International Journal of Advanced Research in Medicine

E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2025; 7(3): 83-88
www.medicinepaper.net
Received: 16-05-2025
Accepted: 20-06-2025

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Pretreatment platelet count and neutrophil/lymphocyte ratio are predictive markers for carboplatin plus pemetrexed therapy-induced thrombocytopenia

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DOI: https://www.doi.org/10.22271/27069567.2025.v7.i3b.655

Abstract
Background: Carboplatin is a platinum-based chemotherapy commonly used for lung cancer treatment. Thrombocytopenia is a major dose-limiting side effect, correlated with the area under the concentration curve (AUC). Predictive markers for carboplatin-induced thrombocytopenia could help identify patients who need reduced doses. Thrombocytopenia caused by carboplatin combined with pemetrexed is notably influenced by carboplatin in commonly used regimens for lung cancer.
Objectives: Is to detect predictive markers for carboplatin-induced severe thrombocytopenia in patients receiving carboplatin plus pemetrexed therapy
Methods: A prospective cohort study was conducted at the Oncology Teaching Hospital Medical Complex in Baghdad, Iraq. The study included 50 Iraqi patients diagnosed with lung adenocarcinoma between May 2022 and January 2023. Data were collected prospectively from the hospital's laboratory and directly from participants during their regular visits to the consultation room.
Results: Fifty patients with lung adenocarcinoma were included in this prospective cohort study. the mean age of the samples was 61.1 ± 11.2 years old. The proportion of males was 66% and for females was 34%. A thirty percent of the patients had a history of smoking. Regarding co-morbidities hypertension was the most common co-morbidity found with a prevalence of 14% followed by diabetes and heart failure. None of the cases had a family history of lung cancer The incidence of ≥ Grade I thrombocytopenia after carboplatin Plus pemetrexed treatment in this dataset was reported to be 24%. 28 patients had N/L ratio > 3 prior to chemotherapy initiation and it was reduced to 40% after treatment (P-value = 0.08). Platelets count was significantly reduced after cycles of chemotherapy treatment from a median of 322.5 to 246.5 (Wilcoxon test, P-value <0.001). On the other hand, N/L ratio was also reduced from a median of 3.3 to 2.2 though not statistically significant.
Conclusion: Pre-treatment platelet count and N/L ratio are potential markers for identifying chemotherapy patients at higher risk of developing thrombocytopenia. Platelet count can predict both the incidence and severity of post-chemotherapy thrombocytopenia, with 258 x 10^9/L identified as the optimal cutoff. However, while the N/L ratio is associated with an increased risk, it was not found to be a reliable predictive factor.

Keywords: Therapy-induced thrombocytopenia, lung cancer, platelet, neutrophil/lymphocyte ratio, carboplatin plus pemetrexed

Introduction

Over the past century, lung cancer has transitioned from being a rare disease to the most common malignancy and the leading cause of cancer-related deaths globally, responsible for about one-quarter of all cancer deaths. The 5-year survival rate is estimated at 18%, varying from 55% for localized cases to 4.5% for advanced stages. More than 95% of lung cancers are classified into four major histologic types: squamous, adenocarcinoma, large cell, and small cell [1].

Carboplatin, a chemotherapy medication used to treat various cancers such as ovarian, lung, head and neck, brain cancers, and neuroblastoma, is administered via injection into a vein. Common side effects include low blood cell levels, nausea, and electrolyte imbalances, while serious side effects may involve allergic reactions and an increased future risk of cancer. Its use during pregnancy can harm the baby [2]. Carboplatin belongs to the platinum-based antineoplastic class and works by inhibiting DNA duplication. Compared to cisplatin,

carboplatin has reduced side effects, particularly the absence of nephrotoxic effects, and is easier to control in terms of nausea and vomiting. However, it can cause significant myelosuppression, reducing blood cell and platelet production in the bone marrow [3]. This effect reaches its lowest point 21-28 days post-treatment, after which blood levels stabilize. Neutropenia, a reduction in white blood cells, may lead to complications such as infections, often requiring hospital readmission and antibiotic treatment [4].

Pemetrexed is a chemotherapy drug that mimics folic acid and works by inhibiting enzymes involved in purine and pyrimidine synthesis, thus preventing the formation of DNA and RNA required for cell growth [5]. It was approved by the FDA in 2008 for use with cisplatin to treat locally advanced and metastatic non-small cell lung cancer (NSCLC) in patients with non-squamous histology. Patients are advised to take folic acid and vitamin B12 supplements and use glucocorticoids around the time of treatment to prevent side effects like skin rashes [6, 7].

Common side effects of pemetrexed include low blood cell counts, fatigue, nausea, vomiting, diarrhea, oral mucositis, loss of appetite, skin rash, and constipation. These can be managed with supportive treatments like antiemetics, oral hygiene, and glucocorticoid therapy [8].

Chemotherapy-induced thrombocytopenia (CIT) is a serious complication of chemotherapy, defined as platelet counts below 100 x 10^9/L. It is classified based on severity using the National Cancer Institute criteria [9]. Severe thrombocytopenia can disrupt cancer treatments, increase bleeding risks, and necessitate platelet transfusions. Several chemotherapies can induce thrombocytopenia by interfering with platelet production through mechanisms such as DNA synthesis inhibition, platelet shedding, and increased platelet destruction. Agents like alkylating agents, platinum analogs, anthracyclines, and nucleic acid analogs inhibit megakaryocyte development, while oxaliplatin can cause antibody-mediated platelet destruction [10].

The neutrophil to lymphocyte ratio (NLR) is a marker of subclinical inflammation, calculated by dividing neutrophil count by lymphocyte count. Elevated NLR is linked to poor cancer prognosis [11-13].

Patients and Method

A single-center bidirectional cohort study was conducted at the Oncology Teaching Hospital Medical Complex in Baghdad, Iraq. The study included 50 Iraqi patients diagnosed with lung adenocarcinoma between May 2022 and January 2023. Data were collected retrospectively from the hospital's laboratory and directly from participants during their regular visits to the consultation room.

The study included 50 patients diagnosed with lung adenocarcinoma. The inclusion criteria specified that all participants were adults over 18 years old, diagnosed with lung adenocarcinoma, and all tested positive for TTF1. Additionally, all patients received combination chemotherapy consisting of carboplatin and alimta.

Exclusion criteria for the study included outpatient chemotherapy recipients, patients who were lost to follow-up within 21 days after chemotherapy for any reason, patients lacking essential laboratory data within 7 days prior to chemotherapy initiation, and those who were transitioned to targeted therapy during the study period.

Data collection was conducted using a questionnaire, which gathered information on the patients' age, cancer stage, risk factors, doses of carboplatin and alimta, platelet count, neutrophil count, lymphocyte count, and the N/L ratio before the first dose and again 21 days later after the second dose.

The respondents were fully informed about the study purpose and verbal consents were taken from all the respondents who were recruited in the study. Confidentiality of the obtained information considered. An official letter of permission from Iraqi board for medical specialties was obtained.

Depending on whether the distribution was normal or skewed, continuous variables were expressed as means and standard deviations or medians with range. Categorical variables were expressed as frequency and percentages. The Welch's t-test (for normally distributed variables) and Wilcox rank-sum test (for non-normally distributed variables) were performed. The difference between categorical variables was investigated using either the χ^2 test with yates correction or Fisher's exact test, depending on the context. Youden method was used for calculating the optimal cut-off point for the post-treatment thrombocytopenia, univariate logistic regression was used to calculate the odds ratio for the likelihood of thrombocytopenia. A P-value less than 0.05 was considered statistically significant. R software packages was used for data processing, administration, and statistical analysis ("R version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria").

Results

Fifty patients with lung adenocarcinoma were included in this prospective cohort study. the mean age of the samples was 61.1 ± 11.2 years old. The proportion of males was 66% and for females was 34%. A thirty percent of the patients had a history of smoking. Regarding co-morbidities hypertension was the most common co-morbidity found with a prevalence of 14% followed by diabetes and heart failure. None of the cases had a family history of lung cancer.

Table 1: Demographics, family history and comorbidities in patients with lung adenocarcinoma.

Characteristics	Cases, N = 50[1]
Age, years	61.1 ± 11.2
Sex	
Males	33 (66.0%)
Females	17 (34.0%)
History of comorbidities	
Smoking	15 (30.0%)
Hypertension	7 (14.0%)
Diabetes	5 (10.0%)
Heart failure	2 (4.0%)
Family history of lung cancer	0 (0.0%)
[1]Mean ± SD; n (%)	

Concerning the stages of lung cancer reported in this study. The most common was Stage IV (44%) followed by stage II (32%) and stage III (22%).

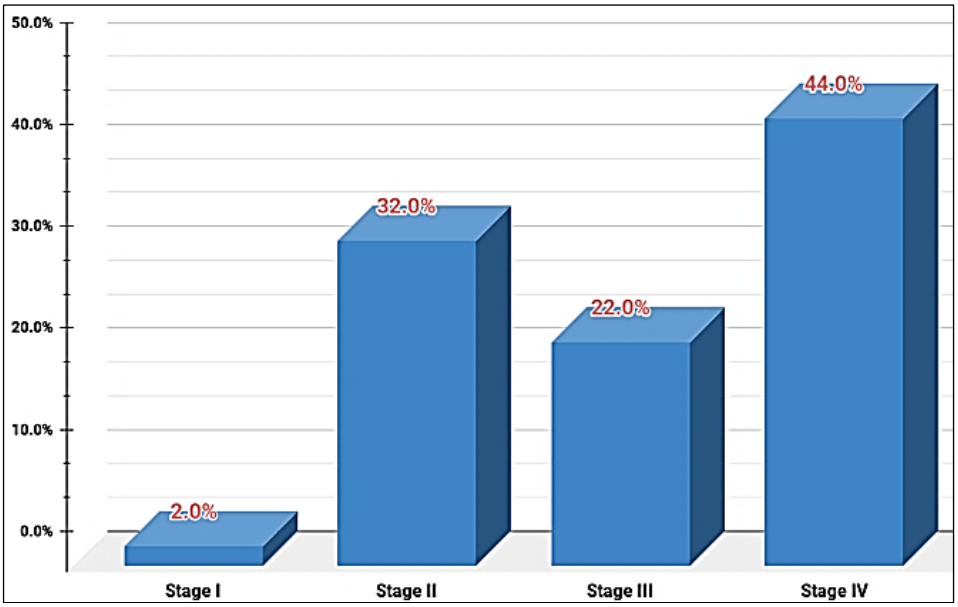

Fig 1: Prevalence of the stages of lung adenocarcinoma

The incidence of ≥ Grade I thrombocytopenia after carboplatin Plus pemetrexed treatment in this dataset was reported to be 24%. 28 patients had N/L ratio > 3 prior to chemotherapy initiation and it was reduced to 40% after treatment (P-value = 0.08).

Table 2: Incidence of ≥ Grade I thrombocytopenia and N/L ratio > 3.

Characteristics	Pre-treatment[1]	Post-treatment[1]	P-value[2]
≥ Grade I thrombocytopenia	0 (0.0%)	12 (24.0%)	NA
N/L ratio > 3	28 (56.0%)	20 (40.0%)	0.08
[1]n (%)			
[2]McNemar's Chi-squared test with continuity correction.			

Platelets count was significantly reduced after cycles of chemotherapy treatment from a median of 322.5 to 246.5 (Wilcoxon test, P-value <0.001). On the other hand, N/L ratio was also reduced from a median of 3.3 to 2.2 though not statistically significant.

Table 3: Blood profile before and after the combination chemotherapy.

Characteristics	Pre-treatment[1]	Post-treatment[1]	P-value[2]
Platelets × 10^9/L	322.5 (275.8, 386.0)	246.5 (167.2, 339.0)	< 0.001
Neutrophils × 10^9/L	5.4 (4.8, 9.5)	3.8 (2.4, 7.7)	0.008
Lymphocytes × 10^9/L	1.9 (1.4, 2.5)	1.6 (1.4, 2.1)	0.14
N/L ratio	3.3 (1.9, 5.3)	2.2 (1.3, 4.0)	0.07
[1]Median (IQR)			
[2]Wilcoxon signed rank test with continuity correction			

Carboplatin and pemetrexed dose were compared between those who developed thrombocytopenia and those who did not. The doses for both drugs were higher in those with ≥ Grade I thrombocytopenia though not statistically significant. Blood profile was also compared before and after treatment (Table 4).

Table 4: Chemotherapy dose and blood profile in patients with and without thrombocytopenia.

Characteristics	≥ Grade I thrombocytopenia, N = 12[1]	Normal platelets, N = 38[1]	P-value[2]
Chemotherapy dose			
Carboplatin mg	516.7 ± 240.9	480.0 ± 93.3	0.6
Pemetrexed mg	833.3 ± 44.4	809.5 ± 90.0	0.2
Before treatment			
Platelets × 10^9/L	284.0 (169.0, 318.0)	329.0 (304.0, 404.0)	0.027
Neutrophils × 10^9/L	4.8 (3.4, 8.3)	5.4 (4.9, 9.6)	0.2
Lymphocytes × 10^9/L	1.5 (1.4, 1.9)	2.1 (1.4, 2.5)	0.2
N/L ratio	3.3 (1.4, 6.0)	3.3 (2.1, 4.6)	0.7
After treatment			
Platelets × 10^9/L	123.0 (74.0, 145.0)	283.0 (224.0, 358.0)	<0.001
Neutrophils × 10^9/L	2.4 (2.0, 3.0)	5.2 (2.8, 7.8)	0.027
Lymphocytes × 10^9/L	1.5 (1.0, 1.5)	1.8 (1.5, 2.1)	<0.001
N/L ratio	1.6 (1.4, 1.9)	2.8 (1.3, 4.1)	0.2
[1] Mean ± SD; Median (IQR)			
[2] Welch Two sample T-test; Wilcoxon rank sum test			

The optimal cut-off points for platelets count and N/L ratio before treatment was calculated using Youden method for the likelihood of developing ≥ grade I thrombocytopenia (Table 5). ROC curve was illustrated in Figure 3. The optimal cut-off point was found to be 258.18 × 10^9/L for platelets count and 5.1 for N/L ratio.

Table 5: Optimal cut-off point for pre-treatment platelets count and N/L ratio for the diagnosis of grade I thrombocytopenia after treatment.

Characteristics	Cut-off point	Sensitivity	Specificity	AUC
Platelets count	258.18	84%	41%	0.71
N/L ratio	5.1654	41%	78%	0.46
*Youden method				

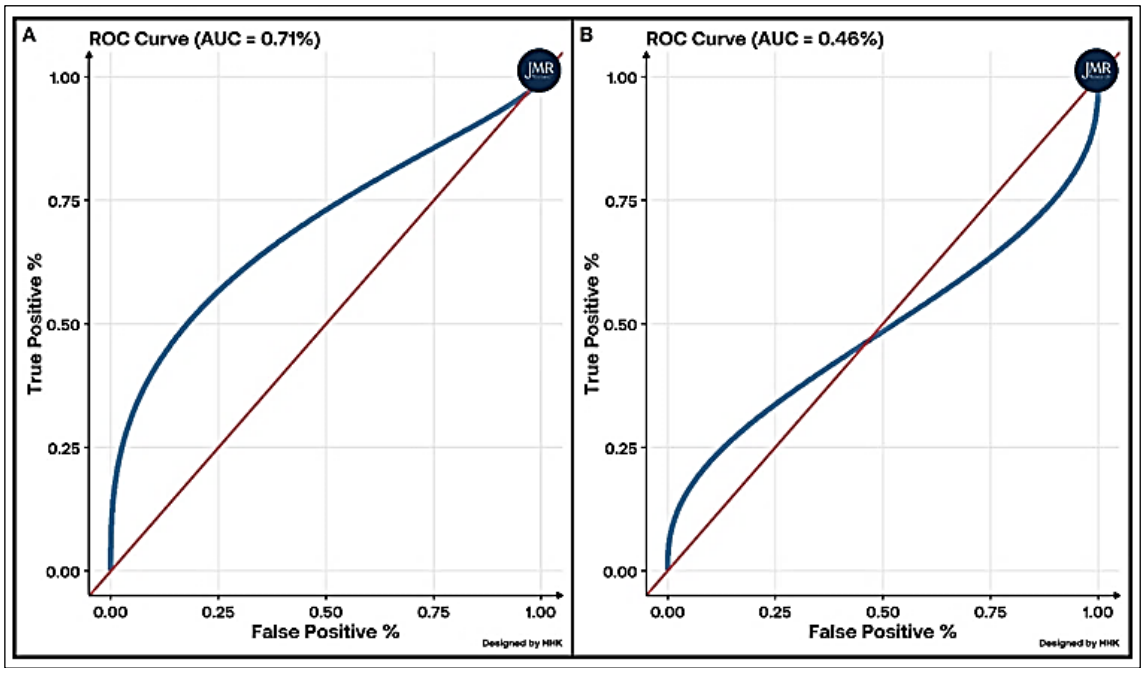

Fig 3: ROC curve showing the area under the curve for the prediction of thrombocytopenia for pre-treatment platelets count (A) and N/L ratio (B).

The odds ratio was calculated using unadjusted binary logistic regression model. The OR for the likelihood of thrombocytopenia was 3.81 for platelets count < 258.18, and 2.68 for N/L ratio and the result was statistically significant only for platelets (P-value = 0.019 and 0.2, respectively).

Table 6: Univariate logistic regression analysis for the likelihood of thrombocytopenia

Characteristics	Odds ratio, OR	95% CI	P-value[1]
Age, years	1.07	1.00, 1.18	0.079
Carboplatin, mg	1.00	1.00, 1.01	0.4
Pemetrexed mg	1.00	1.00, 1.01	0.4
Pre-treatment			
Platelets count	1.00	0.99, 1.00	0.5
N/L ratio	0.94	0.75, 1.08	0.4
Platelets < 258.18	3.81	1.88, 16.6	**0.019**
N/L ratio > 5.16	2.68	0.35, 10.9	0.2
*Unadjusted model			

Discussion

Thrombocytopenia has been known as one of the common chemotherapy-induced hematological adverse effects, particularly related to Carboplatin treatment as a monotherapy or as part of combination chemotherapy [14-16]. The fact that chemotherapy-induced thrombocytopenia could reach life-threatening degrees, which has been reported by many authors [14, 17, 18], certainly calls for active intervention. This includes developing an effective way of predicting the occurrence as well as the severity of thrombocytopenia in patients on chemotherapy so that certain measures could be taken to limit such grave consequences. Many factors have been suggested to work as predictive markers, however, pre-treatment platelet count and Neutrophil/Lymphocyte ratio (N/L ratio) are among the most affordable markers as they are measured as easily as obtaining a peripheral blood sample.

In our study, 50 patients diagnosed with lung adenocarcinoma were included. Of them, about two-thirds were male patients, and the other one-third comprised female participants. Positive smoking history was found in about 30 % of our sample, a much higher figure was reported by Takahashi *et al.* [19]in their study in Japan involving patients with lung cancer (66 % were smokers). Hypertension was identified as a comorbidity in 14 %, with fewer patients having other comorbidities like diabetes and heart failure. None of our participants reported a positive family history of lung cancer. Concerning lung cancer staging, stage IV was found to be the most prevalent among the study sample (44%), while stage I was the least abundant in only 2%. This is close to what Okamoto *et al.* [20] found, that 66 % of their patients were having stage IV disease at the time of the study.

To study whether the platelet count could have a predictive role for chemotherapy-induced thrombocytopenia, the platelet count was measured before and after receiving chemotherapy, and a statistically significant drop in the platelet count was seen after treatment (P-value < 0.001). This drop was observed in 24 % of the treated patients who

were found to have Grade I or more thrombocytopenia (classified according to the CTCAE criteria). Our result came in concordance with that of Takahashi *et al.* and Lawson *et al.* [19, 21] (both studies had a similar figure of 29 % presented with post-chemotherapy thrombocytopenia). On the other hand, Okamoto *et al.* [20] stated that up to 86 % (94 out of 109) of their participants had a drop in their platelet count post-chemotherapy. Such difference in the results might be related to the number of chemotherapy cycles received as well as the method by which the GFR was estimated for the calculation of Carboplatin dose as suggested by some authors [21]. Hanna *et al.* [22] studying chemotherapy in lung cancer patients, came across another finding of note that only 1.9 % of their sample developed thrombocytopenia following Pemetrexed chemotherapy. Such an inference might confirm the greater contribution of Carboplatin rather than Pemetrexed for post-chemotherapy thrombocytopenia.

Furthermore, the pre-treatment platelet count was found to be significantly lower in our patients who developed thrombocytopenia as opposed to those with normal platelet count post-treatment (median count of pre-treatment platelet 284 and 349, respectively; P-value = 0.027). Takahashi *et al.* [19] confirmed our finding and further suggested that those with pre-treatment platelet count < 266 × 10^9/L have a significantly higher incidence of post-chemotherapy thrombocytopenia. Moreover, those patients with the lower pre-treatment platelet count had their platelets drop to a much greater extent than their normal platelet counterpart.

Our results revealed a similarly significant drop in the neutrophil count post-chemotherapy. This corresponds to the result of Okamoto *et al.* [20] who demonstrated post-chemotherapy neutropenia in 56% of their lung cancer patients.

To investigate the potential predictive role of Neutrophil/Lymphocyte ratio (N/L ratio), it was compared before and after chemotherapy treatment, which showed a non-significant drop post-treatment (P-value = 0.07). Likewise, an N/L ratio > 3 was identified in a slightly, and statistically insignificant, lower percentage of the participants following combination chemotherapy treatment (56% pre- and 40% post-treatment). Additionally, a similar conclusion was obtained comparing the pre-treatment N/L ratio between those with post-chemotherapy thrombocytopenia and those with normal platelet count, which culminated in a non-significant difference (P-value = 0.7). Nevertheless, in their study examining the predictive role of N/L ratio for Carboplatin-induced thrombocytopenia, Takahashi *et al.* [19] concluded that a pre-treatment N/L ratio > 2.856 was associated with a much higher incidence of severe (grade III or IV) thrombocytopenia compared to an N/L ratio ≤ 2.856 (OR = 9.51, P-value < 0.001). Explaining their results, the authors claimed, based on another study [23], that an elevated N/L ratio is associated with reduced Carboplatin clearance with subsequent higher exposure to Carboplatin and thus a higher incidence of thrombocytopenia. However, the disparity in the results obtained suggests the need for further research for stronger evidence-based results that can be generalized and practically applied.

When the doses of Carboplatin and Pemetrexed were compared between patients who had thrombocytopenia and those who did not, both doses were seen to be slightly higher, though not statistically significant (P-value > 0.05), among the participants with post-treatment thrombocytopenia. This is in harmony with what other authors [19] found, who further confirmed the lack of association between various AUC values for Carboplatin dose and thrombocytopenia.

Using the Youden method and ROC curve, the optimal cutoff point for pre-treatment platelet count that would highly predict post-chemotherapy thrombocytopenia was found to be 258 x 10^9 /L, with high sensitivity (84%), yet low specificity (41%). A similar figure was suggested by Takahashi *et al.* [19] as well (cutoff point of 266 x 10^9 /L with a sensitivity of 83 % and a specificity of 51 %).

The optimal cutoff point for the pre-treatment N/L ratio was 5.1, which is more specific than sensitive to suggest post-chemotherapy thrombocytopenia. A lower cutoff point of 2.8 with a higher sensitivity (91 %) was concluded by some authors [19]. This difference in the optimal cutoff points between both studies might be justified by using a different method for calculating the cutoff point as well as the variation in the degree (severity) of thrombocytopenia classified based on the CTCAE criteria.

Several factors were examined as potential risk factors that could increase the likelihood for post-chemotherapy thrombocytopenia using logistic regression analysis. Of those factors, pre-treatment platelet count < 258 x 10^9 /L was seen to increase such possibility by up to 4 times (OR 3.8, P-value = 0.019). N/L ratio of more than 5.1 before treatment was associated with more than 2 folds of increasing risk for having chemotherapy-induced thrombocytopenia, yet did not reach statistical significance (OR 2.68, P-value = 0.2). Takahashi *et al.* [19] results agreed with ours and confirmed the presence of a significant predictive role for the pre-treatment platelet with a much higher OR (Platelets OR=24.7, P-value < 0.001). Nevertheless, they found that the N/L ratio was associated with an increased risk for post-chemotherapy thrombocytopenia with a statistical significance (OR=15.1, P-value = 0.0013).

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How to Cite This Article
Alsaheb SHA, Hasan SJ. Pretreatment platelet count and neutrophil/lymphocyte ratio are predictive markers for carboplatin plus pemetrexed therapy-induced thrombocytopenia. International Journal of Advanced Research in Medicine 2025; 7(3): 83-88.