Clinical Consequences and Economic Burden Associated with Febrile Neutropenia in Hospitalized Cancer Patients: A Prospective Study

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Abstract

Objective: *Febrile neutropenia (FN) is viewed as the most decimating oncological crisis particularly in chemotherapy-incited patients. The primary objective of the study was to identify the total direct expenditure of patients during febrile neutropenia with clinical consequences and the secondary aim was to find out the factors associated with higher cost.*

Materials and Method: *This was a single-centered hospital-based study in the largest and only specialized cancer care centre in Bangladesh in the government sector. This prospective study was done in the inpatients' department of the National Institute of Cancer Research and Hospital from April 2020 to January 2021. The primary outcome was the out-of-pocket patient payments (adjusted by government subsidy) per FN episode. Univariate analysis and multiple linear regression were conducted to identify the factors associated with higher costs.*

Results and Discussions: *A total of 101 patients were enrolled in the study. The mean (SD) age was 33.49 (±15.79) years. Of the 101 participants, 63.4% were male. Among the patients, 13.9% died during the episode and 86.1% recovered. Having co-morbidities and COVID-19 were associated with an increased risk of death. The mean cost was US$ 999.44 (±499.05) and the mean length of hospital stay was 21.98 (±9.3) days. The longer hospital stay was significantly associated with higher costs.*

Conclusion: *This study will help to ascertain the hospital cost and clinical outcome of FN which ultimately can help in policymaking strategy.*

Key words: *Febrile neutropenia, economic burden, consequence, oncological emergency.*

Introduction:

Febrile neutropenia (FN) is an oncological emergency that needs to be addressed and managed promptly and properly.[1] FN is defined as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained for one hour.[2,3] Neutropenia is defined as an absolute neutrophil count <1,000/µL (equivalent to <1.0 × 10⁹/L), severe neutropenia as absolute neutrophil count <500/µL (equivalent to <0.5 × 10⁹/L), and profound neutropenia as <100/µL (equivalent to <0.1 × 10⁹/L). The period of neutropenia is considered protracted if it lasts for seven days or longer.[4,5]

Neutropenia and subsequent infections cause a large number of mortality and morbidity in cancer patients. A study from Singapore showed that the inpatient mortality rate of FN is between 4.7% and 9.5%.[3,6] FN frequently leads to a chemotherapy dose reduction and to treatment delays, which subsequently affect the patients' long-term clinical outcomes.[3,7]

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Apart from clinical adversity, FN causes a significant economic burden, especially in hospitalized patients. 80% of patients with haematological malignancies suffer from FN[8]. Many research has been conducted worldwide to correlate the cost-affecting factors with total hospital cost. One study from the USA revealed that the average costs of FN in hospitalized patients ranged from US$18,880 to US$22,086. The costs for outpatient were lower than that of inpatient care.[9] A prospective study from Germany showed the estimated mean direct cost per FN episode requiring hospital care was •3,950.[10,11,12] A study from Singapore revealed that the mean out-of-pocket patient payment was US$2,230 per FN episode.[3]

No specific data were found regarding the mortality and economic burden of patients due to FN in Bangladesh. These types of studies are therefore needed to be done on a large scale to estimate the accurate cost associated with various types of tumor which ultimately will help in policymaking. This prospective study aimed to find out the out-of-pocket expenditure, the factors associated with higher costs, and mortality due to FN in a single episode in hospitalized patients. This study will help to lower future costs. By identifying the risk factor associated with mortality will help us to be more cautious while treating patients with FN and ultimately reducing death.

Methods

Study design and setting

A prospective study was conducted in the inpatients' department of National Institute of Cancer Research and Hospital, Dhaka, Bangladesh from April 2020 to January 2021. 101 patients with neutropenic fever were enrolled in this study.

Patient population

Patients aged ≥13 years were included in the study who received chemotherapy for the treatment of haematological malignances and developed febrile neutropenia. In patients who experienced multiple episodes of FN during the study period, the first episode was selected for analysis. Outdoor patients and neutropenia due to causes other than chemotherapy were excluded from the study. Clinical data (demographic, medical history, medications history, and treatment outcome) and the cost out-of-pocket patient payments were obtained prospectively from patients. The patients were hospitalized till full recovery from low ANC and fever.

The expenditure was estimated from the patients which included the total hospital cost, the reimbursement bill, the out-of-pocket patient payments, and the cost breakdown of out-of-pocket patient payments (consisting of ward charges, food charges, laboratory charges, radiology charges, medicine charges, and other charges). The government subsidizes charges mainly for chemotherapy drugs, antibiotics, room charges but total government charges could not be established properly. The costs associated with the treatment of underlying cancer were not included.

The primary outcome of the study was the out-of-pocket patient payments per FN episode. Univariate and multivariate analyses were performed to identify the factors which had significant associations with a higher cost per FN episode. We evaluated the demographics (age and gender), malignancy types, co-morbidities, days of onset of FN, length of stay (LOS) in hospital, use of stimulators (GCSF and pegylated interferon), and the responsiveness to treatment.

The clinical and demographic characteristics were reported for each patient based on a single admission per patient.

Statistical analysis

We evaluated all of the FN-associated admissions in the hospital. Descriptive analyses were used to summarize the primary study outcome of the study. The means and 95% confidence intervals (CI) were reported. Group comparisons of parametric data were conducted using the Student's t-test or analysis of variance (ANOVA). Scheffe's test with Bonferroni correction was performed if there was a statistically significant finding through the ANOVA test. This step was performed to identify the variables of interest which may affect the outcome of this study. Pearson's correlation coefficient analysis was conducted to identify the variables significantly associated with a higher total hospital cost or out-of-pocket patient payments. After identifying the variables which were significantly associated with higher costs, multiple linear regression models were conducted to estimate the out-of-pocket patient payments. IBM SPSS Statistics 25.0 was used for all of the statistical analyses.

Results

A total of 101 patients with FN completed the study. The mean age was 33.49 (±15.79). Of the 101 participants, 63.4% were male. The most common haematological malignancy was acute lymphoblastic leukaemia (ALL) followed by acute myeloblastic leukaemia (AML), non-Hodgkin's (NHL), and Hodgkin's lymphoma (HL). Only 7 (6.9%) of the study participants had co-morbidities of which diabetes mellitus and ischaemic heart disease (IHD) were the most common ones. Microbiologically documented infection was found in seven (7%) patients. *Klebsiella pneumoniae* (2), *Escherichia coli* (3), *Rhizobium radiobacter* (1), and *Pseudomonas aeruginosa* (1) were found in different samples. As the study was carried out during the COVID-19 pandemic, we have found 6 cases (5.9%) of COVID-19 positive patients. The mean of days of onset of febrile neutropenia was 2.97 (±1.56) days. Stimulators (including G-CSF and peg-interferon) were used in 54% of cases. 87 (86.1%) cases of FN recovered completely and 14 (13.9%) patients died. the mean LOS was 21.98 (±9.3) days. The mean cost was 999.44 (±499.05) USD per FN episode. (Table 1)

Table-1 : *Demographic and clinical characteristics of the patients (n= 101)*

Baseline characteristics	Number of patients (n=101)	Baseline characteristics	Number of patients (n=101)
Age in years		Hypertension	1(1%)
Mean age (±SD)	33.49 (±15.79) years	Chronic viral hepatitis C	1(1%)
13 to 40	77 (76.2%)	Sample which are positive for organism	
41 to 60	16 (15.8%)	Blood	3(3%)
60 to 80	8 (7.9%)	Urine	3(3%)
Gender		Throat	1(1%)
Male	64 (63.4%)	NHL	8 (7.9%)
Female	37 (36.6%)	RT-PCR for COVID-19	
Primary diagnosis- no. (%)		Positive	6 (5.9%)
ALL	47 (46.5%)	Days of onset of febrile neutropenia (±SD)	2.97 (±1.56)
AML	40 (39.6%)	Stimulators-no. (%)	
HL	4 (4%)	G-CSF	50 (49.5%)
CML in blast crisis	1 (1%)	Pegylated-interferon	4 (4%)
MM	1 (1%)	None	47 (46.5%)
Co-morbidities- no. (%)		Outcome- no. (%)	
Diabetes mellitus	3(3%)	Responsive	87 (86.1%)
Ischaemic heart disease	3(3%)	Death	14 (13.9%)
Chronic kidney disease	2(2%)	Mean hospital length of stay (±SD)-days	21.98 (±9.3)
Deep vein thrombosis	2(2%)	Mean cost (±SD)- dollars	999.44 (±499.05)

SD= standard deviation, ALL=acute lymphoblastic leukaemia, AML=acute myeloblastic leukaemia, NHL=non-Hodgkin's lymphoma, HL=Hodgkin's lymphoma, CML= chronic myelod leukaemia, MM=multiple myeloma, GCSF= granulocyte colony stimulating factor.

Having co-morbidities was significantly associated with death (RR 3.55, 95% CI: 1.28-9.82, p-value 0.041). Having COVID-19 was significantly associated with death (RR 4.32, 95% CI: 1.63-11.44, p-value 0.003). (Table 2)

Table 2: *Association of co-morbidities and COVID-19 with the outcome of patients with febrile neutropenia (n=101)*

Characteristics	Death	Responsive	RR	95% CI	p-value
Co-morbidities	3	4	3.55	1.28-9.82	0.01*
RT-PCR for COVID-19	3	3	4.32	1.63- 11.44	0.003*

RR= Risk ratio; CI=confidence interval; *Fisher's exact test

Pearson correlation analysis was carried out to find out if there is a relationship between hospital length of stay (LOS) and cost. The assumptions of normality, linearity, and homoscedasticity were checked, with no violations found. There was a strong positive significant correlation between LOS and cost ($r = .726$, $n = 99$, $p < .001$) with an increase in LOS is associated with higher cost. This relationship can account for 52.7% of variation of scores ($R^2 = .527$).

The association of malignancy type with cost was evaluated. Patients will AML had a significantly higher cost than patients with other haematological malignancies. (Table 3 and Table 4)

Table 3 : *Descriptive analysis of the cost (n=101)*

Variables	No. (%)	Hospital cost Per episode, US$	
		Mean (±95% CI)	p-value
All subjects	101 (100%)	999 (±499)	
Age in years			
13-40	77 (76.2%)	1020 (±463)	
41-60	16 (15.8%)	949 (±520)	0.735@
61-80	8 (7.9%)	898 (±792)	
Gender			
Male	64 (63.4%)	1018 (±530)	0.263#
Female	37 (36.6))	967 (±445)	
Type of malignancy			
ALL	47 (46.5%)	1043 (±511)	
AML	40 (39.6%)	1093 (±465)	0.004@
NHLHL	8 (7.9%)4 (4%)	559 (±298)452 (±369)	
Therapeutic stimulators			
GCSF	50 (49.5%	985 (±509)	
Peg-interferon	4 (4%)	1218 (±640)	0.670@
No stimulator	47 (46.5%)	995 (±483)	

CI= Confidence interval; @p value from ANOVA test; #p value from two-sample t-test, assumed equal variance

Table-4: *Comparison of costs among subsets of variables identified in univariate analysis (n=101)*

Variables	Reference (r)	Comparator (c)		Cost US$
		Mean difference	p-value@	
Type of malignancy	AML	ALL	50	1.00
		HL	640	.071
		NHL	3534	.028*

*Significant at $\alpha=0.05$ after Bonferroni correction; @ Conducted by using Scheffe's test with Bonferroni correction

The LOS (coefficient= 41.37, 95% CI: 33.243 - 49.51, p <0.001) was significantly associated with higher cost. This multivariate model for the cost had an adjusted R^2 of 0.560 (p <0.001). (Table 5)

Table-5 : *Factors associated with higher cost in a regression model (n=101)[a]*

Variables[b]	Unstandardized coefficient (B)	95% CI for B		Standard error coefficient (B)	Standardized	p-value[c]
		Lower bound	Upper bound			
AML	-9.898	-74.353	54.557	32.471	-.022	.761
Length of stay	41.374	33.243	49.505	4.096	.745	<0.001

a= Adjusted R^2 = 0.560 , p <0.001; b= Only clinically relevant variables that were statstically significant at p-value of 0.05 in the univariate analysis were included in the regression model; c= Bolded p are statistically significant

Discussion:

Febrile neutropenia is an independent risk factor for mortality and morbidity in cancer patients, especially in haematogical malignancies.[13,14,15] This present study was carried out among the hospitalized patients in National Institute of Cancer Research and Hospital, Dhaka, Bangladesh with febrile neutropenia to see the response, total out-of-pocket patient cost, and factors associated with higher cost. A higher number of male gender (63.4%)was found here with a mean age of 33.49(±15.79) years, which slightly has differed from that of the study of Singapore where the mean age was 54.8 years and only 37.9% were male.[3] Overall in-hospital mortality was found 13.9% which is higher than that of the study in Turkey [16,17] and study from Iran[18] where mortality was 10.3% and 5.3% respectively, but it was similar to that of Indian studies 13.5%.[19]

Among the malignancies, the most frequent one was ALL (46.5%) and the least ones were MM and CML in blast crisis. However, a study from the southern part of India showed that AML was more frequent in hospitalized febrile neutropenic patients.[19] Culture positivity (blood, urine, throat swab) was found only in 7% of patients whereas 29.62% culture-positive cases were found in an Indian study. This difference could be due to prophylactic antibiotics, a faulty technique of collection procedure, presence of atypical organisms.[3,17] As the study was conducted during the period of the COVID-19 pandemic the RT-PCR for COVID-19 was done in patients where clinical suspicion of COVID-19 was present and we found 6 (5.9%) positive cases and it was statistically significant in comparison to the outcome. A study from Egypt had shown 29.16% COVID-19 positive cases with an increased number of unfavorable outcomes in FN patients.[20] Associated co-morbidities including diabetes, hypertension, IHD, CKD, and chronic viral hepatitis C showed an increased number of unfavorable outcome. This scenario was common to the other studies from Singapore[3] and Iran[17].

The length of stay in the hospital was 21.98 (±9.3) days in the current study. However, the LOS in NHL patients was about eight days in a study from USA[21] and 16 days in a Brazilian study.[22] LOS is associated with a higher economic burden and also unfavorable outcome.[3,4,21,22]

The total out-of-pocket patient cost was US$999.4 (±499.05) which is much lower than that of Singapore (US$2230)[3] and USA ($37555)[21].

The limitation of our study is that it is an observational study. We cannot be certain that we have identified all potential confounding factors. However, the assessment of independent variables by a research group not involved in patient care and the use of a prospective design with an objective endpoint contributed to the methodological strength of this study.

Conclusion:

A longer length of hospital stay was associated with a higher out-of-pocket patient expenditure. Associated co-morbidities and COVID-19 infection showed a bad prognosis in respect of clinical outcome. The study identified factors associated with a higher financial burden on patients despite government subsidies. These results may be used for further economic evaluation to develop appropriate strategies to reduce the cost of FN on cancer patients.

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