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Original Article

Baseline neutrophil–lymphocyte ratio holds no prognostic value for esophageal and junctional adenocarcinoma in patients treated with neoadjuvant chemotherapy.

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*SUMMARY.**Background:*** **Several studies have reported that neutrophil–lymphocyte ratio (NLR) can predict survival in esophageal and gastroesophageal junction adenocarcinoma, as it reflects systemic inflammation. Hence, we aimed to determine whether baseline NLR holds prognostic value for esophageal adenocarcinoma patients treated with neoadjuvant chemotherapy (nCT) followed by surgery.** ***Methods:*** **We studied the data of 139 patients that received nCT before undergoing esophagectomy with curative intent, all identified from a prospectively maintained database (1998–2016). Pretreatment hematology reports were used to calculate the baseline NLR. A receiver operating characteristic curve (ROC-curve) was plotted to determine an optimal cutoff value. NLR quartiles were used to display possible differences between groups in relation to overall survival (OS) and disease-free survival (DFS) using the method of Kaplan–Meier. Cox regression analysis was performed to assess the prognostic value of NLR.** ***Results:*** **The median OS and DFS times were 46 months (interquartile range [IQR]: 19–166) and 30 months (IQR: 13–166], respectively, for the entire cohort. The ROC-curve showed that NLR has no discriminating power for survival status (area under the curve = 0.462) and therefore no optimal cutoff value could be determined. There were no statistically significant differences in median OS times for NLR quartiles: 65 (Q1), 32 (Q2), 45 (Q3), and 46 months (Q4) ($P = 0.926$). Similarly, DFS showed no difference between quartile groups, with median survival times of 27 (Q1), 19 (Q2), 36 (Q3), and 20 months (Q4) ($P = 0.973$). Age, pN, pM, and resection margin were independent prognostic factors for both OS and DFS. On the contrary, NLR was not associated with OS or DFS in univariable and multivariable analyses.** ***Conclusion:*** **Baseline NLR holds no prognostic value for esophageal and gastroesophageal junction adenocarcinoma patients treated with nCT in this study, in contrast to other recently published papers. This result questions the validity of NLR as a reliable prognostic indicator and its clinical usefulness in these patients.**

KEY WORDS: **adenocarcinoma, esophageal carcinoma, lymphocytes, neutrophils, prognostic markers.**

INTRODUCTION

Esophageal adenocarcinoma (EAC) is an aggressive solid tumor and the rising incidence over the last three decades in Western industrialized countries is of concern, given the poor prognosis.[1, 2] Currently used multimodality approaches do not benefit all patients and are associated with a considerable rate of adverse events, creating a need to better identify and differentiate patients that have a poor response to (neoadjuvant) treatment or risk of life-threatening toxicity and may be considered for alternative treatments.[3–6] Complete or major pathologic response as determined in the resection specimen is applied as a prognostic indicator of overall survival (OS) after neoadjuvant therapy.[7] Recent research, however, questions its validity as a surrogate endpoint for OS.[8]

Ideally, pretreatment biomarkers could serve as novel predictors of survival after preoperative therapy plus surgery. As there has been little progress in terms of clinically applicable molecular predictors for EAC, alternative biomarkers are under active investigation. Although the behavior and development of cancer are influenced and determined by numerous molecular

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processes and patient-related factors, there is evidence that both tumor-related inflammation and systemic inflammation play a significant role in the tumorigenesis as it predisposes the microenvironment to tumor development.[9, 10] This has led to an increasing interest in various inflammation-based markers and scores and several of these have been reported to feature prognostic value in solid tumors, as they reflect the extent of antitumor response or systemic inflammation.[11–13]

A marker of systemic inflammation, the neutrophil–lymphocyte ratio (NLR), has also been associated with prognosis in a variety of tumors, including esophageal and gastric carcinomas.[14–16] As the NLR can be calculated from routine blood tests, it is potentially an economical and clinically applicable prognostic biomarker. A handful of studies have reported that NLR determined before therapy is associated with survival in EAC patients after various treatment approaches, but a standardized cutoff value to stratify patients remains undetermined.[17] Therefore, we set out to determine the prognostic value and an optimal cutoff value of pretreatment NLR in patients with esophageal and gastroesophageal junction adenocarcinomas treated with neoadjuvant chemotherapy (nCT).

METHODS

Patients

The prospectively maintained Upper-GI database from the Department of Surgery, Princess Alexandra Hospital (Brisbane, Australia) was searched for patients who underwent curative esophagectomy after nCT for esophageal and gastroesophageal junction adenocarcinomas between February 1998 and August 2016. Approval was granted by the Human Research Ethics Committee to maintain the database (HREC/16/QPAH/614). Patients were considered for neoadjuvant therapy if clinically staged cT1N+ or >cT2N0 and fit for esophagectomy. Hematology reports from routine blood tests were used to calculate the baseline NLR, dividing absolute neutrophil count by absolute lymphocyte count. All blood tests used to calculate NLR were taken prior to chemotherapy treatment, within 1 week of the first consultation. For inclusion, patients needed to have been administered a minimum of two cycles of platinum-based chemotherapy. Exclusion criteria were the absence of pretreatment hematology reports as well as other synchronously active malignancies. Data were collected from eligible patients comprising patient characteristics, clinical staging (7th edition of the American Joint Committee on Cancer-manual[18]), operative details, chemotherapy details, pathological staging and recurrence, and survival status. In case of multiple available reports, the one closest to commencement of chemotherapy was used.

Staging, treatment, and follow-up

Clinical staging included endoscopy and computed tomography (CT) of the chest and abdomen in all patients. Endoscopic ultrasonography was used to clarify tumor and nodal staging when necessary. In 2008 fluoro-deoxyglucose-positron emission tomography scanning was introduced and has been performed as a routine staging procedure since. The majority of patients received a chemotherapeutic regimen based on either a combination of 5-fluoruracil (5-FU) and cisplatin as per OEO2-trial[19] or as per MAGIC-trial[20], administering three cycles preoperative and three cycles postoperative with a combination of 5-FU, cisplatin, and epirubicin (ECF). A small number of patients received two cycles of triplet chemotherapy consisting of docetaxel, cisplatin, and 5-FU (DCF) before surgery, as per a trial regimen. One patient received epirubicin, oxaliplatin, and 5-FU (EOF). Within 3-6 weeks after completing chemotherapy patients underwent curative esophagectomy. The surgical techniques used have been previously described.[21] Follow-up consisted of clinical assessment, including physical and history examination, at three-month intervals after surgery for the first 2 years, 6-month intervals up to five years, where after annually up to ten years. In follow up imaging (typically a CT scan of the chest abdomen and pelvis) and endoscopy were performed when clinically indicated. Additional investigations were carried out on individual basis. Specimens with tumor cells present within 1 mm of the resection margin were considered to be an R1 resection.

Statistical analysis

A receiver operating characteristic curve (ROC-curve) was plotted to determine an optimal cutoff value. NLR quartiles are used to display possible differences between groups in relation to OS and disease-free survival (DFS). Categorical variables are presented as frequencies with percentage and in case of continuous variables as medians with interquartile range (IQR). Pearson's χ^2 test and Fisher–Freeman–Halton exact test were used to compare categorical data, as appropriate, and the Kruskal–Wallis test was used to compare nonparametric continuous data. OS was defined as the time between the date of first consultation and death by any cause or last follow-up. DFS was defined as the time between surgery and histologically proven or radiologically evident recurrence, last follow-up or date of death. OS and DFS curves were estimated by the method of Kaplan–Meier and differences tested with the log-rank test. Cox regression analysis was performed to assess the prognostic significance of NLR and other clinical and pathological variables.

Table 1 Patient characteristics

Variables	*n*
Age, median (IQR, year)	62 (55–67)
Gender (male/female)	123/16
ASA score (1/2/3)	11/93/35
Tumor location (mid/low/GE junction)	30/105/4
cT (T1/T2/T3)	3/58/78
cN (N0/N1/N2)	87/49/3
cM (M0/M1)	139/0
Tumor differentiation (poor/moderate/well)	100/36/3
ypT (T1/T2/T3/T4)	24/21/81/13
ypN (N0/N1/N2/N3)	48/33/36/22
ypM (M0/M1)	136/3
Tumor size, median (IQR, cm)	3 (2–4)
Resection margin (R0/R1/R2)	116/22/1
Mandard score (I/II/III/IV/V/missing)	0/12/25/61/36/5
NLR, median (IQR)	2.46 (1.72–3.23)

IQR, interquartile range; ASA, American Society of Anesthesiologists; GO, gastroesophageal; NLR neutrophil–lymphocyte ratio.

Variables with a P-value < 0.1 in univariable analyses were included in the multivariable model. All tests were two-sided and the threshold for significance was set at $P < 0.05$ (two-sided). Statistical analysis was performed using SPSS v25.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Patients and cutoff value

A total of 144 patients were identified who matched the inclusion criteria and had hematology reports available from blood tests prior to treatment. Five patients did not have sufficient survival data and were excluded from analysis, resulting in 139 eligible patients. Table 1 shows baseline patient characteristics. Median NLR was 2.46 (IQR; 1.72– 3.23) across all patients. The ROC-curve showed that NLR has no discriminating power for survival status (area under the curve = 0.462, Fig. 1) and therefore no optimal cutoff value could be determined. NLR quartiles used to assess the prognostic value of NLR were as follows: ≤1.718 (Q1); 1.72–2.47 (Q2); 2.48–3.15 (Q3); ≥3.16 (Q4). Table 2 displays the distribution of patient and tumor characteristics between the NLR quartiles. None of the assessed variables showed statistically significant differences between NLR quartiles. Also, no trend or statistically significant differences were found regarding grade 3/4 adverse events during chemotherapy among NLR quartiles (P-value = 0.967; data not shown).

OS and DFS

The median OS was 46 months [IQR: 19–166] for the entire cohort. Both uni- and multivariable analyses for OS are shown in Table 3. In univariable analyses, age, resection margin, pathological T-, N-, and M stages were associated with OS ($P < 0.2$) and therefore added to the multivariable model. NLR, assessed as a continuous variable, was not associated with OS in univariable analysis. Multivariable analysis showed that the adjusted hazard ratio (HR) was not predictive for OS (HR 0.922; CI 95% 0.771–1.103; P-value = 0.375). The median (IQR) OS times for NLR quartiles were 65 (20–166) (Q1), 32 (17-not reached) (Q2), 45 (19–95) (Q3) and 46 (19-not reached) months (Q4), with no significant difference ($P = 0.926$). Figure 2A displays the Kaplan–Meier curves for OS for the NLR quartiles.

The median DFS was 27 months [IQR: 10–164] for the entire cohort. Table 4 shows uni- and multivariable analyses for DFS. Age, resection margin, and pathological T-, N-, and M stages were associated with DFS in univariable analyses, whereas NLR was not. In multivariable analysis, the adjusted HR for NLR was 0.951 (CI 95% 0.818–1.107; P-value 0.517) and therefore was not an independent predictor for DFS. The median DFS times showed no difference between NLR quartile groups either, with median DFS times of 27 (13–164) (Q1), 19 (10-not reached) (Q2), 36 (9–93) (Q3) and 20 (9-not reached) months (Q4, $P = 0.973$). Figure 2B displays the Kaplan–Meier curves for DFS for the NLR quartiles.

DISCUSSION

An underlying mechanism that could possibly explain an association between elevated NLR and poor survival has not been clearly established yet. It is evident that both neutrophils and lymphocytes play a fundamental role in the inflammatory response. There is data that suggest that tumors with a significant rate of infiltrating lymphocytes are associated with a better cytotoxic response.[22, 23] Neutrophilia inhibits the antitumor activity of lymphocytes diminishing the beneficial effect of infiltrating lymphocytes on response to therapy and suppresses the cytolytic ability of natural killer cells and activated T cells.[24–26] Moreover, neutrophils are known to release several growth factors, including vascular endothelial growth factor, promoting angiogenesis and can thus stimulate the microenvironment of a tumor.[27] Circulating neutrophil and lymphocyte counts may reflect these tumor-level effects. In this study, however, baseline NLR was not associated with OS or DFS. NLR had no discriminatory power for each quartile and no optimal cutoff point could be determined based on the ROC-curve. Regarding the latter, the area under the curve value (AUC = 0.462) found in the ROC-curve points out that NLR is not a valid marker for predicting survival status. The (adjusted) hazard ratios showed that NLR is not an independent prognostic factor for OS or DFS. Moreover, the NLR was not predictive for pathological response according to Mandard score.

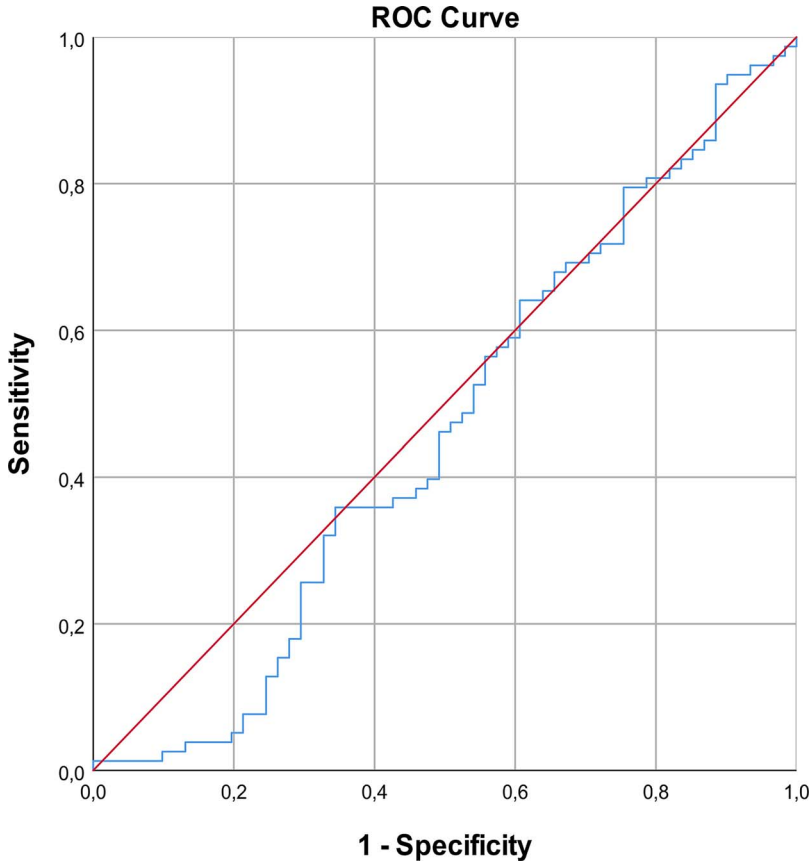

Fig. 1 ROC-curve for survival status; area under the curve = 0.462.

Overall, these findings do not concur with most of the published literature.[14] A meta-analysis of seven studies found NLR to be prognostic for OS in esophageal cancer, but not for DFS (76% squamous cell carcinoma; 20% adenocarcinoma; 4% other).[15] Of note was the significant between-study heterogeneity, partly explained by the variety of treatment approaches. An additional subgroup analysis showed that NLR was not prognostic in patients who underwent surgical resection alone. This corresponds with a recent study including over 1300 patients with gastroesophageal and gastric adenocarcinomas without receiving nCT.[28] In contrast, a study subsequent to the REAL-2 trial, which included 908 patients with both gastric and esophageal carcinoma (88% adenocarcinoma; 10% squamous cell carcinoma; 2% other), all treated with a triplet chemotherapy regimen (ECF/epirubicin, cisplatin, and capecitabine (ECX)/EOF/epirubicin, oxaliplatin, and capecitabine (EOX),[29] reported a predetermined high NLR (>3) was significantly associated with poor survival in a relatively homogeneous group of patients. An important difference to our study, however, is that the majority of the included patients had metastatic disease, reflected by their reported median OS times of 9.1 and 12.7 months for high and low NLR, respectively, compared to our median OS of 46 months for the entire cohort. Interestingly, their median baseline NLR of 3.7 was considerably higher than found in the present study and other comparable literature which did not include metastasized tumors, indirectly suggesting that NLR may reflect the extent of dissemination.[30, 31] A retrospective analysis of 117 patients with adenocarcinoma supports this theory by confirming that the NLR was an independent predictor of the discovery of peritoneal and/or metastatic disease.[32] Moreover, Conway et al. recently reported an NLR ≥3 to be independently associated with early disease progression resulting in unresectable disease in patients receiving nCT for gastroesophageal junction adenocarcinoma.[30] The abovementioned findings, in addition to adequate staging and patient selection, might have played a role in our negative results as no patients with stage IV disease were included.

Despite the wide array of literature reporting NLR to be of prognostic value in various types of solid tumors, there is a lack of consensus regarding the optimal cutoff value to stratify patients.[17] To be of significance as a prognostic tool in the decision-making process, a standardized cutoff value is needed to divide patients into risk groups based on NLR. At this time, this has not been the case and thus the use of NLR has not been implemented in the clinic. Irrespective of our results, the diversity of NLR cutoff values, ranging from 2 to 5, used by previous studies, reporting significant differences in survival times, questions the

Table 2 Distribution of patient and tumor characteristics according to NLR quartiles

Variables	Q1 *n* (%)	Q2 *n* (%)	Q3 *n* (%)	Q4 *n* (%)	*P*-value
Age, median (IQR, year)	63 (55–67)	61 (55–67)	63 (51–68)	61 (56–67)	0.956
Gender					0.487
Female	6 (17.1)	5 (14.3)	2 (5.9)	3 (8.6)	
Male	29 (82.9)	30 (85.7)	32 (94.1)	32 (91.4)	
ASA score					0.509
1	2 (5.7)	2 (5.7)	4 (11.8)	3 (8.6)	
2	24 (68.6)	20 (57.1)	25 (73.5)	24 (68.6)	
3	9 (25.7)	13 (37.1)	5 (14.7)	8 (22.9)	
Tumor differentiation					0.678
Poor	26 (74.3)	26 (74.3)	24 (70.7)	24 (68.6)	
Moderate	7 (20)	9 (25.7)	10 (29.4)	10 (28.6)	
Well	2 (5.7)	-	-	1 (2.9)	
ypT stage					0.748
T1-2	9 (25.7)	11 (31.4)	12 (35.3)	13 (37.1)	
T3-4	26 (74.3)	24 (68.6)	22 (64.7)	22 (62.9)	
ypN stage					0.696
N0	15 (42.9)	11 (31.4)	11 (32.4)	11 (31.4)	
N1-3	20 (57.1)	24 (68.6)	23 (67.6)	24 (68.6)	
ypM stage					0.902
M0	34 (97.1)	35 (100)	33 (97.1)	34 (97.1)	
M1	1 (2.9)	-	1 (2.9)	1 (2.9)	
Tumor size (cm)					0.087
Median (IQR)	3 (1.5–4)	2.5 (2–3.5)	2.8 (2–3.6)	3.5 (2.3–4.5)	
Resection margin					0.186
R0	26 (74.3)	32 (91.4)	27 (79.4)	31 (88.6)	
R1/R2	9 (25.7)	3 (8.6)	7 (20.6)	4 (11.4)	
Mandard score					0.920
TRG I	-	-	-	-	
TRG II	4 (11.8)	3 (9.1)	1 (3)	4 (11.8)	
TRG III	6 (17.6)	5 (15.2)	6 (18.2)	8 (23.5)	
TRG IV	14 (41.2)	15 (45.5)	18 (54.5)	14 (41.2)	
TRG V	10 (29.4)	10 (30.3)	8 (24.2)	8 (23.5)	
Lymph node yield					0.992
Median (IQR)	1 (0–5)	2 (0–6)	1.5 (0–5.25)	2 (0–5)	
Positive lymph node yield					0.843
Median (IQR)	27 (20–34)	26 (19–34)	27.5 (18.75–33.25)	25 (21–33)	

IQR, interquartile range; ASA, American Society of Anesthesiologists; TRG, tumor regression grade; Q1 ≤ 1.718; Q2: 1.72–2.47; Q3: 2.48–3.15; Q4 ≥ 3.16.

reliability of the NLR as prognostic biomarker.[16, 17] Adding the evidence that the NLR is also influenced by ethnical and behavioral characteristics, it explains why measuring the NLR is not being utilized by clinicians.[33]

Despite all the blood tests being taken prior to commencing treatment, a limitation of our study was the considerable variety in point of time the blood tests were taken. Because of this, we cannot rule out that other inflammatory conditions may have affected some NLR values in this data set. However, it is not likely considering the fact that active infection contraindicates systemic therapy. Other limitations are the retrospective nature of this analysis and the relatively small number of patients. However, multiple smaller studies did find an association between pretreatment NLR and survival in esophageal and gastric cancer.[34–36] Moreover, our results do not trend toward being significant suggesting that a lack of statistical power is not likely to be a major factor in our negative findings. To maximize the power of the data, we chose to use the NLR as a continuous variable in the regression analysis.[37] As we could not determine an optimal cutoff value for the NLR in this cohort, we opted to use NLR quartiles as they could virtually display an incremental effect of increasing NLR in a survival curve.

Our primary aim was to assess if the NLR could be used as a stratification tool for risk groups and possibly to predict therapy response. Determining the NLR after chemotherapy would be less useful for that purpose as patients already had therapy, but a change in NLR during chemotherapy might be an area for future research. Currently, there are no studies evaluating a possible association of an increase or decrease of the NLR during chemotherapy and survival outcomes. Note that the NLR can be impacted by the chemotherapy itself, as the chemotherapy regimens used can cause neutropenia. Mayers *et al*.[38] reported that a higher incidence of myelosuppression, possibly correlated with a greater dose of chemotherapy, was associated with better survival in patients with early-stage breast carcinoma treated with adjuvant chemotherapy. Hence, it is possible preoperative NLR, after receiving nCT, might be a better prognosticator.

Table 3 Cox regression analysis for OS

Variables	Univariable analysis				Multivariable analysis		
	n	HR	CI (95%)	*P*-value	HR	CI (95%)	*P*-value
Age (year)	139	0.977	0.953–1.001	0.065	0.961	0.935–0.988	**0.004**
Gender							
Male	123	Ref.	–				
Female	16	0.605	0.263–1.394	0.238			
Tumor differentiation							
Poor	100	Ref.	–				
Moderate	36	0.872	0.523–1.455	0.601			
Well	3	0.326	0.043–2.494	0.281			
Tumor length (centimeter)	139	1.053	0.939–1.181	0.379			
Year of surgery							
1998-2007	61	Ref.	–				
2008-2016	78	0.814	0.515–1.286	0.378			
Resection margin							
R0	116	Ref.	–		Ref.	–	
R1/R2	23	3.801	2.225–6.492	<0.001	2.555	1.4–4.662	**0.002**
ypT stage							
T1-2	45	Ref.	–		Ref.	–	
T3-4	94	2.416	1.391–4.196	0.002	1.101	0.599–2.026	0.756
ypN stage							
N0	48	Ref.	–		Ref.	–	
N1-3	91	5.273	2.829–9.826	<0.001	5.301	2.701–10.404	<**0.001**
ypM stage							
M0	136	Ref.	–		Ref.	–	
M1	3	16.302	4.662–57.500	<0.001	4.619	1.22–17.482	**0.024**
NLR	139	0.944	0.803–1.110	0.486	0.922	0.771–1.103	0.375

HR, hazard ratio; CI, confidence interval; NLR, neutrophil–lymphocyte ratio. For all continuous variables: HR reflects the risk per one absolute unit increase. Bold values are statistically significant ($P < 0.05$).

Table 4 Cox regression analysis for DFS

Variables	Univariable analysis				Multivariable analysis		
	n	HR	CI (95%)	*P*-value	HR	CI (95%)	*P*-value
Age (year)	139	0.979	0.956–1.003	0.084	0.967	0.942–0.992	**0.011**
Gender							
Male	123	Ref.	–				
Female	16	0.629	0.290-1.367	0.242			
Tumor differentiation							
Poor	100	Ref.	–				
Moderate	36	0.811	0.493–1.334	0.410			
Well	3	0.340	0.044–2.608	0.299			
Tumor length (cm)	139	1.041	0.954–1.137	0.365			
Year of surgery							
1998-2007	61	Ref.	–				
2008-2016	78	0.952	0.611–1.484	0.829			
Resection margin							
R0	116	Ref.	–		Ref.	–	
R1/R2	23	3.202	1.915–5.354	<0.001	2.171	1.220–3.865	**0.008**
ypT stage							
T1-2	45	Ref.	–		Ref.	–	
T3-4	94	2.205	1.318–3.688	0.003	1.015	0.570–1.808	0.959
ypN stage							
N0	48	Ref.	-		Ref.	–	
N1-3	91	4.630	2.589–8.280	<0.001	4.549	2.400–8.620	<**0.001**
ypM stage							
M0	136	Ref.	–		Ref.	–	
M1	3	39.359	10.127–152.205	<0.001	14.236	3.453–58.781	<**0.001**
NLR	139	0.974	0.846–1.121	0.709	0.951	0.818–1.107	0.517

HR, hazard ratio; CI, confidence interval; NLR, neutrophil–lymphocyte ratio. For all continuous variables: HR reflects the risk per one absolute unit increase. Bold values are statistically significant ($P < 0.05$).

To conclude, our study showed that, in contrast to some literature, baseline NLR holds no prognostic value for EAC patients treated with nCT plus surgery. In addition to the lack of consensus on a standardized cutoff value, these results question the validity of NLR as a reliable prognostic indicator and thus its role as a clinical tool to stratify EAC patients treated with nCT.

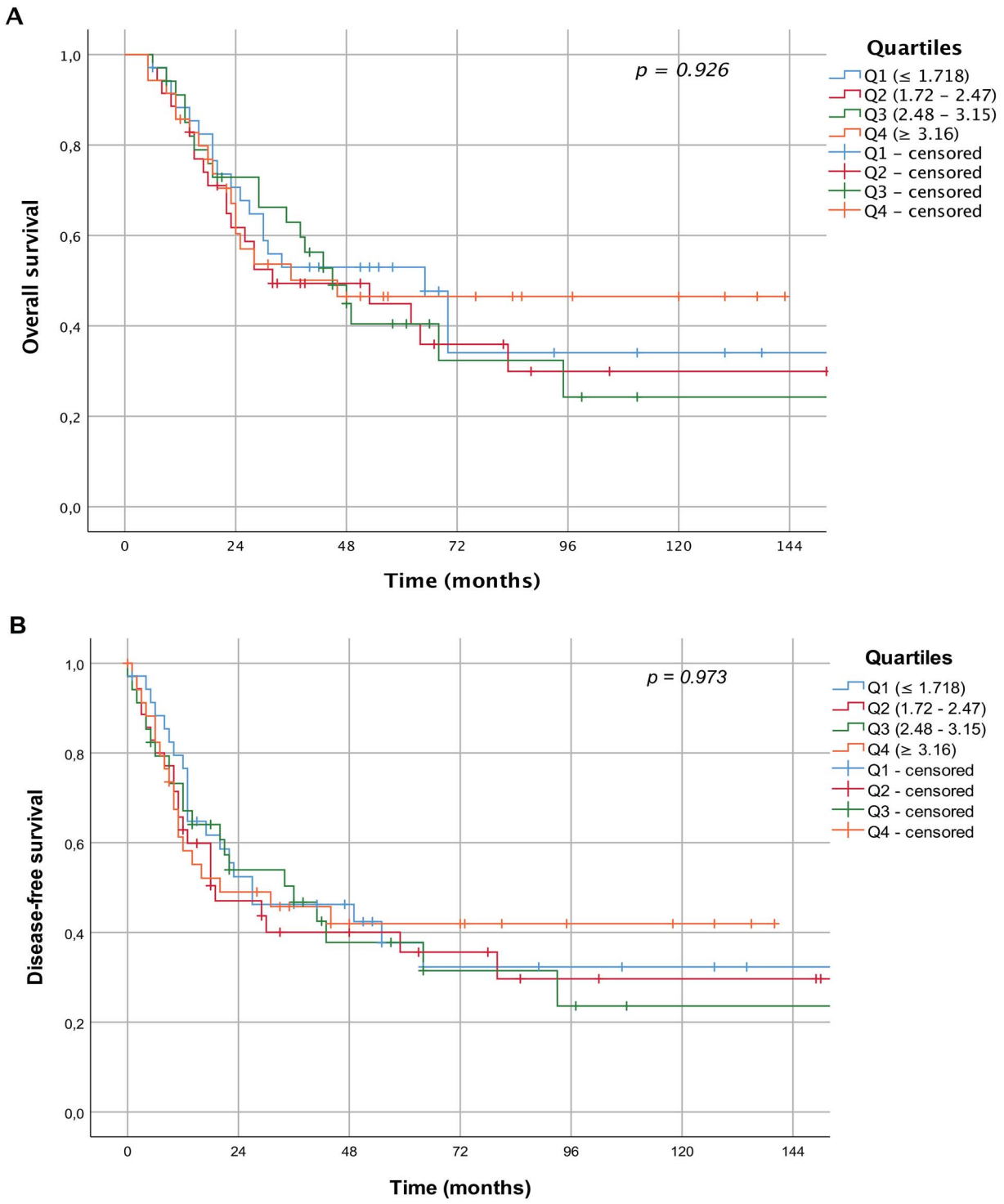

Fig. 2 A-B OS (A) and DFS (B) according to NLR quartiles.

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