Applying Multinational Association of Supportive Care of Cancer Index Score for Identifying Febrile Neutropenia Patients at High Risk of Complications at Tertiary Care Hospital, Pakistan

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Abstract

Introduction: Multinational Association of Supportive Care of Cancer (MASCC) index score is a clinical tool to predict outcomes in Febrile Neutropenia patients. This risk-index score has been authenticated in international trials however local data is deficient. We aimed to determine hospital based incidence rate of serious complications in admitted chemotherapy induced febrile neutropenia patients presenting to a tertiary care hospital. We also aimed to compare proportions of serious medical complications in patients having MASCC score <21 or ≥21. **Methods:** A hospital based prospective close cohort study was designed and conducted at Oncology wards of The Aga Khan University from February to August 2014. Total of 88 patients, aged 16 and above, with chemotherapy induced febrile neutropenia were identified and divided on the basis of MASCC Score into low or high risk {exposure} groups. Follow up was done from day of admission (day zero) to discharge. Outcome was assessed in terms of development of serious complications. Hospital based incidence rate was estimated. The associations between outcome and qualitative variables were evaluated by using Pearson Chi-square and Fisher's exact test. **Results:** Hospital based incidence rate of febrile neutropenia admission was 5.98%, 95%CI [4.88% - 7.08%]. Out of 88 patients with chemotherapy induced febrile neutropenia 85.2% patients were in the high risk group and 14.8% in the low risk group. Serious complications were found in 21.33% and no patients in high and low risk group respectively. Age > 60 (p = 0.039),

MASCC score < 15 (p = 0.002) and an albumin < 2.5 mg/dl (p = 0.046) was associated with higher chance of developing serious complications. Sensitivity, specificity, positive and negative predictive value of MASCC score in predicting risk of serious complications was 21.33%, 100%, 100% and 18.06% respectively. **Conclusion:** MASCC risk-index score is a useful tool to identify patients at low risk of complications. Hospital based incidence rate of serious complications was 18.2%.

Keywords

Febrile Neutropenia, Chemotherapy, Serious Complications

1. Introduction

Febrile neutropenia (FN) is a common complication of chemotherapy. It is considered a medical emergency, in general requiring hospital admission and broad spectrum empiric antibiotics [1]. Among patients receiving chemotherapy 10% - 50% of patients with solid tumours and 80% of those with hematologic malignancies are said to develop FN [2]. Around 10% - 25% patients have documented bacteraemia with most patients having prolonged or severe neutropenia [3] [4] [5]. Such episodes lead to delay in treatment which may compromise outcomes in potentially treatable tumours [6]. Febrile neutropenia may be potentially lethal, with one study reporting inpatient mortality with FN as high as 9.5% [7]. Mortality varies from 5% in patients with solid tumours to around 11% in patients with haematological tumours [8]. Factors associated with high risk of mortality include pneumonia, invasive fungal infections, lung disease, renal disease, liver disease, cerebrovascular disease, congestive cardiac failure, pulmonary embolism and lung carcinoma [7]. Factors associated with a favourable outcome are said to be an albumin level of >2.5 mg/dl, low disease burden, and an absence of respiratory infection [9]. Proven bacteraemia is associated with worst outcomes, with mortality rates of 5% in Gram-positive bacteraemia and 18% in Gram-negative bacteraemia [8].

Various instruments have been established to predict which cases are at high risk for complications. The purpose of such models is to predict the risk of complications at the commencement of FN episode, and to recognize which patient subset would be eligible for outpatient management and less intensive antibiotic therapy. Two such models have been used for risk stratification, which include the Talcott's model and Multinational Association for Supportive Care in Cancer (MASCC) scoring system [10] [11]. Multinational Association of Supportive Care of Cancer (MASCC) index score was developed by Klastersky *et al.* in 2000 to stratify patients into high or low risk and predict their possible outcome, with a score of 21 or more putting the patient at low risk of complications and mortality [11]. The results of this study predicted low risk patients (with a risk index score of ≥21) with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71% [11].

Baskaran *et al.* reported a total of 116 cases of febrile neutropenia out of whom medical complications occurred in 34% of cases. Of the patients identified as low risk, 17.1% developed serious medical complications while patients in the high-risk group, 85% developed serious medical complications [9].

There have been various prospective studies to validate the MASCC scoring system; however most of them have been conducted in developed countries [9] [11]. Hence we carried out this study to assess if MASCC scores of high risk and low risk and consequently high or low risk of complications are applicable in our part of the world. By identifying patients at low risk of complications, a less aggressive treatment may be given (early hospital discharge or outpatient therapy), thus reducing the cost of hospital stay, chances of overtreatment and appropriate use of resources and at the same time, identifying patients with high risk and appropriately treating them [12].

The MASCC risk index score is based on seven independent factors, present at the beginning of FN episode. These seven factors and their weight are given in Table 1.

The list of serious complications is detailed in Table 2. We hypothesized that patients with low MASCC score are at a higher risk of developing serious complications as compared to those with a high score. The primary objective of this study was to estimate hospital based incidence rate of serious complications in cancer patients admitted with febrile neutropenia.

We also aimed to compare proportions of serious medical complications in patients having MASCC score < 21 or ≥21.

2. Methods

2.1. Overview and Study Participants

We adopted a prospective close cohort study design to collect data from Febru-

Table 1. Multinational Association for Supportive Care in Cancer (MASCC) risk model (9)*.

Prognostic Factor	Weight
Burden of febrile neutropenia illness: no or mild symptoms (less than two organ symptoms, not requiring intervention)	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection (in patients with haematological malignancies.)	4
No dehydration	3
Burden of febrile neutropenia illness: moderate symptoms (more than two organ systems or less than two organ systems but requiring intervention)	3
Outpatient status	3
Age < 60 years	2

*The overall score is calculated by adding the individual points, with maximum score of 26 points. A score of ≥21 is defined as low risk and <21 as high risk.

Table 2. Rate of Serious complications.

	High risk (n = 75)	Low risk (n = 13)
Serious complications [n(%)]	16 (21%)	0
Hypotension	9	-
Respiratory failure	8	-
ICU admission	3	-
DIC	1	-
Confusion	3	-
CCF	2	-
Bleeding	2	-
Renal failure	4	-
Death	9	-
Median length of hospital stay [days] (range)	4 (1 - 28)	4 (1 - 7)

ary to August 2014 from the Oncology wards of The Aga Khan University (where both haematology and solid tumours are treated) which is one of the tertiary care hospitals in Karachi, Pakistan receiving patients from all over the country. We recruited a cohort of 88 chemotherapy induced febrile neutropenia patients aged 16-years and above of either gender using consecutive sampling methodology. They were enrolled at their index visit via emergency or oncology clinic requiring ward admission. These patients were followed from the day of hospital admission till discharge.

Patients with confirmed diagnosis of cancer and having history of receiving chemotherapy prior to episode of febrile neutropenia were included. They were excluded if the adult patient presented with febrile neutropenia as a result of their underlying disease, like, aplastic anaemia and myelodysplastic syndrome. Also, patients with no history of chemotherapy were excluded.

2.2. Ethics Statement

Our study protocol was initially accepted from the Ethical Review Committee of our institution with ERC # 2948-Med-14. Therefore, written informed consent was taken from patients before asking them for study participation.

2.3. Ascertainment of Exposure

Trained interviewers screened and enrolled participants within 48 hours of hospital admission based on the standard definition of febrile neutropenia episode with a single oral temperature of 38.3˚C or, oral temperature of 38˚C which persists for more than an hour and an absolute neutrophil count of <1000 cells/mm^3 [1]. Patients were stratified into high {exposed} and low risk {non-exposed} based on MASCC score at the time of admission. The MASCC Score is calculated based on burden of illness, presence of hypotension, chronic obstructive pulmonary disease, fungal infection, solid tumor, outpatient status and age < 60 years [Table 1].

2.4. Ascertainment of Outcome

Patient outcome was recorded by the trained interviewers as development of serious complications or not at the time of hospital discharge, based on presence or absence of any of the following: hypotension, respiratory failure, intensive care admission, disseminated intravascular coagulation, confusion or altered mental state, congestive cardiac failure, bleeding and renal failure. Length of hospital stay was recorded on discharge. Positive cultures were also recorded.

2.5. Covariables

Following covariables were recorded for each patient including demographic information, underlying cancer and chemotherapy, day one of chemotherapy, absolute neutrophil count (ANC), foci of infection, including any positive cultures. The application of G-CSF non-usage versus usage [along with the total number of days administered] was noted.

2.6. Operational Definitions Taken into Account

Patients were stratified as high risk if they had a MASCC score of less than 21 and low risk if score is equal to or more than 21 based on parameters mentioned in **Table 1** [11]. Serious complications [10] were defined as a presence of any one of the following: Hypotension if systolic blood pressure < 90 mm Hg, respiratory failure if arterial oxygen pressure < 60 mm Hg while breathing room air or a need for mechanical ventilation. Intensive care unit admission for hypotension with systolic blood pressure < 90 mm Hg or respiratory failure with an arterial oxygen pressure < 60 mm Hg while breathing room air or a need for mechanical ventilation. Disseminated intravascular coagulation (prothrombin time > 14 seconds and activated prothrombin thromboplastin time (PTT) > 35 seconds, fibrinogen levels < 150 mg/dl, fibrin degradation products > 20 microgram/ml and d-dimer > 0.8 mg/l).

Confusion was defined as (assessed by Confusion Assessment Method diagnostic algorithm based on the presence of two factors: (i) acute onset and fluctuating course and (ii) inattention and presence of any one of the following two factors: (a) disorganized thinking (b) altered level of consciousness [13]. Congestive cardiac failure, as seen on chest X-ray as bilateral lung infiltrates; requiring treatment with diuretics. Bleeding, severe enough to require one packed red cell transfusion. Renal failure defined as increase in Serum Creatinine of 0.3 mg/dl within 48 hours [14]. Data collection schema has been illustrated in **Figure 1**.

2.7. Sample Size Assumptions

The sample size was calculated by taking into consideration the study objectives. Epi Info Version 6 was utilized to compute the sample size. The calculations were based on the assumption that reported proportion of serious complication for febrile neutropenia is 34% [9]. By taking into account this figure together
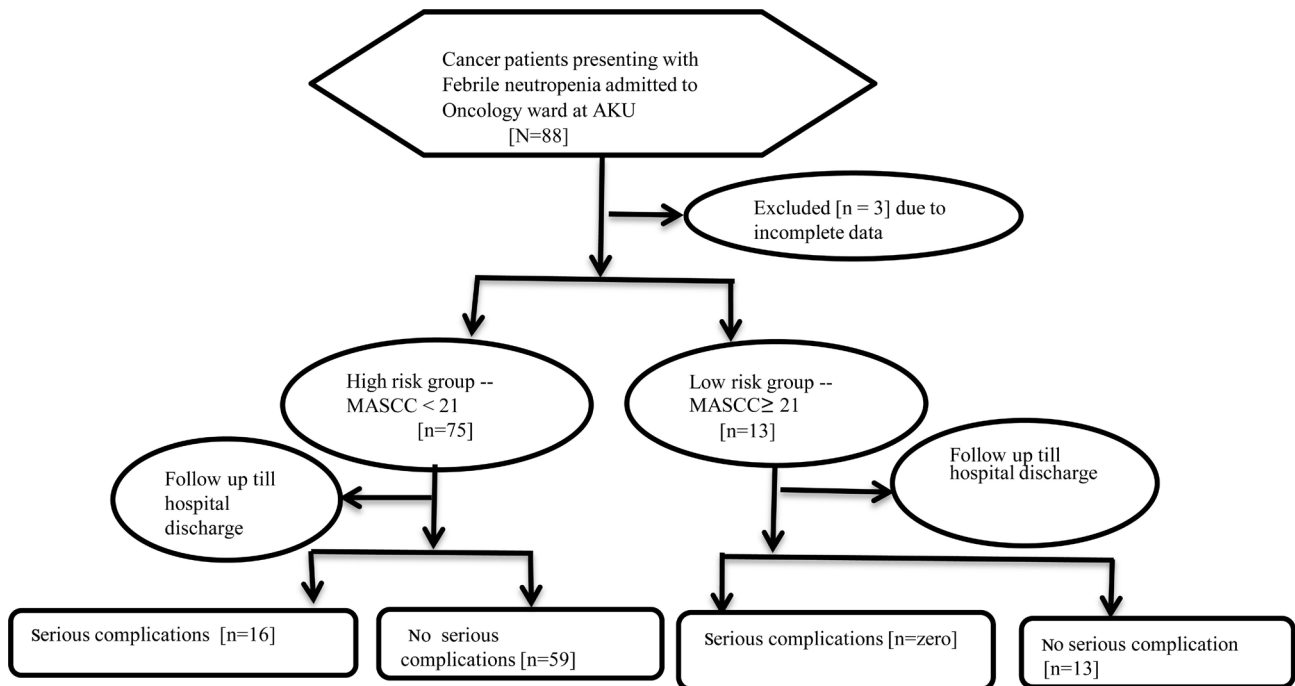
Figure 1. Schematic depiction of study flow chart.

with 95% CI, and exposed to non-exposed ratio of 1:1, with 80% power and risk ratio of 2.0, the sample size calculated to be n = 76. After adjusting for missing or incomplete information, the final sample size was approximately N = 84.

2.8. Data Analysis Plan

Data were entered and analysed in Statistical Package for Social Sciences 20.0 version. (SPSS, Inc., Chicago, IL, USA). Descriptive analysis were run to compute frequencies and proportions for categorical variables like gender, presence or absence of each serious complications (hypotension, respiratory failure, intensive care unit admission, bleeding, disseminated intravascular coagulation, congestive cardiac failure, confusion or altered mental status and death). Means and standard deviations were calculated for quantitative variables.

Number and proportions were calculated for complications in patients with MASCC score ≥ 21 and < 21. Hospital based incidence rate of serious complications was computed. χ^2 or Fischer's Exact test were applied to categorical variables like age, gender, tumour, albumin, ANC, MASCC Score, Microbiology and G-CSF use. Independent samples t test was applied to assess difference between mean length of hospital stay and serious complications A p-value of <0.005 was taken significant for inferential statistics. A 2 × 2 table was employed for calculation of sensitivity, specificity, positive and negative predictive values of MASCC score in accurately predicting risk of serious complications. 95% confidence intervals were computed for the estimates.

3. Results

Data were collected for patients admitted with chemotherapy induced febrile

neutropenia. A thorough review of the hospital medical records system revealed a total of 1471 patients who received chemotherapy between February till August 2014. However among these patients only 88 patients were admitted with chemotherapy induced febrile neutropenia and included for analysis (Figure 1). Thus we compute hospital based incidence rate of occurrence of chemotherapy induced febrile neutropenia to be 5.98%, {88/1471}, 95%CI [4.88% - 7.08%]. Hospital based incidence rate of serious complications in these admitted febrile neutropenia patients was 18.2%, 95%CI [11.5% - 25%]. The mean age of inducted patients was 45.51 ± 15.69 years; range 17 - 75 years. The sample comprised of slightly higher preponderance of males 49 (55.7%). The mean day of febrile neutropenia was 10.26 ± 5.42 days. A total of 75 (85.2%) patients were categorized into high risk (exposed group) and 13 (14.8%) into low risk (non-exposed group) based on criteria defined earlier. Among the high risk patients 16 (21.33%) developed serious complications while none of the patients among low risk developed serious complications. Baseline characteristics based on risk status are given in Table 3. The rate of serious complications is enlisted in Table 2. Hypotension, respiratory failure and death were the most common complications.

3.1. Tumour Types

Forty nine (55%) presented with haematological malignancies and 39 (44.3%) with solid tumours. The most common chemotherapy prescribed for solid tumors was Doxorubicin and Cyclophosphamide, received by five patients. The most common chemotherapy in patients with haematological tumors was Rituximab, Cyclophosphamide, Vincristine, Doxorubicin and Prednisolone, received by six patients.

Table 3. Baseline characteristics based on low and high risk MASCC group.

Characteristics	High risk	Low risk
Number of patients n(%)	75 (85.2%)	13 (14.8%)
Median age in years (range)	48 (17 - 75)	53 (18 - 63)
Gender		
Male	42 (56%)	7 (54%)
Female	33 (44%)	6 (46%)
Tumor		
Solid	34 (45.3%)	5 (38.5%)
Haematological tumors	41 (54.7%)	8 (61.5%)
Mean Haemoglobin gm/dl (range)	9.73 (6.1 - 18.1)	9.62 (8 - 11.4)
Absolute Neutrophil Count (cells/µL)		
<100	62 (82.7%)	10 (76.9%)
>100	13 (17.3%)	3 (23.1%)
Mean Platelet (range) (cells/µL)	99 (1 - 500)	67 (3 - 227)

3.2. Outcome Based on Covariates (Tumour Type, Positive Bacteraemia, Length of Hospital Stay, ANC and Age)

Among the 49 patients who presented with haematological tumours, 8 (16.3%) developed serious complications and among the 39 patients with solid tumours 8 (25.8%) developed serious complications (χ^2 test statistic: 0.256, df = 1, p = 0.613).

Among the entire sample of 88 patients, 23 patients had positive cultures. Amid the high risk group a total of 17 (22.6%) patients' revealed bacteraemia. Out of these 17 patients, 2 (11.7%) patients died. In contrast, 6 (46.1%) patients in the low risk group had bacteraemia and none of them died. However no statistically significant difference was established among the low and high risk group in terms of positive cultures and outcome (serious complication). (χ^2 test statistic: 0.23, df = 3, p = 0.97).

The mean length of hospital stay was 5.3 ± 4.79 days; range 1 - 28 days. The length of hospital stay did not correlate with increased risk of acquiring serious complications, ($t(86) = 0.428$, p = 0.670).

Despite the fact that most patients among the high risk group had an ANC of <100, this did not clinically translate into a high risk of serious complications and was also statistically insignificant (χ^2 test statistic: 1.87, df = 1, p = 0.17).

The mean haemoglobin level was 9.7± 2.1 g/dl with lowest and highest level varying between 6.1 to 18.1 g/dl.

The factors associated with serious complications have been given in a cumulative form in Table 4.

3.3. MASCC Score in Accurately Predicting Risk of Seriou Complications

The sensitivity, specificity, positive and negative predictive value of MASCC score in accurately predicting risk of serious complications was 21.33%, 95% CI [12.72 - 32.32], 100%, 95% CI [75.12 - 100], 100%, 95% CI [79.24 - 100] and 18.06%, 95% CI [9.99 - 28.90] respectively. See Table 5.

4. Discussion

This study helped us find that MASCC risk-index score as a useful tool to identify patients at low risk of complications. Eighty five percent patients comprised the high risk group which is higher than the proportion of patients reported in literature [27.5% - 62%] [15] [16]. Among the high risk patients 16 (21.33%) developed serious complications while none of the patients in the low risk developed serious complications. This is in distinction to the results of similar studies in the past where 85% - 86.3% patients in the high risk group developed serious medical complications. This indicates that the FN population in our part of the world is different from those reported in literature with less risk of developing serious complications. There is a potential that most of the low risk patients were not admitted. There are two possible explanations; one that their treating oncologists may have not admitted them   because of their low risk predisposing

Table 4. Factors associated with serious complications.

Variable	Serious Complications		Test Statistic	p value
	Yes	No		
Age			4.256	0.039 ~
<60	9	58		
>60	7	14		
Gender			0.256	0.613 ~
Male	8	41		
Female	8	31		
Tumor			0.256	0.613 ~
Solid	8	31		
Heme	8	41		
Albumin*			6.137	0.046 ~
<2.5	3	5		
>2.5	8	21		
ANC			___	0.285 §
<100	15	57		
>100	1	15		
MASCC			___	0.002 §
≤15	6	4		
>15	10	68		
Microbiology			7.243	0.404 ~
Positive	4	18		
Negative	11	55		
G-CSF use			2.144	0.143 ~
Yes	12	64		
No	4	8		

*A baseline albumin was checked in 37 patients and not assessed in 51 patients. § Fischer Exact test. ~χ^2 test.

Table 5. MASCC score to predict presence or absence of serious medical complications.

	MASCC Score		
Serious medical complications	High risk (+ve)	Low risk (-ve)	
Present (+ve)	True positive (a)	False Positive (b)	
	16	0	**16**
Absent (−ve)	False Negative ©	True Negative (d)	
	59	13	**72**
Total	**75**	**13**	**N = 88**

features, second in view of Pakistan being a resource poor country these patients may not have reported to the hospital. Data regarding the patients with FN who presented in the outpatient setting and were not later admitted, would have helped in having a robust analysis, however such patients were not a part of this study as per our protocol.

In the original study by Klastersky *et al.*, a score of <15 was associated with 79% chance of serious complications, with MASCC score between 15 - 20 being intermediate in risk with 40% chance of complications [11]. In the current study similar results were found with 60% chance of serious complications in patients with a score of <15% and 15.38% in patients with MASCC score amongst 15 - 20. A subsequent study may be done in the future to assess and stratify factors specific to this very high risk group (with MASCC score of <15, that predispose to higher rate of complications).

Among the 88 patients in this study, 22 had bacteraemia among which 13 (59%) patients had gram negative bacteraemia and 9 (40%) patients had gram positive bacteraemia. In the Western literature, the proportion of gram positive bacteraemia has increased in contrast to gram negative bacteraemia in patients with FN [17]. In a study by Feld *et al.*, the factors predisposing to increased gram positive bacteraemia were said to be increased use of prophylactic antibiotics such as quinolones, central lines, antacids and mucositis (secondary to chemotherapy) [18]. In the developing countries, the situation of bacteraemia is similar to ours. [19] [20]. The reason for lower percentage of gram positive bacteraemia is thought to be due to less frequent use of quinolones and central lines [18]. In our study however prior history of prophylactic antibiotics and presence of central lines were not recorded.

Uys *et al.*, in their study reported 75% mortality among the high risk bacteraemia patients. In the current study, however 11.7% in the high risk group with bacteraemia died.

There have been numerous randomized controlled trials to evaluate the efficacy of granulocyte colony stimulating factors (G-CSF) in FN patients, with results revealing effect on shortening the duration of neutropenia [21] [22] [23]. However none of the studies reveal benefit in terms of reducing the duration of fever, cost or the use of antimicrobial therapy and no effect on reducing mortality. In patients with uncomplicated FN episode, G-CSF is hence not recommended [24]. In our study the use of G-CSF was not associated with decrease in serious complications, [p = 0.14].

There were several factors which were associated with a higher chance of developing serious complications. These factors included age > 60, MASCC score of <15 and an albumin <2.5 mg/dl. However no statistically significant association was found in risk of developing serious complications based on solid or haematological malignancy, ANC, haemoglobin, gender, length of hospital stay and bacteraemia. In a similar study by Baskaran *et al.*, low albumin was associated with a higher chance of serious complications [9]. However in contrast to the present study there was no statistically significant difference found based on

age. Based on our results we recommend that albumin be incorporated in the risk stratification.

In our patient population the sensitivity, specificity, positive and negative predictive value of MASCC score in accurately predicting risk of serious complications was 21.33%, 100%, 100% and 18.06% respectively. In another study from Asia, sensitivity, specificity, negative and positive and negative predictive value of MASCC score in predicting risk of serious complications was 81, 60, 52 and 86% respectively [25]. In another study reported from Malaysia, MASCC score predicted outcome with sensitivity, specificity, and positive predictive value of 93%, 67% and 83% respectively [9]. By far in our patient population MASCC score was more specific and with a greater positive predictive value in comparison to other studies however less sensitive. This study correctly predicted 100% of low risk and 21.3% of high risk patients hence indicating that our high risk patient population need further risk stratification. A total of seventy five patients were predicted to be in the high risk MASCC group and sixteen of them developed serious medical complications. This lead to an obvious finding of a low sensitivity which is in contrast to those reported in earlier studies. This may be attributable to a relatively smaller sample size of our study or it could be a finding by chance alone. The low sensitivity of our study implies a possibility that our high risk group possibly developed less serious complications when compared to international data, or this again could be a chance finding. A probable explanation of this could be that our patient population is different. Another justification is that this study is only representative of a single institution and the inference thus is always taken with caution.

To the best of our knowledge through literature search, we report that this is the first study which applies the MASCC score index in our patient population, from the developing country belt.

There are several strengths of this study; a cohort study design was selected which is ideal in forecasting the causal association of exposure with outcome. Furthermore there was no loss in follow up or drop out of our cohort as these patients were followed up till hospital discharge. Our study has few limitations that need to be taken into account while interpreting the results. As we enrolled all the patients with febrile neutropenia during the study period hence it was hard to select and maintain an equal number of exposed and non-exposed patients. It shall be recognized that this is a single centre study conducted in a tertiary care centre. Hence, generalizability of our study results is reported with caution.

5. Unanswered Questions and Future Directions for Research

Data regarding the patients with FN who presented in the outpatient setting and were not later admitted, would have helped in a robust data analysis, however such patients were not a part of this study.

Among the patients identified to be in the low risk group a prospective study could be done to treat them with oral antibiotics with possibility of an early dis-

charge if a patient remains afebrile for more than 24 hours. This would help in reducing length of hospital stay and hence cost of medical treatment. Similar study has been done in the past by Klastersly *et al.*, in which 44% low risk patients eligible for oral antibiotics were discharged home with a median time to discharge of 26 hours after they were afebrile for at least 24 hours [26]. Only 3.7% of these patients required readmission, however none of the 44% patients developed any serious medical complications [26].

6. Conclusion

We conclude that MASCC risk index score is a tool which is helpful in identifying FN patients at low risk of complications. In future by applying this score it would help in treating high risk patients aggressively from the start and at the same time identifying low risk patients who may be treated less aggressively with a potential early discharge and marked reduction in hospital cost.

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Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Z.S. primarily initiated the concept of the study. Z.S., M.B. and M.S. have made substantial contributions to conception and development of project, design, analysis and interpretation of data. Z.S. and M.B. performed the data analysis.

M.K. was responsible for acquisition of data. Z.S. drafted the initial manuscript; A.A. and A.D. helped in reviewing the article. M.B. and M.S. were involved in critically revising and adding intellectual content to the final version. All authors carefully reviewed and approved the final document.

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List of Abbreviations

ANC	Absolute Neutrophil Count
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
AKUH	Aga Khan University Hospital
CI	Confidence Intervals
DLBCL	Diffuse Large B-Cell Lymphoma
ERC	Ethical Review Committee
FN	Febrile Neutropenia
G-CSF	Granulocyte Colony Stimulating Factors
MASCC	Multinational Association of Supportive Care of Cancer
PCP	Pneumocystis carinii pneumonia
PTT	Prothrombin Thromboplaistn Time
SPSS	Statistical Packages for Social Sciences
TMP-SMZ	Trimethoprim-Sulfamethoxazole