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The Prognostic Significance of Transient Receptor Potential Canonical 1 and Its Association with Vascular Endothelial Growth Factor Receptor 2 in Papillary Thyroid Carcinoma Patients

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Transient receptor potential canonical 1 (TRPC1) facilitates the proliferation, invasion, and metastasis of thyroid cancer cells through up-regulating vascular endothelial growth factor receptor 2 (VEGFR2), while its clinical role in papillary thyroid carcinoma (PTC) is unknown. This study intended to evaluate the prognostic value of TRPC1 and its correlation with VEGFR2 in PTC patients. In this retrospective study, tumor TRPC1 immunohistochemistry (IHC) score was evaluated in 287 PTC patients who underwent surgical resection and 30 thyroid benign lesion (TBL) patients. Moreover, 50 tumor tissue samples from PTC patients were randomly selected for VEGFR2 IHC score evaluation. Our study showed that tumor TRPC1 IHC score was increased in PTC patients versus TBL patients (P = 0.006). Meanwhile, tumor TRPC1 IHC score was related to extrathyroidal invasion (P = 0.028) and pathological node stage 1 (P = 0.011) in PTC patients. Tumor TRPC1 IHC score > 0 was not related to disease-free survival (DFS) or overall survival (OS) (both P > 0.05); however, tumor TRPC1 IHC score > 3 was linked with shortened DFS (P = 0.005) and OS (P = 0.020) in PTC patients. By time-dependent area under curve (AUC) analyses, tumor TRPC1 IHC score showed good values in estimating relapse and death risks over 7 years with all AUCs above 0.7. Furthermore, tumor TRPC1 IHC score > 3 independently predicted shorter DFS (hazard ratio = 2.948, P = 0.045), but not OS (P > 0.05) in PTC patients. Tumor TRPC1 IHC score was positively associated with tumor VEGFR2 IHC score in PTC patients (P = 0.010). Collectively, TRPC1 links with extrathyroidal and lymph node invasion, elevated disease relapse risk, and increased VEGFR2 in PTC patients.

Keywords: clinicopathological features; disease-free survival and overall survival; papillary thyroid carcinoma; transient receptor potential canonical 1; vascular endothelial growth factor receptor 2
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Introduction

Papillary thyroid carcinoma (PTC) accounts for about 79.0%-90.0% of all thyroid cancer cases, which is characterized by a high degree of differentiation and slow growth (Pusztaszeri and Auger 2017; Hu et al. 2021; Jung et al. 2022). Notably, the global incidence of PTC has been increasing in recent years, which leads to a certain degree of burden on the public health system (Sung et al. 2021; Lam 2022). The main modality for PTC treatment is surgical resection followed by postoperative endocrine therapy or radionuclide therapy (Haddad et al. 2022). Although the 10-year survival rate of PTC patients is more than 90%, there is still a certain proportion of patients who suffer from aggressive metastasis and disease recurrence, which seriously threatens their survival (Huang et al. 2021; Spyroglou et al. 2022; Masui et al. 2023). Thus, seeking potential biomarkers that reflect the prognosis of PTC patients is essential, which may contribute to improving their clinical management.

Transient receptor potential canonical 1 (TRPC1) consists of six transmembrane segments with the N- and C-termini located in the cytoplasm (Nesin and Tsiokas 2014). As a member of the Transient receptor potential (TRP) channel superfamily, TRPC1 interacts with a variety of proteins to mediate its effect on Ca^{2+} signaling, thereby affecting basic cell functions, such as proliferation, survival, differentiation, secretion, and migration (Nesin and Tsiokas

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2014). In terms of the role of TRPC1 in cancer, TRPC1 regulates tumor growth, proliferation, metastasis, and survival by promoting store-operated calcium entry (SOCE) (Sobradillo et al. 2014; Ambudkar et al. 2017; Wang et al. 2018; Villalobos et al. 2019; Elzamzamy et al. 2020). In addition, TRPC1 regulates calcium signaling, which is further involved in the progression of cancer epithelial-to-mesenchymal transition, as well as affects the efficacy of chemotherapy agents (El Hiani et al. 2009a, b; Overley-Adamson et al. 2014; Schaar et al. 2016; Bong et al. 2020; Zhang et al. 2020; Sun et al. 2021). Previous studies have revealed that TRPC1 regulates various cell malignant behaviors in head and neck cancers, such as thyroid cancer and nasopharyngeal carcinoma (He et al. 2012; Asghar et al. 2015; Elzamzamy et al. 2020). For example, one study shows that the knockdown of TRPC1 reduces proliferation, invasion, and migration of human thyroid cancer cells (Asghar et al. 2015). Another study illustrates that the blockade of TRPC1 inhibits the invasion of nasopharyngeal carcinoma cells (He et al. 2012). Regarding clinical research, one study reveals that TRPC1 is overexpressed in tongue squamous cell carcinoma tissues; it also reflects lymph node metastasis and higher tumor stage in tongue squamous cell carcinoma patients (Shi et al. 2022).

Currently, TRPC1 has been revealed to participate in the progression of thyroid cancer through up-regulating the expression of the vascular endothelial growth factor receptor 2 (VEGFR2) (Asghar et al. 2015). Notably, VEGFR2 is an angiogenic factor that is considered to be involved in the progression of PTC (Mohamad Pakarul Razy et al. 2019; Chen et al. 2020). One previous study shows that the activation of the VEGFR2 pathway promotes PTC cell proliferation (Chen et al. 2020). Clinically, one research suggests that VEGFR2 is overexpressed in PTC patients (Mohamad Pakarul Razy et al. 2019). Considering the role of TRPC1 in the regulation of head and neck tumor progression and VEGRF2, it is hypothesized that TRPC1 may reflect tumor progression and prognosis, as well as intercorrelate with VEGFR2 in PTC patients. However, relevant studies are still lacking.

Therefore, the purpose of the current study was to investigate the clinical significance and prognostic value of TRPC1; meanwhile, this study also aimed to explore the relationship of TRPC1 with VEGFR2 in tumor tissues in PTC patients.

Methods

Study population

This retrospective study included 287 PTC patients who underwent surgical resection between August 2016 and December 2021. The inclusion criteria were: a) diagnosed as PTC by pathological methods; b) underwent surgical resection; c) aged more than 18 years old; d) had at least one available set of follow-up data for use; e) had completed medical records; f) had identifiable and retrievable tumor tissue sample. Patients with other primary cancers or hematological malignancies were excluded. Meanwhile, thirty thyroid benign lesions (TBL) patients were screened, who were age- and sex-matched with PTC patients. The eligible criteria for TBL patients were: a) diagnosed as TBL by pathological methods; b) aged over 18 years old; c) had identifiable and retrievable tumor samples; d) without other primary cancers. Besides, the Ethics Committee of Harbin Medical University Cancer Hospital gave approval to this study. All subjects or his/her families signed the informed consent.

Data collection

Age, sex, tumor size, extrathyroidal invasion, pathological tumor-node-metastasis (pTNM) stage, radioiodine, and follow-up data of PTC patients were collected from the electronic medical record system. Routine follow-ups (every 2 months in the 1st year, and every 3 months thereafter) were conducted until May 2023. During early follow-up, outpatient visits were recommended for all patients; during long-term follow-up thereafter, telephone return visits were recommended for patients without relapse. Patients who lost to follow-ups were recorded as censored at their last follow-ups. Lost to follow-ups were defined as patients who were not visited or could not be contacted in two follow-up visits (roughly 6 months). Based on the above follow-up data, the accumulating disease-free survival (DFS) rate and accumulating overall survival (OS) rate were calculated. DFS was defined as the duration between surgical resection and the occurrence of disease relapse or death from any cause. OS was defined as the duration between surgical resection and the occurrence of death from any cause. Besides, the age and sex of TBL patients were collected as well.

Tumor TRPC1 detection

After collecting tumor tissue samples from all subjects, the tumor TRPC1 immunohistochemistry (IHC) score was determined by an IHC assay. The goat polyclonal anti-TRPC1 antibody (1:150; No. Cat. ab110837, Abcam, Cambridge, Massachusetts, USA) was applied as the primary antibody, and the donkey anti-goat IgG (H&L) (HRP) (1:2000; No. Cat. ab6885, Abcam, Cambridge, Massachusetts, USA) was applied as the secondary antibody. The experiment was conducted strictly in accordance with the given instructions. After staining, the expression of TRPC1 was assessed based on the intensity and density of stained tissues. The intensity was classified into 0 to 3, and density was classified into 0 to 4. The total IHC score was the product of intensity and density, scaled from 0 to 12. For prognostic analysis, the tumor TRPC1 IHC score was grouped into two categories: = 0 and > 0, or ≤ 3 and > 3.

Tumor VEGFR2 detection

As per the findings of Asghar MY et al., TRPC1 played an important role in regulating the growth and invasion of thyroid carcinoma through VEGFR2 (Asghar et al.

2015). This study also delved into the analysis of the STRING database (https://cn.string-db.org/), which revealed that TRPC1 was capable of regulating multiple VEGF isoforms and other common oncogenes by regulating kinase insert domain receptor (KDR, known as VEGFR2), shown in Supplementary Fig. S1. Therefore, fifty tumor tissue samples from PTC patients were further randomly screened, and the VEGFR2 expression was detected by an IHC assay. The rabbit monoclonal anti-VEGF Receptor 2 (1:200; No. Cat. ab115805; Abcam, Cambridge, Massachusetts, USA) was applied as the primary antibody, and the goat anti-rabbit IgG (H&L) (HRP) (1:2000; No. Cat. ab6721; Abcam, Cambridge, Massachusetts, USA) was applied as the secondary antibody. The total IHC score was scaled from 0 to 12, which was the product of intensity and density. The tumor VEGFR2 IHC score was classified into two categories: = 0 and > 0, or ≤ 3 and > 3.

Statistical analyses

SPSS v. 26.0 (IBM, Armonk, New York, USA) was used for data analyses. The student t-test was used for comparing tumor TRPC1 IHC scores between PTC patients and TBL patients, as well as the differences between tumor TRPC1 IHC scores and characteristics of PTC patients. The Spearman test was used for analyzing the correlation between tumor TRPC1 IHC score and pT stage or pTNM stage. Kaplan-Meier curves were used to display accumulating DFS or OS rates, in which the Log-rank test was used for comparison. The time-dependent receiver operating curve (ROC) method was used for evaluating the ability of tumor TRPC1 IHC score to predict relapse or death, which was displayed via area under curves (AUC). Specifically, the time-dependent ROC was plotted through the following steps: firstly, the time point of interest was selected; secondly, the ROC curve at each time point was calculated; finally, the AUC of each time point was figured out based on the ROC curve. The multivariable Cox regression analyses were used to find factors related to DFS or OS, which was shown through forest plots. Tumor TRPC1 IHC score cut by 3, age, sex, tumor size, extrathyroidal invasion, pT stage, pN stage, and pTNM stage were included in the multivariable analyses, and enter method was used. The Pearson test was used to analyze the correlation between tumor TRPC1 IHC scores and tumor VEGFR2 IHC scores. The Chi-square test was used to compare tumor TRPC1 IHC scores and tumor VEGFR2 IHC scores cut by the IHC score of 0 or 3. Moreover, the tumor TRPC1 and VEGFR2 IHC scores were combined as a union, in which 'High level (0 cut)' was defined as both tumor TRPC1 and VEGFR2 IHC scores were > 0; 'Median level (0 cut)' was defined as either tumor TRPC1 or VEGFR2 IHC scores were > 0; 'Low level (0 cut)' was defined as both tumor TRPC1 and VEGFR2 IHC scores were < 0. Similarly, 'High level (3 cut)', 'Median level (3 cut)', and 'Low level (3 cut)' were defined. A $P < 0.05$ indicated statistical significance.

Results

Clinical features of PTC patients

The enrolled 287 PTC patients included 200 (69.7%) females and 87 (30.3%) males, and their median (interquartile range (IQR)) age was 43.0 (36.0-57.0) years. The median (IQR) value of tumor size was 3.7 (2.3-4.8) cm in PTC patients. There were 121 (42.2%) patients with extrathyroidal invasion. Among 287 PTC patients, there were 197 (68.6%) patients with pTNM stage I, 44 (15.3%) patients with pTNM stage II, 31 (10.8%) patients with pTNM stage III, and 15 (5.2%) patients with pTNM stage IV. A number of 152 (53.0%) PTC patients received radioiodine treatment. Moreover, PTC patients were followed up for a range of 6.0-78.5 months, among which 109 (38.0%) patients lost to follow-up. Other detailed information on PTC patients was displayed in Table 1.

Table 1. Clinical characteristics of PTC patients.

Characteristics	PTC patients (N = 287)
Age (years), median (IQR)	43.0 (36.0-57.0)
Sex, n (%)	
Female	200 (69.7)
Male	87 (30.3)
Tumor size (cm), median (IQR)	3.7 (2.3-4.8)
Extrathyroidal invasion, n (%)	121 (42.2)
pT stage, n (%)	
1	42 (14.6)
2	66 (23.0)
3	84 (29.3)
4a	75 (26.1)
4b	20 (7.0)
pN stage, n (%)	
0	80 (27.9)
1	207 (72.1)
pTNM stage, n (%)	
I	197 (68.6)
II	44 (15.3)
III	31 (10.8)
IV	15 (5.2)
Radioiodine, n (%)	152 (53.0)
Follow-up range (months)	6.0-78.5
Lost to follow-up [a], n (%)	109 (38.0)

PTC, papillary thyroid carcinoma; IQR, interquartile range; pT, pathological tumor; pN, pathological node; pTNM, pathological tumor-node-metastasis. 'a', Lost to follow-ups were defined as patients who were not visited or could not be contacted in two follow-up visits (roughly 6 months). The Kolmogorov-Smirnov test was utilized to verify if the data follows a normal distribution. Age and tumor size were not in normal distribution and were described with median (IQR).

Tumor TRPC1 IHC score between PTC patients and TBL patients

The comparative analysis showed that tumor TRPC1 IHC score was elevated in PTC patients in comparison with TBL patients (4.5 ± 2.9 vs. 3.0 ± 2.5) (P = 0.006) (Fig. 1A). Meanwhile, the IHC examples of TRPC1 expression in TBL patients and PTC patients were exhibited in Fig. 1B.

Linkage of tumor TRPC1 IHC score with clinical features in PTC patients

The association analyses suggested that the tumor TRPC1 IHC score was associated with extrathyroidal invasion (P = 0.028) and pN stage 1 (P = 0.011) in PTC patients. However, no relationship was observed in the tumor TRPC1 IHC score with other characteristics in PTC patients, such as age, sex, tumor size, pT stage, or pTNM stage (all P > 0.05) (Table 2).

Accumulating DFS and accumulating OS of PTC patients

There were 33 (11.5%) relapse cases, and the 3-, 5-, and 7-year accumulating DFS rates of PTC patients were 88.7%, 84.4%, and 84.4%, respectively. Meanwhile, there were 20 (7.0%) deaths, and the 3-, 5-, and 7-year accumulating OS rates of PTC patients were 93.2%, 89.2%, and 89.2%, correspondingly.

Linkage of tumor TRPC1 IHC score with DFS and OS in PTC patients

When the cut-off value of the tumor TRPC1 IHC score was 0, there was no correlation of tumor TRPC1 IHC score with DFS in PTC patients (P = 0.101) (Fig. 2A). Then, when the cut-off value of tumor TRPC1 IHC score was 3, it was found that tumor TRPC1 IHC score > 3 was related to shortened DFS in PTC patients (P = 0.005) (Fig. 2B). When the tumor TRPC1 IHC score of 0 was used as the cut-off value, the data revealed that there was no linkage of tumor TRPC1 IHC score with OS in PTC patients (P = 0.284) (Fig. 2C). However, when the tumor TRPC1 IHC score of 3 was set as the cut-off value, tumor TRPC1 IHC score > 3 was associated with reduced OS in PTC patients (P = 0.020) (Fig. 2D).

Furthermore, the time-dependent AUC curve revealed that tumor TRPC1 IHC score had good values in predicting relapse and death risks over 7 years with all AUCs above 0.7 (Fig. 2E-F).

Independent factors related to DFS and OS in PTC patients

Tumor TRPC1 IHC score > 3 [hazard ratio (HR) = 2.948, P = 0.045], tumor size > 4 cm (HR = 2.458, P = 0.049), extrathyroidal invasion (HR = 6.688, P = 0.006), and pN stage (HR = 4.197, P = 0.020) independently predicted shortened DFS in PTC patients (Fig. 3A). Additionally, tumor TRPC1 IHC score > 3 did not have the ability to independently estimate OS (HR = 3.590, P = 0.095), while extrathyroidal invasion independently forecasted unfavorable OS in PTC patients (HR = 7.638, P = 0.036) (Fig. 3B).

Linkage of tumor TRPC1 IHC score with tumor VEGFR2 IHC score in PTC patients

Based on the analysis of the STRING database, TRPC1 regulated various VEGF isoforms and other oncogenes by mediating VEGFR2. Thus, the correlation of TRPC1 with VEGFR2 in tumor tissues of PTC patients was

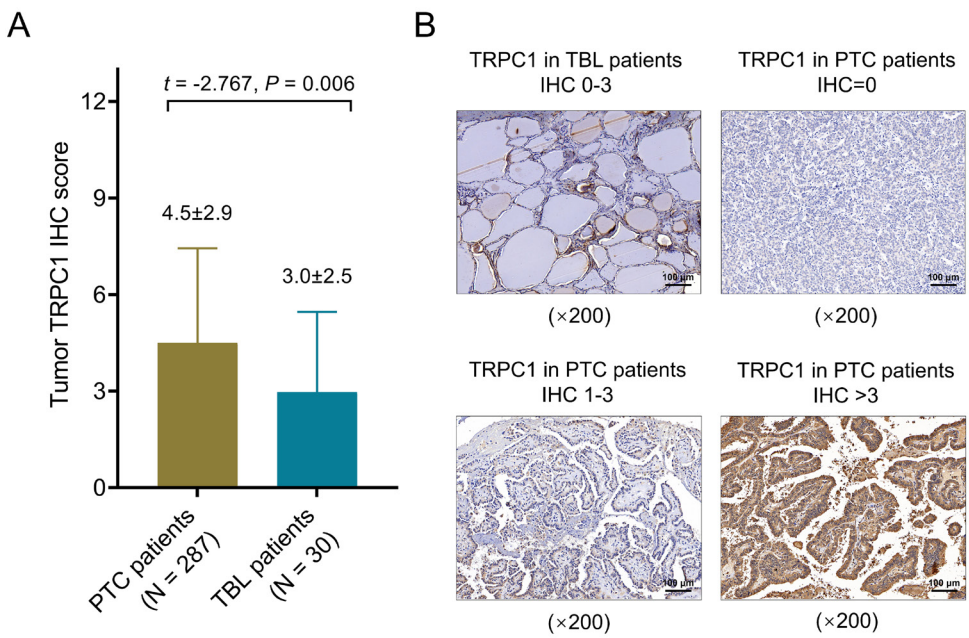


Fig. 1. Tumor TRPC1 IHC score in PTC patients and TBL patients.
Comparison of tumor TRPC1 IHC score between PTC patients and TBL patients (**A**); the examples of TRPC1 expression measured by IHC assay in PTC patients and TBL patients (**B**).

Table 2. Correlation analyses between tumor TRPC1 IHC score and characteristics of PTC patients.

Characteristics	Tumor TRPC1 IHC score, mean±SD	*t/r*	*P* value
Age		–0.778	0.437 $
< 55 years	4.4±2.7		
≥ 55 years	4.7±3.3		
Sex		0.304	0.761 $
Female	4.5±2.9		
Male	4.4±3.0		
Tumor size		–1.501	0.134 $
≤ 4 cm	4.3±3.0		
> 4 cm	4.8±2.9		
Extrathyroidal invasion		–2.209	0.028 $
No	4.2±2.8		
Yes	5.0±3.1		
pT stage		0.097	0.100 $$
1	3.7±2.9		
2	4.2±2.8		
3	5.1±3.1		
4a	4.6±3.0		
4b	4.3±2.2		
pN stage		–2.555	0.011 $
0	3.8±2.7		
1	4.8±3.0		
pTNM stage		0.039	0.507 $$
I	4.4±2.7		
II	4.6±3.4		
III	5.0±3.5		
IV	4.9±2.8		

TRPC1, transient receptor potential canonical 1; IHC, immunohistochemistry; PTC, papillary thyroid carcinoma; SD, standard deviation; pT, pathological tumor; pN, pathological node; pTNM, pathological tumor-node-metastasis. $, indicated that *P* values were determined by the student t-test; $$, indicated that *P* values were determined by the Spearman test.

investigated, which showed that tumor TRPC1 IHC score was positively correlated with tumor VEGFR2 IHC score in PTC patients (r = 0.359, P = 0.010). Tumor TRPC1 and VEGFR2 IHC scores showed high intercorrelation no matter applying their cut-off score at 0 (P = 0.045) or at 3 (P = 0.049) (Fig. 4).

Linkage of the combination of tumor TRPC1 IHC score and tumor VEGFR2 IHC score with DFS and OS in PTC patients

The combination of tumor TRPC1 IHC score and tumor VEGFR2 IHC score was separated into high level, median level, and low level by using 0 and 3 as cut-off values, respectively. When cut off by 0 or 3, the combination of TRPC1 and VEGFR2 was not related to DFS or OS in PTC patients (all P > 0.05) (Supplementary Fig. S2).

Discussion

TRPC1 mediates store-operated Ca^{2+} entry (SOCE) pathways, which is considered to be abnormally expressed in head and neck cancers (Hegde et al. 2022, Shi et al. 2022). For instance, one study shows that TRPC1 is upregulated in tongue squamous cell carcinoma tissue, and its elevation is linked with poor tumor features in tongue squamous cell carcinoma patients (Shi et al. 2022). Moreover, another previous research also reveals that TRPC1 is highly expressed in head and neck squamous cell cancer patients (Hegde et al. 2022). Nevertheless, the clinical role of TRPC1 in the management of PTC patients is unclear. In our study, tumor TRPC1 IHC score was increased in PTC patients versus TBL patients, and it was linked with extrathyroidal invasion and pN stage 1 in PTC patients. The possible reasons included that: (1) TRPC1 high expression might reflect the accelerated proliferation rate of tumor cells; meanwhile, the proliferation speed of tumor cells was faster in PTC patients than in TBL patients (Ke and Long 2022). Thus, tumor TRPC1 IHC score was increased in PTC patients. (2) TRPC1 directly bound to calmodulin (CaM) and promoted the interaction of CaM with phosphoinositol-3 kinase (PI3K), which further activated the

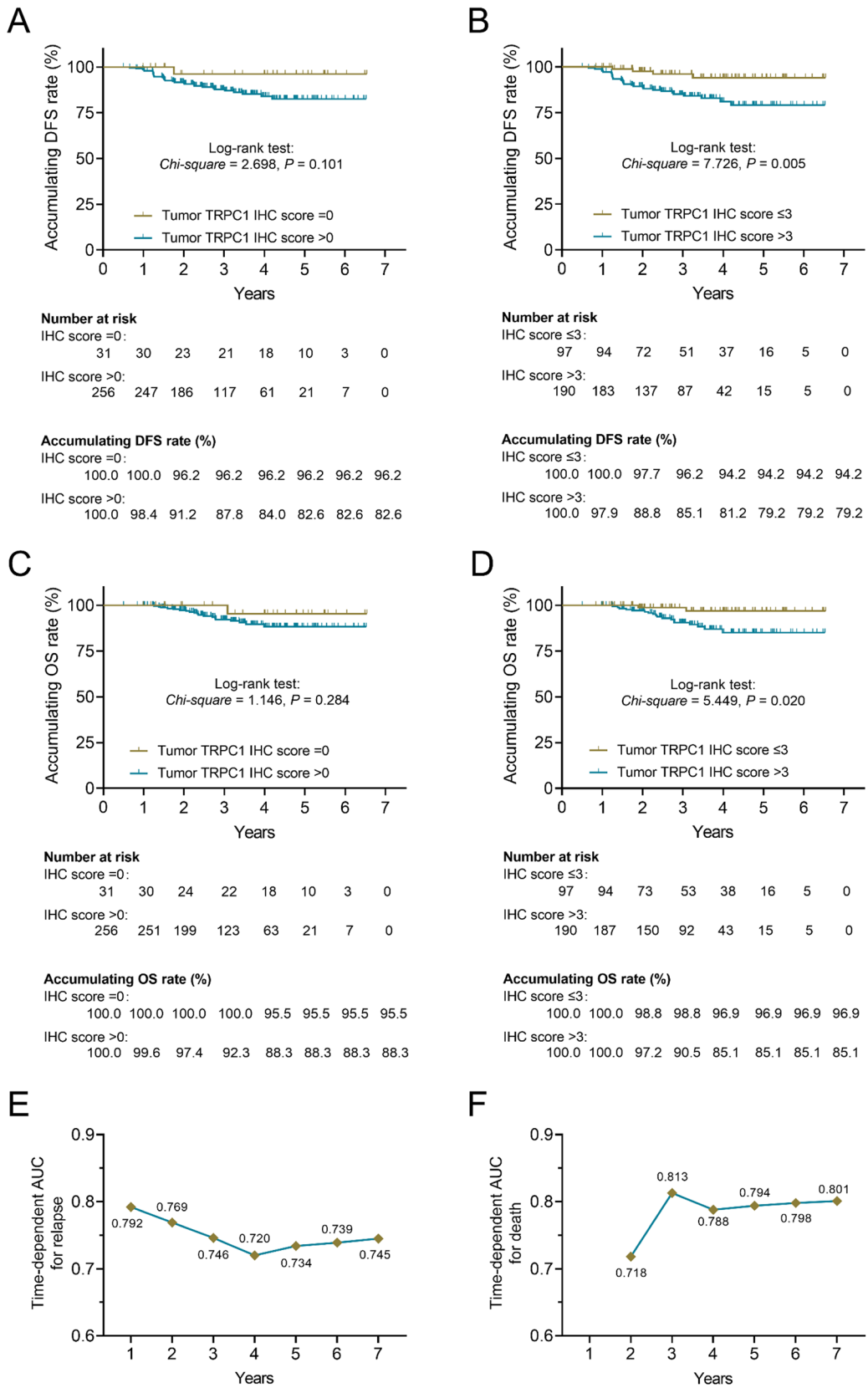


Fig. 2. Association of tumor TRPC1 IHC score with relapse and death in PTC patients.
Relation of tumor TRPC1 IHC score with DFS when the cut-off values of tumor TRPC1 IHC score were 0 (**A**) and 3 (**B**); relation of tumor TRPC1 IHC score with OS when the cut-off values of tumor TRPC1 IHC score were 0 (**C**) and 3 (**D**); time-dependent AUC of tumor IHC score in predicting relapse (**E**) and death risks (**F**) over 7 years in PTC patients.

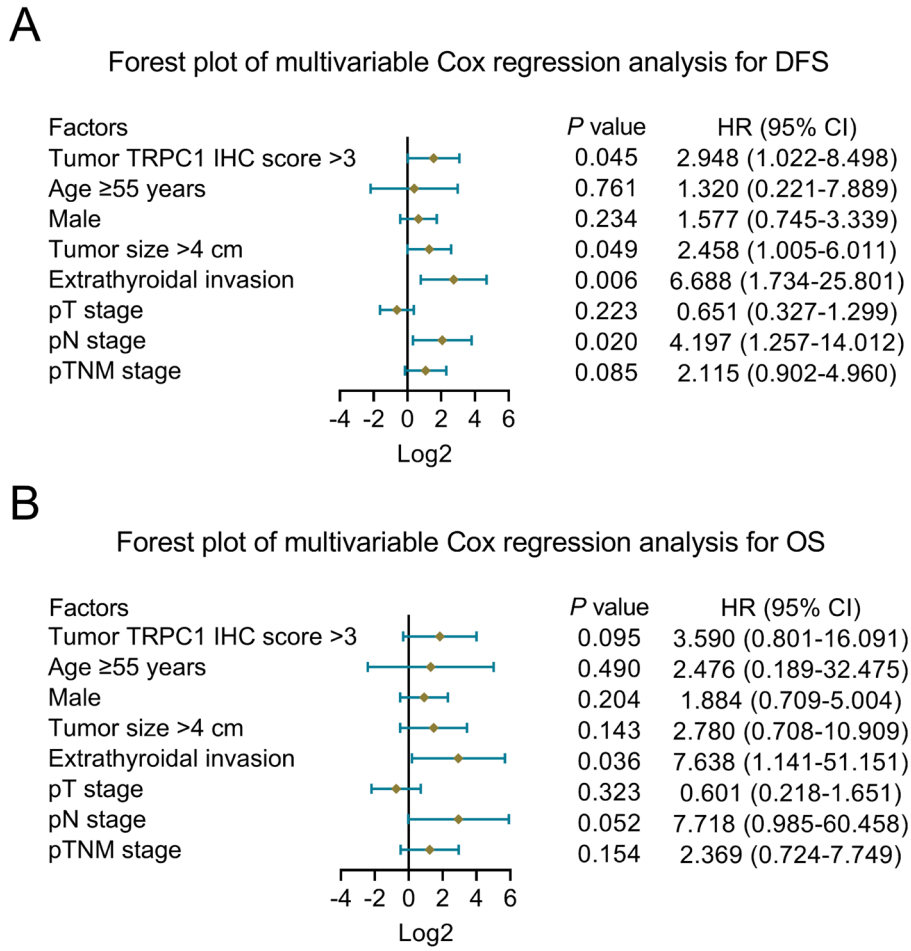
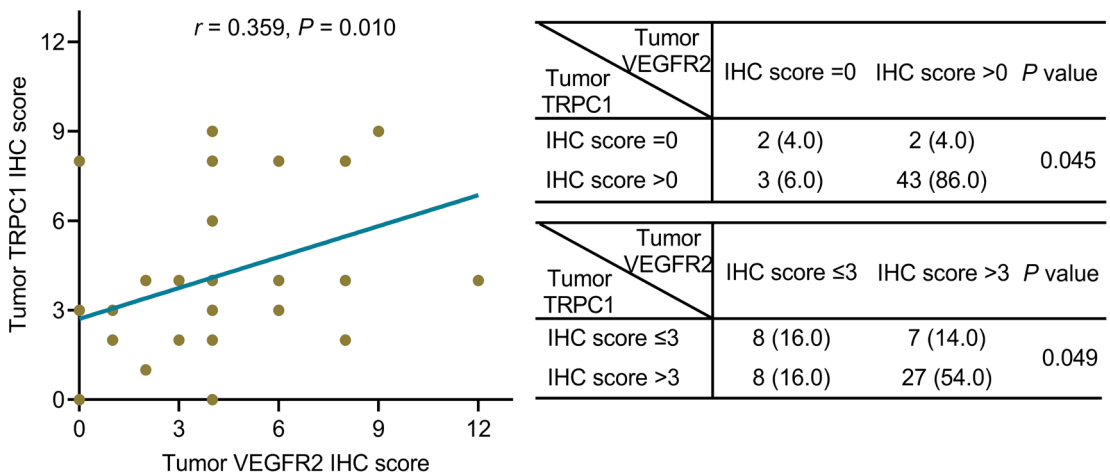


Fig. 3. Multivariable Cox regression analyses for DFS and OS in PTC patients.
The multivariable Cox regression models revealed the independent factors of DFS (**A**) and OS (**B**) in PTC patients.



Tumor TRPC1 \ Tumor VEGFR2	IHC score =0	IHC score >0	*P* value
IHC score =0	2 (4.0)	2 (4.0)	0.045
IHC score >0	3 (6.0)	43 (86.0)	

Tumor TRPC1 \ Tumor VEGFR2	IHC score ≤3	IHC score >3	*P* value
IHC score ≤3	8 (16.0)	7 (14.0)	0.049
IHC score >3	8 (16.0)	27 (54.0)	

Fig. 4. Association of tumor TRPC1 IHC score with tumor VEGFR2 IHC score in PTC patients.

PI3K/protein kinase B (Akt) signaling cascade, thus promoting tumor invasion and migration (Sun et al. 2021). Therefore, tumor TRPC1 IHC score was correlated with extrathyroidal invasion and pN stage 1 in PTC patients. Notably, our study chose TBL as a control group instead of healthy people, which was because we aimed to determine

whether TRPC1 was related to non-malignant thyroid disease or thyroid cancer.

In terms of the prognostic value of TRPC1, previous studies disclose that TRPC1 high expression is linked with shortened survival in patients with head and neck tumors (Hegde et al. 2022, Shi et al. 2022). Notably, our study found that tumor TRPC1 IHC score > 3 was correlated with poor DFS and OS; meanwhile, it independently predicted shorter DFS, but not OS in PTC patients. Furthermore, our study also revealed that the tumor TRPC1 IHC score had a good value in predicting relapse and death risks over 7 years in PTC patients. These results could be explained by: (1) TRPC1 promoted PTC progression through up-regulating $S1P_3$ and VEGFR2, which enhanced the tumor burden of PTC patients, thereby accelerating the recurrence of disease (Asghar et al. 2015). (2) TRPC1 might promote cancer stemness through the PI3K/AKT signaling pathways; meanwhile, cancer stemness increased the risk of tumor recurrence and caused the death of PTC patients, thus TRPC1 could forecast relapse and death risks in PTC patients (Najafi et al. 2019; Jin et al. 2023; Zhou and Jiang 2023). (3) OS might be influenced by patients' individual differences and the effect of subsequent treatment (Ke and Long 2022). Therefore, tumor TRPC1 IHC score > 3 was not independently linked with OS in PTC patients.

Notably, in our study, TRPC1 was 50% higher in PTC versus TBL (4.5 vs. 3.0), which indicated there might be several overlap numbers, thus tumor TRPC1 IHC score cut by 3 had a better performance than its score cut by 0 for predicting prognosis. Moreover, our study only chose tumor TRPC1 IHC score cut by 3 for Cox analysis, which was due to the two reasons as follows: (1) When the tumor TRPC1 IHC score was cut by 0, there was no linkage of tumor TRPC1 IHC score with PFS or OS in PTC patients. (2) Tumor TRPC1 IHC score cut by 3 had a better performance than its score cut by 0 for predicting prognosis of PTC patients.

Above all, in our study, TRPC1 was considered to be linked with worse prognosis in PTC patients. Another study also showed that TRPC1 promoted the proliferation, invasion, and migration of human thyroid cancer cells (Asghar et al. 2015). However, some previous studies also found that the overexpression of TPRC1 could inhibit the proliferation, invasion, and migration of breast cancer and esophageal squamous cell carcinoma, reflecting a favorable prognosis of patients with these cancers (Zhang et al. 2020; Zeng et al. 2021). The above findings suggested a double-edged function of TRPC1 in regulating cancer. It might be because: The emergence and progression of tumors are the result of the combined effects of multiple genes, and the same gene may play different roles in different tumors (Zeng et al. 2021). Future studies are required to further explore detailed mechanisms of TRPC1 in regulating different cancers to clarify this issue.

VEGFR2 is an angiogenic factor, which plays an important part in the progression and invasion of thyroid carcinoma (Asghar et al. 2015, Mohamad Pakarul Razy et al. 2019). Notably, one previous study shows that TRPC1 regulates the proliferation, invasion, and migration of thyroid carcinoma via mediating VEGFR2 (Asghar et al. 2015). Meanwhile, based on the STRING database, it was illustrated that TRPC1 regulated many VEGF isoforms and other common oncogenes by regulating VEGFR2. According to the above studies, it is hypothesized that TRPC1 may be involved in the progression of PTC through regulating VEGFR2. Thus, our study explored the relationship of TRPC1 with VEGFR2 in tumor tissues of PTC patients, which illustrated that tumor TRPC1 IHC score was positively linked with tumor VEGFR2 IHC score in PTC patients. The possible reason was that TRPC1 might up-regulate VEGFR2 by adjusting calcium signaling (Asghar et al. 2015). This finding of our study indicated that TRPC1 might mediate a series of cellular functions of PTC through adjusting VEGFR2, while relevant research was still needed for further verification.

Our study had several limitations: (1) Due to the fact that our study was retrospective, there might be some selection bias. (2) In our study, TRPC1 was measured by IHC assay, and further studies should consider detecting TRPC1 in fresh tissues by quantitative real-time polymerase chain reaction. (3) The number mismatch between PTC patients and TBL patients might influence the statistical effect of our study.

In conclusion, TRPC1 reflects extrathyroidal invasion, elevated tumor stage, and poor survival; meanwhile, TRPC1 positively links with VEGFR2 in tumor tissues of PTC patients. These findings indicate that TRPC1 may be a promising therapeutic target for the management of PTC.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Files

Please find supplementary file(s);
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