Original Article

Prognostic Role of the Lymph Node Ratio in Colorectal Cancer: A Retrospective Study

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Abstract

Background: Studies have been conducted to investigate more practical and useful parameters in determining the prognosis of patients with colorectal cancer (CRC), and some suggest that the lymph node ratio (LNR) may be useful in doing so, especially in patients with inadequate lymph node dissection. **Objectives:** We aimed to evaluate the effect of LNR (number of metastatic lymph nodes/number of total lymph nodes excised) on disease-free survival and overall survival rates in CRC. **Design:** A single-center retrospective cohort study. **Setting:** Tertiary care hospital. **Patients and Methods:** The clinical and pathological features of the patients were analyzed by dividing them into groups according to tumor localization; tumor, node, metastasis staging; and LNR. The Kaplan–Meier method and the log-rank test were used for survival analysis. **Sample Size:** A total of 479 patients with CRC who were operated on between September 1991 and December 2011 were included in this study. The LNR of 439 patients could be calculated, and analyses were according to these patient groups. **Main Outcome Measures:** The primary objective of this study was to determine the effect of LNR on disease-free survival and overall survival in CRC. **Results:** A total of 121 right-sided colon cancers, 202 left-sided colon cancers, and 156 rectal cancers were analyzed. The age of the patients ranged from 20 to 93 years, and the mean age was 66.8 (13.5) years. The cumulative 5-year survival rate was 48.5% in our patients with CRC. When analyzing the tumor, node, metastasis stages of the groups according to their LNRs, the results showed that as the rate of lymph node metastasis increases, so does the tumor stage parameter ($P < 0.001$). The overall survival and disease-free survival rates significantly decreased as LNR increased ($P < 0.001$). **Conclusion:** This study showed that LNR correlates well with the disease-free and overall survival rates. A higher LNR could indicate the aggressiveness of the tumor; therefore, LNR may be a predictor of the poor prognosis of CRC. **Limitations:** Some patients could not be followed-up and we could not evaluate complications because not all patients had data on postoperative complications. As a result, our study results may have been affected. **Conflict of Interest:** The authors have no conflict of interest to declare.

Keywords: Colorectal cancer, lymph node ratio, lymph node staging, metastatic tumor, prognostic factor, survival outcome

Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide.[1] According to the Ministry of Health in Turkey (2019), colorectal malignancies are the third most prevalent type of cancer, with an incidence of 14.2 per 100,000 females and 25.3 per 100,000 males.[2] Approximately, two million new CRC cases with approximately one million deaths were predicted for 2020 globally, making CRC one of the most serious health issues in the world.[1]

The prognosis of CRC is closely related to tumor stage. Five-year survival rates are 90% in early-diagnosed localized disease, 71% in regionally disseminated disease, and 14% in distant metastatic disease.[3]

Published studies have shown that many factors are associated with survival in CRC and that no single prognostic factor is responsible for recurrence or survival. Tumor depth in the intestinal wall, regional lymph node spread, and distant organ metastasis have been accepted as the most important prognostic factors and form the basis of most staging systems.[4-7]

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Many studies have been conducted to investigate more practical and useful parameters in determining the prognosis, and some studies suggest that lymph node ratio (LNR) may be useful in doing so, especially in patients with inadequate lymph node dissection.[8-11]

This study aimed to evaluate the effects of LNR on disease-free survival and overall survival in patients with CRC.

Materials and Methods

Data on patients who underwent colorectal surgery at Istanbul Haydarpasa Military Hospital General Surgery Clinic between September 1991 (mostly after 2002) and December 2011 were retrospectively collected.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the University of Health Sciences, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Number: 85/15.06.2022).

Patients whose patient files could not be accessed and who did not have sufficient data to be evaluated were excluded from the study.

The following parameters were analyzed: demographics, the indication of surgery (emergency, elective, palliative, or curative), tumor location, histopathological type, histologic grade, types of surgery (abdominoperineal resection, low anterior resection, anterior resection, left hemicolectomy, transverse colectomy, right hemicolectomy, total colectomy, total proctocolectomy, Hartmann procedure, or palliative procedures), tumor stage [tumor, node, metastasis (TNM) classification], and LNR. Local recurrence, distant metastasis, disease-free survival, and overall survival were analyzed at the end of the patients' fifth year of follow-up.

For further analysis, the patients were stratified using the following parameters: according to age in years (40, 41–60, and ≥60 years), according to tumor stage [American Joint Commission on Cancer (AJCC) stages I–IV],[12] and according to LNR (number of metastatic lymph nodes/number of total lymph nodes), ranging from 1 to 4 (LNR 1 = 0.00–0.083, LNR 2 = 0.084–0.25, LNR 3 = 0.26–0.50, and LNR 4 = 0.51–1.00).

While determining LNR, a 1/12 (0.083) ratio was determined as the upper limit of the first group (LNR 1) because at least 12 lymph nodes must be excised to make an appropriate decision according to the guidelines.[13] The quarter percentile and half percentile were taken as the second and third cut-off values, respectively.

Disease-free survival and overall survival analyses were performed for the TNM stage and LNR. Patients were divided into the following three groups according to tumor location: right-sided colon cancer (cecum, ascending colon, hepatic flexure, and transverse colon), left-sided colon cancer (splenic flexure, descending colon, and sigmoid colon), and rectal cancer.[14]

The primary objective of this study was to determine the effect of lymph node ratio on disease-free survival and overall survival in CRCs.

Statistical analysis

The Statistical Package for Social Sciences (SPSS Inc. Chicago, IL) program was used to evaluate the findings. Parameters with a probability of <0.025 were included in the multivariate analysis. The Chi-squared and Kruskal–Wallis non-parametric tests and the univariate analysis test was used for descriptive statistical analyses between the groups. Results from the survival time analyses were calculated using the Kaplan–Meier method, and the difference between the survival curves were evaluated using the log-rank test. The effect of LNR on survival time was evaluated using regression analysis. In the parametric data, values were presented as means with standard deviation or standard error. A *P* value of <0.05 was considered to be statistically significant.

Results

After excluding the patients with missing data, 479 patients (121 right-sided colon cancers, 202 left-sided colon cancers, and 156 rectal cancers) were analyzed. The clinicopathologic features, TNM stages, and LNRs of the patients are detailed in Table 1. The patients' ages ranged from 20 to 93 years, and their mean age was 66.8 (13.5) years. The mean follow-up period was 41.1 (2.1) months.

Information on 74 patients could not be obtained because they were unfollowed, and their contact information was unavailable. During follow-up, it was observed that 219 patients were still alive and 186 died due to various reasons. The cause of death in 158 (33%) patients was disease related. In five patients, the cause of death was the development of a secondary malignancy, so they were included in the group that died due to non-disease causes. In addition, 18 (11.5%) out of 156 patients with rectal cancer had neoadjuvant chemoradiotherapy. Six patients with rectal cancer and 13 patients with colon cancer had chemotherapy before surgery.

The pathological T-stage could not be determined in 29 (6.1%) patients because palliative surgery was performed, and these patients were considered to be stage T4 as per the clinical staging. The pN value could not be determined in 29 (6.1%) patients due to no tumor resection and in 11 (2.3%) patients because no lymph nodes were noted in the pathology report. For adequate lymph node staging, ≥12 lymph node dissections were required, and this was performed in 182 (38%) patients. The mean number of lymph nodes excised was 12 (0.4), and the median was 10 (range 1–67). Staging was not performed in three (0.6%) patients in whom resection could not be performed due to locally advanced disease that was not metastatic [Table 1].

Due to missing data, local recurrence in 74 patients and distant metastasis in 111 patients could not be evaluated.

Table 1: Clinicopathological characteristics; TNM Stage; and the lymph node ratio of the patients with colorectal cancer

Characteristic	Total, *n* (%)	Right-sided colon	Left-sided colon	Rectum	*P*
Gender					0.623
Female	207 (43.2)	49	86	72	
Male	272 (56.8)	72	116	84	
Age [years, mean (S.E.M)]	66.8 (13.5)				0.155
40	23 (4.8)	5	9	9	
41–60	103 (21.5)	29	35	39	
≥60	353 (73.7)	87	158	108	
Histopathological type					0.189
Adenocarcinoma	427 (89.1)	103	181	143	
Mucinous adenocarcinoma	37 (7.7)	12	15	10	
Signet ring cell adenocarcinoma	11 (2.3)	3	5	3	
Undifferentiated	4 (0.8)	3	1	0	
Tumor differentiation grade					0.007*
Well differentiated	77 (16.1)	11	38	28	
Moderately differentiated	365 (76.2)	95	148	122	
Poorly differentiated	33 (6.9)	12	15	6	
Undifferentiated	4 (0.8)	3	1	0	
Time to surgery					<0.001*
Emergency surgery	98 (20.5)	26	59	13	
Elective surgery	381 (79.5)	95	143	143	
Types of surgery					0.456
Curative procedure	434 (90.6)	113	182	139	
Palliative procedure	45 (9.4)	8	20	17	
Types of operations					<0.001*
Abdominoperineal resection	35 (7.3)	-	-	35	
Low anterior resection	98 (20.5)	-	-	98	
Anterior resection	89 (18.6)	-	89	-	
Left hemicolectomy	51 (10.6)	-	51	-	
Transverse colectomy	14 (2.9)	3	11	-	
Right hemicolectomy	110 (23)	110	-	-	
Total colectomy	18 (3.8)	6	12	-	
Total proctocolectomy	2 (0.4)	-	-	2	
Hartmann procedure	33 (6.9)	-	29	4	
Palliative procedures	29 (6.1)	2	10	17	
pT Stage					0.905
1	18 (4)	4	8	6	
2	77 (17.1)	20	29	28	
3	309 (68.7)	80	133	96	
4	46 (10.2)	15	22	9	
pN Stage					0.209
0	257 (58.5)	61	118	78	
1	135 (30.8)	41	56	38	
2	47 (10.7)	15	13	19	
Lymph Node Ratio					0.105
LNR 1	281 (64)	71	120	90	
LNR 2	80 (18.2)	28	37	15	
LNR 3	39 (8.9)	10	12	17	
LNR 4	39 (8.9)	8	18	13	
M Stage					0.409
0	388 (81)	103	161	124	
1	91 (19)	18	41	32	
TNM Stage					0.929
I	84 (17.5)	22	34	28	
II	165 (34.4)	39	76	50	
III	136 (28.4)	42	51	43	
IV	91 (19)	18	41	32	

*Statistically significant‘ S.E.M: standard error of mean; TNM: tumor, node, metastasis; LNR: lymph node ratio

Local recurrence was detected in 49 (10.2%) patients, while distant metastases were detected in 129 (26.9%). Five-year survival rates for stages I, II, III, and IV were 77.1%, 59.2%, 42.4%, and 6.6%, respectively. The median survival time of the patients who underwent surgical treatment and follow-up in our clinic due to CRC was 28.7 (0.1–273.1) months, and the mean survival time was 41.1 (2.1) months. While the median disease-free survival was 21.3 (0–273.1) months, the mean survival time was 36.9 (2.1) months.

The examination performed according to the degree of tumor differentiation detected that from stages I to IV, the rate of well-differentiated tumors decreased from 32.1% to 9.9% and the rate of moderately differentiated tumors increased from 66.7% to 81.3%. While poorly differentiated and undifferentiated tumors were 1.2% in stage I tumors, they were 8.5%, 10.3%, and 8.8% in stages II, III, and IV tumors, respectively. Well-differentiated early-stage tumors were found to be statistically significant ($P < 0.001$).

The metastatic lymph node rate could not be determined in 40 (8.4%) patients with no lymph node count information or no total excised lymph nodes noted in the pathology report. Therefore, the LNR of 439 patients could be calculated, and analyses were performed according to these patient groups. The patients' clinicopathological characteristics according to LNR are detailed in Table 2. When analyzing the tumor differentiation grade, statistically significant differences ($P = 0.02$) between LNR groups 1–2 ($P = 0.008$) and LNR groups 1–4 ($P = 0.048$) were found. In addition, the probability of successfully performing curative surgery in patients in LNR group 4 was significantly lower than that in the other groups ($P = 0.004$).

When analyzing the TNM stages of the groups according to their LNRs, the results showed that as the rate of lymph node metastasis increases, so does the tumor stage parameter ($P < 0.001$) [Table 3].

Follow-up results according to LNR are detailed in Table 4. At the time of diagnosis, distant metastasis was found in 7.8% of the patients in LNR 1, 16.2% in LNR 2, 30.7% in LNR 3, and 43.5% in LNR 4.

The probability of distant metastasis significantly increased as LNR increased ($P < 0.001$). During the follow-up period, distant metastasis was detected in 21% of the patients in LNR 1, 46.4% in LNR 2, 52.9% in LNR 3, and 65.5% in LNR 4. The probability of distant metastasis significantly increased as metastatic lymph node rates increased ($P < 0.001$).

During the follow-up period, mortality rates among the patients in LNR 1, 2, 3, and 4 were 33.6%, 57.1%, 58.8%, and 79.4%, respectively. All survival parameters significantly decreased as LNR increased ($P < 0.001$). The survival analysis curve according to LNR is shown in Figure 1a, and the disease-free survival curve according to LNR is shown in Figure 1b.

Table 2: Clinicopathological characteristics of the patients according to the lymph node ratio

Characteristic	LNR 1	LNR 2	LNR 3	LNR 4	*P*
Gender					0.886
Female	118	34	17	19	
Male	163	46	22	20	
Age (years)					0.956
40	9	6	2	4	
41–60	67	16	10	6	
≥60	205	58	27	29	
Tumor location					0.105
Right-sided colon	71	28	10	8	
Left-sided colon	120	37	12	18	
Rectum	90	15	17	13	
Histopathological type					0.310
Adenocarcinoma	254	71	34	31	
Mucinous adenocarcinoma	3	2	1	4	
Signet ring cell adenocarcinoma	22	5	4	4	
Undifferentiated	2	2	0	0	
Tumor differentiation grade					0.020*
Well differentiated	58	6	6	4	
Moderately differentiated	206	67	30	30	
Poorly differentiated	15	5	3	5	
Undifferentiated	2	2	0	0	
Time to surgery					0.017*
Emergency surgery	42	20	8	13	
Elective surgery	239	60	31	26	
Types of surgery					0.004*
Curative procedure	277	74	36	35	
Palliative procedure	4	6	3	4	
Types of operations					0.112
Abdominoperineal resection	24	3	3	4	
Low anterior resection	62	11	14	8	
Anterior resection	56	18	6	6	
Left hemicolectomy	35	9	3	3	
Transverse colectomy	7	4	0	3	
Right hemicolectomy	67	25	8	8	
Total colectomy	9	3	3	3	
Total proctocolectomy	2	0	0	0	
Hartmann procedure	19	7	2	4	

*Statistically significant, LNR: Lymph node ratio

Discussion

CRC commonly causes cancer-related deaths worldwide. Curative resection is the primary treatment option, and survival rates after 5 years have been reported to be 40–69%.[15-17] Seventy percent of recurrences occur within the first 2 years after resection.[18,19] Age, gender, tumor location, tumor stage, local invasion, presence of obstruction/perforation, microscopic features, and lymph node involvement have all been reported to affect prognosis.[20,21] To better determine the prognosis of patients with inadequate lymph node dissection, the ratio of metastatic lymph nodes to total lymph nodes excised can be used.[22,23]

Table 3: TNM stage according to the lymph node ratio

	LNR 1	LNR 2	LNR 3	LNR 4	*P*
pT Stage					<0.001*
1	16	0	0	0	
2	68	4	0	1	
3	180	66	33	25	
4	17	10	6	13	
pN Stage					<0.001*
0	257	0	0	0	
1	23	77	23	13	
2	1	3	16	26	
pM Stage					<0.001*
0	259	67	27	22	
1	22	13	12	17	
TNM Stage					<0.001*
I	78	0	0	0	
II	161	0	0	0	
III	20	67	27	22	
IV	22	13	12	17	

*Statistically significant; TNM: tumor, node, metastasis; LNR: lymph node ratio

The most important factor affecting prognosis is tumor stage. The most widely used staging system at present was developed by AJCC and was based on the TNM criteria.[12,24] While the 5-year survival rate of patients with stage I tumors may exceed 90%, the rate may decrease below 10% in patients with stage IV tumors. Our results showed an overall 5-year survival rate of 48.5%; in particular, the rates of survival of patients with stages I, II, III, and IV tumors were 77.1%, 59.2%, 42.4%, and 6.6%, respectively. Consistent with the literature, we determined that tumor stage has a remarkable effect on disease-free and overall survival.[3,15,25]

At present, the only curative treatment option for CRC is complete removal of the tumor (with adequate surgical margins) and mesenteric lymph nodes. While some investigators believe in the therapeutic benefits of a complete lymphadenectomy, others believe that it merely allows for more accurate staging.[26] When deciding on adjuvant chemotherapy, the most important factor to consider is the involvement of lymph nodes.[27-29] Patients may not benefit from adjuvant therapy and may have low survival rates as a result of insufficient staging. On the

Table 4: Follow-up results according to the lymph node ratio

	LNR 1	LNR 2	LNR 3	LNR 4	*P*
Local recurrence					0.300
Present	23	12	5	4	
Absent	217	55	32	29	
Distant metastasis					<0.001*
Present	47	26	18	19	
Absent	176	30	16	10	
Follow-up					<0.001*
Alive	162	27	14	7	
Dead	82	36	20	27	
Overall survival (month)					0.001*
Median (range)	33.1 (0.1–237.1)	22.9 (0.1–146)	24.9 (0.3–96.2)	15.5 (0.2–127.2)	
Mean±S.E.M	48.6±2.9	33.8±4.6	28.9±3.7	26.9±5.7	
DFS (month)					<0.001*
Median (range)	29 (0.1–237.1)	15.2 (0.1–146)	11.3 (0–96.2)	7.5 (0.2–127.2)	
Mean (S.E.M)	45 (3)	30.3 (4.6)	20.2 (3.9)	19.3 (5.4)	
Five-year survival rate (%)	63.6	32.4	33.2	17.8	

*Statistically significant, S.E.M: standard error of mean, DFS: disease-free survival, LNR: lymph node ratio

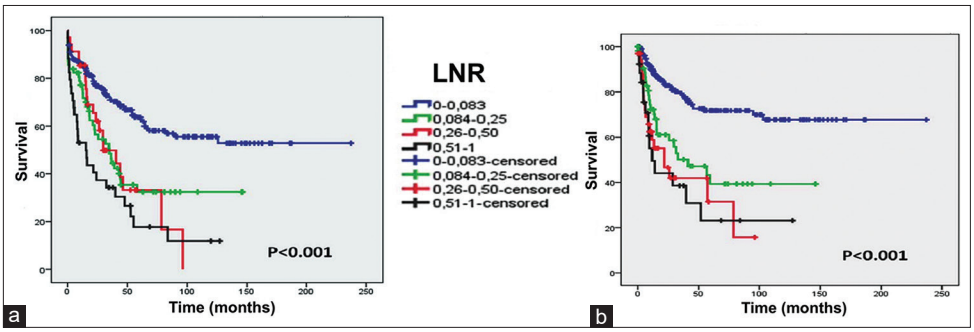

Figure 1: Survival curve of the patients. (a) Overall survival curve according to lymph node ratio. (b) Disease-free survival curve according to lymph node ratio

other hand, overstaging may result in unnecessary exposure to chemotherapy and its side effects. Therefore, using LNR in addition to counting the number of metastatic lymph nodes may be helpful for better staging.

The number of metastatic lymph nodes is important in the TNM staging system and is affected by the width of the resection margin, the surgical technique used, the pathologist's evaluation, and the technique used for lymph node isolation. TNM staging cannot be accurately performed when there is inadequate lymph node dissection. Many organizations, including AJCC, the National Cancer Institute, and the American Society of Clinical Oncology, have stated that at least 12 lymph nodes should be dissected for accurate staging in patients who have undergone CRC resections.[30]

Many studies have determined poor survival rates in patients with node-negative colon cancer who have undergone inadequate lymph node dissections. Researchers attribute this to incorrect staging due to inadequate surgical or pathological evaluation.[31-34]

LNR was shown to have prognostic significance in patients with inadequate lymph node dissections, and our results were consistent with these studies.[9,22,35,36] A meta-analysis of 14 studies involving 90,274 CRC patients revealed that a higher metastatic lymph node ratio was markedly associated with worse overall survival and disease-free survival rates. Regardless of tumor location, the metastatic LNR helps predict the prognoses of CRC patients.[37]

Despite our promising findings, our study has some limitations. First, ours was a single-center retrospective study. In addition, because the hospital's computer-based patient record system was implemented after 2002, some of the data on patients operated on before this time could not be accessed. Furthermore, some control analyses were performed in other hospitals, and some patients could not be followed-up. As a result, our study results may have been affected. Moreover, we could not evaluate the complications because not all patients had postoperative complication data.

In conclusion, this study showed that LNR correlates well with the disease-free and overall survival rates. A higher LNR could indicate the tumor's aggressiveness; therefore, LNR may be a predictor of poor prognosis in CRCs.

Ethical policy and Institutional Review board statement

This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the University of Health Sciences, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee (Number: 85/15.06.2022).

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Conflicts of interest

There are no conflicts of interest.

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