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RESEARCH ARTICLE

The Relationship of Tumor-infiltrating Lymphocyte Ratio with Histopathological Parameters and Effect on Survival in Colorectal Cancers

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ABSTRACT

Introduction: Tumor lymphocyte infiltration demonstrates a positive effect on patient survival in breast cancer, melanoma, renal cell carcinoma, and lung cancer. This study aimed to elucidate the relationship between tumor-infiltrating lymphocyte (TIL) ratio and disease-free survival (DFS) and overall survival (OS) by considering localization, clinical and pathological features, microsatellite instability (MSI) status, mutation status, and demographic data.

Method: Patients (n=248) diagnosed with colorectal cancer stages 1, 2, and 3 were analyzed retrospectively. Patients with an Eastern Cooperative Oncology Group performance score of <2 were excluded. Clinical characteristics, age, gender, histopathologic features, TIL ratio, and carcinoembryonic antigen (CEA) level of the patients were recorded.

Results: Stage, CEA level, TIL ratio, N stage, T stage, and lymphovascular invasion were statistically significant. Early stage (p=0.019), low CEA level (p≤0.001), high TIL ratio (p=0.046), low N stage (p=0.004), low T stage (p=0.016), and absence of lymphovascular invasion (p=0.037 and p=0.046) were associated with longer DFS. Lymphovascular invasion, N stage, CEA levels, and TIL ratio were analyzed using multivariate analysis. According to the results, the hazard ratio (HR) for the TIL ratio was 1.68 (95% confidence interval (CI): 1.005-2.807; p=0.048), and the HR for the CEA level was 0.49 (95% CI: 0.293-0.846; p=0.01).

Conclusion: Regarding the outcomes of this research, the TIL ratio was found to be an effective indicator of DFS, confirmed via multivariate analysis to present a 32% reduction in the risk of recurrence/relapse. The TIL ratio was identified as a prognostic factor beyond the effects of stage, grade, lymphovascular invasion, CEA level, and MSI status. The current data provides substantial evidence to support the ratio's consideration in staging guidelines.

Keywords: Colorectal cancer, tumor-infiltrating lymphocytes, tumor immunology, immune response, prognostic factors

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the leading cause of mortality after lung cancer. Recent evidence indicates that the incidence of CRC, especially in the left colon and rectum, increases in the <50-years age group and decreases in older groups. Therefore, determining prognostic factors and developing new treatment modalities have gained importance, with the increasing use of individualized treatment. Although the etiopathogenesis is unknown, the disease is thought to develop secondary to genetic and environmental factors affecting the colonic mucosa.[1]

Modern immune surveillance theory emphasizes that the human immune system has the ability to detect and destroy tumor cells. In addition, this theory argues that tumor cells are not passive targets for the immune system; they can also escape and neutralize the person's immune system. This

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theory expresses the complexity of the interactions between tumor cells and immune system cells or their products.[2] It is estimated that the immune system cell, not the tumor cell, often dies due to these interactions. Many years ago, it was noted that lymphocytes-immune system cells-exist in varying numbers in malignant tumors. These lymphocytes were later defined as tumor-infiltrating lymphocytes (TILs).

These lymphocytes include antigen-specific B cells, natural killer cells, adaptive immune effector cells, and immune suppressor cells. These are the cells responsible for tumor cell killing and regression.[3] It was initially thought that these TILs indicated chronic inflammation in cancer. It was then later discussed whether TILs create a facilitating environment for cancer growth or whether they emerge as an immune response to cancer or supported prognosis. It was shown that the presence of TILs in the tumor region in advanced stages of diseases such as colon, breast, head, and neck cancers can extend the patient's life expectancy.[4]

Tumor lymphocyte infiltration demonstrates a positive effect on patient survival in breast cancer, melanoma, renal cell carcinoma, and lung cancer. New therapies, such as immune system checkpoint inhibitors, have been introduced in clinical practice. The interaction between immune response and tumor cells plays a crucial role in tumor formation and spread in CRC.[5] Within the scope of this research, we aimed to elucidate the relationship between TIL ratio and disease-free survival (DFS) and overall survival (OS) by considering localization, clinical and pathological features, microsatellite instability (MSI) status, mutation status, and demographic data.

Materials and Method

Setting and Study Population

Patients (n=248) diagnosed with CRC stages 1, 2, and 3 admitted to the department of Internal Medicine, division of Medical Oncology outpatient clinic between 2017 and 2020 were included in this retrospective analysis. The files of the patients included in the study were retrospectively analyzed. Patients with an Eastern Cooperative Oncology Group performance score of <2 were excluded. Clinical characteristics, age, gender, histopathologic features, TIL ratio, and carcinoembryonic antigen (CEA) level of the patients were recorded.

Ethical Statement

All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee approval was granted (approval number: 2020/0216, date: 29.04.2020), while as this was a retrospective analysis, no informed consent was required from the participants.

Pathological Analysis

Disease stages of the patients at the time of diagnosis were recorded. Histological subtypes were grouped as mucinous and non-mucinous adeno cancer. Biopsy specimens of four patients with a stony ring component were included in the mucinous group if they had a mucinous component and in the non-mucinous group if they did not. Tumors were examined in three groups: grade 1, grade 2, and grade 3. Lymphovascular involvement, MSI status (MSI-high and MSI-stable), and T and N stages were obtained. Lymphocyte infiltration level (high and low) was recorded. As shown in Figure 1, the TIL ratio cut-off value was 10% in the preparations evaluated at the tumor invasive margin on hematoxylin-eosin 200x magnification. All TIL ratios ≥10% were recorded as high and those ≤10% as low.

Statistical Analysis

Data recording and statistical analysis were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY). Number, percentage, median, mean, and standard deviation were used as descriptive statistical terms to evaluate the data. The Kaplan-Meier method was used for DFS and OS analysis, and the log-rank test was used to determine

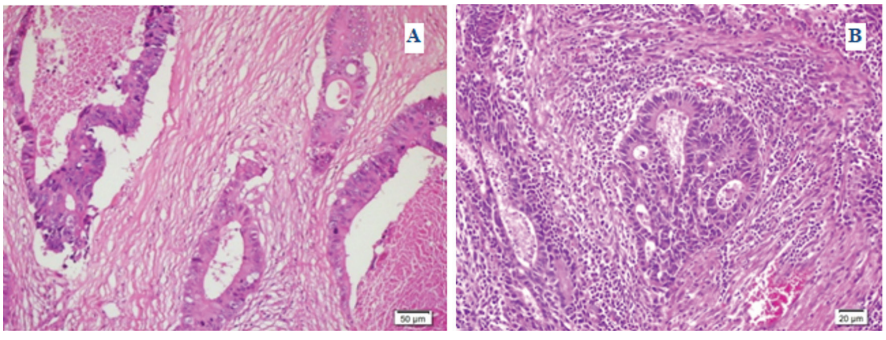


Figure 1. Hematoxylin-eosin 200x results. A: Low TIL (≤10%); B: High TIL (>10%)
TIL: Tumor-infiltrating lymphocyte

the relationship between prognostic factors and DFS. The MedicReS E-PICOS 21.3 program was used for Z-testing. Prognostic factors that showed statistical significance in the proportional hazards analysis test (Cox proportional hazards model) were re-evaluated via multivariate analysis. A p-value of <0.05 was accepted for statistical significance.

Here, G*Power 3.1.9.7 was used for the power analysis. The actual power of the study was calculated as 95% for categorical variables and 49% for censored variables. The required total number of events was 66. The power calculation for DFS was 0.5953, with a hazard ratio (HR) and 72 event count.

Results

Clinical and Pathological Characteristics of Patients

The mean age of the patients was 63.8±13.9 years. Regarding gender, 110 (44.4%) were women and 138 (55.6%) were men. The distribution of other parameters was as follows: Stage (stage 1: stage 2: stage 3-26:111:111 patients), location [right colon: left colon and rectum-81 (32.7%): 167 (67.3%)], CEA level [C0 (CEA<5 ng/mL): C1 (CEA>5 ng/mL) 166:82], grade (G1: G2: G3-37:206:5), histopathology (non-mucinous: mucinous-198:50), mismatch repair status (MSI-high: MSI-stable-23:151); TIL ratio (high: low-161:88), T stage (T1:T2:T3:T4-5:17:24:152:55), N stage (N0:N1:N2-141:76:31), lymphatic invasion (present: absent-69:163), vascular invasion (present: absent-36:196), neoadjuvant chemotherapy (no: yes-147:36), operated primary tumor (no: yes-16:232), adjuvant radiotherapy (no: yes-211:18), adjuvant chemotherapy (no: yes-107:141).

Occurrence of metastasis or recurrence appeared in 74 (29.7%) patients. Detailed clinical features, pathological features, and treatment regimens of the patients in relation to the TIL ratio are presented in Table 1. The median age in the low TIL ratio group was 62, whereas the median age in the high TIL ratio group was 66 (p=0.061).

OS and DFS Outcomes

Of the 248 patients included in the study, the DFS and OS of 32 (12.8%) deceased. The median OS was 102 months. Among the 248 patients, 44 developed metastasis and 30 experienced recurrence. The median time to recurrence and metastasis was 55 months.

OS and DFS Results by TIL Ratio

The number of patients in the low TIL ratio group was 88, and 32 (36.3%) of these patients progressed. In the high TIL ratio group, the number of patients was 160, and 42 (26%) of these patients progressed. While the median OS was not reached in the high TIL ratio group, it was found to be 89 months in the low TIL ratio group. The difference between OS and TIL ratios was not statistically significant. The median DFS was 138 months in the high TIL ratio group and 49 months in the low TIL ratio group. A statistically significant relationship was found between DFS and TIL ratio (p=0.046) (Graph 1) (Table 2).

In summary, the effect of prognostic factors on survival time was calculated. Here, disease stage, CEA level, TIL ratio, N stage, T stage, and lymphovascular invasion were statistically significant. Early stage (p=0.019), low CEA level (p<0.001), high TIL ratio (p=0.046), low N stage (p=0.004), low T stage (p=0.016), and absence of lymphovascular invasion (p=0.037 and p=0.046) were associated with longer DFS.

Lymphovascular invasion, N stage, CEA levels, and TIL ratio were analyzed using multivariate analysis. According to the results, the HR for the TIL ratio was 1.68 (95% confidence interval (CI): 1.005-2.807; p=0.048), and the HR for the CEA level was 0.49 (95% CI: 0.293-0.846; p=0.01).

Discussion

CRCs are diagnosed at earlier stages with the implementation of screening programs. In addition to the classical TNM staging, CRC is classified into high- and low-risk groups for treatment decision-making, treatment protocol, and duration. This risk grouping is based on prognostic markers such as lymphovascular invasion, lymph node status, differentiation status, MSI status, obstruction/perforation, and positive surgical margin.[6]

In current oncology, tumor immunity, the immune response of the organism, and the behavior pattern of the tumor are still part of the process in terms of both treatment and prognosis. Indeed, studies have shown that peritumoral lymphocytic reaction against CRC and TIL ratio are associated with prolonged survival in patients. This may be an indicator of the host's immune response. However, no consensus has been reached in the literature on the prognostic evaluation of the TIL ratio, and it has not yet been included in the guidelines. The reasons for this may be the lack of a sufficient number of studies, different levels of TIL ratio in the studies, and different localizations of TIL ratio in pathological evaluation.[7] When we reviewed the literature, Pagès et al.[8] suggested that the infiltrative growth pattern at the invasive tumor border was a significant independent prognostic factor for patients with CRC. Fuchs et al.[9] compared peritumoral lymphocyte infiltration with intraepithelial lymphocyte infiltration and showed that peritumoral infiltration was superior in survival analysis. The authors used the International Tumor Infiltrating Lymphocytes Working Group system for investigations involving CRC. Based on these studies, the current study examined TIL ratio levels at the tumor invasive margin.

In many types of cancer, intra- and extra-tumoral lymphocytic infiltration is the organism's response to newly emerging

Table 1. The relationship between TIL ratio and other prognostic factors

			TIL ratio						
	Total (n=248)		**Low (<10%) TIL ratio (n=88)**		**High (>10%) TIL ratio (n=160)**			
		n	%	n	%	n	%	p-value	1-β
Sex	Men	138	55.6%	50	56.8%	88	55.0%	NS	
	Women	110	44.4%	38	43.2%	72	45.0%		
Diagnosis age	<65	125	50.4%	49	36.2%	76	60.8%	NS	
	>65	123	49.6%	39	31.7%	84	68.3%		
ECOG performance scale	0	172	69.4%	68	77.3%	104	65.0%	0.045	0.55
	1	76	30.6%	20	22.7%	56	35.0%		
Stage	S1	26	10.5%	5	5.7%	21	13.1%	NS	
	S2	111	44.8%	43	48.9%	68	42.5%		
	S3	111	44.8%	40	45.5%	71	44.4%		
	S4	0	0.0%	0	0.0%	0	0.0%		
Histopathology	Non-mucinous	198	79.8%	68	77.3%	130	81.3%	NS	
	Mucinous	50	20.2%	20	22.7%	30	18.8%		
Grade	1	37	14.9%	10	11.4%	27	16.9%	NS	
	2	206	83.1%	75	85.2%	131	81.9%		
	3	5	2.0%	3	3.4%	2	1.3%		
Location	Right colon	81	32.7%	29	33.0%	52	32.5%	NS	
	Left colon	91	36.7%	34	38.6%	57	35.6%		
	Rectum	76	30.6%	25	28.4%	51	31.9%		
Lymphatic invasion	Absent	163	70.20%	63	38.6%	100	61.3%	NS	
	Yes	69	29.70%	25	36.2%	44	63.7%		
Vascular invasion	Absent	196	84.40%	75	38.2%	121	61.7%	NS	
	Yes	36	15.50%	13	36.1%	23	63.8%		
MSI status	MSI-stable	151	86.8%	55	88.7%	96	85.7%	NS	
	MSI-high	23	13.2%	7	11.3%	16	14.3%		
CEA levels	C0 (<5 mg/dL)	166	66.9%	56	63.6%	110	68.8%	NS	
	C1 (>5 mg/dL)	82	33.1%	32	36.4%	50	31.3%		
Neoadjuvant chemotherapy	No	147	80.3%	49	79.0%	100	82.6%	NS	
	Yes	36	19.7%	13	21.0%	21	17.4%		
Operated primary tumor	No	16	6.5%	5	5.7%	11	6.9%	NS	
	Yes	232	93.5%	83	94.3%	149	93.1%		
Adjuvant radiotherapy	No	211	92.1%	49	79.0%	98	81.0%		
	Yes	18	7.9%	13	21.0%	23	19.0%		
Adjuvant chemotherapy	No	107	43.1%	8	10.0%	10	6.7%		
	Yes	141	56.9%	0	0.0%	0	0.0%		
Adjuvant chemotherapy type	Capecitabine plus oxaliplatin	99	70.2%	42	75.0%	57	67.1%		

Table 1. Continued

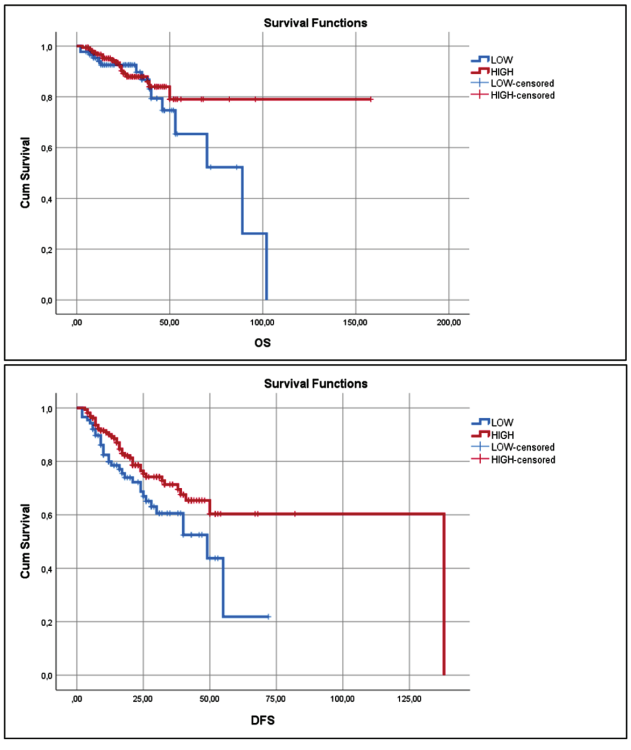
		TIL ratio							
	Total (n=248)		Low (<10%) TIL ratio (n=88)		High (>10%) TIL ratio (n=160)				
	5-fu, folinic acid plus oxaliplatin	9	6.4%	4	7.1%	5	5.9%		
	Capecitabine, 5-fu, folinic acid plus oxaliplatin	1	0.7%	1	1.8%	0	0.0%		
	Capecitabine only	27	19.1%	6	10.7%	21	24.7%	0.039	0.59
	Other	5	3.5%	3	5.4%	2	2.4%		
Mutation type	KRAS positive	16	51.6%	9	52.9%	7	50.0%	NS	
	NRAS positive	2	6.5%	1	5.9%	1	7.1%		
	Wild	13	41.9%	7	41.2%	6	42.9%		

TIL: Tumor-infiltrating lymphocyte, NS: Not significant, ECOG: Eastern Cooperative Oncology Group, MSI: Microsatellite instability, CEA: Carcinoembryonic antigen, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma RAS Viral Oncogene Homolog

Table 2. TIL ratio and survival time

TIL	Number of patients	Number of patients who progressed (percentage)	p-value=0.046	OS median (months)	DFS median (months)
Low	88	32 (36.3%)		89	49
High	160	42 (26%)		Not reached	138

DFS: Disease-free survival, OS: Overall survival



Graph 1. Survival graph of TIL ratio (left to right: OS and DFS)
DFS: Disease-free survival, OS: Overall survival, TIL: Tumor-infiltrating lymphocyte

neoplastic formations. This plays an essential immunological role in tumor regression, and is, therefore, extremely important. Previous literature elaborated that significant lymphocytic infiltration in CRCs was associated with increased survival. Rubio et al.[10] found intense lymphocytic infiltration to be an excellent prognostic indicator in their study of 277 cases of anal squamous cell carcinomas. Similarly, according to Schumacher et al.[11], the presence of lymphocytes positively affects the prognosis in esophageal carcinomas. The opposite is also possible. Scott et al.[12] showed that systemic inflammatory effects in 106 cases of inoperable non-small cell lung tumors reduced the patients' quality of life and negatively affected the prognosis. McArdle et al.[13] emphasized that lymphocytes are a poor prognostic indicator in prostate cancers, as did Curiel et al.[14], albeit in a different tumor type, ovarian cancer.

In the present study, the patients' median DFS was 55 months, and their OS was 102 months. The 3-year DFS rate was 74.2%, and the 5-year DFS rate was 70.6%. In the MOSAIC study, the 5-year DFS rates were 73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups, respectively, with a median follow-up of 37.9 months.[15] The median follow-up period in the NSABP C-07 study was 42.5 months. The 3-year DFS rates were 71.8% in

the FULV arm and 73.2% in the FLOX group.[16] The DFS rates in the present study were comparable with those of previous data.

In this study, prognostic factors such as stage, lymph node metastasis, lymph node invasion, vascular invasion, and CEA level significantly affected DFS. Despite evidence supporting the prognostic value of the TIL ratio, this indicator has not been widely adopted due to previous controversial results. Ogino et al.[17] found that the TIL ratio was less significantly associated with patient survival than the other three components for Crohn-like reaction, peritumoral reaction, intratumoral peri glandular reaction, and lymphocytic reaction score using TIL ratio. On the other hand, Klintrup et al.[18] found a significant association between invasive borderline low-grade inflammatory infiltration and poor survival in a study of 386 patients undergoing surgery for CRC. Roxburgh et al.[19] reported that the degree of TIL ratio was independently associated with cancer-specific survival in patients undergoing curative resection for CRC.

The results of the Cox regression analysis conducted by Huh et al.[20] confirmed that low TIL ratio grade was an independent predictor of poor OS in patients with CRC. Prall et al.[21] showed that patients with stage-III CRC with high tumor density CD8 cells showed significant survival compared with those with low tumor density. In the present study, TIL ratio was examined in two categories, and progression was seen in 42 of 160 patients in the high TIL ratio group, with a TIL ratio of >10%. In contrast, progression was seen in 32 of 88 patients in the low TIL ratio group. This was statistically significant in the DFS curves (p=0.046). The median time to progression was 138 months for the high TIL ratio group and 49 months for the low TIL ratio group. Furthermore, 17% of patients in the low TIL ratio group and 10.6% in the high TIL ratio group died. In terms of OS, the median time was not reached in the high TIL ratio group, whereas it was 89 months in the low TIL ratio group. While the high TIL ratio group was associated with better survival in the OS analysis, it was not statistically significant. Few patients with death, differences in treatment regimens, and follow-up duration may be why the difference found in DFS could not be demonstrated in the case of OS.

Based on multivariate analysis, lymphovascular invasion, lymph node stage, CEA level, and TIL ratio were analyzed in terms of DFS. Here, CEA level and TIL ratio reached statistical significance regarding DFS. The HR for TIL ratio was 1.68 (95% CI: 1.005-2.807), with a risk reduction of 32% (p=0.048). The HR for CEA level was 0.498 (95% CI: 0.293-0.846; p=0.01). Statistical significance was not achieved in the other parameters. The lack of significance in multivariate analysis for parameters found to be significant in univariate analysis may be because of the poor prognostic effect or due to the low number of patients.

In this study, the prognostic effect of lymphocyte infiltration was statistically significant in DFS analysis (p=0.046). Its effectiveness in terms of survival could not be demonstrated due to the extended follow-up period required. We believe that lymphocyte infiltration around the tumor has a prognostic feature in CRCs. Immune response to tumors is effective in controlling the disease in CRC, the treatment options of which are mostly limited to chemotherapy. The present study found a 32% reduction in the risk of recurrence and relapse in the group with a high TIL ratio. Enhancing the immune response with immunotherapy treatments may have promising effects in adjuvant and metastatic diseases.

Study Limitations

The main limitation of this research is its relatively small sample size. Additionally, some of the patient files could not be obtained due to the study's retrospective nature.

Conclusion

Regarding the outcomes of this research, the TIL ratio was found to be an effective indicator of DFS, confirmed via multivariate analysis as presenting a 32% reduction in the risk of recurrence-relapse. The TIL ratio was identified as a prognostic factor beyond the effects of stage, grade, lymphovascular invasion, CEA level, and MSI status. The current data provides substantial evidence to support the ratio's consideration in staging guidelines.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee approval was granted (approval number: 2020/0216, date: 29.04.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., S.A.E., Ö.D., Concept: İ.S.O., M.G., Design: İ.S.O., S.A.E., M.G., Data Collection or Processing: İ.S.O., A.T., Analysis or Interpretation: İ.S.O., Ö.D., M.G., Literature Search: İ.S.O., A.T., Writing: İ.S.O., S.A.E.

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