Evaluation of Pattern and Outcome of Cancer Patients with Febrile Neutropenia Presented in Clinical Oncology Department Assiut University from 2018-2022, A Real Life Study.

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Abstract:

Background and aims: Febrile neutropenia (FN) is the most serious complication of chemotherapy which requires adequate assessment and treatment. The objective of this study was to evaluate the epidemiological pattern and clinical outcomes of chemotherapy-induced FN.

Methods: This was a single center retrospective observational study conducted at the Clinical Oncology Department of Assiut University Hospital Medical records of patients with cancer and FN were reviewed from January 2018 to December 2022.

Results: The incidence of FN was 3.8%. A total of 152 patients were included with a mean age of 51 years and 71% were females. Most patients (92%) had solid malignancies. It occurs most frequently (86.8%) during the first 3 cycles of chemotherapy. Twenty-two patients (14.5%) had a high risk Multinational Association for Supportive Care in Cancer (MASCC) score, and 23 patients (15%) received primary prophylaxis. Twenty patients (13.2%) and 60 patients (39.5%) required chemotherapy dose reduction and cycle delay respectively. Twenty-two patients (14.5%) needed hospitalization and 8 patients (5.3%) died during their admission. Baseline MASCC score (<21), long duration of FN (>4 days), chemotherapy delay and respiratory tract infection were factors significantly associated with mortality.

Conclusions: This study showed that the incidence of FN was common among solid cancer. It occurs most frequently during the first three cycles of chemotherapy. Physicians should be aware of factors associated with mortality to provide a better monitor, management and improve the outcome of FN.

Keywords: febrile neutropenia, cancer, chemotherapy, clinical outcomes

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Introduction:

Cancer patients are at increased risk for infection, as a consequence of immune function impairment and loss of barrier integrity, related to both their underlying malignancy and the toxic effects of anticancer therapy [1].

The association of neutropenia and infection continues to be the commonest life-threatening complication of chemotherapy that predisposes cancer patients to serious infections and reduces their intake of optimal therapeutic doses of chemotherapy [2] and a major cause of morbidity and mortality in this patient population [3,4].

Neutropenic fever is defined as a single oral temperature greater than or equal to 101 F (38.3 C) or a temperature greater than or equal to 100.4 F (38 C) for at least an hour, with an absolute neutrophilic count (ANC) of less than 1500 cells/microliter. In severe neutropenia, the ANC is less than 1500 cells per microliter. Febrile neutropenia is the most common complication of cancer therapy [4].

The presence of fever with neutropenia is associated with multiple microorganisms including bacteria, viruses, and fungi. Gram-positive microorganisms have emerged as the predominant pathogens, being responsible for severe infection in neutropenic patients [5].

Many scientific societies at a national and international level make a distinction between patients with febrile neutropenia who are at high or low risk, depending on defined criteria set out in globally validated scales. One of the most commonly used is the

Multinational Association of Supportive Care in Cancer (MASCC) score, it identified patients suitable for outpatient management of FN (low risk) and patient with high risk of complications and should be hospitalized [6,7].

Another validated scale like The Clinical Index of Stable Febrile Neutropenia (CISNE) score was developed and claims to have improved clinical utility and performance compared with the MASCC score. The CISNE score has been validated to predict major complications in FN patients [8].

Additionally, the risk assessment of febrile neutropenia can be performed by the patient risk score (PRS) which is a tool that has been developed based on the European Organization for Research and Treatment of Cancer (EORTC) guideline in order to evaluate the factors more objectively [9].

Appropriate granulocyte-colony stimulating factor (G-CSF) prophylaxis can be initiated after assessing the risk factors for FN for a patient before planning the chemotherapy. Patients who are receiving a chemotherapy regimen that is related to a high risk of neutropenia benefit from the usage of G-CSFs [10].

Clinical practice guidelines have recommended prophylaxis with G-CSFs to reduce the incidence of FN in patients receiving chemotherapy. G-CSFs used for primary prophylaxis start with the first cycle of chemotherapy and continue through subsequent cycles while secondary prophylaxis with G-CSFs is given to patients who experienced neutropenia or FN during a prior cycle of chemotherapy [11,12].

Primary prophylaxis with G-CSFs should be used for patients receiving chemotherapy regimens that are associated with a high risk of developing FN (>20%). For regimens with a low risk of FN (<10%), routine use of prophylaxis with G-CSFs is not recommended [11].

The consequences of febrile neutropenia are varied; many patients may die from life-threatening infections. At minimum, the resulting chemotherapy dose reductions, delays or even discontinuation may all of which can lead to reduced treatment response and lower survival [13].

This study aimed to evaluate the epidemiological pattern and clinical outcomes of chemotherapy-induced febrile neutropenia (a single-center experience).

Patients and Methods:

Study Design:

This was a single center retrospective cross section study conducted at the Clinical Oncology Department of Assiut University Hospital on cancer patients received chemotherapy and presented with febrile neutropenia from January 2018 to December 2022. The study was approval by the Ethics Committee of Assiut University Hospital before data collection in accordance with the Declaration of Helsinki. The sample size was calculated using EPI, version2, open source calculator—SSPropor. Based on prevalence of febrile neutropenia in cancer patient 15%with confidence interval of 95% and power of the study 80%, sample size equal 151 cases from 2018 to 2022.

Study Protocol and Population:

Data were collected from medical records of patients diagnosed with FN during the 4- year study period. Febrile neutropenia was defined as an absolute neutrophil count (ANC) < 500 cells/ mm3 with a single measurement of 38.5°C or a sustained temperature of >38°C for more than 1 hour. FN were determined and graded using the Common Terminology Criteria for Adverse Events version 4.03[14].

Eligibility Criteria:

1. Male or female adults > 18 years old.
2. Patients histologically proven to have either solid or hematologic malignancy.
3. Patients under chemotherapy treatment and developed FN at any cycle or had more than one episode of FN.

Patients with no initiation cycle data, incomplete medical or laboratory records and follow-up/outcome data were excluded from the study.

Data collection:

The following informations was obtained:

1. Age, sex, performance status of the ECOG scale to assess the functional status of cancer patients, mainly their daily life ability, ranged from 0 (patients with normal activity) to 4 (bed-ridden patients at high risk of complications during febrile neutropenia).
2. Comorbidities (hypertension, diabetes, liver and renal disease, cardiovascular disease).
3. Type of the cancer and TNM stage.
4. Treatment modalities and types of chemotherapy regimens
5. Type of G-CSF administration defined as primary prophylaxis (G-CSF use in the first cycle before a documented FN) or secondary prophylaxis (incorporating G-CSF prophylaxis in cycles other than the first) and G- CSF use as treatment for neutropenia.
6. Patient risk score according to the EORTC guidelines (range, 0–11) and patients with PRS ≥ 3 were considered to have a high risk of developing FN.
7. MASCC risk index at onset of FN identify FN patients with different risk of complications and death. It served to divide patients into low or high-risk groups (values ≥ or < 21 points, respectively).
8. Laboratory investigations data at the onset of FN episode which include biochemstry and hematology studies, renal& liver functions, blood/ urin/stool/sputum cultures, nasal and oral swabs from infected sitesto identify the sourse of infection.
9. Types of antibiotics/antimicrobial used.
10. Number and duration of FN episodes.

Followed-up data recorded until the end of chemotherapy. Criteria for study completion comprised the remission of fever and neutropenia, whether the patient remained in the hospital for other reason or death of the patient.

For the remission of fever, we considered values lower than 38˚C for at latest 48 hours and values higher than 500 neutrophils / mm3 for at least the two preceding days were regarded as neutrophil recovery.

Endpoint:

The primary outcome measure was the incidence and epidemiology of FN according to a multitude of factors such as the type of cancer, the age, and sex of the patient, the type and cycle of treatment, preventive measures, risk assessment procedures and adequate patient management plans.

We also report clinical outcomes using patients and chemotherapy cycles as the unit of analysis. Patient outcomes defined as recovery, duration of febrile neutropenia-related hospitalizations or CIN/FN related death. Percentage of patients receiving full dose of scheduled chemotherapy or chemotherapy disturbance (dose reduction, delay >7 days, cancelation of administration of chemotherapy) was regarded as chemotherapy outcome.

Statistical Analysis:

Data was analyzed using the Statistical Package for Social Science (SPSS), version 26.0 for Windows. Quantitative data was tested for normality by Shapiro-Wilk test and expressed as mean ± SD or median (range) according to their distribution, while qualitative data were presented by frequencies and percentages. Chi square test and Fisher's Exact Test were used to compare proportion between different groups. P value considered significant when <0.0.5.

Results:

In total, 152 cancer patients were enrolled in the study from 2018 to 2022. The incidence of febrile neutropenia was 3.8%. The mean age was 51.31 and most patients (71.1 %) were females.

According to comorbidities, 24 patients had comorbidities, 15 (9.9%) of them had diabetes mellitus and 13 (8.6%) had hypertension.

Tumor stage was represented as stage I in 5 patients (3.3%), stage II in 47 patients (30.9%), stage III in 59 patients (38.8%) and stage IV in 41 patients (27%). Baseline demographic and clinical characteristics are shown in Table 1. The number of patients who received prophylactic G-CSF was 27 patients (17.8%), 23 of these patients received primary prophylactic G-CSF and 4 patients received secondary prophylactic G-CSF.

There were 130 (85.5%) patients with the low risk MASCC score ≥ 21versus 22 (14.5%) patients with high-risk score for complications < 21 (14, 5%). As shown in Table 2.

Regarding patient risk score, there were 97 patients (63.8%) with score <3 and 55 patients (36.2%) with PRS ≥3 as shown in Table 3.

One hundred and twenty patients (78.9%) developed FN once while 32 patients (21.1%) developed more than one episode of FN. The median duration of FN of the enrolled patients was 4 days (range; 3-12 days). The history of episodes of FN and its duration at enrollment is provided in Table 4.

To know Types of cancer among patients with FN, Table 5 showed that breast cancer was the most common with percentage 36.2 followed by genitourinary cancer with percentage 19.1%. Hematological malignancy (lymphoma) represented in 7.9 % of patients with FN.

Table (1): Baseline demographic and clinical characteristics of cancer patients with FN at Clinical Oncology department from January 2018 to December 2022 (n= 152)

Patients' characteristics	N=152	(%)
Age (years)		
Mean ± SD (range)	51.31±14.04 (20-82)	
<65 years	123	80.9%
≥65 years	29	19.1%
Sex		
▪ Male	44	28.9%
▪ Female	108	71.1%
Presence of comorbidities	24	15.8%
Types of comorbidities		
▪ Diabetes mellitus	15	9.9%
▪ Hypertension	13	8.6%
▪ CVD	3	2.0%
Number of comorbidities		
▪ 0	128	84.2%
▪ 1	18	11.8%
▪ ≥2	6	4.0%
Performance status (ECOG)		
▪ 0	125	82.2%
▪ 1	25	16.4%
▪ 2	2	1.3%
TNM stage		
▪ I	5	3.3%
▪ II	47	30.9%
▪ III	59	38.8%
▪ IV	41	27.0%

Data were expressed as frequency and % or mean ± SD: standard deviation.
FN: febrile neutropenia, CVD: cardiovascular disease, ECOG: Easter Cooperative Oncology Group.

Table (2): Clinical risk factors of febrile neutropenia in cancer patients at Clinical Oncology department from January 2018 to December 2022 (n= 152)

Prophylactic G-CSF	N=152	%
Type of prophylaxis		
▪ No	125	82.2%
▪ Primary	23	15.1%
▪ Secondary	4	2.6%
MASCC risk index at onset of FN		
▪ ≥ 21 (Low risk of FN)	130	85.5%
▪ < 21(High risk of FN)	22	14.5%
Mean ± SD (range)	21.81±1.58 (18-26)	

Data were expressed as frequency and % or mean ± SD.
G-CSF: granulocyte-colony stimulating factor,
MASCC: Multinational Association for Supportive Care in Cancer

Table (3): Patient risk score in cancer patients with febrile neutropenia (FN)

Variable	Score	N=152 (%)
Age ≥65	3	29 (19.1%)
History of prior FN	3	32 (21.1%)
Poor performance status	1.5	2 (1.3%)
Female sex	0.5	108 (71.1%)
No antibiotic prophylaxis	0.5	120 (78.9%)
Patient Risk Score (PRS): median (range)	1.00 (0.50-6.50)	
▪ PRS <3	97 (63.8%)	
▪ PRS ≥3	55 (36.2%)	

Data were expressed as frequency and %

Table (4): Episodes and duration of FN among cancer patients at Clinical Oncology department from January 2018 to December 2022 (n= 152)

Variables	N=152	(%)
Episodes of febrile neutropenia (FN)		
▪ Once	120	78.9%
▪ > 1 episode	32	21.1%
Duration of febrile neutropenia (days)		
Median (range)	4.0 days (3-12)	
▪ <4 days	70	46.1%
▪ ≥ 4 days	82	53.9%

Data were expressed as frequency and % or median (range)

Table (5): Types of cancer among patients with FN at Clinical Oncology department from January 2018 to December 2022 (*n* = 152)

Cancer type	N=152	%
Breast cancer	55	36.2%
Genitourinary cancer	29	19.1%
▪ Urinary bladder cancer/ureter/renal pelvis TCC	13	8.6
▪ Vesicular mole	5	3.3
▪ Ovarian cancer	6	3.9
▪ Endometrial/uterine cancer	4	2.6
▪ Testicular cancer	1	0.7
GIT cancer	28	18.4%
▪ Colon cancer	10	6.6
▪ Rectal/sigmoid cancer	9	5.9
▪ Pancreatic cancer	5	3.3
▪ Gastric, esophageal cancer	4	2.6
Head and neck cancer	15	9.9%
Hepatobiliary cancer	5	3.3%
▪ Gall bladder cancer	3	2.0
▪ Cholangiocarcinoma	2	1.3
Lung cancer	4	2.6%
Sarcomas	4	2.6%
Hematological malignancy (lymphoma)	12	7.9%

Data were expressed as frequency and %

Laboratory investigations of patients with FN according to CBC revealed that, the median number of WBCs was 2.40x109 WBC/ liter with range from 0.17x109/L to 5.20x109/L while the median number of neutrophil was 0.50cells/microliter with range from 0.09x109/mL to 1.30x109/ml.

Single modality chemotherapy was most commonly employed at the start of treatment of the patients, and this was used in 96.1% of cases and the remainder (3.9%) received concurrent chemoradiation. According to chemotherapy regimen, 47 patients (30.9%) received anthracycline-based chemotherapy (cyclophosphamide+ doxorubicin) and 44 patients (28.9%) received platinum-based chemotherapy. The majority of the patients (86.8%) developed febrile neutropenia during the first three cycles of chemotherapy while 13.2% of patients developed the episode of FN between 4th to 6th cycles (Table 6).

Table (6): Treatment modalities and number of cycles of episode of FN of cancer patients at Clinical Oncology department from January 2018 to December 2022 (n= 152)

Variables	N=152	(%)
Treatment modalities		
Chemotherapy alone	146	96.1%
▪ Ifosfamide-based	4	2.6%
▪ Platinum-based	44	28.9%
▪ Fluorouracil-based	31	20.4%
▪ Anthracyclin-based	47	30.9%
▪ Taxane	12	7.9%
▪ Others	8	5.3%
Chemotherapy + radiotherapy	6	3.9%
Post cycle FN		
▪ 1-3	132	86.8%
▪ 4-6	20	13.2%

Data were expressed as frequency and %
FN: febrile neutropenia, Others: irinotecan, EMACO (etoposide,dactinomycin, methotrexate, leucovorin,cyclophosphamide, vincristine), FCR(fludarabine, cyclophosphamide, rityximab)

A positive blood culture was found in 60 patients (39.5%). E-coli was the most predominant organism in 30 patients (19.7%). Sputum cultures identified 5 patients (3.3%). Stool cultures were done in 118 patients It revealed that 13 patients (8.6%) were positive for E-COLI. Also, a urine culture was done in 118 patients and 7 patients (4.6%) were positive. One patient was positive for bronchoalveolar lavage with streptococcus. Nasal swabs were done for 7 patients, COVID19 represented in 6 patients (3.9%). One patient was positive for oral swab with fungi (0.7%). The source of infection was identified in 53 patients (61.8%). Data is presented in Table 7.

Table (7): Results of cultures and swab done to cancer patients with FN at Clinical Oncology department from January 2018 to December 2022 (n= 152)

Variables	N=152	(%)
Blood culture		
▪ Negative	92	60.5%
▪ Positive	60	39.5%
▪ E. coli	30	19.7%
▪ CONS/staph hominins	21	13.8%
▪ Klebsiella	7	4.6%
▪ Streptococcus	2	1.3%
Sputum culture		
▪ Negative	147	96.7%
▪ Positive	5	3.3%
▪ E. coli	3	2.0%
▪ streptococcus	1	0.7%
▪ Enterobacter cloacae complex	1	0.7%
Stool culture[#]		
▪ Negative	105	69.1%
▪ Positive (E. coli)	13	8.6%
Urine culture[#]		
▪ Negative	111	73.0%
▪ Positive	7	4.6%
▪ CONS/staph hominins	3	2.0%
▪ E. coli	3	2.0%
▪ Staph aureus	1	0.7%
Bronchoalveolar lavage		
▪ Not Done	151	99.3
▪ Positive (streptococcus)	1	0.7
Nasal swab		
▪ Not Done	145	95.4
▪ Positive	7	4.6%
▪ COVID	6	3.9
▪ E. COLI	1	0.7
Oral swab		
▪ Negative	151	99.3
▪ Positive (Fungi)	1	0.7
Source of infection		
▪ GIT	22	14.5%
▪ Respiratory tract	14	9.2%
▪ Skin& soft tissue	12	7.9%
▪ Urinary tract	5	3.3%

Data were expressed as frequency and %
#34 patients (22.4%) not done to their stool or urine culture.

Eighty percent of patients (122 patients) with low risk MASCC score received empiric antibiotics as penicillin plus fluroquinolone while10 patients (6.6%) with high-risk MASSC score received meropenem as empirical antibiotics. Other patients received antibiotics according to culture results.

The observed outcomes over the course of CTH cycles showed that chemotherapy dose reduction was done in 20 patients (13.2%) and 60 patients (39.5%) had chemotherapy delay. There was no chemotherapy discontinuation due to FN. In the present study, 8 patients (5.3%) died during their admission, according to cause of death, one patient (0.7%) died due to acute kidney injury, and 7 patients (4.6%) died because of sepsis, the remaining patients had a resolved FN completely without sequalae. Data is summarized in Table 8.

Table (8): Clinical outcomes at the patient and chemotherapy cycle level of chemotherapy-induced FN among cancer patients at Clinical Oncology department from January 2018 to December 2022 (*n* = 152)

Unit of analysis	N=152	(%)
FN-related chemotherapy disturbances		
Chemotherapy dose reduction		
▪ Yes	20	13.2%
▪ No	132	86.8%
Chemotherapy delay		
▪ Yes	60	39.5%
▪ No	92	60.5%
FN-related hospitalizations	22	14.5%
Clinical events		
▪ Live	144	94.7%
▪ Inpatient death	8	5.3%
▪ AKI requiring new dialysis.	1	0.7%
▪ Septic shock requiring pressors	7	4.6%

Data were expressed as frequency and %
FN: febrile neutropenia, AKI: acute kidney injury

Table 9 shows the outcome of patients who developed febrile neutropenia in accordance with their demographic and clinical characteristics. There is no statistically significant difference in outcome of patients living or died regarding their demographic or clinical characteristics.

Regarding prophylactic use of G-CSF, there is no statistically significant difference in outcome and prophylactic G-CSF as shown in Table 10. However, there was statistically significant difference between outcome and MASCC score, higher percentage of MASCC risk among died (87.5%) compared to (10.4%) among living patients, P- value <0.001. Moreover, there was statistically significant difference between outcome and duration of FN, higher percentage of duration ≥ 4 days FN among died (100%) compared to (51.4%) among living patients, p-value 0.008.

Table 11 shows there is no statistically significant difference for outcome of patients with treatment modalities and number of cycles.

Table 12 shows statistically significant outcome for patients who had chemotherapy delay with higher percentage among died (87.5%) compared to (36.8%) among living patients with P-value 0.004. Additionally, a statistically significant outcome for patients diagnosed with respiratory tract infection with higher percentage among died (37.5%) compared to (7.6%) living patients with P-value 0.027.

Table (9): Association between demographic and clinical characteristics of cancer patients with FN with their outcome

Variables	Live (n=144)	Died (n=8)	P-Value*
Age (years)			
▪ <65	116 (80.6%)	7 (87.5%)	0.627
▪ ≥65	28 (19.4%)	1 (12.5%)	
Sex			
▪ Male	40 (27.8%)	4 (50.0%)	0.177
▪ Female	104 (72.2%)	4 (50.0%)	
History of Febrile neutropenia	30 (20.8%)	2 (25.0%)	0.778
Presence of comorbidities	22 (15.3%)	2 (25.0%)	0.463
Types of comorbidities			
▪ Diabetes mellitus	13 (9.0%)	2 (25.0%)	0.180
▪ Hypertension	13 (9.0%)	0 (0.0%)	0.999
TNM stage			
▪ I	5 (3.5%)	0 (0.0%)	0.999
▪ II	45 (31.3%)	2 (25.0%)	0.999
▪ III	57 (39.6%)	2 (25.0%)	0.671
▪ IV	37 (25.7%)	4 (50.0%)	0.270

Data were expressed as frequency and %

*Chi Square test/Fisher Exact test compares proportions between groups

Table (10): Association between G-CSF prophylaxis, clinical risk factors& duration of febrile neutropenia in cancer patients with their outcome

Variable	Live (n=144)	Died (n=8)	P-Value*
Prophylactic G-CSF			
▪ Not received	119 (82.6%)	6 (75.0%)	0.582
▪ Received	25 (17.4%)	2 (25.0%)	
MASCC Risk			
▪ Low	129 (89.6%)	1 (12.5%)	<0.001
▪ High	15 (10.4%)	7 (87.5%)	
Duration of FN			
<4 days	70 (48.6%)	0 (0.0%)	0.008
≥ 4 days	74 (51.4%)	8 (100.0%)	

Data were expressed as frequency and %

*Chi Square test/Fisher Exact test compares proportions between groups

Table (11): Association between treatment modalities& number of cycles of episodes of febrile neutropenia in cancer patients and their outcome

Variables	Live (n=144)	Died (n=8)	P-Value*
Treatment modalities			
Chemotherapy alone			
▪ Ifosfomide-based	3 (2.1%)	1 (12.5%)	0.392
▪ Platinum-based	43 (29.9%)	1 (12.5%)	0.538
▪ Flurouracil-based	30 (20.8%)	1 (12.5%)	0.975
▪ Anthracyclin-based	45 (31.3%)	2 (25.0%)	0.999
▪ Taxane	11 (7.6%)	1 (12.5%)	0.980
▪ Others	7 (4.9%)	1 (12.5%)	0.716
Concurrent chemoradiation	5 (3.5%)	1 (12.5%)	
Post cycle febrile neutropenia			
▪ 1-3	124 (86.1%)	8 (100.0%)	0.258
▪ 4-6	20 (13.9%)	0 (0.0%)	

Data were expressed as frequency and %

*Chi Square test/Fisher Exact test compares proportions between groups

Table (12): Association between FN-related chemotherapy disturbances and source of infection in cancer patients with their outcome

Variables	Live (n=144)	Died (n=8)	P-Value*
Chemotherapy dose reduction			
▪ Yes	20 (13.9%)	0 (0.0%)	0.598
▪ No	124 (86.1%)	8 (100.0%)	
Chemotherapy delay			
▪ Yes	53 (36.8%)	7 (87.5%)	0.004
▪ No	91 (63.2%)	1 (12.5%)	
Source of infection			
Respiratory tract			
▪ Yes	11 (7.6%)	3 (37.5%)	0.027
▪ No	133 (92.4%)	5 (62.5%)	
Urinary tract			
▪ Yes	4 (2.8%)	1 (12.5%)	0.240
▪ No	140 (97.2%)	7 (87.5%)	
GIT tract			
▪ Yes	19 (13.2%)	3 (37.5%)	0.091
▪ No	125 (86.8%)	5 (62.5%)	
Skin& soft tissue			
▪ Yes	10 (6.9%)	2 (25.0%)	0.123
▪ No	134 (93.1%)	6 (75.0%)	

Data were expressed as frequency and %

*Chi Square test/Fisher Exact test compares proportions between groups

Discussion:

This epidemiological study includes 152 patients who developed FN during their cancer treatment.

The incidence of FN in the present study was 3.8% which is lower than the incidence in Ethiopia (50%). [15] where as in South Korea and Turkey showed that the incidence of FN was 18% and 49.1% respectively [17] while in Nigeria the incidence of FN among the patients was 5.3% [18].

In a systematic review and meta-analysis of 65 observational and 110 randomizes controlled trials (RCT) cohorts, the FN rate was 11.7% and 7.9% in the observational and RCT cohorts, respectively [19].

There are varying degrees of neutropenia and FN reported by different studies and this difference could be attributed to different patient characteristics, different chemotherapy regimens, or differential use of G-CSF for prophylaxis during chemotherapy cycles.

The mean age of patients in the study is 51.31 (SD±14.04) with female predominance in (71.1%) of cases similar to report from [20,21]. In contrast to study [2], [22] in which male gender was the most predominant.

Most patients had ECOG≤1 score which is consistent with that reported by Bachlitzanaki [23].

More than eighty percent of patients (84.2%) have no comorbidities (DM, HTN, CVD) similar to report in Aras[10] . On the other hand, 6 patients (4%) had multiple comorbidities which is consistent with results in study of Mazzaro [24] that showed 68.86% patients were without comorbidities and two patients had multiple comorbidities.

In a multivariate analysis of a study revealed that advanced age, presence of two or more comorbidities, low baseline WBC, prolonged duration of neutropenia were significantly associated with higher rate of FN [25].

In our study FN episodes were common in solid tumors with percent 92.1%. which is consistent with the study of Pappu [2]. But research conducted by Joudeh et al showed that the hematological malignancy affected 84.7% of patients with FN [26].

Breast cancer was the most common cancer in the present study which represent 36.8% patients similar to study conducted in palestin Rabayah[27] and in tanzania study Safari [21].

On the contrary, a study from palastin, reported FN episodes were common in hematological malignancies in 86 percent [2] and study conducted in spain found that hepatobiliary tumors were the most frequent neoplasm associated with episodes of FN[28].

Most of patients in this study were with cancer stage III. In contrast with that report in study of [23] where most patients were with stage IV.

In our cases, the rate of FN was reported between 1-3 cycled of chemotherapy (86.8%). This is in agreement with the study of Dessalegn, Fantahun [15] who revealed that the magnitude of FN continuously increased up to the 4th cycle and the highest rate was recorded in the fourth cycle (20.7%).

In the current study, the rate of patients who developed <1 episode of FN was 21%, this rate was higher than results reported by others [29], [30], [31]. In real word multinational study, The rate of patients

with ≥ 1 episode of FN was 9% [29] and In the randomised trial, the overall proportion of patients having ≥ 1 occurrence of FN was 5.8% [30]. Another real-world study reported that the rate of patients who developed ≥ 1 episode of FN was 6.1%[31].

According to the MASCC risk index, nearly most of patients fell within low risk category (≥ 21) in 85.5 % of patients, similar to that reported in Joudeh et al. [2]. But in contrast to study of Parodi [32] which revealed that nearly all patients were with high risk category (<21).

Hospitalization due to FN in our cases was reported in 14.5 % of patients. In the study of Jolis [33] reported that 5.6% of breast cancer and 12.7% of lymphoma patients were hospitalized due to FN for a mean of 10.0 days (range 1–41).

Prolonged and sever neutropenia increase risk of mortality rate [34]. In our study, 82 patients (53.9%) had FN with duration more than 4 day with increasing mortality rate (14.5%) between them. Which is similar to that reported in Joudeh et al. [2] study.

Regarding treatment modalities, our study showed 146 patients developed FN during treatment with chemotherapy alone in which anthracycline based regimens were the most predominant regimen particularly cyclophosphamid -doxorubicin regimen in breast cancer which is consistent with the results in other studies [15][20],[23].

The current study used the EORTC guidelines as a framework for evaluating the myelotoxicity of the chemotherapy regimen and the associated FN risk as well as the presence of patient risk factors. In our cases, 23 patients (15%) received primary prophylaxis G-CSF because they had chemotherapy protocol FN risk of >20% and PRS ≥3 in spite of 36% of patients had PRS ≥3. This means that the used G-CSF was inappropriate for this group of patients.

The results were consistent with the previous study [10] which showed that the patterns of G-CSF use were undertreated in 34.7% of patients for the prophylaxis. But the observed rates of CIN/FN-related hospitalizations and the proportions of patients experiencing CIN/FN related chemotherapy disturbances were not statistically different; however, the proportion of cycles with chemotherapy disturbances was highest among under-prophylacted patients. [35]

Regarding blood stream infection we found in our study that 60 cultures were positive for microorganism, 37 cultures (61.6%) were gram negative bacteria (GNB) and 23 cultures (38.4) were gram positive bacteria (GPB). Dominant GNB was E. Coli (81.08%). Concerning GPB, the major organisms isolated were Staphylococcus coagulase negative (CONS) and Streptococci sp, which is consistent with that reported in El Omri et al. [36] study. On the contrary, Gram-positive manifested in about 54% of the cases in Joudeh et al. [2].

Regarding the focus of fever, our study found that 61.8% of patients had positive cultures in compared to that reported in Joudeh et al study 32.7% had an identified focus of fever [2].

In this study, COVID-19 infection constituted 3.9% of febrile neutropenic cases and fungal infections were found in 0.7% compared to that reported in Joudeh, Sawafta [2] study, COVID-19 infections were found in 6.3% oh FN cases and Fungal infections were found in 3.2% of the cases.

According to antimicrobial agents used during FN, our study showed that the most common empiric antibiotics were penicillin (amoxicillin\clavulanate) and fluroquinolone (ciprofloxacin) (92.42%) mostly in low risk patients followed by meropenem (7.58%) mostly in high risk patients. In terms of culture-guided antibiotics, aminoglycosid and meropenem were the most common agent used (20%) followed by rifampicin and cephalosporin. These results are different from results of the study done by Joudeh [2] showed that amikacin was the most common empiric therapy (82.7%), followed by piperacillin/tazobactam (49.33%), ceftazidime (46.7%), and vancomycin (42%).

In terms of culture-guided antibiotics, amikacin was the agent most frequently used (46%), followed by vancomycin (38.7%), then ceftazidime (35.33%).

Chemotherapy dose reductions and delays were observed in 20 (13.2%) and 60 (39,5%) patients, respectively. in contrast to the study of Leon Rapoport [29] which revealed that Chemotherapy dose reductions were observed in 78 patients (22%) and chemotherapy delays were observed in 148 (41%) patients.

In the present study, 8 patients (5.3%) died during their admission, according to cause of death, one patient (0.7%) died due to acute kidney injury, and 7 patients (4.6%) died because of sepsis. On the contrary Mazzaro et al. [24] showed that two patients died, one due to renal failure and the other due to sepsis.

To identify factors significantly associated with mortality in our cases, statistically significant factors were MASCC risk index (<21), duration of FN (> 4 days), ChT delay and respiratory tract infection as a cause of FN.

The study done by Parodi [32] reported that neutropenia lower than 50 cells/mm3, hospitalization at the onset of FN, presence of CVC at presentation, treated infection before the onset FN, hypotension/ tachycardia/ tachypnea/ dehydration at the onset of FN, initial use of vancomycin, unremitted fever at day 7 or unremitted neutropenia at day 14, as well as initial positive blood cultures, an ECOG score >3 and MASCC risk index <15. Upon multivariate analysis, the presence of dehydration and tachycardia, the existence of a treated infection before the onset FN, along with unremitted fever or neutropenia at days 7 and 14 were significantly associated with mortality.

Limitations:

Our study has some limitations. First, it is a single center retrospective study. Second, lack of some data about G-CSF prophylactic in some patients and nutrition status of patient.

Conclusion:

This study showed that the incidence of FN was high among solid cancer. It occurs most frequently

during the first three cycles of chemotherapy. Prognostic factors significantly associated with mortality in our cases were MASCC risk index (<21), duration of FN (> 4 days), chemotherapy delay and respiratory tract infection.

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