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Original Article

Serotonin transporter-linked polymorphic region genotypes in relation to stress conditions among patients with papillary thyroid carcinoma

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Abstract: The serotonin-transporter-linked polymorphic region (5-HTTLPR) gene has been reported to predispose individuals experiencing trauma to affective disorders such as anxiety and depression. We hypothesized that SS genotype of 5-HTTLPR gene would induce stress conditions and poor prognosis of papillary thyroid carcinoma (PTC). The study enrolled 287 patients with or without post-traumatic stress disorder (PTSD) following surgical treatment of PTC with their baseline characteristics collected. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was conducted to detect genotype frequency. Five self-rating scales, including Impact of Event Scale-Revised Edition (IES-R), Medical Coping Modes Questionnaire (MCMO), Hamilton Depression Scale (HAMD), Social Support Rating Scale (SSRS) and Stressful Life Events (SLEs), were used for depressive state assessment. Survival situations were observed through 15-year follow-up visits one time every six months. Survival rate was calculated using Life Table. Logistic regression analysis was used to analyze factors related to prognosis of PTC. Increased SS genotype and decreased LL genotypes were found in patients with PTSD. PTSD is associated with high stress, and inter-group analysis revealed that patients carrying SS genotype exhibited a high stress condition. PTSD and SS genotype correlated to large tumor size, advanced clinical stage, lymph node metastasis, and decreased 10-year and 15-year survival rate. As for patients carrying the same genotype, those suffering from PTSD showed poorer survival. Also, 5-HTTPRL, MCMQ score (confrontation/avoidance/surrender), HAMD score, SSRS total score, SLEs score, tumor size, clinical stage, and lymph node metastasis were relevant factors for prognosis of PTC. The results demonstrate SS genotype of the 5-HTTPRL gene as a contributor of high stress among patients with PTC. Thus, 5-HTTPRL and stress conditions represent potential investigative focus targets for prognosis of PTC.

Keywords: Papillary thyroid carcinoma, post-traumatic stress disorder, serotonin-transporter-linked polymorphic region gene, prognosis, association

Introduction

Thyroid carcinoma is the most frequent malignant tumor arising in the endocrine system with the morbidity experiencing a 3-fold increase in the last 3 decades [1]. According to predominant histology, well-differentiated cases of thyroid carcinoma accounted for about 9/10, consisting of follicular thyroid carcinoma (FTC) or papillary thyroid carcinoma (PTC) [2]. Moreover, PTC manifests itself as the more common type and patients above 45 years old suffering from it usually have extended soft tissue or lymph node metastasis and are even more susceptible to recurrences and death [3]. Unfortunately, it was reported that there are approximately 20% cancer survivors who are subjected to post-traumatic stress disorder (PTSD) [4]. PTSD is a frequently occurring disorder influencing mental and/or physical health as a consequence of extremely harmful events [5]. Patients diagnosed as PTSD tend to think about the unpleasant events endlessly and uncontrollably over a long period [6]. Also, the confidence of cancer survivors is reduced but apprehension of death and recurrence is enhanced due

to PTSD [7]. Therefore, to treat these patients more effectively, greater understanding of the mechanisms improving prognosis of PTC associated with PTSD is needed.

In recent years, the serotonin-transporter-linked polymorphic region (5-HTTLPR) has been highlighted because of its involvement in mental disorder [8]. For instance, the role of 5-HTTLPR polymorphism located in the promoter region of solute carrier family 6 member 4 (SLC6A4) has been revealed in predicting PTSD [9]. In terms of the quantity of base pairs, 5-HTTLPR polymorphisms can be generally divided into two forms, including 'short' (S) or 'long' (L), in three different combinations, including short and long (SL), short and short (SS) and long and long (LL) [10]. Gressier et al. have ever conducted a meta-analysis and claimed that SS genotype is linked to PTSD in subjects exposed to severe trauma [11]. Hence, it is reasonable to build up a hypothesis that 5-HTTLPR polymorphism may play a role in PTSD post-PTC based on the above-mentioned findings. In the current study, we recruited a total of 287 patients with PTC suffering from PTSD or not to investigate the potential roles of 5-HTTLPR gene polymorphisms on the prognosis as well as the clinical manifestation of patients with PTC.

Subjects and methods

Ethics statement

This study was approved by the Ethics Committee of Hainan General Hospital and in accordance with Declaration of Helsinki. Informed consent was obtained from each subject prior to our study.

Study subjects

A total of 287 patients with PTC who had undergone surgical treatment in Hainan General Hospital from August 2015 to August 2017 were recruited. Inclusion criteria were as follows: (1) patients were diagnosed with PTC using thyroid fine-needle aspiration biopsy or ultrasonic imaging [12]; (2) patients experienced thyroidectomy in Hainan General Hospital with complete clinical data; (3) patients had no other malignancy. Exclusion criteria were indicated below: (1) patients were treated with chemotherapy, radiotherapy and immunotherapy before operation; (2) patients had mental retardation; (3) patients took medicine that may affect cognitive function within the past three months.

One month after the operation, each subject was screened concerning psychiatry and neurology one-to-one by medical personnel and researchers of Psychology Department in Hainan General Hospital. Then, qualified patients were assigned into PTSD (n = 112; patients with PTC meeting the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV) and non-PTSD (n = 175; patients with PTC but without any mental illness) groups.

Evaluations

Detailed baseline characteristics were collected from each participant, including age, gender, history of smoking, history of drinking, education years, marriage status, salary, medical history, medication history and history of allergies.

After the operation, paraffin-embedded pathological sections of all patients were prepared. Pathologic staging was conducted on the basis of American Joint Committee on Cancer (AJCC) staging system for thyroid carcinoma (2002). Results are shown below: 218 patients with tumor size < 3 cm, and 69 patients with tumor size ≥ 3 cm; 141 patients with stage I, 95 patients with stage II, 29 patients with stage III, and 22 patients with stage IV; 144 patients with non-lymph node metastasis, and 143 patients with lymph node metastasis. All patients were followed up by mail, telephone or clinic visits at an interval of 6 months, and adverse events and concomitant medication were asked with survival conditions collected. The follow-up lasted for 15 years until June 2017.

All subjects were required to fill out the five following self-rating scales. Impact of Event Scale-Revised Edition (IES-R) contained 22 entries and dimensions, such as avoidance, intrusion, and high vigilance. The symptoms of avoidance was judged by entry 5, 7, 8, 11, 12, 13, 17, and 22, the intrusion was judged by entry 1, 2, 3, 6, 9, 14, 16, and 20, and the high vigilance was judged by 4, 10, 15, 18, 19, and 21. The 25% and 75% of the total score were used as the demarcation points to classify PTSD symptoms into degrees of mild, moderate, and severe. The total score was less than or equal to 22 was regarded as mild degree, the total score was between 22 and 66 as moderate, and total

Table 1. Baseline characteristics of PTC patients were compared to observe the correlation of PTSD with tumor size, clinical stage, and lymph node metastasis (Mean ± SD or n (%))

Characteristics	Total (n = 287)	PTSD (n = 112)	Non-PTSD (n = 175)	*p* value
Age (years)	45.15 ± 10.25	44.01 ± 9.74	45.88 ± 10.5	0.134
Gender				0.674
Female	157 (54.71)	63 (56.25)	94 (53.71)	
Male	130 (43.29)	49 (43.75)	81 (46.29)	
History of Smoking				0.267
Yes	173 (60.28)	72 (61.81)	101 (57.71)	
No	114 (39.72)	40 (38.19)	74 (42.29)	
History of Drinking				0.324
Yes	190 (66.20)	78 (64.28)	112 (64.00)	
No	97 (33.80)	34 (35.72)	63 (36.00)	
Education Years				0.308
≤ 12 years	155 (54.01)	64 (57.14)	91 (52.00)	
> 12 years	132 (45.99)	48 (42.86)	84 (48.00)	
Marriage Status				0.797
Single	105 (46.59)	42 (37.50)	63 (36.00)	
Married	182 (63.41)	70 (62.50)	112 (64.00)	
Salary (yuan)				0.273
≤ 5000	163 (56.79)	67 (59.82)	96 (54.86)	
> 5000	124 (43.21)	45 (40.18)	79 (45.14)	
Tumor Size				0.022
< 3 cm	218 (75.96)	73 (65.18)	145 (82.86)	
≥ 3 cm	69 (24.04)	39 (34.82)	30 (17.14)	
Clinical Stages				< 0.001
I	141 (49.13)	46 (41.07)	95 (54.29)	
II	95 (33.10)	30 (26.79)	65 (37.14)	
III	29 (10.10)	20 (17.86)	9 (5.14)	
IV	22 (7.67)	16 (14.28)	6 (3.43)	
Lymph Node Metastasis				< 0.001
No	232 (80.84)	75 (66.96)	157 (89.71)	
Yes	55 (19.16)	37 (31.24)	18 (10.29)	

Notes: Age (years), belonging to measurement data, is presented by mean ± SD and analyzed using *t* test between two groups; the other characteristics are compared using n (%) and analyzed by chi-square; *p*, the PTSD *vs.* non-PTSD groups; PTC, papillary thyroid carcinoma; PTSD, post-traumatic stress disorder; SD, standard deviation.

score was more than or equal to 66 was regarded as severe. The Medical Coping Modes Questionnaire (MCMO), edited by Feifel H et al., was applied to evaluate the medical coping styles of patients. The scale classified coping styles into 20 entries, including three coping styles (confrontation, avoidance, and surrender), which were consistent with the basic coping styles when people confronted stressful events. The 4-grade scoring method was used to evaluate the score of each entry. There were 8 entries recording scores reversely, which were the average scores obtained from cumulative addition of corresponding entries. Hamilton Depression Scale (HAMD, Annex 1) was used for depressive state assessment. According to Davis, score > 20 was considered as mild-moderate depression, 8 ≤ score ≤ 20 as dubious depression and score < 8 as no depression. Social Support Rating Scale (SSRS) was adopted to evaluate social support consisting of three dimensions (10 entries), including subjective support (4 entries), objective support (3 entries) and support utilization (3 entries). The higher score represents the better degree of social support. Stressful Life Events (SLEs) was employed to determine the number of stressful events. According to NA Gillespie *et al*. [13], all subjects were asked if during the past 12 months any of the following events had oc-

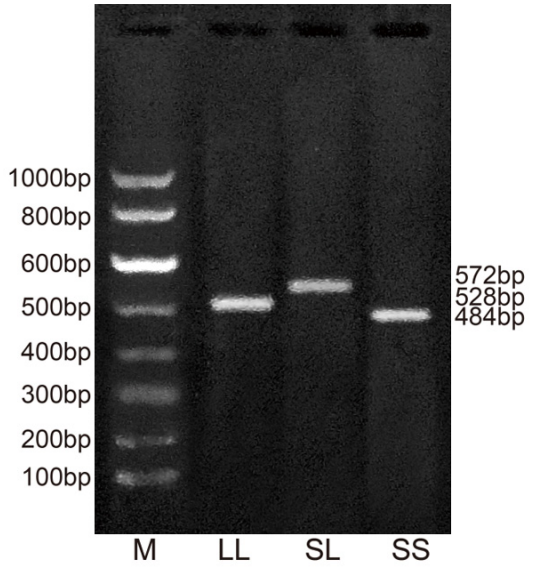

Figure 1. PCR-RELP shows SS, LL and SL genotypes of 5-HTTPRL gene. Notes: M, 100 bp DNA ladder marker; 528 bp, LL genotype; 572 bp, SL genotype; 484 bp, SS genotype; 5-HTTPRL, serotonin-transporter-linked polymorphic region; S, short; L, long; PCR-RELP, Polymerase chain reaction-restriction fragment length polymorphism.

curred: divorce, separation from children, broken steady relationship or being disappointed in love, separation from other loved one or close friend, serious illness or injury; serious accident, being robbed, sacked from job, other serious difficulties at work, major financial problems, legal matters or involvement with police, and living in unpleasant surroundings. The evaluation was performed through scoring. Patients who had not experienced any of the above-mentioned events were scored as 0 point. Every 1-point was added if one event was experienced.

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)

On the second day after patients have signed the informed consent, 5 mL of fasting blood was obtained from arm vein and put into an ethylenediaminetetraacetic acid (EDTA) anticoagulation tube. Whole-genome DNA was extracted using peripheral blood DNA genome extraction kit (DP304-03, Beijing TIANGEN Biotech Co., Ltd., Beijing, China). Absorbance of DNA at 260 nm and 280 nm was measured using spectrophotometer (GENESYS 10S, Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA), and A260 nm/A280 nm was calculated. The higher purity of DNA was ensured > 1.8, which was qualified for subsequent experiments. PCR-RFLP was applied to detect the polymorphism of 5-HTTLPR. Primers were as follows [14]: forward primers, 5'-GGCGTTGCCGCTCTGAATTGC-3'; reverse primers, 5'-GAGGGACTGAGCTGGACAACCCAC-3'. The reaction system of PCR consisted of 200 ng of DNA template, 0.5 uL primers (10 mmol/L), 1.5 uL deoxy-ribonucleoside triphosphate (dNTP, 120 nmol/L) containing 7-deaaze-deoxy-ribonucleoside triphosphate (Roche Life Science, Basel, Switzerland), 5% dimethyl sulfoxide (DMSO, Sigma-Aldrich, Lyon, France), 2.5 uL $MgCl_2$ (1.5 mmol/L) and 0.25 uL Taq polymerase (1.25 U, Eurobio, Brunschwig, Basel, Switzerland), and volume was up to 25 μL by ddH_2O. Reaction conditions were pre-denaturation at 95°C for 5 min, then a total of 35 cycles of denaturation at 95°C for 30 s, anneal at 60°C for 30 s and extending at 72°C for 1 min, and at last extending at 72°C for 10 min. PCR products were put in 1.5% agarose gel electrophoresis and stained with ethidium bromide (EB). Ultraviolet analyzer was applied for electrophoresis images with genotypes detected. Three alleles were listed below in the order of length: SS, 484 bp; LL, 528 bp; SL, 572 bp. The success rate of genotyping was over 98%, 10% out of which was chosen for verification. No incorrect genotype was found in the current experiment.

Statistical analysis

The statistical analysis was conducted with SPSS21.0 (IBM Corp., Armonk, NY, USA). Measurement data were presented by mean ± standard deviation (SD). The t-test was applied for comparison between two groups. Enumeration data were presented by percentage (%) and analyzed using chi-square test. Hardy-Weinberg equilibrium tests were conducted for genotypic distribution. Survival rate was calculated using Life Table. Survival curve was drawn based on Kaplan-Meier (KM). Logistic regression analysis was used to analyze factors related to prognosis. Bilateral $P < 0.05$ was considered statistically significant difference.

Results

PTSD is associated with tumor size, clinical stage, and lymph node metastasis

Initially, detailed baseline characteristics were collected from all subjects. As shown in **Table**

Table 2. 5-HTTPRL SS genotype is associated with increased risk of PTSD (n [%])

Genotypes	Total (n = 287)	PTSD (n = 112)	Non-PTSD (n = 175)	*p* value	OR
SS	92 (32.05)	45 (40.18)	47 (26.86)	0.018	1.829
SL + LL	195 (67.94)	67 (59.82)	128 (73.14)		(1.104-3.030)

Notes: Distribution of 5-HTTPRL genotypes are compared using n (%) and analyzed by chi-square; 5-HTTPRL, serotonin-transporter-linked polymorphic region; PTSD, post-traumatic stress disorder; OR, odd ratio; S, short; L, long.

1, the median age was 45.15 ± 10.25 years, and the subjects were: 157 males and 130 females; 173 patients with history of smoking and 114 patients without history of smoking; 190 patients with history of drinking and 97 patients without history of drinking; 155 patients with ≤ 12 years of education and 132 patients with > 12 years; 105 single patients and 182 married patients; 163 patients with salary ≤ 5000 and 124 patients with > 5000; 141 patients at clinical stage I, 95 patients at stage II, 29 patients at stage III and 22 patients at stage IV; 144 patients without lymph node metastasis and 143 patients with lymph node metastasis. However, no significant difference was observed in age, gender, history of smoking, history of drinking, education years, marriage status and salary between the PTSD and non-PTSD groups ($P > 0.05$). Therefore, tumor size, clinical stage and lymph node metastasis correlate to the occurrence of PTSD.

SS genotype increases the risk of PTSD among patients with PTC

PCR-RELP was performed to detect the distribution of 5-HTTPRL genotypes. With 5-HTTPRL amplified and PCR products experiencing electrophoresis, band at 484 bp was SS genotype, 528 bp was LL genotype and 572 bp was SL genotype (**Figure 1**). Distribution of 5-HTTPRL genotypes in the PTSD and non-PTSD groups is exhibited in **Table 2**. Actual value and theoretical value were both in accordance with Hardy-Weinberg equilibrium with higher goodness of fit ($P > 0.05$). The results revealed that the distribution frequency of the SS genotype was remarkably higher in the PTSD group than that in the non-PTSD group while the opposite situation was observed concerning SL + LL genotype (both $P < 0.05$). The available evidence indicated that patients carrying SS genotype are more susceptible to PTSD post-operation of PTC.

SS genotype is associated with high stress conditions

IES-R, MCMQ, HAMD, SSRS and SLEs were applied for assessment of stress conditions (**Table 3**). Compared with the PTSD group, the non-PTSD group exhibited an increased number of cases with mild, moderate, and severe degree in IES-R, MCMQ score of confrontation, number of cases with HAMD score < 20, and SSRS score but decreased MCMQ score of avoidance and surrender and number of cases with SLE score ≤ 2 (all $P < 0.05$). Intra-group analysis revealed that in the PTSD and non-PTSD groups, compared with patients with SS genotype, patients with SL + LL genotype tended to have higher MCMQ score of confrontation, more cases with HAMD score < 20, and higher SSRS score but lower MCMQ score of avoidance and surrender and less cases with SLEs score ≤ 2 (all $P < 0.05$). The above findings suggested that 5-HTTPRL genotype has no association with the severity of PTSD, and when patients with SS genotype confront stressful events, they tend to avoid and yield rather than to face them. Thus, SS genotype is linked to high stress conditions.

PTSD and 5-HTTLPR SS genotype contribute to the progression of PTC

Next, correlation analysis between 5-HTTLPR and clinical manifestation was carried out, with the results presented in **Table 4**, indicating that 5-HTTLPR was significantly correlated with tumor size, clinical stage, and lymph node metastasis in patients with or without PTSD. Compared with patients carrying SS genotype, the number of cases with tumor size < 3 cm, at stage I, at stage II and without lymph node metastasis increased (all $P < 0.05$). Furthermore, it is noted that patients with PTC suffering from PTSD exhibited a higher possibility of tumor size ≥ 3 cm and lymph node metastasis than those without PTSD (all $P < 0.05$). The findings revealed that among patients carrying the same genotype, significant correlation existed between PTSD and tumor size, clinical stages, and lymph node metastasis post-operation of PTC. The above results revealed that the progression of PTC is associated with PTSD and 5-HTTLPR SS genotype.

Table 3. Self-rating scales demonstrate the correlation of SS genotype of 5-HTTPRL with high stress conditions of patients with PTC after operation (Mean ± SD or n (%))

	PTSD			No PTSD					
	Total (n = 112), A	SS (n = 45), B	SL + LL (n = 67), C	Total (n = 175), D	SS (n = 47), E	SL + LL (n = 128), F	A vs. D	B vs. C	E vs. F
IES-R Score									
Mild	41 (36.61)	16 (35.56)	25 (37.31)	169 (96.57)	44 (93.62)	125 (97.66)	*< 0.001*	*0.849*	*0.67*
Moderate	37 (33.04)	14 (31.11)	23 (34.33)	6 (3.43)	3 (6.38)	3 (2.34)			
Severe	34 (30.35)	15 (33.33)	19 (28.36)	0 (0)	0 (0)	0 (0)			
MCMQ Score									
Confrontation	19.42 ± 3.39	18.00 ± 0.84	20.37 ± 0.81	21.40 ± 3.64	19.70 ± 3.92	22.02 ± 3.34	< 0.001	< 0.001	< 0.001
Avoidance	16.16 ± 2.56	17.40 ± 2.48	15.33 ± 2.27	13.95 ± 1.84	14.60 ± 1.78	13.71 ± 1.81	< 0.001	< 0.001	0.005
Surrender	10.24 ± 2.96	11.47 ± 2.94	9.42 ± 2.69	8.21 ± 2.53	9.28 ± 2.82	7.82 ± 2.30	< 0.001	< 0.001	0.001
HAMD score									
< 20	17 (15.18)	3 (6.67)	14 (20.89)	160 (91.43)	37 (78.72)	123 (96.09)	< 0.001	0.040	*< 0.001*
> 20	95 (84.82)	42 (93.33)	53 (79.10)	15 (8.57)	10 (21.28)	5 (3.91)			
SSRS total score	36.80 ± 8.17	34.40 ± 8.63	38.42 ± 7.50	42.90 ± 9.28	39.64 ± 7.99	44.10 ± 9.46	*< 0.001*	*0.010*	*0.005*
SLEs score									
≤ 2	74 (66.07)	23 (51.11)	51 (76.12)	157 (89.71)	38 (80.85)	119 (92.97)	*< 0.001*	*0.006*	*0.019*
> 2	38 (33.93)	22 (48.89)	16 (23.88)	18 (10.29)	9 (19.15)	9 (7.03)			

Notes: SSRS total score, measurement data, is presented by mean ± SD and analyzed using *t* test between two groups; the other indexes are compared using n (%) and analyzed by chi-square; 5-HTTPRL, serotonin-transporter-linked polymorphic region; PTC, papillary thyroid carcinoma; PTSD, post-traumatic stress disorder; SD, standard deviation; HAMD, Hamilton Depression Scale; SSRS, Social Support Revalued Scale; SLEs, Stressful Life Events.

Table 4. 5-HTTLPR polymorphisms correlates to clinical features post-PTC (Mean ± SD or n (%))

	PTSD		Non-PTSD					
	SS (n = 45), A	SL + LL (n = 67), B	SS (n = 47), C	SL + LL (n = 128), C	A vs. B	C vs. D	A vs. C	B vs. D
Tumor Size								
< 3 cm	23 (51.11)	50 (74.63)	34 (72.34)	111 (86.72)	0.010	0.025	0.036	0.035
≥ 3 cm	22 (48.89)	17 (25.37)	13 (27.66)	17 (13.28)				
Clinical Stages								
I	14 (31.11)	32 (47.76)	22 (46.81)	73 (57.03)	0.007	0.001	0.047	0.008
II	7 (15.56)	23 (34.33)	14 (29.79)	51 (39.84)	0.003	0.001	0.033	0.001
III	13 (28.89)	7 (10.45)	6 (12.76)	3 (2.35)	0.813	0.475	0.983	0.551
IV	11 (24.44)	5 (7.46)	5 (10.64)	1 (0.78)				
Lymph Node Metastasis								
No	20 (80.00)	55 (82.09)	33 (70.21)	124 (96.87)	< 0.001	< 0.001	0.0012	< 0.001
Yes	25 (20.00)	12 (17.91)	14 (29.79)	4 (3.13)				

Notes: Data of correlation analysis between 5-HTTLPR and clinical features post-PTC are presented as n (%) and analyzed by chi-square; 5-HTTPRL, serotonin-transporter-linked polymorphic region; PTC, papillary thyroid carcinoma; PTSD, post-traumatic stress disorder; SD, standard deviation; S, short; L, long.

SS genotype and PTSD resulted in low survival rate

Finally, the prognosis of PTC related to PTSD was evaluated with results shown in **Table 5**. In comparison to patients carrying SS genotype, those with SL + LL genotype exhibited increased 5-year, 10-year and 15-year survival rates (all $P < 0.05$). Furthermore, when patients had the same genotype (SS or SL + LL), those suffering from PTSD had remarkably lower 10-year and 15-year survival rates than those without PTSD (both $P < 0.05$); however, no significant difference was found in 5-year survival rate between the two groups.

According to K-M survival curve (**Figure 2**), the total survival of the PTSD group was significantly lower than that of the non-PTSD group. These results demonstrated that SS genotype

Table 5. 5-HTTLPR SS genotype and PTSD is associated with poor prognosis in PTC

Survival Rate (%)	PTSD		Non-PTSD		A vs. B	C vs. D	A vs. C	B vs. D
	SS (n = 15), A	SL + LL (n = 40), B	SS (n = 19), C	SL + LL (n = 44), D				
5 years	66.67	88.06	89.36	94.53	0.006	0.230	0.008	0.107
10 years	62.22	82.09	80.85	92.19	0.019	0.033	0.047	0.034
15 years	51.11	77.61	74.47	89.06	0.004	0.016	0.02	0.033

Notes: Survival rate is presented by percentage; is compared using Log-rank is used to compare 15-year survival curve between the PTSD and non-PTSD group; survival analysis is performed using Kaplan Meier; 5-HTTPRL, serotonin-transporter-linked polymorphic region; PTC, papillary thyroid carcinoma; PTSD, post-traumatic stress disorder; S, short; L, long.

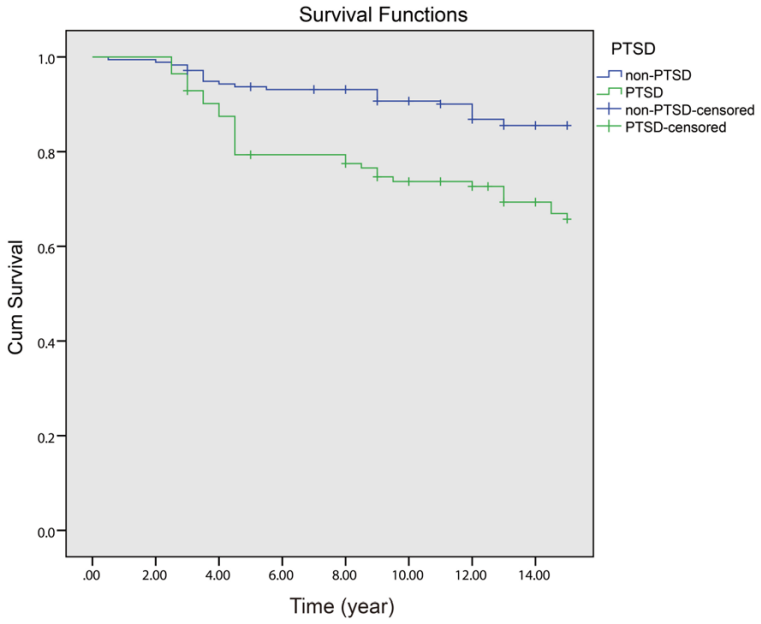

Figure 2. Kaplan-Meier survival curve shows that PTSD contributes to the poor prognosis of PTC. Notes: PTC, papillary thyroid carcinoma; PTSD, post-traumatic stress disorder.

of 5-HTTPRL and PTSD may confer a decreased survival rate to patients with PTC.

Another conclusion based on regression analysis (**Table 6**) was that 5-HTTPRL, MCMQ score (confrontation/avoidance/surrender), HAMD score, SSRS total score, SLEs score, MCMQ tumor size, clinical stages and lymph node metastasis were all critical factors to the prognosis of PTC.

Discussion

A prior study has pointed out that of the rate of well-differentiated thyroid carcinoma is increasing, where follow-up visits are highly recommended especially in a long period [15]. It is said that certain genes may be responsible for the progression of PTC, such as Forkhead box E1 (FOXE1) which exerts negative effects [16]. Considering the following unpleasant mental experiences of cancer, Schillani et al. have identified 5-HTTLPR as an influencing factor of undesirable feelings in psychiatry in breast cancer [17]. Additionally, PTSD is a common and costly disorder with major health care burden in relation to cancer but a tricky one to recognize and deal with [18, 19]. Herein, the present study was designed to uncover the relationship between 5-HTTLPR and susceptibility to PTSD as well as stress conditions in patients with PTC through 15-year follow-up visits and three self-evaluation scales. According to our study, patients with PTC carrying the SS genotype of 5-HTTLPR are more likely to have PTSD, which will lead to the downside outcomes of PTC.

The low death rate of PTC results in, sufferers having to be under observation after operation in case of any recurrence while the chronic feeling of tightness may give rise to psychological problems [20]. A significant finding of our study is that SS genotype of 5-HTTLPR is correlated with PTSD as well as poor clinical performances and outcomes of patients with PTC. As discussed in a functional study, the negative impact on cancer posed by PTSD may lead to damaged immune system which would further weaken the resistance of the body to tumor development while hormones related to stress may also affect the tumor growth [21].

Table 6. Regression analysis reveals that the prognosis of PTC is correlated with 5-HTTPRL, MCMQ score (confrontation/avoidance/surrender), HAMD score, SSRS total score, SLEs score, MCMQ tumor size, clinical stages, and lymph node metastasis

Variants	B	SE	Wald	df	Sig.	Exp (B)	95% CI
5-HTTPRL	-3.385	0.847	15.969	1	< 0.001	0.034	0.006~0.178
HAMD	4.586	0.725	39.965	1	< 0.001	98.054	23.662~406.3
SSRS	-0.069	0.029	5.739	1	0.017	0.934	0.883~0.988
SLEs	1.818	0.771	5.553	1	0.018	6.157	1.358~27.923
Confrontation	-0.22	0.071	9.755	1	0.002	0.802	0.699~0.921
Avoidance	0.628	0.127	24.604	1	< 0.001	1.873	1.462~2.400
Surrender	0.411	0.095	18.869	1	< 0.001	1.509	1.253~1.817
Tumor size	2.372	0.717	10.936	1	0.001	10.72	2.628~43.729
Clinical Stages	2.028	0.882	5.283	1	0.002	7.597	1.348~42.818
Lymph Node Metastasis	-2.673	0.997	7.181	1	0.007	0.069	0.010~0.488

Notes: PTC, papillary thyroid carcinoma; 5-HTTPRL, serotonin-transporter-linked polymorphic region; MCMQ, Medical Coping Modes Questionnaire; HAMD, Hamilton Depression Scale; SSRS, Social Support Revalued Scale; SLEs, Stressful Life Events; SE, standard error; df, degree of freedom; Sig., significance; Exp., Exponential; CI, confidence interval; S, short; L, long.

The involvement of serotonin transporter gene has been previously revealed in the sensitivity to psychopathology and stress [22]. Our results are just in line with the statement proposed by Caspi *et al.* that individuals carrying the LL genotype are less susceptible to depression than those carrying the SL or SS genotype [23]. Likewise, Artero *et al.* have reviewed literature suggesting that young individuals carrying the SS genotype of the 5-HTTLPR polymorphism have a higher risk of being depressed and even committing suicide than those with LL genotype [14]. Karg et al. have also concluded from a majority of relevant studies that the S allele of 5-HTTLPR is concerned with a higher possibility of depression under stress conditions [24]. A research team on surgical outcomes has mentioned that the S allele of 5-HTTLPR is involved in declined expression of serotonin transporter and may serve as a peril allele to depression especially in exposure to SLEs [25]. The transcriptional efficiency may of S allele is lower than that of L allele while S allele is in relation to the brain's function and structure, thus posing impact on gene-related PTSD susceptibility [26]. Similarly, early work indicated that 5-HTTLPR genotype is associated with unfavorable survivalpost-colorectal operation wherein the regulation of 5-HTT activity may be responsible for the altering inflammation [27]. Taken together, we speculated that the SS genotype of 5-HTTLPR could result in adverse mental issues of PTC.

In addition, in terms of the results of Cox regression analysis, tumor size, clinical stage, and lymph node metastasis are all pivotal to prognosis of PTC. A group of Chinese researchers have found that approximately 70% patients with PTC may experience lymph node metastasis [15]. Besides, Somuncu *et al.* have referred to tumor size as one of the influencing factors of prognosis in patients with PTC [16]. In agreement with our finding, Ito *et al.* have ever documented that the prognosis of PTC can be interfered by tumor size and clinical lymph node metastasis [28]. Nevertheless, because of inevitable limitations in our study, much more detailed research is needed in future.

Connectively, the key findings are supported by results suggesting that the SS genotype of 5-HTTLPR allows the identification of patients with PTC in greater risk of PTSD, for which specific intervention may be focused. More importantly, to the results suggest that future research should include a larger cohort of patients and thorough investigations are still required on mental adaptation to cancer in relation to the genetic milieu of patients with the purpose of personalized and more effective intervention.

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Disclosure of conflict of interest

None.

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