

Neutrophil-to-lymphocyte ratio as a predictor of early death in metastatic triple-negative breast cancer

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Abstract

Background The prediction of survival using the neutrophil-to-lymphocytes ratio (NLR) in metastatic breast cancer is still under debate. We aimed to determine the mortality prognostic value of the NLR in female patients with metastatic triple-negative breast cancer. **Methods.** We reviewed 118 medical records of patients diagnosed and treated in a tertiary-care center over a 14-year period. The cut-off value for the NLR (<2.5 and ≥ 2.5) was determined with receiver operating characteristic curves (area under the curve: 0.73; 95% CI: 0.615, 0.851). Survival curves were estimated using the Kaplan-Meier method and compared with the Log-rank test. Multivariate Cox regression was used to identify the risk of mortality at two years. We further performed sensitivity analyses with different cut-off values and subgroup analysis in patients that only received chemotherapy. **Results.** The median follow-up was 24 months. Patients with an NLR ≥ 2.5 had a worse overall survival compared to patients with a NLR <2.5 (6% vs. 28%, $p < 0.001$) at two years. This outcome remained consistent when we stratified for patients that received chemotherapy (8% vs. 36%, $p = 0.001$). Multivariate analysis identified the NLR (≥ 2.5 vs. <2.5) at diagnosis as a prognostic risk factor for mortality in the entire population (HR: 2.12, 95% CI: 1.32-3.39) and in patients that received chemotherapy (HR: 2.68, 95% CI: 1.46 – 4.92). **Conclusions.** The NLR is an accessible biomarker that predicts early mortality in patients with metastatic triple-negative breast cancer. Physicians can use these results to predict survival in these patients.

Introduction

Triple-negative breast cancer (TNBC) is a heterogeneous and aggressive subtype of breast cancer, defined by the lack of expression of estrogen and progesterone hormone receptors, and human epidermal growth factor receptor 2 (HER2). These characteristics make it a tumor with increased lethality, high mutational burden, and few therapeutic options [1]. TNBC is a public health problem in Latin American countries, with few studies addressing its implications on survival prognosis [2–5].

Currently, it is known that the immune system plays an important role in the control of aggressive neoplasms such as TNBC. It has been shown that the presence of a high lymphocyte burden within the tumor improves the prognosis of these patients [6, 7]. In this line, several studies demonstrated that the presence of a high neutrophil-to-lymphocyte ratio (NLR) is associated with poor outcomes in various cancers, including breast cancer [8].

Most of the research on this biomarker in breast cancer did not differentiate between the different subtypes [9, 10], with studies linking a relationship with worse survival in early TNBC [11–16]. However, few studies have addressed the overall survival (OS) according to the NLR in metastatic TNBC (mTNBC) patients, with conflicting results [17–19].

Although patients with TNBC have well-established prognostic factors, determining the importance of the NLR in OS could improve medical decision making, due to the high accessibility of this biomarker. However, studies that focus on metastatic breast cancer tend to include all of its subtypes [18–20].

Therefore, we aim to identify the early-mortality (2y) prognosis value of the NLR at diagnosis in patients with mTNBC.

Material And Methods

Study design and population

This was a retrospective cohort study of female patients with mTNBC, diagnosed and treated at the National Institute of Neoplastic Diseases of Lima, Peru in the period 2000–2014. The study was approved by the center’s institutional review board. Medical records with the International Code for Disease (ICD)-10th edition: “C50, Malignant neoplasm of breast” were identified in the database of the Department of Medical Oncology. We included females with metastasis to other organs at diagnosis, confirmed by computed tomography scan or magnetic resonance imaging and with complete data of receptor status in the immunohistochemistry report.

Patient variables and management

Demographic, clinical, and pathological variables were recorded at the diagnosis of breast cancer. Patient comorbidities were classified using the Charlson comorbidity index (CCI), which is an instrument that assesses 19 diseases and assigns a score from zero to six, based on the impact of the disease on survival outcomes. However, the CCI does not include hypertension in the set of diseases. Hence, we calculated a hypertension-augmented CCI (hCCI) and assigned a weight of “one” to patients with this condition, as in a previous study [21]. Tumor size and lymph node status were classified according to the 7th edition of the American Joint Committee on Cancer [22]. Chemotherapy regimens were chosen following the National Comprehensive Cancer Network (NCCN) guideline on Breast Cancer (Version 3.2018) [23]. The complete list of chemotherapy agents and regimes are shown in Appendix 1.

Exposure definition

The NLR was calculated by dividing the absolute count of neutrophils by the absolute count of lymphocytes. We used receiver operating characteristic (ROC) curves to calculate the area under the curve (AUC) and determine the cut-off values at which the sensitivity equals the specificity (NLR = 2.5; AUC: 0.73; 95% confidence interval [CI]: 0.615, 0.851). We further performed a sensitivity analysis with two different cut-off points, identified with the “Youden” (NLR = 3) and “maximization of specificity” (NLR = 7) methods (Appendix 2).

Data analysis and final outcomes

We described the clinicopathological and treatment characteristics of the entire population and according to the NLR group (< 2.5 vs. ≥2.5). For descriptive purposes, we stratified the age in categories according to the 25th and 75th percentile. Categorical variables were compared with the Chi-square test. We defined OS as the time frame between mTNBC diagnosis and mortality by any cause or the end of the study (November 2017). Due to the high mortality rate in mTNBC, patients were followed for two years. Two

crucial variables had missing values (tumor size and lymph node status). We performed a diagnostic analysis that did not yield a missing pattern. Hence, we assumed the condition missing completely at random (MCAR) and used the listwise deletion technique.

Survival probabilities between the two groups were estimated with the Kaplan-Meier technique and compared with the Log-rank test. Moreover, we calculated the risk of mortality of the NLR with univariate and multivariate Cox regression analysis. Variables in the multivariate model included NLR, age, hCCI, tumor size, lymph node status, number of sites of metastases, and use of chemotherapy. We chose the model based on typical variables related to mortality and their relation to mortality in our dataset. Subgroup analysis included the stratification of patients that received chemotherapy (n = 77, 65.3%), and we calculated the survival probabilities and mortality risk with the previous methods. We reported our outcomes with adjusted hazard ratios (HR) and a 95% CI. Results with a p-value < 0.05 were considered statistically significant. We performed all analyses with R version 3.6.2.

Results

We reviewed the medical records of 118 female patients with mTNBC. Most women were between 41 and 59 years of age at diagnosis, were postmenopausal, had a hCCI score of 6, T4 clinical tumor size status, N1 clinical lymph node status, and a histologic grade III (Table 1). The most frequent type of cancer was ductal carcinoma (87.3%), followed by invasive lobular (3.4%), and others (9.3%). There were 12 different sites of metastases and a total of 205 individual metastases. Of these, the lung (63, 30.7%) was the most frequent, followed by bone (47, 22.9%), the liver (37, 18%), and the brain (22, 10.7%) (Fig. 1).

Table 1

The clinicopathological and treatment characteristics of the patients included in the study.

Characteristics	N of patients (n = 118)	Percentage (%)
Group age in years		
≤ 40	32	27.1
41–59	56	47.5
≥ 60	30	25.4
Menopausal status		
Premenopausal	43	36.4
Postmenopausal	72	61.0
Missing	3	2.5
hCCI		
Score 6		
Score ≥ 7	27	22.9
Clinical tumor size		
T0	3	2.5
T2	13	11.0
T3	14	11.9
T4	85	72.0
Missing	3	2.5
Clinical lymph node status		
N0	14	11.9
N1	48	40.7
N2	25	21.2
N3	27	22.9
Missing	4	3.4
Histologic grade		

hCCI, hypertension-augmented Charlson comorbidity index

Characteristics	N of patients (n = 118)	Percentage (%)
Grade II	11	9.3
Grade III	71	60.2
Missing	36	30.5
nI _r (mean (SD))	5.84 (8.32)	
Site of metastases		
1 organ	58	49.2
2 organs	36	30.5
3 organs	14	11.9
4 organs	9	7.6
5 organs	1	0.8
Chemotherapy	77	65.3
hCCI, hypertension-augmented Charlson comorbidity index		

Table 2 shows a similar distribution of the clinicopathological and treatment characteristics of the patients studied according to the NLR cut-off. Regarding the clinical variables, patients with a NLR ≥ 2.5 were older, had a higher hCCI, and a higher lymph node status, although without statistical significance. Although the differences were not statistically significant, females with low NLR status had a higher histologic grade and received more frequently chemotherapy.

Table 2
 Clinicopathological and treatment characteristics according to NLR status.

Characteristics	NLR < 2.5	NLR ≥ 2.5	P-value
No. of patients	39	79	
Group age in years			0.651
≤ 40	12 (30.8)	20 (25.3)	
41–59	19 (48.7)	37 (46.8)	
≥ 60	8 (20.5)	22 (27.8)	
Menopausal status			0.949
Premenopausal	15 (38.5)	28 (35.4)	
Postmenopausal	23 (59.0)	49 (62.0)	
Missing	1 (2.6)	2 (2.5)	
hCCI			0.507
Score 6	32 (82.1)	59 (74.7)	
Score ≥ 7	7 (17.9)	20 (25.3)	
Clinical tumor size			0.297
T0	0 (0.0)	3 (3.8)	
T2	6 (15.4)	7 (8.9)	
T3	2 (5.1)	12 (15.2)	
T4	30 (76.9)	55 (69.6)	
Missing	1 (2.6)	2 (2.5)	
Clinical lymph node status			0.906
N0	5 (12.8)	9 (11.4)	
N1	18 (46.2)	30 (38.0)	
N2	7 (17.9)	18 (22.8)	
N3	8 (20.5)	19 (24.1)	
Missing	1 (2.6)	3 (3.8)	

hCCI, hypertension-augmented Charlson comorbidity index

Characteristics	NLR < 2.5	NLR ≥ 2.5	P-value
Histologic grade			0.374
Grade II	5 (12.8)	6 (7.6)	
Grade III	25 (64.1)	46 (58.2)	
Missing	9 (23.1)	27 (34.2)	
Site of metastases			0.768
1 organ	22 (56.4)	36 (45.6)	
2 organs	11 (28.2)	25 (31.6)	
3 organs	4 (10.3)	10 (12.7)	
4 organs	2 (5.1)	7 (8.9)	
5 organs	0 (0.0)	1 (1.3)	
Chemotherapy	28 (71.8)	49 (62.0)	0.399
hCCI, hypertension-augmented Charlson comorbidity index			

The median follow-up was 24 months. Patients with a higher NLR had a worse OS (6% vs. 28%, $p < 0.001$) at 2 years (Fig. 2). Similarly, the subgroup analysis of patients that only received chemotherapy, identified a worse OS of females with a higher NLR (8% vs. 36%, $p = 0.001$), see Fig. 3. Multivariate analysis showed a higher risk of mortality with an NLR cut-off value of ≥ 2.5 in the entire population and in patients that received chemotherapy (Table 3). The results of the sensitivity analyses were similar to those of the main analysis (Appendix 2).

Table 3

Multivariate Cox regression analysis of mortality factors in the entire cohort and in patients with chemotherapy.

Characteristics	OS in the entire cohort			OS in patients with chemotherapy		
	HR	95% CI	P-value	HR	95% CI	P-value
NLR						
< 2.5	Ref	-	-	ref	-	-
≥2.5	2.12	1.32–3.39	0.002	2.68	1.46–4.92	0.001
Age	1.00	0.98–1.01	0.748	ref	0.98–1.03	0.821
hCCI						
Score 6	Ref	-	-	ref	-	-
Score ≥ 7	0.77	0.45–1.32	0.342	0.65	0.3–1.41	0.281
Tumor size						
T0-3	1	-	-	ref	-	-
T4	1.15	0.71–1.85	0.577	0.72	0.37–1.39	0.325
Lymph node status						
N0-1	Ref	-	-	ref	-	-
N2-3	1.07	0.7–1.64	0.758	1.35	0.75–2.43	0.319
Site of metastases						
1 organ	Ref	-	-	ref	-	-
≥2 organs	1.17	0.77–1.77	0.473	0.97	0.56–1.68	0.912
Chemotherapy						
No	Ref	-	-	-	-	-
Yes	0.41	0.26–0.64	< 0.001	-	-	-
OS, overall survival; NLR, Neutrophil-to-lymphocyte ratio; hCCI, hypertension-augmented Charlson comorbidity index; CI, confidence interval						

Discussion

The results of this study demonstrate that the NLR is a strong biomarker for OS in women with mTNBC. Previous research found similar results for early-stage TNBC patients. For example, Pistelli et al. analyzed TNBC patients with stage I-IIIa and reported that a NLR > 3 before surgery, followed by adjuvant

chemotherapy and/or radiation, was a prognostic factor for a poor OS [11]. Two other studies that included non-metastatic TNBC support the previous statement [12, 13]. This association was further confirmed in a recent meta-analysis that identified a high NLR as a factor for worse OS in patients with unspecified breast cancer (HR: 1.78) and TNBC (HR: 2.18) [24].

However, the prediction of survival using the NLR in patients with metastatic breast cancer has conflicting results. Takuwa et al. reported a worse OS in patients with a $NLR \geq 1.90$ [25], and Vernieri et al. found the same outcome with a $NLR \geq 2.5$ [17]. In contrast, one of the latest studies found a correlation between NLR and OS in the univariate analysis, but a non-significant association in multivariate Cox regression analysis [26]. The researchers argued that the survival rate with this biomarker depends on the tumor stage at diagnosis, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, and location of the metastasis. Few studies have considered the effect of the ECOG scale in the regression model. Although this variable predicts poor survival outcomes in metastatic breast cancer patients [27, 28], Kumar et al. identified that the NLR was a prognostic factor of OS independently of the ECOG score in a large cohort of oncological patients (15% with breast cancer) [29].

There are several differences between the cited study [26] and ours. While Rubio et al analyzed all subtypes of breast cancer, 14.5% were TNBC, we limited our population to stage IV TNBC. Then, we only focused on patients with metastases at diagnosis, while in the study by Rubio the prevalence of metastasis at diagnosis was 44.5%. Therefore, these differences may explain the significant association between NLR and OS in our multivariate analysis. Moreover, these findings suggest that each subtype of metastatic breast cancer has a different prognostic profile.

Two meta-analyses identified different cut-off values (range: 2–4) to establish the prognostic value of the NLR in breast cancer [9, 10]. Most of these studies relied on the determination by ROC curve estimation. Similar to these experiences, we used the method “sensitivity equals specificity”. Moreover, we used two different methods in the sensitivity analysis and identified the same outcomes. Therefore, with the Youden method, we corroborated the effectiveness of the biomarker. The other method, maximization of specificity, provides a useful threshold to inform a high-confident mortality prediction to mTNBC patients. We made a subgroup analysis including patients that received chemotherapy in order to address the importance of the NLR in this population and control for possible confounding factors by stratifying the patients. Our results remained robust in the sub-population analysis. Hence, these outcomes support the premise that the NLR may be a useful biomarker to predict survival in mTNBC. In addition, we did not exclude females with systemic comorbidities, in order to resemble the daily clinical practice. Then, the hCCI was calculated and controlled in the multivariate analysis.

This study has some limitations. We excluded medical records in the regression analysis due to missing data. Although we did not include the performance status, the hCCI was used to address the distribution of background comorbidities in the patients. Due to the low number of patients that did not receive chemotherapy, we could not perform further analysis in this subgroup. Finally, we assessed patients from a single center, hence, extrapolation of our results should be made with caution.

Conclusions

The present study demonstrates that the NLR is a useful predictor of poor OS in mTNBC. Our analysis also provides the performance of this biomarker with different cut-off values and its utility in patients scheduled for chemotherapy. These results will aid physicians to make evidence-based clinical decisions in a population with an inherent poor prognosis.

Abbreviations

TNBC:	Triple-negative breast cancer
HER2:	Human epidermal growth factor receptor 2
NLR:	Neutrophil-to-lymphocyte ratio
OS:	Overall survival
mTNBC:	Metastatic triple negative breast cancer
ICD:	International Code for Disease
CCI:	Charlson comorbidity index
hCCI:	Hypertension-augmented CCI
NCCN:	National Comprehensive Cancer Network
ROC:	Receiver operating characteristic
AUC:	Area under the curve
CI:	Confidence interval
MCAR:	Missing completely at random
ECOG:	Eastern Cooperative Oncology Group

Declarations

Authorship contributions

GDCK: Conceptualization – Ideas; data curation; methodology; validation; visualization; writing - original draft; writing - review & editing

BSV: Conceptualization – Ideas; data curation; methodology; data analysis; validation; visualization; writing - original draft; writing - review & editing

JTS: Conceptualization – Ideas; data curation; methodology; validation; visualization; writing - original draft; writing - review & editing

DCM: writing - original draft; writing - review & editing

PR: review & editing; visualization

ZM: review & editing

DE: review & editing

CF: methodology, validation

RL: Conceptualization – Ideas

AS: Conceptualization – Ideas

ML: Conceptualization – Ideas

JA: Conceptualization – Ideas, review & editing

HG: data curation, review & editing

JP: Conceptualization – Ideas, review & editing

Ethics approval

This study was approved by the Institutional Research Ethics Committee of the “Instituto Nacional de Enfermedades Neoplásicas”.

Consent for publication

The present study has the institutional consent for publication.

Availability of data and materials

The datasets analyzed during the current study available from the corresponding author on reasonable request.

Competing interests of interest

The authors declare no conflicts of interest.

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Additional File Legends

Appendixes

Appendix 1	Treatment list
Appendix 2	Multivariate analysis of different cut-off values of the NLR
Appendix 3	ROC curve of the NLR biomaker

Figures

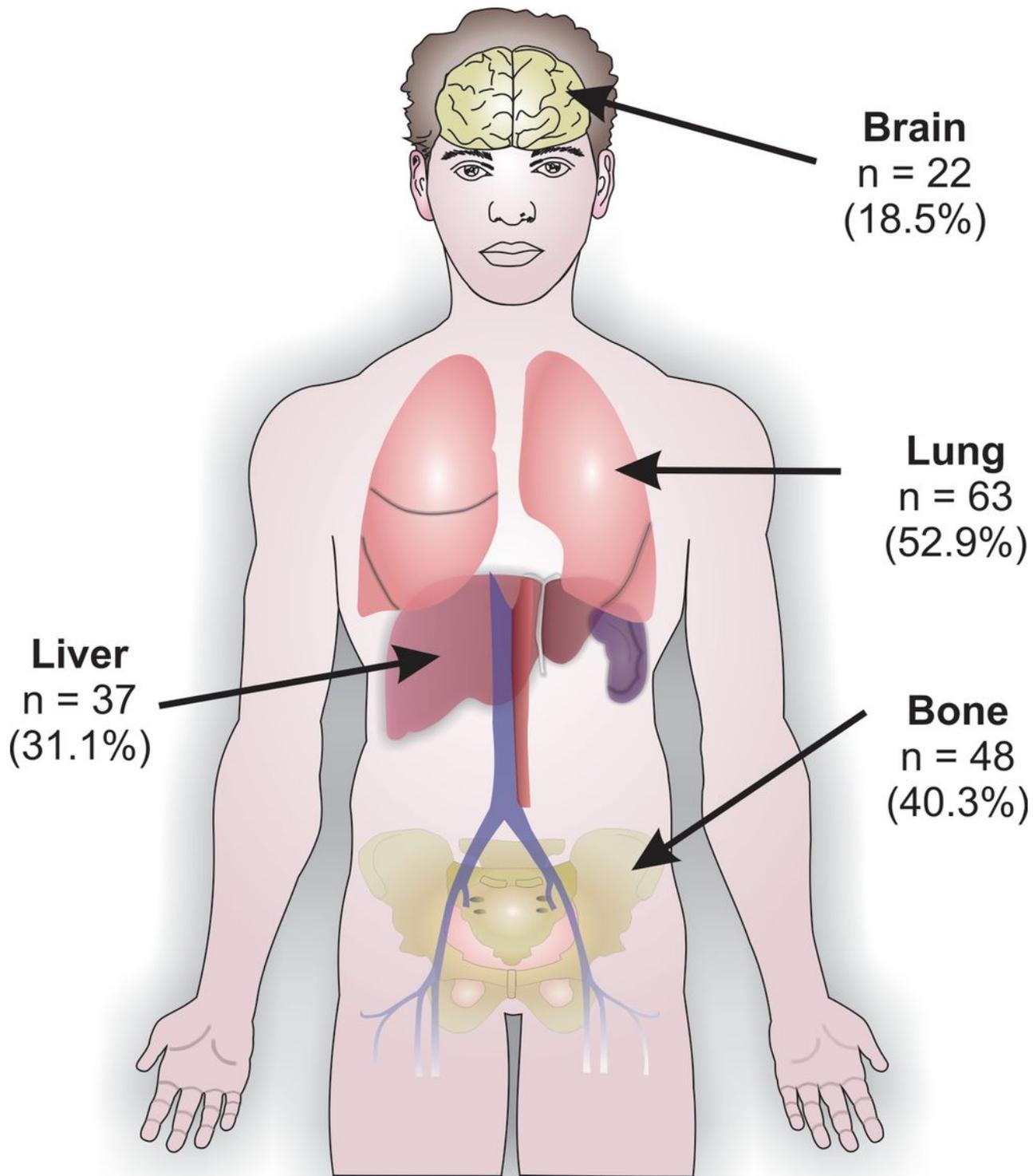


Figure 1

Graphical representation of the metastases

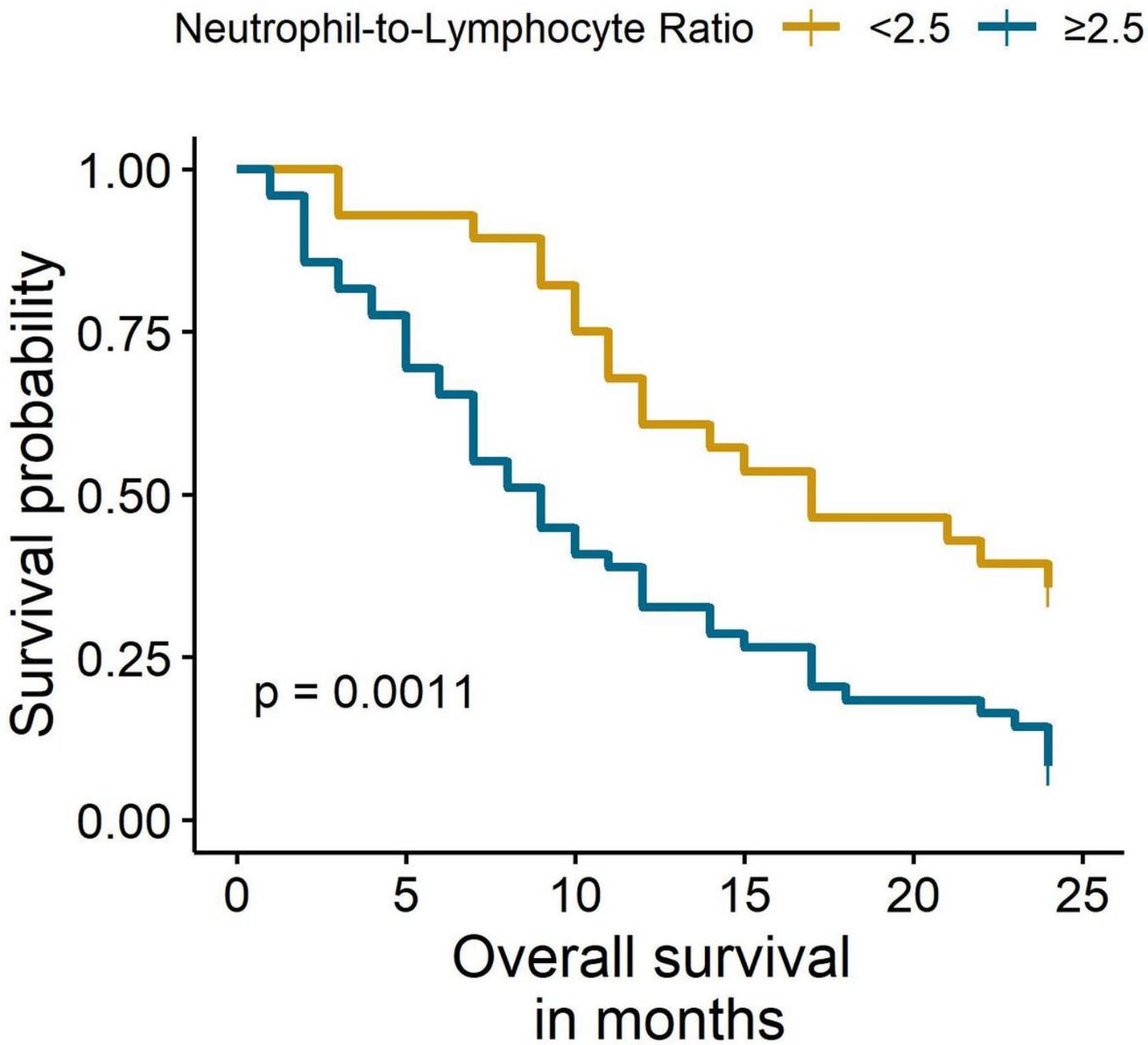


Figure 2

Overall survival of the entire population according to the NLR status

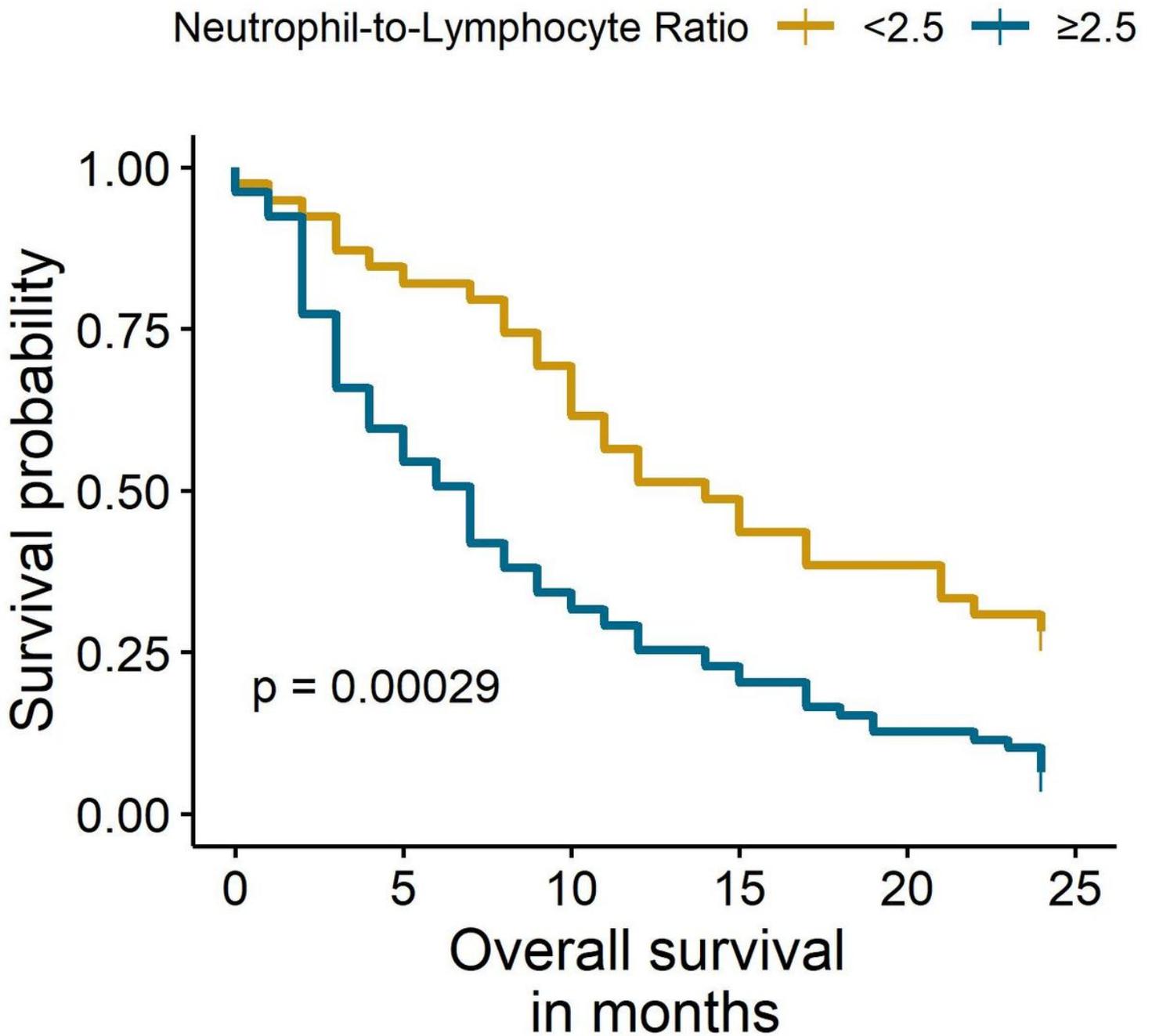


Figure 3

Overall survival of patients with and without chemotherapy according to the NLR status

Supplementary Files

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