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RESEARCH ARTICLE

The Relationship Between the Tumor-Stroma Ratio and Lymph Node Ratio and Survival in Colon Cancer: A Single-Center Experience

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ABSTRACT

Aim: This retrospective analysis aimed to examine the relationship between the tumor-stroma ratio (TSR) and lymph node ratio (LNR) in patients treated with curative-intent surgery for colon cancer and to determine the prognostic value of both parameters for overall survival (OS).

Method: This single-center study included consecutive patients with colon adenocarcinoma who underwent surgical resection between January 2019 and December 2025. The relationships of the TSR and LNR with OS and clinicopathological parameters were investigated.

Results: A total of 113 patients with colon cancer were included in the study. Survival status differed by TSR category. In the low-TSR group, 45 patients (71%) were alive, and 18 (29%) were deceased, whereas the corresponding numbers in the high-TSR group were 23 (46.0%) and 27 (54.0%), respectively. This difference was statistically significant (p=0.006). We also analyzed patients according to survival. Significant differences between survivors and non-survivors were observed in median age, total lymph node count, number of metastatic lymph nodes, and LNR (p=0.04, 0.008, 0.001). No significant association between TSR and LNR was found.

Conclusion: Both TSR and LNR have emerged as promising prognostic indicators. In the present study, both TSR and LNR were associated with OS.

Keywords: Colon cancer, tumor-stroma ratio, lymph node ratio, survival

Introduction

Among gastrointestinal malignancies, colorectal cancer represents a major global health burden, owing to its high incidence and considerable contribution to cancer-related mortality worldwide.[1] Although considerable progress has been made in diagnostic methods and treatment approaches, along with refinements in surgical techniques and approaches, patients with identical clinicopathological stages may exhibit substantial differences in survival outcomes. To better explain this phenomenon, recent research has increasingly focused on the tumor microenvironment and tumor biology, which have emerged as important determinants of clinical outcomes.[2]

Among the histomorphology parameters reflecting the tumor microenvironment, the tumor-stroma ratio (TSR) has emerged as one of the most extensively investigated prognostic parameters. By quantifying the relative proportion of stromal tissue within the tumor, the TSR provides valuable insight into tumor-host interactions and has demonstrated considerable prognostic value in patients with colon cancer.[3] Previous studies have consistently linked a high TSR with more aggressive tumor behavior, including increased invasiveness, advanced pathological stage, a greater likelihood of lymph node involvement, and reduced survival among patients with colon cancer.[4,5]

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Nodal involvement is a key prognostic factor in colon cancer. Despite these considerations, the N category in the existing tumor, node, metastasis staging framework is assigned according to the absolute count of metastatic lymph nodes.[6] However, the total lymph node yield after surgical resection may vary substantially because of differences in surgical technique, the quality of pathological macroscopic examination, and individual anatomical variability, thereby affecting the accuracy of nodal staging. Accordingly, the lymph node ratio (LNR), calculated by dividing the number of metastatic lymph nodes by the total number of lymph nodes examined, has increasingly been recognized as a more objective and reproducible prognostic indicator.[7] We also emphasize that inadequate lymph node retrieval is a clinically relevant factor that may influence staging and subsequent treatment decisions, including adjuvant chemotherapy. However, all surgical procedures were performed with the same surgical unit in the present case.

Accumulating evidence has demonstrated that an elevated LNR is associated with more advanced disease, higher recurrence rates, and poorer survival outcomes in patients with colon cancer.[8]

A biological relationship between lymph node metastasis and the stromal composition of the tumor has been proposed. The tumor stroma is thought to provide a permissive microenvironment that facilitates tumor cell migration and promotes metastatic dissemination. Furthermore, stromal remodeling, angiogenesis, and the activation of cancer-associated fibroblasts have been implicated in lymphatic spread, suggesting that the tumor microenvironment plays a pivotal role in the metastatic process.[9] However, TSR and lymph node involvement have been demonstrated in various other tumor types.

Despite the growing body of evidence supporting the individual prognostic significance of the LNR and TSR, studies evaluating the relationship between these two parameters are scarce, and their combined prognostic impact on survival remains largely unexplored. The present study aims to examine the relationship between the LNR and TSR in patients undergoing curative resection for colon cancer and to assess the prognostic value of both parameters in predicting overall survival (OS).

Materials and Methods

Consecutive patients with colon adenocarcinoma who underwent curative-intent surgical resection at Bolu Abant İzzet Baysal University, İzzet Baysal Training and Research Hospital between January 2019 and December 2025 were retrospectively evaluated in this single-center study. Clinical characteristics and histopathological findings were retrospectively obtained through a review of institutional electronic health records and pathology archives. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (approval number: 2026/296, date: 23.06.2026).

Patient-related demographic and clinical characteristics, histopathological findings, and follow-up data were retrospectively retrieved from institutional electronic records and pathology archives. Eligibility required histopathological confirmation of primary conventional-type colon adenocarcinoma, surgical resection of the tumor, and the availability of survival data.

Exclusion criteria comprised incomplete clinical or histopathological documentation, lack of available pathological specimens, and inadequate follow-up information. Additional exclusion criteria included synchronous malignancies, receipt of neoadjuvant therapy, palliative surgery for metastatic disease, and histological subtypes other than conventional adenocarcinoma, such as mucinous adenocarcinoma or signet-ring cell carcinoma. In addition, patients who died within the 1st postoperative month were also excluded. Patient age, sex, tumor location, total number of examined lymph nodes, number of metastatic lymph nodes, and survival data were recorded. The TSR was retrospectively determined using hematoxylin and eosin-stained histopathological slides. The TSR was evaluated at the invasive tumor front by identifying the microscopic field containing both tumor cells and stromal tissue with the highest proportion of stroma. The percentage of the stromal component within this field was estimated visually at x100 magnification. A 50% cut-off value was used in accordance with the methodology commonly adopted in the literature. Based on the proportion of stromal tissue, the cases were divided into two categories: high TSR, defined as a stromal area of ≥50%, and low TSR, defined as a stromal area of <50% (Figure 1). All types of collagen present in the stromal areas, including keloid-like, mature, and immature collagen, were included in the assessment. Areas affected by crush artifacts, necrosis, and granulocytic infiltration were excluded from assessment. In addition, regions lacking direct tumor-stroma interaction were not considered; only stromal areas immediately adjacent to tumor cells were evaluated.

For each patient, the LNR was derived by dividing the number of lymph nodes with metastatic involvement by the overall number of lymph nodes examined. OS was measured from the date of surgery until death from any cause, with surviving patients censored at their most recent follow-up.

Statistical Analysis

All statistical procedures were performed with IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was applied to assess whether continuous variables conformed to a normal distribution. Data meeting the normality assumption were

summarized as mean ± standard deviation, with group differences assessed by the Independent Samples t-test. For variables with non-normal distributions, values were reported as median and range (minimum-maximum), and comparisons were performed using the Mann-Whitney U test. Categorical variables were summarized as frequencies and percentages, and differences between groups were assessed by the chi-square test. Associations between study variables were examined using Pearson's or Spearman's correlation coefficients, depending on the distribution of the data. Receiver operating characteristic curve analysis was used to determine the sensitivity and specificity of the study variables in predicting survival. A multivariable logistic regression model was used to identify factors independently associated with survival status. Statistical testing was performed on a two-tailed basis, with a p-value of <0.05 regarded as the threshold for statistical significance.

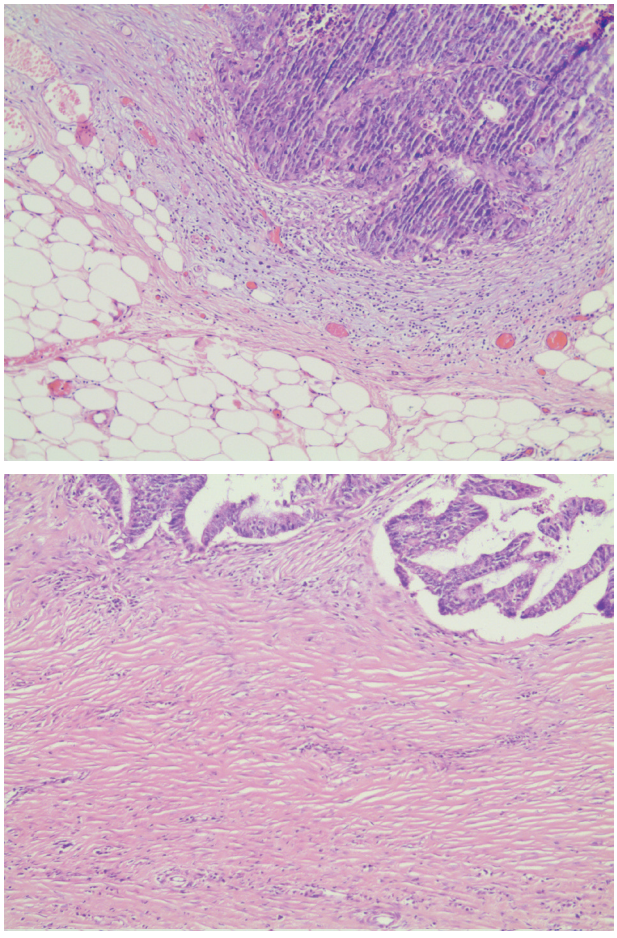

Figure 1. a) Low tumor-stroma ratio (<50%), H&E ×100. b) High tumor-stroma ratio (≥50%), H&E ×100
H&E: Hematoxylin and eosin

Results

The study cohort comprised 113 patients with colon cancer. The sigmoid colon represented the most common tumor site, accounting for 39 cases (34.5%). The remaining tumors were distributed across the rectosigmoid colon (n=32, 28.3%), cecum (n=21, 18.6%), descending colon (n=14, 12.4%), transverse colon (n=4, 3.5%), and ascending colon (n=3, 2.7%). The mean ages of the low- and high-TSR groups were 67 years and 70 years, respectively (p=0.074). Approximately 38% of the low-TSR and 36% of the high-TSR groups were women (p=0.84). Total lymph node count, metastatic lymph node count, LNR, and survival times (in months) were not statistically different among study groups. Survival status differed significantly between the TSR groups. In the low-TSR group, 45 (71%) patients were alive, and 18 (29%) had died, whereas in the high-TSR group, 23 (46.0%) patients were alive, and 27 (54.0%) had died. This difference reached statistical significance (p=0.006). Table 1 summarizes the baseline clinicopathological features of patients in the low- and high-TSR groups.

The cohort was further stratified by survival status. Comparison of survivors and non-survivors revealed statistically significant differences in age (p=0.04), the number of lymph nodes examined (p=0.008), the number of metastatic lymph nodes (p=0.001), and the LNR (p=0.001). The comparative analysis of survival groups is presented in Table 1.

Table 1. Associations of the tumor-stroma ratio (TSR) with clinicopathological characteristics and survival outcomes

Parameters		High TSR (≥50%)	Low TSR (<50%)	p (<0.05)	Survival		p (<0.05)
					Alive	Deceased	
Age (years)		70 (±9)	67 (±11)	0.074	66 (±11)	71 (±9)	0.048
Gender	Female	18 (36%)	24 (38%)	0.084	29 (43%)	13 (29%)	0.133
	Male	32 (64%)	39 (62%)		39 (57%)	32 (71%)	
Total lymph node count (min-max)		19 (8-53)	18 (4-51)	0.161	17 (4-39)	20 (10-53)	0.008
Metastatic lymph node count (min-max)		3.5 (1-25)	2 (1-34)	0.061	2 (1-9)	8 (1-34)	0.001
Lymph node ratio		0.16 (0.04-0.80)	0.12 (0.03-0.82)	0.211	0.13 (±0.12)	0.37 (±0.20)	0.001
Survival times (months)		24 (3-72)	20 (3-72)	0.448	19 (3-50)	24 (3-72)	0.325
Survival status	Alive	23 (46%)	45 (71%)	0.006			
	Deceased	27 (54%)	18 (29%)				

Receiver operating characteristic curve analysis demonstrated that an LNR threshold of >0.16 predicted mortality with a sensitivity of 80% and a specificity of 79% [area under the curve: 0.84; p=0.04; 95% confidence interval (CI): 0.75-0.92] (Figure 2).

In logistic regression analysis, considering total lymph node count, metastatic lymph node count, and TSR, only the metastatic lymph node count remained an independent predictor of mortality (p=0.009, odds ratio: 1.7, 95% CI: 1.03-2.26).

Discussion

Our study showed that a high TSR was associated with high mortality rates and the LNR was significantly associated with mortality. The prognosis of colon cancer is influenced by a variety of factors, including the patient's metabolic status, the pathological and molecular characteristics of the tumor, and the quality of surgical management. In particular, histopathological and molecular biomarkers have emerged as increasingly important prognostic indicators in recent years.[10]

In recent years, the TSR has gained increasing attention as a prognostic biomarker and can be readily determined by pathologists using a standardized assessment of routine histopathological sections. In a recent meta-analysis of 21 studies comprising 7,934 patients with colorectal cancer, a high TSR was identified as a significant indicator of unfavorable outcomes across multiple survival endpoints, including overall, disease-free, cancer-specific, and recurrence-free survival.[11] Similar evidence was provided by Kristensen et al.,[12] who demonstrated that, among patients with stage II colon cancer, a high TSR was associated with a significantly less favorable prognosis than a low TSR. These findings add further support to the prognostic relevance of TSR in colon cancer.[12] With the continued progress of digital pathology technologies, fully automated artificial intelligence-based evaluation of the TSR has shown that a high TSR is an independent prognostic indicator associated with poorer disease-free survival and OS in patients with colon cancer.[13] Our results were consistent with previous evidence, showing a significantly higher mortality rate in the high-TSR group than in the low-TSR group.

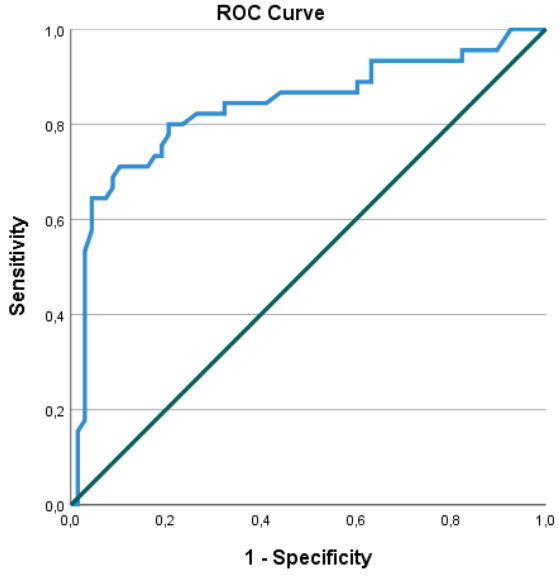

Figure 2. ROC curve of the lymph node ratio for predicting mortality in patients with colon cancer
ROC: Receiver operating characteristic

Elevated LNR values have been associated with an unfavorable prognosis across a variety of malignancies. Several observational studies have reported that higher LNR values are associated with decreased long-term survival across various cancer types, including colorectal, esophageal, breast, and head and neck cancers.[14-16] In a meta-analysis by Ichhpuniani et al.[8] that included 97,631 patients with colon cancer, a higher LNR was found to be significantly associated with reduced OS. In line with previous reports, OS was less favorable among patients with elevated LNR values in our cohort. Moreover, after adjustment for other variables in the multivariable logistic regression model, metastatic lymph node count remained independently associated with mortality.

The TSR is recognized as a marker reflecting the tumor microenvironment, whereas the LNR reflects the nodal tumor burden. These two biomarkers have predominantly been investigated separately, with most studies focusing on their individual prognostic impact on OS. Studies evaluating the combined prognostic value of TSR and LNR are limited. Although no statistically significant association was identified between TSR and LNR in our cohort, the LNR values tended to be higher among patients with a high TSR than among those with a low TSR.

Study Limitations

Several limitations should be considered when interpreting our findings. The retrospective, single-institution nature of the study and the relatively small sample size may limit the extent to which these results can be generalized to broader patient populations. Second, analyses of disease-free and cancer-specific survival could not be performed due to the unavailability of these data.

Conclusion

A growing number of biomarkers have been introduced for the diagnosis, management, and follow-up of patients with colon cancer. Among these, the TSR and LNR have emerged as promising prognostic indicators. In the present study, both TSR and LNR were associated with OS. Further large-scale, multicenter studies evaluating the combined prognostic value of these two biomarkers are warranted to validate our findings and clarify their potential role in prognostic stratification of patients with colon cancer.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (approval number: 2026/296, date: 23.06.2026).

Informed Consent: A retrospective, single-center study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.T., B.Ö., Concept: S.P.Ö., Ç.B., Design: S.P.Ö., C.T., Analysis or Interpretation: Ç.B., Literature Search: S.P.Ö., Writing: S.P.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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Declaration Regarding the Use of AI and AI-Assisted Technologies: The authors declare that no artificial intelligence (AI) or AI-assisted technologies were used in the preparation of this manuscript.

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