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Original Article

Role of the TLR2/NF-κB signaling pathway and the aggregate index of systemic inflammation as prognostic indicators in papillary thyroid carcinoma

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Abstract: Objective: To investigate the expression of the TLR2/NF-κB signaling pathway and the Aggregate Index of Systemic Inflammation (AISI) in patients with papillary thyroid carcinoma (PTC) and to evaluate their clinical relevance to prognosis. Methods: In this retrospective study, we analyzed surgically resected tumor tissue samples from 273 patients with PTC (PTC group) and paired adjacent non-tumorous tissues (PT group), as well as 104 nodular goiter tissues (NG group). The AISI values, along with the positive rates and mRNA expression levels of TLR2, MyD88, and NF-κB, were compared among the three groups. Differences in these indicators were compared across PTC patients with different clinicopathologic features. All PTC patients were followed up for three years and categorized into a survival group (n = 70) and a death group (n = 203) based on prognosis, and between-group comparisons were performed. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic performance of each indicator. Kaplan-Meier survival curves were generated to compare overall survival between high- and low-expression subgroups stratified by TLR2, MyD88, NF-κB mRNA and AISI levels. Cox regression analysis was conducted to identify independent prognostic factors in PTC. Results: Compared to the NG and PT groups, the PTC group showed higher AISI values, and protein positivity and mRNA expression of TLR2, MyD88, and NF-κB (all P<0.05). In the PTC group, the expression levels of these biomarkers and AISI values differed significantly according to tumor stage, lymph node metastasis, degree of differentiation, and extraglandular extension (P<0.05). Significant differences in differentiation grade, lymph node metastasis, extrathyroidal extension, TLR2, MyD88, NF-κB mRNA, and AISI levels were observed between the survival and death groups (P<0.05). The AUC values for predicting patient prognosis based on TLR2, MyD88, NF-κB mRNA, and AISI individually or in combination were 0.802, 0.795, 0.799, 0.815, and 0.818, respectively. Patients with low expression levels of TLR2, MyD88, NF-κB mRNA, and AISI had significantly longer overall survival compared to those with high expression levels (P<0.05). Conclusion: Poor differentiation, extrathyroidal extension, and high AISI expression are independent factors for poor PTC prognosis. The TLR2/NF-κB signaling pathway and AISI are closely associated with tumor progression and have prognostic value.

Keywords: TLR2/NF-κB, aggregate index of systemic inflammation (AISI), papillary thyroid carcinoma (PTC)

Introduction

Thyroid cancer is one of the most common malignant tumors of the head and neck, and its global incidence has risen markedly in recent years [1, 2]. Among all subtypes, papillary thyroid carcinoma (PTC) is the predominant histologic form, accounting for 80%-90% of all thyroid cancer cases [3, 4]. Although the overall prognosis of PTC patients is generally favorable, a subset of patients still experience disease recurrence, metastasis, or other adverse outcomes [5, 6]. Therefore, it is essential to investigate the underlying mechanisms of PTC and to identify effective prognostic indicators.

The innate immune system plays a pivotal role in modulating tumor-associated inflammation. As a key member of the pattern recognition receptor family, Toll-like receptor 2 (TLR2) is widely expressed on the surfaces of immune cells as well as many epithelial cells. TLR2s can

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recognize a variety of pathogen-associated molecular patterns, trigger the expression of the downstream adaptor MyD88, and subsequently activate the NF-κB signaling pathway, which is critically involved in regulating inflammatory responses and other biological processes. Previous studies have demonstrated that aberrant activation of the TLR2/NF-κB signaling pathway is closely associated with tumor aggressiveness and unfavorable clinical outcomes of various malignancies [7]. However, evidence regarding its expression profile and prognostic significance in PTC remains limited.

Inflammatory reaction is closely related to tumor initiation and progression. The Aggregate Index of Systemic Inflammation (AISI), a recently proposed marker reflecting the overall systemic inflammatory status by integrating multiple inflammation-related measurements, offers a more comprehensive and accurate assessment of the body's inflammatory response [8, 9]. Evidence has shown that elevated AISI levels are significantly associated with poor prognosis in various solid malignancies [10, 11]. In PTC, prominent inflammatory cell infiltration and upregulation of inflammatory cytokines within the tumor microenvironment indicate that both systemic and local inflammatory responses may play important roles in pathogenesis.

In this context, this study investigated the involvement of the TLR2/NF-κB signaling pathway and the AISI in the occurrence and progression of PTC, with the aim of providing a theoretical basis for developing targeted therapeutic strategies and establishing an individualized prognostic model for PTC.

Materials and methods

General information

This study included 273 patients with PTC who underwent surgical resection at our hospital from January 2021 to January 2022. Tumor tissues (PTC group) and adjacent non-tumorous tissues (PT group) were collected from these patients. In addition, 104 cases of nodular goiter tissues were included as the normal control group (NC group). The study protocol was reviewed and approved by the Ethics Committee of Xuancheng People's Hospital.

Inclusion and exclusion criteria

Inclusion criteria: PTC group: (1) Newly diagnosed with PTC confirmed by histopathologic examination; (2) Meeting the criteria for surgical intervention and underwent thyroidectomy; (3) Age ≥18 years; (4) No prior history of chemotherapy, radiotherapy, endocrine therapy, or thyroid surgery; (5) Availability of complete clinical data; (6) Provision of informed consent from patients and their families.

NC group: (1) Histopathologically confirmed diagnosis of nodular goiter; (2) Age ≥18 years; (3) No history of thyroid disease, chemotherapy, radiotherapy, or endocrine therapy; (4) Availability of complete clinical data; (5) Provision of informed consent from patients or their family.

Exclusion criteria: PTC group: (1) Coexistence of immune system or hematologic diseases; (2) Acute or chronic infection; (3) Severe cardiac, hepatic, or renal dysfunction; (4) Neurological or psychiatric disorders; (5) Presence of other malignancies or other types of thyroid cancer; (6) Recurrent thyroid cancer; (7) History of preoperative radiotherapy or chemotherapy; (8) Previous thyroid surgery; (9) Pregnancy or lactation; (10) Poor treatment compliance.

NC group: (1) Coexistence of other thyroid diseases; (2) Coexistence of immune system or hematological diseases; (3) Acute or chronic infection; (4) Severe cardiac, hepatic, or renal dysfunction; (5) Neurological or psychiatric disorders; (6) Previous thyroid surgery; (7) Pregnancy or lactation; (8) Poor treatment compliance.

Methods

Data collection: Clinical data of all study subjects were collected and compared, including sex, age, tumor diameter, clinical stage, degree of differentiation, lymph node metastasis status, concomitant Hashimoto's thyroiditis, number of lesions, and presence of extraglandular extension.

Immunohistochemistry: Sections were prepared from surgically resected tissues, including tumor tissues and adjacent non-tumorous tissues from PTC patients, as well as nodular goiter tissues from the NG group. The expres-

sion levels of TLR2, MyD88, and NF-κB in each group were evaluated by immunohistochemistry. For each specimen, five representative sections were examined. Positive staining was identified by the presence of brownish-yellow deposits in the cytoplasm or nucleus. Five fields of view were selected per section for scoring. The IHC score was determined by multiplying the score for positive cell proportion by the score for staining intensity. The proportion of positive cells was scored as: 0 (≤5%, 1 (5%-25%), 2 (26%-50%), 3 (51%-75%), 4 (76%-100%). Staining intensity was scored as 0 (no staining), 1 (yellow), 2 (brownish-yellow), or 3 (brown). A final product ≤1 was defined as negative, and >1 was positive. Among the proteins analyzed, TLR2 was localized to the cytoplasm or nucleus, MyD88 was primarily cytoplasmic, and NF-κB was observed in the cytoplasm or cell membrane.

Reverse transcription polymerase chain reaction (RT-PCR) analysis: Total RNA was extracted from surgically obtained tissue specimens, including tumor tissues and adjacent non-tumorous tissues from PTC patients, as well as thyroid tissues from NG patients. The relative mRNA expression levels of TLR2, MyD88, and NF-κB were quantified using RT-PCR. The primer sequences were as follows: TLR2 forward: 5'-GCTCACCGATGAAGAAG-3'; reverse: 5'-TCCAAGATGTAACGCAA-3'. MyD88 forward: 5'-CGGTCTCCTCCACATCCTCCCTTCC-3'; reverse: 5'-CTGCCAGTGGGGTCCGCTTGTGTCT-3'. NF-κB forward: 5'-AACTGTTCCCCCTCATCTTC-3'; reverse: 5'-TCCTACAAGCTCGTGGGGGT-3'.

Aggregate Index of Systemic Inflammation (AISI) measurement: All participants underwent routine preoperative blood tests. The AISI was calculated based on neutrophil (NEU), monocyte (MON), platelet (PLT), and lymphocyte (LYM) counts, using the following formula: AISI = NEU × MON × PLT/LYM.

Follow-up

Based on the median expression levels of TLR2, MyD88, NF-κB mRNA, and AISI in tumor tissues of PTC patients, subjects were categorized into high- and low-expression groups. All subjects were followed up postoperatively through outpatient visits and telephone interviews for a period of three years. Overall survival (OS) was defined as the interval from the date of surgery to death or the last follow-up.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 software. Categorical data were expressed as n (%) and compared using the Chi-square test. Continuous data were presented as mean ± standard deviation ($\bar{x} \pm s$). For comparisons between two groups, an independent-sample t-test was used. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was used, followed by the Least Significant Difference (LSD) *post hoc* test to identify specific inter-group differences where statistical significance was indicated. The Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the predictive value of various indicators for patient prognosis. Kaplan-Meier survival analysis was performed to compare overall survival between groups stratified by high and low expression levels of TLR2, MyD88, NF-κB mRNA, or AISI. Cox regression analysis was used to identify independent prognostic factors. A *p*-value <0.05 was considered significant.

Results

Immunohistochemical results

The positive rates of TLR2, MyD88, and NF-κB proteins in the PTC group were significantly higher than those in the NG and PT groups (P<0.05). See **Figure 1**.

Comparison of TLR2, MyD88, NF-κB mRNA expression and AISI levels among the three groups

Relative to the NG and PT groups, significantly higher levels of AISI and of TLR2, MyD88, and NF-κB mRNA were observed in the PTC group (P<0.05). See **Table 1**.

Comparison of TLR2, MyD88, and NF-κB mRNA expression and AISI levels in PTC patients with different clinical characteristics

Within the PTC group, patients with clinical stage III-IV, lymph node metastasis, low differentiation, or extrathyroidal extension exhibited significantly higher levels of TLR2, MyD88, NF-κB mRNA, and AISI compared to those with clinical stage I-II, no lymph node metastasis, moderate/high differentiation, or no extrathyroidal extension (P<0.05). See **Table 2**.

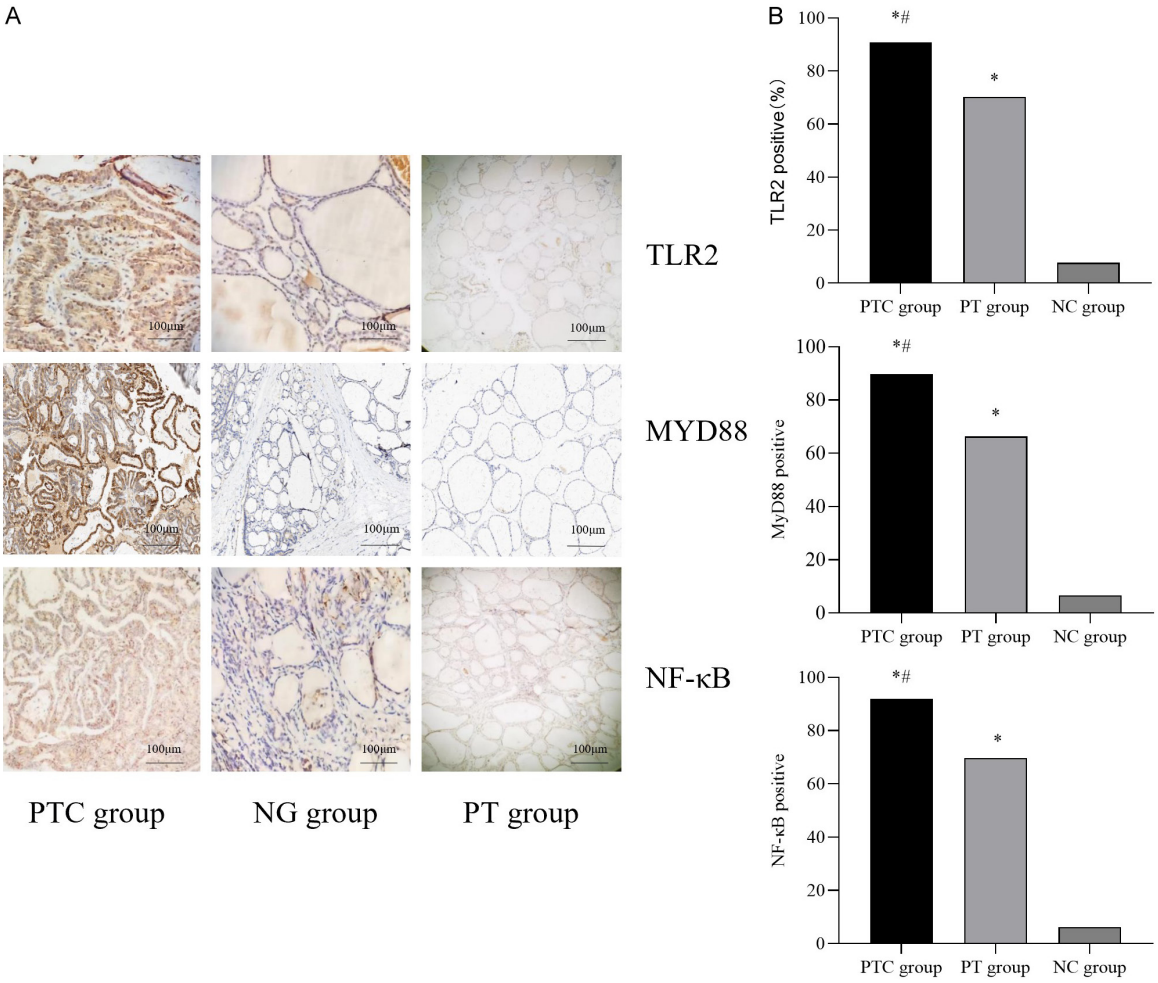

Figure 1. Immunohistochemical results. Note: (A) Immunohistochemical images of each group (×200); (B) Comparison of protein positive rates among the groups. Compared to NC group, *P<0.05; Compared with PT group, #P<0.05.

Table 1. Comparison of TLR2, MyD88, and NF-κB mRNA and AISI levels among the three groups

Group	n	AISI	TLR2 mRNA	MyD88 mRNA	NF-κB positive
PTC	273	428.16±77.39*,#	2.93±0.80*,#	2.91±0.75*,#	3.18±0.72*,#
PT	273	226.28±41.03*	1.22±0.45*	1.31±0.53*	1.74±0.60*
NC	273	159.22±34.91	0.45±0.21	0.57±0.24	0.52±0.29
χ^2		1805.102	1488.383	1300.341	1508.625
P		<0.001	<0.001	<0.001	<0.001

Note: AISI, Aggregate Index of Systemic Inflammation; TLR2, toll-like receptor 2. Compared with the NC group, *P<0.05; Compared to the PT group, #P<0.05.

Comparison of clinical characteristics between survival and deathgroups

Compared to the survival group, patients in the death group exhibited a lower degree of differentiation (grade III-IV) and a higher proportion of lymph node metastasis and extrathyroidal extension (P<0.05). See **Table 3**.

Comparison of TLR2, MyD88, and NF-κB mRNA and AISI levels between survival and death groups

By the end of follow-up, 70 patients had died. The death group exhibited significantly higher levels of TLR2, MyD88, NF-κB mRNA, and AISI compared with the survival group (P<0.05). See **Table 4**.

Table 2. Comparison of TLR2, MyD88, NF-κB mRNA and AISI levels in patients with different clinical characteristics in the PTC group

Characteristic	n	AISI	TLR2 mRNA	MyD88 mRNA	NF-κB mRNA
Gender					
Male	116	430.87±81.65	2.95±0.81	2.94±0.77	3.23±0.73
Female	157	426.15±74.28	2.91±0.70	2.89±0.73	3.14±0.71
	t	0.498	0.415	0.585	0.965
	P	0.619	0.678	0.559	0.336
Age					
<55 years	139	420.08±78.75	2.86±0.79	2.83±0.76	3.12±0.72
≥55 years	134	436.53±75.33	3.00±0.80	2.99±0.72	3.24±0.71
	t	1.762	1.448	1.768	1.367
	P	0.079	0.149	0.078	0.173
Tumor diameter					
≤3 cm	161	432.14±79.35	2.96±0.81	2.94±0.77	3.21±0.72
>3 cm	112	422.42±74.45	2.87±0.77	2.87±0.71	3.14±0.71
	t	1.021	0.923	0.701	0.774
	P	0.308	0.357	0.484	0.440
Clinical stage					
I-II	149	418.31±77.57	2.84±0.77	2.82±0.74	3.09±0.74
III-IV	124	439.99±75.79	3.03±0.81	3.01±0.75	3.29±0.67
	t	2.323	1.983	2.099	2.320
	P	0.021	0.048	0.037	0.021
Degree of differentiation					
Medium/high differentiation	156	406.61±65.17	2.70±0.67	2.69±0.63	3.00±0.66
Low differentiation	117	456.88±83.12	3.22±0.86	3.20±0.79	3.42±0.72
	t	5.601	5.650	5.853	4.920
	P	<0.001	<0.001	<0.001	<0.001
Lymph node metastasis					
No	150	404.19±62.81	2.68±0.65	2.66±0.60	2.98±0.65
Yes	123	457.38±83.46	3.22±0.85	3.21±0.80	3.43±0.72
	t	6.004	5.867	6.553	5.379
	P	<0.001	<0.001	<0.001	<0.001
Hashimoto's thyroiditis					
No	208	427.55±81.53	2.91±0.84	2.90±0.77	3.15±0.74
Yes	65	430.11±62.80	2.97±0.65	2.94±0.65	3.26±0.62
	t	0.232	0.547	0.338	1.049
	P	0.816	0.585	0.736	0.295
Number of lesions					
Single send	168	429.63±74.39	2.93±0.77	2.92±0.73	3.22±0.69
Multiple	105	425.79±82.26	2.92±0.83	2.88±0.76	3.12±0.75
	t	0.399	0.114	0.426	1.030
	P	0.690	0.909	0.670	0.304
Extraglandular extension					
No	201	420.33±74.72	2.85±0.76	2.83±0.70	3.12±0.70
Yes	72	450.01±80.97	3.13±0.85	3.13±0.81	3.34±0.75
	t	2.829	2.556	3.019	2.265
	P	0.005	0.011	0.003	0.024

Note: AISI, Aggregate Index of Systemic Inflammation; TLR2, toll-like receptor 2.

Table 3. Comparison of different clinical characteristics between the survival group and the death group

Index	Survival	Death	χ^2	*P*
Gender			1.424	0.233
Male	34	82		
Female	36	121		
Age			0.207	0.649
<55 years	34	105		
≥55 years	36	98		
Tumor diameter			2.596	0.107
≤3 cm	47	114		
>3 cm	23	89		
Clinical staging			0.796	0.372
I-II	35	114		
III-IV	35	89		
Degree of differentiation			17.651	<0.001
Medium/high differentiation	25	131		
Low differentiation	45	72		
Lymph node metastasis			16.230	<0.001
No	24	126		
Yes	46	77		
Hashimoto's thyroiditis			1.424	0.233
No	57	151		
Yes	13	52		
Number of lesions			0.001	0.983
Single send	43	125		
Multiple	27	78		
Extraglandular extension			86.326	<0.001
No	22	179		
Yes	48	24		

ROC curve analysis

Using cutoff values of AISI (463.87), TLR2 (3.40), MyD88 (3.26), and NF-κB (3.61) mRNA, the area under the curve (AUC) for predicting patient prognosis was 0.815, 0.802, 0.795, and 0.799, respectively. When the four indicators were combined, the AUC increased to 0.818, indicating improved predictive performance. See **Table 5** and **Figure 2**.

Comparison of overall survival between high- and low-AISI expression groups

Patients with low expression of AISI, TLR2, MyD88 and NF-κB mRNA exhibited a significantly longer overall survival than those with high expression (P<0.05). See **Figure 3**.

Cox regression analysis results

Cox regression analysis was performed with prognosis as the dependent variable and clinical stage, lymph node metastasis, differentiation degree, extrathyroidal extension, AISI, and mRNA expression levels of TLR2, MyD88, and NF-κB as independent variables. The analysis revealed that poor differentiation, extrathyroidal extension, and high AISI expression were independent risk factors for poor prognosis in patients. See **Table 6**.

Discussion

Previous studies have shown that although most patients with PTC have a favorable prognosis, a subset of patients still experience poor outcomes, including recurrence and metastasis [12-14]. Therefore, identifying effective biomarkers to assess disease status and predict prognosis in PTC is essential.

TLR2 recognizes pathogen-associated molecular patterns and activates downstream MyD88 and NF-κB signaling, thereby participating in inflammatory responses [15-17]. In this study, immunohistochemical results showed that the positive rates of TLR2, MyD88, and NF-κB proteins in the PTC group were significantly higher than those of the nodular goiter group (NG) and the adjacent non-tumorous tissue group (PT). RT-PCR results further confirmed that the mRNA levels of TLR2, MyD88, and NF-κB were also significantly elevated in the PTC group relative to the NG and PT groups. These findings suggest that in PTC, tumor cells may activate TLR2 by endogenous ligands, subsequently triggering the NF-κB signaling pathway and promoting tumor cell proliferation, survival, and metastasis [18-20]. The AISI is a comprehensive marker reflecting systemic inflammatory status and has been closely asso-

Table 4. Comparison of TLR2, MyD88, NF-κB mRNA, and AISI levels between the survival group and the death group

Groups	n	AISI	TLR2 mRNA	MyD88 mRNA	NF-κB mRNA
Death group	70	491.85±68.36	3.57±0.75	3.49±0.70	3.70±0.58
Survival group	203	406.19±67.65	2.71±0.68	2.71±0.65	3.00±0.67
t		9.111	8.843	8.435	7.723
P		<0.001	<0.001	<0.001	<0.001

Note: AISI, Aggregate Index of Systemic Inflammation; TLR2, Toll-like receptor 2.

Table 5. ROC analysis of TLR2, MyD88, NF-κB, and AISI for predicting patient prognosis individually or in combination

Index	Cutoff value	AUC (95% CI)	P	Sensitivity	Specificity
AISI	463.87	0.815 (0.753, 0.877)	<0.001	0.729	0.797
TLR2 mRNA	3.40	0.802 (0.738, 0.866)	<0.001	0.743	0.772
MyD88 mRNA	3.26	0.795 (0.728, 0.861)	<0.001	0.700	0.797
NF-κB mRNA	3.61	0.799 (0.734, 0.864)	<0.001	0.700	0.807
Joint factor	-	0.818 (0.756, 0.880)	<0.001	0.733	0.786

Note: AISI, Aggregate Index of Systemic Inflammation; TLR2, Toll-like receptor 2.

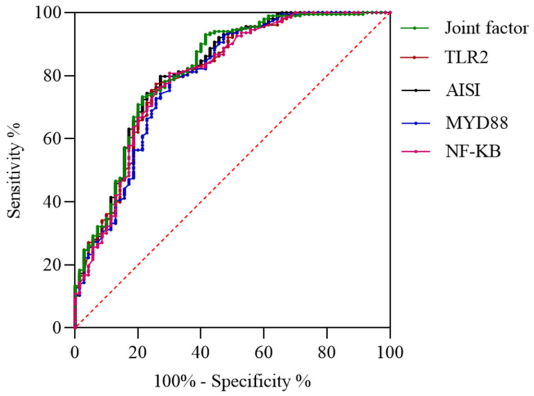

Figure 2. ROC curves.

ciated with tumor progression [21, 22]. In this study, AISI levels in the PTC group were significantly higher than those in the NG and PT groups, indicating that PTC patients exhibit a more pronounced systemic inflammatory response, which may facilitate tumor progression [23, 24].

The study further analyzed PTC patients according to different clinical characteristics. The results demonstrated that TLR2, MyD88, NF-κB mRNA, and AISI levels were significantly higher in patients with advanced clinical stages, lymph node metastasis, extrathyroidal extension, and low tumor differentiation. These findings indicate that the TLR2/NF-κB signaling pathway and systemic inflammatory status (as reflected by AISI) are closely associated with a malignant phenotype of PTC. In patients with advanced-stage disease, activation of the TLR2/NF-κB pathway, together with enhanced systemic inflammatory responses, may promote tumor cell migration and invasion [25, 26]. Furthermore, higher levels of TLR2, MyD88, NF-κB mRNA, and AISI in patients with lymph node metastasis suggest that activation of this signaling pathway and an enhanced inflammatory state may increase tumor cell adhesion, migration, and invasiveness, thereby increasing the likelihood of entry into the lymphatic system and subsequent metastasis.

In this study, PTC patients were followed up for three years. The results found that the patients in the death group had lower tumor differentiation, a higher incidence of lymph node metastasis and extrathyroidal extension, and significantly elevated levels of TLR2, MyD88, NF-κB mRNA, and AISI, suggesting that activation of the TLR2/NF-κB pathway and elevated AISI are closely associated with poor prognosis in PTC patients. Continuous activation of the TLR2/NF-κB signaling pathway may enable tumor cells to evade immune surveillance and promote tumor angiogenesis, thereby providing favorable conditions for tumor growth and metastasis. Concurrently, systemic inflammatory responses can alter the tumor microenvi-

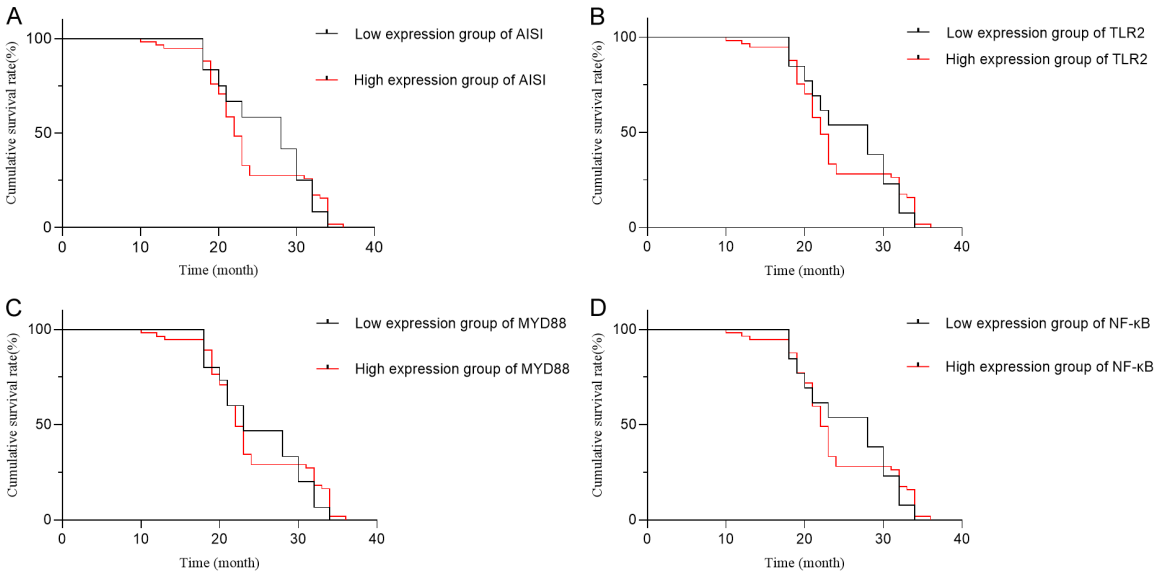

Figure 3. Kaplan-Meier survival curves for high-expression and the low-expression groups of each index. A: AISI; B: TLR2; C: MYD88; D: NF-κB. Note: AISI, Aggregate Index of Systemic Inflammation; TLR2, toll-like receptor 2.

Table 6. Cox regression analysis

Index	B	SE	Wald	P	OR	95% CI	
Clinical stage (III-IV)	-0.395	0.269	2.168	0.141	0.673	0.398	1.140
Lymph node metastasis (Low differentiation)	1.002	0.462	4.713	0.030	2.723	1.102	6.729
Lymph node metastasis (yes)	-0.045	0.465	0.009	0.923	0.956	0.385	2.376
Extraglandular extension (yes)	1.611	0.264	37.352	0	5.008	2.987	8.396
High AISI expression	3.079	1.335	5.316	0.021	21.727	1.587	297.548
High TLR2 mRNA expression	-0.280	0.928	0.091	0.763	0.756	0.123	4.662
High MyD88 mRNA expression	-0.771	0.609	1.604	0.205	0.462	0.140	1.525
High NF-κB mRNA expression	-0.688	0.943	0.532	0.466	0.502	0.079	3.192

Note: AISI, Aggregate Index of Systemic Inflammation; TLR2, toll-like receptor 2; OR, odds ratio; CI, confidence interval.

ronment, promote tumor cell proliferation and survival, and worsen patients' overall physical status and immune function, further increasing the risk of mortality. ROC analysis demonstrated that TLR2, MyD88, NF-κB mRNA, and AISI each had clinical value in predicting patient prognosis, both individually and in combination. Among these, the combined prediction yielded the highest AUC (0.818), indicating that integrated assessment of these markers can more accurately predict the prognosis of PTC patients.

In addition, the study demonstrated that patients in the low-expression groups of TLR2, MyD88, NF-κB mRNA, and AISI had longer overall survival compared to those in the high-expression groups. This finding further supports a negative correlation between the TLR2/NF-κB pathway activity, AISI, and PTC prognosis. Cox regression analysis identified low tumor differentiation, extrathyroidal extension, and high AISI expression as independent risk factors for poor prognosis. Low differentiation reflects an advanced state of tumor progression, while extrathyroidal extension indicates that the tumor has breached the thyroid capsule and infiltrated surrounding vital tissues and organs. This complicates surgical resection, elevates the risk of recurrence and metastasis, and consequently leads to poor patient outcome. High AISI expression reflects a more pronounced systemic inflammatory state, which can promote tumor growth and metastasis through multiple mechanisms. Therefore, interventions such as pharmacological therapy,

nutritional support, and other measures that modulate systemic inflammation may help reduce AISI levels and improve survival.

This study has several limitations. First, the sample size was relatively small, which may introduce selection bias. Second, the study focused on the correlation between TLR2/NF-κB pathway activity, AISI, and prognosis in PTC patients; the specific molecular mechanisms and signaling networks underlying these associations require further investigation. In summary, the TLR2/NF-κB signaling pathway and AISI are closely associated with disease progression of PTC and hold prognostic value.

Disclosure of conflict of interest

None.

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