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RESEARCH ARTICLE

Pretreatment Absolute Neutrophil-to-Lymphocyte Ratio (NLR) Predict the Risk for Febrile Neutropenia in the First Cycle Adjuvant Chemotherapy for Breast Cancer

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Abstract

Background: Chemotherapy-induced febrile neutropenia (FN) is a condition affecting mortality and morbidity. The records show that absolute neutrophil-to-lymphocyte ratio (NLR) is associated with the cancer prognosis and reflects the immune response system on the infection. It can be used as an independent prognostic biomarker and predictive marker in patients with chronic inflammatory diseases, cardiovascular diseases, or malignancies. Therefore, we have been conducted on using absolute NLR to predict FN in a patient with breast cancer who has adjuvant chemotherapy. **Materials and Methods:** The authors retrospectively evaluated the pretreatment absolute NLR of patients with early stage breast cancer who had adjuvant chemotherapy. Then, the relationship to FN was analyzed by using multivariate logistic regression analysis. **Results:** We conducted a retrospective analysis of 339 patients where 21 patients had developed FN (6.19%). The multivariate logistic regression analysis results indicated that the pretreatment absolute NLR cut-off point equal to or greater than 2.4 was a significant independent predictive biomarker of the chemotherapy-induced FN (odds ratio = 2.810, 95%,; CI 1.061 - 7.442; p = 0.038). The predictive performance of the high level of absolute NLR was an acceptable discrimination [AUC= 0.7626 (95% and CI 0.650 - 0.875)]. Furthermore, a calibration curve and the Hosmer-Lemeshow test to assess the accuracy of the predictive model showed a goodness of fit for a logistic predictive model (Hosmer-Lemeshow chi2 = 2.50; p = 0.645). **Conclusions:** Pretreatment absolute NLR would be a useful predictive biomarker for febrile neutropenia after the first cycle of adjuvant chemotherapy for breast cancer that would be simple and easy to integrate in daily practice without extra costs.

Keywords: Biomarker- NLR- Chemoprevention- Breast cancer

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Introduction

Breast cancer is the most commonly found disease in Thai females. According to the National Cancer Institute of Thailand, there were 40.8% new patients in 2018 [1]. Breast cancer treatment with adjuvant chemotherapy plays an important role and its precautionary side effects is febrile neutropenia (FN) although the treatment is the standard chemotherapy regimen, which is not dose-dense chemotherapy [2-3]. FN is mostly found on the first cycle of chemotherapy and is a significant condition, as it increases mortality [4-7]. Recent information illustrated that FN caused 5-20% of mortality [8-9].

Theis et al. [10] found that there were various patient factors affecting FN after the adjuvant chemotherapy. These factors included being female, aged over 65 years, cancer type, disease stage, low albumin, elevated bilirubin, low creatinine clearance, infection before chemotherapy, and number and type of chemotherapy drugs. However, such factors did not directly reflect the granulocyte reservoir or stem cell pool of the bone marrow, which the pretreatment hematological parameters were the white blood cell count [11], platelet count [12], absolute neutrophil count (ANC) [13-14], absolute lymphocyte count (ALC) [15-16], and absolute monocyte count (AMC) [17-19] that were hypothesized to reflect the patients' predisposition to FN.

Some studies applied the clinical predictive model by

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using the pretreatment hematological parameters to predict the FN [13-14-19]. It was found that there were some data that could be used to predict the FN of the patient with cancer in some chemotherapy regimens [13-14]. However, it could not be practical after the validation [19].

Furthermore, a number of studies utilized the absolute neutrophil-to-lymphocyte ratio (NLR) for the prognosis; such as, chronic inflammatory disease, cardiovascular disease and cancer [20-26]. It was discovered that the high cut-off NLR was related to the poor prognosis since the NLR indicated the balance of the inflammatory pathway and anti-immune function and the cut-off of the NLR was unclear [27]. Azab et al. [28] applied NLR > 3.3 as the independent significant predictor to the mortality in patients with chemotherapy. Moreover, Dirican et al. [29] used NLR where four was the independent prognostic factor to the disease free survival (DFS) and overall survival (OS) whereas Krenn-Piko et al. [30] used NLR >3 as the independent risk factor related to the poor DFS. However, it was unable to predict the OS.

In addition, Howard et al. [31] examined the NLR in patients with cancer and discovered that baseline NLR varied with age, gender, race, disease stage, and type of cancer. Thus, in order to apply the NLR, the type of cancer of the population should be studied.

For this reason, this research studied the pretreatment NLR to predict the FN in patients with breast cancer who had adjuvant chemotherapy.

Materials and Methods

The information of the patients with early stage breast cancer during 2016-2019 was collected from the database of the Division of Medical Oncology, Buddhasothorn Hospital, Chachoengsao, Thailand. Exclusion criteria included 1) stage IV breast cancer, 2) a history of other cancers, 3) unavailable essential data, 4) a history of anemia or other hematological disorders, 5) renal and hepatic impairment, 6) the first chemotherapy cycle was not administered at this hospital, and 7)a prophylactic use of granulocyte-colony stimulating factor (G-CSF). The sample size was calculated from the baseline incidence and population variance at a probability of a type-I error of 5% and probability of a type-II error of 20%. Consequently, a size of 238 samples was acquired.

FN was defined as a temperature higher than 38.5°C and an ANC higher than 0.5×10^9/L, or higher than 1.0×10^9/L and expected to fall below 0.5×10^9/L.

Pretreatment NLR and FN after the first cycle of chemotherapy was examined using an explanatory model multivariate (adjusted) and the effects logistic regression analysis. Then, the area under the ROC curve of the NLR used to predict FN and the appropriate cut-off of the pretreatment absolute NLR was investigated.

This study was approved by the Institutional Review Broad of Buddhasothorn Hospital.

Results

From the information of the 339 patients, the average age was 49.74 years. There were four regimens of adjuvant chemotherapy, which were the cyclophosphamide, methotrexate, fluorouracil (CMF) regimen, fluorouracil, adriamycin, cyclophosphamide (FAC) regimen, adriamycin, cyclophosphamide (AC) regimen, and paclitaxel, cyclophosphamide (TC) regimen. The FN at the first cycle of chemotherapy of each regimen is shown in Table 1.

It was discovered that there were 21 patients with FN. From the basic factors of both the patients with and without FN which included age, body surface area (BSA), pretreatment ANC, pretreatment ALC, post-treatment ANC, and pretreatment NLR, the post-treatment ANC was the only one different factor with statistical significance, p=0.002 (Table 2).

When analyzing the pretreatment absolute NLR, which was related to FN, there was the risk of FN at 1.693 times (cOR = 1.693; 95% CI 0.898- 3.190; p = 0.103) (Table 3). However, the confounding effects which were those patients aged over 60 years old (elderly), low BSA (< 1.4 m^2) and chemotherapy regimens had not yet been adjusted. Such factors affected the FN in patients who

Table 1. Comparing the Febrile Neutropenia from Each Chemotherapy Regimen, CMF; FAC; AC; and TC

Regimen	No febrile Neutropenia	Febrile Neutropenia
	Number (%)	Number (%)
CMF	40 (100)	0 (0)
FAC	163 (97.60)	4 (2.40)
AC	113 (87.60)	16 (12.40)
TC	2 (66.67)	1 (33.33)

Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 1.24)	100.00%	0.00%	6.19%	1.0000	
(>= 1.243..)	95.24%	5.03%	10.62%	1.0028	0.9464
(>= 1.25)	95.24%	5.35%	10.91%	1.0062	0.8908
(>= 1.291..)	95.24%	5.66%	11.21%	1.0095	0.8413
(>= 1.47619)	90.48%	9.75%	14.75%	1.0025	0.9770
(>= 1.486..)	90.48%	13.84%	18.58%	1.0501	0.6883
(>= 1.52)	90.48%	14.15%	18.88%	1.0539	0.6730
(>= 1.583..)	85.71%	20.13%	24.19%	1.0731	0.7098
(>= 1.722..)	85.71%	22.96%	26.84%	1.1125	0.6223
(>= 1.76)	80.95%	26.42%	29.79%	1.1001	0.7211
(>= 1.809..)	76.19%	34.59%	37.17%	1.1648	0.6883
(>= 1.833..)	71.43%	40.88%	42.77%	1.2082	0.6989
(>= 2.066..)	71.43%	42.45%	44.25%	1.2412	0.6730
(>= 2.08)	66.67%	46.54%	47.79%	1.2471	0.7162
(>= 2.095..)	66.67%	57.86%	58.41%	1.5821	0.5761
(>= 2.103..)	66.67%	59.12%	59.59%	1.6308	0.5638
(>= 2.111..)	66.67%	59.43%	59.88%	1.6434	0.5608
(>= 2.166..)	66.67%	61.95%	62.24%	1.7521	0.5381
(>= 2.214..)	66.67%	64.15%	64.31%	1.8596	0.5196
(>= 2.4)	66.67%	64.47%	64.60%	1.8761	0.5171
(>= 2.444..)	47.62%	74.84%	73.16%	1.8929	0.6999
(>= 2.476..)	47.62%	75.79%	74.04%	1.9666	0.6912
(>= 2.5)	47.62%	79.87%	77.88%	2.3661	0.6558
(>= 2.533..)	42.86%	81.76%	79.35%	2.3498	0.6989
(>= 2.857..)	28.57%	85.53%	82.01%	1.9752	0.8351
(>= 2.888..)	19.05%	88.36%	84.07%	1.6371	0.9161
(>= 2.933..)	9.52%	89.62%	84.66%	0.9177	1.0095
(>= 3.333..)	9.52%	92.45%	87.32%	1.2619	0.9786
(>= 3.466..)	4.76%	95.60%	89.97%	1.0816	0.9962
(>= 4)	0.00%	96.86%	90.86%	0.0000	1.0325
(> 4)	0.00%	100.00%	93.81%		1.0000

Figure 1. The Sensitivity and Specificity of Each Cut-off Point Value of Pretreatment Absolute NLR.

Table 2. General Quality and white Blood Cell Count Result of the Breast Cancer Patients Comparing between those with and without FN

Factors	No febrile Neutropenia N=318		Febrile Neutropenia N=21		
	mean	±SD	mean	±SD	p-value
Age	49.739	10.749	49.81	10.75	0.977
BSA	1.5885	0.152	1.572	0.118	0.623
Pre ANC	4501.459	1053.2	4733.333	1196.383	0.333
Pre ALC	2185.327	383.905	2061.905	414.097	0.156
Post ANC	1399.047	1763.598	215.143	147.589	0.002
Pre NLR	2.121	0.624	2.352	0.616	0.101

Table 3. The Risk of Pretreatment Absolute NLR (pre NLR) on the FN before Adjusting the Confounding Effects

Risk Factors	Crude Odds Ratio (cOR)	95% Confidence Interval	p-value
pre NLR	1.693	0.898- 3.190	0.103

Table 4. The Sensitivity, Specificity, Positive Predictive value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (LR+), and Negative Likelihood Ratio (LR-) when the Cut-off Point of Pretreatment Absolute NLR was > 2.4.

		95% Confidence Interval
Sensitivity	66.70%	43.0% - 85.4%
Specificity	64.50%	58.9% - 69.7%
Positive predictive value	11.00%	6.2% - 17.8%
Negative predictive value	96.70%	93.3% - 98.7%
Likelihood ratio (+)	1.88	1.34 - 2.63
Likelihood ratio (-)	0.52	0.28 - 0.95

had chemotherapy. Moreover, the pretreatment absolute NLR to be applied to the clinical practice should have the appropriate cut-off point in order to predict the FN.

Then, the cut-off point of the pretreatment absolute NLR to predict the FN was considered (Figure 1). This showed that the cut-off point > 2.4 contained 66.67% of sensitivity (95%CI 43.0% - 85.4%) and 64.47% of specificity (95% CI 58.9% - 69.7%), which was the optimal point because of the highest value of sensitivity and specificity. In addition, at the cut-off point >2.4, the positive predictive value (PPV) was 11.0% (95% CI 6.2% - 17.8%), negative predictive value (NPV) was 96.7% (95% CI 93.3% - 98.7%), positive likelihood ratio (LR+) was 1.88 (95% CI 1.34 - 2.63), and the negative likelihood ratio (LR-) was 0.52 (95% CI 0.28 - 0.95) (Table 4). However, the obtained predictability had not adjusted the confounding effects.

Therefore, when analyzing the pretreatment absolute NLR at the cut-off point > 2.4 and the relationship to the FN by adjusting the confounding effects with the multivariate logistic regression analysis, it was found that the pretreatment absolute NLR > 2.4 had the risk of FN at 2.810 times with statistical significance (aOR = 2.810; 95% CI 1.061 - 7.442; p = 0.038) (Table 5). Additionally, for the overall test accuracy of predicting the FN when using the > 2.4 and adjusting the confounding effects,

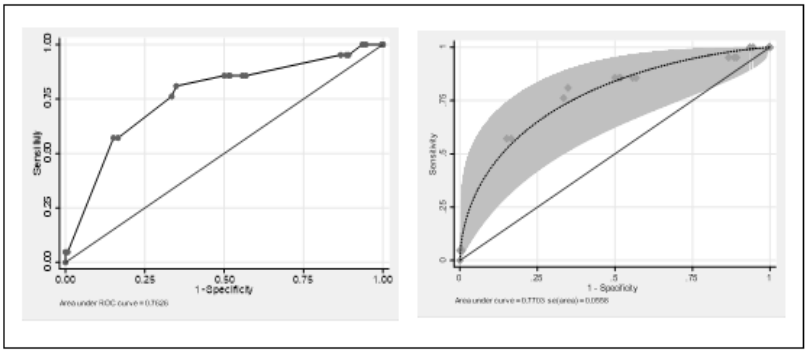

Figure 2. (A; Left, ROC curve) Displaying the Area under the Receiver Operating Characteristic Curve (ROC curve) of the Pretreatment Absolute NLR when using the Cut-off Point > 2.4 to Predict the FN after Adjusting the Effects of the Confounders, and AUC, 0.7626 (95% CI 0.650 - 0.875). (B; right, the fitted ROC curve and simultaneous confidence bands).

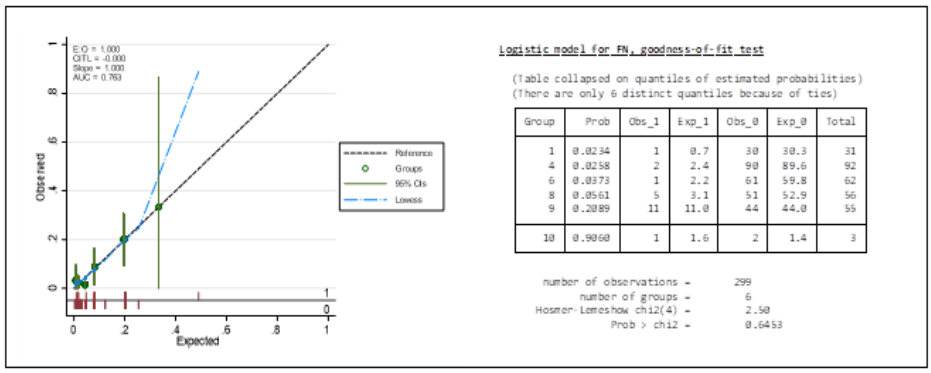

Figure 3. The Calibration Plot Showing the Expected Probabilities (x) Against the Observed Probabilities (y) of the Use of the Pretreatment Absolute NLR >2.4 to Predict the FN. The Hosmer-Lemeshow was chi2 = 2.50, p= 0.645.

the area under the receiver operating characteristic curve (ROC curve) was 0.7626 (95% CI 0.650 - 0.875) (Figure 2).

A logistic regression model is a way to predict the probability of FN based on the values of the pretreatment absolute NLR. Therefore, it is important to be able to assess the accuracy of a predictive model. Thus, the calibration plot was created to qualitatively compare the model's predicted probability of an event to the empirical probability (Figure 3). This illustrated that the obtained calibration curve from the expected probabilities (spike plot) and observed probabilities (Lowess smoother) was close to the diagonal reference line. When testing the model performances with the Hosmer–Lemeshow test, the Hosmer-Lemeshow was chi2 = 2.50 and p = 0.645.

Discussion

After adjusting the confounding effects, the pretreatment absolute NLR at the cut-off point > 2.4 was significantly correlated with the development of FN in the first cycle of the adjuvant chemotherapy (odds ratio = 2.810; 95% CI 1.061 - 7.442; p = 0.038). When applying the ROC curve to examine the overall test accuracy of the FN prediction, AUC = 0.7626 (95% CI 0.650 - 0.875), which was the acceptable

Table 5. The Risk of Pretreatment Absolute NLR (pre NLR) at the Cut-off point >2.4 to the FN after Adjusting the Effects by Using the Multivariate Regression Analysis

Risk Factors	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
pre NLR cut-off point > 2.4	2.81	1.061 - 7.442	0.038
elderly	0.338	0.043 - 2.686	0.305
lowBSA	0.552	0.068 - 4.505	0.579
CMF	1	(Reference category)	
FAC	0.018	0.001 - 0.493	0.017
AC	0.089	0.004 - 2.195	0.139
TC	1	(Reference category)	

Table 6. Comparison of the Studies Using Pretreatment Hematological Parameters to Predict the FN.

	Jenkins's Model (FEC regimen)	Jenkins's Model (TAC Regimen Plus G-CSF prophylaxis)	Chen's Model	This Study (pretreatment absolute NLR cut-off point > 2.4)
Number	741	263	428	339
FN rate	7.15%	11.79%	12.80%	6.19%
FN in cycle 1 high risk group	21%	23.80%	23.10%	11.02%
FN in cycle 1 low risk group	6.03%	4.55%	10.10%	3.30%
P value	0.002	< 0.001	< 0.01	0.038
sensitivity	13.21%	31%	38.20%	66.70%
specificity	95.25%	94%	81.20%	64.50%
PPV	21.21%	24%	23.10%	11.00%
NPV	91.89%	95%	89.10%	96.70%
AUC	NA	NA	0.58-0.6	0.7626

FN, febrile neutropenia; FEC, fluorouracil/epirubicin/cyclophosphamide; TAC, docetaxel/adriamycin/cyclophosphamide; PPV, positive predictive value; NPV, negative predictive value; G-CSF, granulocyte-colony stimulating factor; AUC, area under curve, NA, not available data.

discrimination. Moreover, the results of using a calibration curve along with the Hosmer–Lemeshow test to assess the predictive model performances indicated that there was a goodness of fit for a logistic predictive model (Hosmer-Lemeshow chi2 = 2.50, p = 0.645).

Recently, there were research studies [13-14] that applied pretreatment hematological parameters to predict FN in the first cycle of chemotherapy for breast cancer; this was the Jenkins' model, which combined ANC to ALC where the patients were classified into a low-risk and high-risk group to predict the FN in the patients with breast cancer who had the FEC regimen or TAC regimen. In addition, the study of Chen et al. [19] that validated Jenkins' model indicated that it could not be applied to his population. As a result, he developed the predictive mode that helped to classify the patients in order to predict the FN from the chemotherapy treatment by using ANC, ALC and AMC (Table 6).

Currently, the information about the genetic risk factors affecting the FN from early stage breast cancer presented by Pfeil et al. [32] showed that apart from the clinical risk factors, genetic factors had the impact on the prediction of FN, which involved homozygous carriers of the rs4148350 variant T-allele in MRP1 (odds ratio = 6.7; 95% CI 1.04-43.17), the higher alanine aminotransferase (odds ratio = 1.02; 95% CI 1.01-1.03]), the carriers of the rs246221 variant C-allele in MRP1 (odds ratio = 2.0; 95% CI 1.03-3.86), and the rs351855 variant C-allele in FGFR4 (odds ratio = 2.48; 95% CI 1.13-5.44).

Consequently, the use of pretreatment hematological parameters solely to predict the FN might have less accuracy. Nevertheless, examination of genetic risk factors in the clinical practice was not widely proceeded and the cost-effectiveness was questionable. Thus, the clinical risk factors and pretreatment hematological parameters to predict the FN was vital.

From the predictive model, ANC, ALC or AMC was utilized to classify the patients into the high risk and low risk group of FN; however, there was no use of NLR to predict the FN; the patients with neutropenia from having chemotherapy might not have FN. Chemotherapy induced FN might be related to infection during neutropenia. Recent studies[4-13-14-19-33-37] found that the low pretreatment ANC, ALC, AMC affected the neutropenia and FN positively. This was because neutropenia increased the risk of infection, which might result in FN. On the other hand, NLR reflected the balance between the inflammation pathway activity and anti-immune function. The previous research discovered that the higher NLR was concerned with the poor cancer prognosis and inflammation [20-31-38-39].

The study of Kaushik et al. [40] also reported that the elevated levels of NLR could diagnose and predict the early sepsis and late sepsis by using the cut-off point NLR > 3.3 with AUC= 0.911 at the early sepsis phase, and > 8.3 with AUC = 0.732 at the late sepsis phase. This concurred with the research of Jager et al. [41], which illustrated that NLR was the predictive marker of bacteremia and was more efficient than the conventional marker in the emergency unit at the cut-off point NLR > 10 with AUC = 0.73.

Therefore, the condition of FN, which would be related to the infection in neutropenia that compromised the immune systems using the high absolute NLR obtained from the high levels of neutrophil count associated with the severe inflammation or infection along with the lymphocytopenia indicated that the compromising reflect immune response system was likely one of the predictive markers of chemotherapy induced FN.

The research illustrated that pretreatment absolute NLR could be a useful predictive biomarker for FN after the first cycle of adjuvant chemotherapy for breast cancer, which was simple and easy to integrate in daily practice and without extra costs so to prevent FN in patients with a high risk and minimize the mortality and morbidity.

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