Negative-to-Positive Lymph Node Ratio as an Independent Prognostic Factor for Gastric Adenocarcinoma

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ABSTRACT

Objective: To investigate the association between the ratio of negative/positive lymph nodes (RNP) and other clinic pathological parameters.

Study Design: Descriptive study.

Place and Duration of Study: Faculty of Medicine, Cumhuriyet University, Sivas, Turkey, from February 2008 to December 2019.

Methodology: Consecutive 119 patients with gastric adenocarcinoma, who underwent gastrectomy and D2 lymph node dissection, were included. RNP, other clinicopathological parameters such as tumour grade, type and lymphovascular invasion (LVI) were analysed, as their prognostic impact was investigated.

Results: RNP was an independent prognostic factor for overall survival ($p = 0.003$) and was significantly associated with poor survival ($p < 0.001$). Advanced pathologic T and N stage, presence of perineural invasion (PNI), presence of LVI, high tumour grade, and diffuse-type as per Louren's classification, and the number of the negative lymph nodes were also significantly associated with poor survival (all $p < 0.05$). Although pathologic N stage ($p < 0.01$), PNI ($p < 0.01$), LVI ($p < 0.01$), tumour type as per Louren's classification ($p < 0.01$), tumour grade ($p < 0.01$) and the number of negative lymph nodes ($p < 0.01$) were significantly associated with overall survival in univariate analyses; only gender ($p = 0.025$), gastrectomy type ($p = 0.037$), PNI ($p = 0.028$), tumour type ($p = 0.006$), and number of negative lymph nodes ($p = 0.003$) were meaningfully associated with survival in a multivariate analysis.

Conclusion: The ratio of negative/positive lymph nodes can be used as an independent prognostic marker in patients with gastric cancer, who undergo curative resection, as an alternative prognostic marker to the pathologic N stage.

Key Words: *Stomach neoplasms, Lymph node ratio, Prognosis, Gastrectomy, Lymph nodes.*

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INTRODUCTION

Gastric cancer remains the sixth-leading cancer globally, and the fifth major cause of death, associated with cancer for both males and females.[1,2] Lymph node involvement is one of the most significant prognostic parameters for gastric adenocarcinoma.[3] Staging is based on the correct assessment of lymph node status to predict reliable survival.[4]

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In the American Joint Committee on Cancer's (AJCC) 7th and 8th editions, a count of metastatic lymph nodes determined pathologic N-stage.[5] However, whether this system is effective is controversial, as it is dependent on the count of positive lymph nodes; yet some authors suggest its prognostic ability may be limited and/or may not be applicable to all cases of gastric adenocarcinoma, especially in cases with insufficient lymph node dissection.[6-8]

Recently, the ratio of negative/positive lymph nodes (RNP) was proposed as an alternative prognostic marker in gastric cancer patients.[3,4,7,8]

The aim of this study was to search for the prognostic significance of RNP and its association to other traditional prognostic markers in patients with gastric adenocarcinoma, who had gastrectomy and D2 lymph node dissection.

Table I: Clinicopathologic characteristics of the study group.

Variable	n(%)	R_{NP}			p-value
		$R_{NP}1$	$R_{NP}2$	$R_{NP}3$	
Age (year)					
≤65	50 (42.0)	12 (40.0)	14 (37.8)	24 (46.2)	0.712
>65	69 (58.0)	18 (60.0)	23 (62.2)	28 (53.8)	
Gender					
Female	22 (18.5)	6 (20.0)	6 (16.2)	10 (19.2)	0.909
Male	97 (81.5)	24 (80.0)	31(83.8)	42 (80.8)	
Gastrectomy					
Total	77 (64.7)	19 (63.3)	25 (67.6)	33 (63.5)	0.908
Distal	42 (35.3)	11 (36.7)	12 (32.4)	19 (36.5)	
Pathologic T stage					
T1a	1 (0.8)	-	-	1 (1.9)	
T1b	4 (3.4)	-	3 (8.1)	1 (1.9)	
T2	7 (5.9)	4 (13.3)	2 (5.4)	1 (1.9)	0.128
T3	31(26.1)	11(36.7)	10 (27.0)	10 (19.2)	
T4a	60 (50.4)	13 (43.3)	16 (43.2)	31(59.6)	
T4b	16 (13.4)	2 (6.7)	6 (16.2)	8 (15.4)	
Pathologic N stage					
N1	33 (27.7)	20 (66.7)	9 (24.3)	4 (7.7)	
N2	33 (27.7)	7 (23.3)	18 (48.6)	8 (15.4)	<0.001
N3a	31 (26.1)	3 (10.0)	10 (27.0)	18 (34.6)	
N3b	22 (18.5)	-	-	22 (42.3)	
Tumour location					
Upper third	31(26.1)	9 (30.0)	13 (35.1)	9 (17.3)	0.387
Middle third	37(31.1)	8 (26.7)	11 (29.7)	18 (34.6)	
Lower third	51(42.9)	13 (43.3)	13 (35.1)	25 (48.1)	
Tumour size					
≤4cm	42 (35.3)	12 (40.0)	14 (37.8)	16 (30.8)	0.650
>4cm	77 (64.7)	18 (60.0)	23 (62.2)	36 (69.2)	
Perineural invasion					
Absent	37 (31.1)	22(73.3)	9 (24.3)	6 (11.5)	<0.001
Present	82 (68.9)	8 (26.7)	28 (75.7)	46 (88.5)	
Lymphovascular invasion					
Absent	39 (32.8)	18 (60.0)	9 (24.3)	12 (23.1)	0.001
Present	80 (67.2)	12 (40.0)	28 (75.7)	40 (76.9)	
Tumour type per lauren's classification					
Intestinal type	57(47.9%)62(52.1%)	27 (90.0)	18 (48.6)	12 (23.1)	<0.001
Diffuse type		3 (10.0)	19 (51.4)	40 (76.9)	
Tumour grade					
Low	26 (21.8)	14 (46.7)	9 (24.3)	3 (5.8)	<0.001
Intermediate	42 (35.3)	11 (36.7)	17 (45.9)	14 (26.9)	
High	51 (42.9)	5 (16.7)	11 (29.7)	35 (67.3)	
LNs					
>15	52 (43.7)	8 (26.7)	17 (45.9)	27 (51.9)	0.080
0-14	67 (56.3)	22 (73.3)	20 (54.1)	25 (48.1)	

LNs: Number of negatives, R_{NP}: Ratio of negative-to-positive nodes.

METHODOLOGY

Following the approval of the study protocol by the local Ethics Committee, records of 437 consecutive patients with gastrectomy, due to gastric cancer between February 2008 and December 2019 at Faculty of Medicine, Cumhuriyet University, Sivas, Turkey, were screened and evaluated. Histopathological tumour types, other than adenocarcinoma (gastric lymphoma, gastric neuroendocrine tumour, *etc.*); patients with adenocarcinoma who did not have lymph node metastasis; stage 4 disease; patients receiving neoadjuvant chemotherapy; history of stomach surgery for any cause; an otherwise known malignancy; the presence of a positive surgery border as a result of a pathology specimen; D1 lymph node dissection; patients with a Siewert type 3 tumour of gastroesophageal component, died in the 30 postoperative days, were not included in the study.

An experienced oncologic surgeon performed all procedures. That study consisted of 119 patients, who were included in the criteria.

Table II: Results of the univariate and multivariate analysis between clinicopathologic parameters and prognosis.

Variable	n(%)	Median Survival		Univariate		Multivariate	
		Month	p-value	HR (95%C.I)	p-value	HR (95%C.I)	p-value

Age (year) ≤65 >65	 50 (42.0) 69 (58.0)	 18.1 15	0.789	0.942(0.607-1.462)	0.791		NS
Gender Female Male	 22 (18.5) 97 (81.5)	 18 16	0.300	0.726(0.392-1.344)	0.308	0.470(0.243-0.908)	**0.025**
Gastrectomy Total Distal	 77 (64.7) 42 (35.3)	 17 18	0.998	0.999(0.639-1.563)	0.998	0.588(0.357-0.969)	**0.037**
Pathologic T Stage T1a T1b T2 T3 T4a T4b	 1 (0.8) 4 (3.4) 7 (5.9) 31 (26.1) 60 (50.4) 16 (13.4)	 29 49 49 27.9 14.9 11	 **0.012** 	 0.446(0.058-3.399) 0.369(0.105-1.300) 0.270(0.089-0.821) 0.289(0.139-0.601) 0.572(0.316-1.034)	 **0.020** 0.436 0.121 **0.021** **0.001** 0.064	 	 NS
Pathologic N Stage N1 N2 N3a N3b	 33 (27.7) 33 (27.7) 31 (26.1) 22 (18.5)	 49 15 12 9	 **0.001** 	 0.082(0.038-0.176) 0.251(0131-0.481) 0.598(0.327-1.095)	 **<0.01** **<0.01** **<0.01** 0.096	 0.303(0.121-0.762)	 0.051 **0.011**
Tumour Location Upper third Middle third Lower third	 31 (26.1) 37 (31.1) 51 (42.9)	 21 20 16	 0.855 	 0.963(0.564-1.646) 1.119(0.672-1.863)	 0.859 0.891 0.666	 	 NS
Tumor size ≤4cm >4cm	 42 (35.3) 77 (64.7)	 22 14.9	 0.180 	 0.734(0.464-1.162) 	 0.187 	 	 NS
Perineural Invasion Absent Present	 37 (31.1) 82 (68.9)	 78 11	 **<0.001** 	 0.132(0.067-0.258) 	 **<0.01** 	 0.369(0.152-0.898) 	 **0.028**
Lymphovascular Invasion Absent Present	 39 (32.8) 80 (67.2)	 49 12	 **<0.001**	 0.274(0.159-0.474)	 **<0.01**	 	 NS
Tumour type per Lauren's classification Intestinal type Diffuse type	 57(47.9%) 62(52.1%)	 40 10	 **<0.001**	 0.207(0.125-0.474)	 **<0.01**	 0.416(0.222-0.780)	 **0.006**
Tumour Grade Low Intermediate High	 26 (21.8) 42 (35.3) 51(42.9)	 66 23 9	 **<0.001**	 0.150(0.077-0.295) 0.377(0.228-0.623)	 **<0.01** **<0.01** **<0.01**	 0.459(0.221-0.952)	 0.101 **0.036**
LNs >15 0-14	 52 (43.7) 67 (56.3)	 12 23	 **<0.001**	 2.219(1.421-3.464)	 **<0.01**	 2.149(1.296-3.565)	 **0.003**
R_{NP} R_{NP}1(>15.00) R_{NP}2(2.01-15.00) R_{NP}3(≤2.00)	 30 (25.2) 37 (31.1) 52 (43.7)	 -18.1 8.0	 **<0.001**	 0.047(0.019-0.116) 0.338(0.205-0.558)	 **<0.01** **<0.01** **<0.01**	 0.172(0.057-0.517) 0.443(0.240-0.815)	 **0.003** **0.002** **0.009**

LNs: Number of negatives, RNP: Ratio of negative-to-positive nodes.

Total gastrectomy was done when the stomach cancer was in the proximal area, or distal gastrectomy when the cancer was in the distal area. In locally advanced cases, neighbouring organs such as the colon, spleen, and pancreas were also resected. The pathologic stage was revised according to the AJCC 8th edition.[5] Age, gender, type of gastrectomy, pathologic T and N stages (pT and pN), tumour location and, size, grade, histologic type as per Lauren's classification, presence of lymphovascular (LVI) invasion and perineural (PNI) invasion, count of negative--positive lymph nodes, and RNP, were all noted.[4]

Patients were followed until May 2020. They were evaluated by a clinical examination in 3 to 6 months for the first 2 years, then in 6 to 12 months between 2 to 5 years and annually after the fifth year of follow-up. Laboratory screening was performed when necessary. In addition, patients with stages 2 and 3 were assessed by computed tomography (CT) every 6 to 12 months in the first three years and then annually for five years after their operation. Positron emission tomography (PET) was also used in case of clinical need. Data analyses were conducted using the latest version of IBM-SPSS (Chicago, IL, USA). Categorical data were expressed as percentages, while numerical data were given as mean ± SD and median. Intergroup results were compared *via* the Chi-square test or the likelihood ratio test. Survival analysis was done with the Kaplan-Meier method, and the log-rank test to assess the survival difference. A correlation between overall survival and other variables was investigated backwards with the Cox regression analysis: LR method. The p-value <0.05 was deemed statistically important.

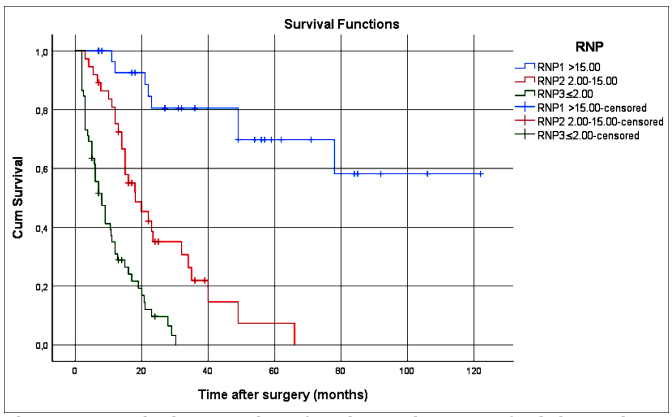

Figure 1: Survival comparison (Kaplan-Meier curves) of the patients according to RNP (p<0.001). RNP: Ratio of negative/positive lymph node.

RESULTS

The majority of the 119 patients were males (81.5%, n = 97). The median age was 66 years, range 40-88 years. The mean count of the dissected lymph nodes was 27.3 ± 11.7. The average count of negative lymph nodes was 17.6 ± 11.3, but the average count of positive lymph nodes was 9.7 ± 9.4. The study's mean in the following period was 22.1 ± 23.0 months (range: 2 - 122 months). More than two-thirds (69.7%, n = 83) of patients died during the follow-up period.

The Chi-square distribution of clinicopathological variables with RNP is summarised in Table I. Pathologic N stage (p <0.01), PNI (p <0.01), LVI (p = 0.01), tumour type (p <0.01), grade (p <0.01), number of negative lymph nodes (p <0.01) and RNP (p <0.01) in univariate analysis, as well as total overall survival, were strongly significant and maintained for gender (p = 0.025), gastrectomy type (p = 0.037), PNI (p = 0.028), tumour type (p = 0.006), and count of negative lymph nodes (p=0.003) in multivariate analyses (Table II).

The RNP was an independent prognostic criterion for overall survival (p = 0.003, Table II). Advanced pathologic T and N stages, presence of PNI, presence of LVI, high tumour grade and diffuse-type as per Lauren's classification, and count of the negative lymph nodes and RNP were also significantly associated with poor survival (p <0.001) (Figure 1).

DISCUSSION

This retrospective study showed that RNP is an adverse prognostic factor for survival with gastric adenocarcinoma, or those who underwent curative gastrectomy with D2 lymph node dissection. The RNP value as an independent prognostic factor is shown in other studies.[3,4,9]

Many studies have shown that the count of negative lymph nodes has a significant impact on the survival of gastric cancer patients as an alternative to the pN stage. [3,10-12] However, this is primarily determined by the extent of lymphadenectomy. Occult lymph node metastasis was associated with shorter survival in patients with N0 gastric carcinoma, and it has been claimed that D2 lymph node dissection may be effective in improving prognosis.[4,10] The present findings support this hypothesis, considering that the patients underwent curative gastrectomy with lymphadenectomy D2. As such, the count of negative lymph nodes was demonstrated to play a role in defence against invasion and metastasis of cancer cells.[13,14] Adequate lymph node sampling *via* curative lymph node dissection contributed to local control of the disease by removing isolated tumour cells and micrometastatic foci.[9] D2 lymph node resection enabled histopathological evaluation of more lymph nodes, with an increased count of dissected nodes, approximating the stage migration effect.[15] Metastatic node count is correlated to cumulative count of dissected lymph nodes.[8] Negative node count (>15) was an independent prognostic factor in univariate and multivariate analyses. D2 lymph node resection, with curative gastrectomy, accurately represents lymph node involvement in gastric cancer.

The AJCC staging manual recommends sampling and histopathological evaluation of 16 regional nodes, but does not provide suggestions regarding extent of lymph node dissection, which represents a shortfall of the AJCC system.[5] In this series, the pN stage was not an independent factor in multivariate analysis, but was associated with survival in the univariate analysis. However, while pN1 stage has been effective as a prognostic factor in multivariate analysis, it was observed how there was no independent prognostic factor in advanced stage pN. Despite this, the authors showed that all 3 subtypes of RNP are independent prognostic factors in multivariate analysis. Other studies support the findings of the present study. Lin *et al*. conducted a study on independent prognostic factors in gastric cancer patients, undergoing curative resection, and found that the pN stage was an independent prognostic factor in one way variance analysis, but failed to confirm this finding in multivariate analysis.[16] Lee *et al.* states that pN is not an independent prognostic marker of gastric cancer.[17] In another study on the prognostic effect of the count of dissected lymph nodes, the pN stage was not found to be an independent marker.[9]

Epithelial tumours usually metastasise *via* lymphovascular channels and/or *via* nerves, (PNI). Although PNI was found to relate to survival in univariate and multivariate analyses, LVI was an independent prognostic marker despite its significant effect on survival in the univariate analysis. Prognostic importance of (PNI) in gastric cancer is controversial. While some authors report that PNI is not a prognostic marker, De Franco *et al.* report it is associated with advanced stage and poor long-term survival, and may act as an adjunctive marker in the intestinal tract's histotype.[18,19] These findings support that PNI is an independent prognostic marker in gastric cancer patients who undergo curative gastrectomy. The authors think the prognostic role of LVI must be investigated in larger groups or by meta-analysis, with conflicting evidence on the prognostic value of LVI, including the results

of this study.[4,20]

Another parameter found to be an independent prognostic marker was histologic tumour type. Diffuse type gastric cancer had a significantly shorter survival. While some studies support our finding, others could not confirm the prognostic value of histologic type in gastric cancer.[4,21,22]

The present authors could not prove the prognostic effect of histologic grade in multivariate analysis, although it was significantly associated with survival in one way variance analysis. Prognostic effect of the histologic grade of gastric carcinoma remains controversial; thus, further investigation is required to demonstrate it is actually an independent prognostic factor.[23,24]

The present study has some limitations. First, there is no standard cut-off value to determine RNP, as the authors used the cut-off in the Yamashita *et al.* study.[4,25] A standard cut-off value should be identified to use RNP as an independent prognostic factor *vs.* the pN stage in gastric cancer patients. The second limitation is the study group size; with more precise results obtained with more patients.

CONCLUSION

RNP can be an alternative, independent prognostic marker for gastric cancer, a new alternative indicator for prognosis assessment following curative gastrectomy and enhancing the current TNM staging system.

ETHICAL APPROVAL:
This study was approved by The Ethics Committee of Cumhuriyet University, Sivas, Turkey (Reference No: 2009-12/25, 11/12/2009).

PATIENTS' CONSENT:
Data of this retrospective research was obtained from the clinical archive.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HA: Conception and design, discussion and literature review.
MK: Acquisition of data, interpretation of data.
MCM: Acquisition of data, search of the literature.
MG: Search of the literature, drafting of manuscript.
HÖ: Analysis and interpretation of data.
KK: Critical revision of the manuscript.

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