Development of a predictive model for febrile neutropenia after chemotherapy in patients with non-Hodgkin's lymphoma and diffuse large B cell lymphoma

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Abstract

Background: Determining risk factors for the development of febrile neutropenia (FN) in patients with non-Hodgkin's lymphoma (NHL) is difficult. We aimed to develop a prediction model for FN occurrence in NHL and diffuse large B-cell lymphoma (DLBCL) based on data commonly available in clinical settings.

Methods: We conducted a multicenter retrospective observational study among lymphoma patients treated with chemotherapy. We collected data on demographic characteristics, disease status, complications, previous illness, and blood parameters. A multivariable logistic regression model was used to analyze the association between these parameters and the incidence of FN. The bootstrapping method was used to evaluate internal validity.

Results: Of 405 patients with NHL in this study, 246 patients had DLBCL and 159 patients had other types of NHL. In the population of patients with DLBCL treated with low-intermediate intensity chemotherapy (194 patients), a predictive risk model was constructed as follows: 2 points for chronic viral hepatitis, 2 points for lymphocyte count $<0.7 \times 10^9$ /L, 1 point for extranodal involvement, and 1 point for soluble interleukin-2 receptor >2000 IU/L. The area under the receiver operating characteristic (ROC) curve was 0.839 (95% CI: 0.764-0.914). Bootstrapped validation beta coefficients of these predictors were identical to those of the original.

Conclusion: This study suggests prediction models for assessing the incidence of FN after chemotherapy in patients with DLBCL and NHL. A prediction model for DLBCL, which included four clinical predictors had high level of accuracy. This risk model is useful for classifying the risk of developing FN before initiating chemotherapy.

Keywords: febrile neutropenia, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma

List of abbreviations

ALC	absolute lymphocyte count
ANC	absolute neutrophil count
AUC	area under the curve
BMI	body mass index
CI	confidence interval
CRP	C-reactive protein
DLBCL	diffuse large B-cell lymphoma
eGFR	estimated glomerular filtration rate
EORTC	European Organization for Research and Treatment of Cancer
FN	febrile neutropenia
G-CSF	granulocyte-colony stimulating factor
IQR	interquartile range
LD	lactate dehydrogenase
NHL	non-Hodgkin's lymphoma
ROC	receiver operating characteristic
sIL2R	soluble interleukin-2 receptor
T-Bil	total bilirubin
WBC	white blood cell

1. INTRODUCTION

1.1. Background Information

Chemotherapy-induced neutropenia is a serious and common clinical condition in the treatment of patients with malignancy. Febrile neutropenia (FN) is the most common complication in patients with malignant disease treated with chemotherapy. FN caused by myelosuppression increases mortality and prolongs hospitalization [1]. Neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hours [2]. FN is defined as the presence of neutropenia accompanied by fever - a single oral temperature measurement of ≥38.3 °C or a temperature of ≥38.0 °C sustained over a 1 hour period [2].

Chemotherapy regimens have been classified as having high, intermediate, or low risk of causing neutropenia and FN, according to previous studies [3]. The European Organization for Research and Treatment of Cancer (EORTC) guidelines state that chemotherapy regimens with an incidence rate of FN ≥ 20%, 10-20%, and <10% are considered as having high, intermediate, and low risk for FN, respectively [4]. Granulocyte colony-stimulating factor (G-CSF) is used to prevent FN after chemotherapy. Several guidelines recommend prophylaxis with G-CSF for patients treated with chemotherapeutic agents with an FN incidence ≥20% [4].

Non-Hodgkin's lymphoma (NHL) is a type of cancer that begins in the lymphatic system, which is part of the immune system. There are many subtypes of NHL, and diffuse large B-cell lymphoma (DLBCL) is the most common. DLBCL is a clinically, biologically, and genetically heterogeneous disease [5]. If the disease relapses after initial treatment, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) treatment for NHL, salvage therapy is used for the second and subsequent lines of treatment. In general, salvage therapy causes more intense myelosuppression and a higher incidence of FN than initial therapy. However, some patients undergoing only initial therapy develop FN more frequently than others. Older age, poor performance status, advanced disease, comorbidities, low blood cell counts, and low body surface area/body mass index are potential risk factors for FN, according to a systematic review [6]. However, there is no comprehensive predictive risk model to guide clinical practice.

Identifying prognostic factors for the development of FN in initially treated patients with lymphoma is a clinically important task. If the causal relationship between the patient's background or disease status and the incidence of FN can be determined, appropriate actions can be taken to prevent the onset of FN.

1.2. Objectives

The purpose of this study is to construct a predictive model for FN after chemotherapy in patients with NHL and DLBCL. Although several potential risk factors for developing FN in patients with malignancy have been reported in the literature, there is no predictive model available for use in clinical settings. In this study, we evaluate the risk factors for the development of FN in association with chemotherapy for NHL.

2. METHODS

2.1. Study design and patients

This was a retrospective multicenter cohort study. Data were collected from Kinan Hospital (Wakayama, Japan) and St. Luke's International Hospital (Tokyo, Japan). The medical records of all adult inpatients and outpatients (≥ 18 years) who were diagnosed with NHL between January 1, 2010 and December 31, 2020 at Kinan Hospital and between January 1, 2010 and December 31, 2018 at St. Luke's International Hospital were reviewed. Because each patient underwent multiple treatments, data were collected for each patient rather than for each episode to avoid duplication of the assessment parameters. We included adult patients with lymphoma treated with chemotherapy containing myelotoxic agents. Excluded patients were those who were too severely ill to receive chemotherapy from the beginning, those who were transferred to our hospital after being diagnosed and treated at other hospitals, and those who were treated with only monoclonal antibody medications, such as rituximab monotherapy.

Because this study was based on existing data from medical records, informed consent from subjects was waived. This study was approved by the research ethics committee of each hospital (Kinan Hospital: 229, St. Luke's International Hospital: 19-R106).

2.2. Data collection

All expected parameters were based on previous studies and clinical insights. Data on the following were collected: patient demographic characteristics including age, sex, height, weight, body mass index (BMI); disease status (pathological diagnosis, Ann Arbor stage, bone marrow infiltration, and extranodal involvement); complications (diabetes mellitus, chronic viral hepatitis [without mention of cirrhosis], chronic kidney disease, cardiac disease, or chronic obstructive lung disease); previous illness (malignancy, surgical history [surgery with general anesthesia], or others); and blood parameters (albumin, total bilirubin, creatinine, estimated glomerular filtration rate, lactate dehydrogenase, C-reactive protein, soluble interleukin-2 receptor [sIL2R], white blood cell count, ANC, ALC, hemoglobin, and platelet count). The following data on treatment were collected: type of chemotherapy regimen, relative dose intensity, prophylactic antibiotics and G-CSF use, and incidence of FN. Chemotherapy regimen was divided into two groups: high-intensity and low-intermediate intensity. Patients who were administered a high-intensity regimen at least once during multiple courses of treatment were in the high-intensity group, and patients who were not administered a high-intensity regimen were in the low-intermediate intensity group. Since the intensity of chemotherapy is clearly related to the development of FN, we evaluated the data separately in the low-intermediate intensity and high intensity groups.

2.3. Study endpoints

The primary endpoint of this study was the incidence of FN in cycle 1 of chemotherapy in patients with DLBCL and NHL. The secondary endpoint was the incidence of FN in all cycles of chemotherapy in patients with DLBCL and NHL. FN was defined as the presence of axillary body temperature ≥ 37.5° C with neutropenia (ANC <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hours).

2.4. Statistical analyses

Descriptive statistics were used to summarize baseline measurements. Continuous and categorical variables are presented as median (interquartile range [IQR]) and n (%), respectively. To create the prediction model, hematological parameters and other continuous variables were converted into binary variables by using clinically important values as cutoffs. We used the χ^2 test to compare parameters between patients with and without FN. Univariable and multivariable logistic regression models were used to explore the risk factors associated with FN onset. All candidate predictors for which the p-value was <0.2 in univariable analysis were included in a backward stepwise logistic regression model, with a p-value of 0.05 for final entry or removal. The scores for each predictor were obtained using the beta coefficient from the final model. A receiver operating characteristic (ROC) curve was drawn, and the area under the curve (AUC) was obtained. For internal validation, a bootstrapping method with 1000 iterations was used to simulate unbiased outcomes. All statistical analyses were conducted using Stata version 17.0 (StataCorp, College Station, Texas 77845 USA).

3. RESULTS

A total of 207 patients (1369 episodes) at Kinan Hospital and 198 patients (1194 episodes) at St. Luke's International Hospital were included in this study. In a total of 405 patients, most were Japanese (Japan: 393, North America: 9, South America: 1, Europe: 2). Their baseline demographic and disease characteristics are summarized for each of DLBCL and non-DLBCL in Table 1. Of the 405 patients, 246 (61%) had DLBCL and 159 (39%) had other types of NHL; follicular lymphoma (69; 17%), Burkitt lymphoma (8; 2.0%), high grade B-cell lymphoma (5; 1.2%), marginal zone lymphoma (18; 4.4%), mantle cell lymphoma (4; 1.0%), peripheral T-cell lymphoma (19; 4.7%), anaplastic large cell lymphoma (2; 0.5%), angioimmunoblastic T-cell lymphoma (16; 4.0%), others (18; 4.4%). The median age of the patients was 70.0 years (IQR: 61.0-78.0), ranging from 25 to 100 years, and there were more women than men. Diabetes (15%) and cardiac disease (15%) were common comorbidities. There were no patients with HIV infection. Nearly half of the patients had Ann Arbor stage IV disease, and approximately one-third had limited disease (I-II: 32%, III-IV: 68%). Approximately a quarter of the patients had bone marrow infiltration, and extranodal involvement was present in more than half of them. Low-intermediate intensity regimen refers to chemotherapy that causes relatively mild myelosuppression, such as R-CHOP, while a high-intensity regimen refers to chemotherapy that causes severe myelosuppression requiring hospitalization, such as E-SHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin). Patients treated with low-intermediate intensity regimens were more in number (total NHL: 302/405 [75 %], DLBCL: 194/246 [79%]). The intensity of chemotherapy was significantly

associated with the onset of FN ($p < 0.001$; data not shown), which is why the results were analyzed by the intensity of the chemotherapy regimen.

Tables 2 and 3 show the univariable analysis for patients who were treated with the low-intermediate intensity regimen, while univariable analysis data of the high-intensity regimen are shown in Appendix B-C. Table 2 shows the association of variables with the incidence of FN in cycle 1 of chemotherapy (primary endpoint), and Table 3 shows that in all cycles of chemotherapy (secondary endpoint). According to these results for DLBCL patients (Table 2), three comorbidities (viral hepatitis, lung disease, and history of surgery), six laboratory findings (platelet, lymphocyte, albumin, lactate dehydrogenase, C-reactive protein, and soluble interleukin-2 receptor), and three items related to lymphoma (Ann Arbor stage, extranodal involvement, and bone marrow infiltration) were selected as candidate predictors for prediction of FN in cycle 1 for DLBCL patients.

Backward stepwise logistic regression analysis was performed for all of the candidate predictors. Based on this analysis, chronic viral hepatitis, extranodal involvement, low lymphocyte count (lymphopenia), and high sIL2R levels were selected as significant prognostic predictors based on a p-value <0.05. Table 4A shows the results of this analysis in cycle 1 for DLBCL. The same analysis was performed for the other three situations; Table 4B shows the factors associated with FN in cycle 1 of chemotherapy for NHL, Table 5A shows the factors associated with FN in all cycles of chemotherapy for DLBCL, and Table 5B shows the factors associated with FN in all cycles of chemotherapy for NHL.

For the factors associated with FN in cycle 1 of chemotherapy for DLBCL, scores for each predictor were obtained on the beta coefficient: chronic viral hepatitis, 2 points; extranodal involvement, 1 point; lymphopenia, 2 points; and high sIL2R levels, 1 point. We calculated the sum of scores for each patient and obtained a ROC curve (Figure 1). The AUC (95% CI) of this model was 0.839 (0.764-0.914). Figure 2 shows the distribution of the prognostic score and FN incidence for each score. When the cutoff value of this score was two out of six, the sensitivity was 85.7%, and the specificity was 73.8%. Other ROC curves were also drawn; Figure A.1 was created using the factors shown in Table 4B, Figure A.2 was created using the factors shown in Table 5A, and Figure A.3 was created using the factors shown in Table 5B.

Finally, we performed bootstrap validation with 1000 iterations for this prediction model. Table 6A shows the observed beta coefficient and bootstrapped validation results for the first FN in DLBCL. Table 6B shows that for first FN in NHL, Table 7A for overall FN in DLBCL, and Table 7B for overall FN in NHL. All simulation data indicated that there was a high internal validity.

Table 1. Demographic and clinical characteristics of study patients

	Total NHL n=405	DLBCL n=246	non-DLBCL n=159
Age, years	70.0 (61.0-78.0)	72.0 (63.0-79.0)	67.0 (58.0-75.0)
Sex			
Female	226 (56%)	146 (59%)	80 (50%)
Male	179 (44%)	100 (41%)	79 (50%)
Comorbidity			
Diabetes	59 (15%)	36 (15%)	23 (14%)
Chronic viral hepatitis	20 (5%)	17 (7%)	3 (2%)
Chronic kidney disease	20 (5%)	14 (6%)	6 (4%)
Cardiac disease	59 (15%)	38 (15%)	21 (13%)
Chronic obstructive lung disease	10 (2%)	5 (2%)	5 (3%)
Malignancy	45 (11%)	31 (13%)	14 (9%)
Surgery history	90 (22%)	55 (22%)	35 (22%)
Ann Arbor Stage			
I	44 (11%)	39 (16%)	5 (3%)
II	86 (21%)	55 (22%)	31 (19%)
III	80 (20%)	44 (18%)	36 (23%)
IV	194 (48%)	108 (44%)	86 (54%)
Bone marrow infiltration			
Yes	98 (24%)	44 (18%)	54 (34%)
No	307 (76%)	202 (82%)	105 (66%)
Extranodal involvement			
Yes	231 (57%)	140 (57%)	91 (57%)
No	174 (43%)	106 (43%)	68 (43%)
Baseline laboratory data			
eGFR <60 ml/min/1.73m^2	96 (24%)	61 (25%)	35 (22%)
T-Bil >1.0 g/dL	55 (14%)	35 (15%)	20 (13%)
Albumin <3.5 g/dL	140 (35%)	87 (36%)	53 (34%)
LD > 222 IU/L	227 (57%)	147 (60%)	80 (51%)
CRP >10 mg/dL	25 (7%)	13 (6%)	12 (8%)
sIL2R >2000 IU/L	159 (41%)	93 (40%)	66 (44%)
WBC <3.5 x 10^9 /L	47 (12%)	29 (12%)	18 (11%)
ANC <1.5 x 10^9 /L	20 (5%)	9 (4%)	11 (7%)
ALC <0.7 x 10^9 /L	84 (21%)	54 (22%)	30 (19%)
Hemoglobin <12.0 g/dL	186 (46%)	114 (46%)	72 (46%)
Platelets <100 x 10^9 /L	58 (14%)	32 (13%)	26 (16%)
Chemotherapy type			
Low-intermediate intensity	302 (75%)	194 (79%)	108 (68%)
High intensity	103 (25%)	52 (21%)	51 (32%)

Abbreviations: eGFR, estimated glomerular filtration rate; T-Bil, total bilirubin; LD, lactate dehydrogenase; CRP, C-reactive protein; sIL2R, soluble interleukin-2 receptor; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count

Table 2. Univariable analysis: factors associated with the incidence of FN in cycle 1 for patients who were treated by low-intermediate intensity regimen

	DLBCL patients with FN n=37	DLBCL patients without FN n=157	p-value	NHL patients with FN n=50	NHL patients without FN n=252	p-value
Age ≥ 65	26 (70%)	112 (71%)	0.9	37 (74%)	168 (67%)	0.31
Sex: male	21 (57%)	88 (56%)	0.94	28 (56%)	131 (52%)	0.6
Comorbidity						
Diabetes	4 (11%)	28 (18%)	0.3	6 (12%)	41 (16%)	0.45
Chronic viral hepatitis	8 (22%)	6 (4%)	<0.001	8 (16%)	9 (4%)	<0.001
Chronic kidney disease	2 (5%)	8 (5%)	0.94	5 (10%)	10 (4%)	0.073
Cardiac disease	7 (19%)	26 (17%)	0.73	8 (16%)	40 (16%)	0.98
Chronic obstructive lung disease	2 (5%)	2 (1%)	0.11	3 (6%)	5 (2%)	0.11
Malignancy	6 (16%)	18 (11%)	0.43	7 (14%)	25 (10%)	0.39
Surgery	3 (8%)	4 (3%)	0.1	7 (14%)	6 (2%)	<0.001
Baseline laboratory data						
WBC <3.5 x 10^9 /L	5 (14%)	17 (11%)	0.64	7 (14%)	30 (12%)	0.68
Hb <12.0 g/dL	20 (54%)	72 (46%)	0.37	30 (60%)	109 (43%)	0.03
Platelets <100 x 10^9 /L	11 (30%)	13 (8%)	<0.001	15 (30%)	25 (10%)	<0.001
ANC <1.5 x 10^9 /L	2 (5%)	6 (4%)	0.67	2 (4%)	12 (5%)	0.81
ALC <0.7 x 10^9 /L	20 (54%)	22 (14%)	<0.001	21 (42%)	36 (14%)	<0.001
T-Bil >1.0 g/dL	6 (16%)	21 (14%)	0.73	7 (14%)	32 (13%)	0.9
Albumin <3.5 g/dL	22 (63%)	49 (31%)	<0.001	30 (62%)	71 (28%)	<0.001
LD > 222 IU/L	27 (75%)	82 (53%)	0.014	37 (76%)	120 (48%)	<0.001
CRP >10 mg/dL	5 (14%)	5 (4%)	0.02	5 (10%)	10 (4%)	0.12
eGFR <60 ml/min/1.73m^2	13 (35%)	39 (25%)	0.2	19 (38%)	59 (24%)	0.034
sIL2R >2000 IU/L	25 (71%)	44 (30%)	<0.001	33 (73%)	79 (33%)	<0.001
Ann Arbor stage: Advanced (III-IV)	30 (83%)	78 (50%)	<0.001	41 (84%)	156 (62%)	0.003
Extranodal involvement	27 (73%)	75 (48%)	0.006	34 (68%)	131 (52%)	0.038
Bone marrow infiltration	12 (32%)	18 (11%)	0.002	17 (34%)	51 (20%)	0.033

Abbreviations: eGFR, estimated glomerular filtration rate; T-Bil, total bilirubin; LD, lactate dehydrogenase; CRP, C-reactive protein; sIL2R, soluble interleukin-2 receptor; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count

Table 3. Univariable analysis: factors associated with the incidence of FN in all cycles for patients who were treated by low-intermediate intensity regimen

	DLBCL patients with FN n=64	DLBCL patients without FN n=130	p-value	NHL patients with FN n=87	NHL patients without FN n=215	p-value
Age ≥ 65	47 (73%)	91 (70%)	0.62	67 (77%)	138 (64%)	0.031
Sex: male	38 (59%)	71 (55%)	0.53	52 (60%)	107 (50%)	0.11
Comorbidity						
Diabetes	10 (16%)	22 (17%)	0.82	15 (17%)	32 (15%)	0.61
Chronic viral hepatitis	9 (14%)	5 (4%)	0.01	10 (11%)	7 (3%)	0.005
Chronic kidney disease	5 (8%)	5 (4%)	0.24	9 (10%)	6 (3%)	0.006
Cardiac disease	12 (19%)	21 (16%)	0.65	15 (17%)	33 (15%)	0.68
Chronic obstructive lung disease	2 (3%)	2 (2%)	0.46	3 (3%)	5 (2%)	0.58
Malignancy	8 (12%)	16 (12%)	0.97	11 (13%)	21 (10%)	0.46
Surgery	17 (27%)	27 (21%)	0.36	27 (31%)	39 (18%)	0.014
Baseline laboratory data						
WBC <3.5 x 10^9 /L	7 (11%)	15 (12%)	0.9	9 (10%)	28 (13%)	0.52
Hb <12.0 g/dL	33 (52%)	59 (45%)	0.42	47 (54%)	92 (43%)	0.076
Platelets <100 x 10^9 /L	14 (22%)	10 (8%)	0.005	20 (23%)	20 (9%)	0.001
ANC <1.5 x 10^9 /L	2 (3%)	6 (5%)	0.62	2 (2%)	12 (6%)	0.22
ALC <0.7 x 10^9 /L	24 (38%)	18 (14%)	<0.001	26 (30%)	31 (14%)	0.002
T-Bil >1.0 g/dL	9 (14%)	18 (15%)	0.92	11 (13%)	28 (14%)	0.79
Albumin <3.5 g/dL	36 (58%)	35 (27%)	<0.001	46 (54%)	55 (26%)	<0.001
LD > 222 IU/L	43 (68%)	66 (51%)	0.025	60 (70%)	97 (46%)	<0.001
CRP >10 mg/dL	5 (8%)	5 (4%)	0.29	5 (6%)	10 (5%)	0.79
eGFR <60 ml/min/1.73m^2	22 (34%)	30 (23%)	0.095	33 (38%)	45 (21%)	0.003
sIL2R >2000 IU/L	36 (60%)	33 (27%)	<0.001	53 (67%)	59 (28%)	<0.001
Ann Arbor stage: Advanced (III-IV)	49 (78%)	59 (45%)	<0.001	70 (81%)	127 (59%)	<0.001
Extranodal involvement	41 (64%)	61 (47%)	0.025	55 (63%)	110 (51%)	0.057
Bone marrow infiltration	16 (25%)	14 (11%)	0.01	24 (28%)	44 (20%)	0.18

Abbreviations: eGFR, estimated glomerular filtration rate; T-Bil, total bilirubin; LD, lactate dehydrogenase; CRP, C-reactive protein; sIL2R, soluble interleukin-2 receptor; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count

Table 4A. Multivariable logistic regression: risk factors associated with the incidence of FN in cycle 1 for DLBCL patients who were treated by low-intermediate intensity regimen

				n=184
	Odds ratio [95% CI]	β coefficient [95% CI]	Score	p-value
Chronic viral hepatitis	9.95 [2.30-43.09]	2.30 [0.83-3.76]	2	0.002
Extranodal involvement	2.90 [1.12-7.49]	1.06 [0.11-2.01]	1	0.028
ALC <0.7 x 10^9 /L	6.02 [2.39-15.17]	1.79 [0.87-2.72]	2	<0.001
sIL2R >2000 IU/L	3.38 [1.36-8.44]	1.22 [0.31-2.13]	1	0.009

Abbreviations: DLBCL, diffuse large B cell lymphoma

Table 4B. Multivariable logistic regression: risk factors associated with the incidence of FN in cycle 1 for NHL patients who were treated by low-intermediate intensity regimen

				n=285
	Odds ratio [95% CI]	β coefficient [95% CI]	Score	p-value
Chronic viral hepatitis	6.11 [1.82-20.47]	1.81 [0.60-3.02]	2	0.003
ALC <0.7 x 10^9 /L	3.11 [1.40-6.88]	1.13 [0.34-1.93]	1	0.005
sIL2R >2000 IU/L	3.33 [1.52-7.30]	1.20 [0.42-1.99]	1	0.003

Abbreviations: NHL, non-Hodgkin's lymphoma

Table 5A. Multivariable logistic regression: risk factors associated with the incidence of FN in all cycles for DLBCL patients who were treated by low-intermediate intensity regimen

				n=191
	Odds ratio [95% CI]	β coefficient [95% CI]	Score	p-value
Ann Arbor stage: Advanced (III-IV)	3.02 [1.44-6.34]	1.10 [0.36-1.85]	1	0.004
ALC <0.7 x 10^9 /L	2.45 [1.10-5.47]	0.90 [0.09-1.70]	1	0.029
Alb <3.5 g/dL	2.44 [1.20-4.94]	0.89 [0.19-1.60]	1	0.013

Abbreviations: DLBCL, diffuse large B cell lymphoma

Table 5B. Multivariable logistic regression: risk factors associated with the incidence of FN in all cycles for NHL patients who were treated by low-intermediate intensity regimen

				n=286
	Odds ratio [95% CI]	β coefficient [95% CI]	Score	p-value
Chronic viral hepatitis	5.33 [1.58-17.95]	1.67 [0.46-2.89]	2	0.007
Ann Arbor stage: Advanced (III-IV)	2.20 [1.09-4.45]	0.79 [0.08-1.49]	1	0.029
ALC <0.7 x 10^9 /L	2.20 [1.10-4.40]	0.79 [0.10-1.48]	1	<0.001
sIL2R >2000 IU/L	3.27 [1.78-5.99]	1.18 [0.58-1.79]	2	0.025

Abbreviations: NHL, non-Hodgkin's lymphoma

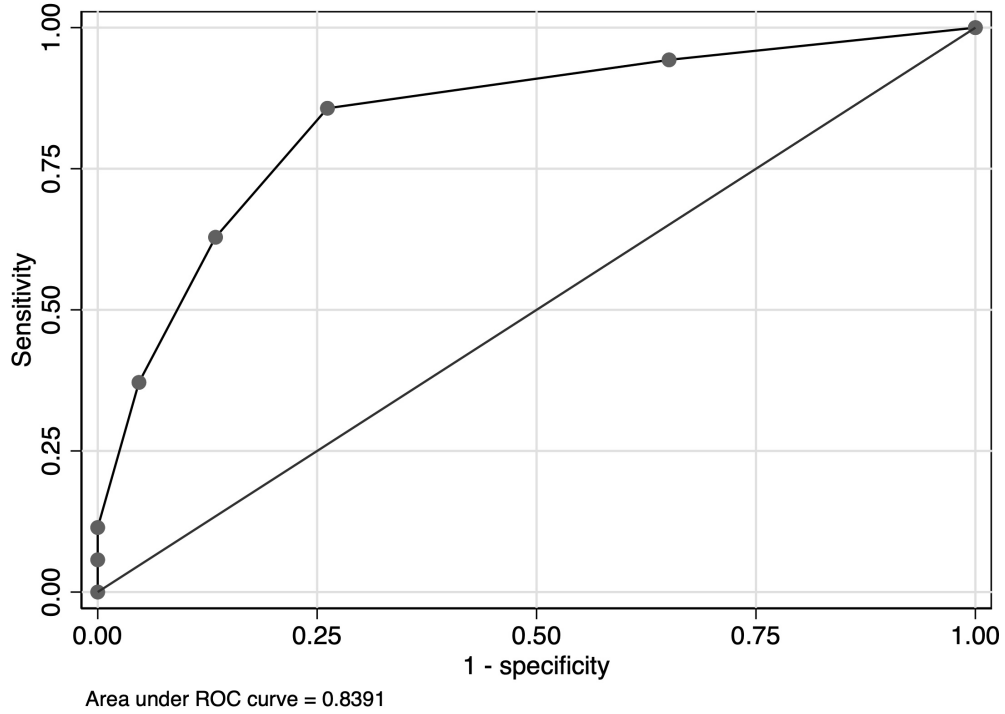

Figure 1. ROC curve of the prediction score for first FN in DLBCL
Area under the curve (AUC) (95% CI) = 0.839 (0.764-0.914)
This ROC was created using factors shown in Table 4A.

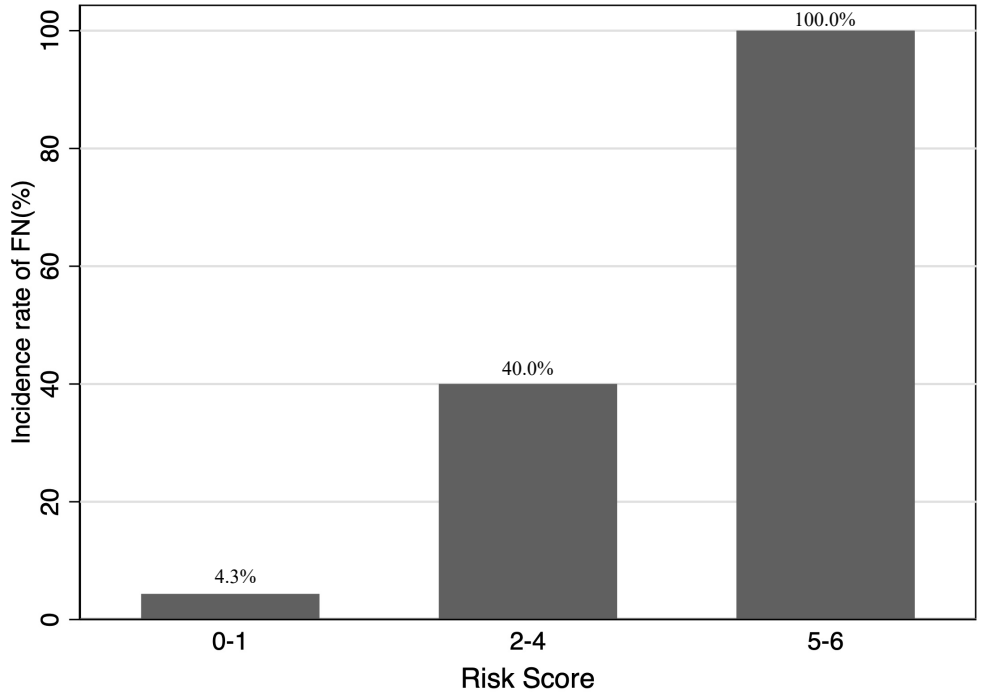

Figure 2. Incidence rate of FN in cycle 1 for DLBCL based on prediction scores

Table 6A. Bootstrap validation of the prediction model for first FN in DLBCL and comparison with the original model

			n=184
	Logistic regression β coefficient [95% CI]	Bootstrapped β coefficient [95% CI]	Score
Chronic viral hepatitis	2.30 [0.83-3.76]	2.43 [0.71-3.88]	2
Extranodal involvement	1.06 [0.11-2.01]	1.15 [0.00-2.27]	1
ALC <0.7 x 10^9 /L	1.79 [0.87-2.72]	1.87 [0.65-2.76]	2
sIL2R >2000 IU/L	1.22 [0.31-2.13]	1.35 [0.14-2.16]	1

Table 6B. Bootstrap validation of the prediction model for first FN in NHL and comparison with the original model

			n=285
	Logistic regression β coefficient [95% CI]	Bootstrapped β coefficient [95% CI]	Score
Chronic viral hepatitis	1.81 [0.60-3.02]	1.88 [0.52-3.10]	2
ALC <0.7 x 10^9 /L	1.13 [0.34-1.93]	1.19 [0.26-2.00]	1
sIL2R >2000 IU/L	1.20 [0.42-1.99]	1.28 [0.34-2.06]	1

Table 7A. Bootstrap validation of the prediction model for overall FN in DLBCL and comparison with the original model

			n=191
	Logistic regression β coefficient [95% CI]	Bootstrapped β coefficient [95% CI]	Score
Ann Arbor stage: Advanced (III-IV)	1.10 [0.36-1.85]	1.15 [0.32-1.89]	1
ALC <0.7 x 10^9 /L	0.90 [0.09-1.70]	0.92 [0.05-1.74]	1
Alb <3.5 g/dL	0.89 [0.19-1.60]	0.92 [0.14-1.65]	1

Table 7B. Bootstrap validation of the prediction model for overall FN in NHL and comparison with the original model

			n=286
	Logistic regression β coefficient [95% CI]	Bootstrapped β coefficient [95% CI]	Score
Chronic viral hepatitis	1.67 [0.46-2.89]	1.79 [0.39-2.96]	2
Ann Arbor stage: Advanced (III-IV)	0.79 [0.08-1.49]	0.80 [0.03-1.55]	1
ALC <0.7 x 10^9 /L	0.79 [0.10-1.48]	0.81 [0.06-1.52]	1
sIL2R >2000 IU/L	1.18 [0.58-1.79]	1.24 [0.56-1.80]	2

4. DISCUSSION

This retrospective observational study identified potential risk factors for FN in patients with lymphoma after chemotherapy. In this study, among 405 patients who received chemotherapy, 156 developed FN at least once during all treatment courses, including 75 (48.1%) who developed FN during the first treatment cycle. These data are consistent with those from a previous report [7]; thus, it is important to focus on the first chemotherapy session. Because the development of FN during the initial treatment for DLBCL is of greatest clinical interest across NHL subtypes, we focused on prognostic factors associated with this phenomenon. The four predictors identified in the multivariable logistic regression analysis were chronic viral hepatitis, extranodal involvement, lymphopenia, and a high sIL2R levels. Although liver cirrhosis is associated with severe infection owing to impaired innate immune function [8], till date, no studies have yet shown a relationship between viral hepatitis and FN occurrence. This study indicated that chronic viral hepatitis is a significant risk factor for the onset of FN in cycle 1 of chemotherapy in patients with DLBCL (OR [95% CI]: 9.95 [2.30-43.09]) (Table 4A), and this has important clinical implications. Extranodal involvement affects the prognosis of DLBCL [9] and is used as a risk factor in the International Prognostic Index (IPI) [10]. Since DLBCL with extranodal involvement requires a higher dose of chemotherapy, the resultant intense myelosuppression may be a reason for the associated risk of developing FN. High sIL2R levels and lymphopenia are important risk factors among hematological parameters. Elevated sIL2R levels before treatment have been reported to be associated with poor prognosis in NHL, including DLBCL [11,12]. Lymphopenia was an important prognostic factor for the entire study population (Tables 4A, 4B, 5A, and 5B). Lymphopenia can be caused by many conditions such as congenital immunodeficiency diseases [13], malnutrition [14], alcohol abuse [15], malignancies [16], systemic autoimmune diseases [17], and infections [18]. A prospective study demonstrated that lymphopenia was associated with a high risk of hospitalization and infection-related death in patients with cancer [19]. Although the causality is unknown, lymphopenia is a clinically important factor in the development of infectious diseases and FN in patients receiving chemotherapy.

To evaluate the prognosis of FN in the first cycle of chemotherapy for patients with DLBCL, we developed a prognostic model comprising four factors: chronic viral hepatitis, extranodal involvement, lymphopenia, and high sIL2R levels. The AUC of this model exhibited a relatively high level of accuracy (AUC = 0.839; 95% CI: 0.764-0.914). The incidence rate of FN was very low (4.3%) among patients whose total score calculated using this model was 0-1 (Figure 2). The sensitivity of the model was 85.7% when the cutoff value of the scores was two out of six. We believe that this model can be used as a tool for identifying patients who are less likely to develop FN in the future. Clinicians always consider the possibility of FN development in patients with DLBCL when they initiate chemotherapy. Patients who have a low score (0-1 points) in this model can be transferred from inpatient to outpatient care relatively earlier without the need for G-CSF administration.

According to the guidelines on the appropriate use of G-CSF [4], the incidence rate of FN in patients undergoing myelosuppressive chemotherapy is 13–21%. In our study, the incidence rate of FN in cycle 1 was 18.5% (75/405), which is consistent with results of

previous reports. FN during chemotherapy is significantly associated with a long-term increase in risk of infections [20]; it can lead to a delayed treatment schedule with early termination and a reduction in the chemotherapy dose, which is associated with high mortality. Therefore, preventing FN can improve overall treatment outcomes for patients. Many studies have indicated that prophylaxis with G-CSF can reduce FN [4,21]; however, the routine use of primary G-CSF prophylaxis in patients with DLBCL is a controversial issue from an economic perspective[22]. If our model can be used to differentiate patients who need G-CSF and those who do not, it can lead to the optimization of treatment of lymphoma.

Although older age (≥65 years) has been reported to be a risk factor for the development of FN [23,24], we did not find any evidence supporting this. A possible reason for this is that the reduction of chemotherapy dose in geriatric patients causes milder myelosuppression than that caused by the usual regimen. Japan is a super-aged society, and the median age of patients in this study was 70 years. Our study is, thus, a significant analysis of FN development in the geriatric population.

4.1. Limitations

This study has some limitations. First, the study population was from only two facilities. St. Luke's International Hospital is located in the center of the capital city, and Kinan Hospital is located in the countryside of Japan. This is good because it shows the diversity of the population; the mean age of patients in each hospital was significantly different ($p = 0.001$). We also performed bootstrapping for internal validation; however, this is not sufficient, and external validation is needed in future studies.

Second, we did not assess the association of prophylactic use of G-CSF and antibiotics with the development of FN. Prophylactic care was often performed at the discretion of the primary physician, and some chemotherapy sessions included prophylaxis while others did not for the same patients. It was difficult to assess prophylaxis as a potential risk factor for this retrospective study because the outcome was for each patient rather than for each episode.

Third, the outcome is the onset and development of FN, but not the frequency of infection-related admission or death. Although FN is associated with longer hospitalization, higher costs, and mortality [1], we could not mention the association between them in this study.

4.2. Implications for Practice

More than half of NHL cases are DLBCL, and clinicians are concerned about FN development during chemotherapy for DLBCL. Since FN more often develops during the first cycle of chemotherapy, prognostic tools for FN onset in cycle 1 are in great demand. In this risk model, the AUC (95% CI) was 0.839 (0.764-0.914). When the total calculated score of this prediction model for DLBCL patients is 0-1 point, clinicians can consider that the

possibility of developing FN in these patients is low. This is significant information before commencing chemotherapy for determining the length of hospital stay and planning outpatient treatment for these patients.

4.3. Conclusions

We suggest a prediction model for FN development in patients with DLBCL consisting of four predictors: chronic viral hepatitis, extranodal involvement, lymphopenia, and high sIL2R levels. This model shows a relatively high AUC and should be used in clinical settings.

5. References

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Appendix A: ROC curve for other populations and outcome

Figure A.1. ROC curve of the prediction score for first FN in NHL
Area under the curve (AUC) (95% CI) = 0.780 (0.711-0.849)

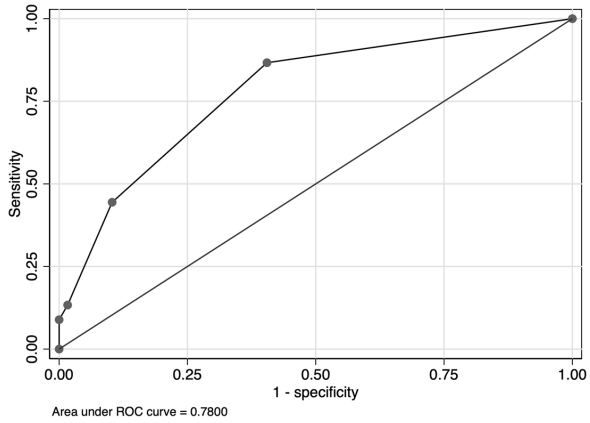


Figure A.2. ROC curve of the prediction score for all FN in DLBCL
Area under the curve (AUC) (95% CI) = 0.739 (0.666-0.811)

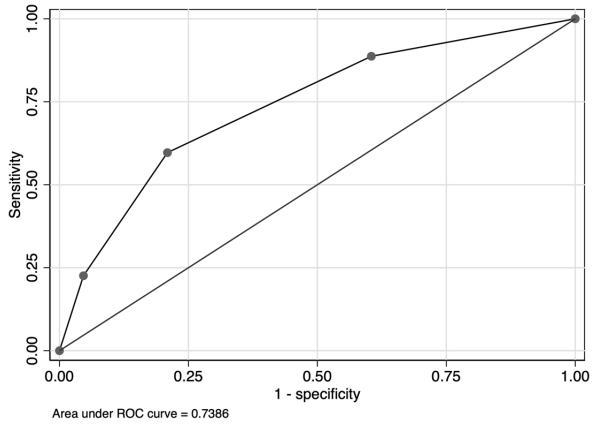
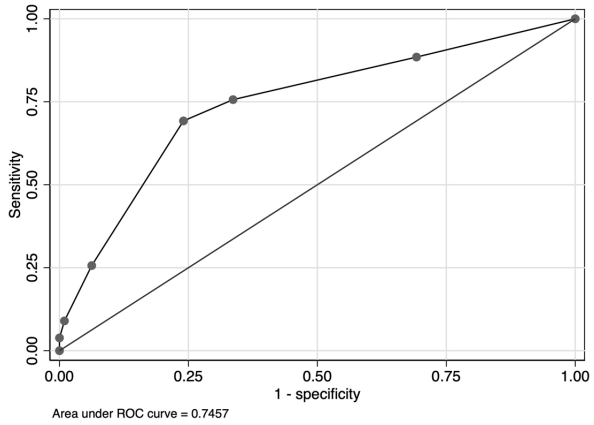


Figure A.3. ROC curve of the prediction score for all FN in NHL
Area under the curve (AUC) (95% CI) = 0.746 (0.680-0.811)



Appendix B: Univariable analyses for patients who were treated by high intensity regimen

Table B.1. Univariable analysis: factors associated with the incidence of FN in cycle 1 for patients who were treated by high intensity regimen

	DLBCL patients with FN n=9	DLBCL patients without FN n=43	p-value	NHL patients with FN n=25	NHL patients without FN n=78	p-value
Age ≥ 65	7 (78%)	29 (67%)	0.54	16 (64%)	49 (63%)	0.92
Sex: male	8 (89%)	29 (67%)	0.2	16 (64%)	51 (65%)	0.9
Comorbidity						
Diabetes	1 (11%)	3 (7%)	0.67	5 (20%)	7 (9%)	0.13
Chronic viral hepatitis	0 (0%)	3 (7%)	0.41	0 (0%)	3 (4%)	0.32
Chronic kidney disease	0 (0%)	4 (9%)	0.34	0 (0%)	5 (6%)	0.19
Cardiac disease	1 (11%)	4 (9%)	0.87	4 (16%)	7 (9%)	0.32
Chronic obstructive lung disease	0 (0%)	1 (2%)	0.64	0 (0%)	2 (3%)	0.42
Malignancy	2 (22%)	5 (12%)	0.4	5 (20%)	8 (10%)	0.2
Surgery	2 (22%)	9 (21%)	0.93	7 (28%)	17 (22%)	0.52
Baseline laboratory data						
WBC <3.5 x 10^9 /L	1 (11%)	6 (14%)	0.82	2 (8%)	8 (10%)	0.78
Hb <12.0 g/dL	3 (33%)	19 (44%)	0.55	12 (50%)	35 (45%)	0.66
Platelets <100 x 10^9 /L	2 (22%)	6 (14%)	0.53	6 (25%)	12 (15%)	0.28
ANC <1.5 x 10^9 /L	1 (11%)	0 (0%)	0.027	3 (13%)	3 (4%)	0.11
ALC <0.7 x 10^9 /L	3 (33%)	9 (21%)	0.42	9 (39%)	18 (23%)	0.14
T-Bil >1.0 g/dL	0 (0%)	8 (20%)	0.17	2 (9%)	14 (19%)	0.25
Alb <3.5 g/dL	6 (67%)	10 (24%)	0.012	15 (60%)	24 (32%)	0.011
LD > 222 IU/L	7 (78%)	31 (72%)	0.73	19 (76%)	51 (65%)	0.32
CRP >10 mg/dL	1 (12%)	2 (5%)	0.41	6 (25%)	4 (6%)	0.007
eGFR <60 ml/min/1.73m^2	2 (22%)	7 (16%)	0.67	5 (20%)	13 (17%)	0.7
sIL2R >2000 IU/L	7 (78%)	17 (41%)	0.048	15 (68%)	32 (43%)	0.035
Ann Arbor stage: Advanced (III-IV)	9 (100%)	35 (81%)	0.16	22 (88%)	55 (72%)	0.11
Extranodal involvement	8 (89%)	30 (70%)	0.24	18 (72%)	48 (62%)	0.34
Bone marrow infiltration	2 (22%)	12 (28%)	0.73	10 (40%)	20 (26%)	0.17

Table B.2. Univariable analysis: factors associated with the incidence of FN in all cycles for patients who were treated by high intensity regimen

	DLBCL patients with FN n=36	DLBCL patients without FN n=16	p-value	NHL patients with FN n=69	NHL patients without FN n=34	p-value
Age ≥ 65	25 (69%)	11 (69%)	0.96	45 (65%)	20 (59%)	0.53
Sex: male	27 (75%)	10 (62%)	0.36	46 (67%)	21 (62%)	0.62
Comorbidity						
Diabetes	2 (6%)	2 (12%)	0.39	7 (10%)	5 (15%)	0.5
Chronic viral hepatitis	2 (6%)	1 (6%)	0.92	2 (3%)	1 (3%)	0.99
Chronic kidney disease	4 (11%)	0 (0%)	0.17	5 (7%)	0 (0%)	0.11
Cardiac disease	4 (11%)	1 (6%)	0.58	8 (12%)	3 (9%)	0.67
Chronic obstructive lung disease	0 (0%)	1 (6%)	0.13	0 (0%)	2 (6%)	0.042
Malignancy	5 (14%)	2 (12%)	0.89	9 (13%)	4 (12%)	0.85
Surgery	8 (22%)	3 (19%)	0.78	17 (25%)	7 (21%)	0.65
Baseline laboratory data						
WBC <3.5 x 10^9 /L	7 (19%)	0 (0%)	0.058	10 (15%)	0 (0%)	0.019
Hb <12.0 g/dL	16 (44%)	6 (38%)	0.64	33 (49%)	14 (41%)	0.48
Platelets <100 x 10^9 /L	7 (19%)	1 (6%)	0.22	16 (24%)	2 (6%)	0.028
ANC <1.5 x 10^9 /L	1 (3%)	0 (0%)	0.5	6 (9%)	0 (0%)	0.07
ALC <0.7 x 10^9 /L	11 (31%)	1 (6%)	0.055	23 (35%)	4 (12%)	0.014
T-Bil >1.0 g/dL	6 (18%)	2 (12%)	0.61	12 (18%)	4 (12%)	0.46
Alb <3.5 g/dL	12 (34%)	4 (25%)	0.51	32 (48%)	7 (21%)	0.008
LD > 222 IU/L	27 (75%)	11 (69%)	0.64	51 (74%)	19 (56%)	0.065
CRP >10 mg/dL	3 (9%)	0 (0%)	0.24	10 (15%)	0 (0%)	0.021
eGFR <60 ml/min/1.73m^2	7 (19%)	2 (12%)	0.54	14 (20%)	4 (12%)	0.28
sIL2R >2000 IU/L	20 (59%)	4 (25%)	0.026	36 (56%)	11 (33%)	0.032
Ann Arbor stage: Advanced (III-IV)	30 (83%)	14 (88%)	0.7	55 (81%)	22 (67%)	0.12
Extranodal involvement	26 (72%)	12 (75%)	0.83	46 (67%)	20 (59%)	0.44
Bone marrow infiltration	11 (31%)	3 (19%)	0.38	24 (35%)	6 (18%)	0.072

Appendix C: Multivariable analyses for patients who were treated by high intensity regimen

Table C.1. Results of backward stepwise logistic regression: risk factors associated with the incidence of FN in cycle 1 for DLBCL patients who were treated by high intensity regimen

			n=49
	Odds ratio [95% CI]	β coefficient [95% CI]	p-value
Alb <3.5 g/dL	5.90 [1.13-30.76]	1.78 [0.13-3.43]	0.035
sIL2R >2000 IU/L	3.40 [0.56-20.61]	1.22 [-0.58-3.03]	0.183

Table C.2. Results of backward stepwise logistic regression: risk factors associated with the incidence of FN in cycle 1 for NHL patients who were treated by high intensity regimen

			n=97
	Odds ratio [95% CI]	β coefficient [95% CI]	p-value
sIL2R >2000 IU/L	2.88 [1.05-7.88]	1.06 [0.05-2.06]	0.04

Table C.3. Results of backward stepwise logistic regression: risk factors associated with the incidence of FN in all cycles for DLBCL patients who were treated by high intensity regimen

			n=50
	Odds ratio [95% CI]	β coefficient [95% CI]	p-value
sIL2R >2000 IU/L	4.29 [1.14-16.07]	1.46 [0.13-2.78]	0.031

Table C.4. Results of backward stepwise logistic regression: risk factors associated with the incidence of FN in all cycles for NHL patients who were treated by high intensity regimen

			n=101
	Odds ratio [95% CI]	β coefficient [95% CI]	p-value
Alb <3.5 g/dL	3.26 [1.23-8.60]	1.18 [0.21-2.15]	0.017
LD > 222 IU/L	1.86 [0.76-4.56]	0.62 [-0.28-1.52]	0.175