Prognostic factors for mortality with febrile neutropenia in hospitalized patients

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ABSTRACT

Background: Febrile neutropenia is a life-threatening complication of cancer treatment that results in hospitalization and delays cancer therapy. The aim of this study is to identify prognostic factors of patients admitted with febrile neutropenia.

Methods: A retrospective study via chart review without direct patient contact was conducted. All adults above 18 years with the diagnosis of febrile neutropenia hospitalized in University Medical Center in Lubbock, Texas, between January 2010 and December 2013 were reviewed. The data were analyzed with IBM SPSS statistics.

Results: One hundred twenty-seven patients were included in this study. The hospital mortality rate was 17.3%, and the 30-day mortality rate was 20.5%. The median length of stay (LOS) was eight days. Hematologic malignancies accounted for 66.1% of the patients. On multivariate analysis, the in-hospital mortality rate was associated with fever duration (adjusted odds ratio [OR] 7.19; 95% CI 1.06-50.00; $p <0.04$), abnormal liver function tests (adjusted OR 63.72; 95% CI 5.95-682.07; $p <0.001$), ICU admission (OR 45.78; 95% CI 4.97-420.99; $p <0.001$) and positive culture (adjusted OR 12.71; 95% CI 1.14-142; $p <0.039$). The independent risk factors for a 30-day mortality rate were abnormal liver enzymes (OR 48.38; 95% CI 5.27-444.29; $p <0.001$), ICU admission (OR 63.66; 95% CI 5.96-680.30; $p <0.001$) and fever duration more than four days (OR 8.26; 95% CI 1.11-62.50; $p=0.039$). The data indicated that diagnosis of hematologic malignancies (OR 4.06; 95% CI 1.34-12.31 $p=0.013$), fever duration (adjusted OR 6.29; 95% CI 1.81-21.92; p 0.004) and neutropenic duration more than five days (OR 3.68; 95% CI 1.44-9.40 $p=0.007$) were associated with LOS more than eight days.

Conclusions: Febrile neutropenia in hospitalized patients results in a significant mortality rate. Factors associated with increased mortality include ICU admission and abnormal liver enzyme tests.

Key words: Febrile neutropenia, cancer, ICU admission, liver enzyme tests, mortality, and length of stay

INTRODUCTION

Febrile neutropenia is a life threatening complication of cancer treatment that results in hospitaliza-

tion and the need for broad spectrum antibiotics. It can affect outcomes during cancer treatment through delays in the treatment cycle, dose reductions, or discontinuation of chemotherapy. Its consequences depend on the severity and duration of the neutropenic phase and vary greatly among patient groups. Febrile neutropenia accounts for approximately 40% to 50% of the total cost of hospitalization in cancer care and results in mortality rates between 3% and 20%, depending on risk factors.[1,2] Risk stratification could influence the medical management in febrile neutropenic patients, and high risk patients might benefit from a more intensive medical approach. The current National Comprehensive Cancer Network (NCCN) guideline recommends the use of the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index (Table 1) as a risk stratification tool to identify low risk febrile neutropenic patients.[3] However, this index stratifies patients into only outpatient and inpatient management groups. There is no risk scoring system available for febrile neutropenic patients who require hospitalization, but there have been studies on prognostic factors to improve risk assessment of these patients based on clinical and laboratory indicators. Some of these factors include the duration and severity of neutropenia, the underlying cancer, disease status, underlying comorbidities, and types of infection.[4,5] In our study we wanted to identify prognostic factors for febrile neutropenia in hospitalized patients.

Table 1 The Multinational Association for Supportive Care in Cancer (MASCC) Risk Index

Characteristic	Weight
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Burden of illness: moderate symptoms	3
Outpatient status	3
Age < 60 years	2

Points attributed to the variable "burden of illness" are not cumulative. The maximum theoretical score is therefore 26. ≥21: low risk patients (positive predictive value 91%, specificity 68%, sensitivity 71%)

MATERIAL AND METHODS

PATIENT POPULATION

A retrospective study via chart review without direct patient contact was conducted. All patients aged greater than 18 years old with a diagnosis of cancer and ongoing chemotherapy treatment with fever (temperature equivalent to ≥ 38.0 ˚c) and neutropenia (absolute neutrophil count less than 500/mcL and/or a predicted decline to less than 500/mcL over next 48 hours) hospitalized in University Medical Center in Lubbock, Texas, from January 1, 2010, to December 31, 2013, were included in the study.

Inclusion criteria were based on the ICD 9 288.00 code for the diagnosis of febrile neutropenia. All data were reviewed and checked for accuracy. Some patients were admitted initially for infection or chemotherapy and did not have febrile neutropenia at the time of admission but later developed it. This group of patients was also included as a secondary diagnosis of febrile neutropenia with the onset of fever occurring as inpatient. Some patients developed multiple episodes of febrile neutropenia, but only the first one was considered in this study. Exclusion criteria included patients who were on palliative care measures and who did not receive or denied treatment. Febrile neutropenia from all causes other than chemotherapy (e.g., primary immunodeficiency or liver disease) was also excluded from the study. All patients' data were deidentified and included the patients' demographics (ages, gender, types of cancer, and comorbidities) and clinical parameters, including complete blood count with absolute neutrophil count (ANC), complete metabolic panel, and culture at diagnosis of febrile neutropenia. All patients' hospital courses were reviewed to determine length of stay (LOS) and discharge outcome. This study was approved by the Institutional Board Review for the protection of human subjects of the Texas Tech Health Sciences Center, Lubbock/Odessa, Texas.

OUTCOME MEASURES

The primary outcome was inpatient mortality. Factors associated with 30-day mortality rates and

LOS were also assessed.

Descriptive analysis was used to describe patient characteristics. Univariate and multi-variable logistic regression models were used to evaluate the association between clinical risk factors and patient mortality and LOS. A *p* value less than 0.05 was considered statistically significant. The data were analyzed with the IBM SPSS software (IBM; version).

RESULTS

The first episodes of febrile neutropenia in 127 patients were included in the study. The cohort included 80 men (63%) and 47 women (37%) with a mean age of 55.7 ± 16.5 (range 19-84). Most patients were more than 55 years. The ethnic/race distribution included 81 Caucasians (63.8%), 43 Hispanics (33.9%), and three African-Americans (2.4%). Twelve patients (9.4%) had metastatic disease at the time of febrile neutropenia diagnosis. Eighty-five patients (66.9%) had one or more comorbidities. The most common comorbidities were essential benign hypertension in 59 patients (46.5%), diabetes in 23 patients (18.1%), and chronic kidney disease in 16 patients (12.6%). Thirty-six patients (28.3%) were admitted to or transferred to the intensive care unit (ICU) during hospitalization.

The mean fever duration was 3.5 ± 3.75 days (median: two days, interquartile range [IQR]:1-4 days; range 1-26 days). The mean absolute neutrophil count at the onset of fever was 629.32 /mcl with mean lowest count at 9.49/mcl. The number of days from onset of fever to lowest ANC count was 2 ± 1.8 days. Colony stimulating factor was given to 96 patients (75.6%). The neutropenic period ranged from 1-22 days with a median of five days. Every patient was on antibiotics at the time that fever developed. The sources of infection were unknown in 46 cases (36.2%), the lung in 21 cases (16%), the gastrointestinal tract in 21 cases (16%), the urinary tract in 16 cases (12.6%), and primary bacteremia in 17 cases (13.4%). Seventy-one cases (55.9%) had positive cultures, including 38 Gram positive cultures (29.9%), 32 Gram negative cultures (25.2%), and one fungal culture (0.8%).

The hospital mortality rate was 17.3%, and the 30-day mortality rate was 20.5%. The LOS ranged from 2-73 days with a median of eight days (IQR 5-14 days). Seventy-one patients (55.9%) had a LOS more than eight days. A MASCC score less than 21 occurred in 22 of 26 patients (84.62%) in the 30-day mortality rate group, but this was not statistically different from the score in 30-day survivors.

Univariate analysis showed that abnormal liver enzymes, ICU admission, fever duration more than four days, and positive cultures were significantly associated with death (Tables 3 and 4). The type of malignancy and neutropenic duration were associated with prolonged LOS (> 8 days) (Table 5). On multivariate analysis, the in-hospital mortality rate was associated with fever duration (adjusted odds ratio [OR] 7.19; 95% CI 1.06-50.00; p <0.04), abnormal liver enzymes (adjusted OR 63.72; 95% CI 5.95-682.07; p <0.001), ICU admission (OR 45.78; 95% CI 4.97-420.99; p <0.001) and positive culture (adjusted OR 12.71; 95% CI 1.14-142; p <0.039). The independent risk factors for a 30-day mortality rate were abnormal liver enzymes (OR 48.38; 95% CI 5.27-444.29; p <0.001), ICU admission (OR 63.66; 95% CI 5.96-680.30; p <0.001) and fever duration more than four days (OR 8.26; 95% CI 1.11-62.50; p=0.039). The data indicated that diagnosis of hematologic malignancies (OR 4.06; 95% CI 1.34-12.31 p=0.013), fever duration (adjusted OR 6.29; 95% CI 1.81-21.92; p=0.004) and neutropenic duration more than five days (OR 3.68; 95% CI 1.44-9.40 p=0.007) were associated with LOS more than eight days (Tables 3, 4 and 5).

DISCUSSION

Febrile neutropenia is a major complication from cancer treatment that carries a high mortality rate. Lyman et al 6 studied a large cohort of patients with cancer and found that patients who developed febrile neutropenia had a higher overall and early mortal-

Table 2 Characteristics of patients in study (total N=127)

		N	Percent
Gender	Male	80	63
	Female	47	37
Race	White	81	63.8
	Hispanic	43	33.9
	African-American	3	2.4
Diagnosis	Leukemia	58	45.7
	Lymphoma	26	20.5
	GI malignancy	10	7.9
	Lung cancer	6	4.7
	Soft tissue	3	2.4
	Head and Neck	3	2.4
	breast cancer	6	4.7
	Other	15	11.8
Comorbidities	Diabetes Mellitus	23	18.1
	Hypertension	59	46.5
	Heart failure	10	7.9
	Chronic kidney disease	16	12.6
	Deep vein thrombosis	6	4.7
	COPD/asthma	11	8.6
	Coronary artery disease	11	8.6
MASCC score	< 21	92	72.4
	> 21	35	27.6
ICU admission		36	28.3
30 day mortality		26	20.5
In hospital mortality		22	18.9
Discharge destination	**Home**	89	70.1
	Nursing facility	5	3.9
	Hospice	9	7.1
CSF		96	75.6

Table 2 Characteristics of patients in study (total N=127) (Continued)

		N	Percent
Source of infection			
	Pneumonia	21	16.5
	UTI	16	12.6
	Primary bacteremia	17	13.4
	gastrointestinal	21	16.5
	Skin/soft tissue	2	1.6
	Other	4	3.1
Culture	Positive	71	55.9
	Negative	56	44.1
Gram	Positive	38	29.9
	Negative	33	26
Readmission in 30 days		36	28.3

Table 3 Prognostic factors associated with in-hospital mortality in febrile neutropenia patients

Variable	In hospital Expired (n=22)	Crude OR (CI)	P-Value	Adjusted OR (CI)	P-Value
Age (years)					
≤60	14(20.6%)	1.65	0.3	1.86	0.57
>60	8(13.6%)	(0.64-4.27)		(0.22-16.13)	
Gender					
Male	15(18.8%)	1.32	0.58	3.61	0.18
Female	7(14.9%)	(0.50-3.51)		(0.55-23.55)	
Race					
White	15(18.5%)	1.1	0.83	1.61	0.522
Hispanic	6(14%)	(0.46-2.64)		(0.37-6.95)	
African-American	1(0.5%)				
Type					
Hematologic Malignancies	16(19%)	1.74	0.32	1.16	0.334
Solid tumor		(0.59-5.13)		(0.13-10.41)	
	5(11.9%)				

Table 3 Prognostic factors associated with in-hospital mortality in febrile neutropenia patients (Continued)

Variable	In hospital Expired (n=22)	Crude OR (CI)	P-Value	Adjusted OR (CI)	P-Value
Comorbidities					
Yes	12(14.1%)	0.526	0.18	1.01	0.717
No	10 (23.8%)	(0.21-1.34)		(0.16-6.40)	
Fever duration					
> 4 day	12(38.7%)	5.43	<0.001	7.19	**0.04****
< 4 day	10 (10.4%)	(2.05-14.40)		(1.06-50.00)	
Liver enzymes					
Abnormal	15(46.9%)	11.43	<0.001	63.72	**<0.001****
Normal	7(7.4%)	(3.27-39.87)		(5.95-682.07)	
Albumin level					
Normal (> 3g/dL)	6(20.7%)	1.34	0.58	3.62	0.38
Low	16(16.3%)	(0.47-3.81)		(0.54-24.39)	
GFR					
< 60	9(24.3%)	1.85	0.21	1.41	0.69
> 60	13(14.8%)	(0.71-4.82)		(0.26-7.68)	
MASCC					
High risk	18 (19.6%)	1.89	0.29	5.39	0.16
Low risk	4(11.4%)	(0.59-6.20)		(0.51-56.63)	
Neutropenic period					
> 5 day	14(20.3%)	1.53	0.38	1.16	0.86
≤ 5 day	8(14.3%)	(0.59-3.95)		(0.24-6.25)	
ICU admission					
Yes	17(47.2%)	15.39	<0.01	45.78	**<0.001****
No	5(5.5%)	(5.05-46.89)		(4.97-420.99)	
Source of infection					
Bacteremia	4(23.5%)	1.57	0.47	1.11	0.73
Other infection	18(16.4%)	(0.46-5.38)		(0.13-9.71)	
Culture					
Positive	19(26.8%)	6.45	0.004	12.71	**0.039****
Negative	3(5.4%)	(1.80-23.13)		(1.14-142)	

Table 4 Prognostic factors associated with 30-day mortality in febrile neutropenia patients

Variable	30 day Mortality Rate	Crude OR (CI)	P-Value	Adjusted OR (CI)	P-Value
Age (years)					
≤60	16(25.4%)	1.36	0.5	4.13	0.21
>60	10(20%)	(0.56-3.33)		(0.45-33.33)	
Gender					
Male	17(24.3%)	1.21	0.68	1.21	
Female	9(20.9%)	(0.49-3.03)		(0.20-7.25)	0.84
Race					
White	16(23.2%)	0.97	0.94	0.76	
Hispanic	9(22%)	(0.44-2.16)		(0.20-3.02)	0.7
African-American	1(33.3%)				
Type					
Hematologic Malignancies	18(24%)	1.35	0.54	3.16	
Solid tumor		(0.51-3.60)		(0.30-33.15)	0.33
	7(18.9%)				
Comorbidities					
Yes	13(20.8%)	1.47	0.41	1.369	0.717
No	12(27.8%)	(0.59-3.66)		(0.25-7.49)	
Fever duration					
>4 days	13(50.0%)	5.69	<0.001	8.26	0.039**
<4 days	13(14.9%)	(2.16-14.9)		(1.11-62.50)	
Liver enzymes					
Abnormal	9(69.2%)	14.82	<0.001	48.38	<0.001**
Normal	17(17.0%)	(3.63-60.52)		(5.27-444.29)	
Albumin level					
Low	7(30.4%)	1.64	0.35	2.26	0.38
Normal (> 3g/dL)	19(21.1%)	(0.59-4.54)		(0.36-14.28)	
GFR					
< 60	11(32.4%)	2.01	0.13	2.02	0.42
> 60	15(19.5%)	(0.81-5.01)		(0.37-11.10)	
MASCC					
High risk	22(27.2%)	2.61	0.1	4.649	0.15
Low risk	4(12.5%)	(0.82-8.30)		(0.58-37.53)	

Table 4 Prognostic factors associated with 30-day mortality in febrile neutropenia patients (Continued)

Variable	30 day Mortality Rate	Crude OR (CI)	P-Value	Adjusted OR (CI)	P-Value
Neutropenic period					
> 5 day	16 (26.7%)	5.69	<0.001	3.79	0.157
≤ 5 day	9(17.6%)	(2.61-15.00)		(0.60-23.81)	
ICU admission					
yes	18(56.2%)	11.73	<0.001	63.66	<0.001**
no	8(9.9%)	(4.272-32.22)		(5.96-680.30)	
Source of infection					
Bacteremia	4(26.7%)	1.26	0.72	1.52	0.73
Other infection	22(22.4%)	(0.36-4.34)		(0.14-16.22)	
Culture					
Positive	20(31.7%)	3.41	0.017	3.32	0.23
Negative	6(12%)	(1.25-9.31)		(0.48-23.11)	

Table 5 Prognostic factor associated with more than 8 days length of stay (LOS) in febrile neutropenia patients

Variable	LOS	Crude OR (CI)	P-Value	Adjusted OR (CI)	P-Value
Age (years)					
≤60	34(50%)	1.68	0.5	2.84	0.07
>60	22(37.3%)	(0.83-3.42)		(0.90-8.93)	
Gender					
Male	35(43.8%)	1.04	0.92	1.2	0.74
Female	21(44.7%)	(0.50-2.14)		(0.41-3.53)	
Race					
White	38(46.9%)	0.83	0.59	0.87	0.76
Hispanic	16(37.2%)	(0.43-1.62)		(0.36-2.14)	
African-American	2(66.7%)				
Type					
Hematologic Malignancy	48(57.1%)	5.67	<0.001	4.06	**0.013****
Solid tumor		(2.34-13.70)		(1.34-12.31)	
	8(19.1%)				
Comorbidities					
Yes	34(40%)	0.6	0.188	0.59	0.33
No	22(52.4%)	(0.29-1.28)		(0.21-1.69)	

Table 5 Prognostic factor associated with more than 8 days length of stay (LOS) in febrile neutropenia patients (Continued)

Variable	LOS	Crude OR (CI)	P-Value	Adjusted OR (CI)	P-Value
Fever duration					
>4 days	24(77.4%)	6.86	<0.001	6.29	0.004**
<4 days	32(33.3%)	(2.67-17.60)		(1.81-21.92)	
Liver enzymes					
Abnormal	6(46.2%)	1.097	0.88	1.97	0.38
Normal	50(43.9%)	(0.35-3.47)		(0.43-8.93)	
Albumin level					
Low	15(51.7%)	1.49	0.35	1.15	0.82
Normal (> 3g/dL)	41(41.8%)	(0.65-3.42)		(0.35-3.72)	
GFR					
< 60	18(48.6%)	1.27	0.54	2.09	0.17
> 60	38(42.7%)	(0.59-2.74)		(0.72-6.05)	
MASCC					
High risk	44(47.8%)	1.75	0.1	2.32	0.19
Low risk	15(34.3%)	(0.78-3.95)		(0.67-8.03)	
Neutropenic period					
> 5 day	42(60.9%)	4.67	<0.001	3.68	0.007**
< 5 day	14(25%)	(2.15-10.21)		(1.44-9.40)	
ICU admission					
yes	20(55.6%)	1.91	0.1	1.29	0.78
no	36 (39.6%)	(0.88-4.17)		(0.41-4.13)	
Source of infection					
Bacteremia	7(41.2%)	0.87	0.87	0.62	0.53
Other infection	49(44.5%)	(0.31-2.46)		(0.14-2.78)	
Culture					
Positive	36(52.7%)	1.85	0.09	1.67	0.38
Negative	20(35.7%)	(0.90-3.80)		(0.53-5.24)	

ity, especially in the non-Hodgkin lymphoma (NHL) group. Besides hematologic malignancy, several factors contributed to prolonged LOS and increased risk of death, including older age, impaired kidney function, and severity of neutropenia. Bacteremia and pneumonia significantly increased the mortality. [2, 4-8] Our study showed similar results in factors that af-

fect LOS, which were neutropenic duration and type of hematologic malignancy. Impaired kidney function could occur with sepsis, dehydration, or chronic kidney disease, but did not show any correlation with outcome in our cohort. Severe clinical burden (e.g., ICU admission) showed a significant correlation with mortality rate.

Invasive fungal infection also contributed to an increased risk of death in some studies.[2, 7] However, in our study there was only one culture proven fungal infection which prevented more analysis. Fever duration was associated with a 30-day mortality rate in our sample, which could reflect inadequate coverage of antibiotics to ongoing infection, severe underlying hematologic malignancy, or an immunosuppressed state.

C-reactive protein (CRP) seems to predict adverse outcomes.[8-10] CRP was not routinely obtained in patients admitted for infection in our hospital; therefore, we did not have enough data to analyze this particular test. Recent studies have shown hematologic parameters could be used as an inflammatory marker. Red blood cell distribution width (RDW) was reported as a predictor of mortality rate among patients with critical illness and infectious disease, such as community acquired pneumonia, sepsis, and septic shock.[11-15] Thrombocytopenia has been associated with poor outcomes in febrile neutropenia. [5, 8, 16] Correlation between sepsis from febrile neutropenia and RDW has never been explored. Our study collected platelet counts and RDW values at the onset of fever and at 24, 48, and 72 hours to assess any relation to mortality rate, but the results were not significant (data not shown). There were two possible explanations for these events. First, RDW and platelet levels are dynamic variables with changes associated with acute disease states. In cancer patients, who have ongoing illness, this response might not occur in patients with chronic disease. The second explanation could be that our study population had received chemotherapy agents which could cause an inadequate bone marrow response and therefore prevent significant change in hematologic parameters.

Our study found significant correlation between abnormal liver enzymes (aspartate aminotransferase, AST; alanine aminotransferase, ALT, and alkaline phosphatase, AKLP) with both in-patient and 30-day mortality rates. These markers had not been used in earlier studies. Low total protein levels do predict outcomes.[8] We suggest that these abnormal liver enzymes developed secondary to liver involvement from severe sepsis and that this could lead to a higher mortality rate in this group of patients.

The MASCC risk index has been used widely to identify low risk febrile neutropenia. Multiple studies have shown that the tool has a sensitivity range from 59 to 95%.[17] Positive predictive values of MASCC score in those studies were 85% or higher when study populations presented with mostly solid tumors. The MASCC might not be accurate in predicting outcomes in hematologic malignancy. As seen in our study with a majority of patients with hematologic malignancy (66.1%), mortality did not show a significant correlation with this risk index. Nevertheless, a score less than 21 has been associated with poor outcomes in febrile neutropenia. [8, 10, 16, 18] Several studies have shown that MASCC could predict an unfavorable outcomes in febrile neutropenia when combined with other inflammatory markers, such as procalcitonin or CRP,[10, 19] when compared to inflammatory markers alone.[20] MASCC is still currently the best risk stratification tool for febrile neutropenia,[21] but it does not include neutropenic duration,[17] which was an independent risk factor for prolonged LOS in our study.

In summary, our study explored clinical risk factors associated with outcomes in febrile neutropenia in chemotherapy patients. Our results were similar to prior studies. The use of MASCC should aid physicians in identifying high risk patients and prompt immediate treatment. Clinical risk factors, such as the type of underlying malignancy and fever and neutropenic duration, should be considered when evaluating patients with febrile neutropenia.

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