The Multinational Association for Supportive Care in Cancer Risk Index: A Multinational Scoring System for Identifying Low-Risk Febrile Neutropenic Cancer Patients

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Purpose: **Febrile neutropenia remains a potentially life-threatening complication of anticancer chemotherapy, but some patients are at low risk for serious medical complications. The purpose of this study was to develop an internationally validated scoring system to identify these patients.**

Materials and Methods: **Febrile neutropenic cancer patients were observed in a prospective multinational study. Independent factors assessable at fever onset, predicting low risk of complications, on a randomly selected derivation set, were assigned integer weights to develop a risk-index score, which was subsequently tested on a validation set.**

Results: **On the derivation set (756 patients), predictive factors were a burden of illness indicating absence of symptoms or mild symptoms (weight, 5; odds ratio [OR], 8.21; 95% confidence interval [CI], 4.15 to 16.38) or moderate symptoms (weight, 3; OR, 3.70; 95% CI, 2.18 to 6.29); absence of hypotension (weight, 5; OR, 7.62; 95% CI, 2.91 to 19.89); absence of chronic obstructive pulmonary disease (weight, 4; OR, 5.35; 95% CI, 1.86 to 15.46); presence of solid tumor or absence of previous fungal infection in patients with hematologic malignancies (weight, 4; OR, 5.07; 95% CI, 1.97 to 12.95); outpatient status (weight, 3; OR, 3.51; 95% CI, 2.02 to 6.04); absence of dehydration (weight, 3; OR, 3.81; 95% CI, 1.89 to 7.73); and age less than 60 years (weight, 2; OR, 2.45; 95% CI, 1.51 to 4.01). On the validation set, a Multinational Association for Supportive Care in Cancer risk-index score ≥ 21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71%.**

Conclusion: **The risk index accurately identifies patients at low risk for complications and may be used to select patients for testing therapeutic strategies that may be more convenient or cost-effective.**

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FEBRILE EPISODES IN cancer patients with chemotherapy-induced neutropenia can be life-threatening and may require administration of empiric, broad-spectrum antibiotics.[1] The accepted standard of care for such patients has been routine hospitalization for administration of parenteral antibiotics, close monitoring for development of complications, and evaluation for response to therapy.[2] This practice, along with the use of substantially improved antimicrobial agents, has resulted in a dramatic decrease in mortality among febrile neutropenic patients.

Many investigations have indicated that neutropenic patients with fever are a heterogeneous population, with subsets with varying risks regarding response to initial therapy, development of serious medical complications, and mortality.[3-7] Over the past decade, several investigators have identified subsets of febrile neutropenic patients who are at low risk for the development of complications, including mortality.[8-11] Several clinical studies involving neutropenic patients with predicted low risk have demonstrated the feasibility of newer approaches, such as outpatient therapy after early discharge from the hospital or outpatient therapy for the entire febrile episode, using parenteral, sequential (intravenous [IV] followed by oral), or oral antibiotic regimens.[12-17] Because these studies were conducted at single centers, using various definitions of low-risk patients and without adequate controls, they cannot be considered as having demonstrated the safety and efficacy of these new approaches. However, the safety of an oral regimen was suggested in an early controlled study.[18] Furthermore, two recent randomized large trials demonstrated the efficacy and safety, in clinically selected low-risk patients, of an oral empiric antibiotic treatment compared with a parenteral regimen[19,20]; however, in both studies, all patients were treated as inpatients. In published guidelines

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on the management of febrile neutropenia, oral therapy has been identified as a possible option for low-risk patients.[21,22]

Pivotal for the adoption of newer therapeutic strategies are a uniformly acceptable definition of low-risk febrile neutropenic patients and a simple but accurate clinical prediction rule that reliably identifies such patients at the onset of a febrile episode.

Talcott et al[23] developed a clinical prediction rule classifying patients into four risk groups. They suggested that neutropenic patients with controlled cancer and no serious comorbidity who developed fever in an outpatient setting would be at low risk, with an expected rate of serious medical complications of less than 5%. This classification scheme was prospectively validated in a study conducted at two United States institutions.[24] It was further tested clinically in a pilot study involving 30 low-risk patients who were discharged after an initial 48-hour hospital stay.[25] Thirteen percent of these patients developed serious complications, and nine patients (30%) were readmitted. However, five of these readmissions were due only to prolonged fever that resolved immediately afterward, and no patient died. In other studies, patients selected using clinical criteria were treated successfully as outpatients with IV or orally administered antibiotics.[14,26]

The purpose of this study, which was designed as a multicenter prospective observational study involving febrile neutropenic cancer patients treated with empiric antibiotic regimens, was to develop an internationally validated scoring system to identify low-risk patients (those defined as having a high probability of fever resolution without development of serious medical complications or death) at the onset of their febrile episodes. The performance of this clinical prediction rule was compared with that of the Talcott model.

The ultimate goal of the scoring system was selection of patients who might be candidates for new therapeutic strategies, including, but not limited to, outpatient management. This led us to register patients already hospitalized at fever onset, most of whom probably could not have been sent home even after initial hospital-based antimicrobial treatment. Inclusion of only outpatients in our study would have been detrimental for the generalizability of our model, given that the indication for hospitalization of cancer patients has changed during the last decade and will probably continue to change.

The study was conducted by the Study Section on Infections of Multinational Association of Supportive Care in Cancer (MASCC).

MATERIALS AND METHODS

Patients

The participating institutions agreed to study prospectively all consecutive febrile episodes (or randomly selected febrile episodes) occurring in patients meeting the following eligibility criteria: diagnosis of malignancy treated by chemotherapy that was causative of or contributive to neutropenia (granulocyte count $< 500/\mu L$, including polymorphonuclear leukocytes and band forms), temperature greater than 38°C (measured orally and documented by the patient or the medical/nursing staff), and age greater than 16 years. In addition, patients' febrile neutropenia had to be treated with an appropriate initial empiric antibiotic regimen based on known distribution of local pathogens and local susceptibilities, including an antipseudomonal beta-lactam in combination with an aminoglycoside, two beta-lactams in combination, or monotherapy with a third-generation cephalosporin or a carbapenem. Appropriateness of each administered empiric regimen was reviewed during a meeting of the authors of the present report and, if necessary, discussed with the local investigator. Because allowing patients to be enrolled several times during successive febrile episodes could induce a covariance structure between outcome data and invalidate statistical comparisons, only the first febrile episode occurring in a patient during the study period was considered. Finally, each participating institution contracted to enroll at least 20 patients.

Outcome

The dependent variable of interest was the final outcome of the patient, categorized as (1) fever resolution for 5 consecutive days without a serious medical complication, with modifications of the initial antibiotic treatment allowed (favorable outcome), or (2) fever resolution for 5 consecutive days with occurrence of a serious medical complication (medical complications considered serious were prospectively defined in the study protocol and are listed in Table 1), including death before fever resolution for 5 consecutive days.

Data Collection

All case report forms were sent to one of the institutions (Institut Jules Bordet), where a central review was performed to verify eligibility as well as homogeneity in outcome assessment and where the database was managed and checked for consistency.

Statistical Methodology

The study sample was divided into a two-thirds derivation set used to construct a prediction model and estimate its coefficients and a one-third validation set used to evaluate the performance of the clinical prediction rule. Because one of the goals of the study was validation of a prediction rule for use in a multinational setting, the two sets were obtained by randomizing the institutions rather than the patients. To account for differences in underlying neoplasms treated at the participating centers, we generated all possible combinations, allocating each institution to the derivation or validation set so that the proportion of patients in the first group was 67% $\pm$ 5% and the difference between the proportions of patients with solid tumors was less than 5%. One of these combinations was randomly selected to obtain the derivation and validation sets.

For both samples, patient baseline characteristics were summarized using descriptive statistics: frequency tabulations for categorical variables and summary parameters (median and range) for continuous variables.

Table 1. Medical Complications Considered Serious

Hypotension: systolic blood pressure less than 90 mmHg or need for pressor support to maintain blood pressure
Respiratory failure: arterial oxygen pressure less than 60 mmHg while breathing room air or need for mechanical ventilation
Intensive care unit admission
Disseminated intravascular coagulation
Confusion or altered mental state
Congestive cardiac failure seen on chest x-ray and requiring treatment
Bleeding severe enough to require transfusion
Arrhythmia or ECG changes requiring treatment
Renal failure requiring investigation and/or treatment with IV fluids, dialysis, or any other intervention
Other complications judged serious and clinically significant by the investigator*

*All reviewed by one investigator. Viral or fungal, microbiologically documented primary infection during the febrile episode, without any described complication and resolving under therapy, was considered a part of the infectious process and was not considered a serious complication.

Model derivation. Logistic regression analysis was applied to the derivation set to assess the association between the covariates and outcome. The covariates considered as potential prognostic factors are listed in Table 2; all were measured at the time of presentation with fever. All continuous variables were categorized on the basis of clinical arguments (the categories are then easy to use and to interpret) using a priori cut points, chosen according to physician judgment or to published reports.[28, 29] Univariate analyses were performed to select a first set of covariates to be tested for inclusion in a multivariate model; all covariates with a *P* value less than .1 for the null hypothesis of no effect were considered. Estimates of the covariate coefficients were obtained using the maximum likelihood method. Estimated odds ratios (ORs) with confidence intervals (CIs) were calculated. A priori second-order interaction terms, selected using clinical judgment and expertise, were also considered, namely diagnosis (solid tumor or hematologic tumor) by age, shock (systolic blood pressure < 90 mmHg), and any comorbidity; control of cancer by any comorbidity; profound neutropenia ($< 100/\mu L$) by fever (temperature $> 39°C$); inpatient status by Acute Physiology and Chronic Health Evaluation (APACHE) II score; burden of illness by any comorbidity; and prophylaxis administration by growth factor administration.

After completion of the univariate analyses, a multiple logistic regression model was fit to the data. A backward and forward step-up procedure was used for selection of the covariates. A *P* value less than .01 was the criterion for entry of a covariate in the model, and a further *P* value greater than .05 led to removal of the variable from the model. All *P* values were two-sided. Determination of APACHE II score (APACHE II was developed and validated in intensive care settings) requires additional computation and the values of some variables not routinely assessed in patients with febrile neutropenia. For these reasons, the score was not included in further assessment. Based on the logistic model, a score for prediction was calculated for each patient. Each coefficient estimate was multiplied by the same factor and rounded to the nearest integer. The multiplicative factor was chosen to obtain the smallest individual weight equal to 2. The global score was the sum of these individual weights and was substituted to the exact value of the logistic equation for ease of clinical implementation. A higher global score indicated a greater likelihood of fever resolution without development of any serious medical complication. High values identified low-risk patients. The accuracy of the scoring system was assessed by plotting observed versus predicted outcomes.

On the basis of this scoring system, several prediction rules were derived with the aim of selecting patients at low risk, using each possible value of the score as a threshold. Patients with scores higher than the thresholds constituted the group at low risk for complications and were predicted to recover favorably from their neutropenic febrile episodes. The sensitivity, specificity, and positive and negative predictive values of these rules were evaluated, with the convention that patients predicted by the rule to be at low risk and indeed recovering without complications represented true positives. Considering that our objective was to select, for therapeutic investigations, patients at low risk, we chose score thresholds to obtain safe positive predictive values with low rates of false identification of patients as being at low risk.

Validation set. The validation set was analyzed to test the performance of the derived prediction rule and to compare that rule with the Talcott prediction rule. Receiver operating characteristic curves were calculated to compare the performance of the rule in the derivation and validation sets.

Missing data. Missing data were handled in the following manner to avoid subsequent patient data exclusions from the analysis: a missing absolute neutrophil count was categorized, on the basis of the WBC count, into two categories ($\leq 100/\mu L$ or $> 100/\mu L$). In case of a WBC count greater than $100/\mu L$, this categorization was impossible and a random assignment was performed, with stratification by institution and, within each institution, with respect to the existing ratio between the two considered categories. Other missing biologic values were assumed to be in the normal defined range.

RESULTS

Eligibility

Between December 1994 and November 1997, 1,351 patients from 20 institutions (in 15 countries) were registered onto the study. Of these patients, 212 (16%) were considered ineligible, for the following reasons: undocumented neutropenia (72 patients), no or undocumented fever (45 patients), no chemotherapy or chemotherapy not contributive to neutropenia (38 patients), previous entry onto the study (30 patients), no empiric treatment or ineligible empiric antibiotic treatment (15 patients), no cancer (four patients), age less than 16 years (three patients), retrospective data collection (three patients), and incomplete (for key variables) case report form (two patients). Therefore, data relative to 1,139 patients were kept for the final analysis. Participating investigators and institutions are listed in the Appendix.

Table 2. Covariates Tested as Potential Predictive Factors

Covariate	Categories
Age	< 60 years, ≥ 60 years
Sex	Male, female
Underlying cancer	Solid tumor or lymphoma, hematologic tumor
Uncontrolled cancer	No, yes (leukemia: absence of complete remission; solid tumor or lymphoma: new lesions, increase of > 25% of lesions or symptoms of progressive disease)
Treatment setting	(Neo)adjuvant treatment, first-line treatment for advanced disease, second (subsequent)-line treatment, BMT
Growth factor administration (prophylaxis)	No, yes at presentation
Expected further neutropenia duration	< 7 days, 7-14 days, > 14 days
ECOG performance status	0-1, 2-4
Burden of illness*	No or mild symptoms, moderate symptoms, severe symptoms or moribund
Physiologic reserve*	Extreme or most stress tolerable, trouble with moderate stress, trouble with mild stress or without stress
Patient already in hospital	No, yes
Temperature	< 39°C, ≥ 39°C
Duration of fever	≤ 24 hours, > 24 hours
Presence of infection site	No, yes
Abnormality on chest x-ray	No or not documented, yes due to tumor, yes due to infection
Prophylactic antimicrobial treatment at presentation	No, yes
Hypotension	No, yes (systolic blood pressure < 90 mmHg)
Pulse	< 120 beats/min, ≥ 120 beats/min
Respiratory rate	≤ 24 breaths/min, > 24 breaths/min
Comorbidities	
Recent surgery	No, yes within 6 weeks
Ischemic heart disease or congestive cardiac failure	No, yes
Chronic obstructive pulmonary disease†	No, yes
Diabetes	No, yes
Confusion or altered mental state	No, yes
Blood loss requiring IV therapy	No, yes
Dehydration requiring IV therapy	No, yes
Weight loss of > 5% within 1 month	No, yes
Previous febrile neutropenia	No, yes
Previous fungal infection	No, yes
Antifungal therapy within 6 months	No, yes
Antiviral therapy within 6 months	No, yes
Other serious comorbidity‡	No, yes
Talcott group	I (inpatient), II (outpatient with comorbidity itself justifying hospitalization), III (outpatient without cancer control but without comorbidity), IV (outpatient without comorbidity and without uncontrolled cancer)
Talcott group dichotomized	I-III, IV
Biologic values	
Hemoglobinemia	≥ 8 g/dL, < 8 g/dL
Absolute neutrophil count	≥ 100/μL, < 100/μL
Platelet count	≥ 5,000/μL, < 5,000/μL
Creatinemia	< 2 mg/dL, ≥ 2 mg/dL
Bilirubinemia	< 2 mg/dL, ≥ 2 mg/dL
Albumin level	≥ 2.5 g/dL, < 2.5 g/dL
APACHE score	< 40, ≥ 40

Abbreviations: BMT, bone marrow transplantation; ECOG, Eastern Cooperative Oncology Group; APACHE, Acute Physiology and Chronic Health Evaluation.
*Severity of illness was estimated at presentation by the attending physician using visual analog scales that measure symptom severity and physiologic reserve.[27]
†Active chronic bronchitis, emphysema, decrease in forced expiratory volumes, and need for oxygen therapy, corticosteroids, and/or bronchodilators.
‡As mentioned by the investigator if judged serious, but all comorbidities were reviewed by one investigator.

Patient Characteristics

The derivation and validation sets, obtained by random allocation of the institutions, included 756 patients (66.4%) and 383 patients (33.6%), respectively, with 43.8% and 41.8% of patients, respectively, having hematologic tumors. The male-to-female ratio in the sample of 1,139 eligible patients was almost 1:1 (565 male patients, 574 female patients), and median age was 52 years. A total of 174 patients (15.3%) underwent bone marrow transplantation. One half of the patients (574) were inpatients when fever occurred (Talcott group I). Among the outpatients, 113 (9.9% of the overall population) presented with comorbidities justifying hospitalization (Talcott group II), 135 (11.9%) had uncontrolled cancer but no comorbidity (Talcott group III), and the remaining 317 patients (28%) were at low risk for the development of serious complications (Talcott group IV). Detailed patient characteristics are listed in Table 3, broken down into the derivation and validation sets.

Outcome Distribution

Complete resolution of fever without complications occurred in 645 patients (85%; 95% CI, 82.7% to 87.9%) in the derivation set and 310 patients in the validation set (81%; 95% CI, 76.9% to 85.0%), whereas 111 in the derivation set (15%; 95% CI, 12.1% to 17.3%) and 73 in the validation set (19%; 95% CI, 15.0% to 23.1%) developed at least one serious medical complication, including death before complete resolution of fever (35 patients in the derivation set and 20 patients in the validation set). The most frequent complications were confusion, hypotension, and respiratory failure. A microbiologically documented infection with bacteremia was reported in 206 patients in the derivation set (27%; 95% CI, 24.0% to 30.5%) and 94 patients in the validation set (25%; 95% CI, 20.1% to 20.9%).

Predictive Factors for Favorable Outcome

Derivation set. The association between each covariate listed in Table 2 and complete resolution of fever without serious medical complications, as tested in univariate analysis, is outlined in Table 4. We estimated the probability of a favorable outcome and chose as the reference category, for binary covariates, the group with the lowest rate of fever resolution without complication, to obtain an OR greater than 1 in the other patient subgroup. The characteristics showing a statistically significant higher rate of favorable outcome ($P < .001$) or, in other words, associated with a lower risk of serious medical complications were age less than 60 years (OR, 2.57; 95% CI, 1.71 to 3.89), controlled cancer (OR, 2.05; 95% CI, 1.36 to 3.08), good Eastern Cooperative Oncology Group performance status (OR, 2.39; 95% CI, 1.58 to 3.62), no or mild symptoms of disease (OR, 13.9; 95% CI, 7.3 to 26.3) as well as moderate symptoms (OR, 5.77; 95% CI, 3.57 to 9.31) compared with severe symptoms, physiologic reserve allowing tolerance of the most extreme stress (OR, 7.89; 95% CI, 4.26 to 14.63) or moderate stress (OR, 3.58; 95% CI, 2.24 to 5.71), outpatient status (OR, 2.15; 95% CI, 1.41 to 3.28), temperature less than 39.0°C (OR, 2.02; 95% CI, 1.34 to 3.04), no abnormality on chest x-ray (OR, 3.77; 95% CI, 2.24 to 6.37), no hypotension (OR, 8.88; 95% CI, 4.08 to 19.36), respiratory rate $\leq$ 24 breaths/min (OR, 3.57; 95% CI, 1.79 to 7.14), absence of chronic pulmonary disease (OR, 4.10; 95% CI, 1.63 to 10.26), absence of diabetes mellitus (OR, 4.77; 95% CI, 2.19 to 10.36), absence of confusion or mental state alteration (OR, 7.15; 95% CI, 3.56 to 14.37), absence of blood loss (OR, 3.30; 95% CI, 1.67 to 6.52), absence of dehydration (OR, 3.48; 95% CI, 2.01 to 6.04), no history of previous fungal infection (OR, 2.96; 95% CI, 1.51 to 5.78), no antifungal therapy within the previous 6 months (OR, 2.42; 95% CI, 1.44 to 4.07), allocation to Talcott group IV (OR, 5.43; 95% CI, 2.68 to 10.97), albumin level $\geq$ 2.5 g/dL (OR, 4.93; 95% CI, 1.90 to 12.79), and APACHE II score less than 40 (OR, 3.92; 95% CI, 2.58 to 5.93).

Among the interaction tests investigated using logistic regression models with two main effects and one second-order interaction term, one was selected to be tested in the multivariate analysis: a term including underlying disease and previous fungal infection status (previous fungal infection is associated with a poorer prognosis in patients with hematologic tumors but not in patients with solid tumor [OR, 0.24; 95% CI, 0.11 to 0.55; $P < .001$]).

Based on multivariate analysis of a set of covariates selected as described earlier, the characteristics included in the final model, which could be considered independent predictive factors of favorable outcome, were (in order of decreasing magnitude of the corresponding ORs) burden of illness with no or mild symptoms or moderate symptoms, absence of hypotension, absence of chronic pulmonary obstructive disease, solid tumor or no previous fungal infection in patients with hematologic tumors, absence of dehydration, burden of illness with moderate symptoms, outpatient status, and age less than 60 years. The coefficient estimates of the covariates included in our model are listed in Table 5 with the corresponding ORs and their CIs and a goodness-of-fit statistic for the model. The integer score derived from the logistic equation of this model gave the following weights to those characteristics: burden of illness with no or mild symptoms, five points; no hypotension, five

Table 3. Patient Characteristics

	Derivation Set (n = 756)		Validation Set (n = 383)	
	No. of Patients	%	No. of Patients	%
Host factors				
Age, years				
Median	52		52	
Range	16-91		16-86	
Sex				
Male	367	48.5	198	52
Female	389	51.5	185	48
Disease factors				
Underlying cancer				
Acute leukemia	212	28	81	21
Chronic leukemia	39	5	24	6
Myeloma	32	4	25	7
Hodgkin's disease	30	4	14	4
Other hematologic malignancy	18	2	14	4
Lymphoma	120	16	65	17
Breast tumor	127	17	48	13
Lung tumor	57	8	27	7
Other solid tumor	121	16	85	22
Burden of illness				
No signs	39	5	9	2
Mild signs	232	31	116	30
Moderate signs	345	46	189	49
Severe signs	126	17	65	17
Moribund	4	< 1	—	
Missing data	10	1	4	1
Physiologic reserve				
Extreme stress tolerable	25	3	15	4
Most stress tolerable	228	30	158	41
Trouble with moderate stress	297	39	158	41
Trouble with mild stress	159	21	44	12
Trouble without stress	37	5	4	1
Missing data	10	1	4	1
ECOG performance status				
0	103	14	75	20
1	332	44	142	37
2	241	32	117	31
3	47	6	43	11
4	14	2	2	< 1
Missing data	19	3	4	1
Fever duration at presentation				
< 24 hours	624	83	284	74
24-48 hours	75	10	66	17
> 48 hours	48	6	29	8
Missing data	9	1	4	1
Presence of infection site	327	43	138	36
Talcott group				
I	377	50	197	51
II	79	10	34	9
III	82	11	53	14
IV	218	29	99	26
APACHE score				
Median	33		32	
Range	7-96		0-80	
Treatment Factors				
Treatment setting				
Adjuvant or neoadjuvant treatment	70	9	42	11
First-line treatment	330	44	165	43
Second (subsequent)-line treatment	253	34	105	27
BMT	103	14	71	19
Autologous BMT	57		46	
Allogeneic BMT, related donor	32		20	
Allogeneic BMT, unrelated donor	7		5	
Peripheral-blood stem-cell transplantation	7		—	
Antimicrobial prophylaxis at presentation	261	35	157	41
Growth factors at presentation	171	23	70	18

Table 4. Univariate Analysis of the Derivation Set for Outcome

Characteristic	No. of Patients	Rate (%)*	OR	95% CI	P
Age					
< 60 years	534	89	2.57	1.71-3.89	< .0001
≥ 60 years	222	76			
Sex					
Female	389	88	1.60	1.06-2.41	.02
Male	387	82			
Malignancy					
Solid tumor or lymphoma	425	88	1.56	1.04-2.33	.03
Hematologic malignancy	331	82			
Cancer					
Controlled	510	88	2.05	1.36-3.08	< .001
Uncontrolled	246	79			
Treatment setting					
Adjuvant or neoadjuvant treatment	70	94	1.77	0.53-5.89	.35
First-line treatment for advanced disease	330	83	0.54	0.26-1.10	.10
Second (subsequent)-line treatment	253	83	0.54	0.26-1.12	.10
BMT	103	90			
Growth factor use					
Growth factor administration	171	89	1.49	0.88-2.50	.13
No growth factor administration at presentation	585	84			
Expected further neutropenia duration					
< 7 days	306	87	1.61	0.95-2.74	.08
7-14 days	301	86	1.41	0.84-2.38	.20
> 14 days	147	81			
ECOG performance status					
0-1	435	90	2.39	1.58-3.62	< .001
2-4	302	79			
Symptoms					
No or mild	271	95	13.90	7.3-26.3	< .001
Moderate	345	88	5.77	3.57-9.31	< .001
Severe or moribund	130	57			
Stress tolerance					
Extreme or most stress tolerable	253	95	7.89	4.26-14.63	< .001
Moderate stress tolerable	297	89	3.58	2.24-5.71	< .001
Trouble with mild stress or without stress	196	68			
Hospitalization status					
Outpatient	379	90	2.15	1.41-3.28	< .001
Inpatient	377	81			
Temperature					
< 39°C	508	88	2.02	1.34-3.04	< .001
≥ 39°C	248	79			
Fever duration					
≤ 24 hours	624	86	1.50	0.91-2.47	.11
> 24 hours	123	81			
Infection					
No infection site	429	88	1.53	1.02-2.29	.04
Presence of infection site	327	82			
Chest x-ray					
No abnormality	622	88	3.77	2.24-6.37	< .001
Abnormality, tumor	54	82	2.24	0.98-5.13	.06
Abnormality, infection	80	66			
Antimicrobial prophylaxis					
No	495	86	1.03	0.68-1.57	.88
Yes	261	85			
Hypotension					
No	728	87	8.88	4.08-19.36	< .001
Yes	28	43			
Pulse					
< 120 beats/min	656	86	1.22	0.70-2.16	.48
≥ 120 beats/min	100	83			
Respiratory rate					
≤ 24 breaths/min	720	86	3.57	1.79-7.14	< .001
> 24 breaths/min	36	64			

NOTE. The last category of each covariate is used as the reference category.

*Rate of episode resolution without occurrence of serious medical complications.

Table 4. Cont'd

Characteristic	No. of Patients	Rate (%)*	OR	95% CI	P
Surgery					
Within 6 weeks	28	89	1.45	0.43 -5.00	.55
No surgery within 6 weeks	728	85			
Cardiac disease as comorbidity					
No	719	86	2.62	1.25 -5.47	.01
Yes	37	70			
Chronic obstructive pulmonary disease					
No	736	86	4.10	1.63-10.26	.003
Yes	20	60			
Diabetes					
No	728	86	4.77	2.19-10.36	< .001
Yes	28	57			
Confusion or alteration of mental state					
No	721	87	7.15	3.56-14.37	< .001
Yes	35	49			
Blood loss					
No	715	86	3.30	1.67 -6.52	< .001
Yes	41	66			
Dehydration					
No	688	87	3.48	2.01 -6.04	< .001
Yes	68	66			
Weight loss of > 5% within 1 month					
No	690	86	2.00	1.10 -3.66	.02
Yes	66	76			
Previous febrile neutropenia					
No	511	86	1.27	0.83 -1.93	.27
Yes	245	83			
Previous fungal infection					
No	712	86	2.96	1.51 -5.78	< .001
Yes	44	68			
Antifungal therapy within 6 months					
No	666	87	2.42	1.44 -4.07	< .001
Yes	90	73			
Antiviral therapy within 6 months					
No	686	86	1.37	0.72 -2.59	.34
Yes	70	81			
Other serious comorbidity					
No	710	86	1.24	0.56 -2.74	.59
Yes	46	83			
Talcott group					
IV	218	96	5.58	2.76-11.31	< .001
III	82	81	0.99	0.54 -1.85	.98
II	79	84	1.22	0.64 -2.33	.55
I	377	81			
IV	218	96	5.43	2.68-10.97	< .001
I-III	538	81			
Hemoglobin level					
≥ 8 g/dL	644	86	1.32	0.78 -2.25	.30
< 8 g/dL	112	82			
Absolute neutrophil count					
≥ 100/μL	233	90	1.74	1.06 -2.83	.02
< 100/μL	523	83			
Platelet count					
≥ 5,000/μL	695	86	1.47	0.76 -2.87	.25
< 5,000/μL	61	80			
Creatinemia					
< 2 mg/dL	747	86	7.56	1.99-28.60	.003
≥ 2 mg/dL	9	44			
Bilirubinemia					
< 2 mg/dL	724	86	2.01	0.88 -4.59	.10
≥ 2 mg/dL	32	75			
Albumin level					
≥ 2.5 g/dL	738	86	4.93	1.90-12.79	< .001
< 2.5 g/dL	18	56			
APACHE score					
< 40	547	91	3.92	2.58 -5.93	< .001
≥ 40	209	71			

Table 5. Selected Multivariate Model (n = 746)

Characteristic	Coefficient	SE	OR	95% CI	P
Burden of illness					
No or mild symptoms	2.11	0.35	8.21	4.15-16.38	< .001
Moderate symptoms	1.31	0.27	3.70	2.18-6.29	< .001
No hypotension	2.03	0.49	7.62	2.91-19.89	< .001
No chronic obstructive pulmonary disease	1.68	0.54	5.35	1.86-15.46	.002
Solid tumor or no previous fungal infection	1.62	0.48	5.07	1.97-12.95	< .001
No dehydration	1.34	0.36	3.81	1.89-7.73	< .001
Outpatient status	1.25	0.28	3.51	2.02-6.04	< .001
Age < 60 years	0.90	0.25	2.45	1.51-4.01	< .001

NOTE. Goodness-of-fit, χ^2 statistic, 710.05 (737 df) ($P = .76$). Odds ratios are expressed using already described reference categories. The modeled probability is the probability of a favorable outcome, ie, the probability of episode resolution without occurrence of any serious complication.

points; no chronic obstructive pulmonary disease, four points; solid tumor or no previous fungal infection in the case of a hematologic tumor, four points; no dehydration, three points; burden of illness with moderate symptoms, three points; outpatient status, three points; and age less than 60 years, two points. The whole score was obtained by summing the individual weights (Table 6). The maximum score is 26, because the points given for the two favorable categories of burden of illness are not cumulative. Plots of the observed and predicted outcomes against score values are presented in Fig 1.

The prediction rules derived using this score, on the derivation set, are listed in Table 7 for different thresholds, with the associated sensitivities, specificities, positive and negative predictive values, and overall misclassification rates. The same parameters were calculated for the Talcott clinical prediction rule. The best overall misclassification rate that can be achieved is 13%. At that level, 616 of 756 patients are identified as low-risk patients; however, at that threshold, the proportion of patients falsely identified as being at low risk (12%) is too high for a safe clinical prediction rule. We propose to use the threshold of 21 because it corresponds to a still relatively low misclassification rate (21%), to a large proportion of patients identified as being at low risk (551 of 756, 73%), and an increased positive predictive value (94%).

Table 6. Scoring System

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

NOTE. Points attributed to the variable "burden of illness" are not cumulative. The maximum theoretical score is therefore 26.

Of the 551 patients identified as being at low risk using the threshold of 21, a total of 32 (6%) developed a serious medical complication, including death (six patients [1%]). In the group considered by the rule to be at high risk for complications (205 patients), 79 patients (39%) had a serious medical complication, including death (29 patients [14%]). The most frequent complications among the patients falsely identified as members of the good-prognosis group were confusion (nine patients), cardiac problems (ECG changes in seven and arrhythmia in seven), respiratory failure (six patients), hypotension (four patients), renal failure (four patients), and bleeding (four patients). Of the six patients who died before fever resolution, three had hematologic malignancies, four had advanced disease treated with first-line chemotherapy, and two had advanced disease treated with second (subsequent)-line chemotherapy; a microbiologic diagnosis was made in four patients (with bacteremia in three). The deaths occurred quite late after fever onset in most of the six patients (two died on day 8 and three died after > 2 weeks); one patient died on day 3. Three of these patients had been allocated to Talcott group IV.

The application of the Talcott model on our derivation set led to the identification of 218 patients (29%) with predicted low risk. The positive predictive value is high (96%), but sensitivity is low (32%) and the misclassification rate is high (59%). The death rate in this Talcott group IV was 1% (three of 218 patients).

Validation set. Of the 383 patients in the validation set, 243 (63%) were predicted, using the chosen prediction rule with a threshold of 21, to be at low risk, with a 91% rate of resolution without complications; whereas 140 were classified as being at high risk, with a rate of resolution without serious complications of 64%. The sensitivity, specificity, negative predictive value, and misclassification rate of the prediction rule were 71%, 68%, 36%, and 30%, respec-

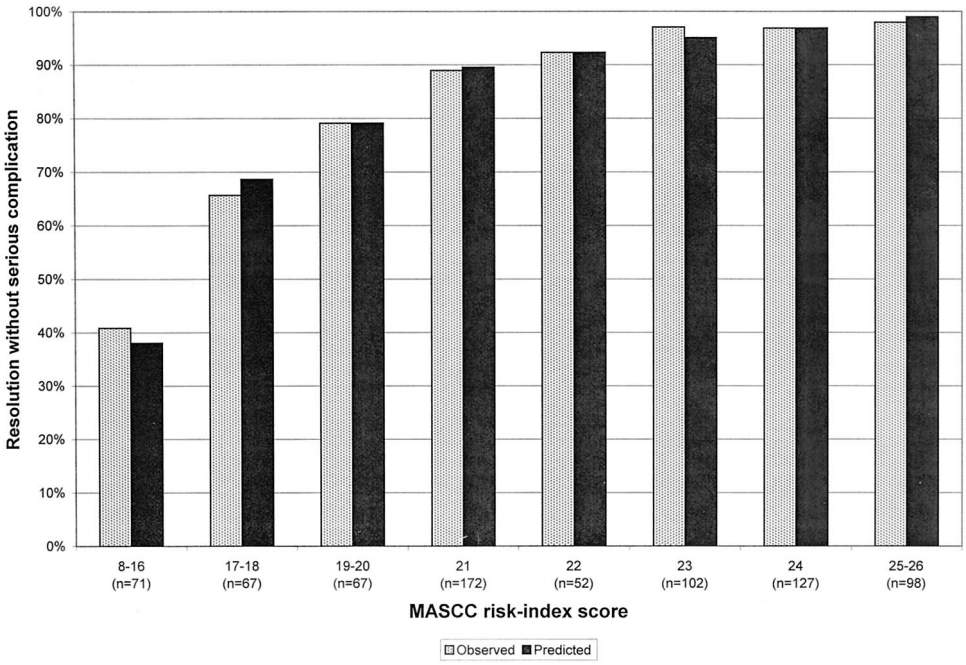

Fig 1. Observed and predicted rates of fever resolution without serious medical complication development for several values of the scoring system.

tively. By comparison, the Talcott prediction rule identified 99 patients (26%) as being at low risk, with a 7% false-positive rate (93% rate of resolution without occurrence of a serious medical problem). Among the other patients, identified as being at high risk, the rate of resolution without complication was 77% (218 of 284 patients). Four (1.6%) of the 243 patients in the low-risk group died. One of these patients had solid tumor, two had advanced disease and received first-line chemotherapy, one had advanced disease treated with second (subsequent)-line chemotherapy, one underwent bone marrow transplantation, two developed bacteremia, a microbiologic diagnosis was made without bacteremia documentation in one patient, and three patients were allocated to Talcott group I. As in the derivation set, these deaths did not occur immediately after the beginning of the febrile episode (one patient died on day 5 and three died after $>$ 2 weeks). The most frequent complications in the false-positive patients were bleeding (three patients) and hypotension (three patients). Renal failure and respiratory failure occurred in one patient each. The sensitivity, specificity, negative predictive value, and misclassification rate of the Talcott prediction rule were 30%, 90%, 23%, and 59%, respectively. Three deaths occurred in Talcott group IV (on days 5, 6, and 8). Two of these patients had an MASCC risk-index score of less than 21 and advanced disease treated with first-line chemotherapy (one had solid tumor and one had non-Hodgkin's lymphoma); both patients developed bacteremia.

In Table 8, we provide the parameters of the MASCC clinical prediction rule at several thresholds, as well as those of the Talcott model, on the validation set. In Fig 2, we present, for both sets, the receiver operating characteristic curves assessing the discriminating ability of the MASCC scoring system.

DISCUSSION

There is general agreement that febrile neutropenic cancer patients constitute a heterogeneous population, with a subgroup having a low risk of serious complications or death. This recognition of risk stratification has led to changes in the treatment of these patients, including changes in antimicrobial therapy (combinations *v* monotherapy), mode of administration (IV *v* orally), and treatment setting (hospital, outpatient center, physician's office, home). Two recently published clinical trials[19,20] demonstrated the safety and efficacy of oral antibiotics for low-risk patients in the inpatient setting. These studies used different definitions to select patients for the trials, which underscores the need for an internationally validated system to identify this low-risk group accurately so that clinical research into new treatment strategies, including outpatient management, can be conducted safely.

In this multinational, multicenter study of more than 1,100 patients with fever and neutropenia, we demonstrated that certain characteristics, easily identifiable at the onset of the febrile episode, predict low risk of medical complications. Using these factors, we developed the simple and

Table 7. Clinical Prediction Rule Performance: Derivation Set (n = 756)

	TP	FP	FN	TN	Se	Sp	PPV	NPV	Miscl
Score ≥ 8	645	111	0	0	1.00	0.00	0.85	—	0.15
Score ≥ 14	643	95	2	16	1.00	0.14	0.87	0.89	0.13
Score ≥ 17	616	69	29	42	0.96	0.38	0.90	0.59	0.13
Score ≥ 19	572	46	73	65	0.89	0.59	0.93	0.47	0.16
Score ≥ 20	523	34	122	77	0.81	0.69	0.94	0.39	0.21
Score ≥ 21	519	32	126	79	0.80	0.71	0.94	0.39	0.21
Score ≥ 22	366	13	279	98	0.57	0.88	0.97	0.26	0.39
Score ≥ 23	318	9	327	102	0.49	0.92	0.97	0.24	0.44
Score ≥ 24	219	6	426	105	0.34	0.95	0.97	0.20	0.57
Talcott rule	209	9	436	102	0.32	0.92	0.96	0.19	0.59

Abbreviations: TP, number of true positives (patients identified as being at low risk and with resolution without serious complications); FP, number of false positives (patients identified as being at low risk but having developed a serious complication); FN, number of false negatives (patients identified as being at high risk but with resolution without serious complications); TN, number of true negatives (patients identified as being at high risk and having developed a serious complication); Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; Miscl, rate of misclassification of patients.

easy-to-use MASCC scoring system and its clinical prediction rule for identification of low-risk patients.

When we were developing our rule, we examined the trade-offs between sensitivity, specificity, positive and negative predictive values, and overall misclassification rate. The rule that we are proposing, with a threshold of 21, has a low, if not minimal, misclassification rate, corresponding to a nearly optimal use of the logistic regression model, and a better sensitivity than rules using higher thresholds would have. If we apply our rule to the subgroup of outpatients, its positive predictive value, on the validation set, is improved (94% [133 of 142 patients]) and is comparable to that of the Talcott model (93%) when that model is applied to our patients. With our model, 142 (76%) of 186 outpatients are identified as being at low risk, compared with 99 Talcott group IV patients (53%). Each user of our model still has the opportunity to choose the threshold defining the clinical prediction rule. However, if we select a clinical prediction rule at a higher threshold (eg, 22), the overall performance of the rule is worse (at a threshold of 22, the misclassification rate is increased to 45%).

Our model has several advantages over prior methods for identifying low-risk patients. Our prospective study involved worldwide participation (investigators were affiliated with 20 institutions in 15 countries); the external validity of the results was increased with a large sample size, ensuring internal validity. As far as external validity is concerned, our patient population is more representative of the varying patterns of clinical practice in the management of these patients. Our sample included patients who were treated with different antibiotic regimens after having undergone a variety of myelosuppressive treatments in various types of institutions. We developed our risk-index score on a derivation set and further tested it on a validation set. The two sets were obtained by randomizing institutions rather than patients, to better assess the validity of our model, even in the presence of varying types of patient management. By this method, we could also address the issue of consideration of subjectively assessed covariates, such as burden of illness, which was included in our final model but was perhaps not consistently measured by the different investigators. The generalizability of our model, in terms of reproducibility and transportability as defined by Justice et al,[30] is confirmed by the fact that the positive predictive value in the validation set (94%) was close to that in the derivation set (91%). A similar decrease in positive predictive value also occurred when the Talcott model was applied to our patients; this was unexpected, because neither the

Table 8. Clinical Prediction Rule Performance: Validation Set (n = 383)

	TP	FP	FN	TN	Se	Sp	PPV	NPV	Miscl
Score ≥ 17	282	55	28	18	0.91	0.25	0.84	0.39	0.22
Score ≥ 19	246	41	64	32	0.79	0.44	0.86	0.33	0.27
Score ≥ 20	221	25	89	48	0.71	0.66	0.90	0.35	0.30
Score ≥ 21	220	23	90	50	0.71	0.68	0.91	0.36	0.30
Score ≥ 22	147	10	163	63	0.47	0.86	0.94	0.28	0.45
Talcott rule	92	7	218	66	0.30	0.90	0.93	0.23	0.59

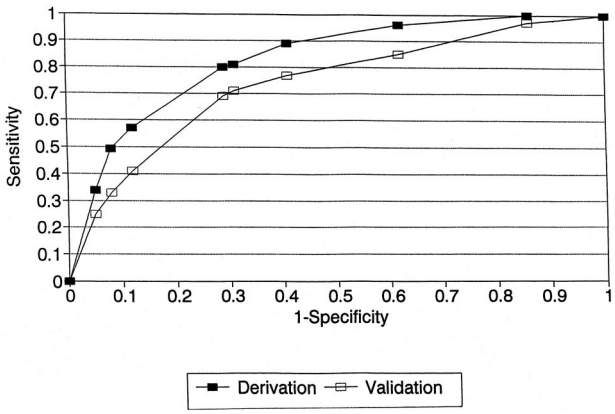

Fig 2. Receiver operating characteristic (ROC) curves for the derivation and validation sets.

derivation set nor the validation set was used for development of the Talcott rule. This suggests that the small loss in the positive predictive value of our rule is due more to a random variation than to a lack of reproducibility.

We acknowledge that the validation of our scoring system is not a static process. Our model will need to be tested repeatedly over time and will probably need to be updated to reflect changes in the management of febrile neutropenic patients.

Data were missing for some of the biologic variables (at rates from < 1% to up to 20%) but not for the covariates included in the final model. The reproducibility of the performance of our model should therefore not be jeopardized by that problem.

Our model represents an improvement over the Talcott classification in that our model has a lower misclassification rate (30% *v* 59%, on the validation set) and a better sensitivity (71% *v* 30%). The positive predictive value was comparable (91% *v* 93%), but our model has a lower specificity (68% *v* 90%). The major advantage of our model is that the rate of identification of patients as being at low risk is substantially increased (63% *v* 26%). The use of a higher threshold to define the clinical prediction rule, a threshold of 22 for instance, would result in a higher positive predictive value (94%) on the validation set and a specificity comparable to that of the Talcott model (86%). However, although this choice might be safer, especially in patients not rigorously monitored, it corresponds to a loss of 22% of low-risk patients. Furthermore, as already mentioned, the positive predictive value of our model (94%), in the outpatients included in the validation set, is comparable to that of the Talcott model (93%) when that model is applied to the same patient population.

Another advantage of our model over the Talcott classification system is that we replaced the uncontrolled cancer variable, not selected in our multivariate model, with measures more specifically associated with the clinical severity of the febrile episode (rather than with the underlying cancer), such as burden of illness, hypotension, and dehydration. The general comorbidity variable was replaced with specific conditions (chronic obstructive pulmonary disease and age). It is not surprising that comorbidities such as diabetes, cardiac disease, and confusion, which were relatively uncommon in our series, are not included in our final model; they were probably replaced by other variables such as burden of illness.

Our group of patients predicted as being at high risk remains heterogeneous; a substantial number of patients in that group recover from fever without complications. This is a common problem that has been encountered by other investigators attempting to predict the occurrence of complicated febrile neutropenia.[31-34] There is a need to evaluate new covariates including variables related to the treatment of the underlying disease, which might be particularly important[11, 35] but were not fully assessed in our study.

Among the factors that we expected to be predictive of development of a serious complication were the underlying disease (hematologic malignancy *v* solid tumor) and the duration of neutropenia. Neither was included in our model. Nevertheless, the role of the underlying disease appears in our model as an interaction between prior fungal infections and hematologic malignancy. Its meaning is not completely clear; it may be a surrogate marker for refractory or relapsed leukemia or prolonged prior episodes of neutropenia. The expected duration of neutropenia, often used by other authors for selecting low-risk patients,[19,20] although not prognostic of final outcome, predicted a higher probability of responding to empiric antimicrobial therapy without need for modification. However, the expected duration of neutropenia did not accurately predict the actual duration of neutropenia, which might be an important factor. Accurate prediction of the severity and duration of neutropenia is an important goal. These aspects should be taken into consideration during the development of future risk models, which should allow us to provide optimal care to febrile neutropenic patients with new therapeutic strategies focusing on patient comfort and quality of life as well as cost efficacy.

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APPENDIX

Participating Investigators and Institutions

The following are participating investigators and institutions, with numbers of eligible patients given in parentheses: L. Elting, K. Rolston, E. Rubenstein, M.D. Anderson Cancer Center, Houston, TX (172 patients); T. Berghmans, J. Klastersky, P. Mommen, M. Paesmans, Institut Jules Bordet, Brussels, Belgium (159 patients); B. De Pauw, J.P. Donnelly, Algemeen Universitair Ziekenhuis, Nijmegen, the Netherlands (91 patients); R. Feld, A. McGeer, Ontario Cancer Institute, Toronto, Canada (83 patients); A. Cometta, G. Zanetti, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (73 patients); W. Feremans, A. Kentos, Hôpital Erasme, Brussels, Belgium (53 patients); I. Malik, National Cancer Institute, Karachi, Pakistan (52 patients); J.L. Michaux, S. Neumeister, Cliniques Saint-Luc, Brussels, Belgium (50 patients); J. Herrstedt, K. Wedervang, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark (49 patients); W. Kern, Medizinisches Universitätsklinik, Ulm, Germany (46 patients); I. Bover, Hospital Sant Joan, Reus, Spain (43 patients); M. Boyer, Royal Prince Alfred Hospital, Camperdown, Australia (41 patients); P. Ljungman, Huddinge University Hospital, Huddinge, Sweden (40 patients); J. Vorlicek, Masaryk University Hospital, Brno, Czech Republic (35 patients); Z. Aziz, Jinnah Hospital, Lahore, Pakistan (27 patients); B.L. Rapoport, Medical Oncology Centre of Rosebank, Johannesburg, and Pretoria Academic Hospital, Pretoria, South Africa (27 patients); J. Gallagher, Geisinger Medical Center, Danville, PA (26 patients); J. Talcott, Dana Farber Cancer Institute, Boston, MA (25 patients); M. Viot, Centre Antoine Lacassagne, Nice, France (25 patients); R. de Bock, Algemeen Ziekenhuis Middelheim, Antwerp, Belgium (22 patients).

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