Research Square

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Pretreatment Neutrophil-to-lymphocyte ratio (NLR) as a potential risk marker for Febrile Neutropenia (FN) in Breast and Ovarian Cancer During First-Cycle Chemotherapy

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Abstract

Purpose

The neutrophil-to-lymphocyte ratio (NLR) is an emerging biomarker for predicting febrile neutropenia (FN) in cancer patients. This study aimed to evaluate the association between pre-treatment NLR and the risk of FN in breast and ovarian cancer patients.

Methods

In this prospective study, 130 patients (109 breast, 21 ovarian) were analyzed. Pre-treatment NLR was measured, and the optimal cutoff was determined using receiver operating characteristic (ROC) curve analysis. Clinical and pathological variables, including age, body surface area (BSA), chemotherapy regimen, cancer type, and stage, were assessed using univariate analyses.

Results

ROC analysis showed an area under the curve (AUC) of 0.628 (95% CI 0.511–0.746) for NLR. An NLR cutoff ≥ 2.1 demonstrated a sensitivity of 72.7%, specificity of 50%, positive predictive value of 27.9%, and a negative predictive value of 90%. Baseline NLR ≥ 2.1 was associated with increased odds of FN (OR 2.67, 95% CI 0.97–7.33, p = 0.057); meanwhile, age, BSA, cancer stage, cancer type, and chemotherapy regimen were not significantly associated with FN.

Conclusion

Pre-treatment NLR ≥ 2.1 demonstrates moderate discriminatory ability for predicting febrile neutropenia, although the association was not statistically significant. These findings suggest NLR may serve as a supportive predictive marker, warranting further validation in larger cohorts.

Introduction

Febrile Neutropenia (FN) is one of the debilitating adverse effects of chemotherapy and is deemed an oncological emergency [1]. FN is defined as a single temperature ≥ 38.3 ˚C or ≥ 38.0 ˚C over the span of 1 hour, checked orally, along with an Absolute Neutrophil Count (ANC) of < 0.5 x10^3/μL or < 1.0 x10^3/μL with an anticipated reduction to ≤ 0.5 x10^3/μL over the next 48 hours [2]. Incidence of FN varies, ranging from less than 10% to more than 20%, with mortality up to 7.0% for adults with solid malignancies [3, 4]. Chemotherapy-induced neutropenia tends to frequently develop in the earlier phase of treatment cycles [5–8]. Along with its significant contribution to morbidity and mortality, economic burden on hospital resources, FN poses a major therapeutic challenge due to treatment delays and dosage limitations [9–13]. Several risk factors that influence the occurrence of FN have been identified, spanning three major domains: patient-related factors, including age ≥ 65, female gender, poor performance status, comorbidities, low body surface area (BSA); disease-related factors, such as genetic predisposition,

tumor type and advanced stage; and treatment related factors, encompassing the type of chemotherapeutic regimen and absence of prophylactic measures [14–18].

In light of the complex interactions among the aforementioned factors that influence neutropenia, there is a compelling need for a clinically applicable prediction tool [19]. Such a tool would enable proactive primary prophylaxis strategies to reduce neutropenia risk effectively and ideally prevent its occurrence altogether [20]. Over the years, diverse hematological parameters such as Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC), Absolute Monocyte Count (AMC), Platelet Count, and others have been explored in the quest to predict FN, because to some extent these indices represent the bone marrow hematopoietic stem cells pool and granulocyte reservoir [7, 19–27]. Despite the development of several predictive models, none have been incorporated into the routine clinical practice of oncologists [2, 28].

Recently, the Neutrophil-to-Lymphocyte Ratio (NLR) has garnered attention for its link to multiple oncologic settings, including prognosis, pathological complete response rates, sarcopenia, and a possible indicator of treatment response [29–35]. Overall, these findings demonstrate the wide range of therapeutic implications of NLR as a versatile biomarker that links host immunological state with disease behavior and treatment results. Furthermore, NLR has also been evaluated in association with predicting FN, as this marker better represents the balance between host immunity and inflammatory status [36, 37].

In this prospective study encompassing a South Asian population, our research scrutinizes the potential of the NLR as a predictive marker for FN in Breast and Ovarian Cancer after the first cycle of chemotherapy. By examining the relationship between NLR and FN, this study aims to seek its clinical relevance and potential use in patient care.

Methods

Study Design & Setting

This prospective observational study was conducted at Institute of Nuclear Medicine & Oncology, Lahore (INMOL) from March,2025 to December,2025. Ethical approval was obtained from the Institutional Review Board/Ethics Committee (IRB/EC Approval No: INMOL-53-216). This study was performed in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before inclusion in the study for participation and publication of data.

Sample Size Calculation

Considering the combined incidence of Breast & Ovarian Cancers as 19.2% (16.5% for Breast Cancer & 2.7% for Ovarian Cancer) from GLOBOCON 2022 for Pakistan [38], taking the confidence level as 95% and margin of error as 5%, a sample size of 130 (109 for Breast Cancer & 21 for Ovarian Cancer) was calculated.

Study Population

Patients aged 18–60 years with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and histologically confirmed invasive carcinoma of the breast or ovary were eligible for inclusion. For breast cancer, patients receiving adjuvant three-weekly Adriamycin-Cyclophosphamide (AC) protocol were included, whereas patients receiving Paclitaxel-Carboplatin (TC) were included in either the adjuvant or neoadjuvant setting. For ovarian cancer, Paclitaxel-Carboplatin (TC) was included in both adjuvant and neoadjuvant settings. Exclusion criteria included metastatic disease, prior malignancy or hematological disorders, hepatic or renal dysfunction, incomplete clinical or laboratory data, administration of the first chemotherapy cycle outside INMOL, or prophylactic use of granulocyte-colony stimulating factor (G-CSF). This approach ensured a homogeneous intermediate-risk population for FN, minimizing confounding from regimens with low or high FN risk, as defined by established guideline-based risk stratification [2]. Standardized clinical and laboratory data collection further reduced potential sources of selection and information bias.

Data Collection Procedure

Demographics and clinical variables, including age, body surface area (BSA), cancer type, disease stage, and chemotherapy regimen, were recorded. A baseline complete blood count (CBC) was obtained within 48 hours prior to initiation of the first cycle of chemotherapy at INMOL, and hematological parameters, including pre-chemotherapy ANC, ALC, and NLR, were documented. Following administration of chemotherapy, patients were prospectively monitored during the first treatment cycle for the development of FN. A follow-up CBC was routinely performed on day 9 after chemotherapy to assess the expected neutrophil nadir. In addition, patients were instructed to undergo immediate CBC testing at INMOL if they developed fever, defined as a single oral temperature ≥ 38.3 ˚C or a sustained temperature ≥ 38.0 ˚C for at least one hour, consistent with the standard definition of FN. The occurrence of FN during the first chemotherapy cycle was recorded for outcome assessment.

Neutrophil to Lymphocyte Ratio (NLR) Assessment

The CBC obtained before chemotherapy commencement was used for the calculation of the neutrophil-to-lymphocyte ratio.

NLR = Absolute Neutrophil Count ÷ Absolute Lymphocyte Count

Baseline NLR values were used for predictive analysis.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 20). Continuous variables, which were age, BSA, pre-chemotherapy ANC, ALC, NLR, and post-chemotherapy ANC, were expressed as mean ± standard deviation and compared between patients who developed FN and those who did not using independent-samples t-tests. In contrast, categorical variables, which were cancer type, cancer stage,

and chemotherapy regimen, were presented as frequencies and percentages and compared across groups by cross-tabulation. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability of baseline NLR for the development of FN. The area under the curve (AUC) was calculated, and the optimal cutoff value was determined based on the best combination of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LR), and crude odds ratio (cOR). Univariate binary logistic regression analysis was performed to evaluate the association between FN and NLR, along with other potential predictive variables, including age, BSA, cancer type, cancer stage, and chemotherapy regimen. Model calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test. Results were reported as odds ratios (OR) with 95% confidence intervals (CI). All statistical tests were two-sided, and p-values < 0.05 (alpha level = 0.05) were considered statistically significant.

AI-assisted language editing

During the preparation of this manuscript, the authors used Grammarly to assist with grammar, punctuation, and language clarity. The authors reviewed and edited the final manuscript version and take full responsibility for the content.

Results

A total of 130 patients were included in the study, comprising 109 (83.8%) patients with breast carcinoma and 21 (16.2%) patients with ovarian carcinoma. Febrile neutropenia developed in 22 (16.9%) patients during the first chemotherapy cycle. Baseline demographic, clinical, and hematological characteristics stratified according to neutropenia are presented in Table 1.

Table 1
Baseline Characteristics According to the Development of Febrile Neutropenia

Variable	Overall (n = 130)	FN (n = 22)	Non-FN (n = 108)	p-value
Age(years)	48.98 ± 8.83	49.27 ± 7.55	48.92 ± 9.102	0.867
BSA(m^2)	1.619 ± 0.093	1.611 ± 0.090	1.620 ± 0.094	0.686
Pre-chemotherapy ANC ($x10^3/\mu L$)	4.483 ± 961	4.672 ± 803	4.444 ± 988	0.314
Pre-chemotherapy ALC ($x10^3/\mu L$)	2.056 ± 451	1.918 ± 494	2.085 ± 439	0.116
Pre-chemotherapy NLR	2.33 ± 0.84	2.59 ± 0.76	2.28 ± 0.85	0.116
Post-chemotherapy ANC ($x10^3/\mu L$)	1.466 ± 1348	0.228 ± 129	1.718 ± 1344	< 0.001*
Cancer Type	• 109(83.8%)	• 18(16.5%)	• 91(83.5%)	
• Breast cancer	• 21(16.2%)	• 4(19%)	• 17(81%)	
• Ovarian cancer				
Stage	• 22(16.9%)	• 4(18.2%)	• 18(81.8%)	
• I	• 41(31.5%)	• 6(14.6%)	• 35(85.4%)	
• II	• 67(51.5%)	• 12(17.9%)	• 55(82.1%)	
• III				
Chemotherapy Regimen	• AC (90; 69.2%)	• 13(14.4%)	• 77(85.6%)	
	• TC (40; 30.8%)	• 9(22.5%)	• 31(77.5%)	

FN: febrile neutropenia; Non-FN: non-febrile neutropenia; BSA: body surface area; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; AC: Adriamycin-Cyclophosphamide; TC: Paclitaxel-Carboplatin; *p < 0.05 indicates statistical significance

The predictive performance of pre-chemotherapy NLR for FN was evaluated using ROC curve analysis. The area under the curve (AUC) was 0.628 (95% CI 0.511–0.746), indicating moderate discriminatory ability, and is shown in Fig. 1.

Multiple NLR cutoff values were evaluated to determine optimal diagnostic performance. An NLR cutoff value of 2.1 demonstrated the best combination of sensitivity and specificity and was selected as the optimal threshold. Diagnostic performance characteristics for multiple NLR cut-offs are shown in Table 2.

Table 2
Diagnostic performance characteristics of various NLR cut-offs

NLR cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	cOR
≥ 2.0	77.27%	46.29%	22.66%	90.90%	1.44	0.49	2.93
≥ 2.1	72.7%	50%	27.9%	90%	1.4	0.5	2.67
≥ 2.2	63.6%	52.8%	21.5%	87.7%	1.35	0.69	1.96
≥ 2.3	54.5%	55.6%	20%	85.7%	1.23	0.82	1.5
≥ 2.4	54.5%	59.3%	21.4%	86.5%	1.34	0.77	1.75

NLR: neutrophil-to-lymphocyte ratio; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; cOR: crude odds ratio

Univariate logistic regression analysis was performed to evaluate factors associated with the development of FN. Baseline NLR ≥ 2.1 was associated with increased odds of FN (OR 2.67, 95% CI 0.97–7.33, p = 0.057), while age, BSA, cancer stage, cancer type, and chemotherapy regimen were not significantly associated with FN (Table 3).

Table 3
Univariate analysis of clinicopathological factors associated with febrile neutropenia

Variable	cOR	95% CI	p-value
NLR ≥ 2.1	2.67	0.970–7.331	0.057
Age	1.005	0.953–1.059	0.866
BSA	0.354	0.002–52.396	0.684
Cancer Type • Ovary vs Breast	• 1.190	• 0.358–3.953	• 0.777
Cancer Stage • Stage II vs I • Stage III vs I	• 0.771 • 0.982	• 0.193–3.088 • 0.281–3.429	• 0.714 • 0.977
Chemotherapy Regimen • TC vs AC	• 1.720	• 0.667–4.431	• 0.262

cOR: crude odds ratio; BSA: body surface area; AC: Adriamycin-Cyclophosphamide; TC: Paclitaxel-Carboplatin

Discussion

In this prospective study, baseline neutrophil-to-lymphocyte ratio (NLR) was evaluated as a potential predictor of febrile neutropenia (FN) in breast and ovarian cancer patients receiving intermediate-risk chemotherapy regimens, for which primary prophylaxis by Granulocyte-Colony Stimulating Factor (G-CSF) is not recommended. An NLR threshold of ≥ 2.1, derived using receiver operating characteristic analysis, demonstrated moderate discriminatory performance and showed a trend toward increased risk of FN on univariate analysis (crude OR 2.67; 95% CI 0.970–7.331; p = 0.057). In contrast, other clinical variables, including age, body surface area, cancer type, disease stage, and chemotherapy regimen, were not significantly associated with FN risk. Taken together, these findings suggest that NLR may possess prognostic utility as a risk marker for FN.

Looking at the baseline blood counts, patients who developed cytopenia had higher mean pre-chemotherapy absolute neutrophil counts and lower mean absolute lymphocyte counts compared with those who did not develop neutropenia. While these differences did not reach statistical significance, the observed trend supports the biological construct underlying NLR, whereby relative neutrophilia reflects systemic inflammatory activation and relative lymphopenia reflects diminished adaptive immune competence. This pattern supports the idea that NLR is more than just a number; it reflects underlying immune balance and hematopoietic reserve [39, 40].

The association of elevated NLR observed in the present study appears to be biologically plausible. Higher neutrophil counts in cancer patients are hypothesized to reflect tumor-driven inflammatory signaling and cytokine-mediated stimulation of disordered myelopoiesis, resulting in a systemic pro-inflammatory state. Furthermore, neutrophils have been associated with suppression of T-cell activity through the formation of reactive oxygen species (ROS) and other inhibitory mediators [41, 42]. In contrast, lymphocytes mediate adaptive immunity, and low lymphocyte counts suggest impaired immune competence and reduced ability to fight infection [43]. When considered together, a higher NLR may therefore represent an imbalance between heightened innate inflammatory activation and weakened adaptive immunity. Such imbalance may indicate reduced host reserve during systemic stress, which could partially explain increased susceptibility to chemotherapy induced myelosuppression.

Our findings are consistent with prior studies linking elevated baseline NLR to hematologic toxicity during systemic therapy. Badran O et al conducted a retrospective study in a Middle Eastern breast cancer cohort receiving CDK4/6 inhibitors; an NLR cutoff ≥ 2.5 was associated with a higher incidence of grade 4 neutropenia events, shorter progression-free survival, and lower 3-year overall survival rate, supporting a relationship between systemic inflammation and treatment toxicity [40]. Similarly, a Japanese cohort of esophageal cancer patients treated with cisplatin and 5-fluorouracil found that NLR ≥ 3.0 independently predicted FN, with a hazard ratio of 4.849 [36]. Chantharakhit et al. also evaluated the usefulness of pretreatment NLR as a predictive marker for FN in Thai women with breast cancer. After adjusting for potential confounding factors and determining an optimal cut-off value, the study found that a pretreatment NLR greater than 2.4 predicted FN with a sensitivity of 66.67% and specificity of 64.47% [37]. Patients with an NLR above this threshold had a 2.81-fold higher risk of developing FN,

with a statistically significant result (p = 0.038). The key findings of previous studies on NLR and FN are summarized in Table 4. The difference in the varied cut-offs of NLR between the previous studies and this one can be attributed to the differences in demographics and clinical characteristics, as Howard et al in their study found that NLR changes with age, race, gender, disease stage, and type [44].

Table 4
Key findings of NLR in febrile neutropenia across prior studies

Study	**Current study**	**Chantharakhit et al.**	**Kumazawa et al.**
Sample size	130	339	114
NLR cutoff	≥ 2.1	≥ 2.4	≥ 3.0
AUC	0.7626 (95% CI 0.650–0.875)	0.628 (95% CI 0.511–0.746)	-
Sensitivity	72.7%	66.7%	-
Specificity	50.0%	64.5%	-
PPV	27.9%	11.0%	-
NPV	90.0%	96.7%	-
OR	2.67*	2.81^	-
HR	-	-	4.849 (95% CI 1.307–17.98)
p-value	0.057	0.038	0.018

NLR: neutrophil-to-lymphocyte ratio; AUC: area under the curve; PPV: positive predictive value, NPV: negative predictive value; OR: odds ratio; HR: hazard ratio;* crude odds ratio; ^ adjusted odds ratio

From a clinical perspective, NLR offers several practical advantages. It is inexpensive, universally available, and derived from routine complete blood counts without additional testing burden. Current clinical tools such as the Multinational Association for Supportive Care in Cancer (MASCC) and Clinical Index of Stable Febrile Neutropenia (CISNE) scores are valuable for risk stratification after febrile neutropenia has already developed; however, they do not assist clinicians in identifying vulnerable patients before chemotherapy initiation [45]. The ability to recognize patients at increased risk prior to chemotherapy could allow closer monitoring, individualized counseling, or selective supportive strategies without deviating from established guideline-based practice. This is particularly relevant in intermediate-risk chemotherapy regimens, such as three-weekly Doxorubicin–Cyclophosphamide and Paclitaxel–Carboplatin schedules evaluated in this study, where routine primary G-CSF prophylaxis is not recommended [2].

The strengths of this study include its prospective design, standardized timing of hematologic assessment, and objective determination of an optimal NLR cutoff using ROC analysis. We also evaluated traditional clinical predictors in our population to gain a comprehensive overview, although

none were significant. Limitations included a single-center design, lesser FN events and a modest sample size, which may have limited statistical power, potentially contributing to borderline significance despite consistent biological trends. Multivariate analysis was not performed due to limited significant predictors. Restriction to intermediate-risk chemotherapy regimens enhanced internal consistency but limited extrapolation to high- or low-risk treatment settings.

Despite these limitations, the findings do demonstrate reasonable clinical generalizability, as NLR is derived from routine laboratory parameters available in almost every healthcare setting. The consistency of observed trends with previously published studies supports the broader applicability of inflammation-based risk assessment, although external validation in larger multicenter cohorts remains necessary.

Future research should focus on combining NLR with clinical, demographic, genetic, and treatment-related factors to improve predictive accuracy. Serial assessment of inflammatory markers may also provide insight into dynamic responses during chemotherapy.

In conclusion, baseline NLR demonstrated a trend toward predictive relevance for chemotherapy-induced neutropenia in this prospective cohort. Although not definitive as a standalone predictor, NLR represents a simple and biologically meaningful biomarker that may assist individualized risk assessment and supportive care planning, particularly within intermediate-risk chemotherapy settings where preventive strategies must be selectively applied.

Statements & Declarations

Funding

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Competing Interests

The authors have no conflicts of interest to declare.

Author Contributions

Faraz Saif conceived and designed the study, collected and analyzed the data, and drafted the manuscript. Fakhra Nain Qureshi and Azaz Ahmed contributed to the study design and assisted with data interpretation. Fakeeda Durrani and Imad Ullah assisted with data collection and literature review. Noor Ul Ain Azam and Ziauddin Ahmed contributed to methodological guidance and critically revised the manuscript. Asif Riaz Khan supervised the study and provided critical revisions to the manuscript. All authors read and approved the final version of the manuscript.

Ethics Approval

Ethical approval was obtained from the Institutional Review Board/Ethics Committee (IRB/EC Approval No: INMOL-53-216). This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate & publish

Written informed consent was obtained from all participants before inclusion in the study for participation and publication of data

Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to institutional policy regarding patient confidentiality considerations, but are available from the corresponding author on reasonable request.

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Figures

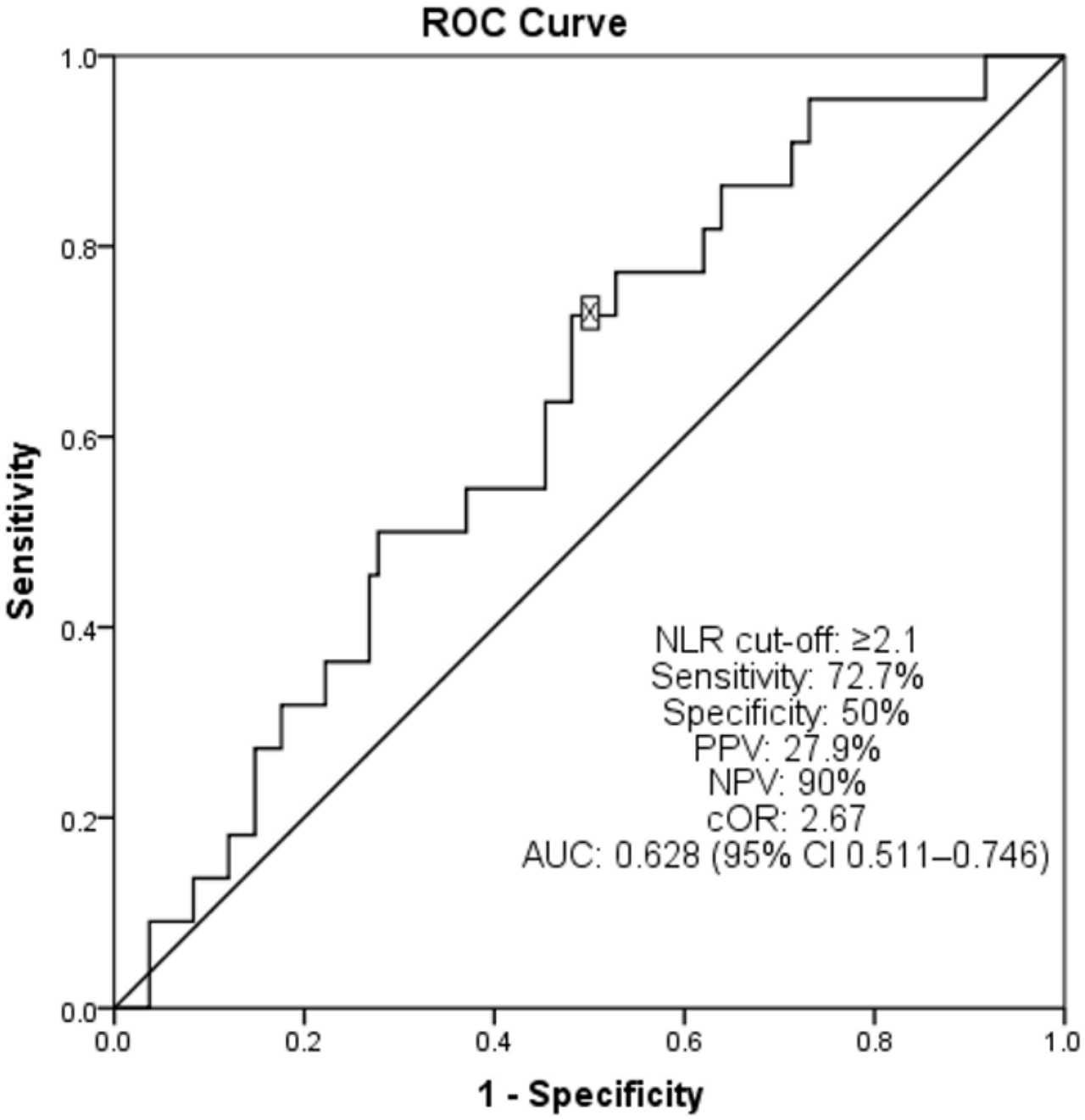


Figure 1

Receiver Operating Characteristic (ROC) curve for neutrophil-to-lymphocyte ratio (NLR) in predicting febrile neutropenia. The black X indicates the optimal cutoff point (NLR = 2.1) with a sensitivity of 72.7% and a specificity 50%. Positive predictive value (PPV), negative predictive value (NPV), crude odds ratio (OR), and area under the curve (AUC) are displayed in the text box.