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Development and validation of a cycle-specific risk score for febrile neutropenia during chemotherapy cycles 2-6 in patients with cancer: The CSRFENCE Score

Theis Aagaard
Tel: +4561337159
Fax: +4535455758
theisaagaard@gmail.com
Download poster at: www.chip.dk

T. Aagaard[1], J. Reekie[1], A. Roen[2], G. Daugaard[3], L. Specht[3], H. Sengeløv[4], A. Mocroft[2], J. Lundgren[1], M. Helleberg[1]

[1]CHIP, Department of Infectious Diseases, Rigshospitalet, [2]Centre for Clinical Research, Epidemiology, Modelling and Evaluation, University College London, [3]Department of Oncology, Rigshospitalet, [4]Department of Haematology, Rigshospitalet

STUDY SUMMARY

Guidelines[1] recommend assessing the risk of febrile neutropenia (FN) at the start of each cycle of a chemotherapy course. However, previous studies have focused on predicting risk of FN in the first cycle[2-4]. 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. 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[2] score (predicting risk of FN in the first cycle) to predict subsequent risk of developing FN in cycles 2-6 based on a combination of the FENCE score and cycle-specific risk factors.

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 FN at cycle initiation was developed and internally validated. The score had good discriminatory ability and is the first published method to estimate cycle-specific risk of FN.

METHODS

Patients with solid cancers treated with standard first-line chemotherapy were included in 2010-2016 from a single site and followed through cycles 2-6. Cycle-specific risk factors were assessed by Poisson regression using generalised estimating equations adjusted for repeated events per patient and random split-sampling.

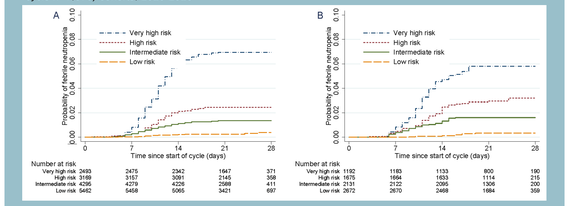
References

[1]Smith et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2015;33:3199-212
[2]Aagaard et al. Development and Validation of a Risk Score for Febrile Neutropenia after Chemotherapy in Patients with Cancer: The FENCE Score. *JNCI Cancer Spectr.* In press. DOI: 10.1093/jncics/pky053
[3]Lyman et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. *Cancer* 2011;117:1917-27
[4]Hosmer et al. Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. *Support Care Cancer* 2011;19:333-41

RESULTS

We included 6,885 patients and randomly split them 2:1 into a derivation and validation cohort (**Table 1**). FN developed in 324/15,419 (2.1%) cycles in the derivation cohort. Higher FENCE[1] risk group, anaemia, 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 predicted FN (**Table 2**). Risk stratification of patients according to the risk score is shown in **Figure 1** with good discriminatory ability and performance of the risk score in the derivation (Harrell's C-statistic 0.79, 95% CI, 0.77-0.81) and validation cohorts (Harrell's C-statistic 0.76, 95% CI, 0.72-0.79) (**Table 3**).

Figure 1. Kaplan-Meier plots of febrile neutropenia during chemotherapy cycles 2-6 according to CSRFENCE 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



Harrell's C-statistic 0.79 (95% CI, 0.77-0.81) **Harrell's C-statistic 0.76 (95% CI, 0.72-0.79)**

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 (%)					
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	
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(xxx FENCE)
*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

Table 2. Multivariable model for the CSRFENCE 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 IRR (95% CI)	Exact coefficient	Coefficient for CSRFENCE score calculation
Intercept*			-9.265	
FENCE groups†				
Low risk	22/4,868 (0.5)	1	0	0
Intermediate risk	62/4,097 (1.5)	2.93 (1.79-4.81)	1.077	3
High risk	86/3,326 (2.6)	3.49 (2.13-5.71)	1.250	3
Very high risk	154/3,128 (4.9)	4.32 (2.65-7.04)	1.463	4
Haemoglobin				
<Normal	273/9,865 (2.8)	2.18 (1.60-2.97)	0.779	2
Normal, above normal or missing value‡	51/5,554 (1.1)	1	0	0
Chemotherapy				
Platinums				
No	68/4,984 (1.4)	1	0	0
Yes	256/10,435 (2.5)	1.47 (1.11-1.94)	0.383	1
Taxanes				
No	154/10,071 (1.5)	1	0	0
Yes	170/5,348 (3.2)	1.46 (1.11-1.92)	0.378	1
Radiotherapy				
No	310/15,021 (2.1)	1	0	0
Yes	14/398 (3.5)	2.27 (1.26-4.06)	0.818	2
Cycle number				
2	110/4,590 (2.4)	1	0	0
3	79/3,912 (2.0)	0.69 (0.51-0.92)	-0.378	-1
4	60/2,803 (2.1)	0.64 (0.46-0.88)	-0.454	-1
5	46/2,246 (2.0)	0.58 (0.41-0.83)	-0.539	-1
6	29/1,868 (1.6)	0.45 (0.29-0.69)	-0.805	-2
FN or neutropenia in previous cycles				
No neutropenia	98/9,911 (1.0)	1	0	0
Neutropenia, but not FN	120/4,350 (2.8)	2.03 (1.53-2.69)	0.707	2
1 FN event	84/1,028 (8.2)	4.99 (3.61-6.89)	1.607	4
>1 FN event	22/130 (16.9)	9.53 (5.47-16.60)	2.255	6
G-CSF prophylaxis				
No	292/13,654 (2.1)	1	0	0
Yes	32/1,765 (1.8)	0.61 (0.39-0.95)	-0.491	-1

FN, febrile neutropenia; IRR, incidence rate ratio; CI, confidence interval; FENCE, FEbrile Neutropenia after ChEmotherapy(xxx FENCE); 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
‡ Individuals with values above normal or missing value for haemoglobin were included in the "normal" category after comparing the coefficients from the multivariable model

Table 3. Performance of the CSRFENCE 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*	324/15,419	162/7,670
Incidence of FN per 1000 PDFU (95% CI)	0.94 (0.84-1.04)	0.94 (0.79-1.08)
Risk score model		
Baseline score, median (IQR)	5 (3-7)	5 (3-7)
Baseline score in cycles with FN, median (IQR)	8 (6-10)	7 (5-9)
Patients with FN by risk score group, low/intermediate/high/very high	15/58/78/173	8/34/51/69
N by risk score group, low/intermediate/high/very high	5,462/4,295/3,169/2,493	2,672/2,131/1,675/1,192
Incidence of FN per 1000 PDFU (95% CI)		
Low risk (score ≤3)	0.12 (0.07-0.20)	0.13 (0.06-0.26)
Intermediate risk (score 4-5)	0.60 (0.45-0.76)	0.71 (0.47-0.95)
High risk (score 6-7)	1.09 (0.85-1.33)	1.34 (0.97-1.71)
Very high risk (score ≥8)	3.06 (2.61-3.52)	2.51 (1.92-3.10)
Incidence rate ratio (95% CI)		
Low risk (score ≤3)	1	1
Intermediate risk (score 4-5)	4.91 (2.78-8.69)	5.32 (2.46-11.49)
High risk (score 6-7)	8.86 (5.09-15.44)	9.99 (4.72-21.17)
Very high risk (score ≥8)	24.87 (14.57-42.45)	18.68 (8.91-39.2)
Incidence rate ratio per point increase in score	1.46 (1.41-1.52)	1.40 (1.33-1.48)

FN, febrile neutropenia; PDFU, person-days of follow-up; CI, confidence interval; IQR, interquartile range

CONCLUSION

- We developed and validated the CSRFENCE risk score for predicting risk of FN in chemotherapy cycles 2-6 using nationwide data sources that allowed almost complete ascertainment of outcomes.
- To the best of our knowledge, this is the first study to present a risk score that estimates cycle-specific risk of FN.
- The score had good discriminatory ability (Harrell's C-statistic 0.79) to predict underlying risk of FN at cycle initiation as guidelines recommend.
- The CSRFENCE risk score can be used to guide initiation of preventive measures and intensity of patient monitoring.
- An online risk calculator will be available at https://chip.dk/Tools-Standards/Clinical-risk-scores.
- External validation of the results is needed.

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