events in 267 episodes of FN (n = 267; 77.1%) as shown in Figure 1. The median number of days for hospital admission for FN was five days (IQR: 3; 7 days).

TABLE 3: Risk factors for febrile neutropenia in study subjects (n = 179).

Variables	Yes		No		Total		OR	95% CI	p
	n	%	n	%	n	%			
Age									
≤ 5 years	42	56.7	32	43.2	74	100.0	0.656	0.669–1.083	0.851
> 5 years	70	66.6	35	33.3	105	100.0			
Gender									
Male	67	63.8	38	36.2	105	100.0	1.136	0.831–1.324	0.400
Female	45	60.8	29	39.2	74	100.0			
Cancer type									
Haematologic	50	79.4	13	20.6	63	100.0	3.345	1.431–4.154	**< 0.001**
Nonhaematologic	62	53.4	54	46.5	116	100.0			
Comorbidity									
Yes	7	63.6	4	36.4	11	100.0	1.132	0.228–2.841	0.524
No	104	62.3	63	37.7	167	100.0			
BM involvement									
Yes	14	63.6	8	36.4	22	100.0	1.606	0.221–1.720	0.252
No	27	51.9	25	48.1	52	100.0			
Disease progress or relapse									
Yes	31	65.9	16	34.0	47	100.0	1.219	0.408–1.647	0.353
No	81	61.4	51	38.6	132	100.0			
Type of chemotherapy†									
Intensive	249	83.8	48	16.2	297	100.0	5.476	1.233–2.409	**< 0.001**
Maintenance	18	48.6	19	51.3	37	100.0			
SCT									
Yes	8	100.0	0	0.0	8	100.0	1.796	1.152–1.943	**0.021**
No	104	60.8	67	39.2	171	100.0			
Concurrent radiotherapy									
Yes	21	61.8	13	38.2	34	100.0	1.016	0.483–1.91	0.531
No	91	62.7	54	37.2	145	100.0			
Central line†									
Yes	131	75.3	43	24.7	174	100.0	1.648	1.050–2.586	**0.018**
No	136	85.0	24	15.0	160	100.0			

Note: Data in bold are statistically significant.

CI, confidence interval; BM, bone marrow; SCT, stem cell transplant; OR, odds ratio.

†, In number of febrile neutropenia episodes (n = 267), others in number of subjects.

TABLE 4: Logistic regression showing independent predictor of febrile neutropenia.

Variables	Odds ratio	95% CI	p
Chemotherapy intensity			
Maintenance	1.000	-	-
Intensive	14.294	37.206–544.200	**< 0.001**
Central line			
No	1.000	-	-
Yes	2.685	0.998–7.226	0.051
Type of cancer			
Brain	1.000	-	-
HD or 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	1.000	-	-
Yes	11.662	3.093–36.013	**< 0.001**

Note: Data in bold are clinically significant.

SCT, stem cell transplant; HD, Hodgkin lymphoma; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; odds ratio; CI, confidence interval.

Microbiologically defined infection was seen in 71 FN episodes (26.6%). 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 because of 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. The cause of death in each case was septic shock.

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; 20.0%) and brain cancers (n = 3; 20.0%) (χ^2 = 23.256, p = < 0.001). Adolescents (age above 10 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 presence of a CVAD and the administration of a blood transfusion at admission emerged as significant risk factors for adverse outcomes (Table 5).

Laboratory markers as indicators of risk for adverse outcomes

A total white cell count below 0.3×10^9/L was a risk factor for adverse outcome (Table 6). Patients with very severe neutropenia with ANC < 0.1×10^9 cells/L (n = 106; 54.9%) were more likely to have adverse outcomes compared to those with severe (ANC: 0.1 to < 0.5×10^9 cells/L; n = 18; 32.7%) and moderate neutropenia (0.5×10^9 cells/L to < 1.0×10^9 cells/L; n = 6; [31.6%] [χ^2 = 10.837, p = 0.004]).

TABLE 5: Clinical risk factors for adverse outcomes in study subjects.

Variables	Presence of adverse outcome						OR	95% CI	*p*
	Yes		No		Total				
	n	%	*n*	%	*n*	%			
Age							1.022	0.850–1.228	0.477
< 5	20	27.0	54	72.9	74	100.0	-	-	-
> 5	30	28.6	75	71.4	105	100.0	-	-	-
Gender†							1.163	0.601–2.251	0.388
Male	28	26.7	77	73.3	105	100.0	-	-	-
Female	22	29.7	52	70.3	74	100.0	-	-	-
Intensity of chemo							1.494	0.768–2.905	0.177
Intense	124	49.8	125	50.0	249	100.0	-	-	-
Maintenance	6	33.3	12	66.7	18	100.0	-	-	-
Type of cancer†							3.215	1.542–5.964	**0.040**
Haematologic	27	42.8	36	57.1	63	100.0	-	-	-
Nonhaematologic	23	19.8	93	80.1	116	100.0	-	-	-
GCSF episode							1.205	0.878–1.655	0.283
Yes	20	57.1	15	42.9	35	100.0	-	-	-
No	110	47.4	122	52.6	232	100.0	-	-	-
Mucositis							2.378	1.188–1.903	**0.001**
Yes	52	63.4	30	36.6	82	100.0	-	-	-
No	78	42.2	107	57.8	185	100.0	-	-	-
Central line							2.043	1.344–2.288	**0.004**
Yes	78	57.4	58	42.6	136	100.0	-	-	-
No	52	39.7	79	60.3	131	100.0	-	-	-
BM involvement†							1.120	0.528–1.665	0.264
Yes	5	22.7	17	77.3	22	100.0	-	-	-
No	7	13.5	45	86.1	52	100.0	-	-	-
Blood transfusion							1.661	1.257–2.196	**< 0.001**
No	42	35.3	77	64.7	119	100.0	-	-	-
Yes	85	58.6	60	41.4	145	100.0	-	-	-

Note: Data in bold are statistically significant with $p = < 0.05$.
OR, odds ratio; BM, bone marrow; GCSF, granulocyte colony stimulating factor; CI, confidence interval.
†, Total number of subjects with FN and not febrile neutropenia episodes.

TABLE 6: Laboratory risk factors for adverse outcomes.

Variables	Yes		No		Total		AOR	CI	*p*
	n	%	*n*	%	*n*	%			
APC (cells/mm^3)							1.649	0.950–1.810	0.079
< 50 000	101	52.1	93	47.9	194	100.0	-	-	-
> 50 000	27	39.7	41	69.3	68	100.0	-	-	-
Haemoglobin (g/dL)							0.783	0.883–1.451	0.268
< 9	79	45.5	91	54.5	167	100.0	-	-	-
≥ 9	51	52.6	46	47.4	97	100.0	-	-	-
WBC (× 10^9/L)							3.082	1.354–2.204	**< 0.001**
< 0.3	67	65.0	36	35.0	103	100.0	-	-	-
> 0.3	61	37.7	101	62.3	162	100.0	-	-	-
Platelet × 10^9/L							1.188	0.847–1.407	0.501
< 50 000	49	51.0	47	49.0	96	100.0	-	-	-
> 50 000	79	46.7	90	53.3	169	100.0	-	-	-

Note: Data in bold are statistically significant with $p = < 0.05$.
WBC, white blood cell; APC, absolute phagocyte count; AOR, adjusted odds ratio; CI, confidence interval.

Independent predictors of adverse outcomes

On multivariate analysis, AML, severe neutropenia and the presence of a CVAD were shown to be independently predictive of an adverse outcome (Table 7).

Discussion

The factors affecting risk of FN and the adverse outcomes have been extensively reviewed in various settings. This study afforded an opportunity to interrogate previously unanswered questions relating to the occurrence of febrile neutropenia and its sequelae in the authors' service. Although they subserve a largely lower socioeconomic population, the treatment options available at their institution are matched in intensity to those found in more resourced settings, given the relative luxury of supportive care available onsite, which includes, amongst others, paediatric intensive care support, haemodialysis and a full palette of specialised paediatric surgical, radiological and rehabilitative care services. Given that identifying and

TABLE 7: Logistic regression showing independent predictors of adverse outcomes.

Variables	Adjusted odds ratio	95% CI	*p*
Type of cancer			
Brain	1.000	-	-
HD or 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	1.000	-	-
No	2.301	0.909–6.091	0.093
Mucositis			
No	1.000	-	-
Yes	1.726	0.944–3.154	0.076
Central line			
No	1.000	-	-
Yes	1.938	1.114–3.370	**0.019**
ANC strata			
Moderate	1.000	-	-
Severe	1.052	0.298–3.720	0.937
Very severe	1.170	0.346–3.960	0.801
WBC strata			
> 0.3	1.000	-	-
< 0.3	2.451	1.318–4.558	**0.005**
Blood transfusion			
No	1.000	-	-
Yes	1.742	0.983–3.086	0.057

Note: Data in bold are clinically significant.

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

managing iatrogenic immune suppression and its sequelae are an integral part of best practice, it seemed timeous for the authors to review their data to identify patients-at-risk for FN as a way to abrogate the adverse outcomes that may arise, most importantly reducing preventable infection-related mortality.

In this analysis, it was demonstrated that a diagnosis of AML, SCT and the use of intensive chemotherapy were independently predictive as risk factors for FN, whilst AML, the presence of CVADs and severe neutropenia (WBC $<0.3\times10^9$) were independently predictive of adverse outcomes as a result of FN.

Patients with haematologic malignancies had a higher propensity for chemotherapy-induced neutropenia (CIN) than their counterparts with solid tumours, and this is consistent with previous reports.[9,18,19] Replacement of haematopoietic cells with blast cells predisposes these individuals to intense bone marrow suppression and an increased risk of FN. Also, the increased intensity of chemotherapy regimens used to treat haematolymphoid malignancies further elevates the risk for FN.[20] In contrast to many haematological treatment regimens which are more intensive in their structure, solid tumour chemotherapy is administered in a cyclical fashion, allowing for count recovery between courses, reducing the effect of chemotherapy-induced leukopenia which may be associated with subsequent episodes of FN. Similarly (and unsurprisingly) then, patients with solid tumours with bone marrow involvement are also at risk for FN, like those with haematologic malignancies.[21] Although a higher proportion of patients with solid tumours with bone marrow involvement experienced FN, this did not reach the threshold for statistical significance.

The presence of a CVAD played a significant role in the predisposition to adverse outcomes consistent with previous reports.[7,18,22] Biofilms, which are aggregates of microbial organisms, have an affinity for artificial catheters and colonise their surfaces. Characteristically, these biofilms form a self-produced protective extracellular matrix that hinders their destruction by the host immune system or systemic antibiotics.[23] The placement of CVADs was identified as an independent risk factor for adverse outcomes, also previously shown,[24] as well as its risk for prolonged hospital admission.[25] Central venous access device-associated bloodstream infection is a common occurrence in patients, and this inadvertently increases FN-related adverse outcomes.[26]

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.[16,27,28] It has been shown that fungal infections, bacteraemia and life-threatening complications increase after five days of admission for FN.[16,17] Consequently, prolonged admission of more than five days was included as a measure of adverse outcome in this study. At RCWMCH, children with FN and severe neutropenia (ANC below 1000/mm^3) are admitted for three days for administration of broad-spectrum intravenous antibiotics contingent on blood culture results, count recovery, defervescence of fever and clinical improvement. Prolonged admissions may occur if fever continues beyond 72 h, if blood cultures flag positive or if an additional complication arises.

Adverse outcomes were observed in almost three-quarters of the episodes of FN in the study's patients. This result is higher than previously reported by Das et al. (26.3%)[4] and Miedema et al. (24.0%).[29] These differences may possibly be explained by the inclusion of prolonged admission as an indicator of adverse outcome in the present study. Notably, previous reports from South Africa have demonstrated a high incidence of adverse events (45.0%), despite the exclusion of prolonged hospital stay.[30] Unfortunately, the variation of indicators used as measures of adverse outcomes between studies complicates any direct comparisons that could be made.[4,29]

Microbiologically confirmed infection accounted for the second-most common adverse outcome in this patient cohort. Some studies have evaluated bacteraemia alone as an adverse outcome, and it has been shown to be the commonest cause of adverse outcomes in several studies.[2,10,18,29,31,32] Isolation of bacterial organisms using conventional blood culture in children with FN is low, and this has resulted in using and applying surrogate research parameters, like prolonged admission to hospital, to help identify individuals at risk of adverse outcomes from FN.[33]

Mortality from FN was 3.6% in this cohort. Mortality rates from FN vary from country to country. In Germany, a mortality rate of 0.7% has been reported.[3] compared to 10.0% in India.[4] This is almost certainly related to access to health care, more specifically the availability of paediatric ICU services. The mortality rate in this study's cohort is heavily influenced by the level of supportive care that is available at RCWMCH, and caution should be taken to not interpret this as a ubiquitous indicator of mortality for the whole country, given the variation in supportive care capability between POUs.

Although these findings are compelling, the authors recognise the limitations inherent in single institutional reviews with relatively small sample sizes. Despite that, however, poor data availability was uncommon (only two patients with missing folders were excluded). Additionally, death could not be evaluated as an outcome for prolonged admission because of low mortality rate.

In conclusion, FN is a common complication in children with cancer treated with chemotherapy. Although these findings do not differ significantly from those reported elsewhere where similar levels of care are available, the analysis has been instructive. Firstly, it is reassuring that there were no additional unknown factors, which may not have been anticipated, which were contributing to the development of FN and its sequelae. Secondly, the analysis will help streamline clinical decision-making through the early identification of patient groups-at-risk in parallel with the development of early intervention standard operating procedures. As an example, RCWMCH continues to hone the criteria for the insertion of CVADs, improve the continuous clinical training of the staff with respect to the management of central lines and infection control in general, as well as introducing commercially available bactericidal, fungicidal, anticoagulant line-locking agents to reduce biofilm growth which predispose to BSI and line failure. As transplantation onsite is a relatively new practice, strict isolation practices and negative pressure ventilation systems help to mitigate the risk of microbiological exposure to highly immunocompromised patients. The early identification of and the prompt response to FN by the clinical team remains a cornerstone of modern oncology care, and the assessment of factors which impact the cause and effect help to shape the care response. These factors require rigorous interrogation to ensure that the environments and practice are fit for purpose and prioritise the safety of the patients.

Acknowledgements

The authors acknowledge the effort of Michelle Karnemeyer for her assistance with folder retrieval.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

M.O.A. was involved in conceptualisation, methodology, data analysis and writing of the original article; A.D. helped in supervision, writing and reviewing the manuscript and resources; M.H. also helped in supervision, writing and editing.

Funding information

The research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data availability

Raw data are available on request from the corresponding author , M.O.A., and there is no restriction on data availability.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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