Validation of MASCC Score for Risk Stratification in Patients of Hematological Disorders with Febrile Neutropenia

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Abstracts

Objectives The purpose of this study is to evaluate the association of MASCC score (Multinational Association for Supportive Care in Cancer Score) in patients with febrile neutropenia (as resultant treatment of hematological disorders) for risk assessment of morbidity and mortality.

Patients and methods Patients presenting with Febrile Neutropenia from November 2011 till December 2013 were enrolled in the study. Initially all patients were hospitalized and their MASCC score was calculated, however those with high risk stayed in hospital till full ANC recovery while low risk group was discharged earlier and keenly followed as out-patient while being on prophylactic oral antibiotics. The MASCC risk-index score was calculated and patients with risk score >21 were regarded as low-risk while <21 were labeled as high-risk.

Results On the basis of 226 febrile neutropenia patient 132(58.4 %) were categorized as low risk while 94(41.5 %) as high risk patients according to MASCC risk index score. In low risk group 123(93 %) had

uncomplicated infection while 9(7 %) had complicated infections. There was no mortality documented in low risk group while eight patients died in high risk group.

Conclusion In this study we correctly predicted outcome of 123(93 %) low risk group patients. The study had positive predictive value of 93 % with both sensitivity and specificity of 65 and 75 % respectively. The MASCC risk score is a valuable tool in determining the outcome in patients with febrile neutropenia.

Keywords MASCC score · Hematological disorders · High-risk febrile neutropenia · Low-risk febrile neutropenia

Introduction

The key to success in the treatment of hematological malignancy is uneventful recovery from FN. The association of fever and neutropenia has been discussed

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extensively in medical literature. The severity and duration of neutropenia have been regarded as the most important factors predicting the prognosis and survival. Immediate hospitalization, rapid initiation of broad spectrum antibiotics and strict vigilance and follow-ups are recommended for prompt management of this devastating complication of chemotherapy. However current guidelines suggest that high risk patients are prone to develop serious medical complications which can be lethal [1–3]. FN has been associated with significant morbidity and mortality ranging from 6.8–20 % in hospitalized patients. Higher rates are being observed in patients with major co-morbidities and documented sepsis or infection [4, 5].

According to the current guidelines chemotherapeutic regimens having ≥ 20 % risk of febrile neutropenia, are considered high-risk [6]. The treatment instituted for hematological malignancies is invariably considered in high risk group. The guidelines considered old age, previous chemotherapy, pre-existing neutropenia, marrow involvement, poor performance status and other medical co-morbidities as risk factors for developing severe neutropenia and complicated course [6].

It is very crucial to identify the patients who are at high risk of developing febrile neutropenia to achieve maximum benefit of therapeutic regimen prescribed. Various studies in past have attempted to identify the risk factors and develop predictive models for chemotherapy induced neutropenia and its complications in patients getting various chemotherapeutic regimens [7]. Currently Multinational Association of Supportive Care in Cancer (MASCC) risk index score is the most widely used model for prediction of complication [8]. This study was designed to validate the MASCC index score in patients of hematological malignancies presenting with febrile neutropenia categorized into low or high risk of developing serious medical complications.

Patients and Methods

Data collected prospectively from November 2011 to December 2013 from all patients presenting with FN at our institution on predesigned Performa. The study was approved by Ethics Committee of the Institute and data of 226 FN episodes collected after an informed signed consent prior to enrollment. All patients had confirmed diagnosis of hematological disease and developed FN as a result of treatment administered (Table 1). Radiotherapy was not given to any of the patient and FN was defined as an absolute neutrophil count of $<500/\mu\text{L}$ or $<1000/\mu\text{L}$ and expected to decline further along with temperature of $>38^{\circ}\text{F}$. MASCC score was calculated with a possible total score ranging from 0 to 26 (Table 2). Patient with score ≥ 21 were regarded as low risk while those with <21 as high risk.

All patients were hospitalized at presentation with FN and were given treatment according to IDSA guidelines [9]. Blood, urine, throat, central line (if present) or any other suspected site cultures were sent along with other baseline investigations as part of institutional protocol. First line empirical therapy included broad spectrum intravenous antibiotics tazobactam/pipracillin and amikacin. If fever was not responding in 72 h, therapy were shifted to second line antibiotics which comprised of carbapenem while amikacin was continued as same. For patients with persistent fever of more than 7 days were administered antifungal therapy (amphotericin or voriconazole). Success of empirical therapy was defined as resolution of fever and clinical signs of infection, eradication of infecting micro-organisms without change in empirical therapy and maintenance of response. MASCC score validation was performed and final outcome of the study was defined as; (a) resolution without complication, (b) resolution with complication and (c) death before

Table 1 Hematological disorders and chemotherapeutic regimens offered

Hematological diseases	N = 226	Type of chemotherapy given	N = 170
ALL	91	UKALL XI protocol	52
AML	61	Induction	18
		Consolidation	34
		ATO/ATRA	14
		FLAG-Ida	8
		Palliative care	9
Aplastic anemia	32	ATG	14
		BMT	3
		R-CHOP	5
Lymphoma	19	FCR	3
Others ^a	23	Miscellaneous	10

^a Others include patients with Allogenic and Autologous Bone marrow transplantation, Myelodysplastic Syndrome, Chronic Myeloid Leukemia, Chronic Lymphocytic leukemia, Multiple Myeloma

Table 2 Multinational association of supportive care of cancer (MASCC) risk-index score [8]

Prognostic factors	Weight
No hypotension (systolic BP >90 mmHg)	5
Solid tumor or hematological malignancy with no previous fungal infection	4
No chronic obstructive pulmonary disease	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Burden of febrile neutropenia (no or mild symptoms) ^a	5
Burden of febrile neutropenia (moderate or severe symptoms) ^{b, c}	3
Age <60 years	2

^a Mild symptoms include—no fever, hemodynamic compromise or clinically significant signs and symptoms of particular site of infection

^{b, c} Moderate/severe symptoms include—high grade fever, any hemodynamic compromise or any of the serious complications described in text, requiring high dependency unit support

resolution. Serious medical complications were regarded as follows; hypotension, respiratory/renal/hepatic failure, Intensive care admission, confusion or altered mental status, congestive cardiac failure, massive bleeding requiring transfusions, ECG changes, arrhythmia requiring treatment, fungal infection or an allergic reaction.

Statistical Analysis

Patient's baseline characteristics were documented as descriptive statistics using SPSS variables. Statistical significance of difference between demographic variables as well as response to empirical therapy and final outcome was calculated and Pearson Chi square test applied. Probability of 0.05 was accepted as statistical significance. Sensitivity, specificity, positive and negative predictive values (PPV and NPV) was calculated statistically for low and high risk groups according to MASCC score.

Results

Data was collected for 226 patients with FN. The median age was 20 years (range 3–81) with 180 patients in less than 50 years of age group. There were 173 males (76.5 %) and fever was the commonest complaint (69.91 %). Frequently diagnosed diseases were, acute lymphoblastic leukemia 91 patients (40.23 %), followed by acute myeloid leukemia 61 (26.9 %) patients and Aplastic anemia in 32 patients (14.15 %) as shown in Table 2. Other salient features of result are shown in Table 3.

First-line empirical therapy was started in 217 patients (96 %) on commencement of fever, while rest of nine received other treatment not following FN protocol. At 72 h 184 patients (84.79 %) continued with first-line treatment while 20 (9.21 %) were shifted to second-line empirical therapy. Colony stimulating growth factors were given to 36 patients who had treatment for acute

leukemia/lymphoma/post bone marrow transplantation. Mean hemoglobin at presentation was 9.3 gm/dl (range 0–14); mean absolute neutrophil count was $0.92 \times 10^9/L$ (range 0–1.6) and mean platelet count was $56 \times 10^9/L$ (range 0–452). Sixty patients (26 %) were already hospitalized at the time of development of FN while rest was admitted from outpatient department. Seventy two patients had central line inserted. The performance status was evaluated prior to the initiation of chemotherapy for respective hematological malignancies for chemotherapy fitness. Ninety four patients (41.5 %) had MASCC index score <21 and were regarded as high risk while 132 (58.4 %) had MASCC score ≥ 21 and were labeled as low risk. Patient's characteristics have been summarized in Table 3. Both the groups had almost equal distribution of gender. There was no major statistical difference in the terms of diagnosis or use of growth factors between two cohorts.

Burden of primary disease was calculated as no or mild signs, moderate signs and severe signs of disease or its complications. The burden of disease was mild in 64 patients (48.5 %) in low risk group while 23 (25 %) patients in high risk group. Severe burden of disease was seen most frequently among high risk group which was 22 (23 %). Both groups had almost equal distribution of disease control, supportive care and given chemotherapy.

Out of 132 low risk patients, there were 33 bacterial isolates which were mostly sensitive to our first line empirical antibiotic therapy for FN. Uncomplicated infection was documented in 123 (93 %) while 9 landed with serious complications but had complete resolution. In complicated infections *Pseudomonas Aeruginosa* was isolated from 2 (2 from blood culture and 1 from urine culture), 1 had *Klebsiella Pneumoniae* (blood culture) and 5 had complicated *Escherichia coli* (blood cultures). One each had *Methicillin resistant staphylococcus Aureus* (MRSA) and *Vancomycin resistant enterococci* (VRE). Therapy was upgraded for four patients with sepsis;

Table 3 Characteristics of low and high risk patients

	Low risk N = 132 (58.4 %)	High risk N = 94 (41.5 %)	P value Pearson Chi square test
Median age			
Years (range)	19(3–77)	22(3–81)	0.854**
Gender			
Male	98(74.2 %)	75(79.8 %)	0.332***
Female	34(52.7 %)	19(20.2 %)	
Underlying disorders			
ALL	55(41.7 %)	36(38.3 %)	
AML	32(24.2 %)	24(25.5 %)	
Aplastic anemia	16(12.1 %)	16(17 %)	
Lymphoma	10(7.5 %)	13(13.8 %)	
Others ~	19(14.3 %)	5(5.3 %)	
Burden of disease			
No or mild signs	64(48.5 %)	23(25 %)	0.000*
Moderate signs	56(42.5 %)	49(52 %)	
Severe signs	12(9.1 %)	22(23 %)	
Patient status			
In-patient	24(18.2 %)	36(38.3 %)	0.001*
Out patient	108(81.8 %)	58(61.7 %)	
Febrile at presentation	114(86 %)	69(73 %)	0.014**
Pulse at presentation			
<120/min	106(80.3 %)	85(90.4 %)	0.461***
>120/min	26(3.7 %)	9(9.6 %)	
Median hospital stay	6 days (range 2–22)	7 days (2–19)	0.554***
Median day of ANC recovery	11 days (4–24)	12 days(3–27)	
Disease status			
Controlled	64(48 %)	24(25 %)	0.000*
Uncontrolled	68(52 %)	70(75 %)	
Treatment setting			
Supportive care	32(24 %)	19(20 %)	
Chemotherapy	95(71.2 %)	72(77 %)	
Bone marrow transplantation	6(4.5 %)	3(3 %)	
Complicated infections	9(7 %)	28(29.8 %)	0.000*
Uncomplicated infections	123(93 %)	66(70.2 %)	
Infection documentation			
Microbiologically documented infection	37(28 %)	40(42.5 %)	
Clinically documented infections	45(34 %)	52(55.3 %)	
Fever of unknown origin	50(37.8 %)	2(3.12 %)	
Number of cultures documented	33(25 %)	42(44.6 %)	0.002*
Response to first line antibiotic therapy			
Success	106(80.3 %)	81(86.2 %)	0.435***
Failure	15(11.4 %)	8(8.5 %)	
Death	0	8	0.001*

* Significant at 0.01 level; ** Significant at 0.05 level; *** Not significant at 0.05 level

Teicoplanin was used to treat MRSA and Linazolid used for VRE. The mortality rate in low risk group was zero.

In our study 93 % of low risk group were correctly predicted for uncomplicated infections and hospital stay.

They had sensitivity and specificity of 65 and 75 % respectively with positive predictive value (PPV) of 93 %.

High risk group had 94 patients (41.5 %), 28(29.8 %) developed complicated infections out of them eight

expired, while 66(70.2 %) had uncomplicated infections with complete resolution. The complications encountered in the high risk group were sepsis, development of invasive fungal infections and intracranial bleed. Total 42 bacterial isolates were documented from high risk group while 2 had invasive fungal infection. Among bacterial isolates 9 were *E. coli* (6 from blood culture, 2 from urine culture, 1 central line and 1 other site), 8 *P. Aeruginosa* (1 from throat culture, 4 from blood, 1 from central line and 2 others), 5 *K. Pneumoniae* (2 from throat culture, 2 from blood and 1 from urine), 8 *Pseudomonas spp* (1 from urine culture, 3 from blood, 1 urine, 2 central line and 1 others), 3 *Klebsiella spp* (1 each from central line, 1 others), one had VRE and 3 had MRSA isolated from blood culture. Among eight expiries, five had sepsis; two had hepatic failure out of which one had severe variceal bleeding while one died of intracranial bleeding.

Microbiological infections were documented in 40 (42.5 %) high risk group patients and 37(28 %) of low risk group patients. Clinically documented infections were seen in 45(34 %) of low risk and 52(55.3 %) of high risk patients.

Discussion

This study was conducted prospectively to classify patients at the onset of FN into high risk and low risk groups according to MASCC score with the aim to predict the probability, rate and severity of complications in both the groups. A recent study has shown that exclusion of patients with complex infection from the low risk group by the MASCC risk index score determined sensitivity of 100 % [10], however in our study the sensitivity and specificity of low risk group was 65 and 75 % respectively with positive predictive value (PPV) of 93 %. This MASCC risk index was validated prospectively in another study and low risk neutropenic patients were identified with accuracy of 98.3 % [12]. The original MASCC study identified low-risk group with PPV of 91 % and sensitivity and specificity of 71 and 68 % respectively [8].

While treating patients with hematological malignancies the final outcome is survival and uneventful recovery from FN. With our current practices the object was attainable as we observed that response to first-line antibiotic therapy was nearly same in both the groups however fewer complications were observed in low risk group. There was no statistical difference in median ANC recovery or median hospital stay.

From 132 low risk patients, 123 had uncomplicated course while only 9 had complicated infections in our study. In another study 57 out of 80 patients were low risk and only one had complicated recovery [11] with

Enterobacter sp, *Candida* and fungal infection but had complete recovery. Our low risk patients had 33 positive isolates (18 from blood, 4 from urine, 4 from throat and 7 from others) and had predominantly *E. coli* infection.

All the mortalities were observed in high-risk group and all of them had severe burden of disease. Sepsis was documented in 5 out of 8 patients and only two had documented isolates (*E. coli* and MRSA). The fatal outcome was due to intracranial bleeding in one patient and two had hepatic failure with massive gastrointestinal bleeding. Out of them one patient with Aplastic anemia developed hepatic veno-occlusive disease along with sepsis. These causes reflect the deterioration primarily because of the actual hematological disease. No mortality was reported in low risk group in a study of Uys et al [11] and cause of mortality of high-risk group was differently reported as of our patients.

The approach to determine MASCC risk index would be helpful to individualize the care with aggressive management to the high risk cohort including early hospitalization, prompt infection control measures and rationalization of colony stimulating factors. Although this high risk index does not enumerate many other factors like the site of infection, level of consciousness of the patient, ongoing coagulopathy/severity of thrombocytopenia, ABG/O2 saturation, renal impairment, procalcitonin levels, intubation status independently but it separates high risk population, who most of the time require intensive care. However the low risk group can be managed conservatively hence making the treatment more cost effective and utilize resources more judiciously. Considering all these facts it can be concluded that MASCC risk index score is an applicable tool in the management of patients with FN and can be more accurately used to predict low risk patients at the onset of FN.

Conclusion

The outcome of 123(93 %) low risk group patients had positive predictive value of 93% with both sensitivity and specificity of 65 and 75 % respectively. Although MASCC risk index score does not evaluate many other aspects of critically ill patients, indeed it highlights high risk population, frequently requiring intensive care. Meanwhile, the low risk group can be managed conservatively hence it can have positive impact on financial burden in developing countries. Hence the MASCC risk score is a valuable tool in determining the outcome of patients with febrile neutropenia, low risk group in particular.

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