

Evaluation of the TRPM protein family as potential biomarkers for various types of human cancer using public database analyses

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Abstract. The Transient Receptor Potential Melastatin (TRPM) protein family members have been demonstrated to be involved in a variety of different types of human cancer. However, to the best of our knowledge, there has not yet been a systematic study regarding the mRNA expression of the TRPM protein family or its prognostic value in human cancer. The present study investigated TRPM expression and its prognostic value in various human cancer types via the Oncomine database, Kaplan-Meier plotter, and the Prognoscan and Gene Expression Profiling Interactive Analysis databases. It was revealed that the transcriptional levels of TRPM1, TRPM3 and TRPM6 were decreased in the majority of cancer tissues, while TRPM2 was increased in most cancer types. In addition, the high or low transcriptional levels of the TRPM protein family members were associated with survival outcomes of different types of solid tumors. The present study suggested that certain TRPM protein family members may serve as useful biomarkers for cancer prognosis and anticancer targets for cancer treatment.

Introduction

Cancer is a complex genetic disease in addition to being one of the leading cause of mortality worldwide (1,2). Despite improving diagnostic techniques and therapeutics, cancer

affects the quality of life of those patients affected, and creates serious social and economic burdens. Therefore, there is an urgent requirement to elucidate the molecular mechanisms underlying cancer development, and to identify novel biomarkers to improve diagnosis, treatment and prognosis. The transient receptor potential (TRP) gene was first cloned in 1989 and categorized into a nonselective cation channel superfamily (3). The human TRP family is divided into six subfamilies: TRPC, TPRV, TRPM, TRPP, TRPML and TRPA. TRPM for 'melastatin' contains 8 members, namely TRPM1, TRPM2, TRPM3, TRPM4, TRPM5, TRPM6, TRPM7 and TRPM8 (4). TRPM2 has been demonstrated to promote the growth of prostate cancer cells (5). TRPM4 was suggested to enhance cancer cell proliferation via upregulating the β -catenin signaling pathway (6). TRPM7 has been considered to regulate the migration and invasion of metastatic breast cancer cells (7). Taken together, the TRPM protein family may be attractive targets for anticancer therapies or prognostic biomarkers in certain types of human cancer (8,9). However, to the best of our knowledge, a systematic study on the transcriptional expression and prognostic value of the TRPM protein family members in human tumors has not been conducted yet. In the present study, the mRNA expression patterns of the TRPM protein family between tumor tissues were investigated and compared with normal tissues through the Oncomine database. Furthermore, the present study analyzed prognostic values using The Cancer Genome Atlas (TCGA) database.

Materials and methods

Oncomine analysis. In the present study, Oncomine (<https://www.oncomine.org>), an online cancer microarray database, was used to analyze the mRNA expression levels of TRPMs in different types of cancer. The cut-offs were set as fold change (FC) =2 and P<0.01, the analysis type was set as cancer vs. normal analysis, and data type as mRNA. The significant differences between cancer and normal tissues, genes, datasets, sample sizes, FC, Student's t-test and P-values were presented.

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Kaplan-Meier plotter analysis. Kaplan-Meier plotter (<https://www.kmplot.com>) (10), which contains gene expression data and clinical data, was used to evaluate the prognostic value of TRPMs mRNA levels. The present study focused on overall survival (OS) patient information with a 10-year follow-up. Patient samples were separated into two groups based on their median expression (high and low expression, the median group was included in the high group) in order to estimate the prognostic value of a certain gene. Kaplan-Meier plots were created by analyzing the OS of patients with cancer. $P < 0.05$ was considered to indicate a statistically significant difference. Both log rank P-value and hazard ratio (HR) with 95% confidence intervals were calculated and summarized. The present study used the best specific probes (JetSet probes) that recognized the TRPM protein family (11).

PrognScan analysis. The results of the survival analyses were downloaded from PrognScan database (<http://dna00.bio.kyutech.ac.jp/PrognScan/index.html/>) (12), which is a public microarray database containing clinical annotations of gene expression and the prognostic value of genes, was used to evaluate the prognostic effects of TRPMs in certain types of cancer in the present study. $P < 0.05$ was considered to indicate a statistically significant difference.

Gene Expression Profiling Interactive Analysis (GEPIA). GEPIA (<http://gepia.cancer-pku.cn/>) (13), an interactive web server for analyzing RNA sequencing expression data, was mined to predict the differential expression levels of TRPM8 in liver and prostate cancer groups compared with the control group. GEPIA was also used to validate gene expression and evaluate the survival analysis of the TRPMs in patients with liver cancer. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

mRNA expression pattern of the TRPM protein family in different types of human cancer. In order to investigate the transcriptional levels of TRPMs in cancerous and control tissues among the multiple different types of cancer, the present study performed an OncoPrint analysis. The database contains a total of 418, 371, 342, 372, 255, 333, 294 and 343 unique analyses for TRPM1, TRPM2, TRPM3, TRPM4, TRPM5, TRPM6, TRPM7 and TRPM8, respectively (Fig. 1). The transcriptional levels of the TRPM family members extracted from the OncoPrint database were significantly increased or decreased compared with the normal group in various types of cancer.

The latest data from GLOBOCAN 2018 has reported that there were 18.1 million incident cancer cases and 9.6 million cancer mortalities in 2018 (1). The top 6 types of cancer to be diagnosed in both sexes combined were lung, breast, prostate, colorectal, stomach and liver cancer (1). Melanoma is the fifth most common malignancy in men and the sixth most common in women (14). Therefore, the present study underlined the expression level and prognosis of TRPMs family in these tumors, and certain other common types of solid tumor.

Expression levels and prognostic values of TRPMs in breast cancer. Firstly, the present study investigated the

expression levels of the TRPMs family in breast cancer using the OncoPrint database. The analysis included 11 datasets in total. According to the TCGA database, TRPM2 was revealed to be upregulated in ductal carcinoma and invasive breast cancer. However, TRPM3 and TRPM6 were downregulated in a variety of different types of breast cancer. Furthermore, TRPM4 was significantly increased only in male breast cancer. No significant differences in TRPM1, TRPM5, TRPM7 and TRPM8 levels were observed between cancerous and control tissues. All the statistically significant results are summarized in Table I.

Breast cancer is now described in terms of intrinsic biological subtypes and is defined into the following four main subtypes: Basal-like (ER-/PR-/HER2-), luminal A (ER+/HER2-/grade 1 or 2), Basal-like B (ER+/HER2-/grade 3) and HER2-enriched (any HER2+ tumor) (15). The Kaplan-Meier curves presenting the OS of four breast cancer subtypes with a 10-year follow-up are presented in Fig. 2. Poor patient outcome was found to be associated with high expression levels of TRPM2 in the patients with HER2+ subtype (Fig. 2D) and low expression of TRPM2 in patients with luminal B subtype (Fig. 2C). High TRPM3 expression was associated with increased OS in luminal B breast carcinoma subtype (Fig. 2G). However, in the patients with the basal (Fig. 2I and M) and HER2+ (Fig. 2L and P) subtypes with a 10-year follow-up, high expression levels of TRPM4 and TRPM6 indicated decreased survival rates.

Expression levels and prognostic values of TRPMs in lung cancer. Using the OncoPrint database, the present study analyzed the transcriptional expression of TRPM members in lung cancer. In a group of datasets including Bhattacharjee *et al.* (16) and Garbe *et al.* (17), the transcriptional expression levels of TRPM1 and TRPM2 in small cell lung carcinoma were significantly increased compared with that in the control tissues. According to Bhattacharjee *et al.* (16), TRPM1 also was upregulated in lung carcinoid tumor. According to the dataset from Garber *et al.* (17), it was revealed that TRPM2 was elevated in squamous cell lung carcinoma and large cell lung carcinoma when compared with the control group. According to Okayama *et al.* (18), TRPM6 was decreased in lung adenocarcinoma; however, this was increased in the lung adenocarcinoma samples in the study of Garber *et al.* (17). However, no statistical differences were observed between lung cancer and control tissue groups for TRPM3, TRPM4, TRPM5, TRPM7 and TRPM8 in the present study. The detailed results are presented in Table II.

The present study employed the Kaplan-Meier plotter to identify the role of TRPM protein family in lung adenocarcinoma and squamous cell lung carcinoma, which are the most common types of lung cancer (19). For patients with lung adenocarcinoma, decreased TRPM1 (Fig. 3A) and TRPM2 (Fig. 3C) levels were associated with improved OS. However, decreased TRPM6 (Fig. 3E) were associated with lower OS rates in the patients with lung adenocarcinoma with a 10-year follow-up. No statistical difference was observed for patients with squamous cell lung carcinoma when regarding OS (Fig. 3B, D and F).

Expression levels and prognostic values of TRPMs in colorectal cancer. As for colon and rectal carcinoma, all

Analysis type by cancer	Cancer vs. Normal	Cancer vs. Normal	Cancer vs. Normal	Cancer vs. Normal	Cancer vs. Normal	Cancer vs. Normal	Cancer vs. Normal	Cancer vs. Normal								
	TRPM1	TRPM2	TRPM3	TRPM4	TRPM5	TRPM6	TRPM7	TRPM8								
Bladder cancer				2												
Brain and CNS cancer		2	1	4			1	2								
Breast cancer		2		3	1		5									
Cervical cancer																
Colorectal cancer	1	3		2	5		22									
Esophageal cancer		1		3				1								
Gastric cancer		1		1			1									
Head and neck cancer		1														
Kidney cancer		3		14	1	3	1	1								
Leukemia		2		1	1		2									
Liver cancer								2								
Lung cancer	2	4					1									
Lymphoma		1		4		2		1								
Melanoma	3	2			1			1								
Myeloma		2		2												
Other cancer		2		2	2	1	1	2								
Ovarian cancer						1										
Pancreatic cancer				1												
Prostate cancer		1		6												
Sarcoma		1		3		4										
Significant unique analyses	6	13	13	3	1	32	17	14	1	1	3	31	1	3	3	5
Total unique analyses	418	371	342	372	255	333	294	343								

Figure 1. mRNA expression levels of TRPM protein family members in human cancer. The number in the cells represents the number of analyses meeting the thresholds. The cell color is determined by the gene rank. Darker red (upregulated) or blue (downregulated) indicates a more highly significant upregulated or downregulated gene. TRPM, transient receptor potential melastatin.

statistically significant datasets are summarized in Table III. According to TCGA datasets, TRPM1 was increased in rectosigmoid cancer compared with the control tissues. It was revealed that TRPM2 was increased in colon and cecum adenocarcinoma from TCGA datasets. According to Skrzypczak *et al* (20), TRPM4 was elevated in colon adenoma epithelia, but decreased in colon carcinoma epithelial and colorectal carcinoma compared with colon tissues. In a group of datasets including TCGA and Hong *et al* (21), TRPM4 was decreased in colon adenocarcinoma, rectal adenocarcinoma and colorectal carcinoma compared with control tissues. This analysis involved 7 datasets in total (20-25), TRPM6 was observed to be upregulated in colon and rectal carcinomas compared with control tissues.

There were no differences in the expression levels of TRPM3, TRPM5, TRPM7 and TRPM8 between colorectal cancer and control tissues.

The associations between TRPM protein family (TRPM1, TRPM2, TRPM4 and TRPM6) and the survival outcomes of patients with colorectal cancer involving OS were determined using the PrognScan database (12). It was revealed that lower expression levels of TRPM1, TRPM2 and TRPM6 were associated with poor prognoses in patients with colorectal cancer. The aberrant regulation of TRPM1, TRPM2 and TRPM6 may contribute to the tumorigenesis and development of colorectal cancer (Fig. 4A, B and D). However, the expression of TRPM4 was not statistically significant in terms of patient prognoses (Fig. 4C).

Table I. Datasets of TRPM protein family in breast cancer.

Gene	Dataset	Normal (n)	Tumor (n)	Fold change	t-test	P-value
TRPM2	TCGA	Breast (61)	Invasive ductal breast carcinoma (389)	2.158	14.181	1.69×10^{-28}
		Breast (61)	Invasive breast carcinoma (76)	2.083	7.516	3.63×10^{-12}
TRPM3	TCGA	Breast (61)	Invasive breast carcinoma (76)	-2.185	-12.894	1.07×10^{-22}
		Breast (61)	Male breast carcinoma (3)	-2.007	-7.258	8.00×10^{-4}
		Breast (61)	Invasive ductal breast carcinoma (389)	-2.185	-14.073	2.56×10^{-22}
TRPM4	TCGA	Breast (61)	Male breast carcinoma (3)	2.108	6.148	5.00×10^{-3}
TRPM6	TCGA	Breast (61)	Invasive ductal breast carcinoma (389)	-5.432	-18.443	3.50×10^{-37}
		Breast (61)	Invasive lobular breast carcinoma (36)	-2.803	-8.379	5.73×10^{-12}
		Breast (61)	Mixed lobular and ductal breast carcinoma (7)	-3.793	-6.679	7.29×10^{-5}
		Breast (61)	Intraductal cribriform breast adenocarcinoma (3)	-5.308	-9.154	2.00×10^{-3}
		Breast (61)	Invasive breast carcinoma (76)	-3.548	-8.71	9.25×10^{-15}

TRPMs, Transient Receptor Potential Melastatin; TCGA, The Cancer Genome Atlas.

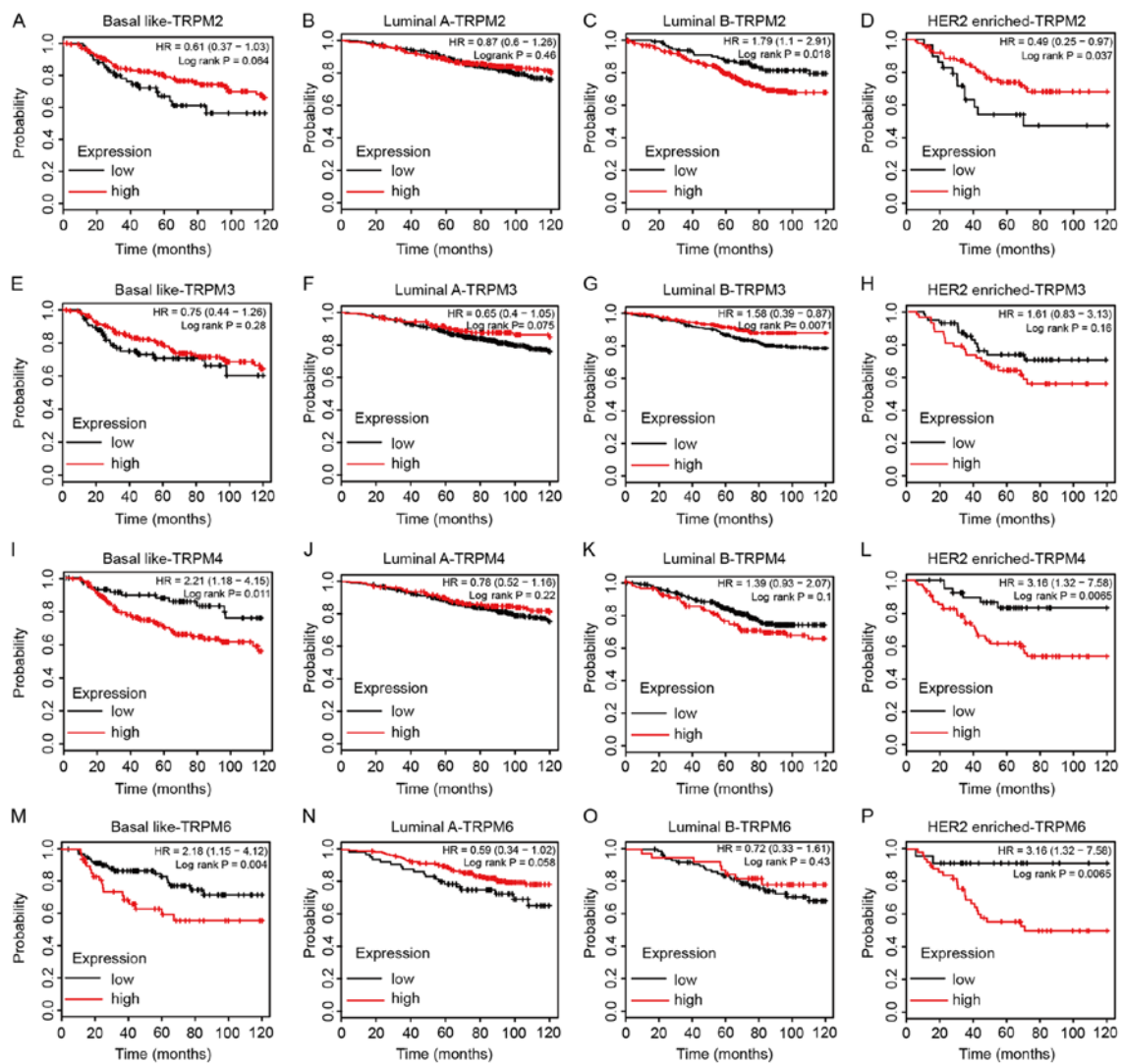


Figure 2. Survival analyses of TRPM protein family in four subtypes of breast cancer: Basallike (ER⁻/PR⁻/HER2⁻), luminal A (ER⁺/HER2⁻/grade 1 or 2), luminal B (ER⁺/HER2⁻/grade 3) and HER2 enriched (any HER2⁺ tumor). (A-D) Prognosis analysis of TRPM2, (E-H) TRPM3, (I-L) TRPM4 and (M-P) TRPM6. TRPM, transient receptor potential melastatin; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.

Table II. Datasets of TRPM protein family in lung cancer.

Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value
TRPM1	Bhattacharjee <i>et al</i> (16)	Lung (17)	Small cell lung carcinoma (6)	2.24	2.664	0.007
		Lung (17)	Lung carcinoid tumor (20)	2.366	2.766	0.005
TRPM2	Garber <i>et al</i> (17)	Lung (5)	Large cell lung carcinoma (4)	4.561	5.046	5.28x10 ⁻⁴
		Fetal lung (1)				
		Lung (5)	Small cell lung carcinoma (4)	4.068	4.404	0.001
		Fetal lung (1)				
		Lung (5)	Lung adenocarcinoma (39)	3.586	5.194	5.85x10 ⁻⁴
		Fetal lung (1)				
TRPM6	Okayama <i>et al</i> (18)	Lung (5)	Squamous cell lung carcinoma (13)	3.53	3.927	7.23x10 ⁻⁴
		Fetal lung (1)				
TRPM6	Okayama <i>et al</i> (18)	Lung (20)	Lung adenocarcinoma (226)	-2.363	-9.369	6.51x10 ⁻¹²

TRPMs, Transient Receptor Potential Melastatin.

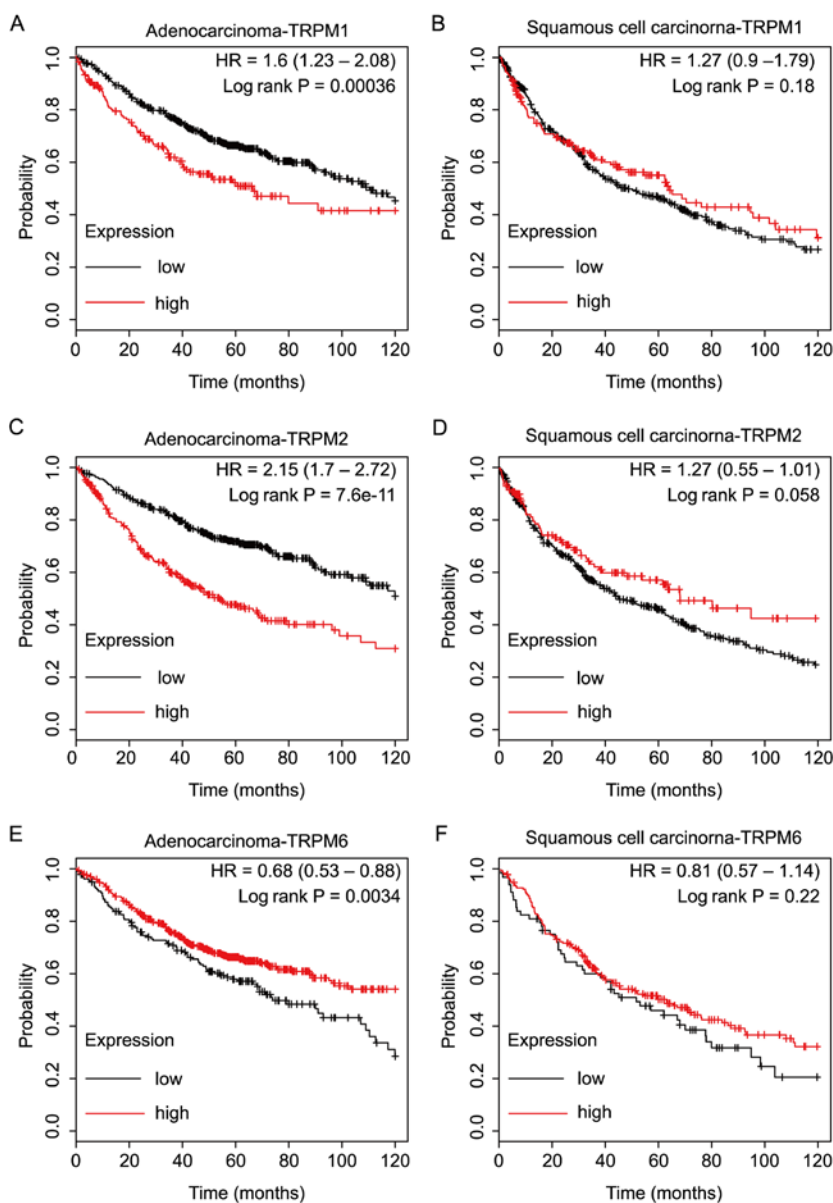


Figure 3. Survival analyses of TRPM protein family in lung adenocarcinoma and squamous cell lung carcinoma. Survival analyses of (A and B) TRPM1, (C and D) TRPM2 and (E and F) TRPM6 were obtained from the Kaplan-Meier plotter database. TRPM, transient receptor potential melastatin; HR, hazard ratio.

Table III. Datasets of TRPM protein family in colorectal cancer.

Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value
TRPM1	TCGA	Colon (19) Rectum (3)	Rectosigmoid adenocarcinoma (3)	3.482	9.492	9.11x10 ⁻⁵
TRPM2	TCGA	Colon (19) Rectum (3) Colon (19) Rectum (3) Colon (19) Rectum (3)	Colon mucinous adenocarcinoma (22) Colon adenocarcinoma (101) Cecum adenocarcinoma (22)	3.352 3.045 3.063	7.898 9.359 7.595	1.71x10 ⁻⁹ 6.79x10 ⁻¹⁵ 3.31x10 ⁻⁹
TRPM4	Skrzypczak <i>et al</i> (20)	Colon (10)	Colon adenoma (5)	2.923	10.06	1.18x10 ⁻⁷
TRPM4	Skrzypczak <i>et al</i> (20)	Colon (10)	Colon carcinoma epithelia (5)	-2.232	-10.598	7.31x10 ⁻⁷
	TCGA	Colon (19) Rectum (3) Colon (19) Rectum (3)	Colon adenocarcinoma (101) Rectal adenocarcinoma (60)	-2.297 -2.264	-10.673 -9.519	1.32x10 ⁻¹⁶ 1.17x10 ⁻¹⁴
	Hong <i>et al</i> (21)	Colon (12)	Colorectal carcinoma (70)	-2.67	-6.172	4.22x10 ⁻⁸
	Skrzypczak <i>et al</i> (20)	Colorectal Tissue (24)	Colorectal carcinoma (36)	-2.133	-4.864	5.00x10 ⁻⁶
TRPM6	Skrzypczak <i>et al</i> (20)	Colorectal Tissue (24) Colorectal Tissue (24)	Colorectal carcinoma (36) Colorectal adenocarcinoma (45)	-15.311 -23.416	-12.377 -17.382	7.31x10 ⁻¹⁸ 3.14x10 ⁻²⁰
	Sabates-Bellver <i>et al</i> (22)	Ascending Colon (4) Sigmoid colon (15) Descending colon (5) Transverse colon (1) Rectum (7) Ascending colon (4) Sigmoid colon (15) Descending colon (15) Transverse colon (1) Rectum (7)	Rectal adenoma (7) Colon adenoma (25)	-10.094 -29.071	-13.134 -14.421	2.76x10 ⁻⁹ 2.09x10 ⁻¹⁷
	Hong <i>et al</i> (21)	Colon (12)	Colorectal carcinoma (70)	-17.076	-18.137	2.29x10 ⁻²⁶
	TCGA	Colon (19) Rectum (3)	Cecum adenocarcinoma (22)	-7.558	-15.345	6.67x10 ⁻¹⁹
	TCGA	Colon (19) Rectum (3)	Colon mucinous adenocarcinoma (22)	-7.851	-13.889	6.58x10 ⁻¹⁷
	TCGA	Colon (19) Rectum (3)	Colon adenocarcinoma (101)	-15.955	-17.402	4.79x10 ⁻²⁷
	TCGA	Colon (19) Rectum (3)	Rectal adenocarcinoma (60)	-16.23	-16.009	1.81x10 ⁻²⁵
	TCGA	Colon (19) Rectum (3)	Rectosigmoid adenocarcinoma (3)	-6.986	-13.172	5.47x10 ⁻⁹
	TCGA	Colon (19) Rectum (3)	Rectal mucinous adenocarcinoma (6)	-2.486	-6.936	3.47x10 ⁻⁶
	Skrzypczak <i>et al</i> (23)	Colon (10)	Colon adenoma (5)	-14.37	-18.47	8.42x10 ⁻¹¹
	Skrzypczak <i>et al</i> (23)	Colon (10)	Colon adenoma epithelia (5)	-23.56	-17.083	6.31x10 ⁻¹⁰
	Skrzypczak <i>et al</i> (23)	Colon (10)	Colon carcinoma (5)	-41.197	-25.401	1.64x10 ⁻¹⁰

Table III. Continued.

Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value
Skrzypczak <i>et al</i> (23)	Colon (10)	Colon (10)	Colon carcinoma epithelia (5)	-15.226	-15.723	7.73x10 ⁻¹⁰
Gaedcke <i>et al</i> (24)	Rectum (65)	Rectum (65)	Rectal adenocarcinoma (65)	-2.345	-17.187	2.83x10 ⁻¹⁰
Kaiser <i>et al</i> (25)	Colon (5)	Colon (5)	Rectal mucinous adenocarcinoma (4)	-3.254	-10.995	6.20x10 ⁻⁵
Kaiser <i>et al</i> (25)	Colon (5)	Colon (5)	Rectal adenocarcinoma (8)	-2.893	-8.959	2.39x10 ⁻⁵
Kaiser <i>et al</i> (25)	Colon (5)	Colon (5)	Rectosigmoid adenocarcinoma (10)	-2.579	-6.526	1.92x10 ⁻⁵
Kaiser <i>et al</i> (25)	Colon (5)	Colon (5)	Colon mucinous adenocarcinoma (13)	-13.448	-9.454	1.72x10 ⁻⁵
Kaiser <i>et al</i> (25)	Colon (5)	Colon (5)	Cecum adenocarcinoma (17)	-2.538	-7.776	3.94x10 ⁻⁵
Kaiser <i>et al</i> (25)	Colon (5)	Colon (5)	Colon adenocarcinoma (41)	-2.785	-9.252	6.54x10 ⁻⁵

TRPMs, Transient Receptor Potential Melastatin; TCGA, The Cancer Genome Atlas.

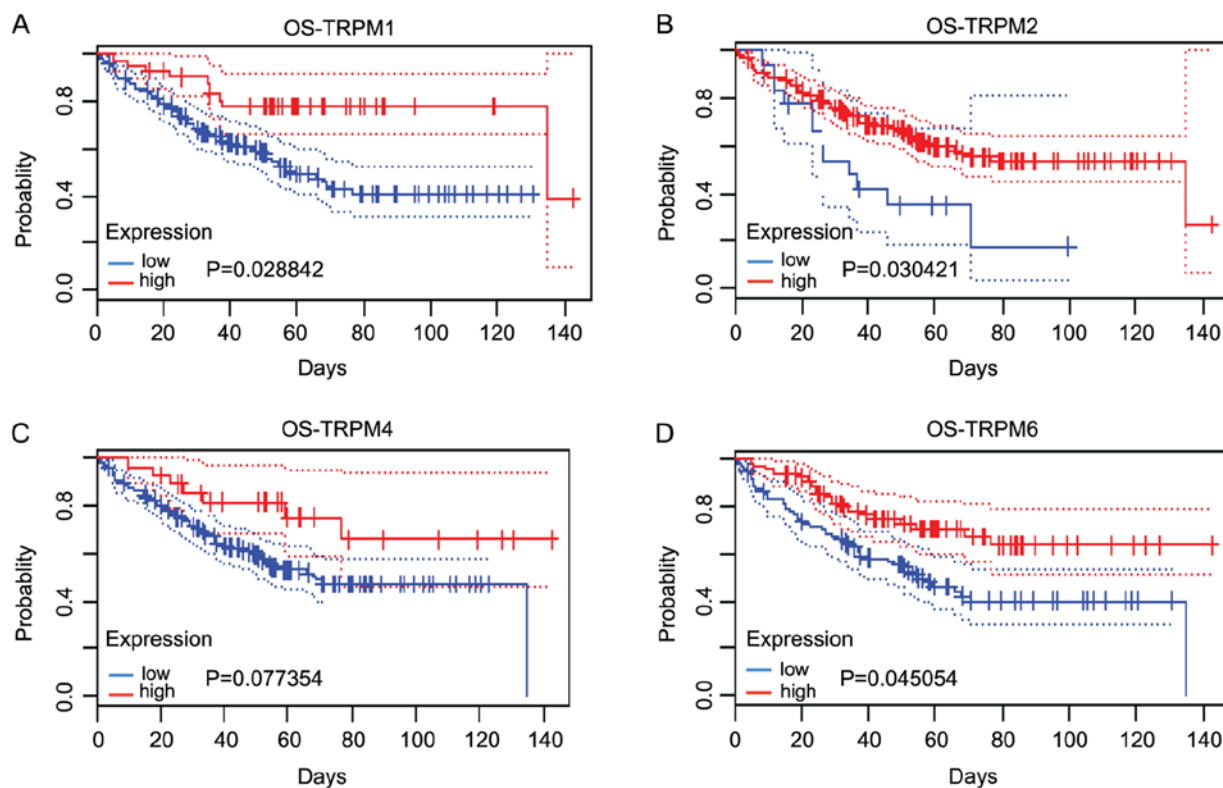


Figure 4. Survival analyses of TRPM protein family in colorectal cancer. Survival analyses of (A) TRPM1, (B) TRPM2, (C) TRPM4 and (D) TRPM6 were obtained from the Kaplan-Meier Plotter database. TRPM, transient receptor potential melastatin; OS, overall survival.

Expression levels and prognostic values of TRPMs in gastric cancer. In the dataset from D'Errico *et al* (26), TRPM1 and TRPM6 were decreased in gastric mixed adenocarcinoma compared with in gastric mucosa. According to Wang *et al* (27), it was revealed that TRPM3 levels were decreased in gastric cancer compared with gastric mucosa and gastric tissue. However, there was no difference observed in the expression levels between gastric cancer and control tissue groups in the other members of the

TRPM protein family. The detailed results are presented in Table IV.

The present study then assessed the prognostic effects of TRPM1, TRPM3 and TRPM6 in gastric cancer. The prognostic effects of these genes are presented in Fig. 5. For intestinal-type patients, high mRNA expression levels of TRPM1, TRPM3 and TRPM6 were significantly associated with improved OS [TRPM1: Hazard ratio (HR)=1.4 (1.02-1.92); P=0.035; TRPM3: HR, 1.68 (1.23-2.31); P=0.0011; TRPM6: HR=1.64

Table IV. Datasets of TRPM protein family in gastric cancer.

Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value
TPRM1	D' Errico <i>et al</i> (26)	Gastric mucosa (31)	Gastric mixed adenocarcinoma (4)	-3.576	-3.638	0.008
TPRM3	Wang <i>et al</i> (27)	Gastric mucosa (12) Gastric tissue (3)	Gastric cancer (12)	-3.251	-3.398	0.001
TRPM6	D' Errico <i>et al</i> (26)	Gastric mucosa (31)	Gastric mixed adenocarcinoma (4)	-2.025	-4.013	0.004

TRPMs, Transient Receptor Potential Melastatin.

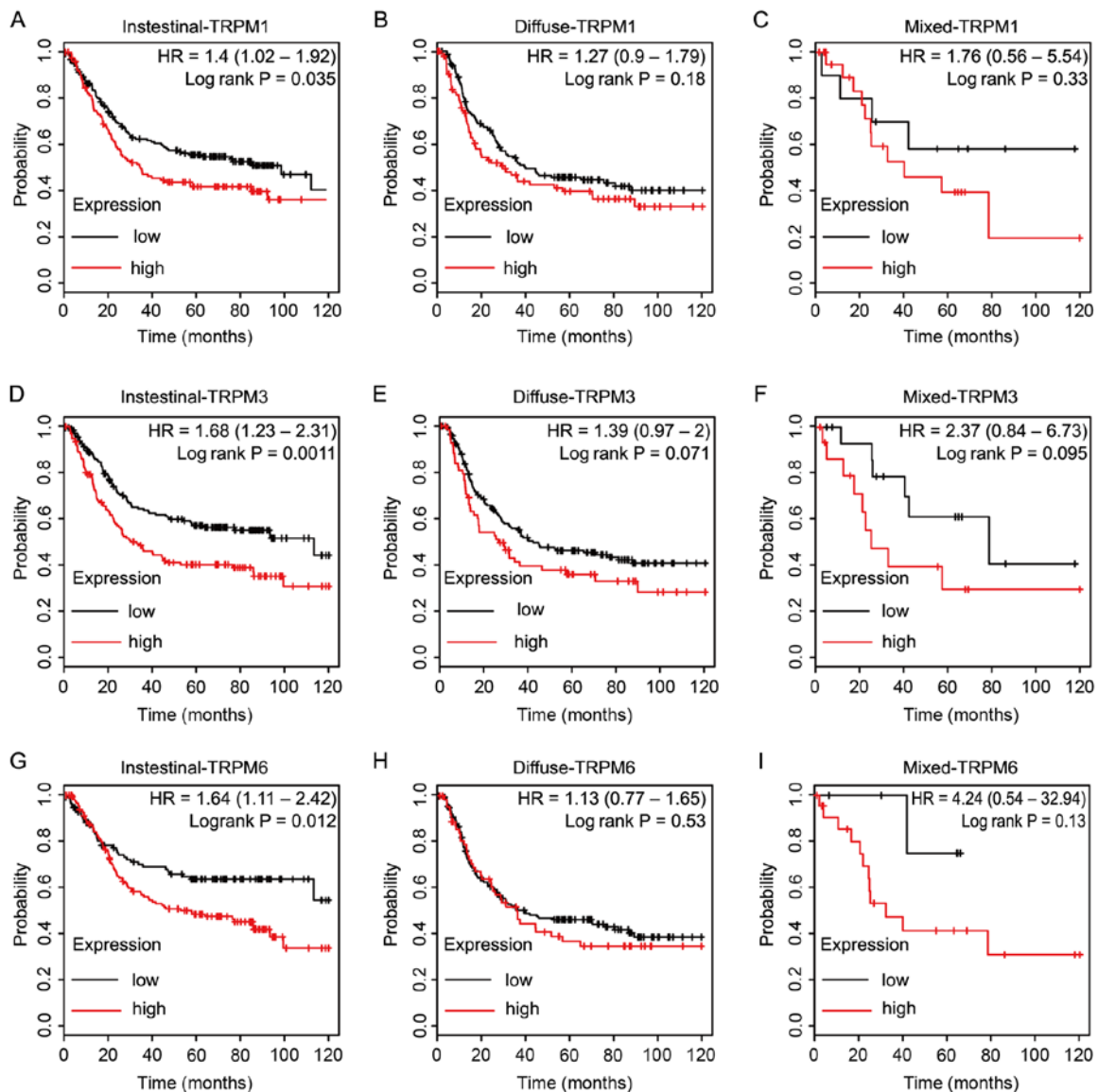


Figure 5. Survival analyses of the TRPM protein family in gastric cancer. Survival analyses of (A-C) TRPM1 (D-F), TRPM3 and (G-I) TRPM6 were obtained from the Kaplan-Meier Plotter database. TRPM, transient receptor potential melastatin; HR, hazard ratio.

(1.11-2.42); $P=0.012$]. However, it was revealed that the mRNA expression levels of TRPM1, TRPM3 and TRPM6 were not associated with longer OS in patients with gastric mixed types and diffuse types of cancer.

Expression levels and prognostic values of TRPMs liver cancer. By analyzing the Oncomine database, only TRPM8 was differentially expressed; its mRNA expression level was significantly increased compared with that in the control liver

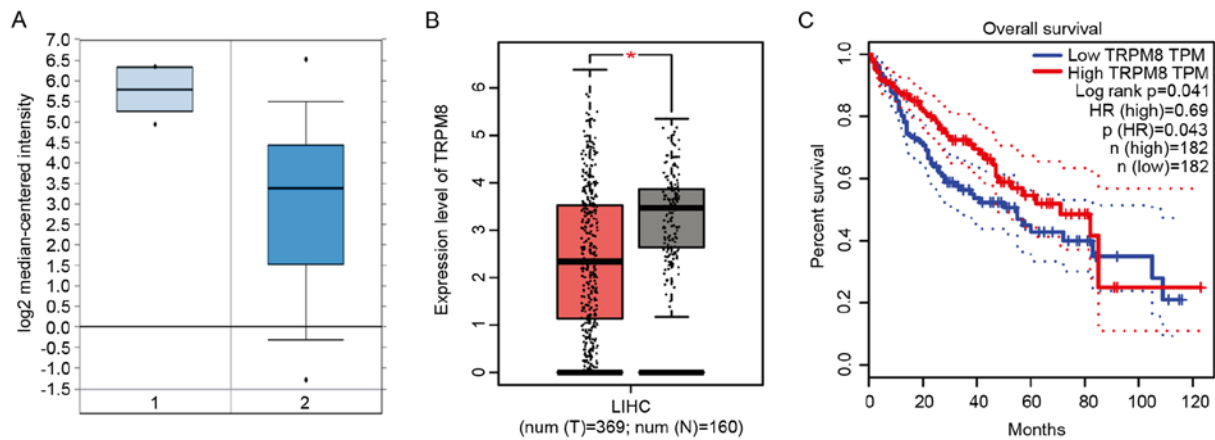


Figure 6. Validation of TRPM8 in liver cancer. (A) Data obtained from the Oncomine database indicated that TRPM8 was significantly downregulated in liver cancer tissues. (B) The GEPIA database also revealed a decreased expression level of TRPM8 in liver cancer tissues compared with control colon tissues. * $P < 0.05$. (C) Kaplan-Meier survival curves obtained from the GEPIA database indicated that patients with liver cancer exhibiting increased expression levels of TRPM8 exhibited improved overall survival time. TRPM, transient receptor potential melastatin; GEPIA, Gene Expression Profiling Interactive Analysis; HR, hazard ratio; LIHC, liver hepatocellular carcinoma.

tissues (FC=-6.512; $P=7.31E-09$; Fig. 6A). In addition, the present study further determined that the TRPM8 levels were significantly elevated in liver cancer tissues by analyzing the GEPIA database ($P < 0.05$; Fig. 6B). In addition, the present study mapped the survival curves of patients with high (red) and low (black) expression of liver cancer from the GEPIA database, demonstrating that the OS time of patients with high TRPM8 gene expression was significantly shorter (HR=0.69; $P=0.041$; Fig. 6C).

Expression levels and prognostic values of TRPMs in prostate cancer. In the Oncomine database, 7 datasets possessed significant differences between prostate cancer and control tissue in total. According to Tomlins *et al* (28), TRPM1 and TRPM2 levels were decreased in prostate cancer (TRPM1: FC=-2.195; $t=-3.77$; $P=3.12 \times 10^{-4}$; TRPM2: FC=-2.455; $t=-4.001$; $P=1.75 \times 10^{-4}$). However, the opposite conclusion was drawn from a series of databases that demonstrated that TRPM4 and TRPM8 were increased in prostate cancer when compared with the normal prostate (29-34). The detailed results are presented in Table V.

Subsequently, the present study evaluated the prognostic effect of the TRPM protein family members (TRPM1, TRPM2, TRPM4 and TRPM8) on the prognosis of prostate cancer through the Prognoscan database. Only TRPM8 expression exhibited a statistically significant association with the prognosis of the patient [$P=0.006968$; HR=0.87 (0.78-0.96); Fig. 7].

Expression levels and prognostic values of TRPMs in melanoma. A total of 3 datasets revealed significant differences between melanoma and control tissues in the Oncomine database. In the studies by Talantov *et al* (35) and Haqq *et al* (36), it was revealed that the level of TRPM1 expression in control skin tissues was low, while it increased markedly in melanoma samples. According to Haqq *et al* (36), TRPM2 was also demonstrated to be upregulated in melanoma tissues when compared with control skin tissues. However, in the study conducted by Riker *et al* (37), the expression levels of TRPM4

and TRPM7 were markedly elevated in cutaneous melanoma samples when compared with control tissues. The results are presented in Table VI.

To further assess the role of TRPM protein family in cancer progression of patients with melanoma, the present study used the Prognoscan database to calculate prognostic values based on cox $P < 0.05$ (12). As presented in Fig. 8, TRPM1 and TRPM4 were significantly associated with OS.

Expression levels and prognostic values of TRPMs in other types of cancer. The present study also analyzed the transcriptional level of TRPMs in certain other types of solid tumor. It was suggested that the most marked differences were observed in kidney cancer, esophageal cancer, brain and central nervous system (CNS) cancer, and head and neck cancer (Fig. 1). All the detailed analyses of the aforementioned cancer types are summarized in Table VII. For clear cell renal cell carcinoma, which is the most common type of kidney cancer, all genes were downregulated (38-42). TRPM4, TRPM5 and TRPM8 in the study by Yusenko *et al* (43) were increased in renal oncocytoma samples when compared with the control group. However, there were no statistically significant differences observed in TRPM2 and TRPM6 levels between kidney cancer and control tissues. TRPM4 expression was upregulated in esophageal cancer, while TRPM1 and TRPM8 expression levels were decreased (44-46). In the cases of brain and CNS cancer, TRPM2, TRPM3 and TRPM6 were expressed at low levels in different types of brain and CNS cancer (47-51). However, TRPM8 was elevated in glioblastoma when compared with control brain tissues in the data by Murat *et al* (51) and Lee *et al* (49). Notably, only TRPM1 was expressed at an increased level in head and neck squamous cell carcinoma when compared with buccal mucosa (FC=-5.324; $t=-8.031$; $P=1.52E-10$) according to the study by Ginos *et al* (52).

Subsequently, the present study further analyzed the association between the TRPMs and the survival rate of patients in all the aforementioned types of cancer using the Prognoscan database (12). In conclusion, the effect of the TRPM protein family on the prognosis of renal cancer was not significant. In particular, the high expression of TRPM8 was

Table V. Datasets of TRPM protein family in prostate cancer.

Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value
TRPM1	Tomlins <i>et al</i> (28)	Prostate gland (23)	Prostatic intraepithelial neoplasia (13)	-2.195	-3.77	3.12x10 ⁻⁴
TRPM2	Tomlins <i>et al</i> (28)	Prostate gland (21)	Prostatic intraepithelial neoplasia (13)	-2.455	-4.001	1.75x10 ⁻⁴
TRPM4	Varambally <i>et al</i> (29)	Prostate gland (6)	Prostate carcinoma (7)	3.622	8.767	3.94x10 ⁻⁶
	Liu <i>et al</i> (30)	Prostate gland (13)	Prostate carcinoma (44)	2.753	5.931	2.57x10 ⁻⁶
	Vanaja <i>et al</i> (31)	Prostate gland (8)	Prostate adenocarcinoma (27)	3.937	6.464	4.24x10 ⁻⁷
	Grasso <i>et al</i> (32)	Prostate gland (28)	Prostate carcinoma (59)	3.059	8.109	7.08x10 ⁻¹¹
	Arredouani <i>et al</i> (33)	Prostate gland (8)	Prostate carcinoma (13)	2.761	4.796	1.13x10 ⁻¹¹
	Wallace <i>et al</i> (34)	Prostate gland (20)	Prostate adenocarcinoma (69)	4.542	4.226	1.59x10 ⁻⁴
TRPM8	Vanaja <i>et al</i> (31)	Prostate gland (8)	Prostate adenocarcinoma (27)	2.883	3.082	0.005

TRPMs, Transient Receptor Potential Melastatin; TCGA, The Cancer Genome Atlas.

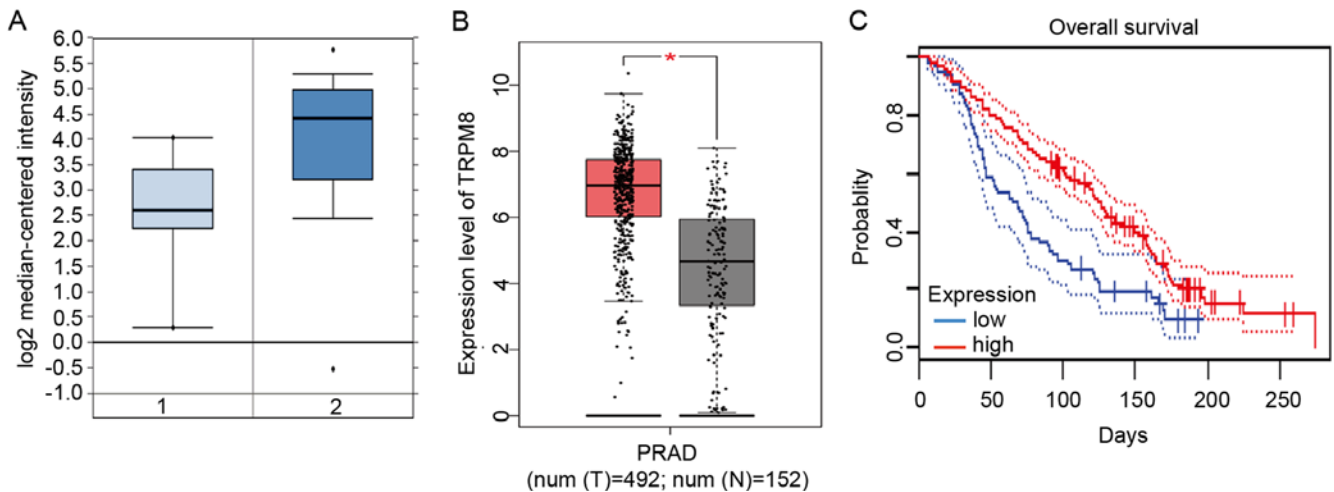


Figure 7. Validation of TRPM8 in prostate cancer. (A) Data obtained from the Oncomine database indicated that TRPM8 was significantly upregulated in prostate cancer tissues. (B) The GEPIA database also revealed a decreased expression level of TRPM8 in prostate cancer tissues compared with normal colon tissues. *P<0.05. (C) Kaplan-Meier survival curves obtained from the PrognScan databases indicated that patients with prostate cancer exhibiting increased expression levels of TRPM8 had a poorer overall survival time. TRPM, transient receptor potential melastatin; GEPIA, Gene Expression Profiling Interactive Analysis; PRAD, prostate adenocarcinoma.

associated with poor OS in patients with esophageal cancer [P=0.001214; HR=225.46 (8.47-6004.05)]. As for brain cancer, increasing TRPM6 levels were associated with poor prognosis [P=0.010649; HR=3.70 (1.36-10.09)]. However, there may be no association between this protein family with the survival outcomes of patients with head and neck cancer.

Discussion

Despite increasing advances in early diagnosis and treatment options, cancer remains a significant cause of morbidity and mortality worldwide (1,53,54). Tumor formation and metastasis is a complex process, and is the result of various gene dysregulation events and cellular processes, including tumorigenesis, basement membrane degradation, matrix permeability, cell adhesion and angiogenesis. Ca²⁺ signaling pathways are necessary for regulation of the cell cycle, cell proliferation and apoptosis, and are involved in the process of tumorigenesis (55). TRPM, one superfamily of the TRP cation

channel, contributes to the regulation of intracellular Ca²⁺ concentration (56,57). The TRPM protein family consists of 8 structural and functional channels that are widely expressed in a number of different types of tissue and have diverse physiological functions (8). The TRPM protein family may serve as triggers for enhanced proliferation and aberrant differentiation, which leads to the pathogenic proliferative and invasive characteristics of cancer (58). Differences in expression of the TRPM channels may provide a new basis for tumor diagnosis, and may be a novel target for cancer therapy. The present study used the Oncomine database to systematically analyze the mRNA expression levels of the TRPM protein family in different types of tumor, and assessed the prognostic values using the Kaplan-Meier plotter, and PrognScan and GEPIA databases.

Breast cancer remains the most common type of malignant tumor and the leading cause of cancer-associated mortality among women worldwide (1,59). Due to its high heterogeneity, it is necessary to constantly investigate new biomarkers

Table VI. Datasets of TRPM protein family in melanoma.

Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value
TRPM1	Talantov <i>et al</i> (35)	Skin (7)	Benign melanocytic skin nevus (18)	34.333	7.586	4.13x10 ⁻⁷
	Talantov <i>et al</i> (35)	Skin (7)	Cutaneous melanoma (45)	19.17	8.278	2.83x10 ⁻⁵
	Haqq <i>et al</i> (36)	Skin (3)	Non-neoplastic nevus (9)	2.634	6.291	5.33x10 ⁻⁵
TRPM2	Haqq <i>et al</i> (36)	Skin (3)	Melanoma (6)	3.106	10.783	6.70x10 ⁻⁶
	Haqq <i>et al</i> (36)	Skin (3)	Non-neoplastic nevus (9)	2.316	7.136	1.58x10 ⁻⁵
TRPM4	Riker <i>et al</i> (37)	Skin (4)	Cutaneous melanoma (14)	-7.112	-5.004	6.51x10 ⁻⁵
TRPM7	Riker <i>et al</i> (37)	Skin (4)	Cutaneous melanoma (14)	-2.601	-3.968	5.59x10 ⁻⁴

TRPMs, Transient Receptor Potential Melastatin.

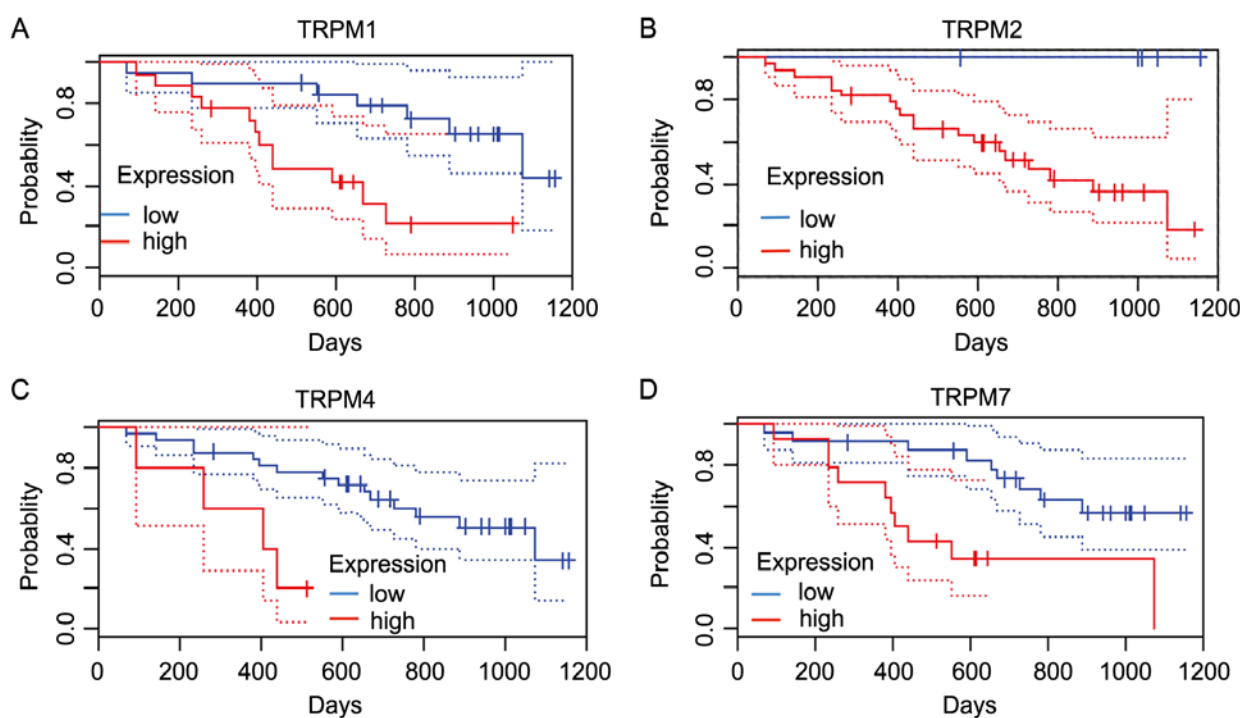


Figure 8. Survival analyses of TRPM protein family in melanoma. Survival analyses of (A) TRPM1, (B) TRPM2, (C) TRPM4 and (D) TRPM7 were obtained from the Kaplan-Meier Plotter database. TRPM, transient receptor potential melastatin.

in order to distinguish different subtypes and predict their clinical behavior and therapeutic response (60-62). The expression of TRPM2 and TRPM4 were upregulated in ductal carcinoma and invasive breast cancer when compared with control breast tissue. By contrast, TCGA database demonstrated that TRPM3 and TRPM6 were downregulated in invasive breast tumors. The results from the present study suggested that TRPM2, TRPM3, TRPM4 and TRPM6 may be used as molecular biomarkers to identify breast cancer invasion (63). The Kaplan-Meier analysis demonstrated that decreased TRPM2 may be used to predict prognosis in patients with Luminal B breast cancer and HER2⁺ breast cancer subtypes. High expression of TRPM4 and TRPM6 indicated lower survival rates in patients with basal and HER2⁺ subtypes. In addition, according to the analysis of the present study, TRPM3 may be used as a biomarker for

the Luminal B breast cancer subtype. The results suggested that certain members of the TRPM family may be potential biomarkers and targets for new breast cancer therapies. Associations between TRPM proteins and breast cancer continue to be identified as a result of rapid advances in molecular biology and genetics research (9). In addition, TRPM6 somatic mutations have also been observed in an independent cohort of breast cancer samples (64).

Lung cancer has the highest rates of incidence and mortality in China (65) and around the world (66). The present study systemically analyzed the expression and prognostic value of TRPMs in lung cancer. The results indicated that the decreased expression levels of TRPM1 and TRPM2, and increased expression levels of TRPM6 in lung adenocarcinoma may serve an important role in lung cancer tumorigenesis. The present study revealed that transcriptional TRPM2 is a novel

Table VII. Datasets of TRPM family in other cancers.

Cancer type	Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value	
Kidney	TRPM1	Cutcliffe <i>et al</i> (38)	Fetal kidney (3)	Renal wilms tumor (18)	-2.541	-3.605	9.45x10 ⁻⁴	
		Jones <i>et al</i> (39)	Kidney (23)	Clear cell renal cell carcinoma (23)	-4.321	-16.61	3.60x10 ⁻¹⁶	
		Jones <i>et al</i> (39)	Kidney (23)	Renal pelvis urothelial carcinoma (8)	-3.927	-15.642	4.53x10 ⁻⁸	
	TRPM3	Cutcliffe <i>et al</i> (38)	Fetal kidney (3)	Renal wilms tumor (18)	-2.484	-9.971	3.28x10 ⁻⁹	
		Cutcliffe <i>et al</i> (38)	Fetal kidney (3)	Clear cell sarcoma of the kidney (14)	-2.3	-8.486	2.07x10 ⁻⁷	
		Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Renal wilms tumor (4)	-15.445	-8.899	3.90x10 ⁻⁵	
		Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Chromophobe renal cell carcinoma (4)	-24.806	-7.897	3.06x10 ⁻⁴	
		Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Renal oncocytoma (4)	-12.037	-6.976	3.16x10 ⁻⁴	
		Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Papillary renal cell carcinoma (19)	-2.491	-3.007	0.004	
		Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Clear cell renal cell carcinoma (26)	-2.155	-2.816	0.006	
		Jones <i>et al</i> (39)	Kidney (23)	Renal pelvis urothelial carcinoma (8)	-2.588	-10.534	1.22x10 ⁻¹¹	
		Jones <i>et al</i> (39)	Kidney (23)	Chromophobe renal cell carcinoma (6)	-2.097	-13.197	2.10x10 ⁻⁹	
		Jones <i>et al</i> (39)	Kidney (23)	Clear cell renal cell carcinoma (23)	-2.48	-6.97	8.02x10 ⁻⁹	
		Gumz <i>et al</i> (40)	Kidney (10)	Clear cell renal cell carcinoma (10)	-3.346	-7.187	6.29x10 ⁻⁷	
		Beroukhim <i>et al</i> (41)	Renal cortex (10) Renal tissue (1)	Non-hereditary clear cell renal cell carcinoma (27)	-5.56	-6.922	5.03x10 ⁻⁸	
		Beroukhim <i>et al</i> (41)	Renal cortex (10) Renal tissue (1)	Hereditary clear cell Renal cell carcinoma (32)	-4.687	-7.061	1.26x10 ⁻⁷	
		Lenburg <i>et al</i> (42)	Kidney (9)	Clear cell renal cell carcinoma (9)	-2.934	-5.54	6.54x10 ⁻⁵	
		TRPM4	Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Renal oncocytoma (4)	3.218	5.827	3.24x10 ⁻⁴
			Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Renal oncocytoma (4)	-8.912	-11.645	5.16x10 ⁻⁶
			Beroukhim <i>et al</i> (41)	Renal cortex (10) Renal tissue (1)	Hereditary clear cell Renal cell carcinoma (32)	-2.236	-8.049	9.29x10 ⁻⁸
Gumz <i>et al</i> (40)	Kidney (10)		Clear cell renal cell carcinoma (10)	-3.562	-4.352	2.26x10 ⁻⁴		
TRPM5	Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Renal wilms tumor (4)	9.955	3.917	0.003		
TRPM7	Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Renal wilms tumor (4)	-2.16	-6.705	6.05x10 ⁻⁴		
TRPM8	Yusenko <i>et al</i> (43)	Fetal kidney (2) Kidney (3)	Papillary renal cell carcinoma (19)	22.217	4.332	5.07x10 ⁻⁴		
Esophageal	TRPM1	Hao <i>et al</i> (44)	Duodenum (13) Esophagus (14)	Esophageal Adenocarcinoma (5)	-3.222	-4.282	3.87x10 ⁻⁴	
	TRPM4	Kimchi <i>et al</i> (45)	Esophagus (8)	Barrett's esophagus (8)	4.661	3.301	0.003	

Table VII. Continued.

Cancer type	Gene	Dataset	Normal (n)	Tumor type (n)	Fold change	t-test	P-value	
	TRPM8	Kimchi <i>et al</i> (45)	Esophagus (8)	Esophageal adenocarcinoma (8)	4.448	3.535	0.002	
		Kim <i>et al</i> (46)	Esophagus (28)	Barrett's esophagus (15)	3.233	8.597	3.60x10 ⁻⁸	
		Kimchi <i>et al</i> (45)	Esophagus (8)	Esophageal adenocarcinoma (8)	-3.315	-3.413	0.003	
Brain and CNS	TRPM2	Liang <i>et al</i> (47)	Brain (2) Cerebellum (1)	Oligoastrocytoma (3)	-2.694	-4.518	0.007	
		Bredel <i>et al</i> (48)	Brain (4)	Anaplastic oligodendroglioma (3)	-4.071	-5.62	0.005	
	TRPM3	Lee <i>et al</i> (49)	Neural stem cell (3)	Glioblastoma (22)	4.661	3.301	5.67x10 ⁻⁵	
		Sun <i>et al</i> (50)	Brain (23)	Oligodendroglioma (50)	-2.286	-8.417	3.95x10 ⁻¹²	
		Sun <i>et al</i> (50)	Brain (23)	Glioblastoma (81)	-2.447	-10.147	2.32x10 ⁻¹⁷	
	TRPM6	TCGA	Brain (10)	Brain glioblastoma (542)	-16.791	-16.791	1.92x10 ⁻⁹	
		Murat <i>et al</i> (51)	Brain (4)	Glioblastoma (80)	-2.46	-5.563	0.001	
		Sun <i>et al</i> (50)	Brain (23)	Diffuse astrocytoma (7)	-2.5	-3.865	0.001	
		TRPM8	Murat <i>et al</i> (51)	Brain (4)	Glioblastoma (80)	2.49	8.432	4.39x10 ⁻¹¹
			Lee <i>et al</i> (49)	Neural stem cell (3)	Glioblastoma (22)	5.257	6.712	4.98x10 ⁻⁶
Head and neck	TRPM1	Ginos <i>et al</i> (52)	Buccal Mucosa (13)	Head and neck squamous cell carcinoma (41)	-5.324	-8.031	1.52 x10 ⁻¹⁰	

TRPMs, Transient Receptor Potential Melastatin; TCGA, The Cancer Genome Atlas; CNS, central nervous system.

prognostic biomarker for lung adenocarcinoma; consistent with the results of Huang *et al* (67), which demonstrate that the knockdown of TRPM2-antisense also significantly inhibited cell proliferation.

Colorectal cancer is the third most common diagnosed type of cancer in humans which poses a significant public health issue worldwide, with >1.8 million cases diagnosed each year (1,68). As a result of the numerous studies investigating TRPM channels and colorectal cancer, tumor treatment options are becoming more diverse and accurate for colorectal cancer. The present study revealed that TRPM1, TRPM2 and TRPM6 may serve as diagnostic markers for the prognosis of colorectal cancer development and are useful targets for pharmaceutical interventions. These data provide evidence to support the hypothesis that TRPM1, TRPM2 and TRPM6 serve a crucial role in tumor growth and metastasis formation (8).

The results of the present study may contribute to a more complete understanding of the expression levels and prognostic values of TRPM family members in certain solid tumors, including gastric cancer, which causes nearly 1 million mortalities worldwide each year (1,69,70). Certain cell channels, including TRP, are more active or are upregulated in gastric cancer cells (70). The present study suggested that the abnormal regulation of TRPM1, TRPM2 and TRPM3 may be vital in the development of intestinal type gastric cancer. They may participate in different stages of tumorigenesis. Not all TRPM channels have been investigated thoroughly and the current literature base remains

inadequate. The results from the present study regarding TRPM2 expression are in concordance with the data from the study by Almasi *et al* (71), which suggested that TRPM2 knockdown inhibits cell proliferation, and promotes apoptosis in gastric cancer cells. However, research is currently focused on TRPM7, and there are few studies on TRPM1 and TRPM3. Therefore, future studies investigating these specific proteins are required.

The present study aimed to assess the importance of TRPMs in liver cancer, the fourth most common cause of mortality associated with cancer (1). The most significant finding from the present study was that the OS time of patients with liver cancer exhibiting increased TRPM8 expression levels was significantly shorter compared with those patients with decreased TRPM8 expression. This suggested that TRPM8 may be a novel marker for liver cancer survival and prognostic accuracy. However, these results must be interpreted with caution, as further work is required in order to establish the viability of this new marker.

Prostate cancer is a common form of cancer in adult males which is responsible for one-fourth of all incident cancer cases in western countries, with its incidence continuing to increase (66,72). The present study suggested that TRPM8 served a key role in mediating the biological behavior of prostate tumors, consistent with the results of numerous independent studies demonstrating that TRPM8 was important for the survival, migration and invasion of prostate cancer cells (73,74).

Deeds *et al* (75) demonstrated that TRPM1 was expressed at high levels in poorly metastatic variants of the melanoma cell line. The Oncomine database and the Kaplan-Meier plotter survival analyses performed in the present study also demonstrated that TRPM1 was considered to be a tumor activator of melanoma. The data implied that low TRPM1 expression levels were associated with decreased OS rates in comparison with high TRPM1 levels. When examining TRPM4, the results of the present study also suggested that it may serve as a factor in regulating melanoma proliferation, apoptosis and necrosis.

In the present study, it was also revealed that the downregulation of TRPM4 expression was associated with improved OS in patients with glioma. In addition, the potential association between TRPM8 and esophageal cancer OS was measured, and the results implied that TRPM8 may be a prognostic marker and potential therapeutic target for esophageal cancer. However, this family appears to not be associated with OS in kidney cancer and head and neck cancer.

In summary, the results of the present study indicated that certain members of the TRPM protein family exhibit significant differences in mRNA expression levels between cancer and control tissues. A number of these proteins may be useful biomarkers for cancer prognosis, and may represent novel anticancer targets.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

FHQ and XLM were responsible for the Oncomine and Kaplan-Meier plotter analysis and writing the original draft. LDL was involved in the PrognoScan analysis and interpretation of the data, and revising the manuscript critically for important intellectual content. MHH was involved in revising the manuscript and participated in the interpretation of data. HT made contributions to the acquisition of data. XHJ was involved in the GEPIA analysis and interpretation of the data. JPZ was responsible for the conception, design of the study and revising the manuscript critically for important intellectual content. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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