BMC Gastroenterology

RESEARCH

Open Access

THSD7A as a novel prognostic factor for colorectal carcinoma

Oktay Halit Aktepe[1*], Olcay Kurtulan[2], Pinar Ezgi Dama[1], Ahmet Melih Arslan[1], Elif Atag[1], Meral Uner[2], Berfu Korucu[3], Aziz Karaoglu[1] and Suayib Yalcin[4]

Abstract

Background Thrombospondin type 1 domain-containing 7 A (THSD7A) expression, an angiogenesis-related protein, has been implicated in various aspects of cancer progression, reflecting its potential as a prognostic marker for various cancers. Therefore, we investigated the prognostic value of THSD7A expression in colorectal cancer (CRC).

Methods A total of 95 patients with CRC were included. The patients were stratified into two groups according to THSD7A expression status determined by immunohistochemistry [negative (no staining), and positive (expression ≥ 1% of cancer cells)]. The overall survival (OS) of prognostic subgroups was estimated by Kaplan Meier method. The prognostic value of THSD7A expression was evaluated by univariable and multivariable Cox regression models.

Results THSD7A was expressed in 42.1% of CRC patients. Patients with no THSD7A expression had inferior OS than patients with THSD7A expression (72.9 months vs. median OS was not reached, $p=0.001$, respectively). Our multivariate analyses revealed that the independent predictors of OS were poor differentiation of tumor (HR: 2.603, $p=0.002$), advanced stage (HR: 3.210, $p<0.001$), and the loss of THSD7A expression (HR: 3.094, $p=0.001$).

Conclusions The present study showed that THSD7A expression could serve as a potential prognostic marker for CRC cancer. Further research is warranted to elucidate the exact underlying THSD7A-mediated cancer progression and to explore its clinical use in improving CRC prognostication and treatment strategies.

Keywords Colorectal cancer, Prognosis, THSD7A

Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide and the second most common cause of cancer-related deaths in the United States [1]. Increasing efforts in screening and early detection policy and recent advances in local and systemic treatment modalities have led to better survival outcomes in CRC. Approximately 20% of CRC patients have metastatic disease at initial presentation, indicating a poor prognosis [2]. The combination of systemic chemotherapy agents with monoclonal agents such as anti-vascular endothelial growth factor (VEGF) antibody bevacizumab and anti-epidermal growth factor receptor antibodies, panitumumab and

*Correspondence:
Oktay Halit Aktepe
oktayhalit.aktepe@deu.edu.tr
[1]Department of Medical Oncology, Dokuz Eylül University Cancer Institute, Izmir, Turkey
[2]Department of Pathology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[3]Department of Nephrology, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey
[4]Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey

cetuximab, has led to an improvement in CRC survival [3–5]. Even though treatment with new modalities like monoclonal antibodies, immune checkpoint inhibitors, and targeted therapy has been associated with superior survival outcomes in CRC [6–9], the prognosis of metastatic CRC (mCRC) remains poor, with 5-year survival rate of 14% [10].

The association between angiogenesis and cancer pathogenesis has been shown in various trials. Thrombospondin type 1 domain-containing 7 A (THSD7A), a glycoprotein involved in cell adhesion and angiogenesis, has emerged as a novel marker for the prognostication of various tumors [11–14]. THSD7A consists of soluble (sTHSD7A) and membrane-bound N-glycoprotein parts. It was shown that the sTHSD7A was the functional part and took part in angiogenesis via inducing sprouting, endothelial cell migration, and formation of filopodia and tube [15] Additionally, THSD7A induces angiogenesis via activation of focal adhesion kinase (FAK)-dependent signaling pathway [15], which has a crucial role in vascular network stability and cell survival [16] In contrast to these findings, several motifs and domains of THSD7A have a regulatory role in angiogenesis, such as thrombospondin type 1 repeats, which contribute to vascular homeostasis via their effects on cell aggregation, cell-cell contact, cell motility and proliferation, and inhibition of angiogenesis [17]. It was also demonstrated that the expressions of VEGF receptor (VEGFR)-1, VEGFR-2, and notch-regulated ankyrin repeat protein (NRARP) a/b, angiogenic markers, were significantly decreased by the knockdown of THSD7A [18] In addition to angiogenesis, THSD7A involves in several parts of cancer pathogenesis. Hou et al. investigated the effect of THSD7A on cell cycle, apoptosis, migratory and invasive capacity, and cell proliferating activity in esophageal squamous cell carcinoma cell lines (Eca 109 and EC 9706) and showed that knocking out THSD7A resulted in decreased of proliferation, invasion, and migration; increased apoptosis and the cell cycle arrest at G1 phase [12]. However, the prognostic impact of THSD7A expression in different tumor types is not consistent. For example, while the loss of THSD7A expression is associated with inferior survival outcomes in renal cell carcinoma (RCC) and CRC, the overexpression of THSD7A expression in prostate cancer is related to poorer outcomes [13]. Our previous study revealed that we showed an inverse relationship between THSD7A expression and pathologic determinants of CRC in a rat model [19]. On the other hand, scant data about the association between THSD7A expression and survival outcomes of CRC is available. Therefore, the present study was conducted to evaluate the significance of THSD7A expression on the clinicopathological parameters and the association between THSD7A expression and overall survival (OS) of CRC. We also aimed to analyze the association between THSD7A expression and OS in de novo mCRC treated with a combination of chemotherapy and monoclonal agents.

Materials and methods

Patients and study design

This retrospective and observational study included 95 CRC patients who were ≥18 years old and treated between January 2009 and December 2019 at the Department of Medical Oncology at Hacettepe University Cancer Institute in Ankara, Turkey. The whole patient population had a history of colectomy for curative or palliative intent in early or advanced stages. Patients with missing clinic-pathologic data, scanty follow-up, and inadequate tissue sampling for immunohistochemical analysis with THSD7A were excluded. Clinical Research Ethics Committee of Hacettepe University approved the study, and written informed consent was obtained from the study population or their relatives. All procedures in this study were carried out in accordance with the 1964 Declaration of Helsinki and its later amendments.

Immunohistochemistry

The immunohistochemical analysis, as described previously [16], was performed by two independent pathologists blinded to patients' prior clinical and pathological data. In brief, the sections with a thickness of 3-µm were obtained from tissue blocks of patients with CRC and transferred to other paraffin blocks. The tissue sections with 4-µm-thickness were deparaffinized at 72° and then incubated with a primary antibody specific for THSD7A ([CL3778], ab243031, Abcam, Cambridge, UK, dilution 1:150) overnight at 4°. The samples were washed in phosphate-buffered saline and counter-stained with hematoxylin. Tumors without any staining were considered negative. Tumors with 1 + staining in < 70% or with 2 + staining in < 30% of cells were considered weakly positive. Tumors with 1 + staining in > 70% and with 2 + staining in > 30% but < 70% and with 3 + staining in < 30% of cells were considered moderately positive. Tumors with 2 + staining in > 70% and with 3 + staining in > 30% of cells were considered strongly positive. The staining status of THSD7A was dichotomized into two prognostic groups for statistical analysis: negative (no expression in any tumor cell) and positive (expression ≥ 1% of cancer cells), as in other studies investigating the prognostic value of THSD7A expression in cancer [11, 20, 21].

Statistical analyses

Non-normally distributed continuous variables were presented as median with interquartile range, and categorical variables were expressed as percentages. Chi-square and Mann–Whitney U tests were applied to measure the associations in categorical and continuous variables,

respectively. The follow-up time was calculated from the day of diagnosis until the day of death or the last contact. OS was measured as the period from the start of treatment to death from any cause. Kaplan Meier procedure was used for the estimation of OS, and the difference in prognostic subgroups was evaluated using the long-rank test. Statistical Package for Social Sciences version 25 (IBM Inc., Armonk, NY, USA) software was used for all the statistical analyses.

Results

Baseline patient characteristics

Overall, 95 CRC patients were enrolled in the present study with a median age of 63 (range: 29–81), and 58.6% of them were males. THSD7A expression was seen in 42.1% of patients with CRC. Representative images for different expression status for THSD7A were shown in Fig. 1, and the clinicopathological characteristics of cases stratified according to THSD7A expression levels were presented in Table 1. Patients without THSD7A expression were more likely to have lymphovascular invasion (LVI) than those with THSD7A expression ($p = 0.014$). Other clinic-pathological determinants, including age, gender, tumor location site, perineural invasion (PNI), T stage, N stage, M stage, and tumor differentiation status, were similar between THSD7A prognostic groups.

Survival outcomes

THSD7A expression was detected in 56.5% of CRCs. However, the percentages of positive staining for THSD7A in localized and metastatic patients were 37.5% and 46.8%, respectively. Fifty-two (54.7%) patients died during the median follow-up time of 69.5 months (35.7–100).

Kaplan-Meier analyses revealed that patients with THSD7A expression had superior OS than those without

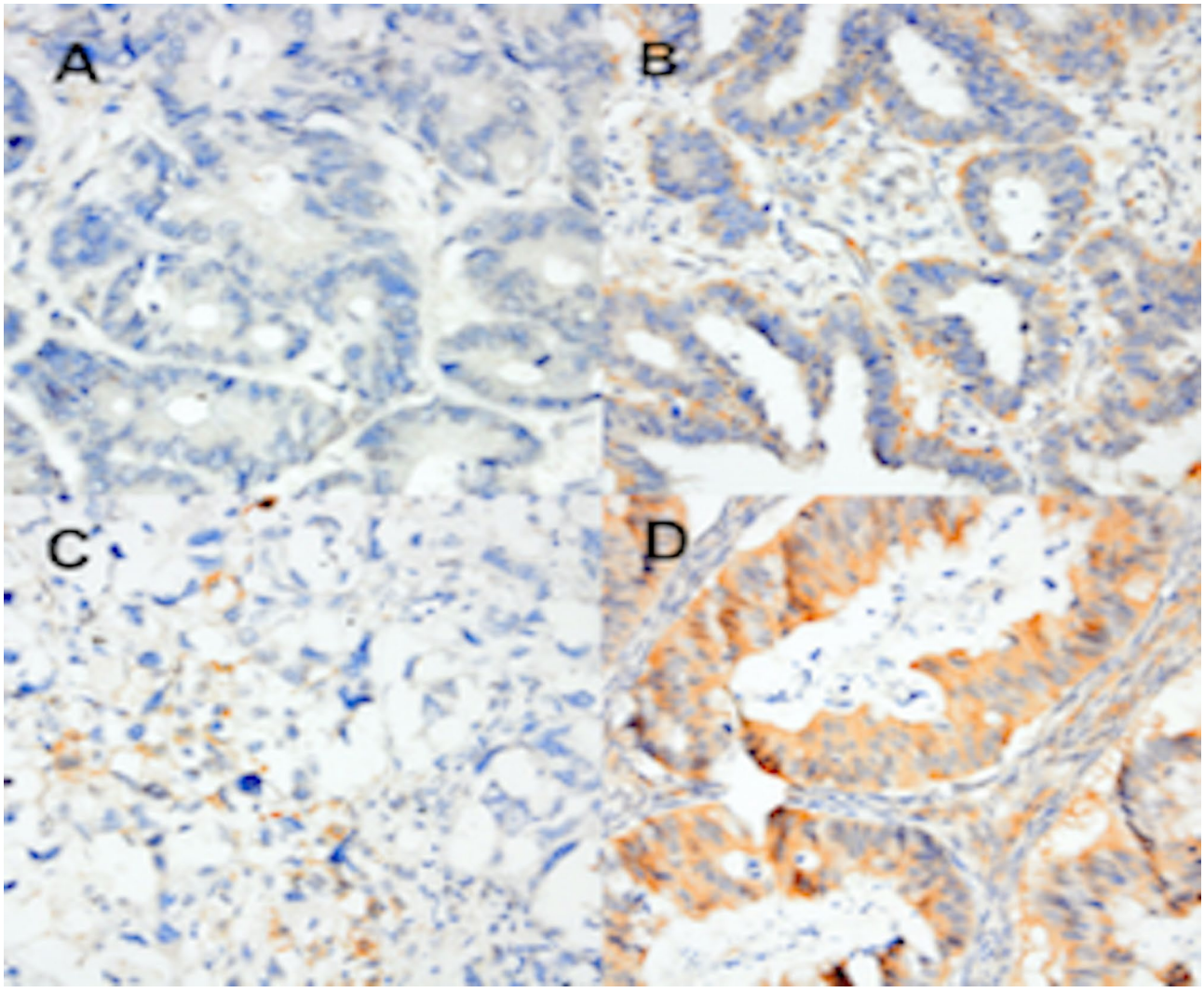

Fig. 1 Immunohistochemical staining showing different expression status for THSD7A with magnification 200x. **A** negative staining for THSD7A. **B** weakly positive THSD7A expression. **C** moderately positive THSD7A expression. **D** strongly positive THSD7A expression staining

Table 1 Patient characteristics stratified based on THSD7A expression status

Variable	THSD7A expression		*P* value
	Negative *n* = 55 (57.9%)	Positive *n* = 40 (42.1%)	
Gender Male	65.5	47.5	0.080
Age, range	64 (30–78)	61 (29–81)	0.151
T2-3 T4	55.6 44.4	52.5 47.5	0.759
N0 N1-2-3	25.5 74.5	30 70	0.817
M0 M1	54.5 45.5	45 55	0.358
LVI Absent Present	23.1 76.9	47.5 52.5	0.014
PNI Absent Present	21.2 78.8	27.5 72.5	0.479
Tumor location Left Right	72.7 27.3	77.5 22.5	0.597
Histology Good Moderate-poor	41.8 58.2	60 40	0.080

Dichotomous and continuous variables were presented as percentages and median with interquartile range, respectively. Abbreviations: LVI: lymphovascular invasion; PNI: perineural invasion; THSD7A: thrombospondin type 1 domain-containing 7 A

THSD7A expression [median OS was not reached vs. 52.6 months (95% CI: 19.4–85.8), $p = 0.001$, Fig. 2A]. Furthermore, taking disease stage into consideration, Patients with THSD7A expression had better median OS than patients with no THSD7A expression in both localized and metastatic disease [median was not reached in THSD7A positive group vs. 93.8 months in THSD7A negative group (95% CI: 87.3-100.3), $p = 0.040$ for localized disease, Figs. 2B and 92.4 months (95% CI: 53-131.9) vs. 36.4 months (95% CI: 32.3–40.5), $p = 0.001$ for metastatic disease, Fig. 2C, respectively]. When considering the prognostic factors associated with OS, univariate analyses showed that LVI, PNI, tumor stage, tumor differentiation and THSD7A expression status all had a significant impact on OS (Table 2). However, as shown in Table 3, multivariate analyses revealed that the independent predictors influencing worse OS were poorly differentiated tumor histology (HR: 2.603, 95% CI: 1.419–4.777, $p = 0.002$), advanced tumor stage (HR: 3.210, 95% CI: 1.693–6.086, $p < 0.001$), and negative expression for THSD7A (HR: 3.094, 95% CI: 1.576–6.074, $p = 0.001$).

Discussion

THSD7A has garnered significant attention in cancer research because of its diverse functions in carcinogenesis and cancer progression. Also, the multifaceted roles of THSD7A include angiogenesis, tumor growth, treatment resistance, and metastasis, reflecting its crucial functions in the tumor microenvironment. In the present study, we investigated the prevalence of THSD7A expression in CRC and whether THSD7A expression has been linked to OS of CRC patients. Our findings showed that THSD7A expression was seen in 42.1% of CRC and negative expression of THSD7A was associated with worse survival outcomes in CRC. We also demonstrated that mCRC patients without THSD7A expression had inferior OS times compared to those with THSD7A expression.

The functional role of sTHSD7A executes its function in the early steps of endothelial cell migration process, which involves chemotaxis mainly driven by VEGF and basic fibroblast growth factor; haptotaxis stimulated by binding of integrins to extracellular matrix (ECM); and mechanotaxis, the directional migration process in response to the mechanical forces [22–24] It also induces filopodia formation, and focal adhesion complex (The assembly of FAK, paxillin, and vinculin) [15], which is compatible with the functionel roles of other key angiogenesis-related proteins such as VEGF-A, and VEGF-C [25] Furthermore, sTHSD7A induces mitogen-activated protein kinase by increasing the phosphorylation levels of Erk1/2 and P38, contributing to the downstream cell migration signaling pathways of THSD7A [15] All these data indicate the roles of THSD7A in angiogenesis.

In addition to angiogenesis, Shen et al. investigated the functional roles of THSD7A in gastric cancer and showed that THSD7A is involved in tumor progression via various processes, including epithelial-mesenchymal transition (EMT), the activity of ECM-receptor interaction, IL2- STAT5 signaling pathway, and vascular smooth muscle contraction (VSMC) [26]. The EMT process has been documented to play an essential role in tumor progression and metastasis in various tumors, including CRC [27–29]. ECM-receptor interaction was reported to have crucial roles in the progression, prognosis, and metastasis of CRC [30]. It was shown that the overexpression and constitutive activation of STAT5 were associated with inferior survival outcomes in CRC [31, 32]. Mahajan et al. demonstrated that there was an important link between VSCMC and cell communication in CRC progression [33] Taking these data together, EMT, the activity of ECM-receptor interaction, IL2-STAT5 signaling pathway, and VSMC might be underlying mechanisms of THSD7A in progression, prognosis, and metastasis of CRC.

Various studies identified a relationship between tumor immune cells (TICs) and survival outcomes of tumors and reponse to therapy in cancers, including CRC [34–36]. Shen et al., for the first time, investigated the relationship between TICs and THSD7A and showed that THSD7A expression was positively correlated with M2 macrophages, resting mast cells, and regulatory T cells,

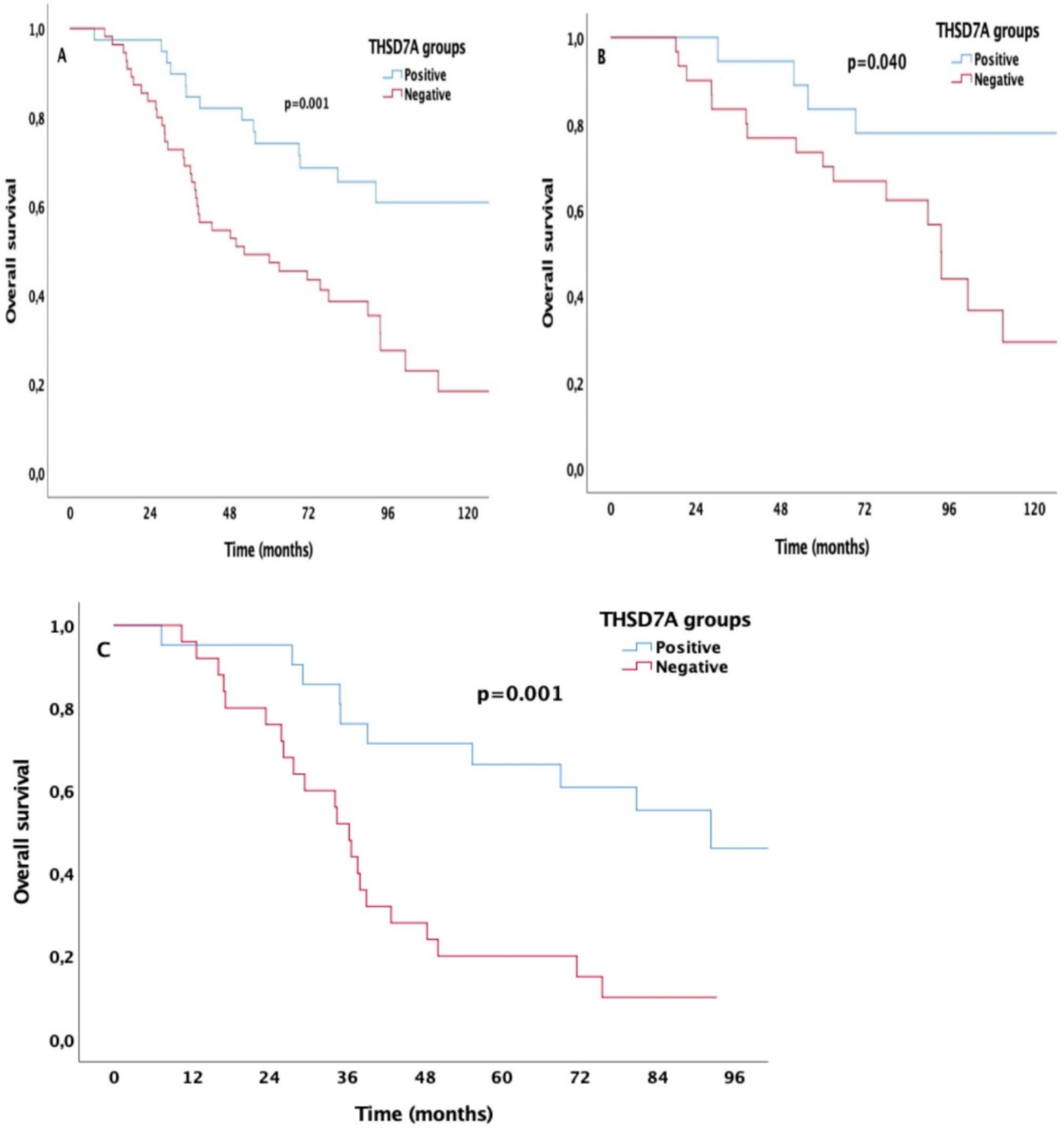

Fig. 2 Kaplan Meier curves estimating OS times stratified according to THSD7A expression status in **A** the whole population; **B** patients with early stage CRC; **C** patients with mCRC

and negatively correlated with M1 macrophages, activated memory CD4 + T cells, and follicular helper T cells in gastric cancer [26] A T-cell dysfunction and exclusion gene expression signature score named as TIDE and tumor mutation burden (TMB) scores have been used to estimate immunotherapy efficacy [37, 38]. Shen et al. revealed that the group with higher THSD7A expression had greater TIDE score and lower TMB compared to those with lower THSD7A expression in gastric cancer, indicating a poor prognosis [26].

Given the intricate role of THSD7A in regulating cancer survival, efforts to elucidate its molecular mechanisms and therapeutic implications are paramount. The role of THSD7A as a prognostic factor was investigated in several studies, and the effect of THSD7A expression on cancer survival varies from one tumor type to

Table 2 Univariate Cox analyses determining the associations between clinic-pathologic variables and OS

Variable	HR (95% CI)	95% CI		*P* value
		Lower	Upper	
Age	1.002	0.958	1.028	0.928
Gender Female vs. Male	0.960	0.608	1.514	0.860
Tumor differentiation Good vs. Moderate-poor	1.999	1.265	3.159	0.003
Tumor location Left vs. Right	1.210	0.714	2.052	0.479
LVI Absent vs. Present	2.379	1.382	4.095	0.002
PNI Absent vs. Present	2.409	1.401	4.142	0.001
Tumor stage Early vs. Advanced	2.837	1.762	4.567	< 0.001
THSD7A expression Positive vs. Negative	2.711	1.464	5.020	0.002

Abbreviations: LVI: lymphovascular invasion; PNI: perineural invasion; THSD7A: thrombospondin type 1 domain-containing 7 A

Table 3 Multivariate Cox regression analyses determining independent variables for OS

Variables	HR	95% CI for HR		*P* value
		Lower	Upper	
THSD7A expression Positive vs. Negative	3.094	1.576	6.074	0.001
Tumor stage Early vs. Advanced	3.210	1.693	6.086	< 0.001
Tumor differentiation Good-moderate vs. Poor	2.603	1.419	4.777	0.002

Abbreviation: THSD7A: thrombospondin type 1 domain-containing 7 A

another [11, 13, 20, 26]. For Instance, Stahl et al. investigated the importance of THSD7A expression on the prognosis of several types of cancers and showed that the loss and gain of THSD7A was associated with inferior survival outcomes in CRC and prostate cancer, respectively [13]. Furthermore, the prognostic significance of THSD7A expression may vary across the stages of a tumor. For example, Stahl et al. demonstrated that considering all stages, THSD7A was not an independent determinant for OS of RCC [13]. However, in our previous report, THSD7A expression was linked to worse survival outcomes in patients with metastatic RCC treated with targeted therapy [21]. Regarding the association between THSD7A expression and pathological parameters and prognosis of CRC, Stahl et al. demonstrated that THSD7A expression was seen in 43% of CRC and the lack of THSD7A expression was related to advanced T stage, N stage, poorer tumor differentiation, and vascular invasion [13]. Also, Li Xian et al. showed that the percentage of CRC patients stained with THSD7A was 97.5% [14]. As compared to these findings, the present study showed that THSD7A expression was detected in 43.5% of CRC, and there was no association between THSD7A expression status and adverse pathological features except LVI. These controversial results about THSD7A positivity might arise due to the clinicopathological differences in each study because our cohort was mostly composed of CRC patients with advanced stage (51.7%), while in the studies by Stah et al. and Li Xian et al., no clinical information was given about this issue.

We, for the first time, investigated and showed the association of THSD7A expression in mCRC patients treated with chemotherapy plus biologic agents. However, the main limitations of the present study are its retrospective nature and relatively small number of patients. Since our study population was relatively small, we could not categorize THSD7A expression into different expression levels, indicating a clear necessity to establish a reliable cut-off point for better prognostication in future trials with a larger number of patients. Furthermore, it is necessary to elucidate the prognostic impact of THSD7A expression in patients with high microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) tumors because all the patients in our study had microsatellite stable (MSS) phenotype. Finally, we could not analyze THSD7A expression in normal colon tissue adjacent to the tumor since TME was used for THSD7A expression.

Conclusions

Overall, the emerging evidence on the role of THSD7A in cancer highlights its association with key pathological hallmarks and prognosis of several types of cancer. The results of our study revealed that THSD7A expression status was an independent prognostic marker in predicting OS in CRC patients who underwent colectomy for curative or palliative purposes at initial presentation. Further prospective and in vitro investigations into the molecular mechanisms underlying THSD7A-mediated effects in different cancer types, including CRC, are warranted to unravel its full potential as a therapeutic target and prognostic marker in oncology.

Abbreviations

CRC	Colorectal cancer
dMMR	Mismatch repair deficiency
ECM	Extracellular Matrix
EMT	Epithelial-Mesenchymal Transition
FAK	Focal Adhesion Kinase
LVI	Lymphovascular invasion
mCRC	Metastatic Colorectal Cancer
MSI-H	High Microsatellite Instability
MSS	Microsatellite Stable
PNI	Perineural Invasion
NRARP	Notch-Regulated Ankyrin Repeat Protein
OS	Overall Survival
RCC	Renal Cell Carcinoma
THSD7A	Thrombospondin type 1 domain-containing 7 A
sTHSD7A	Soluble Thrombospondin type 1 domain-containing 7 A
TICs	Tumor Immune Cells

TMB	Tumor Mutation Burden
VSMC	Vascular Smooth Muscle Contraction
VEGF	Vascular Endotelial Growth Factor
VEGFR	Vascular Endotelial Growth Factor Reseptor

Author contributions
OHA, OK, MU, BK, AK and SY designed research; OHA, OK, MU, BK and SY conducted research; OHA, EA, AK and SY analyzed data; OHA, OK, PED, AMA, EA, MU, BK, AK and SY wrote the paper; OHA had primary responsibility for final content. All authors read and approved the final manuscript.

Funding
This work is supported by the Department of Scientific Research Projects Coordination Unit of Hacettepe University (project no: 19300).

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author (Oktay Halit Aktepe, oktayhalit.aktepe@deu.edu.tr) on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective study involving human participants was reviewed and approved by Clinical Research Ethic Commission of Hacettepe University (decision no: KA-20091/06.10.2020) and adhered to the Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants or their relatives included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 14 December 2024 / Accepted: 11 March 2025
Published online: 17 March 2025

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7–33.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73:17–48.
3. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014;371:1609–18.
4. Van Cutsem E, Köhne C-H, Hitre E, Zaluski J, Chang Chien C-R, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360:1408–17.
5. Douillard J-Y, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369:1023–34.
6. André T, Shiu K-K, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in Microsatellite-Instability–High advanced colorectal cancer. N Engl J Med. 2020;383:2207–18.
7. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018;15:731–47.
8. Yoshino T, Di Bartolomeo M, Raghav K, Masuishi T, Loupakis F, Kawakami H, et al. Final results of DESTINY-CRC01 investigating trastuzumab Deruxtecan in patients with HER2-expressing metastatic colorectal cancer. Nat Commun. 2023;14:3332.
9. Fakih MG, Salvatore L, Esaki T, Modest DP, Lopez-Bravo DP, Taieb J, et al. Sotorasib plus panitumumab in refractory colorectal cancer with mutated KRAS G12C. N Engl J Med. 2023;389:2125–39.
10. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF et al. SEER cancer statistics review, 1975–2009 (vintage 2009 populations). Bethesda, MD: National Cancer Institute. 2012;:1975–2009.
11. Flockerzi FA, Hohneck J, Langer F, Bohle RM, Stahl PR. THSD7A positivity predicts poor survival and is linked to high FAK expression and FGFR1-Wildtype in female patients with squamous cell carcinoma of the lung. Int J Mol Sci. 2023;24:10639.
12. Hou Z, Abudureheman A, Wang L, Hasim A, Ainiwaer J, Zhang H, et al. Expression, prognosis and functional role of Thsd7a in esophageal squamous cell carcinoma of Kazakh patients. Xinjiang Oncotarget. 2017;8:60539–57.
13. Stahl PR, Hoxha E, Wiech T, Schröder C, Simon R, Stahl RAK. THSD7A expression in human cancer. Genes Chromosomes Cancer. 2017;56:314–27.
14. Xian L, Dong D, Luo J, Zhuo L, Li K, Zhang P, et al. Expression of THSD7A in neoplasm tissues and its relationship with proteinuria. BMC Nephrol. 2019;20:332.
15. Kuo M-W, Wang C-H, Wu H-C, Chang S-J, Chuang Y-J. Soluble THSD7A is an N-Glycoprotein that promotes endothelial cell migration and tube formation in angiogenesis. PLoS ONE. 2011;6:e29000.
16. Braren R, Hu H, Kim YH, Beggs HE, Reichardt LF, Wang R. Endothelial FAK is essential for vascular network stability, cell survival, and lamellipodial formation. J Cell Biol. 2006;172:151–62.
17. Adams JC, Tucker RP. The thrombospondin type 1 repeat (TSR) superfamily: diverse proteins with related roles in neuronal development. Dev Dyn. 2000;218:280–99.
18. Liu LY-M, Lin M-H, Lai Z-Y, Jiang J-P, Huang Y-C, Jao L-E, et al. Motor neuron-derived Thsd7a is essential for zebrafish vascular development via the Notch-dll4 signaling pathway. J Biomed Sci. 2016;23:59.
19. Aktepe OH, Sahin TK, Guner G, Guven DC, Yeter HH, Kurtulan O, et al. Correlation between THSD7A expression and tumor characteristics of Azoxymethane-Induced colon cancer model in rats. Turkish J Gastroenterol. 2021;32:1049–56.
20. Flockerzi FA, Hohneck J, Saar M, Bohle RM, Stahl PR. THSD7A positivity is associated with high expression of FAK in prostate cancer. Diagnostics. 2023;13:221.
21. Aktepe OH, Gundogdu F, Kosemehmetoglu K, Yeter HH, Aksoy S, Guven DC, et al. THSD7A expression: a novel immunohistochemical determinant in predicting overall survival of metastatic renal cell carcinoma treated with targeted therapy. Ir J Med Sci. 2022;191:1561–7. (1971 -).
22. Li S, Huang NF, Hsu S. Mechanotransduction in endothelial cell migration. J Cell Biochem. 2005;96:1110–26.
23. Klemke RL, Cai S, Giannini AL, Gallagher PJ, de Lanerolle P, Cheresh DA. Regulation of cell motility by Mitogen-activated protein kinase. J Cell Biol. 1997;137:481–92.
24. Giroux S, Tremblay M, Bernard D, Cardin-Girard J-F, Aubry S, Larouche L, et al. Embryonic death of Mek1-deficient mice reveals a role for this kinase in angiogenesis in the labyrinthine region of the placenta. Curr Biol. 1999;9:369–76.
25. George ML, Tutton MG, Janssen F, Arnaout A, Abulafi AM, Eccles SA, et al. VEGF-A, VEGF-C, and VEGF-D in colorectal cancer progression. Neoplasia. 2001;3:420–7.
26. Shen K, Chen B, Yang L, Gao W. Integrated analysis of single-cell and bulk RNA-sequencing data reveals the prognostic value and molecular function of THSD7A in gastric cancer. Aging. 2023;15:11940–69.
27. Zhu W, Cai M-Y, Tong Z-T, Dong S-S, Mai S-J, Liao Y-J, et al. Overexpression of EIF5A2 promotes colorectal carcinoma cell aggressiveness by upregulating MTA1 through C-myc to induce epithelial–mesenchymaltransition. Gut. 2012;61:562–75.
28. Huang Y, Hong W, Wei X. The molecular mechanisms and therapeutic strategies of EMT in tumor progression and metastasis. J Hematol Oncol. 2022;15:129.
29. Mak P, Leav I, Pursell B, Bae D, Yang X, Taglienti CA, et al. ERβ impedes prostate cancer EMT by destabilizing HIF-1α and inhibiting VEGF-Mediated snail nuclear localization: implications for Gleason grading. Cancer Cell. 2010;17:319–32.
30. Nersisyan S, Novosad V, Engibaryan N, Ushkaryov Y, Nikulin S, Tonevitsky A. ECM–Receptor regulatory network and its prognostic role in colorectal cancer. Front Genet. 2021;12.
31. Du W, Wang Y, Hong J, Su W, Lin Y, Lu R, et al. STAT5 isoforms regulate colorectal cancer cell apoptosis via reduction of mitochondrial membrane potential and generation of reactive oxygen species. J Cell Physiol. 2012;227:2421–9.
32. Xiong H, Su W-Y, Liang Q-C, Zhang Z-G, Chen H-M, Du W, et al. Inhibition of STAT5 induces G1 cell cycle arrest and reduces tumor cell invasion in human colorectal cancer cells. Lab Invest. 2009;89:717–25.
33. Mahajan M, Sarkar A, Mondal S. Integrative network analysis of transcriptomics data reveals potential prognostic biomarkers for colorectal cancer. Cancer Med. 2024;13.

34. Nguyen N, Bellile E, Thomas D, McHugh J, Rozek L, Virani S, et al. Tumor infiltrating lymphocytes and survival in patients with head and neck squamous cell carcinoma. Head Neck. 2016;38:1074–84.
35. Bremnes RM, Busund L-T, Kilvær TL, Andersen S, Richardsen E, Paulsen EE, et al. The role of Tumor-Infiltrating lymphocytes in development, progression, and prognosis of Non–Small cell lung cancer. J Thorac Oncol. 2016;11:789–800.
36. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen P, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol. 2010;11:19.
37. Jiang P, Gu S, Pan D, Fu J, Sahu A, Hu X, et al. Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response. Nat Med. 2018;24:1550–8.
38. Liu L, Bai X, Wang J, Tang X-R, Wu D-H, Du S-S, et al. Combination of TMB and CNA stratifies prognostic and predictive responses to immunotherapy across metastatic cancer. Clin Cancer Res. 2019;25:7413–23.

Publisher's note