Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2025; 42(3): 319-323
doi: 10.52142/omujecm.42.3.15

Relationship between TIM-3 expression and clinicopathological parameters in colorectal carcinomas

Gizem TEOMAN*, İsmail SAYGIN, Zeynep TÜRKMEN USTA, Zeynep SAĞANAK YILMAZ

Department of Pathology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Türkiye

Received: 12.06.2026 • **Accepted/Published Online:** 29.08.2025 • **Final Version:** 30.09.2025

Abstract

Colorectal cancer (CRC) is a biologically heterogeneous malignancy, complicating prognostic assessments and therapeutic responses. T cell immunoglobulin and mucin-domain containing-3 (TIM-3) is an immune checkpoint receptor implicated in immune regulation; however, its prognostic significance in CRC remains unclear. A retrospective analysis was performed on 173 colorectal adenocarcinoma cases. TIM-3 expression in tumor-infiltrating immune cells (ICs) was assessed using immunohistochemistry. Associations between TIM-3 expression and clinicopathological parameters such as patient age and sex, tumor site and size, grade, invasion status, mismatch repair (MMR) protein status, and HER2 expression were examined. The impact on overall survival was assessed. High TIM-3 expression was significantly more frequent in females, rectal tumors, high-grade adenocarcinomas, and tumors invading the muscularis propria. In contrast, lower TIM-3 expression correlated with lymphovascular, venous, and perineural invasion. Elevated TIM-3 expression was associated with microsatellite stability (MSS) and HER2 positivity. High TIM-3 expression predicted reduced overall survival. TIM-3 expression in tumor-infiltrating immune cells may serve as a prognostic biomarker in colorectal carcinoma. Its association with distinct pathological features and survival outcomes highlights its potential role in immune modulation and as a therapeutic target in selected CRC patients.

Keywords: Colorectal neoplasms, TIM-3, Tumor-infiltrating lymphocytes, immune checkpoints, microsatellite instability

1. Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide and represents a major contributor to cancer-related illness and death. It holds the position as the third most common cancer globally and ranks second among the leading causes of cancer mortality (1). About 25% of colorectal cancer cases exhibit recurrence, while approximately 20% of patients present with metastatic disease at diagnosis (2). Early-stage colorectal cancer (CRC) is typically managed effectively through surgical resection and subsequent adjuvant chemotherapy; however, treatment alternatives for advanced and metastatic cases are constrained (3). Advanced stages of colorectal cancer are associated with a poor prognosis, with a five-year survival rate of approximately 12% (4). Targeted therapies aimed at the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways have become key components in the management of metastatic disease. However, the development of primary or acquired resistance to these agents highlights the need for new therapeutic approaches. There is an increasing focus on immunotherapy strategies and the significance of immune-based treatments in colorectal cancer (CRC) (5).

Immune checkpoint inhibitors have significantly changed cancer treatment for multiple tumor types. Their application has been associated with improved survival rates in specific patients with advanced or metastatic cancers, resulting in more positive prognostic outcomes (6).

Immune checkpoints comprise stimulatory and inhibitory molecules that modulate the activation of the immune system. Inhibitors that target checkpoints, including programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and T cell immunoglobulin and mucin-domain containing-3 (TIM-3), have become increasingly significant. These molecules are frequently overexpressed in malignant tumors and are typically linked to unfavorable clinical outcomes (7).

TIM-3, a member of the TIM (T cell immunoglobulin and mucin-domain containing) family, was initially discovered on the surface of Th1 and Tc1 cells (8). Later studies revealed its expression in various tumor types, including renal and colorectal carcinomas (9). When present on immune cells, TIM-3 interacts with its ligand, galectin-9, leading to the apoptosis of TIM-3$^+$ Th1 cells and facilitating tumor immune escape (10). Research has underscored the importance of TIM-3 expression in T cells in relation to tumor development (11). In colorectal cancer specifically, TIM-3 has been implicated in promoting cellular proliferation and invasion. Moreover, it is suggested that TIM-3 could serve as an independent prognostic indicator in patients with colorectal cancer (12).

This study aims to assess the immunohistochemical expression of TIM-3 in tumor-infiltrating lymphocytes (TILs) within colorectal carcinoma specimens and to explore its

*Correspondence: dr.gizemcivelek@gmail.com

association with mismatch repair (MMR) protein status, Her2 expression, and other clinicopathological features.

2. Materials and Methods

2.1. Patients' selection

This study included 173 patients who underwent surgical resection for colorectal carcinoma at Karadeniz Technical University, Faculty of Medicine between 2015 and 2019, with histopathological confirmation of adenocarcinoma in the Department of Medical Pathology. Patients who had received preoperative chemotherapy or had a concurrent diagnosis of a second primary malignancy were excluded from the study.

Formalin-fixed, paraffin-embedded (FFPE) tissue samples were reviewed by a pathologist, who selected the most appropriate tissue blocks for analysis. All cases were confirmed as colorectal adenocarcinoma through histological evaluation, and sufficient clinical and pathological data were available for inclusion. Clinical information was retrieved from the hospital's electronic medical records. It included age, gender, tumor size, tumor location, histological grade, lymphovascular invasion, tumor budding, venous invasion, perineural invasion, lymph node metastasis, mismatch repair (MMR) protein expression status, Her2 expression status, and pathological stage.

2.2. Immunohistochemistry

Immunohistochemical (IHC) analysis was conducted on 4-µm-thick sections obtained from formalin-fixed, paraffin-embedded tissue blocks. The slides were deparaffinized using EZ Prep solution (Ventana Medical Systems, Tucson, AZ, USA), followed by antigen retrieval for 60 minutes using the manufacturer's cell conditioning solution. Staining was carried out with the ultraView Universal DAB Detection Kit (Ventana Medical Systems). For the detection of TIM-3 expression, sections were incubated with a primary antibody targeting T cell immunoglobulin and mucin-domain containing-3 (TIM-3; dilution 1:100; Abcam; catalog no: ab185703) at 37 °C for two hours using an automated staining system (Benchmark XT; Ventana Medical Systems).

2.3. Evaluation

TIM-3 expression in tumor-infiltrating immune cells (ICs) was evaluated using a classification system adapted from the criteria of Fehrenbacher et al. This system categorizes staining intensity based on the proportion of the tumor area occupied by TIM-3-positive immune cells as follows: IC3 (≥10%), IC2 (≥5% to <10%), IC1 (≥1% to <5%), and IC0 (<1%) (13).

2.4. Statistical Analysis

The statistical analyses were performed using SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Data analysis was conducted with R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were summarized as frequencies and percentages, while continuous variables were described using means along with their minimum and maximum values. The Kolmogorov-Smirnov test was applied to evaluate whether continuous data followed a normal distribution. For variables with normal distribution, group comparisons were performed using Student's t-test. When the normality assumption was not satisfied, the Mann-Whitney U test was used instead. A p-value below 0.05 was considered indicative of statistical significance.

2.5. Ethical Considerations

This study was conducted retrospectively using archived tissue samples and patient data. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. Ethical approval for the study was obtained from the Ethics Committee of Karadeniz Technical University, Faculty of Medicine (Approval No: 24237859-612; Date: November 14, 2024). Due to the retrospective design of the study and the use of anonymized archival materials, the requirement for informed consent was waived by the ethics committee.

2.6. Survival Analysis

Survival analysis was performed to evaluate overall survival (OS) according to TIM-3 expression status in tumor-infiltrating immune cells. The time from the date of surgery to the date of death or last follow-up was calculated. Patients who were alive at the last follow-up were censored. Median survival times and their 95% confidence intervals (CI) were estimated using the Kaplan-Meier method. Differences in survival distributions between groups were compared using the log-rank test. Additionally, Cox proportional hazards regression models were used to estimate hazard ratios (HR) and corresponding 95% confidence intervals to assess the association between TIM-3 expression and survival outcomes. The proportional hazards assumption was verified prior to the analysis. A p-value less than 0.05 was considered statistically significant.

3. Results

A total of 173 patients diagnosed with colorectal adenocarcinoma at Karadeniz Technical University, Faculty of Medicine between 2015 and 2019 were included in this study. The average age was 63 years (range: 23–91), with a standard deviation of 12.85. Among these patients, 74 (42.7%) were female, and 99 (57.3%) were male.

Immunohistochemical evaluation revealed that TIM-3 expression was primarily localized to immune cells infiltrating the tumor microenvironment. TIM-3 positivity was identified in lymphocyte-like immune cells, appearing on the cell membrane and/or in the cytoplasm (Fig.1), reflecting both their distribution and density within tumor stroma.

Among the 173 cases, 73 (42.2%) showed less than 1% TIM-3 expression in immune cells and were categorized as IC0 (negative expression). Positive TIM-3 staining was found in the remaining 100 cases (57.8%). Within this group, 48 cases (27.7%) were scored as IC1 (1–5%), 28 cases (16.2%) as IC2 (5–10%), and 24 cases (13.9%) as IC3 (>10%) (Fig. 2).

The mean age for patients with IC0 expression was 61.33 years, while it was 64.21 years for those with positive TIM-3 staining (IC1–IC3). This age difference was not statistically significant (p = 0.146).

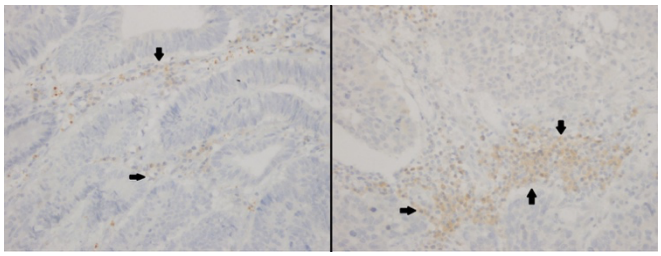

Fig. 1. Immunohistochemical staining of TIM-3 in tumor-infiltrating immune cells (ICs) in colorectal carcinoma. Positive membranous and/or cytoplasmic TIM-3 expression is observed in lymphocyte-like immune cells within the tumor microenvironment (arrows). The staining highlights the distribution and density of TIM-3-positive immune infiltrates in the tumor stroma. (TIM-3 ×200)

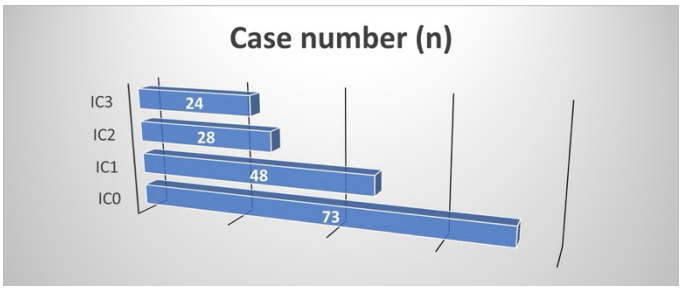

Fig. 2. Distribution of TIM-3 expression levels in tumor-infiltrating immune cells (ICs) in colorectal carcinoma. The bar chart shows the number of cases classified into four categories according to the proportion of the tumor area occupied by TIM-3-positive immune cells: IC3 (≥10%), IC2 (≥5% to <10%), IC1 (≥1% to <5%), and IC0 (<1%). The majority of cases were categorized as IC0, indicating low or absent TIM-3 expression in the immune microenvironment. This distribution highlights the variability in TIM-3-positive immune cell infiltration among the cases

A significant inverse relationship was found between tumor size and TIM-3 positivity. The average tumor diameter in IC0 cases was 5.1 cm, whereas tumors with IC3 scores had a mean diameter of 3.8 cm. This inverse correlation between tumor size and TIM-3 expression was statistically significant (p = 0.025).

Additional clinicopathologic parameters and their association with TIM-3 expression are detailed in Table 1.

In terms of survival, patients in the IC0 group had a mean survival time of 81.9 months (95% CI: 72.6–91.2), while those in the TIM-3-positive group (IC1–IC3) had a mean survival of 74.6 months (95% CI: 67.5–81.8). Although patients with higher TIM-3 expression showed shorter survival, the difference was not statistically significant (p = 0.908). Similarly, survival was not significantly associated with TIM-3 expression in immune cells (HR = 1.12; 95% CI: 0.51–2.47; p = 0.776) (Fig. 3).

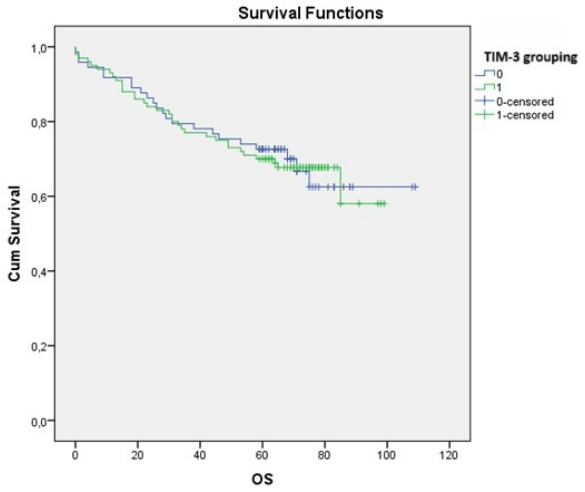

Fig. 3. Kaplan-Meier survival curves depicting overall survival (OS) stratified by TIM-3 expression status in tumor-infiltrating immune cells. Patients were grouped into TIM-3 negative (0; blue line) and TIM-3 positive (1; green line) categories. Censored data points are indicated by vertical ticks along the curves (blue for TIM-3 negative, green for TIM-3 positive). The cumulative survival probability is plotted over time (months). No statistically significant difference in overall survival was observed between the groups

TIM-3, a co-inhibitory receptor, is frequently expressed on T-cell subsets such as CD4+, CD8+, and regulatory T cells in different tumor settings. In this study, we primarily focused on TIM-3 expression in stromal lymphocytes, offering insight into tumor-related immune modulation. We also assessed TIM-3 expression in tumor epithelial cells. Weak focal cytoplasmic positivity in tumor cells was observed in only eight cases; among these, seven showed no corresponding TIM-3 positivity in immune cells (IC0), while just one case showed co-expression.

Table 1. The clinicopathological parameters and the expression status of TIM-3 in immune cells of the cases

		TIM3				
		IC0	IC1	IC2	IC3	p value
Sex	Female	29 (39.2%)	19 (25.7%)	9 (12.2%)	17 (23%)	**0.023**
	Male	44 (44.4%)	29 (29.3%)	19 (19.2%)	7 (7.1%)	
Localization	Rectum	12 (31.6%)	9 (23.7%)	10 (26.3%)	7 (18.4%)	0.677
	Right colon	21 (43.8%)	14 (29.2%)	7 (14.6%)	6 (12.5%)	
	Left colon	38 (46.3%)	23 (28%)	11 (13.4%)	10 (12.2%)	
	Transverse colon	2 (40%)	2 (40%)	0 (0%)	1 (20%)	
Histological type	Adenocarcinoma	67 (41.9%)	43 (26.9%)	27 (16.9%)	23 (14.4%)	0.747
	Mucinous adenocarcinoma	6 (46.2%)	5 (38.5%)	1 (7.7%)	1 (7.7%)	
Histological grade	Grade 1	40 (40.4%)	28 (28.3%)	17 (17.2%)	14 (14.1%)	0.852
	Grade 2	24 (47.1%)	15 (29.4%)	7 (13.7%)	5 (9.8%)	
	Grade 3	9 (39.1%)	5 (21.7%)	4 (17.4%)	5 (21.7%)	
Tumor extent	Submucosa	1 (33.3%)	2 (66.7%)	0 (0%)	0 (0%)	0.156

	Muscularis propria	5 (26.3 %)	3 (15.8%)	5 (26.3%)	6 (31.6%)	
	Pericolonic tissue	56 (42.1%)	39 (29.3%)	22 (16.5%)	16 (12%)	
	Visceral peritoneum	11 (61.1 %)	4 (22.2%)	1 (5.6%)	2 (11.1%)	
Lymphovascular invasion	No	42 (40%)	33 (31.4%)	15 (14.3%)	15 (14.3%)	0.524
	Yes	31 (45.6%)	15 (22.1%)	13 (19.1%)	9 (13.2%)	
Venous invasion	No	64 (40.5%)	45 (28.4%)	25 (15.8%)	23 (14.5%)	0.542
	Yes	9 (56.2%)	3 (18.7%)	3 (18.7%)	1 (6.2%)	
Perineural invasion	No	65 (41.9%)	43 (27.7%)	24 (15.5%)	23 (14.8%)	0.687
	Yes	8 (44.4%)	5 (27.7%)	4 (22.2%)	1 (5.5%)	
Tumoral budding	No	19 (45.2%)	16 (38.1%)	3 (7.1%)	4 (9.5%)	0.121
	Yes	54 (41.2%)	32 (24.4%)	25 (19.1)	20 (15.3%)	
Tumor-infiltrating lymphocytes	No	35 (48.6%)	20 (25.8%)	11 (25.3%)	6 (8.3%)	0.262
	Yes	38 (37.6%)	28 (27.7%)	17 (16.8%)	18 (17.8%)	
Infiltrative border	No	1 (11.1%)	5 (55.6%)	1 (11.1%)	2 (22.2%)	0.095
	Yes	72 (43.9%)	43 (26.2%)	27 (16.5%)	22 (13.4%)	
Metastasis status	No	37 (40.2%)	30 (32.6%)	17 (18.5%)	8 (8.7%)	0.098
	Yes	36 (44.4%)	18 (22.2%)	11 (13.6%)	16 (19.8%)	
Mesenteric tumor nodule	No	60 (43.5%)	39 (28.3%)	23 (16.7%)	16 (11.6%)	0.394
	Yes	13 (37.1%)	9 (25.7%)	5 (14.3%)	8 (22.9%)	
Recurrence status	No	71 (42.8%)	46 (27.7%)	28 (16.9%)	21 (12.7%)	0.141
	Yes	2 (28.6%)	2 (28.6%)	0 (0%)	3 (42.9%)	
MSI status	No	56 (39.2%)	41 (28.7%)	23 (16.1%)	23 (16.1%)	0.171
	Yes	17 (56.7%)	7 (23.3%)	5 (16.7%)	1 (3.3%)	
Her2 status	Negative	72 (42.4%)	46 (27.1%)	28 (16.5%)	24 (14.1%)	0.636
	Positive	1 (33.3%)	2 (66.7%)	0 (0%)	0 (0%)	

4. Discussion

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. Although surgical resection and adjuvant therapy are standard for stage II and III CRC, overall outcomes remain suboptimal (14). Recently, interest in immunotherapy has surged, particularly in inflammation-associated cancers. However, despite the inflammatory nature of CRC, its response to immune checkpoint blockade lags behind other malignancies such as melanoma and lung cancer. This may be due to distinct immune evasion mechanisms and a complex tumor microenvironment. Combination strategies involving immunotherapy, chemotherapy, and targeted agents have shown promise in early trials (15,16).

This study evaluated TIM-3 expression in resected colorectal carcinoma specimens to investigate its association with clinical and pathological characteristics. A statistically significant relationship was observed between TIM-3 positivity and patient sex. No significant correlation was found between TIM-3 expression and features such as tumor location, histologic grade, lymphovascular invasion, or perineural invasion.

Older patients tended to show higher TIM-3 expression, although this difference was not significant. The trend may reflect age-related immune system decline (immunosenescence), which can enhance expression of inhibitory immune checkpoint molecules like TIM-3 (16).

Interestingly, smaller tumors were more frequently associated with high TIM-3 expression in immune cells. Although TIM-3 is commonly linked to immunosuppression, its upregulation in a chronically inflamed tumor microenvironment could reflect an ongoing immune response that constrains tumor growth (17). In larger tumors, TIL density increased, indicating that an intensified inflammatory response may influence TIM-3 expression and tumor progression.

Female patients demonstrated higher TIM-3 positivity. Hormonal influences, particularly estrogen, may underlie this finding, as estrogen is known to modulate immune function and can enhance expression of certain immune markers (18).

Additionally, TIM-3 expression was more common in rectal carcinomas than in colon cancers, consistent with findings by Kuai et al. (19). The rectum's distinct anatomy and immune environment may influence this expression pattern. Factors like local inflammation, microbial flora, and stromal composition could contribute to differences in immune checkpoint profiles (20).

Our results also showed that TIM-3 expression was more frequent in microsatellite stable (MSS) tumors than in MSI-high tumors. Given the strong immunogenicity of MSI-H cancers, which typically rely on the PD-1/PD-L1 axis for immune escape, MSS tumors may instead utilize TIM-3-related mechanisms. This observation warrants further study in larger cohorts.

Moreover, a higher frequency of TIM-3 positivity was noted in HER2-positive tumors. This suggests that HER2-driven signaling might intersect with immune evasion pathways involving TIM-3, though more evidence is needed to substantiate this finding (21).

Survival analysis revealed that patients lacking TIM-3

expression had longer overall survival, though the difference did not reach statistical significance. This trend is in line with previous studies in other tumor types, including gastric and lung cancers, where high TIM-3 levels were linked to poor prognosis (22). The presence of TIM-3 may reflect a state of immune exhaustion within the tumor microenvironment, contributing to ineffective anti-tumor responses and reduced survival.

Collectively, these findings point to TIM-3 as a potential biomarker for prognostication and as a possible target for immunotherapeutic intervention in CRC. However, due to the lack of statistically significant survival outcomes, further research involving larger, prospective cohorts is needed.

This study emphasizes the clinical and immunological relevance of TIM-3 expression in colorectal adenocarcinoma. While statistical significance was limited, several patterns emerged higher TIM-3 expression in older individuals, female patients, rectal tumors, HER2-positive, and MSS subtypes suggesting TIM-3's role in shaping the immune landscape of CRC. Furthermore, the trend toward reduced survival in TIM-3-positive cases highlights its potential utility as a prognostic marker. These findings support the continued exploration of TIM-3 in large-scale studies and its consideration as a therapeutic target in CRC immunotherapy strategies.

Conflict of interest

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Acknowledgments

None to declare.

Authors' contributions

Concept: G.T., Design: G.T., Data Collection or Processing: G.T., İ.S., Z.T.U., Z.S.Y., Analysis or Interpretation: G.T., Z.T.U., Z.S.Y., Literature Search: G.T., İ.S., Writing: G.T.

Ethical Statement

Approval was obtained from Karadeniz Technical University Scientific Research Ethics Committee, the study started. The ethics committee decision date is 14/11/2024 and the number of ethical committee decisions is 24237859-612.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.
2. Ogunwobi OO, Mahmood F, Akingboye A. Biomarkers in colorectal cancer: current research and future prospects. Int J Mol Sci. 2020;21(15).
3. Tørring ML, Falborg AZ, Jensen H, et al. Advanced-stage cancer and time to diagnosis: an International Cancer Benchmarking Partnership (ICBP) cross-sectional study. Eur J Cancer Care (Engl). 2019;28(5):e13100.
4. Messersmith WA. NCCN guidelines updates: management of metastatic colorectal cancer. J Natl Compr Canc Netw. 2019;17(5.5):599-601.
5. Arora SP, Mahalingam D. Immunotherapy in colorectal cancer: for the select few or all? J Gastrointest Oncol. 2018;9(1):170-179.
6. Gupta AK, Melton LJ 3rd, Petersen GM, et al. Changing trends in the incidence, stage, survival, and screen-detection of colorectal cancer: a population-based study. Clin Gastroenterol Hepatol. 2005;3(2):150-158.
7. He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. Cell Res. 2020;30(8):660-669.
8. Joller N, Kuchroo VK. Tim-3, Lag-3, and TIGIT. Curr Top Microbiol Immunol. 2017;410:127-156.
9. Zhang P, Wang Y, Liu XR, et al. Downregulated Tim-3 expression is responsible for the incidence and development of colorectal cancer. Oncol Lett. 2018;16(1):1059-1066.
10. Huang X, Bai X, Cao Y, et al. Lymphoma endothelium preferentially expresses Tim-3 and facilitates the progression of lymphoma by mediating immune evasion. J Exp Med. 2010;207(3):505-520.
11. Zhou E, Huang Q, Wang J, et al. Up-regulation of Tim-3 is associated with poor prognosis of patients with colon cancer. Int J Clin Exp Pathol. 2015;8(7):8018-8027.
12. Yu M, Lu B, Liu Y, et al. Tim-3 is upregulated in human colorectal carcinoma and associated with tumor progression. Mol Med Rep. 2017;15(2):689-695.
13. Wuerdemann N, Pütz K, Eckel H, et al. LAG-3, TIM-3 and VISTA expression on tumor-infiltrating lymphocytes in oropharyngeal squamous cell carcinoma—potential biomarkers for targeted therapy concepts. Int J Mol Sci. 2020;22(1).
14. Smolle MA, Pichler M, Haybaeck J, Gerger A. Genetic markers of recurrence in colorectal cancer. Pharmacogenomics. 2015;16(11):1315-1328.
15. Ngiow SF, Teng MW, Smyth MJ. Prospects for TIM3-targeted antitumor immunotherapy. Cancer Res. 2011;71(21):6567-6571.
16. Kong X, Zhang J, Chen S, et al. Immune checkpoint inhibitors: breakthroughs in cancer treatment. Cancer Biol Med. 2024;21(6):451-472.
17. Sasidharan Nair V, Toor SM, Taha RZ, et al. Transcriptomic profiling of tumor-infiltrating CD4(+)TIM-3(+) T cells reveals their suppressive, exhausted, and metastatic characteristics in colorectal cancer patients. Vaccines (Basel). 2020;8(1).
18. Collins MK, McCutcheon CR, Petroff MG. Impact of estrogen and progesterone on immune cells and host-pathogen interactions in the lower female reproductive tract. J Immunol. 2022;209(8):1437-1449.
19. Kuai W, Xu X, Yan J, et al. Prognostic impact of PD-1 and Tim-3 expression in tumor tissue in stage I-III colorectal cancer. Biomed Res Int. 2020;2020:5294043.
20. Pérez-Ruiz E, Berraondo P. Immunological landscape and clinical management of rectal cancer. Front Immunol. 2016;7:61.
21. Czajka-Francuz P, Prendes MJ, Mankan A, et al. Mechanisms of immune modulation in the tumor microenvironment and implications for targeted therapy. Front Oncol. 2023;13: [makale no].
22. Qin S, Dong B, Yi M, et al. Prognostic values of TIM-3 expression in patients with solid tumors: a meta-analysis and database evaluation. Front Oncol. 2020;10:1288.