Development of a Prognostic Model to Predict the Response to Treatment of Neutropenic Fever in Patients with Hematological Malignancies

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Abstract: Background: A febrile neutropenia remains one of the most commonly encountered oncological emergencies in patients with hematological malignancies. Development of a prognostic system is very critical in those patients **Aim of the study**: The aim of this study was to describe febrile neutropenia in a cohort of Egyptian patients with hematological malignancies and to develop a predictive model for its outcome. **Methods**: This is a prospective observational study including 142 patients with haematological malignancies who presented to Kasr Al Ainy Center of Clinical Oncology during the period of 1st of June 2014 untill October 2015. This group of patients suffered from 270 episodes. According to the MASCC score, high risk patients were treated inpatients. All admitted patients were subjected to blood, sputum, stool and urine culture withdrawal and Galactomann test. PCR (polymerase chain reaction) of sepsis and BAL (broncho alveloar lavage) were done in certain cases. Empirical antibiotics were started immediately, antifungal and antiviral were received according to the guidelines. **Results**: The different diagnostic modalities were analysed in addition to the results of treatment by different classes of antibiotics. The most frequent diagnosis in our study were AML (55 patients), followed by ALL (27 patients, and NHL (35 patients) and others diagnosis (HL, MM, CLL,CML). The disease status of hematological malignancy patient was found highly significant and affects the control of neutropenic fever episode. The more the patient develop neutropenic episodes the more the risk of mortality. In our study, the MASCC score were highly significant. 62% of the identified pathogens were gram positive detected by blood culture. while gram negative bacteria were the commonest pathogens identified by other diagnostic modalitie. The most encountered organisms were MRSA, CONS and Klebsiella. **Conclusions** The management of febrile neutropenia requires the cooperation between several departments. Many risk factors affect the outcome of febrile neutropenia and should be taken in consideration for every pts.

1. Introduction

Neutropenic fever remains one of the most commonly encountered oncologic emergencies, the immune systems in neutropenic patients is impared; so the patients often do not exhibit typical signs and symptoms of infection, the obvious clues in their presentation should always be strongly pursued.[1] According to the Infectious Diseases Society of America, the neutropenic fever was defined as a single temperature measurement $\geq$ 38.3°C (101°F) or a sustained temperature $\geq$ 38°C ($\geq$ 100.4°F) for more than 1 hour in a patient with an absolute neutrophil count (ANC) of either < 500 cells/µL or < 1000 cells/µL, with a predicted nadir of < 500 cells/µL over the subsequent 48 hours.[2] Patient with hematological malignancies are at high risk of infection although they may have normal or even elevated ANCs due to defects in neutrophil function (qualitative neutropenia).[3] These defects include reduction in phagocytosis, decreased bactericidal and fungicidal activity, decreased production of superoxide anions, and defects in

granulocyte locomotion.[4] The greater the risk of infection is directly proportional to the longer the duration of neutropenia.[5] Patient with hematological malignances develop neutropenic fever far more often than patients with solid tumors.[6] It's critical to early diagnose and early administer of anti-infective therapy for the overall survival of cancer patients.[7] Several factors have been implicated in the pathogenesis of febrile neutropenia. These factors may be attributed to the malignancy itself or treatment associated factors.[8] The outcome of patients with febrile neutropenia depends to a great extent on the degree and duration of neutropenia.[9] However, many other factors contribute to the variation in patients' response to treatment and survival.[10] Several attempts have been done to identify the risk group in febrile neutropenia.[11] APACHE (Acute Physiology and Chronic Health Evaluation) was one of the earliest scoring system used for general assessment of febrile neutropenia patients.[12] In 2000, an internationally validated scoring system to identify the risk groups (low vs high) in febrile neutropenia cancer

patients was developed by the Multinational Association of Supportive Care in Cancer. Many risk factors were not included in the MASCC score although they have an important effect on the risk of complication in febrile neutropenia e.g. renal and hepatic disorders.[13]

Aim of the Work

Our aim is to improve the outcome of neutropenic fever treatment in hematological malignancy patient. This is achieved by achieving our goals which are the following: To recognize the responsible risk factors affecting outcomes. To correlate the frequencies of NF episodes with the outcome. To identify the role of different diagnostic modalities for detecting the source of infection; To know the results of treatment of cancer patient in NF. To built up a prognostic score predicting the outcome of NF in patient with hematological malignances. The most common sites of infection encountered in patients with neutropenia are Respiratory tract infections, followed by bacteremia (including central line associated bloodstream infection- CLABSI), urinary tract infections, skin/skin structure infections, and infections originating from the oro-pharynx and intestinal tract.

2. Patients and Methods

This study was a prospective observational study on patient with hematological malignancies who presented with or developed neutropenic fever in the period between May 2014 to the end of October 2015 at Kar Einiy Hospital Oncology Department Cairo University. Patient inclusion criteria Age: ≥18 years. Disease status: in remission, relapsed/ refractory, or newly diagnosed. Exclusion criteri: Pediatric patients younger than 18 years old. Patients who presented with neutropenic fever and improved on oral antibiotics. All patients presented with neutropenic fever were subjected to the following: detailed history including: diagnosis of the primary disease, duration of fever treatment given, previous attacks, last chemo and radiotherapy, recent surgery, examination: vital sign, performance status criteria of MASCC score (low risk or high risk for complications).

Table (1) MASCC score

Characteristic		Score
Burden of illness	no or mild symptoms	5
	moderate symptoms	3
	severe symptoms	0
No hypotension (systolic BP >90 mmHg)		5
No chronic obstructive pulmonary disease (**COPD**)		4
Solid tumor/lymphoma with no previous fungal infection		4
No dehydration		3
Out patient status (at onset of fever)		3
Age <60 years		2

Score >21→ low risk, Score <21→ high risk, Maximum theoretical score of 26

Examination of oral cavity, paranasal sinuses, perianal area, chest, body orifices, skin….etc. Collecting blood cultures Every single patient was subjected to immediate withdrawal of blood culture as soon as possible and is repeated if indicated (2 sets if there was a central line) and the following tests were done if indicated: Urine culture: only patient who had urinary symptoms or suspected urinary tract infection have performed this test, sore swab, wound swab was performed in those with open wound with draining pus. Sputum culture. CSF analysis in cases with suspected CNS infection. PCR for sepsis: was done in selected cases, galactomanan test: was done in patients with suspected fungal infection, BAL: The patient was referred to perform this invasive procedure only if there were positive CT findings. Xray and CT scan for chest, abdomen or paranasal sinuses Empirical antibiotics: The used antibiotics as 1st line of treatment were: Ceftazidine 2gm/ 8h Cefipime 1gm/ 8h Meropenem 1 gm/ 8hr Imipinem 500 mg/ 6hr, Ampicillin/ Tazobactem 3.375gm/ 6hr. We start Amphotericine loading dose 0.5mg/kg IVI over 2-6 hr and maintenance dose maximum 1mg/ kg once daily. The solution should be covered from light. Dose adjustment was done in cases with renal and/ or hepatic impairement. Potassium supplements were prescribed during treatment period. Antiviral protocol: Acyclovir 10mg/Kg IV q8hr for 7 days was used in case with suspected viral infection. G-CSF: Usually was given in patient with ALL or lymphoma having prolonged neutropenia. Filgrastim (Neubogen) was used 5mcg/Kg SC/IV qDay dose was repeated according to duration and severity of ANC.

Statistical Method

The data was statistically described in terms of range, mean, standard deviation (SD), median, frequencies (number of cases) and relative frequencies (percentages) when appropriate comparaison of

quantitative variables between study groups was done using Mann Whitney U test for independent samples for comparing categorical data, Chi square test was performed exact test was used instead when the expected frequencies were less than 5 a probability value (P-value) <0.05 was considered statistically significant. All statistical calculations was done using computer program Microsoft excel version 7 (Microsoft corporation, NY, USA) and SPSS (statistical package for social science, SPSS Inc, Chicago, IL, USA) a statistical program for microsoft window. For the development of a prognostic index, only FN episodes with complete data related to pre-treatment variables will be included. Only one FN for each patient will be considered. For patients who had more than one episode with complete data, the last one was the one taken into consideration. Variables with a significant p value (<0.05) in univariate analysis will be included in logistic multivariate analysis. Based on the odds ratios, a weighed partial score will be assigned for each of variables significant in multivariate analysis. A receiver operating characteristic (ROC) curve analysis will be used to determine the best cutoff value of the developed prognostic index for the prediction of FN episodes outcome.

3. Results

This is a prospective observational study including 142 patients with haematological malignancies who presented to Kasr Al Ainy Center of Clinical Oncology during the period of 1st of June 2014 untill October 2015. This group of patients suffered from 270 episodes. The commonest diagnosis was AML (55), followed by NHL (35) and ALL (27). The other less common diagnoses were CML, CLL, HL and M. M. Patients were categorised according to the disease status whether in remission (44), newly diagnosed (26) or relapsed/ refractory (72).

The different modalities used for the diagnosis of infection were analysed in addition to the results of treatment by different classes of antibiotics. All factors which may affect the prognosis were subjected to analysis Patient characteristics: Age group from 30- 60. Seventy eight (54.9%) of our patients were females while males represented 45.1%. The majority of cases was significant with P value<0.001 between refractory

diseases/ relapsed & newly diagnosed and those in remission. The most common co-morbidity in our patients was diabetes mellitus, followed by HCV infection and COPD. Out of 188 NF episodes with acute leukemias diagnosis, 141 episodes had occurred following induction or consolidation chemotherapy. They were highly significant with Pvalue <0.001.

Diagnostic modalities CT chest was done in 249 episodes of FN. Positive findings were seen in 31% of cases. Similar figure was obtained by CT PNS (32%). Galactomanan was performed in 125 cases; the results were above the cut-off value of 0.5 in 45 cases (36%). Bacterial pathogens (or fungal) were detected in 72 cases (21%) out of 343 samples. Sixty two percent of the identified pathogens were gram positive while gram negative bacteria represented 38%. In the blood culture, gram positive bacteria were identified in 80% of cases. On the other hand, gram negative bacteria were the commonest pathogens identified by other diagnostic modalities (19/28, 68%). The most common gram positive bacteria were MRSA (17) and CoNS (17). Klebsiella and E-coli were the commonest gram neg bacteria detected in our study.

As regard the treatment options: Prophylactic Fluconazole was given in 172 episodes, 20% developed fungal infection on the other hands it was not prescribed in 98 episodes and only 12% developed fungal infection with P value: 0.183. G-CSF was used in a total of 90 episodes in this group 44% of neutropenic fever exceeded 10 days compared to 55.9% of episodes in which G-CSF was not used. 1st line antibiotic usage: At the onset of febrile neutropenia, patient started empiric antibiotics using either 3rd generation Cephalosporins as Ceftazidime (167 episodes) or Cefipime (4th generation Cephalosporins) in 42 episodes or Carbapenems in 54 episodes. Febrile neutropenic episodes were controlled in 61 episodes using 3rd generation Cephalosporins (61/167; 37%). Sixty three percent (30/48; 63%) of episodes were controlled by 1st line Cefipime, while 24/ 54; (44%) were controlled with 1st line carbapenems. High risk patients with MASCC score <21 were predominant in Carbapenems group (68%; 37/54) compared with 3rd generation Cephalosporins (38%; 36/167) and Cefipime group (3%; 15/48) as presented in (Table 1).

Table (2):1st line antibiotics usage among the 270 febrile neutropenic episodes

1st line Antibiotic	Controlled	Not controlled	Total use	MASCC	
				<21	≥21
3rd gen. Cephalosporin	61 (37%)	106 (64%)	167	63	104
4th gen. Cephalosporin	30 (63%)	18 (38%)	48	15	33
Carbapenems	24 (44%)	30 (56%)	54	37	17
P value				0.158	0.011

Antifungal uses. A total of 105 episodes had received Voriconazole or Amphotericin B as 1st line antifungal and 23 of them needed 2nd line antifungal to control the infection, Voriconazole was used in 49 episode (47%) and amphotericin B in 56 episodes (53%). In Voriconazole group, 2nd line was used in 6 episodes (12%) compared to 17 episodes (30%) in Amphotericin group with P value 0.025. When correlating the outcomes of NF episodes in relation to MASCC score and in accordance with diagnosis, it was found that the high risk patients, <21, had poor control. P values were significant with ALL and NHL, 0.001 and 0.003 respectively.

Table (3) showing risk of mortality during neutropenic fever episodes in relation to diagnosis

	Total number	≥21	<21	Total mortality	≥21	<21	P value
AML	125 46%	72 58%	53 42%	13 10.4%	3 23%	10 77%	0.56
ALL	63 23%	34 54%	29 46%	12 19%	1 8 %	11 92%	0.001
NHL	50 18.5%	31 62%	19 38%	8 16%	1 12.5%	7 85.5%	0.003
HL	9 3%	5 56%	4 44%	2 22%	0	2	0.429
MM	10 4%	5 50%	5 50%	1 10%	0	1	1
CML	5 2%	2 40%	3 60%	0	0	0	
CLL	8 3%	5 63%	3 37%	2 25%	0	2	0.1

But the disease status had also a significant role in NF episodes outcome. The patients who were in remission had a better outcome (8.3%) than who were not in remission (40.2%) P value of <0.001. In a way for understanding the relation of mortality and the number of attacks, it was found that the more the development of neutropenic fever episodes the more the incidence of mortality as showed in with a significant P value = 0.025. The positive cultures in relation to number of episodes also revealed a higher incidence of mortality with a P value of 0.008 in 2nd episodes. Predicting score at the onset of neutropenic fever attacks. For developing of a prognostic score, patients with complete data were included in the analysis. Therefore 109 patients were subjected to the analysis. For patients who had more than 1 episodes the last one was taken into consideration. Five pre-treatment variables correlated significantly with the likelihood of death, previous NF episode, severe/moribund disease burden, hypotension, previous fungal infection and uncontrolled malignancy. Variables with a significant p value (<0.05) were included in logistic multivariate analysis. Three variables retained significance in multivariate analysis, severe/moribund disease burden, hypotension and uncontrolled malignancy. Based on the odds ratios, a weighed partial score was assigned for each of these three variables (table 4).

Table (4): Multivariate analysis to determine pre-treatment variables of independent prognostic value (Prognostic score)

Variable	Odds ratio	95% CI		P value	Weighed partial score
Previous NF episode	1.47	0.307	7.023	0.63	--
Severe/ Moribund disease durden	3.677	1.2	11.265	0.023	2
Hypotension	5.609	1.711	18.392	0.004	3
Previous fungal infection	1.905	0.407	8.91	0.413	--
Uncontrolled disease	4.222	1.019	17.493	0.047	2.5

Summing the partial scores of the three significant variables resulted in a prognostic score ranging from 0 (**best prognosis**) to 7.5 (**worst prognosis**). Ideally, the developed prognostic score should be tested in a test set rather than the training set. A cut-off value of 4.5 was determined. It divides patients into two groups, ≤4.5 vs. >4.5 (= at least two positive risk factors including hypotension). A score of >4.5 predicted mortality with a sensitivity of 79% and a specificity of 79%. The overall accuracy was 79%.

Table (5) Correlation between the prognostic score cutoff point >4.5 and the outcome of neutropenic episodes of the training set in univariate analysis

Prognostic score	Death	Episode survival	Odds ratio	95% CI	P value
>4.5	23 (58%)	17 (43%)	14.2	4.99 - 40.44	<0.001
≤4.5	6 (9%)	63 (91%)			

4. Discussion

Our study was a prospective observational study on patients with hematological malignancies who presented with or developed neutropenic fever in the period between May 2014 to the end of October 2015 at Kar Einiy Hospital Oncology Department Cairo University. Patients with acute leukemias (55 patients with AML & 27 with ALL) were the predominant group in our study. This could be attributed to the use of intensive chemotherapy regimens during induction and consolidation therapy. In other studies, acute leukemia, in particular AML, was the predominant hematological malignancy associated with FN (40.5%- 51%).[14] The most common co-morbidities in our study were diabetes, HCV, and COPD. The diabetes in our study was not found to be a significant risk factors (P-value= 0.318) due to strict control of blood sugar levels during neutropenic fever attack. In our study; chronic obstructive pulmonary disease (COPD) was associated with increased risk of pneumonia as documented by CT scan; 14 out of 18 cases developed pneumonia. COPD is one of the risk factors in MASCC score; however in our study, it didn't affect mortality rate. The importance of disease status was very clear in our study.

The risk of mortality in our patients with controlled disease was 4.7% (5/106 episodes) compared to 20% (33/164 episodes) in patients with refractory/ relapsed or newly diagnosed cases. This high number of mortality in refreactory or relapsed cases is not only due to failure to control FN attacks but it is related to the progressive disease. Similar figures was reported by.[15]

As regard the frequency of episodes in relation to diagnosis of patients; the frequency was found to be higher among patients with acute leukemia more than other diagnosis. The average of episodes in patients with ALL (2.9) followed by AML (2.4). This is may be due to the intensive chemotherapy that was used in ALL during induction and consolidation therapy.

We found that sixty two percent of the identified pathogens were gram positive while gram negative bacteria represented 38%. In blood culture; gram positive bacteria represented the majority of the isolates (80%), while gram negative bacteria represented (20%) of isolates. CoNS were the most frequent organisms isolated from 15 blood culture (34%) in the present study. Other studies also reported CoNS as the most common organisms isolated from blood cultures with rates ranged from 30-37%.[16]

On the other hand, gram negative bacteria were the commonest pathogens identified by other diagnostic modalities 68% (19/28). Infections with gram negative bacteria predominated during 1970 and 80, a predominant shift to gram positive infections has been reported in later years. In the current study, there were 18 isolates Staph aureus, 3 of them (16%) were not Methicillin resistant. In correlation with study conducted by Swati et al, he reported all isolate as methicillin sensitive.[17]

However, an Irish study was similar to our current study, Morris et al., reported that 89.3% of all isolates of S. Aureus were Methicillin resistant.[18] In the current study Klebsiella was the most common gram negative organism isolated in 9 episodes (21%) detected by PCR (4), blood culture (3) and urine culture (2).

E-COLI was 2nd common gram negative organism detected in 6 episodes (14%). Similarly, other studies reported the most common gram negative organisms are E-COLI (14 %) and Klebsiella (9%).[19] In the current study, multiplex PCR test from blood samples was done in only 10 % of episodes (27 episodes). It was done in selected cases with prolonged neutropenia with negative blood cultures and negative radiological tests. There were 20 episodes with negative blood cultures and 7 positive results which revealed 12 organisms. Eight out of twelve organisms were gram negative representing 66%. The usage of prophylactic fluconazole had shown increase the incidence of molds infection in our study; it's better to use Posaconazole in leukemia patients especially during induction. The Incidence of fungal infection was higher in the group of patient who received prophylactic fluconazole, fluconazole is active only against candida ALBICAN and inactive against some of candida species like candida Krusei and molds such as Aspergillus and Mucor mycosis.

Posaconazole which is active against molds is recommended by NCCN guidelines, however it is more expensive.[20] As regards to the emprical antibiotic and antifungal coverage, the response rate to 3rd generation Cephalosporin were 37% (61/167) whereas 64% (106/167) required 2nd line antibiotics. Resistance to this group of antibiotics is common including Ceftazidime; therefore they should be used very cautiously in selected cases of FN. Thirty episodes (30/48, 63%) were controlled by 1st line Cefipime, compared with 24 episodes (24/54, 44%) in the group of Carbapenems. The majority of patients in the Carbapenems group were in high risk according to MASCC score (37/54, 68.5% vs. 15/48, 31%) compared to Cefipime group. The risk of death during FN episodes in a trial was 14% (38/270). Klastersky et al. had reported a risk of mortality of 5.2% (64/1223) in patients with hematologic malignancies.[21]

The predominance of patients with uncontrolled disease is another important factor as the mortality rate in patients with controlled disease status was nearly 8%

(5/55) compared to 40% (33/82) in patients with relapsed or refractory disease. Variations in the risk factors in each group of patients and lack of good supportive care may explain increased risk of mortality in our study.

The risk of mortality in patients with high MASCC Score was 3% (5/154), on the other hand it was quit high 28% (33/116) in patients with low MASCC score. MASCC score has been originally designed to predict morbidity in solid tumors and hematologic malignancies. Several studies have demonstrated that the Predictive value of MASCC score decreased with increasing number of patients with hematological malignancies.[22]

In addition many important factors are missing in the MASCC Score for predicting high risk cases. Therefore, we tried to study the important factors which might predict the risk of mortality in FN patients. Four factors in our study (with multivariate analysis) have been identified to be of prognostic significance. Four of them are includes in MASCC score. The aim of using MASCC score in the prediction of serious complication, however our aim was to predict risk of mortality. This may explain the difference in the items included in our analysis and the MASCC score. The three factors which retained significance in multivariate analysis were disease burden, hypotension and uncontrolled disease. These factors were derived purely from cases of hematologic malignancies, easy to apply and depend on single clinical assessment (vs. APACHE II score).

Conflict of interest: None

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