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Prediction of neutropenia and of febrile neutropenia

Marianne Paesmans – MASCC meeting 30/06/2018

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Background

- Neutropenic complications -> reduction of chemotherapy dose intensity
- Febrile neutropenia increases risk for early mortality
- Myeloid growth factors reduce occurrence of neutropenic complications, impact on mortality less obvious
- Costly, not adverse events free
- Need to administer them to the right patients

Background

- Current guidelines : use them when
  - Risk of febrile neutropenia (FN) from chemotherapy > 20% (updated EORTC guidelines, NCCN)
  - Risk of febrile neutropenia from chemotherapy 10%-20% and other risk factors exist (older age, poor PS, comorbidities, female gender, …)
- Requirement of accurate estimate of the risk of FN

Difficulties

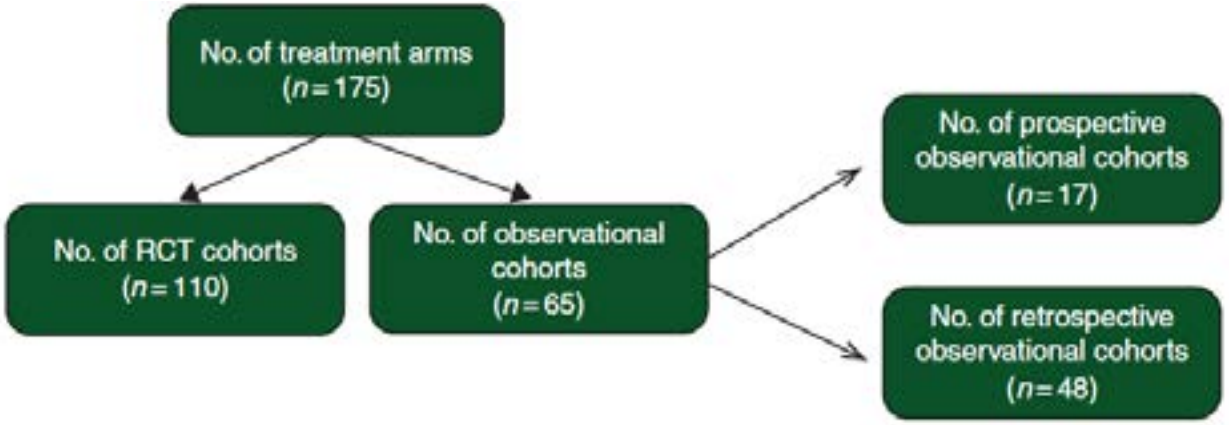
- Baseline risk from chemotherapy regimen :
  - In the guidelines, estimated through clinical trials reports
  - Not often reported in detail
  - Statistical accuracy may be lacking (large confidence intervals)
  - Guidelines updates not frequent enough
  - Patients included in clinical trials are different from those treated in real clinical practice -> expectation of increased rate of FN
  - Currently, better reimbursement of myeloid growth factors -> selection bias for further observational studies
  - Difficult to integrate it into a risk prediction model : how to combine drugs, doses, …

Annals of Oncology 27: 608–618, 2016
doi:10.1093/annonc/mdv619
Published online 27 December 2015

Interpreting febrile neutropenia rates from randomized, controlled trials for consideration of primary prophylaxis in the real world: a systematic review and meta-analysis

J. Truong[1], E. K. Lee[1], M. E. Trudeau[1,2] & K. K. W. Chan[1,2,3,4*]

- Assessment of clinical trials and observational studies using the same chemotherapy regimens in breast cancer
- Inclusion of a regimen : clinical trial + observational study



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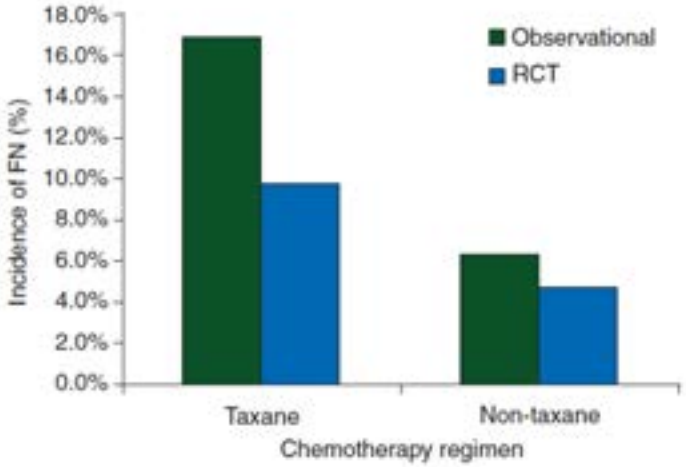
- Clinical trials n=42257, observational studies n=7812



Results: 130 studies involving 29 regimens and 50 069 patients were identified. Sixty-five observational study ($n = 7812$) and 110 RCT ($n = 42\,257$) cohorts were included. The unadjusted FN rate was 11.7% in observational and 7.9% in RCT cohorts. The univariable odds ratio (OR) for FN in the observational study compared with RCT cohorts was 1.58 [95% confidence interval (CI) 1.09–2.28; $P = 0.017$]. The FN rates remained significantly higher in the observational study compared with RCT cohorts (OR = 1.74; 95% CI 1.15–2.62; $P = 0.012$) after adjusting for age, chemotherapy intent, and regimen; this meant that a 13% (95% CI 8.7% to 17.9%) FN rate in RCT would translate into 20% FN rate in observational study.

Conclusions: FN rates in the observational studies are significantly higher than suggested by RCTs. Guidelines should clarify how FN rates from RCTs should be applied in clinical practice. Large population-based studies are needed to confirm FN rates in the real world.

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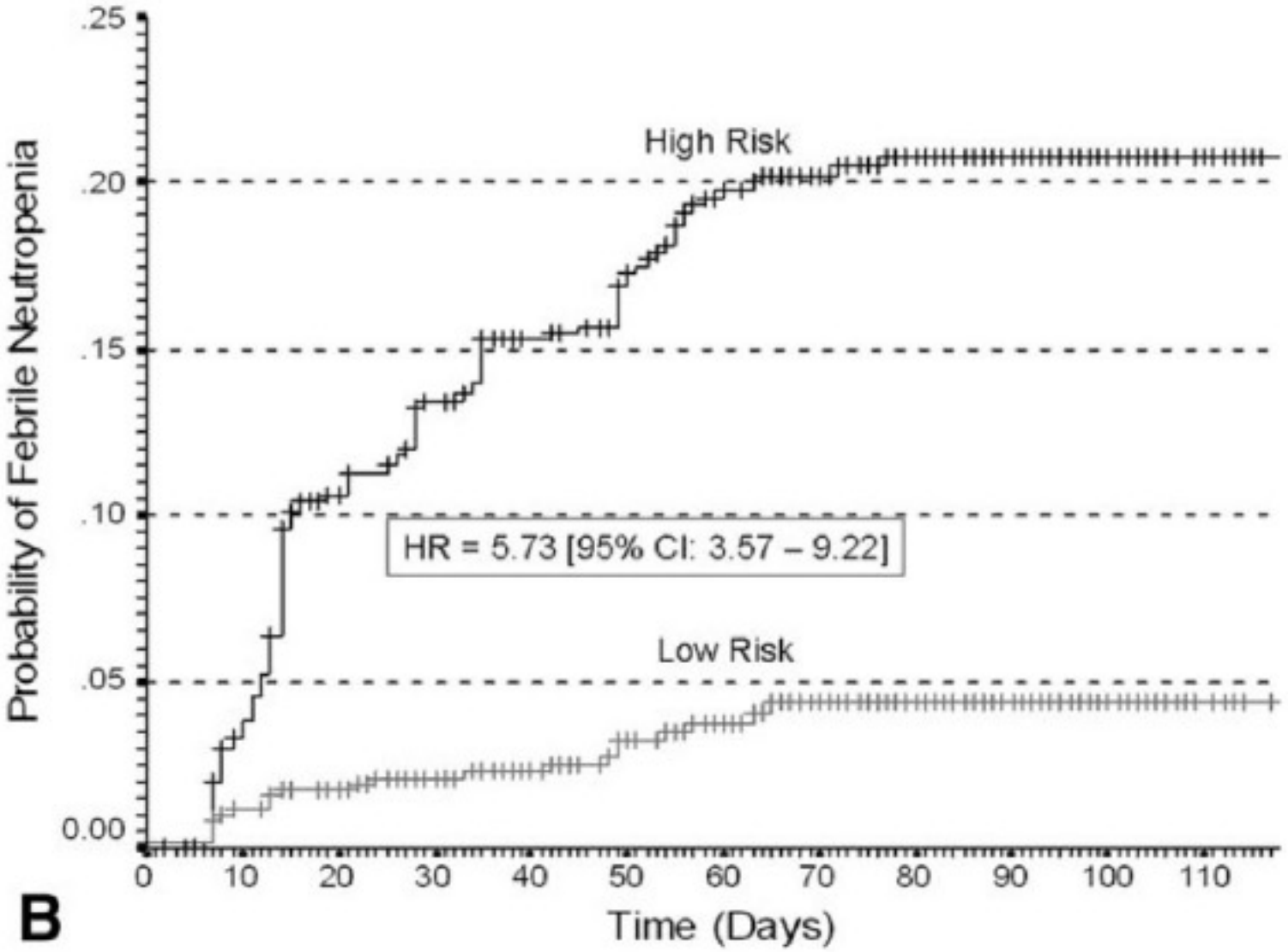
Predicting Individual Risk of Neutropenic Complications in Patients Receiving Cancer Chemotherapy

Cancer 2011

Gary H. Lyman, MD, MPH[1], Nicole M. Kuderer, MD[1], Jeffrey Crawford, MD[1], Debra A. Wolff, MS, PCNP[1], Eva Culakova, PhD, MS[1], Marek S. Poniewierski, MD, MS[1], and David C. Dale, MD[2]

- N=3760, patients with solid tumor or lymphoma
- Development and validation sets
- Controlled sample size (10% risk versus 20% risk)
- Prospective study
- Outcome : severe or febrile neutropenia – cycle 1
- Data collection up to 4 cycles
- Inclusion of patients receiving prophylaxis
- Rates of outcome : 19.5% / 21.2%

High risk : predicted risk > 10%



Multivariate Analysis for Cycle 1 Severe or Febrile Neutropenia (N=2425)

Variables	Odds Ratio	95% CI	*P*
Age, y, ≥65	1.297	.961–1.750	.089
Prior chemotherapy	1.925	1.345–2.755	<.001
Baseline labs			
AST>35 u/L	1.422	.991–2.041	.056
Alkaline phosphatase>120 u/L	1.469	1.058–2.040	.022
Bilirubin>1 mg/dL	2.152	1.235–3.747	.007
GFR mL/min	.993	.989–.997	<.001
WBC×10^3/mm^3	.930	.892–.969	.001
Cancer type[a]			.004
Small cell lung	1.556	.641–3.781	.329
Nonsmall cell lung	.594	.270–1.309	.196
Ovary	.515	.214–1.242	.140
Breast	.842	.377–1.880	.675
Lymphoma	.510	.219–1.188	.118
Medications			
Immunosuppressives	1.554	1.105–2.187	.011
Planned RDI≥85%	2.018	1.449–2.819	<.001
Chemotherapy			
Anthracyclines	7.353	4.577–11.811	<.001
Platinum(s)	1.830	1.075–3.117	.026
Taxanes	2.850	1.860–4.368	<.001
Alkylating agents	5.853	3.215–10.658	<.001
Topoisomerase II inhibitors	8.815	4.411–17.619	<.001
Gemcitabine	3.092	1.696–5.638	<.001
Topoisomerase I inhibitors	18.579	5.366–64.335	<.001
Vinorelbine	4.218	1.896–9.385	<.001
Primary CSF prophylaxis	.120	.079–.180	<.001

Constant Term = −3.423

RDI indicates relative dose intensity; GFR, glomerular filtration rate; AST, aspartate aminotransferase; WBC, white blood count; CSF, colony-stimulating factors.

[a]Reference category: colorectum: OR, 1.00.

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Table 4

Risk Model Performance in the Derivation and Validation Datasets

Derivation and Validation Models Severe or Febrile Neutropenia Risk Based on Median Predicted Risk

Derivation

- **Model Performance**
  - Sensitivity: 90.0% [87.8, 92.4]
  - Specificity: 58.9% [56.6, 61.1]
- **Model Predictive Value**
  - Positive: 34.2% [31.5, 36.9]
  - Negative: 96.1% [94.8, 97.1]
- **Model Likelihood Ratio**
  - Positive: 2.19 [2.05, 2.33]
  - Negative: 0.17 [0.13, 0.23]
- **Model Diagnostic Odds Ratio:**

  12.81 [9.29, 17.67]

Validation

- Model Performance
  - Sensitivity: 85.0% [80.1, 88.9]
  - Specificity: 58.7% [55.5, 61.8]
- Model Predictive Value
  - Positive: 36.1% [32.3, 40.0]
  - Negative: 93.4% [91.1, 95.2]
- Model Likelihood Ratio
  - Positive: 2.06 [1.87, 2.26]
  - Negative: 0.26 [0.19, 0.35]
- Model Diagnostic Odds Ratio:

  8.03 [5.56, 11.62]

Clinical usefulness ?

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Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review

Critical Reviews in Oncology Hematology, 2014

Gary H. Lyman [a,*], Esteban Abella [b], Ruth Pettengell [c]

- Studies reporting univariate / multivariate results
- Heterogeneity in populations, in definition of outcome
- Age, gender, performance status, laboratory abnormalities (lymphocyte & monocyte counts, ANC), low BMI
- Chemotherapy drugs : anthracyclines, taxanes, alkylators, topoisomerase inhibitors, **impact of growth factors**
- Tumor type, advanced disease
- Genetic factors (MBL gene for instance)

- Validated models seldom

Validated risk models for FN

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

Supportive Care Cancer, 2011

Wylie Hosmer · Jennifer Malin · Mitchell Wong

External validation of a risk model of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma

Leukemia & Lymphoma 2013

Matthias Schwenkglenks, Kate Louise Bendall, Alena M. Pfeil, Zsolt Szabo & Ruth Pettengell

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

Supportive Care Cancer, 2015

H. Bozcuk · M. Yıldız · M. Artaç · M. Kocer · Ç. Kaya · E. Ulukal · S. Ay · M. P. Kılıç · E. H. Şimşek · P. Kılıçkaya · S. Uçar · H. S. Coskun · B. Savas

	Hosmer	Schwenkglenks	Bozcuk
Design	Retrospective	Prospective	Prospective
Validation	Internal	External	External
Patients	Elderly; breast, lung, colorectal, prostate cancer	NHL	Breast, lung, colorectal cancer
Data source	SEER; geographical area	Sites from 14 European countries and Australia	Patients from 2 institutions
Inclusion period	1994-2005	?	5/2010-1/2011
Setting	First line CT	R-CHOP chemotherapy, any line	Any line CT
Growth factors	No	Yes	Yes
Outcome	First cycle FN	First and any cycle FN	Any cycle FN
N training	58053	240	1089 pts - 3882 cycles
N validation	28910	1829	960 pts - 1444 cycles
Comment	Limited number of covariates (no biological factors)		36 covariates including laboratory values

Hosmer model

Table 3 Multiple logistic regression predicting febrile neutropenia in the first cycle of chemotherapy (N=63,033)

Predictor (reference)	Odds ratio	P value	95% CI	Prediction model points
Cancer type (breast cancer)				
Lung cancer	2.01	<0.001	1.65–2.44	7
Colon cancer	1.26	0.001	1.09–1.45	2
Prostate cancer	0.27	<0.001	0.22–0.33	−13
Stage at diagnosis (stage 1)				
Stage 2	1.29	0.003	1.09–1.53	3
Stage 3	1.38	<0.001	1.19–1.60	3
Stage 4	1.57	<0.001	1.35–1.83	5
Time from diagnosis to first chemotherapy treatment (<1 months)				
1–3 month	0.70	<0.001	0.62–0.80	−4
>3 month	0.63	<0.001	0.55–0.73	−5
1 or more myelosuppressive chemotherapy agents (chemotherapy with low myelosuppressive potential)	1.11	0.19	0.94–1.32	1
Comorbid conditions at diagnosis				
1	1.13	0.02	1.02–1.28	1
2	1.39	<0.001	1.22–1.57	3
3	1.81	<0.001	1.61–2.04	6

Variables tested but excluded because not statistically significant: age, female sex, chemotherapy interval, race/ethnicity. Model was tested on training dataset (N=63,033)

Hosmer model

Table 4 Observed and predicted proportion of patients with febrile neutropenia (FN) in the first cycle by prediction score in the derivation and validation datasets

	Training dataset			Validation dataset		
Score	*N*	Observed FN, %	Predicted FN, %	*N*	Observed FN, %	Predicted FN, %
0 or lower	37,003	1.6	1.6	18,254	1.6	1.6
1–3	7,055	5.2	5.0	3,543	5.4	5.0
4–6	4,365	7.7	6.6	2,285	6.5	6.6
7–9	5,354	8.6	8.6	2,675	8.3	8.6
10–12	2,443	11.9	11.2	1,241	10.0	11.2
13 or higher	1,833	12.8	15.0	912	15.5	15.0
Overall	58,053	3.9	3.9	28,910	3.9	3.9

The observed FN rate is the actual proportion of subjects who had FN in the sample. The predicted FN rate is the average predicted risk of FN based on the logistic regression model of FN that including the following covariates: cancer type, stage1 or more myelosuppressive chemotherapeutic agents, comorbid conditions (cumulative number: 1, 2, 3) and time from cancer diagnosis to chemotherapy treatment

Schwenkglenks model

Table III. INC-EU model of FN risk in first and any cycle: comparison of original model parameters and re-estimated model parameters based on IMPACT NHL dataset.

	FN in first cycle				FN in any cycle			
	Original model parameters*		Re-estimated model parameters†		Original model parameters*		Re-estimated model parameters†	
Covariate	Odds ratio (95% CI)	*p*-Value‡	Odds ratio (95% CI)	*p*-Value‡	Odds ratio (95% CI)	*p*-Value[3]	Odds ratio (95% CI)	*p*-Value‡
Age§	2.20 (1.21–4.01)	0.01	1.16 (0.96–1.41)	0.13	1.79 (1.16–2.78)	0.01	1.43 (1.24–1.65)	<0.01
Weight¶	0.62 (0.43–0.89)	0.01	0.89 (0.78–1.03)	0.22	0.62 (0.44–0.88)	0.01	0.90 (0.84–0.98)	0.01
Cardiovascular comorbidity	—		—		2.56 (1.04–6.29)	0.04	1.16 (0.82–1.65)	0.39
Low baseline ANC or WBC**	—		—		4.18 (1.82–9.60)	<0.01	1.92 (1.38–2.67)	<0.01
Previous chemotherapy	6.39 (1.72–23.68)	<0.01	1.46 (0.79–2.70)	0.22	1.76 (0.49–6.36)	0.39	1.02 (0.61–1.70)	0.94
Planned cyclophosphamide dose††	1.16 (1.02–1.32)	0.02	1.12 (0.98–1.27)	0.10	1.33 (1.16–1.52)	<0.01	1.14 (1.04–1.26)	0.01
Planned cytarabine dose††	1.06 (0.98–1.16)	0.15	Not administered in IMPACT NHL		1.09 (1.05–1.13)	<0.01	Not administered in IMPACT NHL	
Planned etoposide dose††	1.59 (1.20–2.11)	<0.01			1.27 (1.03–1.57)	0.02		
Dose-dense regimen (cycle length 2 weeks)	—		—		1.84 (0.71–4.78)	0.21	2.07 (1.45–2.95)	<0.01
CSF use before an event occurred‡‡	0.18 (0.03–0.94)	0.04	0.48 (0.30–0.77)	0.00	0.21 (0.10–0.44)	<0.01	0.45 (0.32–0.64)	<0.01
Dose reduction before an event occurred‡‡	—		—		0.24 (0.09–0.63)	<0.01	0.32 (0.21–0.48)	<0.01
Dose delay before an event occurred‡‡	—		—		0.17 (0.07–0.40)	<0.01	0.39 (0.28–0.55)	<0.01
Baseline albumin low§§	4.76 (1.35–16.71)	0.02	3.15 (1.98–5.01)	0.00	—		—	
Baseline albumin missing§§	0.52 (0.09–2.99)	0.46	1.54 (0.99–2.39)	0.06	—		—	
Baseline alkaline phosphatase high¶¶	—		Not recorded in IMPACT NHL		9.07 (1.41–58.50)	0.02	Not recorded in IMPACT NHL	
Baseline alkaline phosphatase missing¶¶					4.75 (0.73–30.84)	0.10		
Recent infection***	3.07 (0.99–9.52)	0.05			3.32 (1.03–10.71)	0.04		

INC-EU, Impact of Neutropenia in Chemotherapy - European Study Group; NHL, non-Hodgkin lymphoma; ANC, absolute neutrophil count; WBC, white blood cell count; CSF, colony-stimulating factor; CI, confidence interval; FN, febrile neutropenia.

*Based on INC-EU dataset and as reported in Pettengell *et al.*, 2009 [16]; $n = 237$ usable observations.

†Based on IMPACT NHL dataset; $n = 1818$ usable observations for cycle 1 models and $n = 1675$ usable observations for any cycle model.

‡Based on general estimating equations-based robust standard error estimates allowing for clustering by study site.

§Per additional 10 years of age.

¶Per additional 10 kg body weight.

**Baseline ANC $< 3.0 \times 10^9$/L or WBC $< 5.0 \times 10^9$/L.

††Per additional mg/m^2 body surface area/week; per additional 50 mg/m^2.

‡‡Myelopoietic growth factor use; chemotherapy dose reduction; chemotherapy dose delay before a FN event occurred.

§§Baseline albumin < 35 g/dL, missing category introduced to avoid loss of observations.

¶¶Baseline alkaline phosphatase > 250 IU/L, missing category introduced to avoid loss of observations.

***During 60 days prior to chemotherapy or ongoing infectious comorbidity.

Schwenkglenks model

Table II. Risk model performance in INC-EU (training) and IMPACT NHL (external validation) datasets.

	FN in first cycle			FN in any cycle		
	INC-EU (training dataset)*	IMPACT NHL (validation dataset)		INC-EU (training dataset)*	IMPACT NHL (validation dataset)	
Choice of cut-off	Optimal for INC-EU model	Optimal for INC-EU model	Optimal for IMPACT NHL model	Optimal for INC-EU model	Optimal for INC-EU model	Optimal for IMPACT NHL model
Cut-off value	0.116	0.116	0.014	0.232	0.232	0.089
Correct predictions (%)	192 (80)	1583 (87)	1074 (59)	180 (76)	1306 (78)	1113 (66)
Area under ROC curve (95% CI)	0.86 (0.79–0.94)	0.64 (0.59–0.69)		0.83 (0.76–0.90)	0.71 (0.68–0.75)	
Sensitivity (%)	81	14	59	76	42	66†
Specificity (%)	80	93	59	76	86	67†
Negative predictive value (%)	98	93	95	92	87	90
Positive predictive value (%)	28	13	10	48	40	30

INC-EU, Impact of Neutropenia in Chemotherapy – European Study Group; NHL, non-Hodgkin lymphoma; ROC, receiver operating characteristic; CI, confidence interval; FN, febrile neutropenia.

*As published previously (Pettengell *et al.*, 2009 [16]).

†Formal criterion for successful validation met.

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Bozcuk model

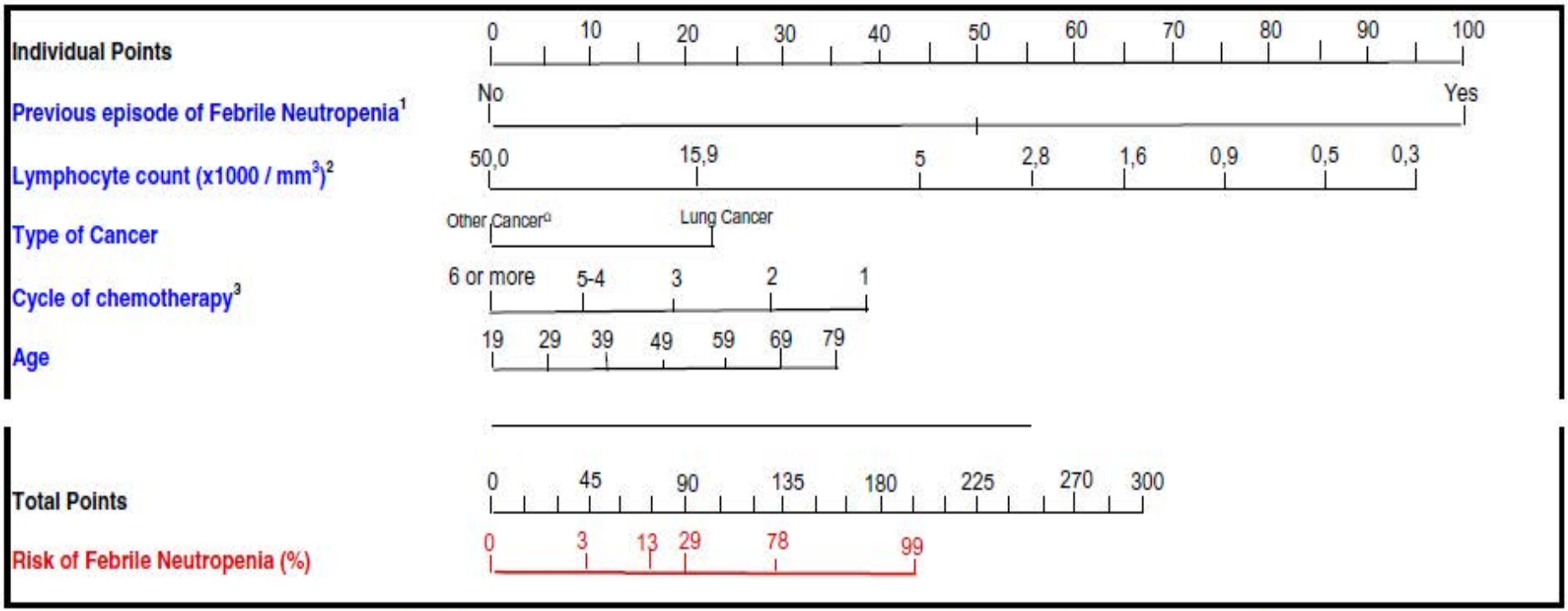

Fig. 1 Nomogram for the risk of febrile neutropenia after standard dose chemotherapy in common solid tumors. [1]Any episode of febrile neutropenia with the current protocol or a previous protocol; [2]based on precycle blood counts; [3]current cycle of chemotherapy with the present protocol; *omega* (Ω)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

Bozcuk model

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

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

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

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Comments

- No «universal » model
- Outcome should be FN at 1st cycle
- Modelling impact of chemotherapy regimen is complex
- Model should be developed without inclusion of patients receiving growth factors
- Model should be externally validated
- More frequent use of growth factors decreases the impact of a model (choice of risk factors adequate ?)
- Within the MASCC Study Group for Infections, very pragmatic study ongoing, observational on patients without growth factors

Such a model might be easy to use …

Predicting neutropenia risk in patients with cancer using electronic data

Pamala A Pawloski,[1,2,3] Avis J Thomas,[1] Sheryl Kane,[1] Gabriela Vazquez-Benitez,[1] Gary R Shapiro,[3,4] and Gary H Lyman[5,6,7]

Journal of the American Medical Informatics Association, 24(e1), 2017, e129–e135

- Feasible to estimate the risk through an algorithm applied on the EHR -> easy to guide growth factors prediction
- Stratification of the patients into 3 risk groups
- Inclusion of patients receiving growth factors
- Compliance with guidelines moderate

And helpful …

Assessing patients' risk of febrile neutropenia: is there a correlation between physician-assessed risk and model-predicted risk?

Cancer Medicine 2015; 4(8):1153–1160

Gary H. Lyman[1], David C. Dale[2], Jason C. Legg[3], Esteban Abella[4], Phuong Khanh Morrow[4], Sadie Whittaker[4] & Jeffrey Crawford[5]

- 124 physicians
- 944 patients
- Poor correlation with physician assessed risk and validated model assessed risk : 0.25 (95% CI : 0.18-0.32)
- Moderate correlation between physician assessed risk and subsequent order for growth factors administration : 0.31 (95% CI : 0.14-0.47)

Conclusions

- Some risk factors are clearly identified
- Limited tools to predict FN
- Further research on that topic ?
- Use of growth factors might be improved