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Article

ARTICLE

Development and Validation of a Risk Score for Febrile Neutropenia After Chemotherapy in Patients With Cancer: The FENCE Score

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Abstract

Background: Febrile neutropenia (FN) after chemotherapy causes a high burden of morbidity and mortality. We aimed to develop and validate a risk score to predict FN in the first cycle of chemotherapy.
Methods: We included patients with solid cancers and diffuse large B-cell lymphomas at Rigshospitalet, University of Copenhagen, 2010-2016. Predictors of FN were analyzed using Poisson regression and random split-sampling.
Results: Among 6294 patients in the derivation cohort, 360 developed FN. Female sex, older age, cancer type, disease stage, low albumin, elevated bilirubin, low creatinine clearance, infection before chemotherapy, and number of and type of chemotherapy drugs predicted FN. Compared with those at low risk (n = 2520, 40.0%), the incidence rate ratio of developing FN was 4.8 (95% confidence interval [CI] = 2.9 to 8.1), 8.7 (95% CI = 5.3 to 14.1) and 24.0 (95% CI = 15.2 to 38.0) in the intermediate (n = 1294, 20.6%), high (n = 1249, 19.8%) and very high (n = 1231, 19.6%) risk groups, respectively, corresponding to a number needed to treat with granulocyte colony-stimulating factors to avoid one FN event in the first cycle of 284, 60, 34 and 14. The discriminatory ability (Harrell's C-statistic = 0.80, 95% CI = 0.78 to 0.82) was similar in the validation cohort (n = 3163) (0.79, 95% CI = 0.75 to 0.82).
Conclusion: We developed and internally validated a risk score for FN in the first cycle of chemotherapy. The FENCE score is available online and provides good differentiation of risk groups.

Febrile neutropenia (FN) is a common complication of chemotherapy associated with a high burden of morbidity and mortality (1). Supportive care measures like treatment with granulocyte colony-stimulating factors (G-CSF) and prophylactic antibiotics can potentially lessen the burden of morbidity and mortality if patients are correctly stratified according to risk of FN (2–4). To minimize the incidence of FN and the associated morbidity, clinical guidelines emphasize the benefit of models that predict FN (5) but also recognize that there is no "consensus nomogram" (6) and do not provide guidance on how to weigh different risk factors when assessing the risk of FN (5–7).

Currently, guidelines recommend prophylactic G-CSF if the risk of FN is more than 20% for a chemotherapy regimen. If the risk is less than 20%, prophylactic G-CSF is recommended in the presence of risk factors. However, the guidelines rely on data from randomized clinical trials, where FN rates are inconsistently reported (8,9). Further, FN rates are higher in observational studies (10) where the patients better resemble the general cancer population.

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Moreover, it is not established how to assess the risk of FN during an entire chemotherapy course. More than one-half of the patients who develop FN do so in the first cycle (11), which will often affect timing and dosing of chemotherapy and prophylactic measures in the following cycles. We therefore found it rational to predict FN during the first cycle (12–14).

Our aim was to develop a model to predict FN in the first cycle of chemotherapy based on pre-therapy risk factors in consecutive treatment-naïve patients with solid cancers or diffuse large B-cell lymphomas (DLBCL). This personalized medicine approach aims to provide clinicians with a tool that potentially can be used to optimize the prescription of G-CSF, prophylactic antibiotics, and intensity of patient monitoring to benefit patients, healthcare systems, and society.

Methods

Study Design and Patient Selection

We assessed all initial visits of patients with solid cancers or DLBCL at the Departments of Oncology and Haematology at Rigshospitalet, University of Copenhagen, to perform a cohort study of consecutive treatment-naïve patients. The patients initiated cycle one of chemotherapy from January 1, 2010 to November 30, 2016 with last follow-up on December 31, 2016.

To be eligible for the study, patients had to be treated with standard first-line chemotherapy. We excluded patients with temporary civil registration numbers, patients registered as initiating two different chemotherapy regimens simultaneously, and patients with stem cell transplantations.

Baseline was defined as the first date of chemotherapy. Patients were followed to the earlier of 1) FN, 2) death, 3) a new cancer diagnosis, 4) change to a different chemotherapy regimen, or 5) end of follow-up (defined as the earlier of end of the first cycle [Supplementary Methods, available online], loss to follow-up, emigration, or December 31, 2016).

The study was approved by the Danish Data Protection Agency (2012-58-0004; RH-2016-47; 04433) and the Danish National Board of Health (3-3013-1060/1/).

Primary Outcome

FN was defined as a blood culture (regardless of whether it was positive or negative) or death within three days of a neutrophil count less than 0.5×10^9/L. Data on temperature measurements were not routinely available before 2014 and were available for only the Capital Region of Denmark; hence, a blood culture was used as a measure of clinical suspicion of infection. If a leukocyte count without neutrophil count was measured, a leukocyte count less than or equal to 2.0×10^9/L was used as a proxy for neutropenia less than 0.5×10^9/L (sensitivity 84%, specificity 94%, Supplementary Figure 1, available online).

In a sensitivity analysis, we used the more narrow definition of FN: fever of at least 38 degrees Celsius within three days of a neutrophil count less than 0.5×10^9/L.

Data Sources, Risk Factors, and Definitions

Data were retrieved from the Centre of Excellence for Personalised Medicine for Infectious Complications in Immune Deficiency data repository of electronic health records, containing nationwide data on biochemistry and microbiology (Supplementary Methods, available online). Furthermore, we used the Danish Lymphoma Registry (15), the National Patient Registry (16), and the Civil Registration System (17). Patients were linked across data sources using the 10-digit unique civil registration number given to all Danish citizens.

We assessed a wide range of patient-, cancer-, and treatment-related risk factors at baseline detailed in the Supplementary Methods (available online). G-CSF and antibacterial prophylaxis were provided according to the guidelines from the American Society of Clinical Oncology (6,18). All risk factors were fitted as categorical variables with a category for missing values if appropriate, and cutoffs were based on reference ranges (19) when possible and otherwise based on the literature (Supplementary Methods, available online).

Statistics

Patients were randomly split 2:1 into a derivation and a validation cohort, stratified on cancer type.

Model Derivation

Risk factors for FN were examined univariably using Poisson regression, and factors with P less than .1 were included in a multivariable model. Subsequently, the factors not included ($P \geq .1$) were added in turn one at a time to assess whether their inclusion improved model fit, either with a lower Akaike information criterion or a P less than .1. As a sensitivity analysis, Cox proportional hazard and Fine-Gray competing-risk regression models with death as a competing risk were investigated to test model robustness.

Using the best fitting multivariable Poisson model, coefficients were scaled by dividing all coefficients by the smallest coefficient greater than 0.01 and rounding to the nearest whole number for easily calculation. A FEbrile Neutropenia after ChEmotherapy (FENCE) score per individual was calculated based on their measured risk factors and the assigned weight from their scaled coefficients. Quintiles of the derived FENCE score were used to define five categories of risk. Because the lowest two quintiles both had a small absolute risk of FN, these were combined, leaving four risk groups; low, intermediate, high, and very high.

Model Validation

The FENCE score was tested in the validation cohort, and the discriminatory ability of the FENCE score model in the cohorts was assessed and compared with Harrell's C-statistic. FENCE score performance was further evaluated by comparison of the crude incidence rates and incidence rate ratios within FENCE score groups, and incidence rate ratios associated with a 10-point increase in the FENCE score.

Calculation of an Individual's Risk of Developing FN

The risk of developing FN can be calculated using the formula:

$$\text{Prob}(\text{FN in cycle one}) = 1 - \exp(t*(-\exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_n X_n))),$$

where t denotes time (i.e., length of cycle one in days), X_n denotes the risk factors, and β_n denotes the parameter coefficients from the Poisson regression model. The FENCE score and a tool to calculate risk of developing FN will be publicly available at https://www.chip.dk/Tools-Standards/Clinical-risk-scores.

Preventive Interventions

Prophylactic treatment with G-CSF and quinolones reduces the incidence of FN by approximately 50% (20) and 25% (21), respectively. We used these estimates for calculations of number needed to treat to avoid one FN event during 21 days. Patients treated with G-CSF were excluded when calculating numbers needed to treat for prophylactic G-CSF.

Sensitivity Analyses

To test the applicability of our definition of FN, we assessed the performance of the FENCE score in three scenarios: 1) using the narrow definition of FN (i.e., documented fever and neutropenia) in the period 2014 to 2016, 2) taking into account only the FN events that met the neutropenia criterion of the FN definition (i.e., not events with a leukocyte count lower than or equal to 2.0×10^9/L and missing neutrophil count), and 3) excluding the patients treated with G-CSF.

Results

We assessed 15 204 patients of whom 11 229 were eligible for the study because they initiated a first cycle of standard first-line chemotherapy. We excluded 251 patients with temporary civil registration numbers, 418 patients who were registered as initiating two different chemotherapy regimens at baseline, 5 patients with stem cell transplantations, and 3 patients who were registered as dead at baseline. Finally, patients treated with weekly cisplatin and concomitant radiotherapy (n = 1095) developed FN with a different time kinetic than other patients, only developing FN on days 30 to 40 after chemotherapy and not in a cycle-dependent manner as shown in Supplementary Figure 2 (available online). Hence, we excluded them.

We included 9457 patients with 24 types of solid cancers and DLBCL treated with 83 different chemotherapy regimens. The patients were randomly split into a derivation cohort (n = 6294) and a validation cohort (n = 3163). The random-split method provided a similar distribution of the risk factors (Supplementary Table 1, available online).

Derivation Cohort

Of the 6294 patients with a median age of 64 years (interquartile range [IQR] = 55–71 years), 3056 (48.6%) were female (Table 1). The most common cancer types were gastric (n = 866, 13.8%), colorectal (n = 802, 12.7%), breast (n = 773, 12.3%), and non–small cell lung cancer (n = 725, 11.5%). FN developed in 360/6294 (5.7%) patients. Ninety-four (1.5%) patients died during follow-up and 11 of these deaths met the FN definition. A total of 884 patients stopped chemotherapy after the first cycle. In univariate analyses female sex, older age, higher Charlson Comorbidity Index score, cancer type, disease stage, abnormal baseline hemoglobin, lymphocyte, platelet, albumin, bilirubin, alkaline phosphatase, lactate dehydrogenase, estimated glomerular filtration rate, and C-reactive protein counts, elevated neutrophil-to-lymphocyte ratio, infection before baseline (a blood culture sample was used as a proxy for infection), concurrent radiotherapy, treatment with three or four chemotherapy drugs as compared with one, and treatment with taxanes, vinca alkaloids, and prophylactic G-CSF were associated with an increased risk of FN (Supplementary Table 2, available online).

In the multivariable analysis, factors associated with an increased risk of FN were female sex; older than 65 years; cancer

Table 1. Characteristics of the patients in the derivation cohort (n = 6294) who developed febrile neutropenia in the first cycle of standard first-line chemotherapy and those who did not*

Characteristic	Developed FN No. or median (% or IQR)	Did not develop FN No. or median (% or IQR)
All	360 (100)	5934 (100)
Sex		
Male	162 (45.0)	3076 (51.8)
Female	198 (55.0)	2858 (48.2)
Age, y	66 (55 to 72)	64 (55 to 71)
Charlson Comorbidity Index	2 (2 to 3)	2 (2 to 3)
Cancer type		
Gastric	36 (10.0)	830 (14.0)
Brain	3 (0.8)	522 (8.8)
Head and neck	7 (1.9)	32 (0.5)
Oesophageal	12 (3.3)	282 (4.8)
Breast	37 (10.3)	736 (12.4)
Mesothelioma	8 (2.2)	322 (5.4)
Non–small cell lung	46 (12.8)	679 (11.4)
Small-cell lung	47 (13.1)	184 (3.1)
Colorectal	3 (0.8)	799 (13.5)
Ovarian	48 (13.3)	336 (5.7)
Cervical/endometrial	2 (0.6)	142 (2.4)
Bladder	5 (1.4)	194 (3.3)
Prostate	18 (5.0)	157 (2.6)
Testicular	30 (8.3)	191 (3.2)
Neuroendocrine	16 (4.4)	151 (2.5)
Lymphoma (DLBCL)	32 (8.9)	222 (3.7)
Other	10 (2.8)	155 (2.6)
Disease stage		
Adjuvant/Ann Arbor I	49 (13.6)	1281 (21.6)
Neoadjuvant or concomitant/ Ann Arbor II	56 (15.6)	1615 (27.2)
Locally advanced or disseminated/Ann Arbor III+	255 (70.8)	3038 (51.2)
Radiotherapy		
No previous radiotherapy	320 (88.9)	5330 (89.8)
Initiated 0–30 days before chemotherapy	15 (4.2)	137 (2.3)
Initiated 30–365 days before chemotherapy	10 (2.8)	254 (4.3)
Initiated >365 days before chemotherapy	15 (4.2)	213 (3.6)
Number of chemotherapy drugs		
1	120 (33.3)	1769 (29.8)
2	138 (38.3)	3170 (53.4)
3	94 (26.1)	934 (15.7)
4	8 (2.2)	61 (1.0)
Chemotherapy		
Platinums	257 (71.4)	4011 (67.6)
Non-platinum alkylating agents	73 (20.3)	1458 (24.6)
Taxanes	109 (30.3)	892 (15.0)
Topoisomerase inhibitors	121 (33.6)	1888 (31.8)
Antimetabolites	74 (20.6)	2052 (34.6)
Vinca alkaloids	44 (12.2)	390 (6.6)
Other chemotherapy	24 (6.7)	394 (6.6)
Prophylactic G-CSF	32 (8.9)	209 (3.5)

*FN = febrile neutropenia; DLBCL = diffuse large B-cell lymphomas; G-CSF = granulocyte colony-stimulating factors; IQR = interquartile range.

Table 2. Multivariable model for the FENCE score for febrile neutropenia in the derivation cohort (n = 6294)

		FENCE score model			
Characteristic	FN/total	Adjusted incidence rate ratio (IRR)	Exact coefficient	Coefficient to use in FENCE score calculation*	Example patient
Intercept†			−7.561		
Sex					
Male	162/3238	1	0	0	0
Female	198/3056	1.39 (1.06 to 1.81)	0.327	8	
Age, y					
<65	164/3250	1	0	0	
65–74	143/2181	1.42 (1.09 to 1.85)	0.351	9	9
≥75	53/863	1.17 (0.80 to 1.70)	0.154	4	
Cancer type					
Gastric	36/866	1	0	0	
Brain	3/525	0.41 (0.03 to 5.11)	−0.891	−22	
Head and neck	7/39	7.95 (3.19 to 19.79)	2.073	52	
Oesophageal	12/294	6.33 (1.91 to 20.93)	1.845	46	
Breast	37/773	3.58 (0.29 to 44.74)	1.276	32	
Mesothelioma	8/330	2.99 (0.87 to 10.25)	1.096	28	
Non–small-cell lung	46/725	6.49 (2.03 to 20.70)	1.870	47	
Small-cell lung	47/231	20.37 (6.81 to 60.90)	3.014	75	
Colorectal	3/802	0.41 (0.09 to 1.84)	−0.897	−23	
Ovarian	48/384	3.05 (1.11 to 8.43)	1.116	28	
Cervical/endometrial	2/144	0.27 (0.05 to 1.49)	−1.299	−33	
Bladder	5/199	3.18 (0.83 to 12.23)	1.156	29	
Prostate	18/175	1.28 (0.38 to 4.30)	0.244	6	6
Testicular	30/221	30.16 (9.78 to 93.07)	3.407	85	
Neuroendocrine	16/167	8.93 (2.66 to 29.95)	2.189	55	
Lymphoma (DLBCL)	32/254	1.32 (0.18 to 9.59)	0.281	7	
Other	10/165	1.49 (0.53 to 4.20)	0.398	10	
Disease stage					
Adjuvant/Ann Arbor I	49/1330	1	0	0	
Neoadjuvant or concomitant/Ann Arbor II	56/1671	0.65 (0.34 to 1.27)	−0.426	−11	
Locally advanced or disseminated/Ann Arbor III+	255/3293	1.31 (0.70 to 2.43)	0.267	7	7
Albumin‡,§					
<Normal	140/1554	1.51 (1.18 to 1.94)	0.413	10	10
Normal	167/3505	1	0	0	
>Normal	9/217	0.75 (0.38 to 1.48)	−0.284	−7	
Missing	44/1018	0.90 (0.54 to 1.51)	−0.104	−3	
Bilirubin‡					
<5 μmol/L	81/1253	1.04 (0.80 to 1.34)	0.035	1	
5–25 μmol/L	264/4883	1	0	0	0
>25 μmol/L	14/78	1.99 (1.13 to 3.50)	0.687	17	
Missing	1/80	0.31 (0.02 to 4.41)	−1.174	−29	
Estimated glomerular filtration rate (CKD-EPI) ‡					
≤60 mL/min	45/487	1.65 (1.14 to 2.39)	0.502	13	
60–90 mL/min	143/2602	1.19 (0.92 to 1.52)	0.170	4	4
≥90 mL/min	171/3161	1	0	0	
Missing	1/44	2.11 (0.15 to 29.93)	0.747	19	
C-reactive protein‡					
<10 mg/L	92/1592	1	0	0	0
≥10 mg/L	184/2490	1.07 (0.82 to 1.41)	0.072	2	
Missing	84/2212	0.70 (0.50 to 0.98)	−0.362	−9	
Infection before chemotherapy‡,‖					
No	290/5557	1	0	0	
Yes	70/737	1.51 (1.13 to 2.00)	0.409	10	10
Number of chemotherapy drugs					
1	120/1889	1	0	0	0
2	138/3308	1.46 (0.43 to 4.92)	0.376	10	
3	94/1028	6.59 (0.83 to 52.25)	1.886	47	
4	8/69	9.18 (0.65 to 129.47)	2.217	56	

(continued)

Table 2. (continued)

Characteristic	FN/total	FENCE score model: Adjusted incidence rate ratio (IRR)	FENCE score model: Exact coefficient	FENCE score model: Coefficient to use in FENCE score calculation*	FENCE score model: Example patient
Chemotherapy					
Platinums					
No	103/2026	1	0	0	0
Yes	257/4268	0.34 (0.09 to 1.28)	−1.073	−27	
Non-platinum alkylating agents					
No	287/4763	1	0	0	0
Yes	73/1531	0.94 (0.16 to 5.58)	−0.065	−2	
Taxanes					
No	251/5293	1	0	0	
Yes	109/1001	3.46 (1.11 to 10.81)	1.241	31	31
Topoisomerase inhibitors					
No	239/4285	1	0	0	0
Yes	121/2009	0.83 (0.24 to 2.87)	−0.189	−5	
Antimetabolites					
No	286/4168	1	0	0	0
Yes	74/2126	0.53 (0.14 to 2.03)	−0.627	−16	
Vinca alkaloids					
No	316/5860	1	0	0	0
Yes	44/434	0.85 (0.22 to 3.28)	−0.163	−4	
Other chemotherapy					
No	336/5876	1	0	0	0
Yes	24/418	0.14 (0.04 to 0.47)	−1.982	−50	

*For each risk factor, only one level contributes to a patient's risk of FN. For example, a 77-year-old patient gets 4 points for age. DLBCL = diffuse large B-cell lymphomas; FN = Febrile neutropenia; IRR = incidence rate ratio.
†Needed if exact risk is to be calculated.
‡Assessed closest to and up to 90 days before baseline.
§The reference range differs based on sex and age; see Supplementary Methods (available online).
‖A blood culture was used as a proxy for infection.

type; disease stage; low albumin; elevated bilirubin; low estimated glomerular filtration rate; infection before baseline; treatment with two, three, or four chemotherapy drugs compared with one; and receiving taxane chemotherapy (Table 2). Most patients treated with G-CSF had either testicular cancer or DLBCL (181/241, 75%), which caused collinearity for G-CSF and cancer type. Therefore, we could not include G-CSF in the model. Cox and Fine-Gray regression showed similar results (results not shown).

A bilirubin level below normal yielded the smallest coefficient greater than 0.01 and was used to scale the other coefficients listed in Table 2. Kaplan-Meier plots of FN according to risk groups are shown in Figure 1. Compared with those at low risk (n = 2520, 40.0%), the incidence rate ratio of developing FN was 4.8 (95% confidence interval [CI] = 2.9 to 8.1), 8.7 (95% CI = 5.3 to 14.1), and 24.0 (95% CI = 15.2 to 38.0) in the intermediate (n = 1294, 20.6%), high (n = 1249, 19.8%), and very high (n = 1231, 19.6%) risk groups. The discriminatory ability was good with a Harrell's C-statistic of 0.80 (95% CI = 0.78 to 0.82).

Validation Cohort

FN developed in 156/3163 (4.9%) patients. The FENCE score model showed similar discriminatory ability as assessed by Harrell's C-statistic in the validation cohort (0.79, 95% CI = 0.75 to 0.82) (Table 3). Crude incidence rates and incidence rate ratios increased across those with a low, intermediate, high, and very high risk of FN, and the incidence rate ratios associated with a 10-point increase in the FENCE score were similar in the two cohorts.

Calculation of an Individual's FENCE Score and Risk of Developing FN

Using Table 2, a 68-year-old (+9) patient with disseminated (+7) prostate (+6) cancer treated with docetaxel (+31), with an albumin of 32 g/L (+10), an eGFR of 80 mL/min (+4) and an infection (+10) two months before chemotherapy would get 77 points and be classified as very high risk. There was no contribution to the FENCE score calculation from the remaining risk factors because these were all in the reference groups. The risk of FN in cycle one would be:

$$\text{Prob}(FN\ in\ cycle\ one) = 1 - exp(21(days\ in\ cycle) * (-\exp(-7.561\ (intercept) + 0.351(age\ 65-74y) + 0.267(disseminated) + 0.244\ (prostate) + 1.241(docetaxel) + 0.413(albumin < normal) + 0.170\ (estimated\ glomerular\ filtration\ rate\ 60-90\ mL/min) + 0.409\ (infection\ before\ chemotherapy)))) = 21.4\%$$

Preventive Interventions

The number needed to treat to avoid one FN event during 21 days with G-CSF was 284, 60, 34, and 14 for the low, intermediate, high, and very high risk groups and 569, 120, 69, and 27 with prophylactic quinolones, respectively.

Sensitivity Analyses

In 2014 to 2016 there were 241 FN events in the two cohorts. There were documented temperatures of 38.0 degrees Celsius or

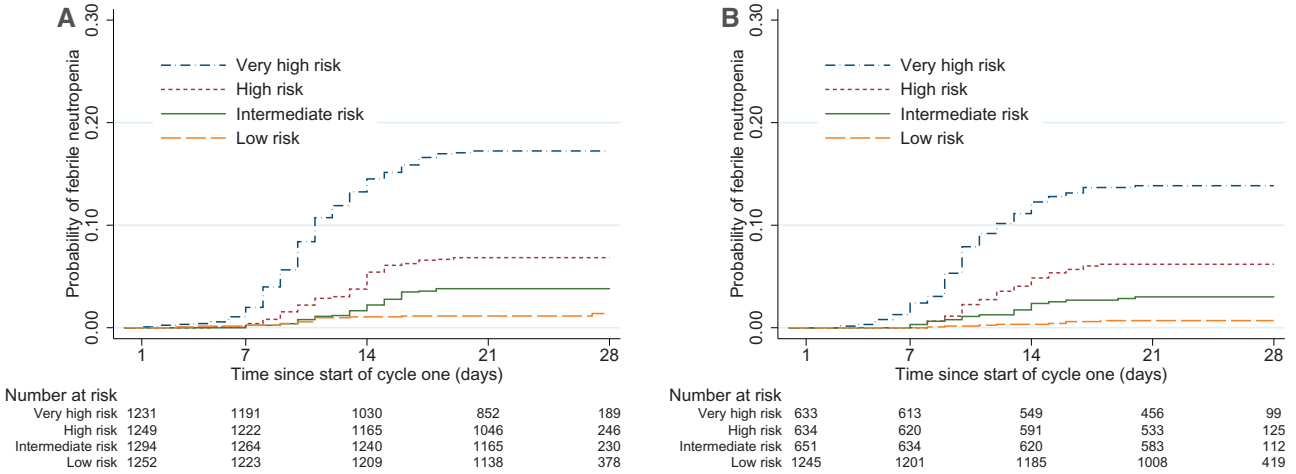

Figure 1. Kaplan-Meier plots of febrile neutropenia after chemotherapy according to FENCE risk groups in the **A)** derivation (n = 6294) and **B)** validation (n = 3163) cohorts.

higher in 179/202 (89%) patients with available temperature measurements. The narrow definition of FN identified 156 FN events, and 7 (4.5%) of these were not identified by the wider definition of FN. Using the narrow definition, the incidence rate was 0.17 (95% CI = 0.14 to 0.19) and the incidence rate ratios in the intermediate, high, and very high risk groups compared with the low risk group were 8.1 (95% CI = 3.0 to 21.3), 14.1 (95% CI = 5.5 to 36.1), and 39.1 (95% CI = 15.9 to 96.0), respectively. The discriminatory ability was similar with a Harrell's C-statistic of 0.81 (95% CI = 0.78 to 0.84).

In the derivation cohort, 39/360 (10.8%) FN events were identified using the leukocytes criterion because neutrophils were not measured. The discriminatory ability of the FENCE score was similar in analyses counting only the FN events that met the neutropenia criterion of the FN definition and in analyses excluding the 241 (3.8%) patients treated with G-CSF in the first cycle (results not shown).

Discussion

We have developed and internally validated a prediction model for FN with good discriminatory ability in both the derivation and validation cohorts. The study included more than 9000 consecutive treatment-naïve patients with solid cancers and DLBCL. We assessed risk factors that could potentially predict FN based on previous studies (22) and used a nonbiased approach to define cutoffs for risk factors and a systematic approach to risk factor selection in our model. We used a diverse population of patients with cancer representative for the general cancer population and data readily available for the clinician when initiating cycle one. This approach allowed us to stratify patients according to risk of FN based on a simple risk score. The FENCE score and the tool to calculate an individual's risk will be available online and can be incorporated into a clinical system allowing for instant calculation of a risk estimate of developing FN that can be used to guide prophylactic measures such as G-CSF, antibiotics, and intensity of patient monitoring.

The change in risk of FN associated with an individual risk factor can be exemplified by a patient with metastatic pancreatic cancer and no other risk factors for whom addition of a taxane to gemcitabine is considered. The risk of FN in cycle one would increase approximately 5-fold (incidence rate ratio ≈3.5 for taxane multiplied with incidence rate ratio ≈1.5 for two chemotherapy drugs instead of one) from 1.1% to 5.6%.

Personalized medicine like this is only possible if it is based on evidence of correct risk stratification from large cohort studies with high quality data. To transition to an era of precision medicine (23) we need to implement risk score models in clinical practice. Implementing even a simple electronic prescription tool in high risk chemotherapy regimens with a risk of FN more than 20% according to guidelines (ie, just reminding physicians to prescribe G-CSF) has been shown to increase correct use of prophylactic G-CSF and reduce the rate of FN (24). To further guide clinicians, we plan to develop a risk score model for FN in cycles two to six to allow for cycle-specific estimation of FN risk as guidelines recommend (5,6).

The previous studies addressing this issue have generally included fewer risk factors. The sufficiently powered studies often rely on administrative data and claims databases (12,14,25) and the few prospective studies (26–32) include fewer patients with inherent power issues restricting the number of included risk factors. The main exception is a prospective study by Lyman et al. (13) that included 3638 patients with breast, lung, colorectal, and ovarian cancer and lymphoma using split-sample methods to develop and validate a prediction model for a combined outcome of severe or FN in cycle one. Between previous studies, there is little overlap on included risk factors (33).

The pathophysiological importance of the risk factors for developing FN is not established. Evidently, a myelosuppressive chemotherapy regimen is required for FN to develop and preexisting myelosuppression appears to exacerbate this (13,14,22,33), but otherwise not much is known about the biological mechanisms responsible for the risk factors' associations with FN. The poor biological understanding of the risk factors and the small overlap in risk factors identified in this and other studies (12,13) call for studies using a systems biology approach to identify the biological pathways that lead to FN.

The major strength of this study was that we developed a risk score that is easily calculable with an online tool from a common set of risk factors available for patients with cancer that reliably predicted FN in the first cycle of chemotherapy. Another advantage was that we included unselected consecutive patients from the general cancer population and used data generated through routine care. Furthermore, we had access to nationwide data, which ensures almost complete ascertainment of outcomes.

Table 3. Performance of the FENCE score in the derivation and validation cohorts*

Variable	Derivation cohort	Validation cohort
Developed FN/No.	360/6294	156/3163
Incidence of FN per 100 PDFU (95% CI)	0.25 (0.23 to 0.28)	0.22 (0.19 to 0.25)
Risk score model		
Baseline score, median (IQR)	29 (-16 to 48)	30 (-15 to 48)
Baseline score for those who developed FN, median (IQR)	57 (42 to 70)	56 (43 to 70)
Patients with FN by risk score group, low/intermediate/high/very high	20/49/84/207	10/19/40/87
N by risk score group, low/intermediate/high/very high	2520/1294/1249/1231	1245/651/634/633
Incidence of FN per 100 PDFU (95% CI)		
Low risk (score ≤16)	0.03 (0.02 to 0.05)	0.03 (0.02 to 0.06)
Intermediate risk (score 17–35)	0.16 (0.12 to 0.22)	0.13 (0.08 to 0.20)
High risk (score 36–52)	0.29 (0.24 to 0.36)	0.27 (0.20 to 0.37)
Very high risk (score ≥53)	0.81 (0.71 to 0.93)	0.65 (0.53 to 0.81)
Incidence rate ratio (95% CI)		
Low risk (score ≤16)	1 (ref.)	1 (ref.)
Intermediate risk (score 17–35)	4.84 (2.88 to 8.14)	3.65 (1.70 to 7.86)
High risk (score 36–52)	8.68 (5.33 to 14.13)	7.86 (3.93 to 15.72)
Very high risk (score ≥53)	24.03 (15.18 to 38.02)	18.86 (9.80 to 36.3)
Incidence rate ratio per 10-point increase in score	1.49 (1.43 to 1.56)	1.44 (1.35 to 1.54)
Harrell's C-statistic	0.80 (0.78 to 0.82)	0.79 (0.75 to 0.82)

*IQR = interquartile range; PDFU = person-days of follow-up.

The inherent limitations of retrospective studies apply to this study with a few additional limitations. We used collection of a blood culture instead of a temperature measurement in our definition of FN, which does not conform with clinical guidelines (6,7). Therefore, confirmation of the results, preferably in a prospective cohort using a guideline-based definition, is needed. However, for the FN events with available temperature measurements, 89% had a documented fever and the discriminatory ability of the FENCE score was similar when we only analyzed FN events identified by the narrow definition (i.e., documented fever and neutropenia). Further, in our setting, blood cultures are collected only when there is fever or clinical suspicion of infection and not for routine surveillance in neutropenic patients.

Collinearity with cancer type hindered inclusion of data on prophylactic G-CSF in the multivariable model; however, only a small subset of patients (241/6294, 3.8%) received prophylactic G-CSF and when we excluded these patients the discriminatory ability of the FENCE score was similar. Another limitation was the lack of information on treatment with prophylactic antibiotics. However, prophylactic antibiotics are rarely used because they are not recommended except for patients anticipated to have neutrophils lower than 0.1×10^9/L for more than seven days (18). Immunomodulation by corticosteroids was also not ascertainable. Despite these limitations, we were able to build a model with good discriminatory ability in both cohorts, which indicates that the variation in risk of FN is well captured by the risk factors in the FENCE score.

In conclusion, we have developed a risk score that reliably predicts the risk of FN in the first cycle of chemotherapy and may be useful for personalizing patient management including prescription of G-CSF and prophylactic antibiotics and guidance for intensity of patient monitoring. Validation in external cohorts and prospective validation of the FENCE score with assessment of impact on rates of FN, mortality, and other patient-relevant outcomes is needed before a general recommendation of use of the FENCE score can be substantiated.

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