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Original Research

Risk Factors Predicting Chemotherapy-induced Severe Neutropenia and Outcome in Advanced Stage Non-small Cell Lung Cancer: Data from the Limited Resource in Thailand

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Introduction: Chemotherapy-induced severe neutropenia requires dose reduction, delay in treatment, or discontinuation, and induces neutropenic complications resulting in poor outcomes and increased healthcare costs. This study aims to identify the risk factors for chemotherapy-induced severe neutropenia and outcome in advanced-stage NSCLC.
Method: From July 2014-January 2019, advanced-stage NSCLC who received chemotherapy were retrospectively analyzed. Demographic and risk factors data were collected from the electronic medical record system. Univariate and multivariate logistic regression analyses were performed to identify risk factors for severe neutropenia. Survival curves were estimated using the Kaplan–Meier method.
Results: Among 259 patients, 37 (14.28%) and 3 patients (1.2%) developed severe neutropenia and febrile neutropenia respectively. In multivariate analysis, restriction of protein diet (OR 9.54; 95%CI 2.44-37.24; P=0.001), concomitant use herbal medicine (OR 8.66; 95% CI 1.04-72.07; P=0.045), high BMI (OR3.1; 95% CI 1.07-8.99; P=0.04), renal disease (OR 3.9; 95% CI 1.7-8.91; P=0.001), number of cycle chemotherapy > 4 (OR 3.97; 95% CI 1.11-14.18; P=0.03) were significant predictors of Chemotherapy-induced severe neutropenia. No difference in response rate, progression-free survival and overall survival among groups (RR 18.9% vs 26.7%; median PFS; 9.6 vs 8.2 months, P=0.32 and median OS 13.8 vs 16.7 months, P=0.79 in severe and non-severe neutropenia respectively).
Conclusions: The present study indicates that protein-restricted diet, concomitant use of herbal medicine, BMI ≥ 25 kg/m^2, renal disease, and more than 4 cycles of chemotherapy are significant risk factors for chemotherapy-induced severe neutropenia. Therefore, patients with these risk factors should be more carefully monitored.

Introduction

Lung cancer is the second most common cancer worldwide, with an estimated 2.2 million new cases and 1.2 million deaths of lung cancer in 2020 [1]. Approximately 85% of all lung cancer patients have Non- Small Cell Lung Cancer (NSCLC) and are often diagnosed with advanced-stage cancer [2]. Nowadays, there are many treatment options for advanced-stage NSCLC such as chemotherapy, targeted therapy or immunotherapy [3- 5]. However, chemotherapy is a backbone treatment for non-targetable mutations or doesn't access novel treatment NSCLC on the basis of improvement in survival and quality of life [5-8].

Chemotherapy—although an effective treatment for lung cancer—has multiple side effects including neutropenia, a serious hematologic toxicity; it requires dose reduction, delay in treatment or discontinuation resulting in poor oncologic outcomes [9, 10]. Moreover, severe neutropenia often induces neutropenic complications or fatal infection and requires antibiotics or hospitalization; this increases healthcare costs [9, 11, 12]. Therefore, it is important to recognize the risk factors for

chemotherapy- induced severe neutropenia (CISN) in advanced-stage NSCLC. In previous studies, general risk factors for CISN includes elderly age, poor Eastern Cooperative Oncology

Group (ECOG) performance, advanced-stage disease, hematologic malignancy, low baseline WBC, neutrophil count, hemoglobin, serum albumin, multiple comorbid diseases [13-20]. However, data largely comes from literature in breast cancer and hematologic malignancy, with multiple compound treatments. The predictive factors of CISN specifically in NSCLC patients treated with limited resources remain lack of information. Therefore, the purpose of this study is to find NSCLC-specific predictive factors and implications for patient's response rate and survival.

Materials and Methods

Patients were eligible for inclusion in the study if they were 18 years of age or older, had histological/cytological confirmation for new case or recurrence of stage IIIB-IV NSCLC who received at least one cycle of chemotherapy, and one toxicity case report from the medical oncology unit at Sawanpracharak hospital, Thailand.

Data collection and assessment. All data were collected from the electronic medical record. The information was evaluated regarding age, sex, body weight, Body Mass Index (BMI), smoking history, ECOG, histology, stage, organ metastasis, comorbid disease, concomitant medications, blood cell count, serum albumin, serum creatinine, details of prior treatment, regimen chemotherapy, number of cycles chemotherapy and side effects. All patients were assessed by history taking, physical examination, and laboratory testing assessment (blood count and chemistry report) before each cycle of chemotherapy administrated. The chemotherapy regimen was selected depend on oncologist.

The severity of adverse events is classified according to the Common Toxicity Criteria of Adverse Events (CTCAE) version 4.0. This study defines severe neutropenia as grade 3-4 neutropenia. Tumor response was assessed by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. The primary objective was to recognize the risk factors of chemotherapy-induced severe neutropenia. The secondary objective was to determine outcomes in advanced-stage NSCLC.

Statistical analyses. Wilcoxon rank-sum tests were used to compare continuous data and data are reported as mean ± standard deviation (SD) or as median (range). Chi-square test or Fisher exact test were used to compare categorical data. To identify the factors associated with severe neutropenia, univariate and multivariate logistic regression were performed. Factors with a P-value < 0.10 in univariate analysis were evaluated as potential covariates in multivariate stepwise logistic regression analysis with backward selection. Survival curves were estimated using the Kaplan–Meier method. All reported P-values are two-tailed; a value below 0.05 was considered statistically significant. All analyses were performed using Stata version 15.1 (Stata Corp., College Station, TX, USA).

Results

Patient Characteristic. Between July 2014 and January 2019, there were 259 patients with advanced-stage NSCLC who received chemotherapy; their toxicity information is available. The patient's characteristics and pretreatment laboratory results are summarized in table1.

	Total (N=259)	Severe Neutropenia (N=37)	No severe neutropenia (N=222)	P-value
Age (years), mean (SD)	62.7 (9.4)	62.1 (8.3)	62.8 (9.6)	0.68
Female, n (%)	117 (45.2)	20 (54.1)	97 (43.7)	0.24
Smoking, n (%)	145 (56.2)	17 (46)	128 (57.9)	0.17
Smoking Pack-year,	31.5 (15.7)	31.6 (16.1)	30.8 (13.2)	0.84

mean (SD)				
Restriction of protein diet, n (%)	11 (4.3)	6 (16.2)	5 (2.3)	<0.001
Concomitant use herbal medicine, n (%)	4 (1.5)	2 (5.4)	2 (0.9)	0.1
Concomitant use anticoagulant, n (%)	12 (4.6)	1 (2.7)	11 (5)	0.55
BMI (kg/m^2), median (IQR)	18 (22.7-22.7)	17.9 (24-24)	18 (22.6-22.6)	0.17
Amount of weight loss (kg), median (IQR)	5 (3-8)	4.5 (3-6)	5 (4-8)	0.19
ECOG n (%)				0.002
ECOG0	51 (19.7)	15 (40.5%)	36 (16.2)	
ECOG1	146 (56.4)	19 (51.4)	127 (57.2)	
ECOG2	58 (22.4)	3 (8.1)	55 (24.8)	
ECOG3	4 (1.5)	-	4 (1.8)	
Baseline Laboratory				
Albumin (g/dl), median (IQR)	3.6 (3.1-4)	3.8 (3-4)	3.6 (3.1-4)	0.84
GFR (ml/min/1.73m^2), median (IQR)	76 (56-92)	60 (49-85)	78.3 (60-92)	0.006
Hemoglobin (g/dl), median (IQR)	11.8	11.5	11.8	0.43
	(10.5-12.8)	(10.1-12.4)	(10.6-12.8)	
WBC (mm^3), median (IQR)	9100	8410	9205	0.43
	(7360-11590)	(6990-10800)	(7450-11595)	
Neutrophil count (mm^3), median (IQR)	6117	5740	6165	0.31
	(4509-8250)	(4224-7640)	(4545-8475)	
Lymphocyte count (mm^3), median (IQR)	1714	1978	1708.5	0.12
	(1230-2349)	(1404-2508)	(1220-2335)	
Platelets (x10mm^3), median (IQR)	341	319	345.5	0.16
	(277-435)	(289-382)	(276.5-444)	
N/L Ratio, median (IQR)	3.5 (2.4-5.2)	2.9 (2.3-3.8)	3.5 (2.5-5.4)	0.08
Comorbid disease, n (%)	166 (64.1)	30 (81.1)	136 (61.3)	0.02
Renal disease, n (%)	59 (22.8)	15 (40.5)	44 (19.8)	0.01
Cardiovascular disease, n (%)	14 (5.4)	0 (0)	14 (6.3)	0.23
Diabetes mellitus, n (%)	25 (9.7)	2 (5.4)	23 (10.4)	0.55
COPD, n (%)	18 (7)	1 (2.7)	17 (7.7)	0.48
Liver disease, n (%)	4 (1.5)	1 (2.7)	3 (1.4)	0.54
Diagnosis				0.46
Newly diagnosis	255 (98.5)	36 (97.3)	219 (98.7)	
Recurrence disease	4 (1.5)	1 (2.7)	3 (1.4)	
TNM Stage				0.87
IIIB	26 (10)	22 (9.9)	4 (10.8)	
IV	233 (90)	200 (90.1)	33 (89.2)	
Histology n (%)				0.67
Adenocarcinoma	178 (69)	154 (69.7)	24 (64.9)	
SCCA	49 (19)	40 (18.1)	9 (24.3)	
Others	31 (12)	27 (12.2)	4 (10.8)	
EGFR Status n (%)				0.218

mutation	9 (3.5%)	3 (8.1%)	6 (2.7%)	
wide type	12 (4.6%)	1 (2.7%)	11 (5%)	
Number of organ metastasis				0.58
1	85 (32.8)	15 (40.5)	70 (31.5)	
2	80 (30.9)	8 (21.6)	72 (32.4)	
≥ 3	64 (24.7)	9 (24.3)	55 (24.8)	
Site of metastasis				
13 (5)	0 (0)	13 (5.9)	0.23	
Lung	139 (53.9)	20 (54.1)	119 (53.9)	0.98
liver	30 (11.6)	4 (10.8)	26 (11.7)	0.87
Bone/Soft tissue	51 (19.7)	6 (16.2)	45 (20.3)	0.57
Lymph node	47 (18.2)	6 (16.2)	41 (18.5)	0.74
Adrenal gland	30 (11.6)	2 (5.4)	28 (12.6)	0.21
Pleural	124 (47.9)	18 (48.7)	106 (47.8)	0.92

Table 1. Baseline Characteristics.

Abbreviation; BMI, Body Mass Index; GFR, Glomerular filtration rate; WBC, White Blood cell; NLR, Neutrophil/lymphocyte ratio; COPD, Chronic Obstructive Pulmonary disease; SCCA, Squamous Cell Carcinoma

There were 37 (14.28%) patients in the severe neutropenia group, 54.1% were female. The mean age was 62.7 ± 9.4 years old. Of the 259 patients, 145 were smoking and the mean of cigarette smoking was 31.5 ± 15.7 pack-year. Based on the 11 patients with a restricted protein diet, the likeliness of developing severe neutropenia was significant (16.2% vs 2.3%, P<0.001). Median baseline GFR was significantly lower in severe neutropenia than non-severe neutropenia (60 vs 78.3, p=0.006). The comorbid and renal disease were significantly more likely in severe neutropenia than in non-severe neutropenia (81.1% vs 61.1%, P<0.02 and 40.5% vs 19.8%, P<0.01 respectively). 255 patients (98.5%) were newly diagnosed with advanced-stage NSCLC. 178 patients have adenocarcinoma sub-type. The metastasis site was not different among groups.

246 (95%) patients received treatment with palliative chemotherapy; almost all chemotherapy regimens were platinum-based (Table 2).

	Total	Severe Neutropenia	No severe neutropenia	P-value
	(N=259)	(N=37)	(N=222)	
Prior RT, n (%)	38 (14.7)	34 (15.3)	4 (10.8)	0.47
Total Dose RT (Gy) (N=41), mean (SD)	33.7 (13)	31.9 (11.7)	49.8 (15.5)	0.01
Treatment, n(%)				0.16
Palliative CMT	246 (95)	34 (91.9)	212 (95.5)	
Concurrent Chemoradiation	2 (0.8)	1 (2.7)	1 (0.5)	
Sequential CMT then RT	9 (3.5)	1 (2.7)	8 (3.6)	
Sequential RT then CMT	2 (0.8)	1 (2.7)	1 (0.5)	
Regimen Chemotherapy				<0.001
Single-agent platinum	36 (13.9)	0 (0)	36 (16.2)	
Platinum/Gemcitabine	44 (17)	20 (54.1)	24 (10.8)	
Platinum/Taxane	176 (68)	16 (43.2)	160 (72.1)	
Cycle, median (IQR)	4 (3-6)	6 (4-6)	4 (3-6)	0.04
Duration of treatment,	77 (49-110)	93 (67-119)	73.5 (43-106)	0.006

Mean (days)				
Dose reduction				<0.001
1 level, n (%)	84 (32.43)	27 (73)	57 (25.7)	
2 level, n (%)	2 (0.007)	0 (0)	2 (0.9)	
Dose interrupt, n (%)	77 (29.72)	29 (78.4)	48 (21.7)	<0.001
Infection	23 (11.9)	2 (5.4)	21 (9.5)	0.55

Table 2. Treatment and Side Effects.

Abbreviation; CMT, Chemotherapy; RT, radiation

The highest incidence of severe neutropenia (54.1%) was found in patients with a platinum/ gemcitabine regimen. There was a significant difference in the median of cycle chemotherapy and duration of treatment among groups (6 vs 4 cycles; P=0.004 and 93 vs 73.5 days respectively). 38 (14.7%) patients received radiation before systemic treatment. The mean total dose radiation was 31.9 ± 11.7 and 49.8 ± 15.5 Gy in severe neutropenia and non-severe neutropenia with statistically significant (P=0.01). Febrile neutropenia was found in 1.2% (3 patients). The infection rate was not different among groups (P=0.55).

Univariate analysis for severe neutropenia revealed that restriction of protein diet (OR 8.4; 95% CI 2.42-29.17; P=0.001), concomitant use herbal medicine (OR 6.29; 95% CI 0.86-46.08; P=0.007), high BMI (BMI ≥ 25) (OR 2.79; 95% CI 1.12-6.91; P=0.03), GFR < 60 mL/min/1.73m^2 (OR 2.95; 95% CI 1.44-6.02; P=0.003), comorbid disease (OR 2.71; 95% CI 1.14-6.44; P=0.02), renal disease (OR 2.76; 95% CI 1.32-5.75; P=0.01), number cycles > 4 (OR 4.59; 95% CI 1.36-15.48; P=0.01), Platinum/ Gemcitabine (OR 8.33; 95% CI 3.8-18.27; P=0.001) were significantly associated with CISN. Multivariate stepwise logistic regression analysis with backward selection revealed that restriction of protein diet (OR 9.54; 95% CI 2.44-37.24; P=0.001), concomitant use herbal medicine (OR 8.66; 95% CI 1.04-72.07; P=0.045), high BMI (OR 3.1; 95% CI 1.07-8.99; P=0.04), renal disease (OR 3.9; 95% CI 1.7-8.91; P=0.001), number of cycle chemotherapy > 4 (OR 3.97; 95% CI 1.11-14.18; P=0.03) were significant predictors of severe neutropenia (Table 3).

Factors	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-Value
Age > 60	1.04 (0.5-2.15)	0.92		
Female	1.52 (0.75-3.05)	0.24		
Smoking	0.62 (0.31-1.24)	0.18		
Restriction of protein diet:	8.4 (2.42-29.17)	0.001	9.54 (2.4437.24)	0.001
Concomitant use of herbal medicine	6.29 (0.86-46.08)	0.07	8.66 (1.04-72.07)	0.045
Concomitant use anticoagulant	0.53 (0.07-4.25)	0.55		
BMI ≥ 25 kg/m^2	2.79 (1.12-6.91)	0.03	3.1 (1.07-8.99)	0.04
Amount of weight loss (kg)	0.93 (0.84-1.02)	0.13		
Albumin (mg/dL)	1.12 (0.62-2.03)	0.7		
GFR< 60 mL/min/1.73m^2	2.95 (1.44-6.02)	0.003		
Hemoglobin (g/dL)	0.93 (0.76-1.14)	0.48		
WBC (x10^3/mm^3)	0.99 (0.98-1)	0.6		
Neutrophil Count (x10^3/mm^3)	0.99 (0.98-1)	0.85		
Lymphocyte count (x10^3/mm^3)	0.99 (0.98-1)	0.17		

platelets count ($x10^3/mm^3$)	0.99 (0.98-1)	0.11		
N/L Ratio > 2.5	1.42 (0.67-3.02)	0.36		
Comorbid disease	2.71 (1.14-6.44)	0.02		
Renal disease	2.76 (1.32-5.75)	0.01	3.9 (1.7-8.91)	0.001
Platinum/Gem	8.33 (3.8-18.27)	<0.001		
Platinum/taxane	1			
Number of Cycle > 4	4.59 (1.36-15.48)	0.01	3.97 (1.11-14.18)	0.03
Radiation	0.67 (0.22-2.01)	0.48		

Table 3. Univariate and Multivariate Analysis for Severe Neutropenia.

The Data cutoff was June 30, 2021. At this time the median follow-up period was 2 years. 244 patients had progression events and 70 patients passed away. The response rate was similar among groups (Table 4).

	Total	Severe Neutropenia	No severe neutropenia	P-value
	(N=244)	(N=37)	(N=207)	
Response treatment				0.2
Partial response	61 (25.5)	7 (18.9)	54 (26.7)	
Stable disease	116 (48.5)	23 (62.2)	93 (46)	
Progressive disease	62 (25.9)	7 (18.9)	55 (27.2)	
6 months PFS (%)	69.5 (63.2-75)	81 (64.2-90.5)	67.4 (60.4-73.4)	0.04
1 year OS (%)	54.3 (42-65.1)	53.9 (24.8-76)	75.4 (62.1-84.7)	0.35
2 years OS (%)	40 (28.6-51.2)	38.5 (14.1-62.8)	40.4 (27.7-52.7)	0.95

Table 4. Treatment Outcomes.

Abbreviation; PFS, Progression-Free Survival; OS, Overall Survival.

The median progression-free survival (mPFS) in severe neutropenia and non-severe neutropenia were 9.6 (6.8-15.6) and 8.2 (4.9-14.8) months respectively (P=0.32). No difference in overall survival (median OS 13.8 vs 16.7 months, P=0.79) (Figure 1 and 2).

Figure 1. Progression-free Survival.

Figure 2. Overall Survival.

Discussion

The present study examined the risk factors associated with chemotherapy-induced severe neutropenia in patients with advanced-stage NSCLC. The result revealed that low baseline GFR, comorbid disease, platinum/gemcitabine regimen, and long duration of exposure to chemotherapy were associated with severe neutropenia. Multivariate logistic regression analysis found that restriction of protein diet, concomitant chemotherapy use of herbal medicine, BMI ≥ 25 kg/m^2, renal disease, and more than 4 cycles of chemotherapy were significant risk factors for CISN.

Dietary restriction-induced sarcopenia and increased risk of cachexia. Therefore, the dietary restriction may not be suitable for patients undergoing cancer treatment. As Hastreiter (2020) reported that protein malnutrition decreased hematopoietic stem cells and promote cell cycle

arrest [21]. Few studies of protein-restricted diet in cancer treatment were identified. One study was a randomized crossover trial in 27 patients treated with irinotecan found that a protein-restricted diet did not demonstrate the difference in WBC and neutrophil count after irinotecan treatment. Protein-restricted diet and toxicity during cancer treatment and oncological outcome require further exploration. However, the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline recommended that protein intake should be above 1 g/kg/day and if possible, up to 1.5 g/kg/day in cancer patients [22].

Nowadays, Herbs have an increasingly significant role in the treatment of cancer with conventional treatment. Based on Naja et al (2017), the incidence of herbal medicine usage in cancer patients were 22-54% [23]; however, the prevalence in this study was 1.5%. This may be due to the doctors' and teams' advice to refrain from using herbs during treatment, or the patients' history was hidden. Many studies explored the efficacy and safety to use herbal medicine with chemotherapy for treatment of cancer, especially in China. Chinese herbal medicine (CHM) alongside chemotherapy showed benefits in reduced non-hematologic toxicity [24,25] and does not show an increased risk of neutropenia in breast cancer [26]. Currently, a meta-analysis evaluated the efficacy of traditional herbal medicine (THM) combined with first-line platinum-based chemotherapy (PBCT) for the treatment of advanced NSCLC revealed that THM combined with PBCT lower the incidence of thrombocytopenia but does not affect neutropenia [27]. A systematic review of fifteen Chinese trials involving 862 participants found that CHM combined with chemotherapy reduces the risk of myelosuppression in stages III-IV NSCLC (RR 0.42, 95% CI 0.22-0.82, p=0.01) compared to chemotherapy alone [28]. However, all trials possessed a noticeable risk of bias, with omissions of potential adverse effects of CHM. The results of previous studies were inconsistent with the findings in this study. This may be due to the different types of herbs used in Thailand and their pharmacogenetic effects, as compared to medicinal herbs researched in literature. The efficacy and safety to use of herbal products as complementary or alternative medicine need to be further explored. The larger sample size of high-quality randomized control trials (RCTs) are necessary to reduce study heterogeneity. In Chotipanich et al. (2019) [29], complementary and alternative medicine use in cancer patients was associated with delayed time to receive standard treatment. Therefore, fixation on complementary and alternative medicine use can be a serious impediment to standard healthcare.

Based on this study, BMI ≥ 25 mg/m^2 is a risk factor for severe neutropenia. Bodyweight affects chemotherapy dose calculation; obese people will get a high dose of the drug, which may result in a higher occurrence of side effects. Kashiwabara et al. (2013) [30] compared the onset of hematologic toxicity in patients with chemotherapy treatment for lung cancer who were categorized into BMI < 25 mg/m^2 and ≥ 25 mg/m^2. They found that grade 4 neutropenia is significantly more common among patients with BMI ≥ 25 mg/m^2 than BMI < 25 mg/m^2 group (43% vs 24%, P<0.005); patients with BMI ≥ 25 mg/m^2 also required G-CSF and a reduction in carboplatin dose. Fernando Gutierrez et al (2016) [31] categorize patients with hematologic toxicity in gynecologic malignancy, who received full-dose carboplatin, into overweight (BMI ≥ 27 mg/m^2) and normal weight (BMI < 27 mg/m^2). The overweight group showed a higher incidence of grade III-IV hematologic toxicity, albeit without statistical significance. Similarly, Furlanetto et al (2016) [32] showed that obese breast cancer patients were more likely to have hematologic side effects but no difference in grade III- IV neutropenia. Other studies revealed obesity did not increase the risk of grade III-IV neutropenia. Therefore, it was unnecessary to use uncapped chemotherapy doses by body size in patients with solid tumors [33-35]. Recently, the ASCO guideline provided evidence that myelosuppression is the same in obese and non-obese patients [36]. However, the ASCO guidelines based its research on mostly Caucasian and African-American cancer patients pool. Future research should focus on total body drug distribution and the impact of obesity on side effects of chemotherapy, specifically in the Asian population.

Comorbid diseases and renal diseases were associated with CISN. However, only renal diseases were strong predictors of severe neutropenia, which is consistent with prior studies [37]. Renal diseases impair neutrophil function [38] resulting in an increased risk of CISN and neutropenic

complications. Patients receiving more than 4 cycles of chemotherapy is a risk factor for CISN which is consistent with past studies [27]. The data may indicate the false association between the number cycle of chemotherapy and severe neutropenia; patients who received more cycles of treatment had a greater accumulation of chemotherapy drugs, resulting in a higher incidence of severe neutropenia. There was no difference in response rate, progression-free survival and overall survival between severe and non-severe neutropenia consistent with prior study [39]. Gargiulo et al (2021) [40] report the pooled analysis of 6 RCTs reveals that CISN was a predictive factor of prognosis in lung cancer (hazard ratio of death 0.71; 95%CI: 0.53–0.95, p=0.048. However, it was an unclear association between the severity of CIN and a prognostic factor. The response of cancer cells to chemotherapy depends on the sufficiency of active drugs, the sensitivity of cancer to chemotherapy, cancer cells' resistance to the drug, genetic predisposition, and pharmacokinetics of chemotherapy. There were many factors that affected cancer mortality. This suggested different performance status, immune status, tumor burden, oncogenic mutations, and subsequent treatment may affect the prognostic value of CISN.

In conclusion, our data indicate that protein-restricted diet, concomitant use of herbal medicine, BMI ≥ 25 kg/m^2, renal disease, and more than 4 cycles of chemotherapy are significant risk factors for CISN in advanced-stage NSCLC. Therefore, patients with these risk factors should be more carefully monitored or adjusted dose of chemotherapy. However, the limitation of this study was the retrospective design, resulting in some relevant information on medical records not being recorded. Further investigation will develop and assess the accuracy of predictive models that clinicians can use to assess a patient's risk for the development of severe neutropenia and neutropenic complications during the course of chemotherapy.

Conflict of interest

The authors declare that no conflict of interests was present during the making of the study

Ethical Declaration

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for- profit sectors

Ethics Approval

This study has been approved by The Committee of The Medical Research Ethics of Sawanpracharak Hospital with reference no. 44/2564

Author Contribution Statement

S.N – contributed to the conception, design, data analysis, and manuscript writing.

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