ART & TECHNOLOGY PUBLISHING PTE. LTD.

Progress in Applied Microbiology

2024 Volume 5, Issue 1

ISSN: 2630-4791

Factors Associated with Chemotherapy-Induced Neutropenia in Diffuse Large B-Cell Lymphoma Patients Undergoing Combination Chemotherapy: A Case-Control Study

Su Yeon Lim[1], Ja Yun Choi[2]*

[1]Department of Nursing, Chonnam National University Hwasun Hospital, Hwasun 58128, Republic of Korea

[2]College of Nursing, Chonnam National University, Gwangju 61469, Republic of Korea

***Corresponding author:** Ja Yun Choi, choijy@jnu.kr

Abstract

Purpose: This study aimed to identify the factors associated with chemotherapy-induced neutropenia (CIN) in diffuse large B-cell lymphoma (DLBCL) patients undergoing combination chemotherapy. *Methods:* A total of 111 patients with DLBCL participated in this study at C University Hospital. The CIN group consisted of patients with an absolute neutrophil count (ANC) lower than 1,000 cells/μL. Clinical factors, the level of depression, and the level of healthy lifestyle were measured on the chemotherapy administration day, and the ANC was measured on the next follow-up day. *Results:* Binary logistic regression analysis showed that the factors associated with CIN in DLBCL were the presence of B symptoms at diagnosis (β = 4.69) and low-risk CIN regimen (β = 0.10) among clinical factors, and the level of healthy lifestyle (β = 0.17). *Conclusion:* Oncology nurses should focus on the patients vulnerable to CIN having B symptoms at diagnosis, receiving a low-risk CIN regimen, and showing non-adherence to healthy lifestyle practice. Administration of granulocyte colony-stimulating factor can be considered for the patients receiving low-risk CIN regimen to reduce CIN. Education programs including healthy lifestyle practice for improving the immune system should be applied to DLBCL patients.

Keywords

Diffuse large B-cell lymphoma
Chemotherapy-induced febrile neutropenia
Precipitating factors

1. Introduction

1.1. Research significance

Non-Hodgkin lymphoma (NHL) is the most common blood cancer worldwide, accounting for 2.8% of cancer diagnoses and 2.6% of cancer mortality [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL [2]. DLBCL is aggressive and more than 70% of patients are diagnosed at an advanced stage, but responds well to six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with rituximab every two or three weeks [3]. Chemotherapy-induced neutropenia (CIN) is a common side effect of cytotoxic chemotherapy, especially combination chemotherapy regimens such as CHOP used to treat NHL [4]. However, the occurrence of CIN is associated with increased hospitalization and healthcare costs due to the need for dose modification, delayed dosing intervals, and repeated use of granulocyte colony-stimulating factors (G-CSF) [5]. In addition, a recent study showed a high correlation between severe CIN and poor quality of life in cancer patients [6]. Therefore, oncology nurses should be alert to the development of CIN in DLBCL patients.

In previous studies on factors associated with the development of CIN or febrile neutropenia (FN) in NHL, comorbidities, bone marrow involvement, and female gender were risk factors for FN in DLBCL patients treated with R-CHOP [7]. In addition, a serum albumin concentration of 3.5 g/dL or less, higher-than-normal serum lactate dehydrogenase (LDH) levels, and bone marrow involvement were significant predictors of severe CIN or FN [8]. More than 60% of DLBCL patients experienced at least one episode of grade 4 severe CIN during the first cycle of R-CHOP, and approximately 50% of patients experienced FN [7]. In addition, a systematic review supported factors including patient age, activity level, dose intensity, serum LDH, myelosuppression, and low pre-chemotherapy blood counts as influential factors in the development of CIN [9]. To summarize the literature, patient-specific and disease-related factors associated with the development of CIN have been mainly explored, but a review of psychological and lifestyle factors is still lacking.

The relationship between psychological or lifestyle factors and the development of CIN is unclear. However, physical activity and structured exercise improved neutrophil function in older adults, and neutrophil function in older adults who regularly engaged in physical activity and exercise did not differ from younger controls [10]. In addition, pre-transplant depression negatively affected neutrophil recovery time after hematopoietic stem cell transplantation [11]. Although not associated with the development of CIN or FN, a higher neutrophil-to-lymphocyte ratio was associated with a higher risk of inflammation, and this ratio was influenced by gender, age, race, marital status, body mass index, physical activity, smoking history, and alcohol consumption [12]. Therefore, in addition to patient-specific characteristics and disease-related factors, lifestyle and psychological factors, such as depression and a history of alcohol and smoking, may affect the immune system and contribute to the development of CIN in DLBCL patients.

Therefore, in this study, we aimed to identify a comprehensive set of factors related to the development of CIN, including factors that have been supported in previous studies as influential factors in the development of CIN, as well as depression and lifestyle factors that affect the immune system of DLBCL patients.

1.2. Research objectives

The purpose of this study is to identify factors influencing the development of CIN in DLBCL patients receiving combination chemotherapy, with the following specific objectives:

(1) To identify the clinical factors, lifestyle, and depression of the subjects.
(2) To identify differences in the incidence of CIN

according to clinical factors, lifestyle, and depression.

(3) To identify factors that affect the occurrence of CIN.

2. Research methods

2.1. Study design

This is a prospective, case-control study that aims to identify factors influencing the development of CIN in DLBCL patients receiving combination chemotherapy, comparing those who develop CIN with those who do not.

2.2. Study subjects

The study subjects were patients diagnosed with DLBCL at C University Hospital who were either ambulatory or hospitalized, and were receiving combination chemotherapy for remission induction, consolidation, or salvage chemotherapy. Patients were excluded if the treatment schedule was interrupted due to the patient's condition during combination chemotherapy. Since CIN is most severe on days 7 to 14 after combination chemotherapy [13], patients with absolute neutrophil count less than 1,000 cells/μL corresponding to grades 3 and 4 according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 on blood tests performed on day 7 (± 3) after combination chemotherapy were selected for the CIN group [14]. On the other hand, the control group included patients with an absolute neutrophil count of more than 1,000 cells/μL at the same time as the patients after combined chemotherapy treatment for the same disease at the same hospital. Patients and controls were matched by gender [7] and no subjects were excluded based on patient gender and control gender. Given the recent decrease in the frequency of CIN due to the use of prophylactic G-CSF and the fact that subjects were selected regardless of the cycle of the combination chemotherapy regimen, the patient-to-control ratio was not considered due to the low incidence of CIN, which would have resulted in a longer study period if the patient-to-control ratio was considered.

The number of subjects was calculated using G*Power 3.1.9. The odds ratio was set at 2.02, the lowest crossover ratio value, based on a study that analyzed the influencing factors of CIN after combined chemotherapy among Korean studies with a similar design to this study [7], and the proportion of the patient group that developed CIN after combined chemotherapy in the logistic regression analysis was 60.2 to 72.0% in studies of non-Hodgkin lymphoma patients [7,15], so the lowest ratio, pl = 0.60, was set. Assuming a normal distribution of explanatory variables, $\mu = 0$, $s = 1$, two-tailed test, significance level of 0.05, and power of $1-\beta = 0.90$, a minimum of 107 patients was required. Based on this, we intentionally sampled 117 participants who agreed to participate, accounting for a 10% dropout rate. After excluding 6 patients (3 in the patient group and 3 in the control group) who were unable to complete their chemotherapy regimen at the time of double-blind sampling or who declined to participate during the survey, a total of 111 patients (29 in the patient group and 82 in the control group) were included in the final sample, with no non-compliant or missing data based on blood tests performed on day 7 (± 3) post-chemotherapy (**Figure 1**).

2.3. Research instruments

2.3.1. Clinical factors

A clinical questionnaire that was drafted by the researcher based on previous studies was used [7-9] and face validity was checked by one nursing professor and one oncology ward nurse. Clinical factors that have been identified as risk factors for CIN in previous studies were divided into three categories: patient-related factors, disease-related factors, and treatment-related factors. The details are as follows.

(1) Patient-related factors

Patient-related factors are related to an individual's physiological and biological characteristics, such as gender, age, weight,

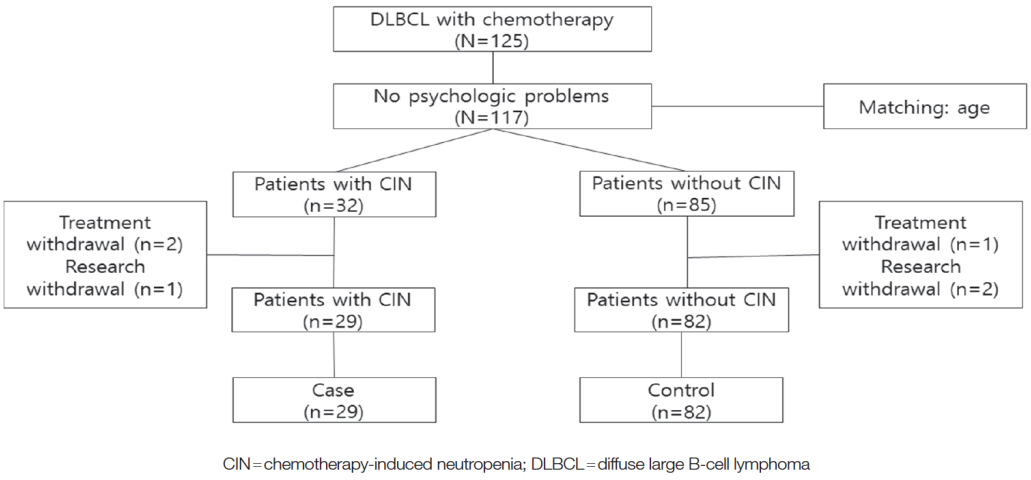

Figure 1. Participants selection flow

body surface area, body mass index, activity performance, and pre-treatment blood levels [white blood cells, hemoglobin, platelets, absolute neutrophil count, LDH, aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatinine], and comorbidities.

Height, weight, and pre-treatment blood values were taken on the first day of combination chemotherapy, one hour before and one hour after meals. The measured height and weight were used to calculate body surface area and body mass index, with a cutoff point of 1.9 m^2 for body surface area and 23 and 25 for body mass index according to Lyman *et al.* [9]. Activity performance was assessed using the Eastern Cooperative Oncology Group Performance Scale (ECOG PS), which ranges from 0 to 5, with a score closer to 0 indicating higher activity performance [16]. Based on previous studies, AST was cut off at 35 U/L [9], hemoglobin at 12 g/dL [17], and platelets at 150,000 cells/μL [17]. For comorbidities, we examined the presence or absence of 17 conditions classified by Quan *et al.* [18] based on ICD-10 codes using Charlson comorbidity index among all disease names entered in the electronic medical record. We excluded lymphoma as the main diagnosis from the cancer comorbidity group, and did not double-count comorbidities when they were found in the same comorbidity group.

(2) Disease-related factors

Disease-related factors are factors related to DLBCL disease characteristics, including stage, extranodal involvement, B symptoms, and bone marrow involvement. The disease stage, extranodal involvement, B symptoms, and bone marrow involvement were determined by the Ann Arbor staging classification [19].

(3) Treatment-related factors

Treatment-related factors are factors related to the treatment of DLBCL, including prior radiation therapy, prior treatment with a regimen different from the current regimen, prior hematopoietic stem cell transplantation, regimen, and cycle, relative dose intensity (RDI), prophylactic granulocyte colony-stimulating factor administration prior to combination chemotherapy, and the presence and number of prior neutropenic episodes.

Combination chemotherapy regimens were categorized into high-, intermediate-, and low-risk based on the risk of FN according

to the National Comprehensive Cancer Network (NCCN) guidelines [20]. Pegfilgrastim (Neulasta) was used 24 hours after combination chemotherapy to prevent FN in all patients treated with high- and intermediate-risk regimens. A cycle of consolidation chemotherapy refers to this treatment cycle, and the number of cycles was calculated as the cumulative number of treatments. Relative dose intensity was cut off at 85% [21]. Lenograstim (Granocyte) was administered prophylactically prior to combination chemotherapy [22]. Previous history of neutropenia was defined as neutropenia with an absolute neutrophil count of less than 1,000 cells/μL that occurred during the course of treatment, not just during the combination chemotherapy, and the frequency was measured as the number of episodes of neutropenia.

2.3.2. Lifestyle

Two aspects of lifestyle were measured: alcohol consumption and smoking history, as scored by the lifestyle tool.

(1) Lifestyle severity

The Health Promoting Lifestyle Profile II (HPLP II) by Walker *et al.* [22] translated and modified by Seo [23] was used, and permission to use the tool was obtained from both the original author and the translator. The HPLP II consists of 50 questions in six subdomains: health responsibility (8 questions), physical activity (8 questions), nutrition (9 questions), spiritual growth (9 questions), interpersonal relationships (8 questions), and stress management (8 questions). Each item is rated on a 4-point Likert scale ranging from 1 for "never" to 4 for "always," and the higher the average rating of the total score divided by the number of items, the higher the level of healthy lifestyle behavior. In Seo's study [23], Cronbach's α was 0.92, and in this study, Cronbach's α was 0.95.

(2) Drinking and smoking history

Drinking status was checked based on the monthly drinking rate, which is one of the drinking status indicators of the National Health and Nutrition Examination Survey. Smoking history was divided into non-smoking, smoking, and quitting smoking in the past year.

(3) Depression

Depression was measured using a Korean instrument from Korea Psychology Corporation, which has the right to publish Beck's Beck Depression Inventory-II (BDI-II). This tool reflects major depressive symptoms such as sadness and guilt, with a total of 21 questions, each question on a 4-point scale from 0 to 3, and a total score ranging from 0 to 63. In this study, a total score of 22 was examined as a cutoff point for depression [24]. The reliability of the tool was shown to be above 0.80 in both patients and normal controls, with a Cronbach's α coefficient of 0.90 for the Korean version of the BDI-II in a normal adult population [24]. In this study, the Cronbach's α coefficient was 0.90.

2.4. Data collection

The data collection period for this study was from September 20, 2019 to March 31, 2020. A trained research assistant obtained written informed consent in the hospital room on the day of admission. Data collection through electronic medical records was performed by a researcher and one trained research assistant. They independently coded the electronic medical records of 10 subjects, and the agreement was r = 0.80. Discrepancies in coding were resolved by consensus as comorbidities and CIN occurrence. The first data collection point of the study was the starting date of combination chemotherapy for outpatients or inpatients, and clinical factors, lifestyle, and depression were examined. Clinical factors were collected through electronic medical records, and lifestyle and depression were self-reported in a structured questionnaire,

which was read and answered by a research assistant if needed. The second data collection time point was 7 (± 3) days after completion of the combination chemotherapy, and the occurrence of CIN was investigated according to the absolute neutrophil count criteria based on blood tests performed at outpatient visits or in the inpatient ward.

2.5. Data analysis

The data collected in this study were analyzed using SPSS Statistics 27.0. The clinical factors, lifestyle, and depression of the subjects were calculated as frequencies and percentages, means and standard deviations (SD). The normality test for lifestyle and depression was performed using the Shapiro-Wilks test and followed a normal distribution. Differences in the incidence of CIN according to clinical factors, lifestyle, and depression were analyzed by independent *t*-test, chi-square test, and Fisher's exact test. Factors affecting the occurrence of CIN were analyzed by binary logistic regression.

2.6. Ethical considerations

This study was approved by the Research Ethics Committee of C University Hospital (CNUHH-2019-150). Written informed consent was obtained on the day of the subject's admission to the hospital by a research assistant trained in accordance with the Declaration of Helsinki. The data collected will be used only for research purposes, anonymity will be guaranteed, and will be destroyed after three years.

3. Results

3.1. Differences in the incidence of chemotherapy-induced neutropenia based on clinical factors

3.1.1. Patient-related factors

Differences in the incidence of CIN according to patient-related factors are shown in **Table 1**. Among the patient-related factors, weight and platelets showed statistically significant differences between the two groups. Weight was significantly different in the CIN and non-CIN groups, with a mean of 62.22 ± 9.61 kg and 67.02 ± 10.36 kg, respectively ($t = 2.19$, $P = 0.031$). Platelets were less than 150,000 cells/μL with 11 (37.9%) in the CIN group and 16 (19.5%) in the non-CIN group, showing a significant difference ($\chi^2 = 3.95$, $P = 0.047$).

Otherwise, there were no statistically significant differences between the two groups in gender, age, body surface area, body mass index, physical performance, white blood cells, hemoglobin, absolute neutrophil count, LDH, AST, total bilirubin, BUN, creatinine, and comorbidities.

3.1.2. Disease-related factors

Differences in the incidence of CIN according to disease-related factors are shown in **Table 2**. Among the disease-related factors of the subjects, B symptoms showed a statistically significant difference between the two groups. There was a significant difference between 10 (34.5%) cases in the CIN group and 12 (14.6%) cases in the non-CIN group ($\chi^2 = 5.31$, $P = 0.021$).

There were no statistically significant differences in other stages, extranodal involvement, or bone marrow involvement between the two groups.

3.1.3. Treatment-related factors

Differences in the incidence of CIN according to treatment-related factors are shown in **Table 2**. Among the treatment-related factors of the subjects, the presence or absence of treatment with a regimen different from the current combination chemotherapy regimen and the presence or absence of a history of combination chemotherapy regimen and neutropenia showed statistically significant differences between the two groups. There was a significant difference between 13 (44.8%) in the CIN group and 14 (17.1%) in the non-CIN group in the history of treatment with a regimen different from the current combination chemotherapy regimen ($\chi^2 = 8.97$, $P = 0.003$). According to the combination chemotherapy regimen,

Table 1. Difference in developing chemotherapy-induced neutropenia according to patient-related factors

Variables	**Categories**	**Total (n = 111)**	**CIN (n = 29)**	**Non-CIN (n = 82)**	χ^2 **or** *t*	***P***
		n (%) or mean ± SD	**n (%) or mean ± SD**	**n (%) or mean ± SD**		
Gender	Male	84 (75.7)	22 (75.9)	62 (75.6)	0.00	0.978
	Female	27 (24.3)	7 (24.1)	20 (24.4)		
Age (year)		61.05 ± 13.08				
	< 65	56 (50.5)	16 (55.2)	40 (48.8)	0.35	0.554
	≥ 65	55 (49.5)	13 (44.8)	42 (51.2)		
Weight (kg)		65.77 ± 10.33	62.22 ± 9.61	67.02 ± 10.36	2.19	0.031
BSA (m^2)		1.87 ± 1.47				
	< 1.9	95 (85.6)	25 (86.2)	70 (85.4)	-	> 0.999*
	≥ 1.9	16 (14.4)	4 (13.8)	12 (14.6)		
BMI (kg/m^2)		24.39 ± 4.41				
	< 23	38 (34.2)	13 (44.8)	25 (30.5)	1.97	0.374
	23–24.9	31 (27.9)	7 (24.1)	24 (29.3)		
	≥ 25	42 (37.8)	9 (31.0)	33 (40.2)		
ECOG PS	0	38 (34.2)	11 (37.9)	27 (32.9)	-	0.418*
	1	60 (54.1)	14 (48.3)	46 (56.1)		
	2	12 (10.8)	3 (10.3)	9 (11.0)		
	3	1 (0.9)	1 (3.4)	0 (0.0)		
	4	0 (0.0)	0 (0.0)	0 (0.0)		
WBC (cells/μL)		6,827.93 ± 2,766.72	6,379.31 ± 2,292.59	6,986.59 ± 2,912.20	1.02	0.312
Hgb (g/dL)		11.48 ± 1.40				
	< 12	70 (63.1)	21 (72.4)	49 (59.8)	1.47	0.225
	≥ 12	41 (36.9)	8 (27.6)	33 (40.2)		
PLT (cells/μL)		22,8945.95 ± 10,3624.45				
	< 150,000	27 (24.3)	11 (37.9)	16 (19.5)	3.95	0.047
	≥ 150,000	84 (75.7)	18 (62.1)	66 (80.5)		
Pre ANC (cells/μL)		4,979.28 ± 2,649.86	4,238.62 ± 2,226.08	5,241.22 ± 2,748.97	0.52	0.470
LDH (IU/L)		543.82 ± 367.58	682.10 ± 613.64	494.91 ± 209.90	-1.61	0.118
AST (U/L)		26.67 ± 15.25				
	≤ 35	92 (82.9)	21 (72.4)	71 (86.6)	-	0.093*
	> 35	19 (17.1)	8 (27.6)	11 (13.4)		
Total bilirubin (mg/dL)		0.50 ± 0.19	0.55 ± 0.21	0.48 ± 0.18	-1.71	0.090
BUN (mg/dL)		14.86 ± 6.76	15.04 ± 7.06	14.80 ± 6.69	-0.17	0.867
Cr (mg/dL)		1.05 ± 1.16	1.24 ± 1.80	0.98 ± 0.84	-1.06	0.293
Comorbidity	No	48 (43.2)	11 (37.9)	37 (45.1)	0.45	0.502
	Yes	63 (56.8)	18 (62.1)	45 (54.9)		
Post ANC (cells/μL)		4,947.66 ± 4,714.65	6,563.54 ± 4,475.77	378.62 ± 323.18		

Abbreviations: ANC = absolute neutrophil count; AST = aspartate transaminase; BMI = body mass index; BSA = body surface area; BUN = blood urea nitrogen; CIN = chemotherapy-induced neutropenia; Cr = creatinine; ECOG PS = Eastern Cooperative Oncology Group performance status; Hgb = hemoglobin; LDH = lactate dehydrogenase; PLT = platelet; WBC = white blood count; *Fisher's exact test.

there were 11 (37.9%) high-risk and 13 (44.8%) intermediate-risk in the CIN group and 65 (79.3%) intermediate-risk in the non-CIN group, showing a significant difference (χ^2 = 12.18, *P* = 0.002). Previous neutropenic events were 16 (55.2%) in the CIN group and 27 (32.9%) in the non-CIN group, showing a significant difference (χ^2 = 4.47, *P* = 0.035).

There were no statistically significant differences between the two groups in the number of other radiotherapy treatments, hematopoietic stem cell transplantations, cycles of combined chemotherapy, relative dose intensity, prophylactic granulocyte colony-stimulating factor administration, and number of CIN events.

Table 2. Difference in developing chemotherapy-induced neutropenia according to disease- and treatment-related factors

Variables	Variables	Total (n = 111)	CIN (n = 29)	Non-CIN (n = 82)	χ^2 or *t*	*P*
		n (%) or mean ± SD	n (%) or mean ± SD	n (%) or mean ± SD		
Stage	I	30 (27.0)	8 (27.6)	22 (26.8)	2.77	0.428
	II	23 (20.7)	3 (10.3)	20 (24.4)		
	III	26 (23.4)	8 (27.6)	18 (22.0)		
	IV	32 (28.8)	10 (34.5)	22 (26.8)		
Extranodal involvement	No	21 (18.9)	6 (20.7)	15 (18.3)	0.08	0.777
	Yes	90 (81.1)	23 (79.3)	67 (81.7)		
B symptoms	No	89 (80.2)	19 (65.5)	70 (85.4)	5.31	0.021
	Yes	22 (19.8)	10 (34.5)	12 (14.6)		
BM involvement	No	98 (88.3)	24 (82.8)	74 (90.2)	-	0.319*
	Yes	13 (11.7)	5 (17.2)	8 (9.8)		
Previous RT	No	100 (90.1)	26 (89.7)	74 (90.2)	-	> 0.999*
	Yes	11 (9.9)	3 (10.3)	8 (9.8)		
Other regimen CTx	No	84 (75.7)	16 (55.2)	68 (82.9)	8.97	0.003
	Yes	27 (24.3)	13 (44.8)	14 (17.1)		
Previous SCT	No	106 (95.5)	27 (93.1)	79 (96.3)	-	0.470*
	Yes	5 (4.5)	2 (6.9)	3 (3.7)		
Regimen	High-risk	23 (20.7)	11 (37.9)	12 (14.6)	12.18	0.002
	Intermediate-risk	78 (70.3)	13 (44.8)	65 (79.3)		
	Low-risk	10 (9.0)	5 (17.2)	5 (6.1)		
Cycle of CTx		3.95 ± 9.72	2.10 ± 1.54	4.60 ± 11.21	1.19	0.237
RDI		91.86 ± 15.66				
	< 85	30 (27.0)	8 (27.6)	22 (26.8)	0.01	0.937
	≥ 85	81 (73.0)	21 (72.4)	60 (73.2)		
Prophylaxis G-CSF	No	95 (85.6)	25 (86.2)	70 (85.4)	-	> 0.999*
	Yes	16 (14.4)	4 (13.8)	12 (14.6)		
Previous neutropenia	No	68 (61.3)	13 (44.8)	55 (67.1)	4.47	0.035
	Yes	43 (38.7)	16 (55.2)	27 (32.9)		
Number of neutropenia experience (n = 43)		2.86 ± 2.64	3.88 ± 3.34	2.26 ± 1.95	-1.76	0.092

Abbreviations: BM = bone marrow; CIN = chemotherapy-induced neutropenia; CTx = chemotherapy; G-CSF = granulocyte-colony stimulating factor; RDI = relative dose intensity; RT = radiation treatment; SCT = stem cell transplantation; *Fisher's exact test.

3.2. Differences in the incidence of chemotherapy-induced neutropenia based on lifestyle

Differences in the incidence of CIN based on lifestyle are shown in **Table 3**. The mean lifestyle scores of the subjects were 2.43 ± 0.41 and 2.68 ± 0.49 in the CIN and non-CIN groups, respectively, showing a statistically significant difference between the two groups (t = 2.42, P = 0.017).

For alcohol consumption, 23 (79.3%) responded as "never" and 6 (20.7%) responded as "drink" in the CIN group, and 76 (92.7%) responded as "never" and 6 (7.3%) responded as "drink" in the non-CIN group, which was not statistically significant between the two groups (P = 0.076). Smoking history included 11 (37.9%) non-smokers in the CIN group and 28 (34.1%) in the non-CIN group, 3 (10.3%) current smokers in the CIN group and 8 (9.8%) in the non-CIN group, and 15 (51.7%) quitters in the CIN group and 46 (56.1%) in the non-CIN group, with no statistically significant difference between the two groups (χ^2 = 0.17, P = 0.919).

3.3. Differences in the incidence of chemotherapy-induced neutropenia according to depressive status

Differences in the incidence of CIN by depression status are shown in **Table 3**. The mean depression level of the subjects was 14.71 ± 9.64, with 15 (51.7%) and 30 (36.6%) depressed in the CIN and non-CIN groups, respectively, which was not statistically significant between the two groups (χ^2 = 2.04, P = 0.154).

3.4. Factors affecting the development of neutropenia

To determine the factors affecting the occurrence of CIN in subjects, a binary logistic regression analysis was performed, selecting the seven variables that showed significant differences in the univariate analysis as independent variables: weight, platelets, B symptoms, treatment history with a regimen different from the current combination chemotherapy regimen, combination chemotherapy regimen, previous occurrence of CIN, and lifestyle score.

The regression model was statistically significant (χ^2 = 35.14, P < 0.001), and the explanatory power was 39.7% by the Nagelkerke coefficient of determination. The classification accuracy was 80.2%, and the Hosmer-Lemeshow test for model fit did not reject the hypothesis that there is no difference between the observed and predicted values of the model (χ^2 = 2.99, P = 0.935), indicating that the model presented in this study fits the data well.

Table 3. Difference in developing chemotherapy-induced neutropenia according to the levels of healthy lifestyle and depression

Variables	Categories	Total (n = 111)	CIN (n = 29)	Non-CIN (n = 82)	χ^2 or t	P
		n (%) or mean ± SD	n (%) or mean ± SD	n (%) or mean ± SD		
Level of lifestyle		2.62 ± 0.48	2.43 ± 0.41	2.68 ± 0.49	2.42	0.017
Alcohol	No	99 (89.2)	23 (79.3)	76 (92.7)	-	0.076*
	Yes	12 (10.8)	6 (20.7)	6 (7.3)		
Smoking	None	39 (35.1)	11 (37.9)	28 (34.1)	0.17	0.919
	Yes	11 (9.9)	3 (10.3)	8 (9.8)		
	Quit	61 (55.0)	15 (51.7)	46 (56.1)		
Depression	No	66 (59.5)	14 (48.3)	52 (63.4)	2.04	0.154
	Yes	45 (40.5)	15 (51.7)	30 (36.6)		

Abbreviation: CIN = chemotherapy-induced neutropenia; *Fisher's exact test.

Table 4. Factors associated with chemotherapy-induced neutropenia

Variables	B	SE	*P*	OR	95% CI
Weight	-0.05	0.03	0.060	0.95	0.90–1.00
PLT (ref: < 150,000 cells/μL)	-0.87	0.62	0.156	0.42	0.13–1.40
B symptoms (ref: No)	1.55	0.62	0.012	4.69	1.40–15.70
Other regimen CTx (ref: No)	1.04	1.51	0.492	2.83	0.15–55.00
Regimen (ref: Low-risk)					
Intermediate-risk	-1.38	1.30	0.160	0.16	0.01–2.07
High-risk	-2.31	0.99	0.020	0.10	0.01–0.70
Previous neutropenia (ref: No)	0.60	0.63	0.336	1.83	0.54–6.23
Level of healthy lifestyle	-1.80	0.62	0.003	0.17	0.05–0.55

Abbreviations: CI = confidence interval; CTx = chemotherapy; OR = odds ratio; PLT = platelet; SE = standard error

Factors influencing the occurrence of CIN were B symptoms at diagnosis, low-risk combination chemotherapy regimen, and low lifestyle score. The odds ratios of the parameter estimates showed an odds ratio of 4.69 (β = 4.69, p = 0.012) for CIN in the presence of B symptoms, an odds ratio of 0.10 (β = 0.10, p = 0.020) for CIN in the high-risk combination chemotherapy regimen compared to the low-risk combination chemotherapy regimen, and an odds ratio of 0.17 (β = 0.17, p = 0.003) for CIN for an average increase of 1 point in lifestyle score (**Table 4**).

4. Discussion

In this study, the risk factors for CIN in DLBCL patients were B symptoms at diagnosis, a low-risk combination chemotherapy regimen, and a low lifestyle score.

Based on the results, low-risk combination chemotherapy regimens were the strongest predictors of CIN in DLBCL patients. The National Comprehensive Cancer Network (NCCN) recommends that G-CSF can be used prophylactically to prevent the development of CIN immediately after combination chemotherapy, depending on the risk of developing FN [20]. In this study, all patients received prophylactic G-CSF within 24 hours after high- and intermediate-risk combination chemotherapy to reduce the likelihood of CIN according to NCCN guidelines. The European Organization for Research and Treatment of Cancer (EORTC) most recently updated its guidelines on the use of G-CSF after NHL treatment in 2010, recommending the use of prophylactic G-CSF after R-CHOP for the treatment of NHL and discussing more aggressive consideration of G-CSF administration not only for R-CHOP but also for patients receiving lower-risk combination chemotherapy regimens who may be more vulnerable to developing CIN by not receiving prophylactic G-CSF [4]. Although not all CINs result in FN, the occurrence of CIN alone can cause fatigue, disruption of daily activities, negative emotions, and social isolation [14], resulting in increased hospitalization and hospital costs [5]. In this study, patients receiving combination chemotherapy classified as high and intermediate risk for FN were given prophylactic G-CSF, but patients receiving low-risk combination chemotherapy were not given prophylactic G-CSF. Consequently, the lack of prophylactic G-CSF increased the likelihood of CIN in DLBCL patients receiving low-risk combination chemotherapy regardless of the risk of FN on the combination chemotherapy regimen. Therefore, we believe that the NHL treatment guidelines should strongly consider including a recommendation for prophylactic G-CSF administration in the guidelines regardless of the risk of FN.

The second factor associated with the development of CIN in this study was a low lifestyle score. The lower the lifestyle score, the higher the incidence of

CIN in DLBCL patients. In a recent study, regular participation in leisure-time exercise improved neutrophil function, lowered myeloperoxidase levels, and increased total antioxidant capacity in healthy middle-aged men, potentially slowing the immune aging process [25]. In a study of older adults, regular habitual physical activity was associated with efficient neutrophil migration, a critical step in resolving infections that is impaired with age [10]. A healthy diet can also help to reduce the side effects associated with combination chemotherapy. Malnutrition and decreased muscle mass are frequent in cancer patients and have a negative impact on clinical outcomes [26]. Univariate analysis in this study showed that higher body weight was associated with the development of CIN, but the relationship was not supported by multivariate analysis by a narrow margin (P = 0.060). It is thought that a healthy diet or optimal nutrition may protect DLBCL patients from the side effects of combination chemotherapy, including the development of CIN. A healthy lifestyle helps to maintain a normal body weight, thus a healthy, balanced diet consisting of nutrient-dense, whole foods, including vegetables, fruits, protein sources, and healthy fats, along with regular physical activity or exercise, is important. On the other hand, smoking habits were inversely associated with the development of CIN or FN in previous studies. In patients receiving gemcitabine chemotherapy alone or in combination with oral chemotherapeutic agents, non-smokers had a 3.5-fold higher incidence of CIN compared to smokers, and this was more pronounced with increasing pack-years of smoking [27]. However, pharmacodynamic markers of gemcitabine-induced neutropenia concomitantly reduced the efficacy of gemcitabine. Thus, smoking reduced the efficacy of the chemotherapeutic agent against cancer cells while simultaneously reducing the incidence of CIN or FN as a toxic response. Previous studies have confirmed that implementing a healthy lifestyle such as exercise, diet, and drinking habits can be beneficial for neutrophilic immunity, but since neutrophil function is not the same as neutrophil count, it is not yet sufficient to confirm the relationship between healthy lifestyle and the occurrence of CIN, and further studies are needed to establish the causal relationship.

The last factor influencing the development of CIN in DLBCL patients was the presence of B symptoms at diagnosis. B symptoms are a triad of non-specific symptoms of fever of 38°C or higher, night sweats, and weight loss of 10% or more in the previous 6 months, which are common in high-grade lymphomas such as DLBCL, and have been associated with poorer survival in DLBCL patients [28]. In phase III of the British National Lymphoma Investigation (BNLI), approximately 50% of 664 patients with DLBCL had B symptoms, and after adjustment for age, functional status, bone marrow involvement, chemotherapy regimen type, and G-CSF administration, the occurrence of severe CIN was associated with B symptoms [29]. B symptoms were strongly associated with an increase in the systemic inflammatory response index (SIRI), a measure of decreased activity of CYP3A4, a key enzyme in drug metabolism [29]. Most drugs used to treat NHL are metabolized by CYP3A4. Decreased activity of CYP3A4 reduces hepatic metabolism, leading to strong chemotherapy-induced toxicity, resulting in CIN [30]. Therefore, an individualized approach, including the use of prophylactic G-CSF, is needed to reduce systemic inflammatory responses prior to combination chemotherapy in patients with B symptoms at the time of DLBCL diagnosis.

The results of this study should be interpreted with caution because it was a prospective, case-control study, and subjects were recruited at a time when the occurrence of CIN after combination chemotherapy was unknown, hence the proportion of patients with CIN was relatively low compared to the control group, and the proportion of controls per patient group could not be taken into account. In addition, lifestyle and depression were measured at 1-week intervals in this

study, which may not sensitively reflect the changes in lifestyle or depression at 1-week intervals, and there were limitations in measuring the changes in drinking and smoking habits at 1-week intervals. Lastly, we cannot exclude the possibility that CIN may have occurred in the control group after the time of secondary data collection.

5. Conclusion

Oncology nurses should monitor the development of CIN in DLBCL patients with B symptoms at diagnosis, those who do not receive prophylactic G-CSF after combination chemotherapy, or those who are noncompliant with healthy lifestyle behaviors. DLBCL treatment guidelines should actively include a recommendation to administer G-CSF to all patients after combination chemotherapy regardless of their risk of developing CIN or FN, and educational programs should be developed to include healthy lifestyle practices to improve the immune system.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al., 2018, Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2018(68): 394–424.

[2] van Leeuwen MT, Turner JJ, Joske DJ, et al., 2014, Lymphoid Neoplasm Incidence by WHO Subtype in Australia 1982–2006. Int J Cancer, 2014(135): 2146–2156.

[3] Pfreundschuh M, Kuhnt E, Trümper L, et al., 2011, CHOP-Like Chemotherapy with or Without Rituximab in Young Patients with Good-Prognosis Diffuse Large-B-Cell Lymphoma: 6-Year Results of an Open-Label Randomised Study of the MabThera International Trial (MInT) Group. Lancet Oncol, 2011(12): 1013–1022.

[4] Aapro MS, Bohlius J, Cameron DA, et al., 2011, 2010 Update of EORTC Guidelines for the Use of Granulocyte Colony-Stimulating Factor to Reduce the Incidence of Chemotherapy-Induced Febrile Neutropenia in Adult Patients with Lymphoproliferative Disorders and Solid Tumours. Eur J Cancer, 2011(47): 8–32.

[5] Boccia R, Glaspy J, Crawford J, et al., 2022, Chemotherapy-Induced Neutropenia and Febrile Neutropenia in the US: A Beast of Burden that Needs to be Tamed? Oncologist, 2022(27): 625–636.

[6] Lalami Y, Klastersky J, 2017, Impact of Chemotherapy-Induced Neutropenia (CIN) and Febrile Neutropenia (FN) on Cancer Treatment Outcomes: An Overview About Well-Established and Recently Emerging Clinical Data. Crit Rev Oncol Hematol, 2017(120): 163–179.

[7] Choi YW, Jeong SH, Ahn MS, et al., 2014, Patterns of Neutropenia and Risk Factors for Febrile Neutropenia of Diffuse Large B-Cell Lymphoma Patients Treated with Rituximab-CHOP. J Korean Med Sci, 2014(29): 1493–1500.

[8] Usami E, Kimura M, Iwai M, et al., 2016, Chemotherapy Continuity and Incidence of Febrile Neutropenia with CHOP Therapy in an Outpatient Setting. Mol Clin Oncol, 2016(4): 591–596.

[9] Lyman GH, Abella E, Pettengell R, 2014, Risk Factors for Febrile Neutropenia Among Patients with Cancer Receiving Chemotherapy: A Systematic Review. Crit Rev Oncol Hematol, 2014(90): 190–199.

[10] Bartlett DB, Fox O, McNulty CL, et al., 2016, Habitual Physical Activity is Associated with the Maintenance of Neutrophil Migratory Dynamics in Healthy Older Adults. Brain Behav Immun, 2016(56): 12–20.

[11] Tavakoli-Ardakani M, Beyraghi N, Mirjalili M, et al., 2019, Effect of Pretransplant Depression on Neutrophil Recovery Following Hematopoietic Stem Cell Transplantation. Transpl Res Risk Manag, 2019(11): 1–9.

[12] Howard R, Scheiner A, Kanetsky PA, et al., 2019, Sociodemographic and Lifestyle Factors Associated with the Neutrophil-To-Lymphocyte Ratio. Ann Epidemiol, 2019(38): 11–21.

[13] American Society of Clinical Oncology, n.d., Coping with Cancer, viewed September 11, 2022, https://www.cancer.net/coping-with-cancer/physicalemotional-and-social-effects-cancer/managing-physical-side-effects/neutropenia

[14] Freites-Martinez A, Santana N, Arias-Santiago S, et al., 2021, Using the Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr (Engl Ed), 2021(112): 90–92.

[15] Hassan BA, Yusoff ZB, Othman SB, 2015, A Close Look at Neutropenia Among Cancer Patients: Risk Factor and Management, in Updates on Cancer Treatment, IntechOpen, London, 1–23.

[16] Oken MM, Creech RH, Tormey DC, et al., 1982, Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol, 1982(5): 649–655.

[17] Lee M, Yee J, Kim JY, et al., 2019, Risk Factors for Neutropenia and Febrile Neutropenia Following Prophylactic Pegfilgrastim. Asia Pac J Clin Oncol, 2019(15): 231–237.

[18] Quan H, Li B, Couris CM, et al., 2011, Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data from 6 Countries. Am J Epidemiol, 2011(173): 676–682.

[19] Carbone PP, Kaplan HS, Musshoff K, et al., 1971, Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res, 1971(31): 1860–1861.

[20] Becker PS, Griffiths EA, Alwan LM, et al., 2020, NCCN Guidelines Insights: Hematopoietic Growth Factors, Version 1.2020. J Natl Compr Canc Netw, 2020(18): 12–22.

[21] Lyman GH, Kuderer NM, Crawford J, et al., 2011, Predicting Individual Risk of Neutropenic Complications in Patients Receiving Cancer Chemotherapy. Cancer, 2011(117): 1917–1927.

[22] Walker SN, Sechrist KR, Pender NJ, 1987, The Health-Promoting Lifestyle Profile: Development and Psychometric Characteristics. Nurs Res, 1987(36): 76–81.

[23] Seo HM, 2001, Construction of Health Promoting Behaviors Model in Elderly, thesis, Seoul National Univ., Seoul.

[24] Sung HM, Kim JB, Park YN, et al., 2008, Study on the Reliability and the Validity of Korean Version of the Beck Depression Inventory-II (BDI-II). J Korean Soc Biol Ther Psychiatry, 2008(14): 201–212.

[25] Moghaddam SR, Elmieh A, Chafy MR, 2021, The Effect of Leisure Time Regular Exercise on Neutrophil Function, Myeloperoxidase Levels, and Antioxidant Capacity in Middle-Aged Men. Med Sci J Islamic Azad Uni, 2021(31): 413–424.

[26] Arends J, Bachmann P, Baracos V, et al., 2017, ESPEN Guidelines on Nutrition in Cancer Patients. Clin Nutr, 2017(36): 11–48.

[27] O'Malley M, Healy P, Daignault S, et al., 2013, Cigarette Smoking and Gemcitabine-Induced Neutropenia in Advanced Solid Tumors. Oncology, 2013(85): 216–222.

[28] Vusqa U, Jayakrishnan TT, Bakalov V, et al., 2022, Predictors and Long-Term Outcomes for Diffuse Large B-Cell Lymphoma (DLBCL) Patients Undergoing Surgery Prior to Systemic Therapy: A Nationwide Analysis. Cureus, 2022(14): e24448.

[29] Sharma R, Cunningham D, Smith P, et al., 2009, Inflammatory (B) Symptoms are Independent Predictors of Myelosuppression from Chemotherapy in Non-Hodgkin Lymphoma (NHL) Patients--Analysis of Data from a British National Lymphoma Investigation Phase III Trial Comparing CHOP to PMitCEBO. BMC Cancer, 2009(9): 153.

[30] Makihara K, Shimeda Y, Matsumura T, 2021, Influence of Concomitant Polypharmacy on Docetaxel-Induced Febrile Neutropenia. Cancer Diagn Progn, 2021(1): 135–141.