ORIGINAL ARTICLE

C-reactive protein and the MASCC risk index identify high-risk patients with febrile neutropenia and hematologic neoplasms

Juan F. Combariza · Milton Lombana · Luis E. Pino · Marcos Arango

Abstract

Objective The objective of this study is to assess the prognostic usefulness of the Multinational Association of Supportive Care in Cancer (MASCC) risk score in association with the value of C-reactive protein (CRP) to identify high-risk patients with febrile neutropenia and hematologic neoplasms.

Methods A retrospective cohort study in which the MASCC score and the CRP values were used to assess the mortality risk at 30 days among patients with febrile neutropenia and hematologic malignancies was performed.

Results Two hundred thiry-seven patients with febrile neutropenia were analyzed; the mortality rate within 30 days was 9 %. High-risk patients according to the MASCC score were significantly more likely to experience adverse outcomes, such as being transferred to the intensive care unit (RR 3.55; CI 95 % 2.73–6.62, $p<0.001$) and death (RR 2.21; CI 95 % 1.74–2.79, $p<0.001$). Multivariate analysis showed a strong association between the high-risk group identified by the MASCC score (HR 3.0; CI 95 % 1.12–13.54, $p=0.032$) and the mean levels of CRP (HR 17; CI 95 % 2.21–136.48, $p=0.007$) and survival. The survival rate within 30 days was 100 % for the patients with a low-risk MASCC score and a mean CRP less than 15 mg/dL. This rate was only 64 % for high-risk patients with a mean CRP greater than 15 mg/dL.

Conclusion The MASCC risk score combined with the mean CRP value successfully identifies patients with febrile neutropenia and hematological malignancies and a high risk of death.

Keywords Febrile neutropenia · C-reactive protein · Hematologic neoplasms

J. F. Combariza (✉) · M. Arango
Hematology department, Hospital Pablo Tobón Uribe, Calle 78B No. 69-240, Medellín, Colombia
e-mail: combariza@yahoo.com

M. Lombana
Hematology–Oncology department, Clínica Imbanaco, Cali, Colombia

L. E. Pino
Hematology–Oncology department, Clínica Medellín, Medellín, Colombia

Introduction

Patients with hematologic malignancies may develop neutropenic fever after chemotherapy in up to 80 % of the cases. The clinical presentation may vary from undocumented clinical infection up to bacteremia, septic shock, and death [1–5]. Due to the heterogeneity of the clinical presentation and the diversity of the complications associated with febrile neutropenia, the Multinational Association of Supportive Care in Cancer (MASCC) developed a prognostic score for patients with febrile neutropenia. This score divides patients into two mutually exclusive risk groups and could serve as a basis for selecting therapeutic strategies [5]. C-reactive protein (CRP) is a global marker of inflammatory activity; high values had been associated with an increased risk of mortality [6, 7]. We have previously found that the mean value of CRP during the first 5 days of the febrile neutropenia episode was useful to identify patients more likely to die due to infection (unpublished observations).

The MASCC risk model has been mainly used among patients with solid neoplasms, the information regarding its usefulness as a prognostic tool in the hematological malignancies setting is more limited [5, 8]. CRP is an inexpensive and widely available laboratory test that can improve the accuracy of the MASCC risk score for assessment of

prognosis in this group of patients. One previous study has suggested that this combination could be a convenient option that improves patient risk stratification [7].

In this study, the authors wanted to assess the prognostic usefulness of the MASCC risk score in association with the mean CRP value to identify patients with febrile neutropenia and hematologic malignancies and a higher risk of death.

Methods

A retrospective cohort study assessing survival rates based on the MASCC score and the CRP values of patients diagnosed with febrile neutropenia at the Pablo Tobón Uribe Hospital in Medellin, Colombia was performed. The study was conducted between May 1, 2009 and December 3, 2012.

Patients older than 15 years, with febrile neutropenia and a diagnosis of hematologic neoplasms or aplastic anemia who appeared in the institutional records of the hematology group were included in the study. Conversely, patients with incomplete information or with a follow-up of less than 30 days were excluded. Each episode of febrile neutropenia occurring in the same patient was included in the analysis.

Mortality rates were analyzed. These rates were calculated from the moment in which the febrile neutropenia was diagnosed until the 30th day after such episode. The data found in the clinical records was used to identify the presence of febrile neutropenia, the clinical variables, the MASCC score, the CRP values upon diagnosis, and the mean CRP values within the first 5 days of the episode. The MASCC score was calculated for all episodes of febrile neutropenia as suggested by the authors. Patients were considered to be at low risk when their scores were above 21 points and at high risk when their scores were equal to or less than 20 points (Appendix 1) [5]. Febrile neutropenia was defined in accordance with the recommendations of the Infectious Diseases Society of America as a single oral temperature higher than 38.3 °C or a temperature higher than 38.0 °C if sustained for more than 1 h in a patient with an absolute neutrophil count below 500 cells per mm^3 (or expected to fall below this level in the next 48 h) [6]. As for the CRP, it was defined as high when it had a value above 15 mg/dL measured either at the moment in which febrile neutropenia was diagnosed or as the mean value during the first 5 days after diagnosis. The CRP was measured through latex agglutination using the immunoassay technique and was expressed in milligrams/deciliter (mg/dL).

After confirming the prognostic value of the mean CRP as well as that of the MASCC score, we evaluated the usefulness of this association to identity four different risk groups: low-risk MASCC score and mean CRP <15 mg/dL, low-risk MASCC score and mean CRP >15 mg/dL, high-risk MASCC score and mean CRP <15 mg/dL, and high-risk MASCC score and mean CRP >15 mg/dL.

Statistical analysis

A sample size of 236 patients was estimated (using Yates correction) after considering the following aspects: a 30-day mortality rate of 30 % for patients with high CRP values or with a high-risk MASCC score along with a mortality rate of 10 % for patients with low risk or low CRP values. In addition, the significance level was 0.05, the power was 90 %. The hypothesis and tests of independence were analyzed using either the chi-square test or Fisher's exact test as required. The association between the analyzed variables and the need for being transferred to the intensive care unit was determined with a logistic regression using relative risk and odds ratio. The Kaplan-Meier nonparametric method was used to analyze survival rates. The comparison of the groups' survival rates was performed using the log-rank test. The association between dependent variables was determined through the hazard ratio using the Cox regression method. The significance level was set at 5 %, and the confidence intervals were calculated at 95 %. The statistical analysis was conducted using the Stata 11.2 software.

This study was previously approved by the Research and Ethics Committee of the Pablo Tobón Uribe Hospital.

Results

A total of 237 patients with febrile neutropenia were analyzed between May 1, 2009 and December 1, 2012. See Table 1 for the characteristics of the study population. For 73.8 % of the cases, the onset of febrile neutropenia occurred during the hospitalization period. Furthermore, 5.9 % of the episodes occurred among patients that were having hematopoietic stem cell transplantation. Most patients had a diagnosis of acute leukemia (68 %); they were followed by patients with lymphoma (23 %) or other neoplasms (9 %).

The MASCC score classified as low risk, 56.5 % of the cases and as high risk, 43.5 % of them. The baseline values for CRP were above 15 mg/dL for 26 % of the patients. Similarly, for 36 % of the cases, the mean value during the first 5 days of the febrile episode was above 15 mg/dL. In 26 % of the cases, admission to the ICU was necessary. The reasons for admission were either shock or respiratory failure in all of them. Finally, 9.3 % of the patients died within 30 days after diagnosis.

Association between the MASCC risk score, CRP, and the mortality rates

Upon categorizing the variables composing the MASCC model, we found that 103 patients (43.5 %) had moderate or severe symptoms at the time of diagnosis, 66 (27.9 %) had

Table 1 Characteristics of the study population (*N*=237)

Characteristic	Number (%) mean [range]
Age	41 years [15–82]
Male gender	133 (56.12)
Duration of the neutropenia (days)	13 [2–77]
Neutrophils at the time of diagnosis (per mm^3)	170 [0–1000]
Documented infection	140 (59.07)
Type of infection	Bacterial 135 (96.4)
	Fungal 4 (2.9)
	Tuberculosis 1 (0.7)
Site of infection	Isolated bacteremia 69 (57.5)
	Urinary tract infection 27 (22.5)
	Respiratory tract infection 24 (20)
Bacteremia isolates	*E. coli* 30 (33)
	Klebsiella sp. 24 (27)
	Streptococcus sp. 7 (8)
	E. coli + *K. pneumoniae* 7 (8)
	S. aureus 6 (7)
	P. aeruginosa 6 (7)
	K. pneumoniae + *P. aeruginosa* 3 (3)
	E. coli + *P. aeruginosa* 1 (1)
	Other gram-negative 5 (6)
Germ resistant to initial empiric antibiotic therapy	24 (22)
Initial empiric antibiotic therapy	Piperacillin/tazobactam 205 (86.5)
	Meropenem 24 (10.1)
	Cefepime 8 (3.4)

arterial hypotension, 3 (1.3 %) had chronic obstructive pulmonary disease (COPD), 17 (7.2 %) had a history of previous fungal infection, 103 (43 %) showed dehydration requiring parenteral fluids, 175 (73.8 %) were hospitalized at the moment of the episode, and 186 (76.8 %) were younger than 60. The variables of the MASCC score that better identified patients with a higher risk of mortality were symptom burden, hypotension, and dehydration requiring intravenous fluids (Table 2). Upon analyzing the survival rates within 30 days based on the MASCC score, we found a survival rate of 97 %

for the population with a low-risk MASCC score. Patients with a high-risk score were found to have a survival rate of 87 % (*p*<0.001) (Fig. 1). Likewise, when compared with low-risk patients, high-risk patients according to the MASCC score showed a greater probability of dying (RR 2.21; CI 95 % 1.74–2.79, *p*<0.001) or being transferred to the intensive care unit due to severe infection (RR 3.55; CI 95 % 2.73–4.62, *p*<0.001).

Upon conducting a univariate analysis, the following predictive variables for mortality were found: a high-risk MASCC score, a baseline CRP value greater than 15 mg/dL, a mean CRP value greater than 15 mg/dL, documented infection, bacteremia, infection with a resistant germ, and admission to the intensive care unit. After multivariate analysis, the following variables retained prognostic power: a high-risk MASCC score, a mean CRP greater than 15 mg/dL, and admission to the intensive care unit (Table 3).

Four groups were established by the prognostic model based on mean CRP values and MASCC risk score. These groups had different death risks. The rate of survival within 30 days was 100 % for patients with low-risk MASCC scores and a mean CRP <15 g/dL, whereas the same rate was only 64 % for patients with high-risk MASCC scores with high CRP (Fig. 2).

Discussion

The MASCC risk score was initially designed as a tool to identify low-risk subjects with febrile neutropenia that can be managed as outpatients. We found that this risk score can be used for assessing the risk of mortality and the need for being transferred to the ICU among Colombian patients with hematologic neoplasms and febrile neutropenia. When trying to optimize the prognostic models, including CRP values along with the MASCC score was extremely useful, especially for a better stratification of the high-risk group.

Table 2 MASCC risk score variables and 30-day mortality risk

|	Death		
	Relative risk	CI 95 %	*p* value
Severe symptom load (present vs absent)	6.38	1.94–21.00	<0.001
Hypotension (present vs absent)	3.74	1.67–8.33	<0.001
Chronic obstructive pulmonary disease (present vs absent)	Not applicable	–	–
History of previous fungal infection (present vs absent)	0.61	0.08–4.30	0.5167
Dehydration requiring parenteral fluids (present vs absent)	8.23	2.50–27.09	<0.001
Inpatient at the moment of the episode (yes vs no)	0.83	0.31–2.15	0.7005
Age <60 years (yes vs no)	0.43	0.19–0.96	0.0389
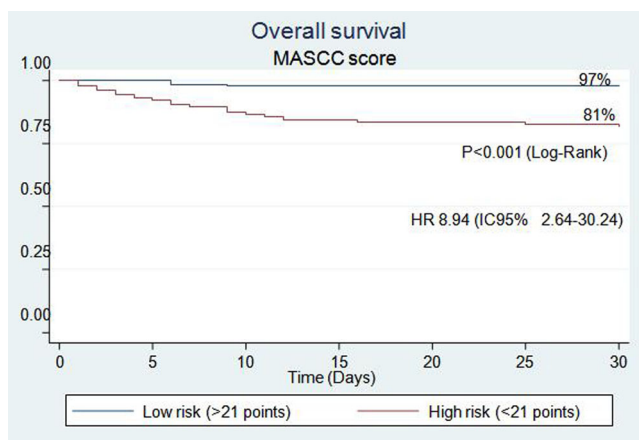
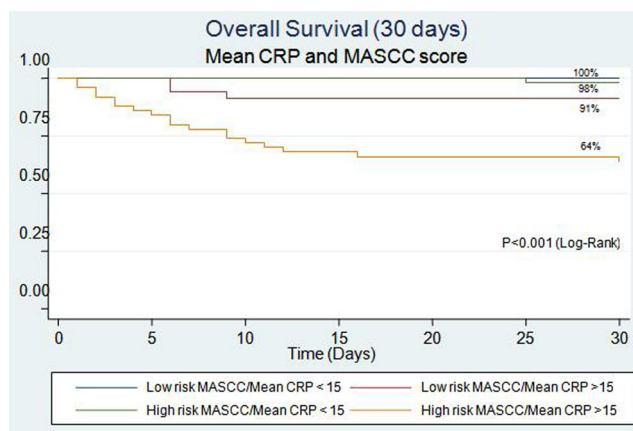**Fig. 1** 30-day survival according to the MASCC risk score

Fig. 2 Survival rates at 30 days according to the mean CRP values and the MASCC risk score

Klastersky et al. documented that out of 551 patients identified as being at low risk, 6 % experienced serious medical complications and 1 % died. As for the group considered to be at high risk (205 patients), 39 % of the patients had serious complications and 14 % died [5]. These results are consistent with ours but in this cohort, fewer patients had a low-risk MASCC score (56 vs 73 %). This could be due to the fact that the present study only included patients with hematologic neoplasms. Furthermore, most febrile neutropenia episodes (68 %) were secondary to acute leukemia, and 73 % of them occurred in hospitalized patients; for this reason, not all the individual variables had the same weight for the prognosis assessment. The individual variables of the MASCC scale with the highest statistical and prognostic weight for this study were symptom load, hypotension, and dehydration requiring intravenous fluids. In different parts of the world, the MASCC scale has been validated as a prognostic tool for patients with

febrile neutropenia. Moreover, various treatment guidelines recommend its application so that low-risk patients can be managed as outpatients [7–13].

Upon reviewing the literature on the usefulness of inflammatory markers as predictors of bacteremia or severe infections, we found several studies that evaluated CRP, procalcitonin, interleukin-6, or interleukin-8 [14–22]. Two findings are worth mentioning. First, most of these studies were carried out among pediatric patients [14–17, 21], whereas the present study included adults with diverse hematologic malignancies. Secondly, there is no clear association between the levels of CRP measured at the time of onset of neutropenia and the severity of the infection or bacteremia [16–22]. It is well known that CRP is a sensitive indicator of inflammation, albeit its specificity is low. In a previous observation, we found that specificity could be improved by using mean CRP value (measurements obtained during the first 5 days

Table 3 Univariate and multivariate analysis of variables associated with mortality

Variable	Univariate analysis			Multivariate analysis		
	HR	CI 95 %	p value	OR	CI 95 %	p value
Male sex	0.94	0.41–2.19	0.9024	–	–	–
High MASCC Score	8.94	2.64–30.24	<0.001	3.90	1.12–13.54	0.032
Episode occurring during stem cell transplantation	0.49	0–3.45	0.2279	–	–	–
Baseline CRP >15 mg/dL	3.71	1.60–8.59	0.001	1.78	0.76–4.17	0.182
Mean CRP >15 mg/dL	42.79	5.75–318.24	<0.001	17.36	2.21–136.48	0.007
Documented infection	15.51	2.08–115.35	<0.001	2.79	0.28–27.42	0.379
Bacteremia	7.15	2.42–21.14	<0.001	1.73	0.49–6.09	0.387
Resistant microbial isolate	4.60	1.87–11.30	<0.001	1.31	0.51–3.35	0.561
Admission to intensive care	32.82	7.66–140.52	<0.001	16	3.04–94.09	0.001
Baseline diagnosis of acute leukemia	1.03	0.42–2.54	0.9356	–	–	–
Duration of neutropenia ≥7 days	1.28	0.47–3.49	0.8340	–	–	–
Duration of neutropenia ≥14 days	1.15	0.48–2.74	0.7502	–	–	–

of each neutropenic episode) instead of a lone baseline value. This has not been reported elsewhere and could be a useful tool in resource-poor settings such as ours.

Our study has several limitations. The retrospective nature of the design and the fact that the study was carried out in a single institution could lead to bias. On the other hand, the external validity of our findings is high as the MASCC risk score can be used in almost every setting, and CRP is widely available. We recommend validating these findings in prospective studies with different populations in order to confirm their usefulness.

In conclusion, the combination of the MASCC risk score and mean CRP value during the first 5 days of a neutropenic episode successfully identifies a group of patients with hematologic malignancies and a high risk of death.

References

1. Klastersky J (2004) Management of fever in neutropenic patients with different risks of complications. Clin Infect Dis 39(Suppl 1): S32–S37

2. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328–340

3. Rosenberg PS, Alter BP, Bolyard AA, Bonilla MA, Boxer LA, Cham B et al (2006) The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood 107:4628–4635

4. Ramphal R (2004) Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Clin Infect Dis 39(Suppl 1):S25–S31

5. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R et al (2000) 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 18:3038–3051

6. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:427–431

7. Ahn S, Lee YS, Chun YH, Kwon IH, Kim W, Lim KS et al (2011) Predictive factors of poor prognosis in cancer patients with chemotherapy-induced febrile neutropenia. Support Care Cancer 19:1151–1158

8. Hui EP, Leung LK, Poon TC, Mo F, Chan VT, Ma AT et al (2011) 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 19:1625–1635

9. Ahn S, Lee YS, Lim KS, Lee JL (2013) Adding procalcitonin to the MASCC risk index score could improve risk stratification of patients with febrile neutropenia. Support Care Cancer 21:2303–2308

10. Elligsen M, Walker SA, Walker SE, LePiane F, Lathia N, De'Angelis C et al (2012) Comparison of mortality between nosocomial and community-acquired febrile neutropenia patients treated initially with cefazolin plus tobramycin: retrospective chart review. Eur J Clin Microbiol Infect Dis 31:1141–1150

11. Paesmans M, Klastersky J, Maertens J, Georgala A, Muanza F, Aoun M et al (2011) Predicting febrile neutropenic patients at low risk using the MASCC score: does bacteremia matter? Support Care Cancer 19: 1001–1008

12. Nakagawa Y, Suzuki K, Masaoka T (2009) Evaluation of the risk factors for febrile neutropenia associated with hematological malignancy. J Infect Chemother 15:174–179

13. Baskaran ND, Gan GG, Adeeba K (2008) Applying the Multinational Association for Supportive Care in Cancer risk scoring in predicting outcome of febrile neutropenia patients in a cohort of patients. Ann Hematol 87:563–569

14. Haeusler GM, Carlesse F, Phillips RS (2013) An updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment of fever during neutropenia in children with cancer. Pediatr Infect Dis J 32:e390–e396

15. Lin SG, Hou TY, Huang DH, He SY, Lin YD, Zhang LY et al (2012) Role of procalcitonin in the diagnosis of severe infection in pediatric patients with fever and neutropenia—a systemic review and meta-analysis. Pediatr Infect Dis J 31(10):e182–e188

16. Phillips RS, Wade R, Lehrnbecher T, Stewart LA, Sutton AJ (2012) Systematic review and meta-analysis of the value of initial biomarkers in predicting adverse outcome in febrile neutropenic episodes in children and young people with cancer. BMC Med 10:6

17. Miedema KG, de Bont ES, Elferink RF, van Vliet MJ, Nijhuis CS, Kamps WA et al (2011) The diagnostic value of CRP, IL-8, PCT, and sTREM-1 in the detection of bacterial infections in pediatric oncology patients with febrile neutropenia. Support Care Cancer 19: 1593–1600

18. Schuttrumpf S, Binder L, Hagemann T, Berkovic D, Trumper L, Binder C (2006) Utility of procalcitonin concentration in the evaluation of patients with malignant diseases and elevated C-reactive protein plasma concentrations. Clin Infect Dis 43:468–473

19. Aznar-Oroval E, Sanchez-Yepes M, Lorente-Alegre P (2010) Valor diagnostico de la procalcitonina, la interleucina 8, la interleucina 6 y la proteína C reactiva en la detección de bacteriemia y fungemia en pacientes con cáncer. Enferm Infecc Microbiol Clin 28:273–277

20. Ortega M, Rovira M, Almela M (2004) Measurement of C-reactive protein in adults with febrile neutropenia after hematopoietic cell transplantation. Bone Marrow Transplant 33:741–744

21. Kitanovski L, Jazbec J, Hojker S, Derganc M (2014) Diagnostic accuracy of lipopolysaccharide-binding protein for predicting bacteremia/clinical sepsis in children with febrile neutropenia: comparison with interleukin-6, procalcitonin, and C-reactive protein. Support Care Cancer 22:269–277

22. Massaro K, Costa S, Leone C (2007) Procalcitonin (PCT) and C-reactive protein (CRP) as severe systemic infection markers in febrile neutropenic adults. BMC Infect Dis 7:137