Development and validation of a cycle-specific risk score for febrile neutropenia during chemotherapy cycles 2-6 in patients with solid cancers: the ^{CSR}FENCE score

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Abbreviations

CI: confidence interval; CISNE: Clinical Index of Stable Febrile Neutropenia; ^{CSR}FENCE: Cycle-Specific Risk of FEbrile Neutropenia after ChEmotherapy; FENCE: FEbrile Neutropenia after ChEmotherapy; FN: febrile neutropenia; G-CSF: granulocyte colony-stimulating factors; IQR: interquartile range; MASCC: Multinational Association of Supportive Care in Cancer; NNT: number needed to treat

What's new?

Guidelines recommend assessing the risk of febrile neutropenia at the start of each cycle of a chemotherapy course. We followed a large cohort of patients with solid cancers treated with standard first-line chemotherapy through cycles 2-6. A risk score for predicting risk of febrile neutropenia at each cycle initiation was developed and internally validated. The score has good discriminatory ability and is the first published method to estimate cycle-specific risk of febrile neutropenia.

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Abstract

The absolute risk reduction by prophylaxis in chemotherapy-induced febrile neutropenia (FN) is largest in patients at highest underlying risk. Therefore, reliable predictive models are needed. Here, we develop and validate such a model for risk of FN during chemotherapy cycles 2-6. A prediction score for risk of FN during the first cycle has recently been published[1]. Patients with solid cancers initiating first-line chemotherapy in 2010-2016 were included. Cycle-specific risk factors were assessed by Poisson regression using generalised estimating equations and random split-sampling. The derivation cohort included 4,590 patients treated with 15,419 cycles, wherein 326 (2.1%) FN events occurred. Predictors of FN in multivariable analyses were: higher predicted risk of FN in the first cycle, platinum- or taxane-containing therapies, concurrent radiotherapy, treatment in cycle 2 compared to later cycles, previous FN or neutropenia, and not receiving granulocyte colony-stimulating factors. Each predictor added between -2 to 8 points to each patient's score (median score 4; interquartile range, 1-6). The incidence rate ratios for developing FN in the intermediate (score 1-4), high (score 5-6), and very high risk groups (score ≥7) were 7.8 (95% CI, 2.4-24.9), 18.6 (95% CI, 5.9-58.8), and 51.7 (95% CI, 16.5-162.3) compared to the low risk group (score ≤0), respectively. The score had good discriminatory ability with a Harrell's C-statistic of 0.78 (95% CI, 0.76-0.80) in the derivation and 0.75 (95% CI, 0.72-0.78) in the validation cohort (patient *n*=2,295, cycle *n*=7,670). The ^{CSR}FENCE score is the first published method to estimate cycle-specific risk of FN.

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Introduction

Febrile neutropenia (FN) induced by chemotherapy is a critical complication. FN is associated with an increased risk of suboptimal treatment effect due to dose delays, dose reductions, and treatment discontinuations[2–4]. Fortunately, mortality, morbidity, and patient management associated with FN have improved with increased awareness amongst physicians and patients leading to prompt initiation of empiric antibiotics as advocated in clinical guidelines[5,6]. Moreover, management of FN has been reformed by risk scores. Risk scores, such as the MASCC[7] and CISNE[8] scores, can identify those patients presenting with FN who are at low risk and who can be treated as outpatients. Similarly, risk stratification of patients according to the risk of developing FN before chemotherapy delivery could further improve patient care. Ultimately, initiation of preventive measures in high-risk groups could lead to better outcomes due to fewer complications ensuring greater adherence to treatment protocols.

We previously presented the FEbrile Neutropenia after ChEmotherapy (FENCE) score for identifying patients at high risk of developing FN in the first cycle based on pre-treatment risk factors[1]. Others have published similar methods[9–11]. These methods assume that the risk of FN in the first cycle can be extrapolated to the remainder of the chemotherapy course. However, guidelines recommend assessing the risk of FN at the start of each cycle to initiate preventive measures for FN in high-risk patients, such as prophylaxis with granulocyte colony-stimulating factors (G-CSF)[12–14].

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Amongst the few studies that have assessed the risk of FN in multiple chemotherapy cycles, some have assessed pre-treatment risk factors such as patient age, chronic comorbidities, or performance status[15,16], while others have assessed cycle-specific risk factors such as neutropenic events[3], prophylactic G-CSF[17,18], or Day 5 lymphopenia[19]. However, no study to our knowledge has presented a method to calculate cycle-specific estimates of risk of FN.

Inevitably, those at highest risk of FN in the first cycle and who survive to start a subsequent cycle are at greater risk during subsequent cycles[9]. However, some risk factors—for example FN in a previous cycle or having a dose delay—can appear only in cycle 2 and onwards. That being the case, we sought to expand our initial FENCE score to predict subsequent risk of developing FN in cycles 2-6 based on a combination of the FENCE score and cycle-specific risk factors. Subsequently, this scoring system will be made available as an online tool for clinicians.

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Methods

Study design and patient selection

We included all patients with solid cancers who initiated cycle 2 of standard first-line chemotherapy regimens at Rigshospitalet, University of Copenhagen. Thus, all analyses were conditional on surviving the first cycle. The study period was 15 January 2010 to 30 November 2016 with last follow-up on 31 December 2016. Patients in our institution are treated according to commonly used international standards for each cancer group and disease stage.

We excluded patients with temporary civil registration numbers, patients registered as initiating two different chemotherapy regimens simultaneously, patients with bone marrow transplants, and patients treated with platinums with a cycle length of seven days. We also excluded patients treated with oral regimens as we did not have information on dose delays and reductions which we deemed were necessary for the study.

Baseline was defined as the first date of chemotherapy in cycle 2. Assessment of cycle length is described in the Supporting Information, Methods. Patients accrued follow-up for any given cycle from the start of the cycle to one of the following events: 1) FN, 2) end of the cycle, 3) death, 4) a new cancer diagnosis, 5) change to a different chemotherapy regimen, or 6) end of follow-up, defined as: termination of chemotherapy, administration of maximum 6 cycles, loss-to-follow-up, emigration, or 31 December 2016. If the patients only experienced 1) or 2) within a cycle, they re-entered the study at the first date of the

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next cycle while patients censored due to 3), 4), 5) or 6) were excluded from any further analysis.

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 or death within three days of a neutrophil count $<0.5x10^9$/L or a leucocyte count $\leq 2.0x10^9$/L if neutrophils were not measured[1]. Data on temperature measurements were not routinely available before 2014 and were only available for the Capital Region of Denmark and hence a blood culture was used as a measure of clinical suspicion of infection. This definition has been shown to be in good concordance with a narrower guidelines-based definition of FN: neutropenia $<0.5x10^9$/L and fever ≥38 degrees Celsius[1].

Data sources, risk factors, and definitions

The data sources have been described previously[1]. Briefly, we used the Centre of Excellence for Personalised Medicine for Infectious Complications in Immune Deficiency (PERSIMUNE) data repository of electronic health records, including nationwide data on biochemistry and microbiology and regional data on medication. We also used data from

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the National Patient Register[20] and the Civil Registration System[21]. Patients were linked across data sources using the 10-digit unique civil registration number given to all Danish citizens with subsequent pseudo-anonymization of patient data before data extract and analyses.

For pre-therapy risk factors we assessed the FENCE score groups for risk of FN in the first cycle[1] (based on pre-therapy data on: sex, age, cancer type, disease stage, albumin, bilirubin, estimated glomerular filtration rate and C-reactive protein counts, infection before chemotherapy, number of and type of chemotherapy drugs) as a measure of underlying predisposition for FN, and comorbidity as measured by the Charlson Comorbidity Index (CCI) score[22,23].

Cycle-specific risk factors included were: body surface area, haemoglobin, leucocyte and platelet counts, number of and type of chemotherapy drugs, concurrent radiotherapy, cycle number, previous FN or neutropenia, dose delays, dose reductions, and prophylactic G-CSF treatment (see Supporting Information, Methods for details).

Statistics

Patients were randomly split 2:1 into a derivation and a validation cohort, stratified on cancer type and number of cycles. Poisson regression with generalized estimating equations and adjustment for repeated events per patient was used to determine risk factors associated with developing FN.

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Model building in the derivation cohort

In the primary approach, risk factors for FN were univariably assessed and risk factors with $p<0.1$ were included in a multivariable model. We then omitted risk factors with a $p\geq0.1$, one at a time, depending on their importance. All variables not included were then added to the model in turn to examine whether inclusion improved model fit, assessed as a $p<0.1$. To keep the model as simple as possible, we used Harrell's C-statistic to assess whether removing risk factors with a $p\geq0.05$ significantly changed the discriminatory performance of the model. Finally, we used forwards and backwards selection methods including all potential risk factors to assess if the same risk factors were identified. We tested one á priori defined interaction of FENCE score groups and cycle number.

The risk factors included in the multivariable model were scaled to each other for simpler use. Scaling was performed by dividing all the exact coefficients with the smallest coefficient and rounding to the nearest whole number. For each patient's individual cycles, we summed the scaled coefficients of that patient's risk factors as the Cycle-Specific Risk of FEbrile Neutropenia after ChEmotherapy (^{CSR}FENCE) score. We then grouped the patients in quintiles of their ^{CSR}FENCE score and collapsed the second and third quintiles as the incidence rates were almost identical, leaving four ^{CSR}FENCE score groups: low, intermediate, high, and very high risk.

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^{CSR}FENCE score performance in the derivation and validation cohorts

The discriminatory ability of the ^{CSR}FENCE score was assessed in the two cohorts by Harrell's C-statistic. We internally validated the ^{CSR}FENCE score performance in the validation cohort as compared to the derivation cohort by comparison of the crude incidence rates and incidence rate ratios within ^{CSR}FENCE score groups and the incidence rate ratios per point increase in the ^{CSR}FENCE score. In addition, to assess the added value of including cycle-specific risk factors we compared a model including only the FENCE score to the ^{CSR}FENCE score model using Harrell's C-statistic.

Preventive interventions

Studies have shown that the incidence of FN can be reduced by approximately 50% using G-CSF[24] and approximately 25% with prophylactic quinolones[25]. We calculated numbers needed to treat (NNT) to avoid one FN event over 21 days. NNT for G-CSF were calculated in patients without G-CSF prophylaxis. We also calculated NNT for G-CSF in patients without G-CSF prophylaxis who had not experienced a dose delay ≥15% or dose reduction ≥15%.

Sensitivity analyses

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We tested the discriminatory ability of the ^{CSR}FENCE score 1) using events identified by a guidelines-based definition of FN of fever ≥38 degrees Celsius and neutropenia <0.5x10^{9}/L in the period 2014-2016 when temperature measurements were routinely available for most patients and 2) in patients not receiving G-CSF.

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Results

There were 10,826 patients who initiated standard first-line chemotherapy in the study period. We excluded 251 patients with temporary civil registration numbers, 418 patients who were registered as initiating two chemotherapy regimens simultaneously, 4 patients with bone marrow transplantations, 3 patients who were registered as dead before initiation of the first cycle, 1,095 patients treated with weekly platinums, and 979 patients treated with oral monotherapy. Of the remaining 8,076 patients, 153 (1.9%) died and 1,038 (12.9%) did not initiate cycle 2. The patients not included were more often males, had more advanced disease, and the distribution of cancer types differed from the patients included. We thus included 6,885 patients with 24 types of solid cancers who accumulated 23,089 cycles of chemotherapy in 76 different chemotherapy regimens with a median follow-up of 3 cycles per patient (IQR, 2-5).

The cohort was randomly split 2:1 into a derivation cohort (patient *n*=4,590, cycle *n*=15,419) and a validation cohort (patient *n*=2,295, cycle *n*=7,670). Patient characteristics were similar in the two cohorts, although a higher proportion of patients in the derivation cohort had experienced FN in the first cycle (5.3% versus 4.2%, *p*=0.03) (Table 1).

Description of the derivation cohort

The 4,590 patients, median age of 64 years (interquartile range (IQR), 54 to 71) and 2,252 (49.1%) men, were followed for a median of three cycles (IQR, 2 to 5) with a median cycle

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length of 21 days (IQR, 20 to 23) (Table 1). FN developed in 326/15,419 (2.1%) cycles. Prophylactic G-CSF was used in 768/4,590 (16.7%) patients for 1,765/15,419 (11.6%) cycles with the majority being patients with breast cancer (550/768, 71.6%), of whom most (367/550, 66.7%) initiated prophylactic G-CSF when switching from epirubicin and cyclophosphamide to docetaxel. Dose delays ≥15% and dose reductions ≥15% occurred in 3,199/15,419 (20.7%) and 1,947/15,419 (12.6%) cycles, respectively.

Model building in the derivation cohort

Risk factors univariably associated with FN during cycles 2-6 were FENCE groups, Charlson Comorbidity Index score, body surface area, haemoglobin, leucocyte and platelet counts, number of and type of chemotherapy drugs, concurrent radiotherapy, previous FN or neutropenia, dose delays, and dose reductions (Supporting Information, Table S1).

Forward and backwards selection methods identified the same risk factors as did our primary approach: higher FENCE group, platinum- or taxane-containing therapies, concurrent radiotherapy, treatment in cycle 2 compared to later cycles, previous FN or neutropenia, and not receiving prophylactic G-CSF were associated with increased risk of FN (Table 2). There was no interaction between FENCE score and cycle number (p=0.67), indicating that the risk factors included in the FENCE score had a similar effect on risk of FN in each of the cycles 2-6. Treatment in cycle 3 yielded the smallest coefficient and was used to scale the other coefficients in the score.

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The median ^{CSR}FENCE score was 4 (IQR, 1-6) in all patients and 7 (IQR, 5-10) in patients who developed FN. The scores for the four ^{CSR}FENCE groups were: low risk (score ≤0, cycle *n*=2,609), intermediate risk (score 1-4, cycle *n*=6,143), high risk (score 5-6, cycle *n*=3,567) and very high risk (score ≥7, cycle *n*=3,100). The methods for calculating a ^{CSR}FENCE score and a cycle-specific estimate of risk of FN are detailed in the Supporting Information, Methods and Supporting Information, Results, and illustrated with an example patient.

^{CSR}FENCE score performance in the derivation cohort

Kaplan-Meier plots of FN according to ^{CSR}FENCE groups are shown in Figure 1. FN developed in 3 of 2,609 (0.1%) cycles, 55 of 6,143 (0.9%) cycles, 79 of 3,567 (2.2%) cycles, and 189 of 3,100 (6.1%) cycles in the low, intermediate, high, and very high risk groups, respectively. Compared to those at low risk, the incidence rate ratios of developing FN were 7.8 (95% CI, 2.4-24.9), 18.6 (95% CI, 5.9-58.8), and 51.7 (95% CI, 16.5-162.3) in the intermediate, high, and very high risk groups, respectively. The ^{CSR}FENCE score had a better discriminatory ability (Harrell's C-statistic 0.78, 95% CI, 0.76-0.80) than the FENCE score (Harrell's C-statistic 0.72, 95% CI, 0.69-0.75) for predicting FN in cycles 2-6 ($p<0.001$).

^{CSR}FENCE score performance in the validation cohort

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In the validation cohort there were 2,295 patients and FN developed in 164/7,670 (2.1%) cycles. There were no FN events in the low risk group in the validation cohort, why the reference groups for comparison of incidence rate ratios between the derivation and the validation cohorts were the intermediate risk groups (Table 3). The increase in incidence rates and incidence rate ratios across those with a low, intermediate, high, and very high risk of FN, and the incidence rate ratios per point increase in the ^{CSR}FENCE score were similar in the two cohorts. The discriminatory ability of the ^{CSR}FENCE score model was good, although slightly lower in the validation cohort with a Harrell's C-statistic of 0.75 (95% CI, 0.72-0.78).

Preventive interventions

NNT with G-CSF to avoid one FN event over 21 days were 1,822, 254, 99, and 37 for the low, intermediate, high, and very high ^{CSR}FENCE groups and for prophylactic quinolones the NNT were 3,666, 474, 201, and 74, respectively. In patients without G-CSF prophylaxis who had not experienced a dose delay or dose reduction the NNT for G-CSF prophylaxis were 1,317, 233, 103 and 43 for the low (cycle *n*=617), intermediate (cycle *n*=2,219), high (cycle *n*=1,024), and very high (cycle *n*=871) ^{CSR}FENCE groups.

Sensitivity analyses

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There were 209 FN events in the two cohorts combined in 2014-2016. Amongst those with temperature measurements, 146/172 (85%) had a fever of ≥38.0 degrees Celsius. There were 123 FN events identified by the narrow definition of FN (i.e. documented fever and neutropenia) of which 8 (6.5%) were not identified by the wider definition of FN. Using the events identified by the narrow definition of FN, the incidence rate was 0.58 (95% CI, 0.48-0.69) per 1,000 person-days of follow-up with similar increases in incidence rate ratios across risk groups and per point increase in ^{CSR}FENCE score (results not shown) and with a similar, albeit slightly lower, Harrell's C-statistic of 0.74 (95% CI, 0.70-0.79).

Sensitivity analyses censoring patients the first time they received prophylactic G-CSF and excluding G-CSF as a variable from the final model were consistent with the main analyses (Harrell's C-statistic 0.79, 95% CI, 0.76-0.81).

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Discussion

We have developed and internally validated a cycle-specific risk score for predicting FN in cycles 2-6 of standard first-line chemotherapy in patients with solid cancers. The ^{CSR}FENCE score had good discriminatory ability in both the derivation and validation cohorts. Risk factors identified were higher FENCE[1] score groups (i.e. higher underlying risk of FN), platinum- or taxane-containing therapies, concurrent radiotherapy, treatment in cycle 2 as compared to later cycles, previous FN or neutropenia, and not receiving G-CSF prophylaxis. In the model we incorporated pre-treatment data reflecting underlying risk of FN and cycle-specific risk factors measuring the effect of treatment and events occurring during the chemotherapy course to best resemble clinical practice and the risk factors clinicians usually assess when estimating risk of FN. To the best of our knowledge, this is the first study to present a risk score that estimates cycle-specific risk of FN. The tool to calculate a cycle-specific estimate of a patient's risk of FN will be available online (https://www.chip.dk/Tools-Standards/Clinical-risk-scores).

The ^{CSR}FENCE score discriminated better than the FENCE score indicating that a model utilising cycle-specific risk factors discriminates better than a model using only pre-therapy data. Additionally, we found that underlying risk of FN as measured by the FENCE score, and previous FN or neutropenia are the most important risk factors for FN in cycles 2-6. Neither dose delays nor dose reductions were retained in the model after adjusting for other risk factors. Dose delays and dose reductions are often elicited by neutropenia, as they are recommended in clinical guidelines as preventive measures to lower the risk of

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FN after neutropenic events[13]. Thus, there is likely a high level of correlation between these variables and prior FN or neutropenia which were identified as strong predictors of future FN and included in the final model.

Assessing the cycle-specific risk of FN is recommended by clinical guidelines[13] and knowing the risk can be used to guide intensity of patient monitoring and initiation of preventive measures. However, at what cycle-specific risks of FN patients should initiate prophylactic G-CSF or antibiotics are not established. Cycle-specific cost-effectiveness studies should be carried out with recent methodologies[26] to establish cycle-specific risk cut-offs and hereby facilitate the full potential of the ^{CSR}FENCE score to enable preventive interventions in the right patients to possibly avoid dose delays, dose reductions, and treatment discontinuations.

The major strength of this study is that it is the first study to our knowledge to present a risk score to estimate risk of FN at the initiation of chemotherapy cycles 2-6 as guidelines recommend. We used nationwide data generated through routine care that allowed almost complete ascertainment of outcomes in a large cohort of consecutive patients with many types of cancers providing a sound base for the model.

The main limitation of the study was using a definition of FN that does not conform to current guidelines; however, we have previously shown good concordance between our definition and a narrower guidelines-based definition based on documented fever and neutropenia[1], and reproduced the concordance in this study. Moreover, our definition of FN missed only a few of the FN events identified by the narrow definition. Additional

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limitations include the study being single-centre and without validation in an external cohort. We did not have data on prophylactic antibiotics, which alters the risk of FN. However, prophylactic antibiotics are generally not recommended in guidelines[5]. Another limitation was the lack of data on treatment with corticosteroids. Consequently, as the ^{CSR}FENCE score needs validation in external cohorts, addition of these risk factors in exploratory analyses may improve the discriminatory ability of the score.

In summary, we have developed a reliable risk score that is easily calculable with an online tool that estimates cycle-specific risk of FN induced by chemotherapy in patients with solid cancers. The score had good discriminatory ability to predict underlying risk of FN at cycle initiation. However, validation in prospective studies and external cohorts is needed.

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Conflicts of interest

There are no conflicts of interest related to this study. Professor Specht is a member of the advisory board and principal investigator for Takeda, a member of the advisory board for Merck, has a research agreement with Varian Medical Systems and Merck Serono, and is a principal investigator for Nanovi outside the submitted work. Professor Mocroft has received personal honoraria, travel support or consultancy fees from ViiV Healthcare and Gilead Sciences outside the submitted work. All remaining authors have declared no conflicts of interest.

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Figure legends

Figure 1. Kaplan-Meier plots of febrile neutropenia during chemotherapy cycles 2-6 according to ^{CSR}FENCE groups in the A) derivation (patient *n*=4,590, cycle *n*=15,419) and B) validation (patient *n*=2,295, cycle *n*=7,670) cohorts, 2010-2016

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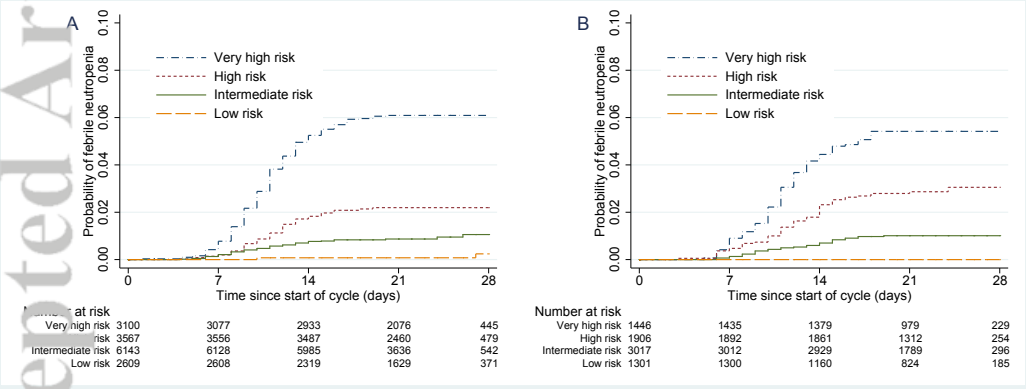

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Novelty & Impact Statement:

Febrile neutropenia (FN), involving fever and abnormally low neutrophil count, is a severe complication of chemotherapy. Current guidelines suggest assessing FN risk at the start of each chemotherapy cycle in order to prevent or better manage the condition if it arises. Here, to improve FN prediction, the authors developed a cycle-specific risk FEbrile Neutropenia after ChEmotherapy (^{CSR}FENCE) score. Risk factors were analyzed by Poisson regression for 6,885 patients with solid cancers who received standard first-line chemotherapy in cycles 2-6. In derivation and validation cohorts, the ^{CSR}FENCE score was found to successfully predict FN risk at cycle initiation.

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Table 1. Characteristics of the derivation and validation cohorts of patients with solid cancers initiating chemotherapy cycles 2-6, 2010-2016

	Derivation cohort		Validation cohort		*P*-value
Patients, n (%)	4,590	66.7	2,295	33.3	
Sex, n (%)					
Men	2,252	49.1	1,155	50.3	0.32
Women	2,338	50.9	1,140	49.7	
Cancer type, n (%)					
Gastric	684	14.9	358	15.6	0.78
Central nervous system	32	0.7	11	0.5	
Head and neck	28	0.6	19	0.8	
Oesophageal	227	4.9	110	4.8	
Breast	736	16.0	376	16.4	
Mesothelioma	287	6.3	149	6.5	
Non-small-cell lung	581	12.7	274	11.9	
Small-cell lung	162	3.5	87	3.8	
Colon/rectal	550	12.0	274	11.9	
Ovarian	359	7.8	163	7.1	
Cervical/endometrial	119	2.6	66	2.9	
Bladder	146	3.2	86	3.7	
Prostate	172	3.7	95	4.1	
Testicular	201	4.4	97	4.2	
Neuroendocrine	158	3.4	62	2.7	
Other	148	3.2	68	3.0	
Disease stage, n (%)					

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Adjuvant	1,107	24.1	532	23.2	0.34
Neoadjuvant or concomitant	924	20.1	495	21.6	
Locally advanced or disseminated	2,559	55.8	1,268	55.3	
FENCE groups*, n (%)					
Low risk	1,571	34.2	804	35.0	0.37
Intermediate risk	1,119	24.4	580	25.3	
High risk	1,006	21.9	503	21.9	
Very high risk	894	19.5	408	17.8	
Febrile neutropenia in the first cycle, n (%)	245	5.3	96	4.2	0.03
Cycle total, n (%)	15,419	66.8	7,670	33.2	
Last cycle, n (%)					
2	678	14.8	353	15.4	0.96
3	1,109	24.2	556	24.2	
4	557	12.1	268	11.7	
5	378	8.2	189	8.2	
6	1,868	40.7	929	40.5	
Age (years), median (IQR)	64	54-71	64	55-71	0.15
Charlson Comorbidity Index, median (IQR)	2	2-3	2	2-3	0.78
Cycle n (per patient), median (IQR)	3	2-5	3	2-5	0.87

IQR, interquartile range; FENCE, Febrile Neutropenia after ChEmotherapy[1]

*Assessed at the start of the first cycle based on pre-therapy risk factors: sex, age, cancer type, disease stage, albumin, bilirubin, estimated glomerular filtration rate and C-reactive protein counts, infection before chemotherapy, number of and type of chemotherapy drugs

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Table 2. Multivariable model for the ^{CSR}FENCE score for predicting febrile neutropenia during chemotherapy cycles 2-6 in the derivation cohort (patient *n*=4,590, cycle *n*=15,419) of patients with solid cancers, 2010-2016

	FN/cycle *n* (%)	Adjusted incidence rate ratio (95% CI)	Exact coefficient	Scaled coefficient to use in ^{CSR}FENCE score calculation
Intercept*			-8.927	
FENCE groups†				
Low risk	23/4,868 (0.5)	1	0	0
Intermediate risk	63/4,097 (1.5)	3.28 (2.04-5.29)	1.189	4
High risk	86/3,326 (2.6)	3.60 (2.22-5.86)	1.282	4
Very high risk	154/3,128 (4.9)	4.76 (2.93-7.72)	1.560	5
Chemotherapy				
Platinums				
No	68/4,984 (1.4)	1	0	0
Yes	258/10,435 (2.5)	1.54 (1.18-2.03)	0.435	1
Taxanes				
No	156/10,071 (1.5)	1	0	0
Yes	170/5,348 (3.2)	1.49 (1.13-1.96)	0.398	1
Radiotherapy				
No	311/15,021 (2.1)	1	0	0
Yes	15/398 (3.8)	2.28 (1.30-4.01)	0.825	3
Cycle number				
2	110/4,590 (2.4)	1	0	0
3	81/3,912 (2.1)	0.74 (0.55-0.98)	-0.305	-1
4	60/2,803 (2.1)	0.69 (0.50-0.96)	-0.368	-1

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5	46/2,246 (2.0)	0.63 (0.44-0.90)	-0.459	-2
6	29/1,868 (1.6)	0.49 (0.32-0.76)	-0.712	-2
FN or neutropenia in previous cycles				
No neutropenia	100/9,911 (1.0)	1	0	0
Neutropenia, but not FN	120/4,350 (2.8)	2.09 (1.58-2.77)	0.737	2
1 FN event	84/1,028 (8.2)	5.36 (3.89-7.40)	1.680	6
>1 FN event	22/130 (16.9)	10.38 (6.00-17.95)	2.340	8
G-CSF prophylaxis				
No	294/13,654 (2.2)	1	0	0
Yes	32/1,765 (1.8)	0.65 (0.42-1.00)	-0.430	-1

FN, febrile neutropenia; CI, confidence interval; FENCE, FEbrile Neutropenia after ChEmotherapy[1]; G-CSF, granulocyte colony-stimulating factors

* Needed if exact risk is to be calculated

† Assessed at the start of the first cycle based on pre-therapy risk factors: sex, age, cancer type, disease stage, albumin, bilirubin, estimated glomerular filtration rate and C-reactive protein counts, infection before chemotherapy, number of and type of chemotherapy drugs

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Table 3. Performance of the ^{CSR}FENCE score in the derivation (patient *n*=4,590) and validation (patient *n*=2,295) cohorts predicting febrile neutropenia during chemotherapy cycles 2-6 in patients with solid cancers, 2010-2016

	Derivation Cohort	Validation Cohort
FN/cycle *n*	326/15,419	164/7,670
Incidence of FN per 1000 person-days of follow-up (95% CI)	0.94 (0.84-1.05)	0.95 (0.80-1.10)
Risk score model		
Baseline score, median (IQR)	4 (1-6)	4 (1-6)
Baseline score in cycles with FN, median (IQR)	7 (5-10)	6 (5-8)
Patients with FN by risk score group, low/intermediate/high/very high	3/55/79/189	0/30/55/79
N by risk score group, low/intermediate/high/very high	2,609/6,143/3,567/3,100	1,301/3,017/1,906/1,446
Incidence of FN per 1000 person-days of follow-up (95% CI)		
Low risk (score ≤0)	0.05 (0.01-0.15)	0 (0-0.13)
Intermediate risk (score 1-4)	0.41 (0.30-0.51)	0.45 (0.29-0.61)
High risk (score 5-6)	0.96 (0.75-1.18)	1.26 (0.93-1.59)
Very high risk (score ≥7)	2.69 (2.31-3.07)	2.37 (1.85-2.89)
Incidence rate ratio (95% CI)		
Low risk (score ≤0)	0.13 (0.04-0.41)	NA
Intermediate risk (score 1-4)	1	1
High risk (score 5-6)	2.38 (1.69-3.36)	2.82 (1.81-4.41)
Very high risk (score ≥7)	6.64 (4.88-9.04)	5.31 (3.49-8.08)
Incidence rate ratio per point increase in score	1.34 (1.31-1.38)	1.31 (1.25-1.37)
Harrell's C-statistic	0.78 (0.76-0.80)	0.75 (0.72-0.78)

FN, febrile neutropenia; CI, confidence interval; IQR, interquartile range

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