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RESEARCH ARTICLE

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Neutrophil-lymphocyte ratio is associated with prognosis in patients who underwent potentially curative resection for gastric cancer

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Background and Objectives: The role of inflammation in cancer development is a well-known phenomenon that may be represented by the neutrophil-lymphocyte ratio (NLR). The present research intends to determine the impact of NLR on the survival outcome of patients with gastric cancer (GC), and to evaluate its use as a stratification factor for the staging groups.

Methods: Data regarding clinical characteristics, surgery, pathology, and follow-up were retrospectively collected from our single-center prospective database. Blood samples were obtained before surgery.

Results: A total of 383 patients (231 males) who underwent gastrectomy with lymphadenectomy were evaluated between 2009 and 2016. NLR established cutoff was 2.44, and patients were divided in NLR ≥2.44 (hNLR) and <2.44 (lNLR). hNLR patients (38.4% of the cases) had lower disease-free survival and overall survival (OS) compared to lNLR patients ($P = 0.047$ and $P = 0.045$, respectively). Risk stratification according to NLR value was done in same tumor depth (T4 and <T4), stage (III and <III) and lymph node status (N+ and N−) group of patients. The OS was significantly lower when NLR was high in same tumor depth ($P = 0.032$) and stage ($P = 0.020$), but not in same lymph node status patients ($P = 0.184$). In a multivariate analysis, NLR was an independent factor of worse OS (HR 1.50 95%CI 1.27-4.21, $P = 0.048$).

Conclusion: A high NLR was an independent risk factor for reduced survival in GC patients submitted to potentially curative resection. Calculating NLR is easily reproducible and may be incorporated in pre-operative evaluation.

KEYWORDS
gastrectomy, gastric cancer, neutrophil-lymphocyte ratio

1 | INTRODUCTION

The role of inflammation in cancer development is a well-known phenomenon, described since the 19th century.[1] Several studies showed that systemic inflammatory status can predict prognosis in different types of tumors.[2,3] Serum markers like C-reactive protein and neutrophil/lymphocyte ratio (NLR) gained relevance and may add information to the TNM classification.[4] Serum levels of neutrophils and lymphocytes may reflect the inflammatory cells present in tumoral stroma.[5] Neutrophilia and lymphopenia, for instance, originate a

pro-tumoral microenvironment. If individual prognosis becomes more accurate, treatment and follow-up may be individualized. The association between NLR and cancer has been investigated in different tumors.[2] In gastric cancer (GC) patients, this association was mostly studied in the general population, irrespective of stage or type of treatment.[6,7] Few articles analyze GC patients who underwent potentially curative resection,[8–11] which is our focus in this research.

The present research intends to answer whether NLR is a prognostic factor associated with overall survival (OS) and disease-free survival (DFS). Additionally, we also examined the relationship between clinico pathological characteristics and NLR levels and if patients with the same pathological status have different prognosis depending on their NLR level.

2 | METHODS

2.1 | Patients

All patients with gastric adenocarcinoma who underwent potentially curative resection in our institution between 2009 and 2016 were considered. Gastrectomy extension and lymph node dissection were performed according to the guidelines of the Japanese Gastric Cancer Association.[12] Patients who underwent D1 or D2 lymphadenectomy were included. Pathologic staging was performed according to the guidelines of the College of American Pathologists.[13] Patients who underwent preoperative chemotherapy, emergency surgery or R1-R2 resection were excluded. Data regarding clinical characteristics, surgery, pathology, and follow-up were retrospectively collected from our prospective database. The study was approved by the hospital ethics committee (NP993/16).

2.2 | Blood analysis

Peripheral blood was obtained after diagnosis and before surgery. The NLR was calculated from the preoperative blood sample by dividing the absolute neutrophil count by the absolute lymphocyte count.

2.3 | Statistical analysis

A cutoff point in the NLR variable was established using the Lausen method, which maximizes the log-rank statistic obtaining the point that best separates two groups in relation to survival.

Comparison of clinicopathological characteristics was performed using chi-square tests for categorical variables and *t*-test for continuous variables. OS and DFS analyses were undertaken using the Kaplan-Meier method and the comparison of curves was obtained through the log-rank test. Multivariate Cox proportional hazard analysis was performed to determine independent risk factors for DFS and OS. Only variables that were significant on univariate analysis were included as co-variables in the multivariable analyses. Survival time, in months, was calculated from the date of diagnosis until the date of death/recurrence. The patients alive were censored at the date of last contact. The level of significance applied in the tests was 5%, always considering two-tailed alternative hypothesis. Software R version 3.4.1 was used to perform all analyzes

3 | RESULTS

In the period considered, among the 423 patients who underwent surgery with curative intent, 383 patients fulfilled the inclusion criteria and were evaluated in this study. The mean age was 62.9 years (range 25-94) and 231 (60.3%) were male. Subtotal gastrectomy with D2 lymphadenectomy was performed in most cases (64% and 86% of cases, respectively).

The median NLR was 2.12 (mean of 2.53, range 0.37-17). Mean neutrophil and lymphocyte counts were 4294.9/mm^3 (range 550-19100) and 1954.7/mm^3 (range 260-11 370), respectively. Mean albumin level was 3.98 g/dL (SD ± 0.59, range 1.4-5.4). The median interval between surgery and blood test was 2 days (range 1-103 days).

The NLR cutoff was 2.44 (Figure 1). Accordingly, patients were divided in high NLR (hNLR, n = 147, 38.4%) and low NLR (lNLR, n = 236, 61.6%). Clinicopathological data for these groups are presented in Table 1. Older age (P = 0.038), male sex (P < 0.001), higher platelet count (P = 0.005) and more advanced pT status (P = 0.027) were associated with hNLR.

With a mean follow-up of 28.5 months (median of 24.3, range 1-90 months), a total of 91 patients had disease recurrence and 112 died. The DFS and OS rate for the entire cohort was 76.2% and 70.8%, respectively.

According to the NLR cutoff, the DFS and OS were significantly worse for hNLR group than lNLR patients (P = 0.047 and P = 0.045, respectively) (Figure 2). Risk stratification according to NLR value was done in same tumor depth (T4 and <T4), same pTNM (III and <III) and same lymph node status (N+ and N−) patients. The OS was significantly

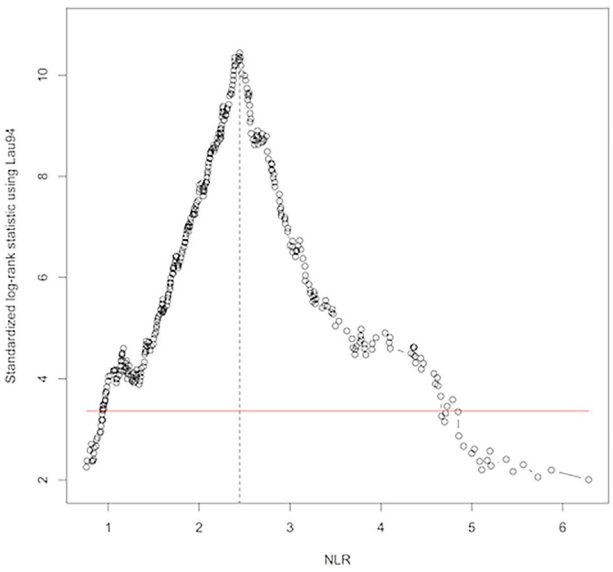

FIGURE 1 NLR cutoff obtained by Lausen curve. NLR, neutrophil-lymphocyte ratio

TABLE 1 Clinicopathologic characteristics of gastric cancer patients with NLR <2.44 and NLR ≥2.44 (n = 383)

	NLR <2.44	NLR ≥2.44	
Variables	***n* = 236 (61.6%)**	***n* = 147 (38.4%)**	***P***
Age (years)			**0.038**
Mean (±SD)	61.9 (12.2)	64.6 (12.8)	
Gender			**<0.001**
Male	125 (53)	106 (72.1)	
Female	111 (47)	41 (27.9)	
Albumin (mg/dL)			0.821
Mean (±SD)	4.0 (0.5)	4.0 (0.6)	
Platelet count × 10^9/L			**0.015**
Mean (SD)	252 (88.6)	305 (250.3)	
Type of Resection			0.377
Subtotal gastrectomy	155 (65.7)	90 (61.2)	
Total gastrectomy	81 (34.3)	57 (38.8)	
pT status			**0.027**
pT1/T2	109 (46.2)	51 (34.7)	
pT3/T4	127 (53.8)	96 (65.3)	
Harvested lymph nodes			0.121
Mean (±SD)	40.2 (18.3)	37.3 (16)	
pN status			0.234
pN negative	111 (47)	60 (40.8)	
pN positive	125 (53)	87 (59.2)	
TNM Stage			
I-II	137 (58.1)	76 (51.7)	0.224
III-IV	99 (41.9)	71 (48.3)	

Bold values signifies $P < 0.05$ is statistically significant.

lower when NLR was high in same tumor depth (P = 0.032) and pTNM (P = 0.020), but not in same lymph node status patients (P = 0.184) (Figure 3).

Table 2 shows the independent prognostic factors for DFS and OS identified by multivariate analysis performed with significant factors identified by univariate analysis. Prognostic factors associated with worse DFS were albumin level, type of gastrectomy, depth of tumor invasion (pT), and lymph node metastases (pN). Regarding OS, analysis revealed that lower albumin level, hNLR, pT3/pT4, and lymph node metastasis were associated to poor survival. So, multivariate analysis confirmed hNLR as an independent factor associated with significantly worse OS.

4 | DISCUSSION

Prognosis in cancer patients is usually based on clinical and pathological staging, which take into account characteristics such as tumor size, depth of invasion, nodal involvement, distant metastasis, histological type, among others. Nevertheless, patients with equivalent pathological status may show different prognosis, suggesting that other factors are involved in disease progression. Serum markers levels including CEA, CA19-9, and AFP,[14] gene expression profile[15] and inflammatory markers (NLR, platelet-lymphocyte ratio, and c-reactive protein)[16] can provide additional information in order to stratify risk among patients, especially among those with same stage disease.

The idea that inflammation is related to cancer was first hypothesized by Virchow in 1863, when a "lymphoreticular infiltrate" was observed inside tumoral stroma.[1] The first time that NLR have been cited in literature was in 1967.[17] In 1976, the association between NLR levels and tumor progression was described in murine models.[18] In humans, neutrophilia as a sign of worse prognosis in cancer was shown in 1978[19] and in 1987 the term NLR and its relationship with prognosis was first utilized in lung cancer population.[20]

Leukocyte recruitment to inflammatory sites plays a dual role, once it benefits the host's defense but also creates a pro-tumoral microenvironment.[1] Neutrophils play a major role in pro-tumoral activity by secreting different sub products, like reactive oxygen species, that cause DNA damage, and vascular endothelial growing factor, an angiogenesis promoter.[21] Also, neutrophils escaping from vasculature to the lesion's site create a channel in which tumor cells may utilize to escape to the vasculature.[22] Distant sites of metastasis

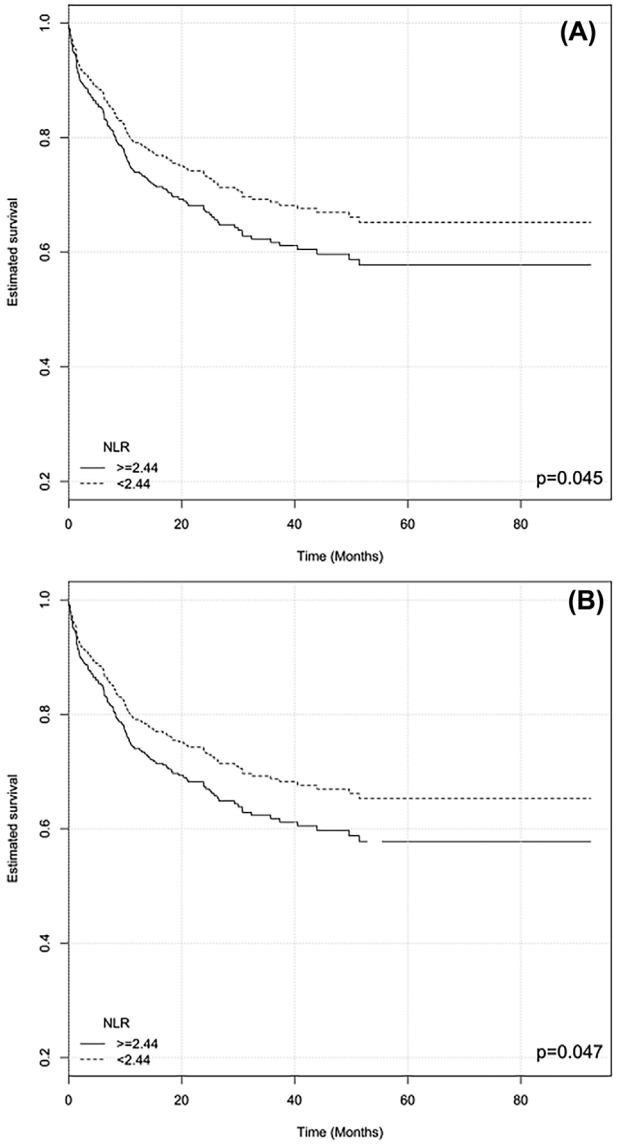

FIGURE 2 Overall survival (A) and disease-free survival (B) curves stratified by preoperative NLR. NLR, neutrophil-lymphocyte ratio

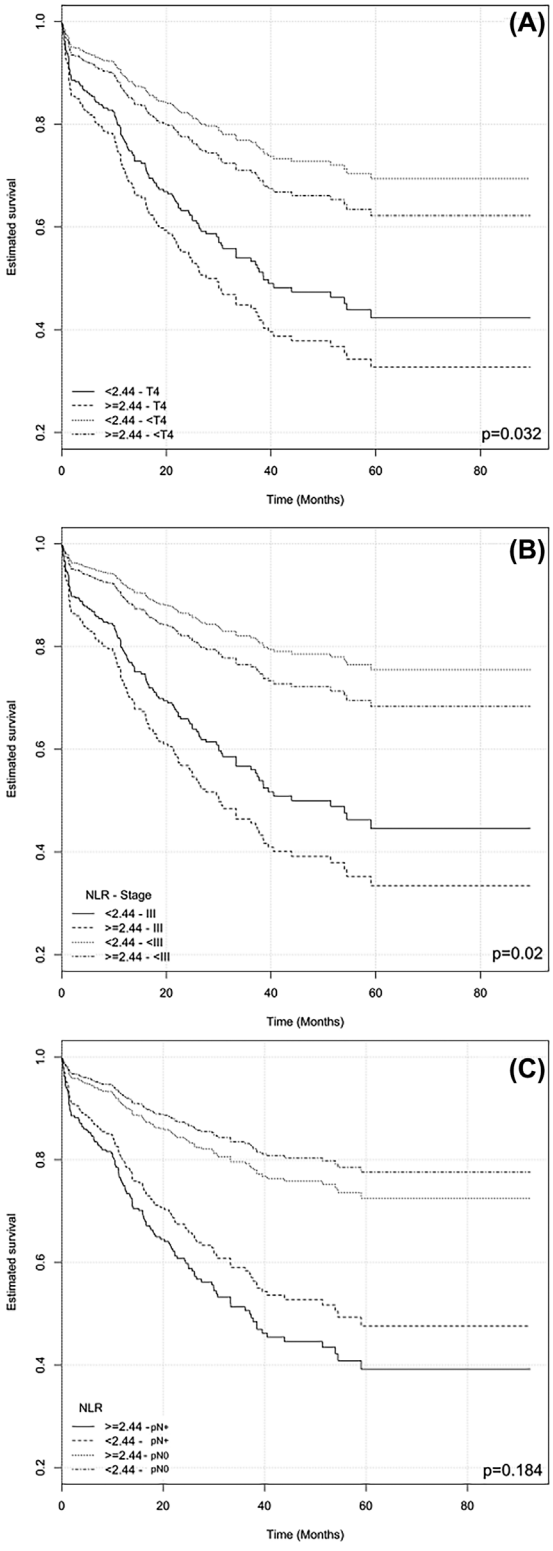

FIGURE 3 Kaplan-Meier curve comparing overall survival and NLR according to: A, tumor depth (B). stage (C). nodal involvement. NLR, neutrophil-lymphocyte ratio

are also affected by neutrophils, who creates tissue for engraftment of metastatic cells.[23] On the other hand, lymphocytes have antitumoral properties by recognizing tumor antigens and displaying cytolytic activity,[24] via the death ligand/death receptor system or by granule exocytosis.[25]

The effect of inflammation on tumoral development was studied in tumor-bearing rabbits who underwent extracorporeal granulocyte depletion. Once NLR was normalized, tumoral regression occurred.[26] Thus, the ratio of neutrophils and lymphocytes reflects the balance between pro- and anti-tumor immune activities.

Although the impact of NLR on worse prognosis still not a consensus,[27] the vast majority of reports demonstrate that higher NLR values predicts worse prognosis in patients with solid tumors, for example, breast,[28] lung,[29] bladder,[30] pancreas,[31] liver,[32] esophagus,[33] colon and rectum,[34] and thyroid.[35]

The relation between gastric cancer and NLR was first demonstrated by an univariate analysis in 1998[36]; the confirmation of worse prognosis in a multivariate analysis was reported 9 years later.[4] In a recent meta-analysis including 2952 patients from five different

TABLE 2 Univariate and multivariate analyses for disease-free survival and overall survival ($n = 383$)

Disease-free Survival	Univariate			Multivariate		
Variables*	**Hazard ratio**	**95%CI**	***P***	**Hazard ratio**	**95%CI**	***P***
Age >65 vs <65 years	0.82	0.54-1.24	0.347	-	-	-
Female vs Male	1.29	0.84-1.98	0.251	-	-	-
Albumin (mg/dL)	0.65	0.48-0.88	**0.006**	0.58	0.41 - 0.81	**0.002**
Platelet count × 10^9/l	1.00	0.99-1.00	0.804	-	-	-
NLR < 2.44 vs NLR > 2.44	1.56	1.03-2.35	**0.034**	1.42	0.91-2.21	0.122
Subtotal vs Total gastrectomy	2.13	1.41-3.21	**<0.001**	1.75	1.23-2.71	**0.013**
pT1/T2 vs pT3/T4	13.4	5.87-30.77	**<0.001**	5.57	2.12-14.68	**0.001**
pN0 vs pN1/2/3	7.59	4.04-14.26	**<0.001**	4.64	2.09-10.29	**<0.001**
Overall Survival	**Univariate**			**Multivariate**		
Variables*	**Hazard ratio**	**95%CI**	***P***	**Hazard ratio**	**95%CI**	***P***
Age >65 vs <65 years	1.48	1.02-2.15	**0.037**	1.42	0.95-2.11	0.088
Female vs Male	1.29	0.87-1.89	0.200	-	-	-
Albumin (mg/dL)	0.73	0.55-0.98	**0.038**	0.69	0.50-0.94	**0.019**
Platelet count × 10^9/l	0.79	0.99-1.00	0.788	-	-	-
NLR < 2.44 vs NLR > 2.44	1.68	1.16-2.43	**0.006**	1.50	1.01-2.23	**0.048**
Subtotal vs Total gastrectomy	1.64	1.13-2.38	**0.009**	1.38	0.93-2.10	0.107
pT1/T2 vs pT3/T4	3.37	2.13-5.33	**<0.001**	2.31	1.27-4.21	**0.006**
pN0 vs pN1/2/3	2.91	1.90-4.47	**<0.001**	2.18	1.24-3.82	**0.007**

*The first variable serve as reference category.
Bold values signifies $P < 0.05$ is statistically significant.

countries, high NLR predicted poor OS regardless of sample size and cut-off values.[37] Different gastric cancer populations are addressed by available reports, varying in pTNM status and treatment approach. The current gap in literature regarding NLR is its value demonstration among non-metastatic surgical patients, especially on those submitted to curative resection, focus of the present report.

As mentioned, few studies identified high NLR as an independent prognostic factor in non-metastatic resectable disease.[4,9,10] Since different methods are applied to calculate NLR cut-off (median, ROC curve, previous studies), none of these reports have the same value. We decided to use the Hothorn-Lausen method in order to obtain the value that best separate two groups according to their overall survival.[38] In spite of the different NLR cut-off values, all the studies reported worse OS when NLR was above the cut-off.

Our univariate and multivariate analysis proves the idea of cancer-inflammation relationship. From all the significant parameters of the univariate analysis and besides pathological parameters (tumor depth and lymph node involvement), only albumin and NLR had a significantly correlation with OS in a multivariate analysis. These data confirm the influence of inflammation on prognosis.

The evidence provided in this study is in accordance with previous reports regarding worse OS.[14,39] Interestingly, we demonstrated that same stage disease or same tumor depth tumors presented different OS according to their NLR values. This information may provide a scientific basis to alter treatment and follow-up, that is, once a subgroup of worse prognosis is identified among patients with same stage disease, it would be worthwhile offering a closer follow-up or make modifications in the neoadjuvant/adjuvant therapies.[40] With the recent developments in cancer immunotherapy, NLR is a potential tool for predicting tumor response to treatment.[41,42]

Our study has some limitations inherent to its retrospective nature. This is a single-center study and follow-up was relatively short for some patients. Also, information about adjuvant treatment is not available for all patients, which may have influence in survival. Moreover, we did not evaluate potential interactions between comorbid conditions and GC.

In our research, all patients were treated in a cancer reference center and were operated by high volume gastric surgeons. We used a standardized definition of high and low NRL based on the establishment of a cutoff value which could be easily reproducible to identify patients with poor prognosis. The advantages of NLR utilization are its cost-effectiveness and simplicity. In addition, it may also stratify the risk in same stage disease patients. Accordingly, once identified subgroups of worse prognosis, a closer follow-up and modifications in systemic treatment may be proposed. However, it is important to mention that, to date, there is no consensus about an NLR cut-off value. Therefore, identifying the optimal cut-off value is still necessary to accurately predict prognosis for GC patients.

In conclusion, a high NLR was an independent risk factor for reduced survival in GC patients, and it may be used as an additional marker to identify patients with a poor prognosis after curative resection.

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DISCLOSURES

The authors report no conflicts of interest.

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SYNOPSIS

This study investigates the relationship between neutrophil-lymphocyte ratio and prognosis in gastric cancer patients who underwent potentially curative resection.