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ORIGINAL ARTICLE

A prospectively validated nomogram for predicting the risk of chemotherapy-induced febrile neutropenia: a multicenter study

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Abstract
Purpose There is clinical need to predict risk of febrile neutropenia before a specific cycle of chemotherapy in cancer patients.
Methods Data on 3882 chemotherapy cycles in 1089 consecutive patients with lung, breast, and colon cancer from four teaching hospitals were used to construct a predictive model for febrile neutropenia. A final nomogram derived from the multivariate predictive model was prospectively confirmed in a second cohort of 960 consecutive cases and 1444 cycles.
Results The following factors were used to construct the nomogram: previous history of febrile neutropenia, pre-cycle lymphocyte count, type of cancer, cycle of current chemotherapy, and patient age. The predictive model had a concordance index of 0.95 (95 % confidence interval (CI)=0.91–0.99) in the derivation cohort and 0.85 (95 % CI=0.80–0.91) in the external validation cohort. A threshold of 15 % for the risk of febrile neutropenia in the derivation cohort was associated with a sensitivity of 0.76 and specificity of 0.98. These figures were 1.00 and 0.49 in the validation cohort if a risk threshold of 50 % was chosen.
Conclusions This nomogram is helpful in the prediction of febrile neutropenia after chemotherapy in patients with lung, breast, and colon cancer. Usage of this nomogram may help decrease the morbidity and mortality associated with febrile neutropenia and deserves further validation.

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Introduction

Febrile neutropenia is an important risk factor for morbidity and mortality in patients with cancer and may lead to a reduction in the dose of chemotherapy delivered [1–4]. Even when a standard dose of chemotherapy is used, febrile neutropenia may be a non-rare event in daily practice in different settings, for example an incidence rate of 9 % after adjuvant chemotherapy with vinorelbine and cisplatin in patients with non-small cell lung cancer (NSCLC) as shown in the ANITA trial, or more than 20 % for docetaxel and trastuzumab chemotherapy in patients with metastatic breast cancer [5, 6]. Thus, primary or secondary prevention, in particular, through the administration of colony-stimulating factor (CSF) is recommended by various guidelines when there is a considerable risk of febrile neutropenia [7, 8].

Although there exist models to predict the risk of febrile neutropenia, they are either derived from groups of solid cancer patients mixed with cases of hematological malignancy or have not been prospectively validated [4, 9–12]. For these reasons, the 2006 ASCO update on the use of hematopoietic CSFs underlines the need for further studies to develop and prospectively validate an accurate risk model to improve the efficacy and cost-effectiveness of growth factor prophylaxis [8]. At the present time, the criteria for the use of CSF and/or other measures to minimize the risk of febrile neutropenia are to some extent arbitrary and based on low quality evidence. Moreover, they have not been fully validated. In this study, we aimed to develop a clinically useful model to predict the individual risk of febrile neutropenia in patients with solid tumors only and validate this model both internally and externally.

Materials and methods

Patients and data collection

Patients with three types of common cancer (breast, lung, and colorectal cancer) who were receiving any line and any cycle of chemotherapy and were at any stage of disease were prospectively and consecutively entered into the study from two institutions over a course of 8 months between May 2010 and January 2011 for the initial cohort (model derivation cohort) and from four institutions during November 2011 and December 2011 for the external validation cohort. The local ethical committee of Akdeniz University approved the study protocol, prior to the onset of the study. Outpatients receiving chemotherapy at the outpatient chemotherapy units and inpatients receiving chemotherapy in the oncology wards were both enrolled. Disease and patient characteristics, as well as details of present and past treatment, specifics of the chemotherapy protocol, number of cycles, any history of febrile neutropenia, and use of CSF were recorded. Chemotherapy regimens administered during the study were categorized with respect to their risk of inducing febrile neutropenia as previously described [7]. Each patient was carefully observed after each cycle for the development of febrile neutropenia. Febrile neutropenia was defined as the occurrence of a fever of 38.3 °C orally or 38.0 °C for over an hour and a neutrophil count <500 or 500–999/mm^3 with a predicted decline to <500/mm^3 over the next 48 h [13]. Regular telephone meetings with the investigators from other participating centers were carried out to ensure timely and accurate data management. Our main reason to use a predictive model to estimate the risk of febrile neutropenia was to be able to initiate some preventive measures: CSF, dose reduction, or prophylactic antibiotics. For example, CSF can be initiated in patients without CSF coverage, or dose reduction and/or prophylactic antibiotics can be started in cases that are already on CSF. All data were entered daily into the main database by the participating centers. The outcome of each febrile neutropenia episode was carefully followed or queried. Two centers (Akdeniz University, Department of Medical Oncology and Antalya Training and Research Hospital, Department of Medical Oncology, both in the city of Antalya) recruited patients for model derivation and four centers recruited for validation (Necmettin Erbakan University, Meram Faculty of Medicine, Dept. of Medical Oncology, Konya, and Süleyman Demirel University, Department of Medical Oncology, Isparta, in addition to the two listed above).

Statistical analysis

Derivation of the model The main outcome variable was the development of febrile neutropenia after a specific cycle of chemotherapy. As the unit of analysis is the cycle of chemotherapy and not the patient, and data are dependent within the same patient, we used univariate and multivariate generalized estimating equation (GEE) models, taking into account the correlation structure within patients. Any factor with a P value <0.10 in the univariate analysis was entered into multivariate analysis. A P value <0.05 was considered necessary for statistical significance.

Validation of the model External validation was performed to test the robustness of the model in a separate validation cohort of patients who were prospectively recruited from four centers. The risk of febrile neutropenia before a specific cycle of chemotherapy in the validation cohort was calculated using a nomogram of the initial model obtained from the derivation

cohort. If score calculated with the use of nomogram prior to a specific cycle of chemotherapy exceeded a certain threshold for the risk of febrile neutropenia, for example 15 %, then it was assumed that the predicted and the actual outcomes for febrile neutropenia were in accordance.

Performance of the model After applying different threshold levels for the risk of febrile neutropenia, the sensitivity and specificity values of each scenario were calculated. Concordance index (CI) was determined to assess the discrimination of the model.

Results

General characteristics

The derivation cohort comprised 1089 patients and 3880 chemotherapy cycles from two centers. The median age was 55 years (range, 26 to 86), 44.8 % had stage 4 disease, and 25.6 % were using CSF prior to a cycle. Most of the cycles (62.1 %) consisted of a chemotherapy protocol that had a 10–20 % risk of febrile neutropenia. During the study duration, a total of 59 episodes of febrile neutropenia were observed (1.5 % of total cycles) (Table 1). With respect to the cycle of chemotherapy administered, 2.7 % of the first cycle, 1 % of the second cycle, 1.6 % of the third, 1.2 % of the fourth and the fifth, and 0.6 % of the sixth cycles and beyond were effected by febrile neutropenia.

The external validation cohort consisted of 960 patients and 1444 cycles of chemotherapy from four centers. The characteristics of this cohort were similar to those of the derivation cohort with a 25.3 % lung cancer frequency, 17.4 % CSF usage rate for prophylaxis, and 18 episodes of febrile neutropenia (1.2 % of total cycles) (Table 2).

Derivation of the generalized estimating equations model

In the univariate analysis, 16 of the 36 factors tested were associated with the occurrence of febrile neutropenia. Five of these 16 factors retained their significance in the multivariate analysis: four factors had significant *P* values; cycle of current chemotherapy, previous history of febrile neutropenia, type of cancer, and pre-cycle lymphocyte count. In addition, because patient age had a marginal significance in the multivariate model, and previous literature suggested it might be a significant factor, it was also incorporated into the final multivariate model. The specifics of the predictors of febrile neutropenia in the derivation cohort are presented in Table 3.

The resultant coefficients of this final model were then used to construct a nomogram. Please refer to the table in Fig. 1 for details of the nomogram.

External validation of the model

The validity of the derived model and the nomogram was tested in a second prospective cohort of consecutive patients from four centers. When a cut off threshold of 0.50 for the risk of febrile neutropenia was chosen, sensitivity and specificity values were 1.00 and 0.49, respectively. The performance details of external validation are shown in Table 4.

Performance of the model

If a cut off level of 0.15 for febrile neutropenia was specified, the sensitivity and specificity values in the derivation cohort were 0.76 and 0.98, respectively (see Table 4 for details of the performance of the model). The predictive model had a concordance index of 0.95 (95 % confidence interval (CI)=0.91–0.99) in the derivation cohort, and 0.85 (95 % CI=0.80–0.91) in the external validation cohort. Also, in the derivation cohort, for patients who did not use CSF, the concordance index was 0.96 (95 % CI=0.92–0.99), as opposed to 0.93 (95 % CI=0.84–1.00) in patients that did use CSF, and these figures were very close.

Discussion

This is an externally validated predictive model to define the risk of febrile neutropenia after chemotherapy in patients with common cancers. This model thus allows pretreatment identification of patients who are likely to develop febrile neutropenia after a specific cycle of chemotherapy. Thus, we think that the nomogram derived from our model will be helpful in daily clinical practice to guide efforts for the prophylaxis of febrile neutropenia. Previous predictive models for febrile neutropenia are either derived from mixed populations including patients with hematological malignancies or have not been externally validated [4, 9–15]. Although Bley et al. prospectively tested their model in two cohorts, the data were very limited for patients with solid tumors; among the 104 patients prospectively tested, only 53 had heterogeneous solid tumors [16]. For these reasons, we believe that the current model represents significant progress in predicting febrile neutropenia and optimizing protection against it. Usage of growth factors, dose reduction or prophylactic antibiotics are among the potential preventive measures in this setting.

The cycle number of the current chemotherapy is two important factors of the current model, and our results indicate that earlier cycles of chemotherapy have a greater risk of febrile neutropenia. This is in accordance with previous studies, in which various investigators have shown that the first cycle of chemotherapy in particular has a greater risk for the

Table 1 Disease, patient, treatment, and laboratory characteristics of the derivation cohort

Factors	Number[a]	Percent	Mean (SD)	Median	Min-Max
Patients	1089				
Cycles	3882	100			
Disease factors					
Type of cancer					
Breast cancer	1526	39.3			
Colon cancer	1333	34.3			
Lung cancer	1023	26.4			
Stage					
1 to 3	2141	55.2			
4	1739	44.8			
Histology					
Adenocarcinoma	1801	46.4			
Other	2081	53.6			
Number of organ systems involved			0.9 (1.1)	1	0–6
Number of metastatic sites involved					
≤3	1988	51.2			
>3	1335	34.4			
Disease status					
No evidence of disease or progression	3476	89.5			
Progression	400	10.3			
Patient factors					
Number of smoking pack years	3868	99.6	20.9 (30.9)	4	0–300
Gender					
Male	1800	46.4			
Female	2061	53.1			
Social security status[b]					
Social security system for workers	1884	48.5			
Other	1976	49.9			
ECOG performance status	3878	99.9	0.7 (0.7)	1	0–4
Comorbidity					
Heart failure or coronary heart disease	302	7.8			
Hypertension	849	21.9			
Diabetes mellitus	505	13.0			
Renal failure	57	1.5			
Chronic obstructive pulmonary disease	213	5.5			
Non-specified comorbidity	639	16.5			
Global quality of life[c]	3600	92.7	5.3 (1.2)	6	1–7
Age	3834	98.8	55.1 (11.3)	55	26–86
Treatment factors					
Center					
Akdeniz University Hospital	3121	80.4			
Antalya Research and Training Hospital	761	19.6			
Place of chemotherapy administration (outpatient vs. inpatient)					
Outpatient	3694	95.2			
Inpatient	188	4.8			
Previous radiotherapy					
Yes	1044	26.9			
No	2825	72.8			
Number of lines of chemotherapy	3880	99.9	1.8 (1.2)	1	1–10

Table 1 (continued)

Factors	Number[a]	Percent	Mean (SD)	Median	Min-Max
Number of sum of cycles of chemotherapy over all lines	3876	99.8	7.4 (8.1)	5	1–79
Cycle of chemotherapy on the current protocol[d]	3881	100.0	3.4 (2.7)	3	1–27
Number of drugs in the current protocol[e]	3882	100.0			
1 or 2 drugs	2246	57.9			
3 or more drugs	1636	42.1			
Baseline febrile neutropenia risk of the protocol (%)[f]					
<10	1087	28.0			
10–20	2410	62.1			
>20	380	9.8			
Colony-stimulating factor (CSF) usage[g]					
Yes	995	25.6			
No	2880	74.2			
Previous history of febrile neutropenia					
Yes	245	6.3			
No	3637	93.7			
Dose reduction[h]					
Yes	329	8.5			
No	3552	91.5			
Febrile neutropenia during study period					
Yes	59	1.5			
No	3823	98.5			
Laboratory factors					
LDH (U/L)	3583	92.3	390.2 (239.9)	363	46–3896
Creatinine (mg/dL)	3824	98.5	0.8 (0.2)	0.7	0.1–2.2
ALT (U/L)	3819	98.4	22.2 (20.7)	18	1–527
Albumin (g/dL)	3518	90.6	4.2 (0.5)	4.2	1.7–8.6
CRP (mg/dL)	3530	90.9	3.2 (7.2)	0.8	0–99
Hemoglobin (g/dL)	3865	99.6	11.8 (1.5)	11.8	6.9–18.3
Monocyte (×1000/mm^3)	3863	99.5	0.6 (0.5)	0.5	0.0–10.9
Neutrophil (×1000/mm^3)	3863	99.5	4.3 (2.8)	3.7	1.0–43.2
Lymphocyte (×1000/mm^3)	3865	99.6	1.9 (1.4)	1.7	0.1–49.8
Thrombocyte (×1000/mm^3)	3868	99.6	305.6 (130.4)	286	72–1235
Mean platelet volume (fL)	3862	99.5	8.5 (3.5)	8.2	0.5–8.9

[a] Missing cases are not separately demonstrated

[b] Four different types of social security as in effect

[c] Global quality of life score of EORTC-QLQ-C30

[d] Cycle of chemotherapy of the current protocol

[e] Number of drugs in the current protocol

[f] Baseline febrile neutropenia risk associated with the protocol on an ordinary scale (<10 %, between 10 and 20 %, >20 %)

[g] CSF usage before a specific cycle

[h] Dose reduction on a specific protocol before a specific cycle

development of febrile neutropenia compared with subsequent cycles [17, 18]. The reduced risk of febrile neutropenia after subsequent cycles might be because the nadir of blood counts and clinical characteristics of a patient while on chemotherapy give the clinician extra time and opportunity to lessen the risk, such as by decreasing the chemotherapy drug dosages and/or starting CSF. For example, current guidelines suggest the use of CSF as a secondary prophylaxis in patients who develop febrile neutropenia on the same or equitoxic chemotherapy protocol, taking into consideration a patient's previous tolerance to chemotherapy [2, 7]. Thus, a history of febrile neutropenia in a patient is a widely recognized risk

Table 2 Selected characteristics of the external validation cohort

Factors	Number[a]	Percent	Mean (SD)	Median	Min-Max
Patients	960				
Cycles	1444	100			
Age			55.4 (12.2)	56	21–85
Type of cancer					
Breast or colon cancer	1078	74.7			
Lung cancer	366	25.3			
Center					
Akdeniz University Hospital	640	44.3			
Antalya Research and Training Hospital	171	11.8			
Konya Meram University Hospital	484	33.5			
Isparta University Hospital	149	10.3			
Number of sum of cycles of chemotherapy over all lines			10 (10.5)	6	1–66
Cycle of chemotherapy on the current protocol[b]			4.7 (4.8)	3	1–56
Colony-stimulating factor (CSF) usage[c]					
Yes	251	17.4			
No	1193	82.6			
Previous history of febrile neutropenia					
Yes	91	6.3			
No	1353	93.7			
Febrile neutropenia during study period					
Yes	18	1.2			
No	1426	98.8			
Lymphocyte (×1000/mm^3)			1.7 (0.8)	1.6	0–6.6

[a] Missing cases are not separately demonstrated

[b] Cycle of chemotherapy of the current protocol

[C] CSF usage before a specific cycle

factor for the development of other febrile neutropenia episodes and was also the most significant factor associated with febrile neutropenia in our analysis.

In our model, a higher baseline lymphocyte count appears to be protective against febrile neutropenia. We believe that higher lymphocyte counts may reflect higher resistance to infection, as these patients may have the potential to activate their humoral or cellular immunity more readily. The precise role of lymphocytes in the development of febrile neutropenia remains to be determined. Interestingly, it has also been demonstrated that baseline or fifth-day lymphocyte counts independently predict the risk of febrile neutropenia [15, 16]. In addition, we found that lung cancer patients had a higher rate of developing febrile neutropenia than breast and colorectal cancer patients. This may be related to the more aggressive nature of this disease, as reflected by poorer survival figures in advanced disease, and/or the more toxic nature of some of the chemotherapy protocols used in our cohort.

We had enriched our model with an additional variable: patient age. Clinicians are aware of the fact that myelosuppression is more common in the elderly cancer patient population. Indeed, this factor was significant in the univariate analysis, with a borderline significance in the multivariate analysis, as well. It is also well known that use of CSF decreases the risk of febrile neutropenia [7, 19]. Numerous analyses have estimated the protective effect of CSF to be around 50 %. In our study, CSF usage was also associated with a reduced risk of febrile neutropenia, although this was not statistically significant. This statistical nonsignificance may stem from the fact that CSF use for prophylaxis was already more frequent in our cohort than expected.

One shortcoming in our study is the low prevalence of febrile neutropenia episodes in the derivation and validation cohorts: 1.5 and 1.2 %, respectively, of the chemotherapy cycles administered. Secondly, the rate of CSF use prior to a cycle, either for primary or secondary prophylaxis, appears to be high in both the derivation and validation cohorts: 25.6and 17.4 %, respectively. We believe that these two shortcomings reflect a highly cautious strategy to minimize the risk of febrile neutropenia. We showed the validity of our nomogram in patients with breast, lung, and colorectal cancers. However, using our nomogram in different patient populations with

Table 3 Predictors of febrile neutropenia in the derivation cohort by generalized estimating equations method

Factors	Univariate analysis			Multivariate analysis*,**		
Disease factors	β	χ^2	*P* value	β	χ^2	*P* value
Type of cancer						
Other vs. breast cancer	0.68	2.16	0.142			
Other vs. lung cancer	1.71	14.91	<0.001	1.15	7.20	0.007
Stage (1 to 3 vs. 4)	0.25	0.70	0.403			
Number of organ systems involved	0.33	9.00	0.003	0.11	0.66	0.418
Number of metastatic sites involved (≤3 vs. >3)	−0.33	1.28	0.257			
Disease status (no disease or progression vs. progression)	0.81	6.13	0.013	0.23	0.23	0.630
Patient factors						
Number of smoking pack years	0.01	9.83	0.002	0.01	0.60	0.439
Gender (male vs. female)	0.38	1.69	0.194			
Social security status[a]	0.49	0.09	0.763			
ECOG performance status	1.35	18.14	<0.001	0.01	0.01	0.981
Comorbidity						
Other vs. heart failure or coronary heart disease	−0.93	6.12	0.018	−0.15	0.09	0.769
Other vs. chronic obstructive pulmonary disease	−0.71	3.12	0.077	−0.32	3.40	0.065
Global quality of life[b]	−0.34	9.09	0.003	−0.30	1.96	0.161
Age	0.03	5.26	0.022	0.03	2.63	0.105
Treatment factors						
Place of chemotherapy administration (outpatient vs. inpatient)	0.36	0.50	0.481			
Previous radiotherapy (no vs. yes)	0.59	4.30	0.038	0.36	0.80	0.372
Number of lines of chemotherapy	0.02	0.03	0.862			
Number of sum of cycles of chemotherapy over all lines	0.04	2.05	0.152			
Cycle of chemotherapy on the current protocol[c]	−0.30	7.53	0.006	−0.48	11.28	0.001
Number of drugs in the protocol[d] (1, 2 vs. 3 or more drugs)	−0.77	5.25	0.022	−0.01	0.00	0.983
Baseline febrile neutropenia risk of the protocol[e]	0.36	0.65	0.723			
Colony-stimulating factor (CSF) usage[f] (yes vs. no)	0.70	7.07	0.008	0.05	0.02	0.897
Previous history of febrile neutropenia (yes vs. no)	4.78	150.22	<0.001	5.10	124.04	<0.001
Dose reduction[g] (no vs. yes)	0.20	0.22	0.640			
Laboratory factors[h]						
LDH	1.11	2.54	0.111			
Creatinine	1.07	0.78	0.377			
ALT	0.18	0.09	0.764			
Albumin	−4.58	1.11	0.170			
CRP	0.35	2.90	0.089	−0.18	0.38	0.540
Hemoglobin	−0.84	0.50	0.479			
Monocyte	0.01	0.00	0.992			
Neutrophil	0.68	1.14	0.286			
Lymphocyte	−2.02	11.38	0.001	−2.22	5.80	0.016
Thrombocyte	−0.42	0.26	0.607			
Mean platelet volume	−1.13	2.33	0.127			

*Multivariate analysis conducted in 3227 cases, 655 cases not included due to missing data

**Multivariate analysis with six factors after excluding LDH and including 2 additional clinically significant variables

[a] Four different types of social security as in effect

[b] Global quality of life score of EORTC-QLQ-C30, although significant in the univariate analysis, not subjected to multivariate analysis as significant correlation with ECOG performance status exists

[c] Cycle of chemotherapy of the current protocol

[d] Number of drugs in the current protocol

[e] Baseline febrile neutropenia risk associated with the protocol on an ordinary scale (<10 %, between 10 and 20 %, >20 %), although not significant in the univariate analysis, subjected to multivariate analysis due to clinical significance

[f] CSF usage before a specific cycle

[g] Dose reduction on a specific protocol before a specific cycle

[h] All variables are log transformed in the analyses

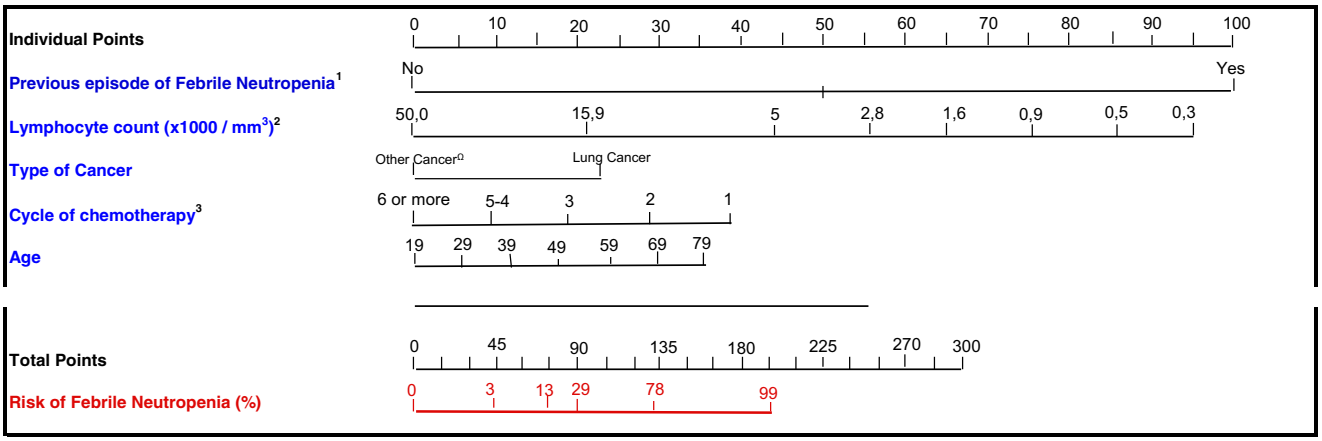

Fig. 1 Nomogram for the risk of febrile neutropenia after standard dose chemotherapy in common solid tumors. [1]Any episode of febrile neutropenia with the current protocol or a previous protocol; [2]based on precycle blood counts; [3]current cycle of chemotherapy with the present protocol; *omega* (Ω) symbol indicates breast or colorectal cancer. In order to calculate risk of febrile neutropenia, add up individual points (on the individual point line) to find total points (on the total point line) which correspond to a risk of febrile neutropenia (on the risk of febrile neutropenia line)

different cancers, or treated with different approaches or strategies, may yield slightly different results and could affect the generalizability of our findings. Thus, our results preferably need to be replicated by other investigators and in different settings.

It is to be kept in mind that the decision of growth factors was not guided in this study. Although this may be regarded as a limitation of the nomogram as it should also be a tool for guiding the decision to use or not growth factors, we used data on the use of growth factors as they are used in the real clinical life from four hospitals; thus, this approach to some extent reflects applicability to daily clinical routine.

Nomograms have been used in the field of oncology for many years [20, 21]. In the construction of our nomogram, we used the most recent methodology [22], and we believe that this is the first validated nomogram to estimate the risk of febrile neutropenia in three common cancers. The performance of the model underlying this nomogram and the potential to reduce the morbidity and mortality associated with febrile neutropenia make this model a candidate for clinical use at oncology clinics to estimate the risk of febrile neutropenia.

In short, we describe in this paper a prospectively validated model to estimate the risk of febrile neutropenia. Using this model, it may be possible to take additional preventive measures against the development of febrile neutropenia and consequently decrease the associated morbidity and mortality. Application of this nomogram in daily practice may help with the risk stratification and the prevention of febrile neutropenia. Thus, our nomogram deserves further validation by other groups.

Table 4 Efficacy of the model in the derivation and validation cohorts

Cohorts		Febrile neutropenia as observed		
		No	Yes	Total
Derivation				
Febrile neutropenia as predicted by the model (cutoff risk ≥0.15)	No	3017	13	3030
	Yes	84	41	125
	Total	3101	54	3155
	Sensitivity	76 %		
	Specificity	97 %		
	NPV	100 %		
	PPV	33 %		
Validation				
Febrile neutropenia as predicted by the model (cutoff risk ≥0.50)	No	691	0	691
	Yes	734	18	752
	Total	1425	18	1443
	Sensitivity	100 %		
	Specificity	49 %		
	NPV	100 %		
	PPV	2 %		

Performance of the model when different thresholds are used in the derivation and validation cohorts for the estimated risk of febrile neutropenia

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All named authors have read the manuscript, have agreed to the submission and have participated in the study to a sufficient extent to be named as authors.

Conflict of interest Authors do not have any conflict of interest to declare.

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