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Original Article

Clinical and Prognostic Value of TIMP1 in Colorectal Cancer

Hyeok-Jun Moon[1,†], Yujoon Cha[1,†], Jae-Ho Lee[2], Junchae Lee[1]

[1]*Medical Course, School of Medicine, Keimyung University*
[2]*Department of Anatomy, Schoolof Medicine & Institute for Medical Science, Keimyung University*

Abstract : Tissue inhibitor of metalloproteinases 1 (TIMP1) is a multifunctional molecule that acts as the primary endogenous inhibitors of metalloproteinases (MPs). The imbalance between MMPs and TIMPs can lead to various cancers. We aim to prove the clinical and prognostic value of TIMP1 gene in colorectal cancer (CRC). TIMP1 mRNA expression was examined in various cancer types. We further evaluated survival to determine the prognostic significance of TIMP1 mRNA in CRC using The Cancer Genome Atlas (TCGA) data. The patients were divided into two subgroups, based on the TIMP1 gene expression levels to assess the clinical characteristics associated with TIMP1 expression. In rectal cancer, higher TIMP1 expression was linked to venous invasion, and there was also a correlated with histological type, location, and MSI types in colon cancer. Survival analysis showed that higher TIMP1 group was statistically associated with poorer prognosis. Our findings suggest that elevated TIMP1 mRNA expression is significantly associated with aggressive clinicopathological features and poor prognosis in CRC. TIMP1 may serve as a potential biomarker for risk stratification and a therapeutic target in CRC management.

Keywords : TIMP1, Colorectal cancer, Colon cancer, Rectal cancer, TCGA

INTRODUCTION

Colorectal cancer (CRC) is the fourth leading cause of cancer-related deaths worldwide, accounting for approximately 9.2% of all cancer deaths [1,2]. It ranks as the second most common cancer among women and the third among men. In 2020 alone, CRC was responsible for 9.4% of global cancer-related mortality [2]. Both genetic and environmental factors contribute to the development of CRC [3]. Approximately 70~80% of CRC cases are sporadic, while 20~30% have a hereditary component, often due to rare, high-risk susceptibility syndromes such as Lynch syndrome (3~4%) and familial adenomatous polyposis (around 1%) [4]. A hallmark of CRC is genetic instability, which arises through at least two distinct molecular mechanisms [5]. The adenoma-carcinoma sequence, representing the most common pathway in CRC development, involves the accumulation of mutations in key genes including APC, K-ras, and p53 [6]. Despite extensive global research on the molecular pathogenesis of CRC, further investigation is needed to identify novel biomarkers and therapeutic targets.

Tissue inhibitor of metalloproteinases 1 (TIMP1) is a multifunctional regulator that modulates extracellular matrix homeostasis primarily by inhibiting matrix metalloprotein-

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Correspondence to: Junchae Lee (Medical Course, School of Medicine, Keimyung University, Daegu 42601, Republic of Korea)
E-mail: chai1703@naver.com

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ases (MMPs), which degrade collagen, elastin, and other matrix components [7]. Beyond its canonical inhibitory role, TIMP1 interacts with various molecular partners and exerts cytokine-like activity, contributing to processes such as cell cycle control, differentiation, angiogenesis, and resistance to apoptosis [8,9]. Elevated circulating or tissue levels of TIMP1 have been consistently reported in multiple inflammatory and malignant conditions and are frequently linked to unfavorable clinical outcomes [10-14]. In particular, TIMP1 overexpression has been identified as a poor prognostic indicator in several cancers, including breast [15,16], prostate [17], and gastric cancer [18]. However, despite its biological relevance, the clinical and prognostic implications of TIMP1 in colorectal cancer remain insufficiently characterized.

Therefore, in this study, we aim to investigate the clinical and prognostic implications of TIMP1 gene expression in CRC, utilizing data from The Cancer Genome Atlas (TCGA). We also explore its correlation with other gene expression profiles to better understand its role in CRC progression.

MATERIALS AND METHODS

1. TCGA data analysis

We utilized primary data from The Cancer Genome Atlas (TCGA) portal (http://cancergenome.nih.gov/) in February 2025. The data provided *p*-value rankings for the prognostic significance of TIMP1 expression across various cancer types (Fig. 1). Among these, rectal and colon cancers showed the most significant associations and were therefore selected for detailed analysis. A total of 440 colon cancer patients and 158 rectal cancer patients were included for clinical and survival analyses.

2. Statistical analysis

Data were analyzed using SPSS software (version 25.0; IBM SPSS, Armonk, NY, USA). Tumor staging was determined according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system. Clinicopathological characteristics—including age, sex, carcinoembryonic antigen (CEA) level, and pathological TNM stage—were analyzed using the chi-square test. Spearman's correlation coefficient was used to assess correlations between TIMP1 expression and clinical variables in rectal cancer. Univariate survival analysis was conducted using Kaplan-Meier survival curves and the log-rank test. Overall survival was defined as the time from diagnosis to death. A *p*-value of <0.05 was considered statistically significant.

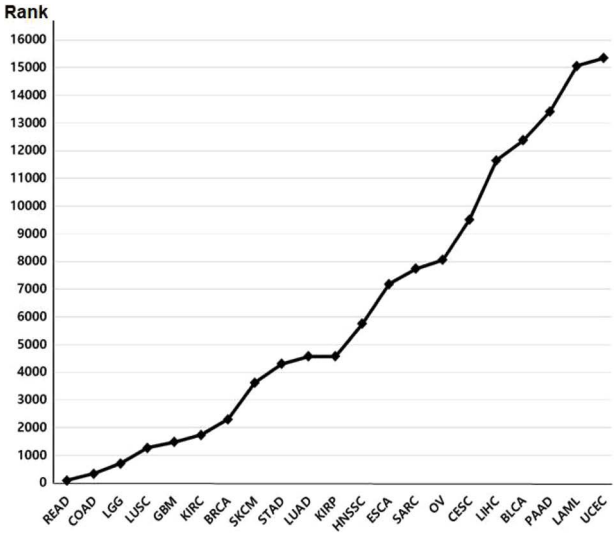

Fig. 1. The rank of survival value of TIMP1 in various cancers.

RESULTS

1. TIMP1 expression in The Cancer Genome Atlas (TCGA) data

To evaluate the clinical significance of TIMP1 expression, rectal and colon patients were divided into two subgroups based on the median value of TIMP1 expression (Tables 1 and 2). In rectal cancer, higher TIMP1 expression was significantly associated with venous invasion ($p=0.033$). However, no statistically significant associations were observed between TIMP1 expression and other clinical characteristics. In colon cancer, higher TIMP1 expression was significantly associated with histological type ($p<0.001$), tumor location ($p<0.001$), and microsatellite instability (MSI) status ($p<0.001$). Although not statistically significant, a trend toward an association with venous invasion was also observed ($p=0.089$).

An overall survival analysis was performed to determine the prognostic value of TIMP1 in colon cancer (Fig. 2A) and rectal cancer (Fig. 2B). TIMP1 expression had statistically significant prognostic value (2372.04±233.98 vs

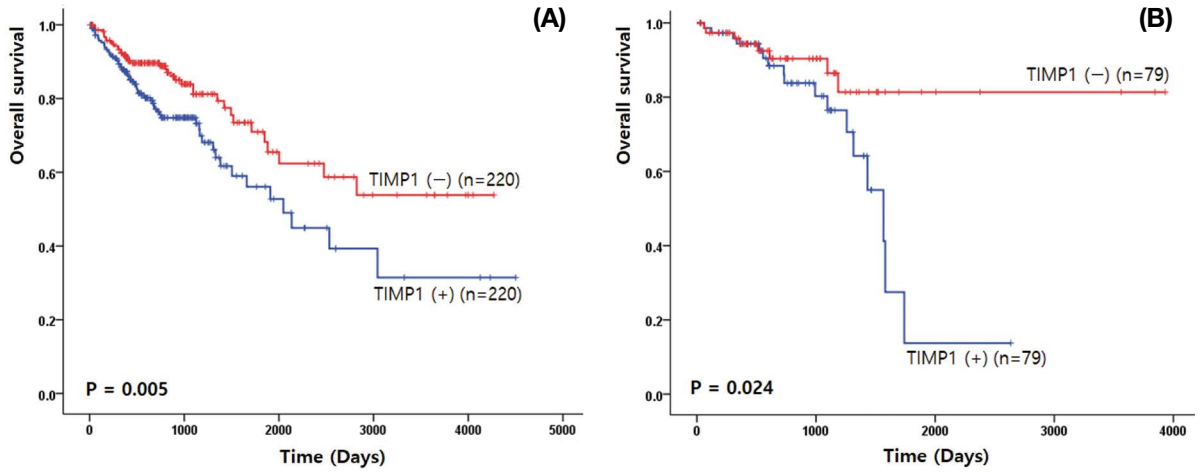

Fig. 2. Overall survival analysis in colon cancer (A) and rectal cancer (B).

2950.82 ± 193.25 days, $\chi^2 = 7.9$ $p = 0.005$) in colon cancer. Additionally, it is statistically significant (1479.71 ± 150.31 vs 3337.07 ± 210.77 days, $\chi^2 = 5.08$, $p = 0.024$) in rectal cancer.

DISCUSSION

In this study, we investigated the clinical and prognostic significance of TIMP1 expression in colorectal cancer (CRC) using TCGA data. Our findings demonstrate, for the first time, that elevated TIMP1 expression is significantly associated with adverse pathological features and reduced overall survival in both colon and rectal cancers. These results support emerging evidence that TIMP1 functions not merely as an endogenous inhibitor of metalloproteinases, but as an active participant in tumor progression and metastasis.

Tissue inhibitors of metalloproteinases (TIMPs) comprise a family of four matrisome proteins and represent the primary endogenous regulators of matrix metalloproteinases (MMPs) [19]. By inhibiting MMPs and members of the ADAM family, TIMPs contribute to extracellular matrix (ECM) homeostasis while also exerting broader effects on cell signaling pathways implicated in cancer, inflammation, and degenerative diseases [20]. The balance between MMPs and TIMPs is essential for maintaining ECM integrity; disruption of this balance can promote pathological remodeling and oncogenesis [22]. Notably, MMPs and ADAMs are key regulators in a range of solid tumors, including breast, lung, prostate, and colorectal cancers [22].

Table 1. Clinical characteristics of TIMP1 expression in rectal cancer

	TIMP1		
	High (N, %)	Low (N, %)	*p*-value
Age			
<65	34 (45.3)	41 (54.7)	0.232
≥65	45 (54.9)	37 (45.1)	
Gender			
Female	36 (51.4)	34 (48.6)	0.803
Male	43 (49.4)	44 (50.6)	
Lymphatic invasion			
No	41 (49.4)	42 (50.6)	0.490
Yes	31 (55.4)	25 (44.6)	
CEA			
≤5	29 (46.8)	33 (53.2)	0.893
>5	20 (45.5)	24 (54.5)	
Venous invasion			
No	48 (46.6)	55 (53.4)	0.033
Yes	23 (67.6)	11 (32.4)	
Pathologic stage			
Stage I	10 (34.5)	19 (65.5)	0.256
Stage II	26 (55.3)	21 (44.7)	
Stage III	27 (56.25)	21 (43.75)	
Stage IV	12 (50)	12 (50)	
M stage			
M0	61 (51.7)	57 (48.3)	0.734
M1	11 (47.8)	12 (52.2)	
N stage			
N0	37 (46.8)	42 (53.2)	0.283
N1	20 (46.5)	23 (53.5)	
N2	20 (62.5)	12 (37.5)	
T stage			
T1	3 (33.3)	6 (66.7)	0.415
T2	11 (40.7)	16 (59.3)	
T3	56 (52.3)	51 (47.7)	
T4	8 (61.5)	5 (38.5)	

Table 2. Clinical characteristics of TIMP1 expression in colon cancer

	TIMP1		
	High	Low	*p*-value
Age			
<65	81 (47.6)	89 (52.4)	0.456
≥65	138 (51.3)	131 (48.7)	
Gender			
Female	108 (52.7)	97 (47.3)	0.273
Male	111 (47.4)	123 (52.6)	
Lymphatic invasion			
No	120 (49.4)	123 (50.6)	0.164
Yes	86 (56.6)	66 (43.4)	
CEA			
≤5	96 (50.8)	93 (49.2)	0.960
>5	46 (51.1)	44 (48.9)	
Venous invasion			
No	141 (48.6)	149 (51.4)	0.089
Yes	53 (58.9)	37 (41.1)	
Pathologic stage			
Stage I	35 (48.6)	37 (51.4)	0.948
Stage II	84 (49.4)	86 (50.6)	
Stage III	66 (52.4)	60 (47.6)	
Stage IV	31 (50.8)	30 (49.2)	
M stage			
M0	167 (51.4)	158 (48.6)	0.935
M1	31 (50.8)	30 (49.2)	
N stage			
N0	122 (47.5)	135 (52.5)	0.190
N1	60 (57.7)	44 (42.3)	
N2	37 (47.4)	41 (52.6)	
T stage			
T1	6 (54.5)	5 (45.5)	0.409
T2	35 (47.3)	39 (52.7)	
T3	147 (48.7)	155 (51.3)	
T4	31 (60.8)	20 (39.2)	
Histological type			
Colon adenocarcinoma	173 (46.3)	201 (53.7)	<0.001
Colon mucinous adenocarcinoma	43 (71.7)	17 (28.3)	
MSI			
Indeterminate	0 (0)	2 (100)	<0.001
MSI-H	55 (72.4)	21 (27.6)	
MSI-L	37 (46.8)	42 (53.2)	
MSS	123 (44.9)	151 (55.1)	
Colon polyps			
No	114 (47.1)	128 (52.9)	0.272
Yes	69 (53.1)	61 (46.9)	
Anatomic neoplasm			
Ascending colon	52 (61.2)	33 (38.8)	<0.001
Cecum	50 (49.5)	51 (50.5)	
Descending colon	8 (42.1)	11 (57.9)	
Hepatic flexure	16 (59.3)	11 (40.7)	
Sigmoid colon	62 (42.8)	83 (57.2)	
Splenic flexure	1 (14.3)	6 (85.7)	
Transverse colon	19 (50)	19 (50)	

In rectal cancer, high TIMP1 expression was significantly associated with venous invasion ($p=0.033$), a well-established marker of tumor aggressiveness and an independent predictor of recurrence and metastasis [2,3]. Although other clinicopathological factors did not reach statistical significance, this association suggests that TIMP1 may facilitate vascular infiltration through ECM remodeling and pro-angiogenic activity [8,21]. In contrast, the influence of TIMP1 was more pronounced in colon cancer, where significant associations were observed with histological subtype, tumor location, and microsatellite instability (MSI) status. These findings align with growing evidence of the molecular heterogeneity of CRC, including distinct biological behaviors between right-sided and left-sided tumors [4-6]. The observed relationship between TIMP1 expression and MSI status may reflect TIMP1-mediated modulation of immune responses or pro-inflammatory signaling pathways characteristic of MSI-high tumors [10,12].

Importantly, survival analyses revealed that high TIMP1 expression was significantly associated with shorter overall survival in both colon and rectal cancers. This is consistent with previous studies reporting that aberrant TIMP1 expression is linked to poor prognosis in gastric cancer, papillary thyroid carcinoma, cutaneous melanoma, breast cancer, and prostate cancer [23,24]. Mechanistic studies further support its oncogenic role: TIMP1 knockdown in CRC reduces phosphorylation of FAK, Akt, ERK1/2, and JNK, indicating involvement of the FAK-PI3K/Akt and MAPK pathways in TIMP1-mediated proliferation, invasion, epithelial-mesenchymal transition, and resistance to apoptosis [25]. Additionally, in melanoma, TIMP1 interaction with CD63 and β1-integrin promotes cell survival through PI3K and PDK1 signaling [26]. Collectively, these findings highlight TIMP1 as a multifunctional mediator of tumor progression through both MMP-dependent and MMP-independent mechanisms and underscore its promise as a potential therapeutic target.

This study has several limitations. First, the TCGA cohort for CRC contains a smaller sample size compared to other cancer datasets, limiting the statistical power of certain analyses. Larger, multicenter cohorts with comprehensive clinicopathological annotations are needed to confirm these results. Second, our analysis relied solely on transcriptomic data. mRNA expression does not always correlate with protein levels or functional activity due to post-transcriptional and post-translational regulation. Protein-level validation using immunohistochemistry, Western blotting, or ELISA

assays in independent patient samples is required to substantiate the clinical relevance of TIMP1 overexpression. Third, although our results suggest that TIMP1 contributes to aggressive tumor features and worse survival outcomes, mechanistic experiments were beyond the scope of this study. In vitro and in vivo studies—including gene knockdown, overexpression systems, and pathway inhibition assays—are necessary to clarify the biological functions of TIMP1 in CRC development, invasion, and metastasis.

CONCLUSIONS

This study identified a significant association between TIMP1 gene expression and clinicopathological characteristics and survival outcomes in colorectal cancer, based on large-scale TCGA data analysis. These findings suggest that TIMP1 may serve as a promising prognostic biomarker in colorectal cancer. However, further studies integrating comprehensive clinical datasets, proteomic validation, and functional experiments are warranted to confirm the biological role of TIMP1 and to evaluate its utility in clinical practice.

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