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Prediction of Febrile Neutropenia Based on Pre-treatment Risk Factors in Patients with Cancer

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INTRODUCTION

Febrile neutropenia (FN) is a common complication to chemotherapy and is associated with a high burden of morbidity and mortality[1]. Identification of those at highest risk may optimise the use of granulocyte-colony stimulating factors, prophylactic antibiotics and intensity of patient monitoring[2].

AIM OF THE STUDY

We aimed to develop a risk stratification model based on pre-treatment risk factors to predict FN in the 30 days after initiation of chemotherapy.

METHODS AND DESIGN

We included consecutive treatment-naïve patients with solid cancers including diffuse large B-cell lymphomas (DLBCL) at Copenhagen University Hospital, 2010 to 2015. Data were obtained from the PERSIMUNE repository of electronic health records. FN was defined as neutrophils <= 0.5 x 10^9/L within 3 days of a proxy for fever: a blood culture sample or death. Time from initiation of chemotherapy to FN was analysed using Fine-Gray regression models with death as a competing event. Risk factors investigated were: age, sex, body surface area, haemoglobin, albumin, neutrophil-to-lymphocyte ratio, Charlson Comorbidity Index (CCI) and chemotherapy drugs. Parameter estimates were scaled and summed to create the risk score. The scores were subsequently grouped into four: low, intermediate, high and very high risk.

Table 1

Risk factors for febrile neutropenia

Risk factor	N (%)	Hazard ratio (95% CI)	P-value
Female sex	4,372 (51)	1.35 (1.13-1.61)	0.001
Age > 65 years	3,952 (46)	1.37 (1.15-1.64)	0.001
Body surface area < 2 m²	6,253 (73)	1.45 (1.14-1.86)	0.003
Haemoglobin < 8 mmol/L	3,918 (46)	1.56 (1.30-1.86)	<0.001
Neutrophil-to-lymphocyte ratio > 3.3	3,516 (41)	1.28 (1.05-1.56)	0.013
Albumin < 39 g/L	3,145 (37)	1.74 (1.44-2.11)	<0.001
Charlson Comorbidity Index > 2	1,820 (21)	1.75 (1.45-2.12)	<0.001

Fine and Gray competing-risks regression with death as a competing event was used and sub-distribution hazard ratios reported. Chemotherapy drugs were included as one variable with 23 indicator variables and are not shown for simplicity, overall Wald test was <0.001.

Table 2

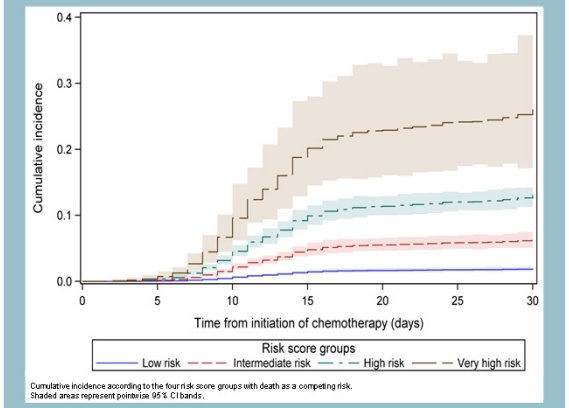
Model for risk score for febrile neutropenia

Risk factor	N (%)	Parameter estimate[a]	Scaled estimate used for risk score	P-value
Age > 65 years	3,952 (46)	0.30673	1	0.002
Albumin < 39 g/L	3,145 (37)	0.36407	1	<0.001
Charlson Comorbidity Index > 2	1,820 (21)	0.38167	1	<0.001
Chemotherapy drugs				
Oxaliplatin	1,204 (14)	-1.29920	-4	<0.001
Carboplatin	2,357 (27)	1.02252	3	<0.001
Cyclophosphamide	1,321 (15)	1.32812	4	0.002
Temozolomide	624 (7)	-1.60360	-5	0.005
Docetaxel	977 (11)	0.62944	2	<0.001
Paclitaxel	260 (3)	-1.38323	-5	0.001
Etoposide	287 (3)	1.05402	3	<0.001
Pemetrexed	384 (4)	-1.38534	-5	<0.001
Capecitabine	1,174 (14)	-0.42165	-1	0.018
Cetuximab	13 (0)	1.91747	6	<0.001

Fine and Gray competing-risks regression with death as a competing event was used and sub-distribution hazard ratios reported.
[a]Adjusted for sex, body surface area, haemoglobin level, neutrophil-to-lymphocyte ratio and use of the following drugs: cisplatin, doxorubicin, epirubicin, irinotecan, fluorouracil, gemcitabine, vincristine, vinorelbine, bleomycin, trastuzumab.

Figure 1

Cumulative incidence of febrile neutropenia



Cumulative incidence according to the four risk score groups with death as a competing risk.
Shaded areas represent pointwise 95% CI bands.

Table 3

Final prediction model

Risk group	Number of patients (%)	Risk score	Incidence rate per 30 person-days (95% CI)	Hazard ratio[a] (95% CI)
Low	4,859 (57)	<3	0.02 (0.02-0.02)	Reference
Intermediate	1,881 (22)	3-4	0.07 (0.06-0.08)	3.4 (2.6-4.4)
High	1,747 (20)	5-7	0.14 (0.13-0.16)	7.2 (5.7-9.2)
Very high	98 (1)	8+	0.31 (0.21-0.45)	15.5 (9.9-24.3)

[a]Fine and Gray competing-risks regression with death as a competing event was used and sub-distribution hazard ratios reported

RESULTS

Among 8,585 patients with twenty-six types of solid cancer or DLBCL, FN was experienced by 467 patients. The incidence rate was 0.06 (95% CI, 0.05-0.06) per 30 person-days. Univariate analyses of risk factors are shown in **table 1**. Multivariable analyses used to calculate parameter estimates for the risk factors are shown in **table 2**. Age (1 point if > 65 years), albumin (1 point if < 39 g/L), CCI (1 point if > 2) and chemotherapy (range of -5 to 6 points per drug) predicted FN. Median score at chemotherapy initiation was 2 points (range –5 to 9). The cumulative incidence and the incidence rates and hazard ratios of developing FN are shown in **figure 1** and **table 3**, respectively, for the four risk groups.

CONCLUSION

We developed a risk score for prediction of febrile neutropenia the first month after initiation of chemotherapy.

PERSPECTIVES

The score is easy to use and provides good differentiation of risk groups, but needs to be validated in an independent population.

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