

Received: 2014.08.18
Accepted: 2014.09.24
Published: 2014.10.05

Independent Factors for Prediction of Poor Outcomes in Patients with Febrile Neutropenia

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Source of support: Departmental sources

Background: Febrile neutropenia (FN) is a life-threatening condition that requires urgent management in the emergency department (ED). Recent progress in the treatment of neutropenic fever has underscored the importance of risk stratification. In this study, we aimed to determine independent factors for prediction of poor outcomes in patients with FN.

Material/Methods: We retrospectively evaluated 200 chemotherapy-induced febrile neutropenic patients who visited the ED. Upon arrival at the ED, clinical data, including sex, age, vital signs, underlying systemic diseases, laboratory test results, estimated GFR, blood cultures, CRP, radiologic examinations, and Multinational Association of Supportive Care in Cancer (MASCC) score of all febrile neutropenic patients were obtained. Outcomes were categorized as "poor" if serious complications during hospitalization, including death, occurred.

Results: The platelet count <50 000 cells/mm³ (OR 3.90, 95% CI 1.62–9.43), pulmonary infiltration (OR 3.45, 95% CI 1.48–8.07), hypoproteinemia <6 g/dl (OR 3.30, 95% CI 1.27–8.56), respiratory rate >24/min (OR 8.75, 95% CI 2.18–35.13), and MASCC score <21 (OR 9.20, 95% CI 3.98–21.26) were determined as independent risk factors for the prediction of death. The platelet count <50 000 cells/mm³ (OR 3.93, 95% CI 1.42–10.92), serum CRP >50 mg/dl (OR 3.80, 95% CI 1.68–8.61), hypoproteinemia (OR 7.81, 95% CI 3.43–17.78), eGFR ≤90 mL/min/1.73 m² (OR 3.06, 95% CI 1.13–8.26), and MASCC score <21 (OR 3.45, 95% CI 1.53–7.79) were determined as independent risk factors for the prediction of poor clinical outcomes of FN patients. Platelet count, protein level, respiratory rate, pulmonary infiltration, CRP, MASCC score, and eGFR were shown to have a significant association with outcome.

Conclusions: The results of our study may help emergency medicine physicians to prevent serious complications with proper use of simple independent risk factors besides MASCC score.

MeSH Keywords: Antineoplastic Agents • Chemotherapy-Induced Febrile Neutropenia • Emergencies

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/892269>

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Background

Advances in cancer treatment have resulted in improved relative survival rates [1]. However, many oncology patients are faced with treatment-related symptoms and conditions that lead to increased use of health services, including emergency departments (EDs). Febrile neutropenia (FN) is such a condition and remains one of the most common causes of oncological patient presentation to the ED [2].

Febrile neutropenia is a life-threatening treatment-related condition that requires urgent management in the ED. Although there have been many advances in the treatment of FN, such patients are known to be at risk of serious infections that are associated with 12–42% mortality [3,4].

The management of febrile neutropenic patients should be based on their clinical course and possible infection source. Early prediction of bacteremia with timely and tailored empiric antimicrobial therapy will improve the prognosis of patients with FN. Recent progress in the treatment of neutropenic fever has underscored the importance of risk stratification and indicated the need to evaluate predictive factors for outcomes in FN [5].

Patient-specific risk factors, comorbid conditions, performance status, type of cancer and stage, age, number of previous febrile neutropenic episodes, and the severity and duration of neutropenia have been considered important predictors of outcomes. Based on the characteristics of FN patients, several predictive models have been developed to classify patients into low- or high-risk groups [6].

Klastersky et al. (2000) developed an internationally validated scoring system called the Multinational Association of Supportive Care in Cancer (MASCC) risk index score. The MASCC score also allows the selection of low-risk patients who can be safely treated with orally administered antibiotics. A MASCC score ≥ 21 indicates that the patient is at low risk of complications and mortality [7] (Table 1).

The clinical risk-prediction model proposed by the MASCC is widely used in clinical practice to define low-risk febrile neutropenia [8]. In the present study, we analyzed the clinical factors predictive of poor outcomes in patients with chemotherapy-induced FN at initial patient evaluation in the ED.

Material and Methods

All adult chemotherapy-induced FN patients who presented to the ED of the University of Ankara Hospital from January 1, 2011 to December 31, 2013 were included in this study. Approval to

Table 1. MASCC Risk Index score.

Prognostic factor	Weight
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension (systolic blood pressure >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumour or no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age <60 years	2

conduct the study was granted by the Ethics Committee of the University of Ankara. Overall, 200 chemotherapy-induced FN patients over 18 years of age and with hematological and oncological malignancies were evaluated retrospectively. FN was defined as an absolute neutrophil count of <500 cells/mm³ [9]. Fever was defined as body temperature greater than 38.3°C at triage or a temperature of 38°C for 1 h or longer during the first 24 h [10]. A C-reactive protein (CRP) cut-off value of 50 mg/dl was used, as proposed in a previous study [11].

Clinical data were obtained from medical records in the electronic patient record system. Upon arrival in the ED, we collected information regarding clinical data (sex, age, vital signs, underlying systemic diseases), laboratory test results (assessment of complete blood count, blood chemistry with differential, liver and renal function tests, blood glucose, electrolytes, protein, estimated glomerular filtration rate [eGFR], blood cultures, CRP concentration), and radiological examinations (a chest radiograph of all febrile neutropenic patients). eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) study equation [12].

The MASCC risk index score was calculated for all patients with chemotherapy-induced neutropenic fever. Outcomes were categorized as “good” if the patient could be discharged without any serious complications and “poor” if there were serious complications during hospitalization or if death occurred. Serious complications included refractory hypotension (defined as systolic blood pressure less than 90 mmHg that required treatment with vasopressors agents), respiratory failure (defined as the need for mechanical ventilation), need for intensive care unit (ICU) admission, renal failure, need for treatment with fluids or hemodialysis, severe bleeding and

Table 2. Clinical characteristics of 200 patients.

Characteristics	n	%
Patients	200	
FN episodes	200	
Gender		
Male	118	55.5
Female	88	44.5
Age, Mean ($\pm$ SD)	56.4 ($\pm$ 13.46)	
Categories of febrile episodes		
Unexplained fever of origin	128	64.0
Bacteremia	72	36.0
MASCC Score		
≥ 21	114	57.0
< 21	86	43.0
Serious complications	105	52.5
Death	64	32.0
Comorbidities		
DM*	32	16.0
CHF**	9	4.5
COPD#	19	9.5
CAD##	7	3.5
Other	60	30.0

* Diabetes mellitus; ** chronic heart failure, # chronic obstructive pulmonary disease, ## coronary artery disease.

need for transfusion, fungal infection, altered mental status, arrhythmia requiring treatment, chronic heart failure, and allergic reactions to treatment. This list of serious medical complications was adapted and modified from Klastersky et al. [7].

The following data were collected: a) variables that were available at presentation, such as age, sex, laboratory variables (hemoglobin, neutrophil count, CRP, eGFR, protein, platelet count), chest X-ray, and comorbidities (e.g., diabetes mellitus, heart failure, COPD, acute coronary syndromes); b) other variables that were determined at triage such as vital signs (respiratory and pulse rates, systolic blood pressure); and c) variables related to blood cultures and complications during hospitalization.

Statistical analyses

Differences between the 2 groups were evaluated using the t-test for continuous variables. Categorical variables were assessed using the chi-square test, and odds ratios were calculated. To define the risk factors of the outcome variables

Table 3. Serious medical complications developed in patients during hospitalisation.

Complications	n (%)
Respiratory failure	28 (14.0%)
Severe bleeding (need for transfusion)	26 (13.0%)
Need for Intensive Care Unit	18 (9.0%)
Renal failure	11 (5.5%)
Fungal infection	6 (3.0%)
Refractory Hypotension	5 (2.5%)
Altered mental status	4 (2.0%)
Arrhythmia requiring treatment	3 (1.5%)
Chronic Heart Failure	2 (1.0%)
Allergic reactions	2 (1.0%)

(mortality and complications), multiple logistic regression analysis was used, and adjusted odds ratios were calculated. The sensitivity, specificity, and positive and negative predicted values were calculated for diagnostic performance of the multiple logistic regression model. P values of less than 0.05 were considered significant.

Results

Patient characteristics and clinical features

During the study period, there were 200 episodes of FN in 200 patients with cancer. The mean and median age of the study patients were 56.4 ± 13.46 (mean $\pm$ standard deviation) and 57.5, respectively. Of the 200 patients, 89 (44.5%) were female. Of the 200 febrile episodes, 72 (36%) had bacteremia and 128 (64%) were categorized as an unexplained fever (Table 2). Serious medical complications were observed in 105 (52.5%) patients and 64 (32%) patients died during hospitalization (Table 3).

Risk stratification for serious complications

Univariate analyses of the clinical parameters available from the ED and MASCC scoring system were performed (Table 4).

In the multiple logistic regression analysis, a platelet count $< 50,000$ cells/mm³ (OR 3.93, 95% CI 1.42–10.92), serum CRP > 50 mg/dl (OR 3.80, 95% CI 1.68–8.61), hypoproteinemia (OR 7.81, 95% CI 3.43–17.78), eGFR ≤ 90 mL/min/1.73 m² (OR 3.06, 95%

Table 4. Univariate analysis of serious complications for febrile neutropenic patients.

Variables	Total n (200)	Without serious complication n (95)	With serious complication n (105)	p value	OR**	95% CI for OR
Age >65 years	52 (26.0%)	13 (13.7%)	39 (75.0%)	<0.001*	3.73	1.84–7.55
Male	111 (55.5%)	48 (43.2%)	63 (56.8%)	0.178	1.47	0.84–2.57
Laboratory findings						
Neutrophils <100 cells/mm ³	48 (24.0%)	20 (41.7%)	28 (58.3%)	0.353	1.36	0.70–2.62
Platelets <50000 cells/mm ³	55 (27.5%)	7 (12.7%)	48 (87.3%)	<0.001*	10.59	4.48–25.02
Hemoglobin ≤10 gr/dl	123 (61.5%)	46 (37.4%)	77 (62.6%)	<0.001*	2.93	1.62–5.30
CRP >50 mg/L	124 (62.0%)	39 (31.5%)	85 (68.5%)	<0.001*	6.10	3.23–11.53
Total Protein <6 gr/dl	122 (61.0%)	31 (25.4%)	91 (74.6%)	<0.001*	13.42	6.61–27.23
eGFR ≤90 mL/min/1.73 m ²	158 (79.0%)	64 (40.5%)	94 (59.5%)	<0.001*	4.14	1.94–8.83
Pulmonary infiltration	111 (55.5%)	41 (36.9%)	70 (63.1%)	0.001*	2.63	1.48–4.68
Comorbidities	127 (63.5%)	38 (29.9%)	89 (70.1%)	<0.001*	8.34	4.26–16.34
Vital signs						
Respiratory rate >24/min	20 (10.0%)	4 (20.0%)	16 (80.0%)	0.009*	4.09	1.32–12.71
Pulse rate >100/min	109 (54.5%)	28 (25.7%)	81 (74.3%)	<0.001*	8.08	4.28–15.23
Systolic blood pressure ≤90 mmHg	57 (28.5%)	8 (14.0%)	49 (86%)	<0.001*	9.52	4.19–21.60
Bacteremia	72 (36.0%)	19 (26.4%)	53 (73.6%)	<0.001*	4.08	2.17–7.70
MASCC <21	86 (43.0%)	23 (26.7%)	63 (73.3%)	<0.001*	4.70	2.60–8.65

* Indicates a significant impact on the risk of serious complication by the univariable logistic regression analysis; ** OR – Odds Ratio.

Table 5. Independent predictors of serious complications by multiple logistic regression analysis.

Variables	Adj. OR*	95% CI for Adj. OR	p
Platelets <50000 cells/mm ³	3.93	1.42–10.92	0.009
eGFR ≤90 mL/min/1.73 m ²	3.06	1.13–8.26	0.027
Total Protein <6 gr/dl	7.81	3.43–17.78	<0.001
CRP >50 mg/L	3.80	1.68–8.61	0.001
MASCC <21	3.45	1.53–7.80	0.003

** Adj. OR – Adjusted Odds Ratio.

CI 1.13–8.26), and MASCC risk-index score <21 (OR 3.45, 95% CI 1.53–7.79) were determined to be independent risk factors for the prediction of poor clinical outcomes of FN patients admitted to the ED (Table 5). These risk factors were predictive of serious complications with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 81%, 78%, 81%, and 79%, respectively.

Risk stratification for death

As shown in Table 6, the clinical parameters and MASCC scores were evaluated with univariate analysis.

In the multiple logistic regression analysis, a platelet count <50 000 cells/mm³ (OR 3.90, 95% CI 1.62–9.43), pulmonary infiltration (OR 3.45, 95% CI 1.48–8.07), hypoproteinemia <6g/dl

Table 6. Univariate analysis of death for febrile neutropenic patients.

Variables	Total n (200)	Survivors n (136)	Exitus n (64)	p value	OR**	95% CI for OR
Age >65 years	52 (26.0%)	23 (44.2%)	29 (55.8%)	<0.001*	4.07	2.10–7.92
Male	111 (55.5%)	69 (62.2%)	42 (37.8%)	0.048*	1.85	1.00–3.43
Laboratory findings						
Neutrophils <100 cells/mm ³	48 (24.0%)	29 (60.4%)	19 (39.6%)	0.196	1.56	0.80–3.06
Platelets <50000 cells/mm ³	55 (27.5%)	21 (38.2%)	34 (61.8%)	<0.001*	6.20	3.16–12.20
Hemoglobin ≤10 gr/dl	123 (61.5%)	72 (58.5%)	51 (41.5%)	<0.001*	3.49	1.74–7.00
CRP >50 mg/L	124 (62.0%)	76 (61.3%)	48 (38.7%)	0.009*	2.37	1.22–4.58
Total Protein <6gr/dl	122 (61.0%)	67 (54.9%)	55 (45.1%)	<0.001*	6.30	2.90–13.74
eGFR ≤90 mL/min/1.73 m ²	158 (79.0%)	103 (65.2%)	55 (34.8%)	0.098	1.96	0.87–4.40
Pulmonary infiltration	111 (55.5%)	62 (55.9%)	49 (44.1%)	<0.001*	3.90	2.00–7.61
Comorbidities	127 (63.5%)	72 (56.7%)	55 (43.3%)	<0.001*	5.43	2.50–11.87
Vital signs						
Respiratory rate >24/min	20 (10.0%)	8 (40.0%)	12 (60.0%)	0.005*	3.70	1.42–9.56
Pulse rate >100/min	109 (54.5%)	60 (55.0%)	49 (45.0%)	<0.001*	4.13	2.11–8.08
Systolic blood pressure ≤90 mmHg	57 (28.5%)	22 (38.6%)	35 (61.4%)	<0.001*	6.25	3.20–12.23
Bacteremia	72 (36.0%)	37 (51.4%)	35 (48.6%)	<0.001*	3.23	1.38–6.00
MASCC <21	86 (43.0%)	35 (40.7%)	51 (59.3%)	<0.001*	11.32	5.51–23.30
Serious complication	105 (52.5%)	47 (44.8%)	58 (55.2%)	<0.001*	18.31	7.35–45.56

* Indicates a significant impact on the risk of exitus by the univariable logistic regression analysis; ** OR – Odds Ratio.

Table 7. Independent factors of death by multiple logistic regression analysis.

Variables	Adj. OR*	95% CI for Adj. OR	p
Platelets <50000cells/mm ³	3.90	1.62–9.43	0.002
Pulmonary infiltration	3.45	1.48–8.07	0.004
Total Protein <6 gr/dl	3.30	1.27–8.56	0.014
Respiratory rate >24/min	8.75	2.18–35.13	0.002
MASCC <21	9.20	3.98–21.26	<0.001

* Adj. OR – Adjusted Odds Ratio.

(OR 3.30, 95% CI 1.27–8.56), respiratory rate >24/min (OR 8.75, 95% CI 2.18–35.13), and MASCC risk-index score <21 (OR 9.20, 95% CI 3.98–21.26) were determined to be independent risk factors for death (Table 7). These parameters were predictive of death with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 75%, 89%, 77%, and 88%, respectively.

Discussion

The development of multi-drug chemotherapy protocols in the treatment of hematological conditions and solid organ tumors, use of high-dose drugs, and improved supporting treatment options have improved the chances of survival for cancer patients in recent years. However, these treatment

regimens also result in immunosuppression and neutropenia, conditions that make patients prone to developing severe infections. Currently, clinicians are aiming to prolong life with these new anti-cancer treatments while also reducing adverse effects such as FN.

Patients who develop FN show varying clinical courses. One of the most important subjects of recent research is the ability to predict the prognosis of these patients. Guidelines have been developed to categorize FN patients into low- or high-risk groups. A commonly used scoring system for this purpose is the MASSC. This scoring system, which predicts prognosis, is believed to be more useful in low-risk patients. High fever in a neutropenic patient requires prompt treatment with broad-spectrum antibiotics until the culture results are obtained. This urgent approach requires emergency physicians to predict independent risk factors for FN apart from those indicated by the MASSC risk-scoring system. However, only a few studies have been conducted in the ED setting to identify independent factors associated with serious complications after the emergent diagnosis of FN.

In this study, independent predictive factors for serious complications in patients diagnosed with FN were identified with a sensitivity of 81% and specificity of 78%. Previous studies that aimed to predict complicated FN in the ED found that laboratory parameters (e.g., platelet count, CRP, and pulmonary infiltration as revealed by chest X-ray) identified patients likely to develop complications [5,11]. Our results are in agreement with these studies; platelet counts of $\leq 50\,000$ cells/mm³ and CRP, an indicator of inflammation, were associated with serious complications. Platelets are unique blood cells with specialized molecular repertoires that have evolved to accomplish crucial functions in host integrity, defense, and repair. Growing evidence shows that platelets play an active role in fighting infection and innate immunity, and thrombocytopenia is frequently observed in systemic infections. Previous studies have found that the severity of thrombocytopenia is associated with increased mortality rates [13–15]. In our study, the level of serum CRP was also recognized as an independent factor. Because infections are the major cause of morbidity and mortality in neutropenic patients, considerable attention has focused on the value of acute-phase reactants in identification of high-risk patients. However, results from previous studies have been inconsistent, and their cut-off points are variable [6]. Moreover, the predictive value of the CRP concentration remains unclear. We used a cut-off value of CRP of 50 mg/dL, as proposed in a previous study [11]. Several studies have reported that CRP is a significant predictor of severe sepsis, while other studies have stated that CRP was not useful in predicting infectious complications in neutropenic patients. However, in our study, we found CRP (OR 3.8, 95% CI 1.68–8.61) to be a significant predictor of serious complications.

In our study, eGFR < 90 mL/min/1.73 m² is associated with increased risk of serious complications. The observed increased risk of serious complications from neutropenic patients with reduced eGFR is considerable, and we suggest that decreased kidney function itself is a predictor of poor outcomes. There are a few potential reasons for this suggestion. First, previous studies have shown that patients with chronic kidney diseases (CKD) are less likely to undergo cancer screening, and patients with CKD also have multiple comorbid conditions [16]. Second, the management of cancer in patients with decreased kidney function is complex. There is little information regarding the optimal timing and necessary dose adjustment of cytotoxic agents for patients with reduced kidney function. In a previous study, Iff et al. stated that an eGFR < 60 mL/min/1.73 m² is a risk factor for cancer deaths and is also a predictor of poor cancer outcomes in the older population [17]. Except for their study, we were unable to find another study that evaluated the eGFR threshold associated with an increased risk of cancer death. In another study, hypoproteinemia (< 62 g/L) was found to be associated with severe sepsis in neutropenic patients [18]. In our study, hypoproteinemia was another independent factor that could predict serious complications in febrile neutropenic patients. This finding can be explained by the fact that intensive chemotherapy can lead to energy consumption and high protein catabolism. Malnutrition and altered oral intake can cause protein-losing enteropathy resulting in hypoproteinemia. These are common features in progressive advanced cancer and are responsible for increased severe hematological toxicity. Clinical malnutrition, which negatively affects patient response to therapy, increases the incidence of treatment-related adverse effects and can decrease survival [19]. Numerous studies have shown that patients with a MASCC risk index score of less than 21 should be considered at high risk for complications, as we did in our study [6,20,21].

In this study, independent predictive factors for death in patients diagnosed with FN have been identified with a sensitivity of 75% and specificity of 89%. We found that hypoproteinemia, platelet counts of $\leq 50\,000$ cells/mm³, and the MASCC risk index score were independent predictive factors. Additionally, a respiratory rate > 24 /min (OR 8.75, 95% CI 2.18–35.13) was the only component in vital signs that was predictive of exitus in multivariate analysis. In a recent study of patients with hematological malignancies, tachypnea was a predictor of septic shock and of poor prognosis of febrile neutropenic patients [22,23].

In previous studies, infiltration or abnormality in the chest X-ray was significantly associated with poor outcome. Both aspects could be responsible for the mortality rate of up to

25–50% (24–26). In our study, pulmonary infiltration was significantly predictive for mortality (OR 3.25, 95% CI 1.47–8.07).

This was a retrospective analysis of a small population in a single-center study. There are limited data about the types of chemotherapy and the duration of neutropenia. Therefore, our results may not be representative of all other institutions and require validation.

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Conclusions

The results of our study may help emergency medicine physicians to prevent the development of serious complications and death in FN patients by the proper use of simple independent risk factors in addition to the MASCC score. Early stratifications of patients into low- and high-risk groups with timely and tailored empiric antimicrobial therapy can improve the prognosis of patients with FN.