



Development of a simplified multivariable model to predict neutropenic complications in cancer patients undergoing chemotherapy

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Abstract

Purpose Neutropenic complications remain the major dose-limiting toxicities of cancer chemotherapy. The aim of this study was to develop and internally validate a comprehensive and easily measurable scoring system for prediction of severe or febrile neutropenia in the first chemotherapy cycle of patients with solid tumors or lymphoma.

Methods This prospective cohort study included consecutive patients at a tertiary referral hospital. Many clinical and laboratory-independent variables were measured at baseline. A multivariable logistic regression analysis was applied after unadjusted analysis, and the multivariable model was transformed into a simplified risk score based on 6 bootstrapped regression coefficients. The simplified scoring system was internally validated using cross-validation. All statistical tests were two-sided.

Results A total of 305 patients were enrolled and followed during 1732 chemotherapy cycles. Of these, 259 were eligible for analysis. The multivariable model revealed 6 predictive factors for severe or febrile neutropenia (scores in parentheses): high-risk regimen without colony-stimulating factor (4 points), intermediate-risk regimen without colony-stimulating factor (3 points), age > 65 years and elevated ferritin (3 points), body mass index < 23 kg/m² and body surface area < 2 m² (2 points), estimated glomerular filtration rate < 60 mL/min/1.73m² (2 points), and elevated C-reactive protein (1 point). The receiver operating characteristic curve was 0.832 (95% confidence interval [CI], 0.767–0.897) for the simplified model and 0.816 (95% CI, 0.771–0.860) for the cross-validation.

Conclusions We developed and internally validated a user-friendly prediction model to guide personalized decision-making using available clinical data and few cost-effective laboratory tests. External validation in other centers with different patients is required.

Keywords Cancer · Neutropenia · Febrile neutropenia · Clinical prediction rule · Chemotherapy

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Introduction

Chemotherapy-induced neutropenia continues to represent a serious and prevalent complication of many chemotherapy regimens, and it is often associated with hospitalization, treatment interruption, and dose reduction, which may compromise treatment outcomes [1–4].

Although granulocyte colony-stimulating factors (G-CSFs) have been shown to be prophylactically effective, they are expensive and associated with increased health-care costs [2]. Therefore, selective use of prophylactic G-CSFs in patients at high risk for neutropenic complications may optimize the health-care costs [5]. International clinical practice guidelines in oncology recommend prophylactic administration of a G-CSF if the risk of febrile neutropenia (FN) is 20% or higher [6–9]. Although these guidelines suggest FN risk calculation for each individual patient prior to chemotherapy and look

forward to find a user-friendly risk prediction tool, no such comprehensive and clinically usable model has yet been widely accepted [6]. Thus, it seems essential to develop of a comprehensive and simplified model for prediction of neutropenic events.

Some previous studies have attempted to develop prediction models for neutropenia-related complications [10–19]. In a systematic review [20], Lyman et al. summarized several patient-, treatment-, and disease-related risk factors for FN and discussed the limitations of developed models. The retrospective design, small sample size, and lack of validation were mentioned the main limitations. In this systematic review, older age, poor performance status, low baseline white blood cell counts, low body mass index (BMI) or body surface area (BSA), advanced disease, use of myelosuppressive chemotherapy regimens, and the presence of comorbidities such as renal or hepatic disorders were considered as major significant predictors for the neutropenic events. Furthermore, the value of inflammatory markers in prediction of chemotherapy-induced myelotoxicity has been shown [19, 21]. Alexandre et al. hypothesized that the stimulation of acute phase protein responses (APPR) could be responsible for increased severe hematologic toxicity of chemotherapy [21]. Moreover, in a prospective study, patients with evidence of inflammation at baseline were more susceptible to FN [19]. Consequently, they recommended the baseline assessment of inflammatory status before initiation of cytotoxic chemotherapy. In the light of these studies, in addition to the majority of well-known and previously identified risk factors, we used a panel of cost-effective laboratory markers as the possible predictors in our study.

A simplified scoring system based on regression coefficients of a final multivariable model can help us to develop a clinically applicable model [22, 23]. Concerns about the overuse and underuse of G-CSFs, as well as their related complications, led us to develop a simplified scoring system for a better individualized decision-making. Since the first episode of severe neutropenia (SN) or FN occurs most frequently in the first cycle of cytotoxic chemotherapy [13], our primary outcome was the occurrence of SN or FN as a composite endpoint in the first cycle of a new chemotherapy regimen. This model could be externally validated later in other centers for all standard chemotherapy regimens.

Methods

Study design and participants

We reported this study based on the TRIPOD and STROBE statements [23, 24]. The study design was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (approval number 93.11.22.164). Written informed consent was obtained from the patients.

Between February 2015 and March 2016, a total of 305 consecutive adult patients with solid tumors or lymphoma who were beginning a new chemotherapy line were prospectively included in this cohort study and followed until June 2016. Patients for whom the nadir (days 10–14 after start of treatment) complete blood count (CBC) in the first cycle was not documented were considered as lost to follow-up and were excluded from the analysis. A total of 259 patients receiving at least one cycle of chemotherapy in a tertiary referral medical center (Shohada-e-Tajrish Medical Center, Tehran, Iran) were considered for the complete-case analysis. Data regarding types of cancers and treatment regimens of this study are summarized in Supplementary Table 1 (Online Resource).

Outcome and predictors

Our primary endpoint as a composite outcome was the occurrence of SN or FN in the first cycle of chemotherapy. Some previously identified predictors in addition to a panel of cost-effective inflammatory markers were considered as the primary possible predictors for the outcome of interest. Twenty-three readily accessible laboratory covariates were evaluated at baseline (Supplementary Table 2, Online Resource). A total of 14 laboratory and clinical candidate predictors were assessed in unadjusted analysis (Table 1). Final selected predictors were assessed in adjusted analysis (Table 2). Further details regarding the predictors and outcome assessment are explained in the Supplementary Methods (Online Resource).

Statistical methods

A detailed report regarding the statistical methods used, predictor handling, selection procedure, collinearity and interaction terms, model development, validation, sample size, missing data, and risk groups is provided in the Supplementary Methods (Online Resource). Briefly, the univariable and multivariable logistic regression analyses were used. The model discrimination and calibration were assessed. To improve the model applicability, we transformed the multivariable model into a simplified scoring system. The simplified model was internally validated using fivefold cross-validation. The statistical analyses were performed using the IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). All statistical tests were two-sided.

Results

Participants

A total of 305 patients were prospectively included in this study and followed through 1732 cycles. Of these, 46

Table 1 Unadjusted association between the candidate predictors and the first cycle SN or FN

Predictor	% of patients with the predictor in each group		β coefficient (95% CI)	P	Risk ratio (95% CI)
	No SN or FN (<i>n</i> = 203)	SN or FN (<i>n</i> = 56)			
eGFR < 60 mL/min/1.73 m ²	10.8	44.6	1.89 (1.26–2.55)	< .001	3.63 (2.48–4.74)
FN risk group					
High risk	25.6	25.0	0.71 (–0.20–1.69)	.097	1.82 (0.88–3.30)
Intermediate risk	29.6	53.6	1.33 (0.60–2.20)	< .001	2.86 (1.64–4.41)
No G-CSF use	74.9	98.2	18.45 (1.64–20.39)	.004	13.85 (2.42–38.20)
BMI < 23 kg/m ²	15.8	41.1	1.31 (0.67–2.00)	< .001	2.58 (1.67–3.59)
Elevated ferritin ^a	9.9	28.6	1.29 (0.56–2.07)	.001	2.47 (1.53–3.49)
Elevated CRP ^b	36.0	53.6	0.72 (0.11–1.32)	.018	1.74 (1.10–2.56)
BSA < 2 m ²	87.2	94.6	0.95 (–0.13–20.00)	.130	2.22 (0.77–4.90)
Age > 65 years	19.2	32.1	0.68 (–0.014–1.34)	.041	1.67 (1.01–2.50)
Elevated haptoglobin ^c	17.2	25.0	0.47 (–0.41–1.14)	.192	1.42 (0.82–2.23)
Total bilirubin > 1 mg/dL	13.8	19.6	0.42 (–0.48–1.17)	.281	1.37 (0.74–2.30)
Hemoglobin < 11 g/dL	14.8	19.6	0.34 (–0.55–1.07)	.381	1.29 (0.70–2.13)
Neutrophil count < 3.1 billion cells/L	14.3	10.7	–0.31 (–1.61–0.46)	.515	0.77 (0.33–1.56)
Lymphocyte count < 0.800 billion cells/L	6.4	7.1	0.13 (–1.5–1.2)	.820	1.1 (0.40–2.30)
Previous CTX/RT	10.8	12.5	0.16 (–0.96–1.06)	.727	1.12 (0.53–2.06)

Abbreviations: *SN*, severe neutropenia; *FN*, febrile neutropenia; *CI*, confidence interval; *G-CSF*, granulocyte-colony stimulating factor; *eGFR*, estimated glomerular filtration rate; *BMI*, body mass index; *BSA*, body surface area; *CRP*, C-reactive protein; *CTX*, chemotherapy; *RT*, radiotherapy

^a Elevated ferritin was defined as serum ferritin level greater than 200 and 300 ng/mL in women and men, respectively

^b Elevated CRP was defined as CRP level greater than 6 mg/L

^c Elevated haptoglobin was defined as haptoglobin level greater than 200 mg/dL

were considered lost to follow-up and were excluded from the regression analyses. The median number of chemotherapy cycles was 6 (range, 1–16). The patient flow diagram is shown in Supplementary Fig. 1 (Online Resource).

Thirty-two patients developed at least one episode of FN during all cycles of chemotherapy. Results showed that 51% of the first FN events occurred in the first cycle. Of 259 eligible patients, 56 (21.6%) experienced severe

Table 2 Adjusted association between the final predictors and the first cycle SN or FN

Predictor	% of patients with the predictor in each group		β coefficient (BCa 95% CI)	Bootstrap P	Risk ratio (95% CI)	Score
	No SN or FN (<i>n</i> = 203)	SN or FN (<i>n</i> = 56)				
FN risk group × no G-CSF use						
High risk × no G-CSF use	4.4	25.0	4.12 (2.41–7.70)	.001	7.67 (5.68–8.37)	4
Intermediate risk × no G-CSF use	25.6	51.8	3.08 (1.85–6.44)	.001	6.38 (4.16–7.73)	3
Age > 65 (years) × elevated ferritin ^a	1.0	10.7	3.63 (0.99–26.66)	.001	4.54 (2.60–4.96)	3
eGFR < 60 mL/min/1.73m ²	10.8	44.6	2.66 (1.33–5.21)	.001	4.86 (3.20–5.97)	2
BMI < 23 kg/m ² × BSA < 2 m ²	15.3	41.1	1.92 (0.74–3.92)	.001	3.53 (2.10–4.80)	2
Elevated CRP ^b	36.0	53.6	1.15 (0.16–2.41)	.003	2.32 (1.26–3.60)	1

Intercept = – 5.09

Abbreviations: *SN*, severe neutropenia; *FN*, febrile neutropenia; *BCa*, bias corrected accelerated; *CI*, confidence interval; *G-CSF*, granulocyte-colony stimulating factor; *eGFR*, estimated glomerular filtration rate; *BMI*, body mass index; *BSA*, body surface area; *CRP*, C-reactive protein

^a Elevated ferritin was defined as serum ferritin level greater than 200 and 300 ng/mL in women and men, respectively

^b Elevated CRP was defined as CRP level greater than 6 mg/L

Table 3 Baseline characteristics of patients included in regression analysis

Characteristic	No SN or FN (<i>n</i> = 203)	SN or FN (<i>n</i> = 56)	<i>P</i>
	No. (%)		
Sex			.048
Male	72 (35.5)	28 (50.0)	
Female	131 (64.5)	28 (50.0)	
Tumor type			< .001
Breast cancer	86 (42.4)	14 (25.0)	
GI cancers	50 (24.6)	9 (16.0)	
Bladder cancer	13 (6.4)	7 (12.5)	
Testicular cancer	8 (3.9)	7 (12.5)	
Sarcomas	6 (3.0)	7 (12.5)	
Other cancers	40 (19.7)	12 (21.5)	
FN risk group			.001
Low risk	91 (44.8)	12 (21.4)	
Intermediate risk	60 (29.6)	30 (53.6)	
High risk	52 (25.6)	14 (25.0)	
	Mean (SE)		
Age, years	51.9 (0.8)	54.5 (2.3)	.104
Weight, kg	72.1 (1)	64.5 (1.7)	< .001
BSA, m ²	1.74 (0.01)	1.68 (0.02)	.034
BMI, kg/m ²	28.2 (0.4)	24.6 (0.6)	< .001
eGFR, mL/min/1.73 m ²	74.7 (0.9)	66.4 (2.3)	< .001
Ferritin, ng/mL	116 (10)	196 (31)	.047
CRP, mg/L	12.9 (1.7)	24.6 (5.3)	.003
Haptoglobin, mg/dL	126 (5)	159 (12)	.015
Neutrophil count, billion cells/L	4.93 (0.17)	5.37 (0.36)	.357
Lymphocyte count, billion cells/L	1.76 (0.05)	1.61 (0.07)	.266
Hemoglobin, g/dL	12.4 (0.1)	12.1 (0.2)	.524
Total bilirubin, mg/dL	0.7 (0.02)	0.8 (0.07)	.449

Abbreviations: *SE*, standard error; *SN*, severe neutropenia; *FN*, febrile neutropenia; *GI*, gastrointestinal; *BSA*, body surface area; *BMI*, body mass index; *eGFR*, estimated glomerular filtration rate; *CRP*, C-reactive protein

or febrile neutropenia in the first chemotherapy cycle. Patients' characteristics are summarized in Table 3.

Model development and specification

The predictor selection procedure is shown in Supplementary Fig. 1 (Online Resource). Unadjusted associations between 14 candidate predictors and the outcome are indicated in Table 1. The components and characteristics of the adjusted model (e.g., the regression coefficients, bootstrap *P* values, risk ratios, and scores of the predictors) are summarized in Table 2. After bootstrapping, the model was transformed into a clinically usable scoring system. Based on the point score of each predictor (Table 2), a total risk score was calculated for each patient. Although the total score of the patients in this study ranged between 0 and 8, the maximum possible score in the scoring system was 12. Patients with a total risk score of ≥ 4 were expected to experience the outcome. By using this cutoff

score, we predicted a group of patients with a high probability of SN or FN occurrence, for whom the prophylactic G-CSF could be considered. Figure 1 demonstrates a relation between the risk score and percent of the event in each score. Three clinical examples indicating how to use the simplified model are presented in Supplementary Table 3 (Online Resource). In total, 181 patients had a risk score of less than 4 points. Of these, only 10 patients (5.5%) experienced the outcome. In contrast, among 78 patients identified as being at high risk for the neutropenic events (using a cutoff score of ≥ 4 points), a total of 46 (58.9%) experienced the outcome.

Model performance

The final bootstrapped model was well calibrated (Hosmer-Lemeshow *p* = .708, Supplementary Table 4, Online Resource). A cutoff probability of 0.18 for the full model and a cutoff score of 4 points for the simplified model provided the optimal

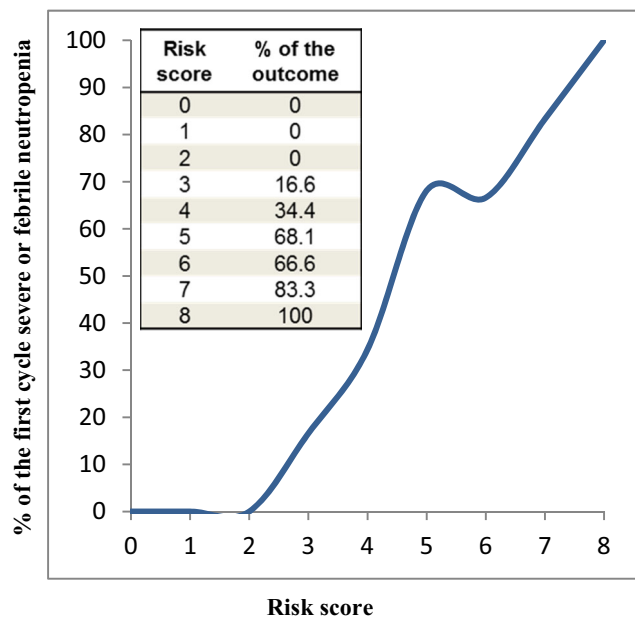


Fig. 1 Relation between risk score and percent of the first cycle severe or febrile neutropenia in each score

sensitivity and specificity on the basis of the receiver operating characteristic (ROC) curve. As indicated in Fig. 2, the full model and simplified model had the area under the ROC curve of 0.845 (95% confidence interval [CI], 0.788–0.903) and 0.832 (95% CI, 0.767–0.897), respectively. The simplified model retained the ability to predict the outcome as excellently as the full model (the ROCs between 0.8 and 0.9 are considered excellent

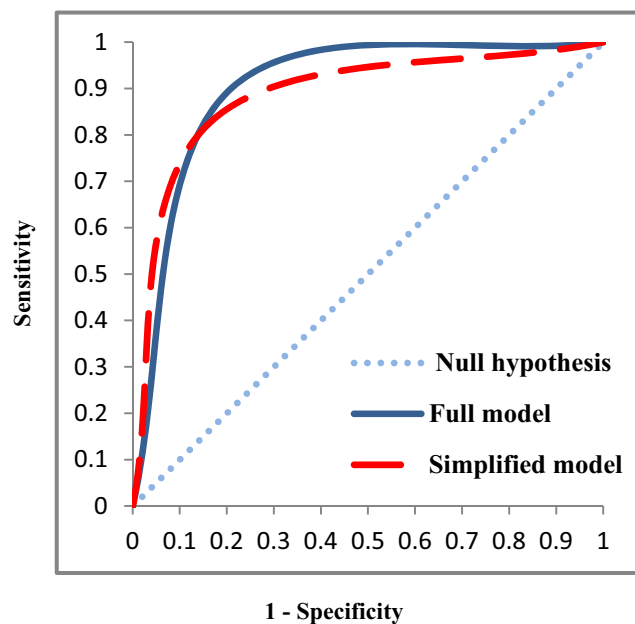


Fig. 2 Receiver operating characteristic (ROC) curve of the outcome predicted group for the full model and simplified model. The straight line shows the relation between sensitivity and 1-specificity under the null hypothesis of no discrimination. The area under the ROC curve was 0.845 (95% confidence interval [CI], 0.788–0.903) and 0.832 (95% CI, 0.767–0.897) for the full model and simplified model, respectively

discrimination) [25]. The scoring system had the sensitivity of 82.1%, specificity of 84.2%, positive predictive value (PPV) of 58.9%, and negative predictive value (NPV) of 94.5%. The simplified model was internally validated by cross-validation. The area under the ROC curve for the cross-validation was 0.816 (95% CI, 0.771–0.860).

Discussion

Interpretation

Multivariable model

Development of a unique, comprehensive, and clinically usable model to predict the chemotherapy-induced neutropenic complications in patients with different tumor types is highly recommended [6]. Lyman et al. have developed an adjusted model based on some laboratory and clinical predictors [13]. However, this model has not been simplified for clinical decision-making. By “simplified model or scoring system,” we mean a simplified format of the underlying regression model to ease its use in practice [22]. As stated in the Supplementary Methods (Online Resource), this simplification could be done, for example, by transforming (such as rounding) the regression coefficients of predictors included in the final model to easy-to-sum integers which are then associated with outcome. It should be noted that a simple unadjusted analysis based on the baseline values and significant differences indicated in Table 3 is not adequate to predict the risk in place of the model. All final predictors in the model have been adjusted for the other independent variables. In fact, adjusted regression coefficients of a multivariable model would provide an improved estimation of the risk. In a prospective study, López-Pousa et al. presented a prediction model for the first cycle chemotherapy-induced neutropenia in patients with different solid tumors [15]. In another study of patients with non-Hodgkin lymphoma, a multivariable model was also developed by Pettengell et al. for the first cycle FN occurrence [17]. The PPVs of these two models were markedly lower (17% for López-Pousa et al.’s model and 28% for Pettengell et al.’s model) compared with that of ours (i.e., 58.9%) in patients either with solid tumors or lymphoma. The low PPV of these models denotes that they classified many patients as high risk, while they did not actually develop the event. Furthermore, using genetic factors in addition to patient-related and chemotherapy-related risk factors, Pfeil et al. developed a multivariable prediction model for FN occurrence in early breast cancer patients receiving chemotherapy [11]. Nevertheless, overall predictive ability of the model remained poor even after including some genetic factors in the model.

There are only few studies which have developed a simplified risk score for prediction of neutropenic complications in patients with different tumor types. In a SEER-based study,

Hosmer et al. developed a simplified risk score to predict the first cycle occurrence of FN in elderly patients with breast, lung, colorectal, and prostate cancer [14]. Of note, the model sensitivity and PPV were considerably low (24 and 12%, respectively). In another study of 266 patients with hematologic malignancies, Moreau et al. developed a general myelotoxicity score to predict the occurrence of FN [16]. A score (0–4) was assigned to each drug according to its expected rate of SN. The major characteristics of the mentioned models are summarized in Table 4.

Predictors

The use of some certain myelosuppressive agents or regimens has been known as a key independent predictor for the neutropenic events in prior studies [13, 16, 26]. However, it is not possible to include all myelosuppressive regimens as separate covariates in a single model. One of the ideal predictors, which could be included in a multivariable prediction model, is the FN risk category of chemotherapy regimens. We demonstrated that the interaction between the risk group of regimens and prophylactic G-CSF use could be considered as a highly potent and significant independent predictor for the occurrence of FN or SN. This sensible interaction was surprisingly ignored in the previous prediction models. Thus, the inclusion of this novel potent predictor into the prediction model could result in a reduced omitted-variable bias in our study compared to prior studies. Moreover, since the FN risk category is not specific to particular chemotherapy regimens, it can be simply used in the future even with the emergence of new chemotherapy regimens.

Previous studies have indicated that low BMI or low BSA is associated with an increased risk of neutropenic events [12, 16, 27, 28]. In the study performed by Pettengell et al., a higher weight was also found to have a protective role against developing FN in the first cycle of the treatment [17]. Capping the dose in obese patients and using the ideal body weight in dose calculation may explain these associations [29, 30]. In fact, reducing the total dose or using idealized body weight (i.e., expected weight of a healthy normal person calculated

based on age, sex, and height) rather than actual body weight in chemotherapy dose calculation could lead to reduced toxicity. In addition, the altered pharmacokinetics of some cytotoxic drugs in overweight patients may be another explanation [30, 31]. Thus, further pharmacokinetics research is recommended [30]. When the rational interactions were assessed in this study, the interaction between BMI ($< 23 \text{ kg/m}^2$) and BSA ($< 2 \text{ m}^2$) was found to be a stronger and more significant predictor for the outcome than any individual variable.

The association between renal disease as a chronic comorbidity and neutropenic complications is widely reported [13, 32–34]. In an adjusted analysis by Hurria et al., a creatinine clearance $< 50 \text{ mL/min}$ estimated by the Cockcroft-Gault equation was associated with an increased risk of FN in older breast cancer patients receiving adjuvant chemotherapy [34]. Moreover, in agreement with our study, Lyman et al. also found a significant association between estimated glomerular filtration rate (eGFR) as a continuous variable and first cycle SN or FN in an adjusted analysis [13]. To generate an easily measurable risk score, we used the eGFR as a dichotomous variable (i.e., the $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$). In patients with renal disorders, metabolism and excretion of a drug might be altered even if the drug is eliminated by non-renal transport and metabolism [35]. Additionally, increased toxicity as a result of drug accumulation may be related to altered plasma protein binding and distribution volume of the drug [36].

Consistent with this study, some previous reports have indicated that higher levels of serum ferritin and C-reactive protein (CRP) were associated with an increased risk of infection or FN after either chemotherapy or allogeneic hematopoietic cell transplantation [37–39]. Moreover, in a non-homogenous population of patients with advanced cancers, Alexandre et al. indicated that an elevated inflammatory status is correlated with increased risk of chemotherapy-induced severe hematologic toxicity [21]. Possible explanations for this association are reduced cytochrome P450 3A (CYP 3A) activity and consequently overexposure to any substrate of CYP 3A, bone marrow sensitivity to a given exposure, and also increased cytotoxicity of chemotherapy-induced DNA damage in the case of APPR stimulation [21]. In a pharmacokinetic study by Alexandre et al.,

Table 4 Comparison between the performance characteristics of different prediction models

Study	Outcome	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cancer type
Lyman et al. [13]	SN or FN in cycle 1	90	58.9	34.2	96.1	Solid tumors and lymphoma
Lopez-Pousa et al. [15]	Neutropenia \geq grade 3 in cycle 1	63	67	17	94	Solid tumors
Pettengell et al. [17]	FN in cycle 1	81	80	28	98	Non-Hodgkin lymphoma
Pfeil et al. [11]	FN	61.3	61.3	23.8	88.9	Breast cancer
Moreau et al. [16]	FN	78.6	62.3	42.7	89.1	Hematologic cancers
Hosmer et al. [14]	FN in cycle 1	24	93	12	97	Elderly patients with solid tumors
Our study	SN or FN in cycle 1	82.1	84.2	58.9	94.5	Solid tumors and lymphoma

Abbreviations: *PPV*, positive predictive value; *NPV*, negative predictive value; *SN*, severe neutropenia; *FN*, febrile neutropenia

ferritin plasma concentration was correlated with increased concentration of midazolam, representing a reduced CYP 3A activity [19]. Although elevated ferritin was found to be an independent prediction factor in our study, a stronger relationship was identified for its interaction with age > 65 years. Of note, in spite of highly significant *p* value, the fairly wide range of CI for the relative risk of this interaction should be considered. This uncertainty may be related to the low exposure rate of this combined variable (approximately 10 and 1% in patients with and without the outcome, respectively). However, further investigation is warranted to validate this potent interaction and also to clarify the rationale behind it.

Our reason for not considering the performance status as a candidate predictor of the event in spite of prior promising evidences was its subjective nature and bias associated with inter-observer variability [40].

Limitations

The lack of external validation is the main limitation. Furthermore, although we included patients with different geographic characteristics and a wide range of tumor types referred from across the country, we declare that no single population is completely representative of the entire population. Thus, external validation in other centers with different patients is necessary before implementing this prediction rule in clinical practice. Moreover, we emphasize that the number of events in our study is fairly small. Of note, the reported CIs are relatively wide, and thus, results should be interpreted with caution. In addition, the systematic error related to the estimation of eGFR should be mentioned as another limitation.

Implications

All clinical and laboratory parameters included in this model are readily available and easily measurable in clinical setting. After external validation in a large population of patients across different centers and geographical locations, this scoring system might be easily used in clinical practice for better stratifying patients at higher risk of neutropenic complications and those who might benefit from prophylactic G-CSF administration. We declare that this fairly small study should be considered as a pilot study and further research with a sufficiently large sample size is required to be sure for clinical applicability of the model as a risk score.

Conclusions

We developed an internally validated scoring system based on few readily accessible and easily assessable predictors to define a group of patients who are at high risk of neutropenic complications. This clinical prediction rule may rationalize the

use of myeloid growth factors, minimize the health-care costs, and maximize the patients' quality of life. However, before using this prediction rule in clinical practice, it should be prospectively tested and/or updated in other centers with different patients to assess its generalizability and external validity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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