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

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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/mm$^3$ (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/mm$^3$ (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 m$^2$ (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

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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].

Klustersky 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 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) treatment, renal failure, need for treatment with fluids or hemodialysis, severe bleeding and

| 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 |
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 (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 ± 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% CI 1.14–8.08), respiratory failure, severe bleeding (need for transfusion), need for Intensive Care Unit, renal failure, fungal infection, refractory hypotension, arrhythmia requiring treatment, chronic heart failure, and allergic reactions were independent risk factors for the outcome variables (mortality and complications).
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.

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/mm³ | 48 (24.0%)    | 20 (41.7%)                          | 28 (58.3%)                      | 0.353   | 1.36 | 0.70–2.62    |
| Platelets <50000 cells/mm³| 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 m²    | 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/mm³ | 3.93      | 1.42–10.92         | 0.009 |
| eGFR ≤90 ml/min/1.73 m²    | 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), hypoproteinaemia <6g/dl
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/mm³ | 48 (24.0%) | 29 (60.4%) | 19 (39.6%) | 0.196 | 1.56 | 0.80–3.06
Platelets ≤50000 cells/mm³ | 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 <6 gr/dl | 122 (61.0%) | 67 (54.9%) | 55 (45.1%) | <0.001* | 6.30 | 2.90–13.74
eGFR ≤90 mL/min/1.73 m² | 158 (79.0%) | 103 (65.2%) | 55 (34.8%) | 0.098 | 1.96 | 0.87–4.40
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

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 ≤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 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 MASSC 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 ≤50 000 cells/mm³, and the MASSC 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 eGFR <60 mL/min/1.73 m². We found that hypoproteinemia and increased body temperature >38°C (OR 8.75, 95% CI 2.18–35.13) were independent predictive factors. In our 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 [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.

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.

References:

1. Canadian Cancer Society (2011) Canadian Cancer Society’s Steering Committee on Cancer Statistics: Canadian Cancer Statistics 2011. http://www.cancer.ca/Canadianwide/About%20cancer/Cancer%20statistics/PowerPoint%20slides.aspx?sc_lang=en. Accessed 15 May 2011

2. Mamtani M, Conlon LW: Can We Safely Discharge Low-Risk Patients With Febrile Neutropenia From the Emergency Department? Ann Emerg Med, 2014; 63: 48–51

3. Lim C, Bawden J, Wing A et al: Rowe Febrile neutropenia in EDs: the role of an electronic clinical practice guideline. Am J Emerg Med, 2012; 30: 5–11

4. Averbuch D, Orasch C, Cordonnier C et al., ECL4, a joint venture of EBM4, EGRT, ICHS, ESGUCH/ESCAMID and ELN: European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica, 2013; 98(12): 1826–35

5. Moon JM, Chun BJ: Predicting the complicated neutropenic fever in the emergency department. Emerg Med J, 2009; 26: B2–6

6. Ahn S, Lee YS: Predictive factors for poor prognosis febrile neutropenia. Curr Opin Oncol, 2012; 24: 376–80

7. Klastersky I, Paesmans M, Rubenstein EB et al: The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol, 2000; 18: 3038–51

8. Flowers CR, Seidenfeld J, Bow EJ et al: Antibacterial prophylaxis and outpatient management of febrile neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical guideline. J Clin Oncol, 2013; 31: 794–810

9. Moores KG: Safe and effective outpatient treatment of adults with chemotherapy-induced neutropenic fever. Am J Health-System Pharm, 2007, 64: 717–22

10. Hughes WT, Armstrong D, Bodey GP et al: 2002 guidelines for the use of antipseudomonal beta-lactams in neutropenic patients with cancer. Clin Infect Dis, 2002; 34: 730–51

11. Lynn JJ, Chen KF, Weng YM, Chiu TF: Risk factors associated with complications in patients with chemotherapy-induced febrile neutropenia in emergency department. Hematol Oncol, 2013; 31: 189–96

12. Levey AS, Coresh J, Greene T et al: Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med, 2006; 145: 247–54

13. Gründler K, Angstwurm M, Hilge R et al: Platelet mitochondrial membrane depolarization reflects disease severity in patients with sepsis and correlates with clinical outcome. Crit Care, 2014; 18(1): R31

14. Gafter-Gvili A, Mansur N, Bivas A et al: Thrombocytopenia in Staphylococcus aureus bacteremia: risk factors and prognostic importance. Mayo Clin Proc, 2011; 18: 389–96

15. Vandijck DM, Blot SI, De Waele JJ et al: Thrombocytopenia and outcome in critically ill patients with bloodstream infection. Heart Lung, 2010; 18: 21–26

16. Williams NC, Tong A, Howard K et al: Knowledge, beliefs and attitudes of kidney transplant recipients regarding their risk of cancer. Nephrology, 2012; 17(3): 300–6

17. Iff S, Craig IC, Turner R et al: Reduced estimated GFR and cancer mortality. Am J Kidney Dis, 2014; 63(1): 23–30

18. Jeddi R, Achour M, Amor RB et al: Factors associated with severe sepsis: prospective study of 94 neutropenic febrile episodes. Hematology, 2010; 15(1): 28–32

19. Davies M: Nutritional screening and assessment in cancer-associated malnutrition. Eur J Oncol Nurs, 2005; 9(Suppl.2): 564–73

20. Gupta D, Vashi PG, Lammersfeld CA, Braun DP: Role of nutritional status in predicting the length of stay in cancer: a systematic review of the epidemiological literature. Ann Nutr Metab, 2011; 59(2–4): 96–106

21. Hui EP, Leung LK, Poon TC et al: Prediction of outcome in cancer patients with febrile neutropenia: a prospective validation of the Multinational Association for Supportive Care in Cancer risk index in a Chinese population and comparison with the Talcott model and artificial neural network. Support Care Cancer, 2011; 19: 1625–35

22. Innes H, Lim SL, Hall A et al: Management of febrile neutropenia in solid tumours and lymphomas using the Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in routine clinical practice. Support Care Cancer, 2008; 16: 485–91

23. Ahn S, Lee YS, Chun YH et al: Predictive factors of poor prognosis in cancer patients with chemotherapy-induced febrile neutropenia. Support Care Cancer, 2011; 19: 1151–58

24. Mato A, Fuchs BD, Heijtjan DF et al: Utility of the systemic inflammatory response syndrome (SIRS) criteria in predicting the onset of septic shock in hospitalized patients with hematologic malignancies. Cancer Biom Ther, 2009; 8: 1095e100

25. Sebben C, Dussart S, Fuhrmann C et al: Oral moxifloxacin or intravenous ceftriaxone for the treatment of low-risk neutropenic fever in cancer patients suitable for early hospital discharge. Support Care Cancer, 2008; 16: 1017–23

26. Offidani M, Corvatta L, Malerba L et al: Risk assessment of patients with hematologic malignancies who develop fever accompanied by pulmonary infiltrates: a historical cohort study. Cancer, 2004; 101: 567–77