EXPERIMENTAL ONCOLOGY

https://doi.org/10.15407/exp-oncology.2024.01.045

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PROGNOSTIC VALUE OF THE DENSITY OF TUMOR-INFILTRATING LYMPHOCYTES AND ITS ASSOCIATION WITH CLINICAL-MORPHOLOGICAL FEATURES OF COLON ADENOCARCINOMAS

Aim. To study the prognostic value of the density of tumor-infiltrating lymphocytes (TILs) and its association with other clinical-morphological parameters in colon adenocarcinomas (CAC). **Materials and Methods**. 236 CAC samples were examined. TILs density was estimated as the percentage of tumor stromal area occupied by TILs. By the index of TILs density, the patients were divided into 3 groups: TILs 0—9% (n = 88); TILs 10—39% (n = 106); TILs > 40% (n = 42). Dependent on this index, their overall survival (OS) was analyzed. **Results**. Kaplan — Meier curves revealed a significant ($p < 0.001$) difference in the OS for patients with different TILs infiltration intensities. Multivariate Cox's proportional hazard regression model analysis has confirmed that patients with moderate TILs density (HR 0.57, 95% CI 0.34—0.96, $p = 0.035$) had better OS rates compared to low TILs density. TILs were associated with the stage ($p < 0.001$), lymph node metastasis pN ($p < 0.001$), distant metastasis M ($p < 0.001$), and the patient's outcome ($p < 0.001$). **Conclusion**. TILs can be considered an additional prognostic tool during regular histological examination and are strongly associated with the most significant clinical-morphological features of CAC.

Keywords: tumor-infiltrating lymphocytes, colon cancer, overall survival, prognosis, adenocarcinoma.

Colorectal cancer (CRC) is a burden on the health care system, being the second leading cause of cancer-related death and causing a steady increase in the annual incidence of cancer [1, 2]. Such an increase is closely related to the "western lifestyle". The greatest increase in morbidity and mortality is observed in low- and middle-income countries. In well-developed countries, the stabilization and reduction of morbidity and mortality trends are noted, in strict correlation with the available preventive measures [3]. Enhancement of diagnostic procedures and tumor features assessment can improve overall patient outcomes, so the search for additional prognostic instruments is still actual [4—6].

Most mutations that occur in sporadic CTC usually follow the DNA mismatch repair pathway (MMR) [7]. FDA has approved Nivolumab with low-dose ipilimumab as a first-line immunotherapy for MSI-high/MMR-deficient metastatic CRC [8].

Citation: Shkurupii B, Zakhartseva L. Prognostic value of the density of tumor-infiltrating lymphocytes and its association with clinical-morphological features of colon adenocarcinomas. *Exp Oncol.* 2024; 46(1): 45-52. https://doi.org/10.15407/exp-oncology.2024.01.045

Despite the clinical decision-making value of the MMR status, there are still gaps in prognostication for CRC patient outcomes. Tumor-infiltrating lymphocytes (TILs) can be utilized as an additional strong prognostic factor for treatment response and overall survival (OS) of CRC patients [9, 10]. TILs can be easily calculated during the regular diagnosis assessment by pathologists. The methodology of TILs count does not require any additional cost as it is done on regular hematoxylin-eosin (H&E) slides.

Materials and Methods

236 formalin fixed paraffin embedded tumor samples from colon adenocarcinoma (CAC) resections were used for this study.

The study was approved by the Commission on Bioethical Expertise (expert conclusion No. 118 from 18.01.2019).

The tumor histological type and grade were accessed based on the 5th edition of the WHO classification of tumors of digestive system 2019 [11]. For scoring the tumor to stroma ratio (TSR), we used the recommendations proposed by Pelt et al. [12].

The calculation of TILs density was based on the recommendations of the International Working Group on TILs evaluation in breast cancer [13]. Only lymphocytes that are situated in tumor stroma must be considered part of TILs. The calculation should not include granulocytes. The TILs density is considered as a percentage of lymphocytes compared to the amount of stroma component. For the following statistical calculations, patients were divided into 3 groups dependent on the TILs density: group A, TILs 0—9%; group B, TILs 10—39%; and group C, TILs 40—100%.

All samples were examined by two independent pathologists to determine the level of agreement in TILs evaluation. Both pathologists were provided with the same recommendations described above and were blinded to any patient`s clinical data.

For statistical analysis, we used an EZR 1.35 software package (R statistical software version 3.4.3. R Foundation for Statistical Computing, Vienna, Austria) [14]. The Kaplan — Meier method with a log-rank test was used to analyze survival data. OS rates were calculated by the univariate and multivariate Cox's proportional hazard regression models. The chi-square test was used for estimation of association between significant prognostic factors. To determine the consistency between pathologists, the Kappa Cohen coefficient (k) was used. $k < 0.20$ was considered as a poor level of agreement; $k = 0.21$—0.41 – fair; $k = 0.41$—0.61 – moderate; $k = 0.61$—0.81 – high; and $k > 0.81$ – almost perfect. p-values less than 0.05 were considered significant.

Results

We analyzed 236 cases of CAC. The mean overall survival (OS) period was 3.2 years (range 0.08—7.3 years). The main clinical and pathological characteristics of the CAC cases are presented in Table 1.

Based on the percentage of lymphocytic infiltrate, all the CAC samples were divided into the following groups: group A — no lymphocytic infiltration or a small number of TILs, n = 88; group B — with a moderate number of TILs, n = 106; and group C — with a high lymphocytic infiltration, n = 42 (Figs. 1—3).

The one-year OS in patients with CAC was 87.2 ± 2.1%; 2-year OS was 78.2 ± 2.6%; 3-year OS was 72.0 ± 2.9%, and in group A these indices were 79.3 ± 4.3%; 66.6 ± 5.0%; and 58.0 ± ± 5.3%, respectively; in group B — 89.6 ± 2.9%; 84.9 ± 3.4%; and 78.5 ± 4.0%, respectively; and in group C 1-year OS and 2-year OS were 90.5 ± ± 4.5% and 85.6 ± 5.4%, respectively.

The Kaplan — Meier curves showed that the differences in OS between groups A, B, and C were statistically significant ($p < 0.001$ by log-rank test) (Fig. 4).

Using univariant Cox's proportional hazard regression model, we showed that OS rates in the group A were significantly lower compared to groups B and C ($p = 0.001$ and 0.001, respectively) (Table 2). Also, the tumor stage ($p < 0.001$), presence of metastases in lymph nodes pN ($p < 0.001$), presence of distant metastases M ($p < 0.001$), and tumor stroma TSR ($p < 0.001$) showed a statistically significant influence on OS (Table 2).

However, multivariate Cox's proportional hazard regression model analysis using Akaike's Information Criterion (AIC) for stepwise selection of the most significant prognostic features revealed that TILs density ($p = 0.039$), TSR ($p = 0.019$), and the presence of metastases in lymph nodes pN ($p < 0.001$) have the greatest impact on the OS of CAC patients (Table 3).

Table 1. **The main clinical-pathological characteristics of the CAC cases**

Parameter	Number of patients	
	n = 236	%
Age		
≤40	5	1.7
>40 < 60	59	25.0
≥60	173	73.3
Stage		
I	11	4.7
II	107	45.3
III	65	27.5
IV	53	22.5
Histological type		
Adenocarcinoma	205	86.9
Adenocarcinoma mucinous	11	4.6
Adenocarcinoma mucous producing	17	7.2
Signet ring cell carcinoma of colon	3	1.2
pT (Tumor)		
pT2	15	6.4
pT3	173	73.3
pT4	48	20.3
pN (Lymph nodes)		
pN0	125	53.0
pN1	80	33.9
pN2	31	13.1
pM (Metastasis)		
M0	183	77.5
M1	53	22.5
Differentiation grade		
G1	13	5.5
G2	208	88.1
G3	15	6.4
Necrosis		
Yes	68	28.8
No	168	71.2
Tumor-infiltrating lymphocytes		
Group A	88	37.3
Group B	106	44.9
Group C	42	17.8
Tumor-to-stroma ratio		
Low	142	60.2
High	94	39.8
Tumor budding		
Low budding	202	85.6
Intermediate budding	22	9.3
High budding	12	5.1
Outcome		
Alive	163	69.1
Dead	73	30.9

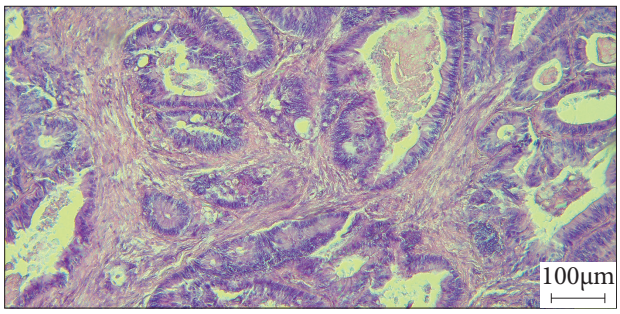

Fig. 1. Adenocarcinoma of the colon, group A, low number of TILs (0—9%). H&E staining, ×100

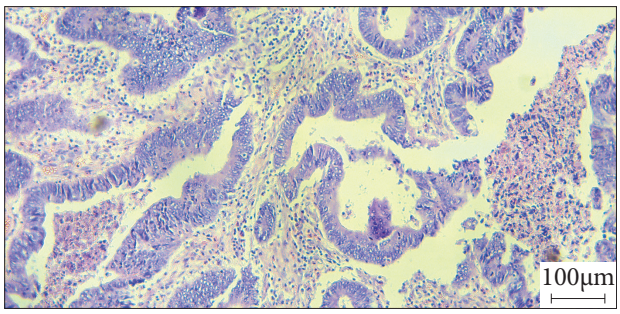

Fig. 2. Adenocarcinoma of the colon, group B, moderate number of TILs (10%—39%). H&E staining, ×100

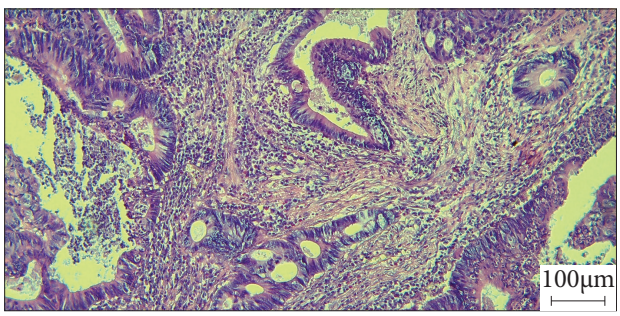

Fig. 3. Adenocarcinoma of the colon, group C, high number of TILs (> 40%). H&E staining, ×100

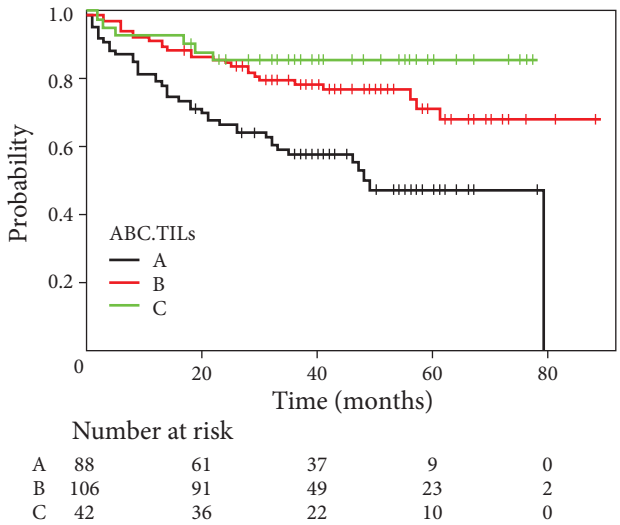

Fig. 4. Kaplan — Meier curve for OS of patients stratified by the TILs density

Table 2. **Univariate Cox regression analysis of factors predicting OS of CAC patients**

Parameter	Overall survival		
	Hazard ratio	Relative risk with 95% confidence interval	*p*
Stage			<0.001
I	Referent		
II	1.15	0.14—8.84	0.893
III	3.24	0.43—24.27	0.250
IV	15.81	2.16—115.7	0.006
pT (Tumor)			0.263
pT2	Referent		
pT3	2.28	0.55—9.36	0.251
pT4	3.02	0.70—13.01	0.136
pN (Lymph nodes)			<0.001
pN0	Referent		
pN1	3.20	1.82—5.61	<0.001
pN2	5.84	3.07—11.10	<0.001
pM (Metastasis)			
M0	Referent		
M1	8.52	5.22—13.91	<0.001
Histological type			0.800
Adenocarcinoma	Referent		
Adenocarcinoma mucinous	0.27	0.03—1.98	0.199
Adenocarcinoma mucous producing	0.78	0.28—2.15	0.639
Signet ring cell carcinoma of colon	1.18	0.16—8.54	0.866
Level of differentiation			0.190
G1	Referent		
G2	1.90	0.46—7.79	0.371
G3	3.51	0.72—16.92	0.117
Necrosis			
Yes	Referent		
No	0.80	0.46—1.39	0.447
TILs density			<0.001
Group A (0—9%)	Referent		
Group B (10—39%)	0.43	0.26—0.71	0.001
Group C (> 40%)	0.25	0.13—0.77	0.001
Tumor-to-stroma ratio			
High	Referent		
Low	0.45	0.28—0.72	<0.001
Tumor budding			0.156
Low budding	Referent		
Intermediate budding	1.07	0.36—3.14	0.898
High budding	0.59	0.23—1.50	0.271

So based on these data, TILs density can be considered an independent prognostic factor.

Based on the analysis of the relationship between clinical-morphological parameters and TILs, we revealed that the TILs density was associated with the stage ($p < 0.001$), presence of lymph node metastases pN ($p < 0.001$), presence of distant metastases M ($p < 0.001$), and the outcome ($p < 0.001$). There was no statistically significant relationship between TILs density and histological tumor type, grade, depth of invasion pT, TSR, presence of necrosis, and tumor budding (Table 4).

Table 3. **Multivariate Cox regression analysis of factors predicting OS of CAC patients**

Parameter	Overall survival		
	Hazard ratio	Relative risk with 95% confidence interval	*p*
TILs density			0.039
Group A (0—9%)	Referent		
Group B (10—39%)	0.57	0.34—0.96	0.035
Group C (>40%)	0.41	0.17—1.01	0.054
Tumor-to-stroma ratio			
High	Referent		
Low	0.56	0.35—0.91	0.019
pN (Lymph nodes)			
pN0	Referent		
pN1	2.65	1.48—4.71	<0.001
pN2	4.26	2.17—8.34	<0.001

The TILs density was equally scored in 199 of 236 cases by both pathologists, and the overall agreement was 86%. The expected frequency of the agreements that would have been expected by chance was calculated by Pearson's Chi-squared test: it was equal to 31.32 for group A (TILs 0—9%); 48.05 for group B (TILs 10%—39%); and 8.02 for group C (TILs > 40%). The Kappa Cohen coefficient (0.75) demonstrated a high level of the agreement between pathologists scoring TILs.

Discussion

Despite the progress in the understanding of CAC development, surgery is a basic treatment option, and the administration of chemotherapy is still majorly based on TNM [15—18].

Nowadays, the tumor microenvironment (TME) is considered one of the keys to the mechanisms of tumor origin, development, progression, and interaction with the host [19]. The major TME compartments are tumor stroma and tumor immune infiltrate, which include tumor-associated macrophages, tumor-associated neutrophils, and TILs [20, 21]. The numerous studies support the prognostic value of TSR for patient's outcome. TSR-rich triple-negative breast carcinomas and colon carcinomas have better overall and disease-free survival. Additionally, statistical data confirm that TSR can be considered an independent prognostic marker for breast cancer [23, 24]. In gall bladder tumors, TSR has also been confirmed to have a prognostic significance but cannot be utilized as an independent tool [24]. TSR did not show any prognostic value in pancreatic ductal adenocarcinoma [25].

Lymphocytes play a leading role in antitumor immune reactions. Several studies specifically showed that B-cells perceive tumor antigens and produce antitumor antibodies assisting T-helper cells in tumor recognition. CD8+ T-cells directly lyse the tumor cells. On the other hand, $CD4^+$ T-cells (Treg) are responsible for tumor immune tolerance by effector T-cell suppression [26, 27]. Naito et al. [28] showed that the higher number of $CD8^+$ T-cells, the better patients' outcomes and suggested to utilize it as a prognostic factor. Also, CD8+ T-cells showed prognostic significance in endometrial and lung cancer [29, 30]. Lymphocyte population distinction with IHC gives more possibilities for precise lymphocyte calculation and allows us to make sure that other immune cells are excluded. However, the procedure requires additional tissue processing, which takes time and increases the cost of diagnostics.

Yet, in the current study we aimed to investigate the potential of TILs detection in general, without division into subpopulations. The advantage of such TILs count is their calculation on regular H&E-stained slides during routine diagnostics without additional expenses.

The TILs density showed its utility as a prognostic tool in triple-negative breast cancer. The high number of TILs is associated with the better OS [31, 32]. The calculation methodology we used had been proposed by the International TILs

Table 4. **Association of TILs density with other clinical-morphological parameters in colorectal adenocarcinomaCAC**

Parameter	Group A (mean age 63.0)		Group B (mean age 65.6)		Group C (mean age 67.8)		*p*
	n	%	n	%	n	%	
Histologic type							
Adenocarcinoma	72	81.8	93	87.7	40	95.2	0.072
Adenocarcinoma mucinous	7	8.0	3	2.8	1	2.4	
Adenocarcinoma mucous producing	8	9.1	8	7.6	1	2.4	
Signet ring cell carcinoma of colon	1	1.1	2	1.9	0	—	
Grade							
1	5	5.7	5	4.7	3	7.1	0.672
2	76	86.3	96	90.6	36	85.8	
3	7	8.0	5	4.7	3	7.1	
Stage							
I	2	2.3	2	1.9	7	16.7	<0.001
II	29	32.9	54	50.9	24	57.1	
III	25	28.4	34	32.1	6	14.3	
IV	32	36.4	16	15.1	5	11.9	
pT							
T2	3	3.4	4	3.8	8	19.1	0.311
T3	68	77.3	81	76.4	24	57.1	
T4	17	19.3	21	19.8	10	23.8	
pN							
N0	35	39.8	56	52.8	34	81.0	<0.001
N1	33	37.5	42	39.6	5	11.9	
N2	20	22.7	8	7.6	3	7.1	
M							
M0	56	63.6	90	84.9	37	88.1	<0.001
M1	32	36.4	16	15.1	5	11.9	
Tumor-to-stroma ratio							
High	43	48.9	36	34.0	15	35.7	0.072
Low	45	51.1	70	66.0	27	64.3	
Necrosis							
Yes	23	26.1	37	34.9	8	19.0	0.727
No	65	73.9	69	65.1	34	81.0	
Tumor budding							
Low	72	81.8	92	86.8	38	90.5	0.370
Intermediate	13	14.8	6	5.6	3	7.1	
High	3	3.4	8	7.6	1	2.4	
Outcome							
Alive	47	53.4	80	75.5	36	85.7	<0.00
Dead	41	46.6	26	24.5	6	14.3	1

Working Group 2014 [13]. A high level of the agreement between pathologists confirms a good reproducibility of the method. In our study, the Kappa coefficient was 0.75. There are other methodologies that confirm the prognostic value of TILs. Dülgar et al. [33] divided tumors due to TILs density into group 0 without lymphocytic infiltrate, group 1+ with low TILs number (<30%), group 2+ (with moderate TILs count (30%—60%), and group 3+ with more than 60% of TILs. The variations of methodologies that can be utilized during the TILs calculations mean that there is a need for standardization. However, the fact that the TILs density shows a prognostic value regardless the calculation method confirms its hidden potential.

Unfortunately, in our research, we had limited data on OS in group C with the highest TILs intensity (just 2-year OS). Our study has several other limitations. It is a retrospective study that included patients treated in 2012—2020. During this period, treatment strategies have varied by treatment protocols, as well as by the number of chemotherapy cycles.

In conclusion, our study has shown a prognostic significance of TILs density for OS in patients with CAC. Due to simplicity, assessment of TILs density can be carried out during regular histological examinations. The association of TILs density with other prognostically significant clinical features testifies in favor of its major importance in CAC progression. The extended studies of TILs can help develop precise treatment strategies for CRC patients.

Funding

The work was performed within scientific research project "Development of Histological and Molecular-Biological Criteria of Differential Diagnosis of Tumors and Precancerous Changes in Organs and Their Prognostic Value" (0119U101131).

Conflict of interest

The authors have no conflict of interests to declare.

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Submitted: December 7, 2023

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ПРОГНОСТИЧНЕ ЗНАЧЕННЯ ПУХЛИНО-ІНФІЛЬТРУЮЧИХ ЛІМФОЦИТІВ ТА ЇХ ЗВ'ЯЗОК З КЛІНІКО-МОРФОЛОГІЧНИМИ ХАРАКТЕРИСТИКАМИ АДЕНОКАРЦИНОМИ ТОВСТОЇ КИШКИ

Мета дослідження: вивчити прогностичне значення пухлино-інфільтруючих лімфоцитів (ПІЛ) та їх зв'язок з клініко-морфологічними параметрами при аденокарциномах товстої кишки. **Матеріали та методи**: для цього дослідження було використано 236 зразків аденокарциноми товстої кишки. ПІЛ оцінювали як відсоток площі строми пухлини, яка була зайнята ПІЛ. За інтенсивністю інфільтрації ПІЛ пацієнтів було розділено на 3 групи: ПІЛ 0—9% (n = 88); ПІЛ 10—39% (n = 106); ПІЛ > 40% (n = 42). **Результати**. На основі кривої виживаності Каплана — Мейєра існує статистично значуща ($p < 0,001$) різниця в загальній виживаності для пацієнтів з різною інтенсивністю ПІЛ. Аналіз моделі пропорційних ризиків Кокса підтверджує, що ПІЛ має статистично значущий вплив на загальну виживаність. Пацієнти з помірним ПІЛ (HR 0,57, 95%; CI 0,34—0,96, p = 0,035) мають кращі загальні показники виживаності порівняно з групою з низьким відсотком ПІЛ. ПІЛ пов'язані зі стадією ($p < 0,001$), метастазами в лімфатичних вузлах pN ($p < 0,001$), віддаленими метастазами M ($p < 0,001$) і виживаністю ($p < 0,001$). **Висновки**. ПІЛ можна розглядати як додатковий прогностичний інструмент під час звичайного гістологічного дослідження. Він має сильний зв'язок із впливовими клініко-морфологічними ознаками.

Ключові слова: пухлино-інфільтруючі лімфоцити, рак товстої кишки, загальна виживаність, прогноз, аденокарцинома.