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Original Article

Predictive Factors of Neutropenia Following First Cycle of Chemotherapy in Patients with Non-Hodgkin's Lymphoma in Bali, Indonesia

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Abstract

Background: Chemotherapy-induced neutropenia (CIN) is a common hematologic toxicity that increases infection risk, hospitalization, and treatment delay. Limited data exist on predictive factors of CIN among non-Hodgkin's lymphoma (NHL) patients in Indonesia, particularly in Bali.

Objective: To identify predictive factors of neutropenia following the first cycle of chemotherapy in patients with NHL at Prof. I.G.N.G Ngoerah General Hospital, Bali, Indonesia.

Methods: This retrospective cohort study included all NHL patients treated from 2020–2023. Eligible patients were aged ≥18 years, received CHOP-based regimens with or without rituximab, and did not receive G-CSF prophylaxis. Data were obtained from medical records. Assessed risk factors were age, gender, BMI, comorbidities, histopathology grading, extranodal involvement, ECOG status, Ann Arbor stage, IPI score, chemotherapy regimen, pre-treatment blood count, eGFR, LDH, and albumin. The incidence of neutropenia was evaluated after the first chemotherapy cycle.

Results: The mean age of the eligible patients (n=112) was 54.53 ± 14.64 years; 46 of them (41%) developed neutropenia. Significant factors associated with neutropenia were histopathology grading (p=0.030), Ann Arbor stage (p=0.048), IPI score (p=0.037), chemotherapy regimen (p=0.019), and LDH above normal (p=0.049). Multivariate analysis identified high IPI scores (p = 0.016; OR 6.375; 95% CI 1.416–28.698) and CHOP regimen (p=0.016; OR 3.033; 95% CI 1.230–7.476) as independent predictors of CIN.

Conclusion: High IPI scores and CHOP regimens are strong predictors of neutropenia after the first chemotherapy cycle in NHL patients. Early identification of high-risk patients is essential for preventive management and improved treatment outcomes.

Keywords: Chemotherapy-induced neutropenia, risk factor, non-Hodgkin lymphoma.

Introduction

Neutropenia is one of the adverse effects that occurs due to chemotherapy containing myelotoxic agents in non-Hodgkin's lymphoma (NHL) patients. Chemotherapy-induced neutropenia (CIN) would increase medical costs, serious infections, aggressive management, morbidity, and mortality of the patients.[1] According to the Common Terminology Criteria for Adverse Events (CTCAE), neutropenia is defined based on

a decrease in the absolute neutrophil count (ANC) to less than 2000/mm^3. Neutropenia can also be classified into four grades based on the CTCAE: Grade I if ANC < 2000/mm^3, Grade II if ANC <1500/mm^3, Grade III if ANC <1000/mm^3, and Grade IV if ANC < 500/mm^3.[2] On the other hand, other studies define neutropenia as an ANC <1500/mm^3, with classifications as follows: mild when ANC is between 1000 and <1500/mm^3, moderate when ANC is between 500 and <1000/mm^3, and severe when ANC is <500/mm^3.[3] Neutropenia can develop into febrile neutropenia (FN), which is the most serious emergency in hematological cases, as it can develop infection progressively. Previous research found that the mortality rate in patients treated for FN was 17.3% while the 30-day mortality rate was 20.5%.[4] Looking at these conditions, the timing and severity of CIN will influence the patient's prognosis and have a predictive role in determining cancer management. By knowing the incidence of neutropenia from the beginning, it will provide consideration for providing prophylaxis so that patient mortality rates can decrease.[1]

Multiple factors may contribute to the development of CIN. According to the National Comprehensive Cancer Network (NCCN), advanced age, previous radiotherapy or chemotherapy, bone marrow involvement, persistent neutropenia, hepatic or renal dysfunction, poor performance status, and immunodeficiency states increase the risk of neutropenia in NHL patients undergoing chemotherapy. Additionally, disease stage, NHL subtype, and the chemotherapy regimen used have been associated with CIN. Pretreatment laboratory parameters—particularly low peripheral blood counts reflecting inadequate bone marrow reserve—are also important considerations.[1] By knowing the risk factors associated with CIN, susceptible individuals can be given appropriate prevention and treatment. In accordance with clinical guidelines, G-CSF prophylaxis is recommended for NHL patients undergoing chemotherapy if the risk of CIN is higher than 20%.[5]

The CHOP regimen, as the standard chemotherapy in NHL cases, consists of cyclophosphamide, doxorubicin, vincristine, and prednisone. When combined with rituximab, the regimen is called R-CHOP. Giving CHOP-based therapy chemotherapy with or without rituximab can cause neutropenia. Myelotoxicity complications in these two regimens are relatively high, with the incidence of febrile neutropenia in the R-CHOP regimen being 20.4%.[6] Patients who have experienced neutropenia after the first cycle of chemotherapy will have the tendency to experience neutropenia in the next cycle. Therefore, the absolute number of neutrophils observed after the first cycle of chemotherapy can predict the occurrence of neutropenia in subsequent cycles and an individual's susceptibility to chemotherapeutic agents. Low initial ANC after the first cycle will have a more severe chance of neutropenia in the next cycle.[1]

Given these considerations, investigating the incidence of neutropenia after the first chemotherapy cycle and identifying associated risk factors is essential. Understanding the determinants of CIN enables clinicians to implement targeted interventions to reduce treatment costs and improve quality of life. In Bali, research on predictive factors regarding chemotherapy-induced neutropenia specifically in NHL has not been conducted. Therefore, this study aims to assess the predictive factors of chemotherapy-induced neutropenia after first cycle of chemotherapy in patients with NHL in Bali.

Methods

This research has a single-center retrospective cohort study design conducted at RSUP Prof. I.G.N.G Ngoerah Denpasar, Bali. A total of 303 patients had confirmed NHL and were registered during January 2020–January 2023. The inclusion criteria for research subjects were patients aged ≥18 years, confirmed with NHL, undergoing first-line chemotherapy (CHOP or R-CHOP), and not receiving Granulocyte colony-stimulating factor prophylactic agents (G-CSF). Patients with incomplete medical record data from both clinical and laboratory data were excluded from this study. After selection, 77 patients did not undergo chemotherapy, 16 patients were <18 years old, 53 patients did not have complete data, and 45 patients were lost to follow-up. Thus, the number of subjects who met the requirements to take part in this research was 112 patients. The patient's clinical data were obtained from medical records, while laboratory parameters were taken from the results of the patient's examination immediately before undergoing chemotherapy. The ANC outcome value was observed after the first cycle of chemotherapy to assess the condition of neutropenia that occurs in the patient.

Factors influencing the incidence of

neutropenia due to chemotherapy were found to vary in each study. The factors assessed from this study were age, gender, body mass index (BMI) according to Asia-Pacific regulations, comorbidities, histopathological grade from working formulation, extranodal involvement, Eastern Cooperative Oncology Group (ECOG) performance status, Ann Arbor staging, International prognostic index (IPI) score, and chemotherapy regimen. Pre-treatment laboratory parameters, such as baseline complete blood count (CBC), estimated glomerular filtration rate (GFR), lactate dehydrogenase (LDH), and albumin, were also assessed as predictive factors in this study which were adjusted to hospital-determined cutoffs.

The age variable was divided into ≤60 years or >60 years to distinguish elderly and non-elderly groups. Gender was categorized as male or female. Body mass index was divided according to the Asia Pacific BMI classification into underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (≥25 kg/m^2).[7] Comorbidities such as heart disease, diabetes mellitus, kidney disorders, pulmonary disease, and others were determined to be present or absent based on history taking and medical records. Histopathological grading was categorized into low, intermediate, and high grade based on the Working Formulation (WF). Low-grade lymphoma is considered indolent, whereas high-grade lymphoma is classified as highly aggressive and often resistant to treatment. Intermediate-grade lymphoma is regarded as potentially curable with combination chemotherapy. This grading is determined through histopathological examination. Low-grade lymphomas include small lymphocytic, follicular small cleaved cell, and follicular, mixed small cleaved and large cell types. Lymphomas classified as intermediate-grade consist of follicular large cell, diffuse small cleaved cell, diffuse mixed small and large cell, and diffuse large cell types. High-grade lymphomas include immunoblastic, lymphoblastic, diffuse small noncleaved cell, as well as Burkitt and non-Burkitt lymphomas. Extranodal involvement was categorized as ≤1 or >1 site, based on the findings from the CT scan examination.[8]

Eastern Cooperative Oncology Group (ECOG) performance status is assessed based on patient or caregiver interview results, physical function observations, and evaluation of time spent in bed/chair. There are several categories of ECOG performance status, consisting of a score of 0 to 5. A score of 0 if the patient is fully active and can perform work without limitations, a score of 1 if patient is limited to perform heavy activities but still able to perform light or sedentary work, a score of 2 if the patient is still able to walk and perform self-care but unable to perform any work activities up to and about more than 50% of waking hours, a score of 3 if the patient only able to perform limited self-care and predominantly bedridden or chaired for more than 50% of waking hours, a score of 4 if completely unable to perform self-care and only bedridden or chaired, while a score of 5 means that the patient has died. ECOG scores in this study will be divided into <2 or ≥2.[9] The Ann Arbor staging system is divided into four stages. Stage I refers to the involvement of a single lymph node region. Stage II indicates the involvement of two or more lymph node regions on the same side of the diaphragm. Stage III involves lymph node regions on both sides of the diaphragm, often accompanied by infiltration of the spleen. Stage IV is characterized by diffuse or disseminated infiltration of one or more extra lymphatic organs or tissues, with or without lymphadenopathy as determined through physical examination and imaging studies such as CT scans. Ann Arbor staging is categorized as I, II or III, IV.[10] The International Prognostic Index (IPI) is a prognostic marker for NHL consisting of five components, each assigned a score of +1 for the following criteria: age >60 years, stage III/IV disease, elevated LDH levels, ECOG performance status ≥2, and involvement of ≥2 extranodal sites. The total IPI score is calculated by summing the points and is categorized into four risk groups: low (score 0–1), intermediate-low (score 2), intermediate-high (score 3), and high (score 4–5).[11] Chemotherapy regimens were categorized into CHOP and R-CHOP. The CHOP regimen is a chemotherapy combination consisting of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and prednisone 40 mg/m^2 while the R-CHOP regimen adds rituximab 375 mg/m^2 to the CHOP combination.[12]

Pre-treatment laboratory parameters were also generated from medical records, including hemoglobin, white blood cells, platelets, glomerular filtration rate (GFR), lactate dehydrogenase (LDH), and albumin. The blood test data collected were initial tests conducted upon patient admission. The GFR was calculated using

the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, based on variables including age, sex, and serum creatinine levels. Each laboratory value was presented as numerical data. Meanwhile, the dependent variable in this study is the incidence of chemotherapy-induced neutropenia. Baseline neutropenia was categorized as absolute neutrophil count (ANC) >1,500/mm^3 and ≥1,500/mm^3. This study will also include neutropenia grading based with the following distribution: mild when ANC is between 1000 and <1500/mm^3, moderate when ANC is between 500 and <1000/mm^3, and severe when ANC is <500/mm^3. Neutropenia following the first cycle of chemotherapy is defined as a condition that meets the criteria for neutropenia and occurs on day 7 or earlier, up to day 21 after chemotherapy.[3] In our hospital, complete blood count assessments are routinely performed on day 1 and one week after chemotherapy. In this study, the assessment of chemotherapy-induced neutropenia (CIN) was conducted uniformly one week after the first chemotherapy cycle.

Demographic data and clinical characteristics of patients were presented using descriptive analysis. Bivariate analysis between neutropenia and clinical characteristics was conducted using the chi-square test. Meanwhile, the relationships between CIN and numerical variables, such as laboratory results, were assessed using either the independent t-test or the Mann–Whitney U test. Variables that showed an association with CIN in the bivariate analysis were subsequently included as independent variables in a multivariate logistic regression analysis. All data were analyzed using SPSS software. A variable was considered statistically significant if the p-value was ≤0.05. This study received ethical approval from the Ethics Committee of RSUP Prof. I.G.N.G. Ngoerah (Approval No. 1829/UN14.2.2.VII.14/LT/2023).

Results

Patient demographic and clinical data can be seen in Table 1. Most of the patients were aged ≤60 years (67%), male (58.9%), had a normal BMI (58%), and accompanied by comorbidities (54.5%). Based on histopathological examinations, most patients were classified as intermediate grade (75.9%). Subjects in this study tended not to have extranodal involvement >1 (93.8%). From other NHL characteristics, most patients were

Table 1 Demographic and Clinical Characteristics of the Study Subjects

Characteristic	n (%) / Mean ± SD / Median (Range)
Age	
≤60	75 (67%)
>60	37 (33%)
Gender	
Male	66 (58.9%)
Female	46 (41.1%)
Body Mass Index	
Underweight	18 (16.1%)
Normal	65 (58%)
Overweight	18 (16.1%)
Obese	11 (9.8%)
Comorbidity	
Yes	61 (54.5%)
No	51 (45.5%)
Histopathology Grading	
Low grade	10 (8.9%)
Intermediate grade	85 (75.9%)
High grade	17 (15.2%)
Extranodal Involvement	
≤1	105 (93.8%)
>1	7 (6.3%)
ECOG performance status	
0,1	60 (53.6%)
≥2	52 (46.4%)
Ann Arbor staging	
I	20 (17.9%)
II	41 (36.6%)
III	25 (22.3%)
IV	26 (23.2%)
IPI Score	
Low	57 (50.9%)
Intermediate-low	22 (19.6%)
Intermediate-high	21 (18.8%)
High	12 (10.7%)
Chemotherapy regimen	
CHOP	67 (58.9%)

Table 1 Continued

Characteristic	n (%) / Mean ± SD / Median (Range)
RCHOP	45 (40.2%)
Hemoglobin (g/dL)	
Mean ± SD	11.7±1.77
Median (Range)	11.65 (6.78–15.76)
WBC (cells×10^3/µL)	
Mean ± SD	11.07±10.56
Median (Range)	8.29 (0.98–76.7)
Platelet (cells×10^3/µL)	
Mean ± SD	334.67±135.65
Median (Range)	327.85 (49–721.7)
GFR (mL/min/1.73 m^2)	
Mean ± SD	87.45 ± 26.58
Median (range)	90.27 (5.95–144.4)
LDH (U/L)	
Mean ± SD	523.70 ± 498.29
Median (range)	371.50 (94–3622)
Albumin (g/dL)	
Mean ± SD	3.21 ± 0.83
Median (range)	3.20 (0.4–5.3)

classified as ECOG ≥2 (55.4%), Ann Arbor stage II (36.6%), with a low IPI score (50.9%). Treatment in this study was categorized into CHOP and RCHOP with a greater percentage of CHOP regiments (58.9%). Laboratory test results, including complete blood count (hemoglobin, WBC, and platelet), GFR, LDH, and albumin, are presented as mean, median, and range values.

The incidence of CIN can be seen in Table 2. This study found that 46 individuals (41%) experienced CIN, with the distribution of neutropenia as follows: mild in 12.5%, moderate in 8%, and severe in 20%. Meanwhile, 66 individuals (59%) did not experience CIN following the first cycle of chemotherapy.

Factors associated with neutropenia can be seen in Table 3. Based on bivariate analysis, histopathology grading (p=0.030), Ann Arbor staging (p=0.048), IPI score (p=0.037), and chemotherapy regimen with CHOP (p=0.019) demonstrated significant relationship with CIN. Meanwhile, other patient characteristics such as age, gender, body mass index, comorbidities, extranodal involvement, and ECOG status were not significantly related to CIN (p>0.05).

Bivariate analysis of pretreatment laboratory findings between neutropenic and non-neutropenic patients is shown in Table 4. Patients who developed neutropenia after the first chemotherapy cycle tended to have higher hemoglobin, platelet counts, and LDH levels compared with non-neutropenic patients. In contrast, WBC, GFR, and albumin levels were lower in patients who developed neutropenia. Among these variables, only LDH showed a significant association with CIN (p=0.049), while CBC parameters, GFR, and albumin were not significantly related (p>0.05).

Table 5 presents the multivariate analysis of variables associated with CIN. Multivariate logistic regression indicated that an IPI score of 4 or 5 (odds ratio [OR], 6.375; 95% CI, 1.416–28.698; p=0.016) and receiving the CHOP chemotherapy regimen (OR, 3.033; 95% CI, 1.230–7.476; p=0.016) were significant predictive factors for CIN in NHL patients. Histopathological grade was not identified as an independent risk factor for CIN in the multivariate analysis.

Table 2 Incidence of Neutropenia After the First Cycle of Chemotherapy

Variables	Frequency (%)
Neutropenia	
Mild (ANC 1000 and <1500/mm^3)	14 (12.5%)
Moderate (ANC 500 and <1000/mm^3)	9 (8.0%)
Severe (ANC <500/mm^3)	23 (20.5%)
Non-neutropenia	66 (59.0%)

Discussion

This study consisted of 112 patients with confirmed NHL. A total of 41% of patients experienced CIN, and 20.5% of all patients developed severe neutropenia. The absolute neutrophil count (ANC) was evaluated following the first cycle of chemotherapy to assess the presence and severity of neutropenia in the patient. The high rate of neutropenia in NHL patients who received chemotherapy agents was also found in

Table 3 Factors Associated with Neutropenia

Variable	Neutropenia	Non-Neutropenia	p-value
Age			0.901
≤60	30 (65.2%)	45 (68.2%)	
>60	16 (34.8%)	21 (31.8%)	
Gender			0.587
Male	29 (63.0%)	37 (56.1%)	
Female	17 (37.0%)	29 (43.9%)	
Body Mass Index			0.682
Underweight	9 (19.6%)	9 (13.6%)	
Normal	27 (58.7%)	38 (57.6%)	
Overweight	7 (15.2%)	11 (16.7%)	
Obese	3 (6.5%)	8 (12.1%)	
Comorbidity			0.831
Yes	24 (52.2%)	37 (56.1%)	
No	22 (47.8%)	29 (43.9%)	
Histopathology Grading			0.030*
Low grade	8 (17.4%)	2 (3.0%)	
Intermediate grade	31 (67.4%)	54 (81.8%)	
High grade	7 (15.2%)	10 (15.2%)	
Extranodal Involvement			0.121
≤1	41 (89.1%)	64 (97.0%)	
>1	5 (10.9%)	2 (3.0%)	
ECOG			0.111
0,1	20 (43.5%)	40 (60.6%)	
≥2	26 (56.5%)	26 (39.4%)	
Ann Arbor staging			0.048*
I, II	19 (41.3%)	41 (62.1%)	
III, IV	27 (58.7%)	25 (37.9%)	
IPI Score			0.037*
Low	20 (43.5%)	37 (56.1%)	
Intermediate-low	10 (21.7%)	12 (18.2%)	
Intermediate-high	7 (15.2%)	14 (21.2%)	
High	9 (19.6%)	3 (4.5%)	
Chemotherapy Regiment			0.019*
CHOP	34 (73.9%)	33 (50%)	
RCHOP	12 (26.1%)	33 (50%)	

*Chi-square test ($p<0.05$)

Table 4. The Association of Laboratory Findings with Neutropenia

Variable	Neutropenia (n=46)	Non-neutropenia (n=66)	p-value
Hb (g/dL), mean±SD	11.67±1.73	11.63±1.81	0.908[a]
PLT (cells×10^3/µL), mean±SD	325.41±136.51	341.11±134.30	0.549[a]
WBC (cells×10^3/µL), median (range)	8.29 (0.98–76.41)	8.28 (4.00–76.70)	0.428[b]
GFR (mL/min/1.73 m^2), mean±SD	86.75±30.67	87.92±23.54	0.820[a]
LDH (U/L), median (range)	438 (180–3622)	322 (94–3078)	0.049[b*]
Albumin, mean±SD	3.09±0.76	3.29±0.86	0.202[a]

* [a] analyzed with *independent T-test*; [b] analyzed with *Mann-Whitney test* (p<0,05)

Table 5 Multivariate Analysis

	B	S.E.	95% CI	OR	p-value
Histopathology grading (high grade)	1.675	0.853	0.35–0.997	0.187	0.051
IPI high score (4 or 5)	1.852	0.768	1.416–28.698	6.375	0.016*
Regiment (CHOP)	1.109	0.460	1.230–7.476	3.033	0.016*

*Using regression logistic test

Lyman *et al*., who stated that the prevalence of CIN grade ≥3 in standard CHOP-like reached 51% of patients. Chemotherapy agents that are myelosuppressive can cause neutropenia, requiring hospitalization with broad-spectrum antibiotics. Therefore, this condition is associated with increased morbidity and mortality rates in NHL patients.[13] Prevention of CIN can be done by administering G-CSF. However, the administration of prophylactic agents, such as G-CSF, is currently not mandatory according to guidelines and is not routinely practiced in Bali, so it is important to know patients who are at risk of developing CIN. Several clinical trials have been conducted with different risk factors. Factors that are implicated in the development of CIN in NHL cases generally include advanced age, history of exposure to radiotherapy or chemotherapy, bone marrow involvement, persistent neutropenia, liver or renal dysfunction, poor performance status, and immunodeficiency states.[5]

This study found that several factors, such as histopathology grading, Ann Arbor staging, IPI score, LDH levels, and chemotherapy regimen, were associated with the occurrence of CIN. Among all these factors, the IPI score and chemotherapy regimen were the most influential as predictive factors for CIN. The prognosis of NHL patients can be categorized based on the IPI score. The IPI score is currently used as a tool to assess the overall survival of NHL patients. The IPI score consists of various components such as age, Ann Arbor staging, LDH level, extranodal involvement, and ECOG status so that it can better define the patient's condition. In clinical practice, the IPI score incorporates key patient- and disease-related factors, effectively capturing tumor burden, systemic inflammation, and marrow infiltration, all of which contribute to reduced hematopoietic reserve and increased susceptibility to myelosuppression. Therefore, patients with higher IPI scores are more vulnerable, including a greater risk of developing CIN. Therefore, all patients should have their IPI score calculated from the outset to enable close monitoring and to consider early initiation of prophylactic treatment.[14]

This study found that the CHOP regimen was significantly more likely to cause CIN than RCHOP based on bivariate and multivariate analysis. Based on the patient distribution in this study, patients who received the CHOP regimen tended to have high-grade NHL, poorer ECOG performance status, and higher IPI scores. Patients on the CHOP regimen also experienced a higher incidence of severe neutropenia compared to those on the R-CHOP regimen. This finding supports the notion that CHOP is more likely to cause CIN in this population compared to R-CHOP. The addition of rituximab to the CHOP regimen was found to

improve the outcomes of patients with DLBCL as the most common form of NHL.[12] Although the agent rituximab, the monoclonal antibody (MoAb) directly against CD20-positive B cells, could reduce ANC, research found that the addition of rituximab to the CHOP regimen can provide good efficacy with high overall and complete response rates reaching 96.7% and 90%, respectively. In addition, there was no treatment-related mortality. RCHOP chemotherapy is a promising treatment for NHL patients assessed from its toxicity and efficacy. Therefore, from a clinical perspective, the administration of R-CHOP may be considered to achieve better outcomes.[15]

Histopathology grading had a significant association with CIN. An advanced stage of disease is associated with various expressions of genes that play a role in apoptosis, differentiation, and cell survival. In addition, the higher the NHL grading, the more aggressive the cancer cells tend to be. Late-stage cancers tend to have high levels of oncogenes that increase the risk of DNA damage. In advanced cancers, chemotherapy can cause genomic instability, so it tends to experience neutropenia.[16] The results of this study are also supported by Evens *et al*., who revealed that NHL with high-grade histopathology has significant toxicity, with the most common prevalence of toxicity being grade 4 neutropenia at 88%. NHL patients with more aggressive histologic subtypes tend to experience greater marrow suppression or neutropenia. This implication suggests that, in addition to being the standard diagnostic tool, histopathological examination may also serve as a predictive marker of NHL aggressiveness in relation to neutropenia.[17]

Higher Ann Arbor staging was a predictive factor for CIN in this study bivariate but not multivariate. Ann Arbor staging defines disease severity. Early-stage NHL patients based on Ann Arbor staging tend to have a limited amount of disease burden. Therefore, the more severe the patient's condition, the greater the risk of a poor prognosis. Non-Hodgkin lymphoma patients with advanced Ann Arbor stages typically present with a higher tumor burden and greater bone marrow involvement. More advanced Ann Arbor staging also impairs hematopoietic reserve. In addition, advanced-stage NHL is often intrinsically more myelosuppressive, making patients more prone to developing neutropenia.[18]

The only pre-treatment laboratory finding that had a significant association with CIN was LDH levels, although multivariate analysis did not show this. Elevated LDH is associated with poor prognosis in NHL because LDH reflects disease progression. Elevated LDH levels reflect rapid cell turnover, systemic inflammation in NHL, and a high tumor burden, all of which compromise bone marrow reserve and increase vulnerability to myelosuppressive chemotherapy. This indicates that the more progressive NHL a patient suffers from, the higher the risk of CIN.[19]

This study found that age did not have a significant relationship with neutropenia. In this population, both younger and older patients were predominantly diagnosed with intermediate-high grade NHL and high IPI scores, resulting in no significant differences related to the patients' chronological age. This research is supported by the study of Dessalegn *et al*., which also found that age did not have a significant relationship with the incidence of neutropenia. The theory suggests that using biological age is more accurate in defining individual health outcomes than chronological age. The existence of different biological and pathogenic mechanisms for each individual supports that biological or physiological age is better used to compare patient conditions.[20]

This study also found that gender did not have a significant relationship with CIN. Research conducted by Davidson *et al*. supports that there was no significant difference in hematological toxicity between men and women. The dose of the chemotherapy regimen in this case was the same, while the difference in toxicity was influenced by the absolute number of cycles and the percentage of the chemotherapy dose received, thereby making gender a non-contributing factor to chemotherapy toxicity.[21] In this study population, a closer analysis revealed that both male and female patients had nearly equal proportions in terms of NHL histopathology grading and IPI scores, indicating no significant risk differences of CIN when assessed by gender.

Other patient characteristics, such as body mass index, were not significant predictive factor for CIN in this study. Likewise, the previous research found that BMI was not a risk factor for neutropenia after the first cycle of chemotherapy in NHL. Most of the samples in this study had normal nutritional status with comparable proportions between the neutropenic and non-neutropenic groups in all nutritional groups. The administration of chemotherapy regimens is personalized, allowing both malnourished and well-

nourished patients to receive appropriate dosing. Therefore, no significant difference was observed between BMI and the incidence of CIN in this population. The insignificance of CIN with BMI is supported by previous studies that recommend that chemotherapy doses should use body surface area (BSA) without considering BMI, especially if the goal is curative, so that patients can receive proportional chemotherapy doses.[22]

In this study, the presence or absence of patient comorbidities on the incidence of CIN did not have a significant effect. A study conducted by Yokoyama *et al*. found that other diseases, such as diabetes mellitus, hepatic, renal, or cardiac disease were not associated with neutropenia in lymphoma patients using chemotherapy. Nevertheless, this study also stated that poor general conditions with various comorbidities can cause poor performance status so that the relative dose intensity given will be lower and more at risk of neutropenia. Comorbidities are often not considered independent predictors of CIN, as their effects are overshadowed by more proximate disease- and treatment-related factors. In clinical practice, even when a patient has comorbidities, some of these conditions may be well-controlled, and the patient may adhere to treatment. Therefore, rather than simply assessing the presence or absence of comorbidities, evaluating other factors such as treatment adherence or the severity of the comorbid conditions has more significant implications for the patient's overall status.[18]

Extranodal involvement did not affect CIN in NHL patients in this study. This study found that most patients with ≤1 extranodal involvement tended to experience neutropenia compared to patients with >1 extranodal involvement so the results of this study did not show significance between extranodal involvement and CIN. Although extranodal involvement often reflects more extensive disease, its impact on the risk of neutropenia is typically mediated by stronger predictors such as bone marrow involvement, physiological reserves, and chemotherapy intensity. Moreover, extranodal involvement does not directly affect hematopoiesis and therefore does not impair neutrophil production.[6]

In this study, performance status by ECOG score also did not provide significant results. In this population, this condition can be assessed from the comparable number of patients experiencing neutropenia and non-neutropenia with an ECOG score ≥2. Research by McAndrew found that even patients with an ECOG performance status of 0 could experience an increased incidence of neutropenia even though they were not grade 3-4 of neutropenia. Assessment of ECOG status can be of insignificant value considering that ECOG is a subjective assessment estimated by the patient himself. ECOG can show an underestimation of patients' performance.[23]

Many studies mention that NHL patients have abnormal laboratory results as a risk factor for CIN. However, in this study, pre-treatment hemoglobin, WBC, and platelet counts did not show a significant association. This may be due to the fact that pre-treatment CBC is a single time-point measurement and may be transient. Various influencing factors, such as infection exposure or steroid use, can introduce measurement noise that weakens the observed associations.[24] On the other hand, GFR is a marker that shows kidney function. Patients with poor kidney function generally have an increased risk of neutropenia. However, the threshold for renal impairment is also an important factor. Mild to moderate reductions in GFR often do not reach statistical significance in predicting neutropenia. Unlike agents that are primarily excreted through the kidneys, standard NHL chemotherapy is not predominantly dependent on renal clearance but rather on hepatic metabolism. Therefore, decreased GFR is less likely to increase systemic drug exposure or the risk of myelosuppression.[25]

This study did not use a large sample size which may not represent broader population and reduce statistical power. Therefore, a larger sample size is required to enhance the validity of the study and ensure representation of the broader population. In addition, there are several other factors that were not assessed in this study such as psychological conditions, physical activity, liver disease, and self-care behavior, which may affect CIN. This study also only assessed CIN after the first cycle of chemotherapy. Therefore, further research is needed to assess other factors and the incidence of CIN in subsequent cycles with a larger sample.

This study shows that histopathology grading, Ann Arbor staging, IPI score, chemotherapy regimen, and LDH level above normal are associated with chemotherapy-induced neutropenia. Of these factors, the high IPI score and CHOP regimen require more attention as predictors of neutropenia in patients with NHL in Bali, Indonesia. The identification of risk factors for chemotherapy-induced neutropenia will

facilitate consideration of further treatment in NHL. Given that both a high IPI score and the use of the CHOP regimen were identified as significant predictors of chemotherapy-induced neutropenia (CIN), these findings should inform clinical decision-making, particularly in resource-limited settings such as Bali. Patients with high IPI scores or those receiving CHOP may benefit from closer hematologic monitoring during the initial chemotherapy cycles. Early consideration of prophylactic measures, such as G-CSF administration, could also be warranted in these high-risk groups to reduce the incidence and severity of CIN. Integrating these predictive factors into routine risk stratification may help optimize patient safety and treatment outcomes, especially in settings where routine prophylaxis is not yet standard practice.

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