ORIGINAL ARTICLE

Exploring Febrile Neutropenia in a Tertiary Care Hospital: Current Trends, Economic Implications, and Clinical Insights

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Abstract

Background: Febrile neutropenia (FN) to date remains a significant cause of morbidity, mortality, and increased healthcare costs among oncology patients. Existing data on its economic implications in low- and middle-income countries (LMICs) is limited.

Objective: To assess the trends of FN admissions in the inpatient setting and their resultant economic burden in patients with solid organ malignancies within an LMIC setting.

Methods: We conducted a retrospective chart review study at the Aga Khan University Hospital, Karachi, Pakistan, from June 2023 to September 2024. One hundred adult patients with solid malignancies who were admitted with FN were included. Demographic, clinical, and economic data were collected and analyzed. Patients were stratified by risk using the Multinational Association for Supportive Care in Cancer (MASCC) score. The primary outcomes of our study included the length of stay (LOS), antibiotic duration, and cumulative hospitalization cost.

Results: Of the 100 patients, 49% were considered low risk (MASCC ≥21). The mean patient age was 54 (SD=13.6) years. High-risk patients had a longer LOS (6.3 *vs.* 3.2 days) and a longer antibiotic therapy duration (8 *vs.* 5 days). Grade 4 neutropenia was found in 60%. The mean hospitalization cost was approximated at $1,200-$1,800 USD per admission (average $350/day), with intravenous antibiotics accounting for 20% and granulocyte colony-stimulating factor 3% of the total costs.

Conclusion: Implementing FN risk-based protocols in LMICs can enable safe outpatient management of low-risk patients, reduce healthcare costs by lowering admissions, and lessen the financial burden on patients in out-of-pocket payment healthcare settings.

Keywords: *Febrile neutropenia, economic burden, low- and middle-income countries, MASCC score, solid malignancies.*

INTRODUCTION

Febrile Neutropenia (FN) is a serious adverse event often seen in patients who are undergoing chemotherapy. Newer drugs have been reported to be less myelosuppressive agents; FN remains a clinical challenge. Individual patient-related risk factors that impact outcomes include age (>65 years), pre-treatment neutropenia, impaired performance status, and presence of significant comorbidities [1, 2]. Risk factors related to treatment include the type of cancer, the chemotherapeutic agents used, and their duration and dosing. Patients with hematological malignancies are reportedly more prone to developing FN [3]. In solid malignancies, it is variable, and about 10-50% of patients have been reported across the literature to experience this complication during the course of their treatment [4]. Because of this, patients often require dose reductions, unplanned delays, and even discontinuation of the treatment. FN's impact on patient outcomes is quite significant, and it has therefore emerged as a notable source of concern in tertiary care hospitals. Furthermore, its implications for the utilization of healthcare resources and the overall quality of care make it an important consideration.

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Since growth stimulants such as granulocyte colony-stimulating factor (G-CSF) have been included in care plans, the incidence of FN has reportedly decreased substantially. Pooled data from randomized controlled trials using prophylactic G-CSF have shown a significant benefit in reducing the risk of developing FN [5]. Not only that, but it has also reduced the mortality rates in these patients. However, real-world data on current trends in the development of FN in low- and middle-income countries are limited. An observational study conducted by Al-Ahwal *et al*. determined the clinical course of FN-related admissions in Saudi Arabia [6]. They analyzed a cohort that included 56 patients with solid tumors. Their findings showed that 16.4% of the patients had severe neutropenia with a mortality rate of approximately 10% among these patients. The study highlighted that FN patterns vary across institutions and should be explored in all major cancer centers to develop appropriate institutional guidelines that improve clinical outcomes in these patients [6].

Therefore, in this study, we aim to determine the trends of inpatient FN admissions at our institute and their socioeconomic implications. We explore the association between FN and different malignancy types, the frequency of admissions, and the risk stratification of FN at admission according to the Multinational Association for Supportive Care in Cancer (MASCC) [7].

MATERIALS AND METHODS

A retrospective chart review study encompassing all FN episodes confirmed through clinical and laboratory documentation in solid malignancies was conducted at the Aga Khan University Hospital, Karachi, Pakistan. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was reviewed by the Ethics Review Committee at the Aga Khan University Hospital and was granted exemption (Ref #: 2023-9224-27359).

The final sample comprised 100 patients. A comparable prior study by Bachlitzanaki *et al*. included 63 cases, whereas our larger cohort enabled more robust estimation of clinical trends and outcomes [8]. Consecutive sampling was applied, including all eligible patients admitted with FN over 15 months (June 2023-September 2024).

Demographic data were collected from patient charts and electronic medical records (EMRs), including age, gender, type of solid cancer, cancer stage at admission, and absolute neutrophil count at presentation. FN was defined as a single oral temperature of ≥38.3 °C or a sustained temperature of ≥38.0 °C for at least 1 hour, with an absolute neutrophil count (ANC) of <1500 cells/μL or an ANC expected to fall below 1500 cells/μL within the following 48 hours [8, 9]. Neutropenia was categorized as mild (ANC 1000-1500 cells/μL), moderate (ANC 500-1000 cells/μL), and severe (ANC <500 cells/μL).

The study received an exemption from the Institutional Ethical Review Committee because it involved no direct patient contact or intervention and posed minimal risk to patients. Furthermore, all pertinent information was recorded on a pretested proforma. All patients aged 18 and above with a histologically proven diagnosis of solid cancer who were admitted to the Oncology service were enrolled in the study. Patients with incomplete or missing data, hematological malignancies, a history of any chronic infection, or an active infection within the 3 days prior to chemotherapy administration were excluded. Repeat FN cases were included in the study.

Data were collected during inpatient admission, and laboratory results were recorded. The following variables were recorded: patient demographics, type of malignancy, stage, grade, chemotherapy regimen, length of hospital stay, duration of antibiotic treatment, treatment outcomes, level of care (intensive care, special care or general care), development of septic shock requiring vasopressor support, development of respiratory failure, need for invasive *vs* non-invasive mechanical ventilation, development of acute kidney injury and the requirement of hemodialysis. Intensive care was defined as requiring Level 2-3 ICU care, while special care was defined as requiring Level 1 ICU care. General care included patients admitted to general ward beds with intermittent monitoring.

We conducted the economic analysis from a direct hospital-based cost standpoint. We calculated the daily cost using estimates provided by our institution's finance department, reflecting the average cost per inpatient day for the studied population. This included inpatient bed charges, nursing care, routine laboratory testing, standard imaging, pharmacy costs, and basic medical consumables. Total hospitalization cost per patient was determined by multiplying the average daily inpatient cost by the length of hospital stay.

The data were analyzed using version 24 of the Statistical Package for Social Sciences. (SPSS Inc., Chicago, IL, USA). Data were analyzed using descriptive statistics (mean, median, and percentage values), independent-samples t-tests, and linear regression, with multivariable models used to adjust for potential confounders. Independent-samples t-tests were used to compare mean differences in continuous variables (such as age, antibiotic duration, and length of stay) between high- and low-risk groups based on the MASCC score, as the groups were independent. A p-value of less than 0.05 was statistically significant.

RESULTS

Patients' Characteristics

A total of 100 patients were included in our study, with equal numbers of males and females. The mean age of our study cohort was 54 years (SD: 13.6). The sample was stratified according to risk of serious complications from FN based on the MASCC criteria. The MASCC score was calculated for each patient based on their characteristics at admission. A score of ≥21 was considered low risk, and a score of <21 was regarded as high risk, according to the criteria. According to the MASCC criteria, half (51%) of our patients were categorized as high-risk, while the remaining (49%) were considered low-risk for serious FN-related complications. Table **1** outlines the baseline characteristics, clinical parameters, and outcomes of patients admitted with febrile neutropenia as stratified by the MASCC risk score.

When stratified by risk, the mean age of patients was 58.1±12.2 years in the high-risk group and 49.9±13.8 years in the low-risk group. The majority (53%) of the patients had stage IV solid malignancies. Table **2** outlines the frequency of each specific malignancy in

Table 1: Baseline characteristics, clinical parameters, and outcomes of patients admitted with febrile neutropenia, stratified by MASCC risk score.

Variable	High Risk (<21) n=51	Low Risk (≥21) n=49	Total n=100	p-value
Demographics				
Age, mean (SD)	58 (12)	49 (13)	54 (13)	<0.001
Gender, n (%)				
Male	26 (50)	24 (49)	50 (50)	0.902
Female	25 (49)	25 (51)	50 (50)	
Cancer Stage, n (%)				
Stage I	3 (6)	3 (6)	6 (6)	0.654
Stage II	11 (21)	11 (22)	22 (22)	
Stage III	7 (13)	12 (24)	19 (19)	
Stage IV	30 (58)	23 (46)	53 (53)	
Neutropenia Grade, n (%)				
Mild	18 (35)	22 (45)	40 (40)	0.410
Moderate	20 (39)	15 (30)	35 (35)	
Severe	16 (31)	12 (24)	28 (28)	
Laboratory Values, mean (SD)				
Hb (g/dL)	9.1 (1.8)	9.7 (1.7)	9.4 (1.8)	0.090
WBC ($\times 10^9$/L)	0.8 (0.6)	1.1 (0.6)	0.9 (0.6)	0.040
ANC (cells/µL)	417 (410)	470 (380)	443 (396)	0.470
Platelets ($\times 10^9$/L)	106.2 (95.7)	136.4 (89.0)	121.3 (92.0)	0.110
Creatinine (mg/dL)	1.2 (0.5)	0.9 (0.6)	1.0 (0.5)	0.020
Treatment & Hospital Course, mean (SD)				
G-CSF days	3.3 (2.4)	2.6 (1.6)	3.0 (2.0)	0.100
Length of stay	6.2 (4.7)	3.2 (1.5)	4.7 (3.7)	<0.001
Antibiotic days	8.1 (4.3)	5.7 (1.8)	6.9 (3.7)	<0.001
ANC recovery (days)	3.4 (2.4)	2.7 (2.0)	3.0 (2.3)	0.120
Level of Care, n (%)				
General Care	19 (37)	43 (88)	62 (62)	<0.001
Special Care	32 (63)	6 (12)	38 (38)	
Outcomes, n (%)				
Mortality	7 (13.7)	0 (0)	7 (7)	0.010

our cohort. The most common type of cancer was breast cancer, followed by head and neck cancer and soft tissue sarcomas.

Moderate neutropenia and stage IV disease were more prevalent in those who were high-risk patients. These patients more often required specialized care (62%) than the low-risk group (12%).

Following admission for FN, almost all (95%) patients received G-CSF, regardless of MASCC score. The mean duration of G-CSF therapy was 3.3 days in the high-risk group and 2.6 days in the low-risk group. The mean length of stay (LOS), as expected, was higher in the high-risk group at 6.2 days *versus* 3.2 days in the low-risk group. The mean MASCC score for the study population was 18.97 ± 3.77 (range: 10-26). High-risk patients also received longer intravenous antibiotics during their hospital stay (8.1 *versus* 5.7 days).

Table 2: Distribution of malignancies among patients admitted with febrile neutropenia, categorized by primary cancer type.

Cancer Type	Frequency
Breast	27
Head and neck	20
Soft Tissue Sarcomas	12
Gastrointestinal	10
Genitourinary	9
Lung and Thoracic	6
Central Nervous System	2
Other Rare Malignancies	14
Total	**100**

Association between MASCC and Length of Stay (LOS)

Linear regression further confirmed this relationship, with LOS negatively associated with MASCC scores (β = -0.27, 95% CI: -0.46 to -0.09, p=0.005). This suggests that a higher MASCC score (lower risk) may be associated with shorter hospital stays.

Association between ANC Recovery and Length of Stay (LOS)

The mean LOS was 4.46 days (SD: 3.78) for patients with ANC recovery in ≤5 days and 6.92 days (SD: 3.88) for those with ANC recovery in >5 days. A two-sample t-test showed a statistically significant difference in LOS between the two groups (p=0.031, 95% CI: 0.23 to 4.70). This suggests that delayed ANC recovery (>5 days) may be associated with more extended hospital stays.

Association between Antibiotic Duration and Length of Stay (LOS)

A significant positive association between the duration of antibiotic therapy and the length of hospital stay was observed in our study. A simple linear regression analysis revealed that with each additional day of antibiotic therapy, the length of hospital stay increased by an average of 0.89 days (p<0.05). In a multivariable regression model, after adjusting for factors such as hemodialysis, days of G-CSF, and care level, the relationship remained significant.

Mortality and Clinical Outcome

Among our study participants, the majority of patients (n=93) were discharged alive at the end of their hospital admission with FN, while seven patients unfortunately succumbed to death. All deaths were seen in the high-risk patient group. A statistically significant difference was observed between the two groups (p=0.010).

DISCUSSION

In this observational study evaluating inpatient hospital trends in FN among patients with solid malignancies, nearly half of those admitted in our setting were categorized as low risk for serious medical complications based on the MASCC risk index. Despite their low risk, all patients received intravenous antibiotics during their hospital stay. Current ASCO/IDSA guidelines recommend using an oral fluoroquinolone plus amoxicillin/clavulanate (or clindamycin if penicillin-allergic) for such patients in an outpatient setting [10]. However, our patients received intravenous antibiotics, primarily reflecting our hospital's antibiogram. Standardized criteria for transitioning to oral regimens could help with the overuse of intravenous antibiotics. In our study, high-risk patients had significantly longer hospital stays, required an extended period of antibiotics, and experienced mortality. Earlier recovery of the absolute neutrophil count was associated with a shorter hospital stay, suggesting it could be a real-time indicator of prognosis in FN management.

Our findings are consistent with the existing literature, which has shown the MASCC risk score's reliability for risk stratification in both high-income and low- and middle-income countries. Similar to previously published data by Al-Ahwal *et al*., all FN-related mortality in our study occurred only in high-risk patients, reinforcing the score's accuracy in predicting outcomes in our healthcare setting [6]. However, the high proportion of low-risk admissions in our setting raises concerns, suggesting possible systemic over-admission of clinically stable FN cases. One potential cause of this may be limited outpatient monitoring infrastructure, physician caution, and patients' or caregivers' preference for hospital-based treatment. All of these could be due to LMIC-related healthcare barriers, which include health literacy, travel distance for appropriate healthcare services, or insufficient support at home.

From a healthcare system's perspective, our findings underscore the urgent need to establish standardized outpatient care programs for low-risk FN patients in LMIC settings. Given resource constraints and limited inpatient capacity even at large tertiary care centers in LMICs, correctly identifying low-risk patients preemptively could free up critical resources for clever use while maintaining quality of care and patient safety. The literature has extensively shown that ambulatory management for these patients results in a significant reduction in healthcare expenditure [11-14]. In our study, the 49 low-risk patients had an average hospital length of stay of 3 days. If they had been managed as outpatients, this could have freed up approximately 156.8 bed days over the study period. Given that the average daily cost of FN admission is approximately PKR 100,000, translating to an estimated PKR 15.68 million (approximately USD 55,000) in potential annual savings in healthcare expenditure, from our center alone. Beyond financial relief, it could also help prevent the significant incidence of hospital-acquired infections and improve the overall quality of life for these patients [8]. More importantly, patients' perspectives have also shown to support this approach as reported by Tueffel *et al*. in their study. They found that patients preferred an outpatient approach to inpatient management for low-risk FN [15].

Use of additional existing risk stratification tools, such as the Clinical Index of Stable Febrile Neutropenia (CISNE) score, alongside the MASCC risk index, may further refine outpatient eligibility, especially in clinically stable patients [16]. Locally tailored predictive models are emerging; however, they are not yet employed at other centers and require validation in larger studies [17]. Mohindra *et al*. concluded that the two-tier CISNE score can be highly effective in identifying low-risk patients [18]. Zheng *et al*., in their systematic review and meta-analysis, pooled data of 6617 patients to compare MASCC *vs*. CISNE in the identification of serious complications from FN [19]. Their results showed that MASCC had higher specificity, while CISNE had higher sensitivity, especially in acute settings. While we chose the MASCC score due to prior institutional validation, larger studies are required to assess combining both scores to optimize triage accuracy.

LIMITATIONS

This study has several limitations: (1) it was conducted at a single tertiary care center study with a moderate sample size which limits generalizability; (2) only the MASCC risk index was used and the CISNE score was not incorporated, which could have added further value to risk stratification performance; (3) only inpatient FN cases were considered which could have potentially underestimated the FN burden; (4) we did not look at the readmission rates or long-term outcomes associated with this complication, which could provide a more comprehensive picture of the FN burden; and (5) although all admitted cases meeting eligibility criteria were recruited, exclusion of records of patients with incomplete or missing data might have resulted in selection bias or information bias, potentially limiting the generalizability of the findings in case those cases had significant differences.

CONCLUSION

Nearly half of the patients in our study admitted with FN were stratified as a low risk for serious medical complications. This data reflects a potentially avoidable strain on healthcare infrastructure, especially in low- and middle-income countries with out-of-pocket payment structures. Implementing standardized outpatient care protocols that facilitate strict patient monitoring for stable, low-risk FN cases can reduce overutilization of healthcare resources, decrease the risk of hospital-acquired infections, and minimize unnecessary exposure to intravenous antibiotics. Future multicentric cross-regional institutional studies can guide context-specific FN management guidelines in resource-constrained settings.

ETHICAL APPROVAL

The study was reviewed by the Ethics Review Committee at the Aga Khan University Hospital and was granted exemption (REF letter No. 2023-9224-27359). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

The anonymized datasets generated and analyzed in the current study are not publicly available due to institutional and ethical restrictions regarding patient confidentiality and safety. However, de-identified data can be made available to the corresponding author upon reasonable request, after institutional approval, as explained. Data requests will be reviewed by the Aga Khan University Hospital Ethics Review Committee to ensure compliance with institutional and national data-protection requirements. All shared data will exclude any information that could identify individual participants.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

SN conceived the study concept.

SN, DS, MNK, AH, MYS, UT, YAR, and MM contributed to study design and methodology.

SN, DS, MNK, and AH collected the data and performed the statistical analysis.

SN, DS, MNK, AH, MYS, UT, YAR, and MM contributed to data interpretation and analysis of results.

SN, DS, MNK, AH, and MYS drafted the initial version of the manuscript.

SN, DS, MNK, AH, MYS, UT, YAR, and MM critically reviewed and revised the manuscript for important intellectual content.

GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the author(s) limitedly used ChatGPT (GPT-4, OpenAI) to get language suggestions and do minor proofreading in some parts of

the manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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