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*Original Article*

# Serum Chemerin and thyrotropin expression levels in patients with thyroid cancer and roles in predicting survival

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**Abstract:** Objective: In the current study, the relationship between expression levels of Chemerin (Chemerin), thyrotropin (TSH), and prognosis in serum of patients with thyroid cancer was explored. Methods: Serum TSH levels in 110 patients with thyroid cancer (observation group) and 100 patients with benign thyroid lesions (control group) were measured using enzyme-linked immunosorbent assays (ELISA). Expression patterns of Chemerin and TSH of the observation group were analyzed. Survival analysis was performed on patients in the observation group. Kaplan-Meier estimates were performed with recurrent and non-recurrent patients as dependent variables. ROC curves were used to analyze the diagnostic value of Chemerin and TSH for thyroid cancer. Results: Chemerin and TSH expression levels in serum of the observation group were significantly higher than those of the control group ($P<0.05$). There was a correlation between TNM stage and lymph node metastasis ($P<0.05$). The area under the ROC curve of Chemerin, TSH, and their combination for diagnosis of thyroid cancer was 0.854 (95% CI: 0.803~0.905), 0.701 (95% CI: 0.630~0.773), and 0.880 (95% CI: 0.834~0.926), respectively. The 5-year overall survival of 110 patients with thyroid cancer was 54.55%. Further analysis found that 5-year survival rates of the Chemerin high expression group were significantly lower than those of the Chemerin low expression group ($P=0.001$). TSH high expression and TSH low expression groups showed a similar trend ($P=0.007$). Conclusion: Chemerin and TSH have diagnostic value in thyroid cancer. They are expected to be potential predictors of survival.

**Keywords:** Thyroid cancer, Chemerin, thyroid stimulating hormone, survival situation

## Introduction

Thyroid cancer, the most common malignant tumor in the endocrine system, accounts for 1% of all tumors. It can be divided into papillary carcinoma, follicular carcinoma, undifferentiated carcinoma, and medullary carcinoma. Papillary carcinoma is the most common [1, 2]. Statistics have shown that the proportion of patients with papillary carcinoma in thyroid cancer is as high as 80%, occurring mostly in women. The thyroid cancer ratio of males to females is about 1:2.5~3, with a wide range of onset age. The average is around 40 years [3, 4]. There were 208,000 new cases of thyroid cancer, worldwide, in 2012 [5]. In 2017, there were 56,900 new cases of thyroid cancer and 2,000 related deaths in the United States [6]. Although the mortality rate is low, patients that are not treated in time are still at risk of death. Studies have shown that 5-year survival rates of thyroid cancer patients can reach 95.8% after early diagnosis and timely and effective treatment [7].

Chemerin is a newly discovered inflammatory agent that exists in cancer patients. Chemerin interacts with tumor necrosis factor alpha, interleukin 6, and adiponectin. It is also known as a chemokine because it acts as a chemokine [8]. It is involved in systemic inflammatory state and has different expression levels in lung cancer and esophageal cancer. It is expected to be a potential diagnostic indicator for patients with papillary carcinoma thyroid cancer [9-11]. However, no previous studies were found showing whether there was a link between Chemerin and thyroid cancer. Thyroid stimulating hor-

mone (TSH) is the most basic examination item for thyroid nodular diseases. Studies have shown that changes in expression of thyrotropin [12] are independent risk factors for thyroid cancer.

Therefore, the current study explores the relationship between expression levels of thyrotropin and Chemerin in serum and clinicopathological features of patients with thyroid cancers. The current study explores whether these levels can be potential diagnostic indicators for thyroid cancer, providing reference for clinician treatment or diagnosis.

## Materials and methods

### *Patient information*

Form January to October 2013, 110 patients with thyroid cancer were enrolled. The patients were sent to the Department of Pathology for biopsy puncturing or surgery. Thyroid cancer was confirmed by pathological diagnosis in these 110 patients (observation group). Of these, there were 48 males and 62 females, aged from 35 to 78, with an average age of 50.2±5.8 years. This study was based on UICC (Union for International Cancer Control) and AJCC (Alternate Joint Communications Center) guidelines [13, 14]. Patients were classified at different TNM stages with pathological diagnosis. Another 100 patients with benign thyroid lesions were enrolled as the control group. This group included a total of 42 males and 58 female patients. They were aged between 30-76 years, with an average age of 49.3±6.9 years. The current study was approved by the Medical Ethics Committee of China-Japan Union Hospital of Jilin University. All study participants provided written informed consent before participating in the study.

*Inclusion criteria for the observation group:* Patients with thyroid cancer that did not receive radiotherapy and chemotherapy before treatment; Age ≥18 years; Patients that provided informed consent; Patients that could be followed-up annually for 5 years to assess the objectives of the study.

*Inclusion criteria for the control group:* Patients with benign thyroid lesions; Age ≥18 years; Patients providing informed consent; Patients that could be followed-up annually for 5 years to assess the objectives of the study.

*Exclusion criteria for the two groups:* Patients with other malignant tumors or endocrine diseases; Patients with defects in immune function; Patients with diseases identified to influence Chemerin and TSH expression, such as inflammatory diseases; Patients with any kind of disorder that may compromise his/her ability to give written informed consent and/or to comply with study procedures.

### *Kit source*

Chemerin and TSH were tested by ELISA (USA R&D Systems inc., DCHM00, MAB65341).

### *Sample collection and testing*

A total of 5 mL of fasting venous blood (heparin anticoagulation) was collected in the early morning on the day before surgery in the observation group and the morning after physical examinations in the control group. The sample were left to rest for 15-30 minutes, then centrifuged at 3,000 RPM for 10 minutes. Serum was collected and dispensed into EP tubes. Some of the serum was taken for subsequent experiments. The Chemerin and TSH detection method operated in strict accordance with ELISA kit instructions. The specific plan was as follows. A 96-well plate was taken, then 100 μL of assay diluent was added to each well. A standard orifice was set up. The control orifices were added to 50 μL of the standard solution and the remaining wells were added to 50 μL of patient serum. The plates were incubated for 2 hours at room temperature. When washing the plate, the washing liquid in each well was guaranteed to be full without overflowing for 30 seconds. It was then discarded and patted dry 5 times. Enzyme label solution of 200 milliliters was added to each well. The plate was sealed, incubated at room temperature for 1 hour, and washed. Next, 200 μL of the substrate solution was added to each well, followed by incubation at 37°C for 30 minutes. Lastly, 50 of stop buffer of μL/well was added. Detection was carried out using a microplate reader within 15 minutes. The maximum absorption wavelength at 450 nm was measured. Three sets of repeat wells were set and the experiment was repeated 3 times.

### *Follow-ups*

Patient survival was followed-up by telephone and other methods. Patients were followed-up

**Table 1.** Clinical data of patients

| Factor | | Observation group (n=110) | Control group (n=100) | $t/c^2$ value | *P* value |
|---|---|---|---|---|---|
| Sex | | | | | |
| | Male | 48 (43.64) | 42 (42.00) | 0.057 | 0.811 |
| | Female | 62 (56.36) | 58 (58.00) | | |
| Age (year) | | | | | |
| | ≥50 | 50 (45.45) | 51 (51.00) | 0.645 | 0.422 |
| | <50 | 60 (54.55) | 49 (49.00) | | |
| BMI ($kg/m^2$) | | 22.84±1.84 | 23.10±1.92 | 1.002 | 0.318 |
| Anamnesis | | | | | |
| | Hypertension | 34 (30.91) | 30 (30.00) | 0.020 | 0.886 |
| | Diabetes mellitus | 32 (29.09) | 31 (31.00) | 0.091 | 0.763 |
| | Hyperlipemia | 25 (22.73) | 25 (25.00) | 0.149 | 0.669 |
| | Coronary disease | 18 (16.36) | 20 (20.00) | 0.467 | 0.494 |
| Residence | | | | | |
| | City | 68 (61.82) | 70 (70.00) | 1.556 | 0.212 |
| | Village | 42 (38.18) | 30 (30.00) | | |
| Degree of education | | | | | |
| | ≥Senior middle school | 47 (42.73) | 49 (49.00) | 0.830 | 0.362 |
| | <Senior middle school | 63 (57.27) | 51 (51.00) | | |
| Pathological type | | | | | |
| | Glandular papillary | 72 (65.45) | | | |
| | Follicular carcinoma | 16 (14.55) | | | |
| | Undifferentiated carcinoma | 12 (10.91) | | | |
| | Cephaloma | 10 (9.09) | | | |
| Differentiation degree | | | | | |
| | Well-differentiated | 54 (49.09) | | | |
| | Moderately differentiated | 26 (23.64) | | | |
| | Poorly differentiated | 30 (27.27) | | | |
| TNM staging | | | | | |
| | I+II | 44 (40.00) | | | |
| | III+IV | 26 (23.64) | | | |
| Lymphatic metastasis | | 24 (21.82) | | | |
| | Yes | 16 (14.55) | | | |
| | No | | | | |
| Pathological type | | 40 (36.36) | | | |
| | Glandular papillary | 70 (63.64) | | | |

**Table 2.** Expression of Chemerin and TSH in serum of the two groups of patients

| | Chemerin (ng/L) | TSH (mIU/L) |
|---|---|---|
| Observation group (n=110) | 2.404±0.491 | 3.431±1.843 |
| Control group (n=100) | 1.684±0.324 | 2.219±1.543 |
| t value | 12.411 | 3.306 |
| *P* value | <0.001 | 0.001 |

every 6 months after discharge and deaths were counted.

*Outcome measures*

Expression levels of Chemerin and TSH in the serum of the two groups were compared. The relationship between Chemerin, TSH, and the clinical data of patients in the observation group was observed. ROC curves were drawn according to expression levels of Chemerin and TSH in the two groups. According to the median expression level of Chemerin and TSH, the observation group was divided into the Chemerin high expres-

**Table 3.** Relationship between Chemerin expression and clinical data in the observation group

| Factor | | Observation group (n=110) | Chemerin (ng/L) | t/F value | *P* value |
|---|---|---|---|---|---|
| Sex | | | | | |
| | Male | 48 (43.64) | 2.451±0.268 | 1.751 | 0.083 |
| | Female | 62 (56.36) | 2.299±0.553 | | |
| Age (year) | | | | | |
| | ≥50 | 50 (45.45) | 2.392±0.472 | 0.517 | 0.607 |
| | <50 | 60 (54.55) | 2.344±0.496 | | |
| BMI (kg/m$^2$) | | | | | |
| | ≥23 | 58 (52.73) | 2.417±0.255 | 1.384 | 0.169 |
| | <23 | 52 (47.27) | 2.309±0.500 | | |
| Pathological type | | | | | |
| | Glandular papillary | 72 (65.45) | 2.178±0.268 | 1.830 | 0.146 |
| | Follicular carcinoma | 16 (14.55) | 2.284±0.294 | | |
| | Undifferentiated carcinoma | 12 (10.91) | 2.341±0.288 | | |
| | Cephaloma | 10 (9.09) | 2.269±0.252 | | |
| Differentiation degree | | | | | |
| | Well-differentiated | 54 (49.09) | 2.268±0.284 | 0.349 | 0.706 |
| | Moderately differentiated | 26 (23.64) | 2.324±0.275 | | |
| | Poorly differentiated | 30 (27.27) | 2.288±0.281 | | |
| TNM staging | | | | | |
| | I+II | 70 (63.64) | 2.298±0.482 | 4.046 | <0.001 |
| | III+IV | 40 (36.36) | 2.641±0.309 | | |
| Lymphatic metastasis | | | | | |
| | Yes | 40 (36.36) | 2.842±0.321 | 6.028 | <0.001 |
| | No | 70 (63.64) | 2.484±0.284 | | |

sion group, Chemerin low expression group, TSH high expression group, and TSH low expression group. Five-year overall survival rates of the two groups were analyzed. Multifactorial Cox regression was used to analyze survival factors of thyroid cancer.

*Statistical analysis*

SPSS 20.0 was used for statistical analysis. GraphPad Prism 7 was used to map data. Count data utilization rates (%) are expressed using Chi-squared tests. Measurement data are expressed as mean ± standard deviation (Mean ± SD). Comparisons between the two groups were performed using independent sample t-tests, denoted by t. Comparisons between more than 2 groups were analyzed using one-way variance, expressed as F. Lsd-t testing was used after pairwise comparisons. Survival analysis was performed using Kaplan-Meier and patient survival was examined with log-rank tests. ROC curves were used to analyze the diagnostic value of Chemerin and TSH in thyroid cancer. P<0.05 indicates statistical differences.

## Results

*Comparison of baseline clinical data between the two groups*

Clinical data of the patients was compared. There were no statistical differences in gender, age, BMI, previous medical history, place of residence, and degree of education between the two groups (P>0.05) (**Table 1**).

*Chemerin and TSH expression levels in serum of the two groups of patients*

Expression levels of Chemerin and TSH were detected in the serum of the two groups. Expression levels of Chemerin and TSH in the serum of the observation group were 2.404±0.491 ng/L and 1.684±0.324 mIU/L, respectively. Expression levels of Chemerin and TSH in the serum of the control group were

**Table 4.** Relationship between TSH expression and clinical data in the observation group

| Factor | | Observation group (n=110) | TSH (mIU/L) | t/F value | *P* value |
|---|---|---|---|---|---|
| Sex | | | | | |
| | Male | 48 (43.64) | 3.347±1.952 | 0.299 | 0.766 |
| | Female | 62 (56.36) | 3.454±1.794 | | |
| Age (year) | | | | | |
| | ≥50 | 50 (45.45) | 3.214±1.950 | 0.516 | 0.607 |
| | <50 | 60 (54.55) | 3.398±1.788 | | |
| BMI (kg/m$^2$) | | | | | |
| | ≥23 | 58 (52.73) | 3.381±1.899 | 0.177 | 0.860 |
| | <23 | 52 (47.27) | 3.418±1.824 | | |
| Pathological type | | | | | |
| | Glandular papillary | 72 (65.45) | 3.216±1.892 | 0.040 | 0.989 |
| | Follicular carcinoma | 16 (14.55) | 3.201±2.031 | | |
| | Undifferentiated carcinoma | 12 (10.91) | 3.318±1.885 | | |
| | Cephaloma | 10 (9.09) | 3.411±1.802 | | |
| Differentiation degree | | | | | |
| | Well-differentiated | 54 (49.09) | 3.437±1.912 | 0.117 | 0.889 |
| | Moderately differentiated | 26 (23.64) | 3.252±2.027 | | |
| | Poorly differentiated | 30 (27.27) | 3.478±1.649 | | |
| TNM staging | | | | | |
| | I+II | 70 (63.64) | 2.751±1.581 | 3.108 | 0.002 |
| | III+IV | 40 (36.36) | 3.695±1.442 | | |
| Lymphatic metastasis | | | | | |
| | Yes | 40 (36.36) | 3.864±1.682 | 2.322 | 0.022 |
| | No | 70 (63.64) | 3.184±1.348 | | |

**Table 5.** ROC curve data

| Factor | AUC | SD | 95% CI | Specificity | Sensitivity | Cut-off | Youden index |
|---|---|---|---|---|---|---|---|
| Chemerin | 0.854 | 0.026 | 0.803~0.905 | 64.64% | 96.00% | 2.200 | 59.63% |
| TSH | 0.701 | 0.036 | 0.630~0.773 | 60.00% | 80.00% | 3.091 | 40.00% |
| Combination detection | 0.880 | 0.023 | 0.834~0.926 | 70.91% | 93.00% | 0.3702 | 63.91% |

Note: AUC: area under the curve.

3.131±2.162 ng/L and 2.519±1.843 mIU/L, respectively. The two groups showed significant differences (P<0.05) (**Table 2**).

*Chemerin and TSH expression levels across clinicopathological patterns*

Based on expression levels and clinical data of Chemerin and TSH, there were no statistical differences in expression of Chemerin and TSH found between gender, age, BMI, pathological type, and differentiation (P>0.05). However, there was a correlation between TNM stage and degree of lymph node metastasis (P<0.05) (**Tables 3** and **4**).

*ROC*

ROC curves were plotted for Chemerin and TSH. The area under the Chemerin curve was 0.854, 95% CI: 0.803~0.905. The value for TSH and the combination of these two indicators was 0.701 (95% CI: 0.630~0.773) and 0.880 (95% CI: 0.834~0.926) (**Table 5** and **Figure 1**).

*Analysis of 5-year survival rates of Chemerin and TSH and patients*

The 5-year overall survival rate of patients with thyroid cancer was 54.55%. Further studies

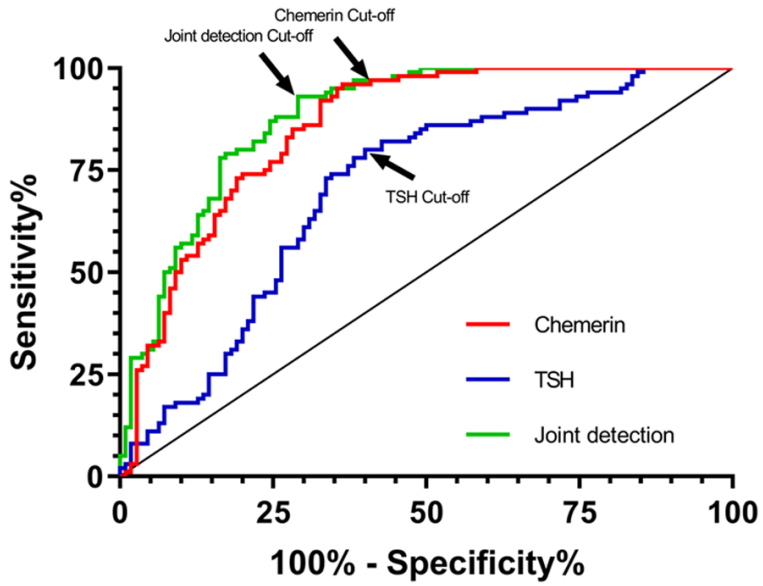


**Figure 1.** ROC curve. When the specificity and sensitivity of Chemerin are 64.64% and 96.00%, the optimal cutoff value is 2.200. When the specificity and sensitivity of TSH are 60.00% and 80.00%, the optimal cutoff value is 3.091. When the specificity and sensitivity of combination of both indicators are 70.91% and 93.00%, the optimal cutoff value is 0.37.

showed that the 5-year survival rate of the Chemerin high-expression group was significantly lower than that of the Chemerin low-expression group (P=0.001). The 5-year survival rate of the TSH high-expression group was also significantly lower than that of the TSH low-expression group (P=0.007) (**Figure 2**).

## Discussion

Thyroid cancer can be divided into four types, including papillary carcinoma, follicular carcinoma, undifferentiated carcinoma, and medullary carcinoma. Papillary carcinoma accounts for 80%~85% of thyroid cancer [15]. There were 90 thousand new cases of thyroid cancer and 68 thousand deaths in China in 2015 [16]. Although incidence and mortality rates of thyroid cancer are lower than other tumors, it still has a certain impact on patient quality of life. Another study showed [3] that early and timely treatment could extend the life span of 80% patients with thyroid cancer by 35 to 40 years. In recent years, the diagnostic rate of thyroid cancer has been improved. This may be related to improvements in the level of clinical equipment and instrument detection. However, diagnosis of thyroid cancer and benign thyroid tumors is mainly via thyroid biopsies. Although sensitivity and specificity are good, lymph node puncturing is an invasive test. This can cause certain trauma to patients [17]. Therefore, finding a less invasive test to determine thyroid cancer and benign thyroid tumors is urgent.

In this study, expression of Chemerin and TSH in the serum of patients was explored. Chemerin is located on human chromosome 7q36.1. It is expressed in the lungs, liver, pancreas, ovaries, and adipose tissue. Chemerin could affect immune function [18-20]. Zhang et al. [21] showed that Chemerin levels can be used as prognostic indicators for patients with gastric cancer. However, whether Chemerin is also differentially expressed in thyroid cancer has not been reported. TSH is a glycoprotein hormone that promotes thyroid growth through gland secretion. It promotes the metabolism of thyroid epithelial cells and synthesis of nucleic acids and proteins in white, promoting the development of thyroid cells [22]. Haymart et al. [23] showed that an increase in TSH is closely related to the clinical stage of thyroid cancer patients. In the study of Wang et al. [24], results showed that an increase of Chemerin expression is closely related to cell invasion in gastric cancer patients. It is not clear whether there is a relationship between expression of Chemerin and clinical data of patients with thyroid cancer. Therefore, analyzing expression levels of Chemerin and clinical data of patients with thyroid cancer, the current study found that expression of Chemerin and TSH is closely related to TNM stage and lymph node metastasis of thyroid cancer patients. This suggests that Chemerin is closely related to occurrence and development of thyroid cancer. Detecting expression levels of Chemerin and TSH in the serum of the obeservation group and the control group, expression of Chemerin and TSH in the serum of the observation group was shown to be higher than that of the control group. This indicates that these two indicators are poten-

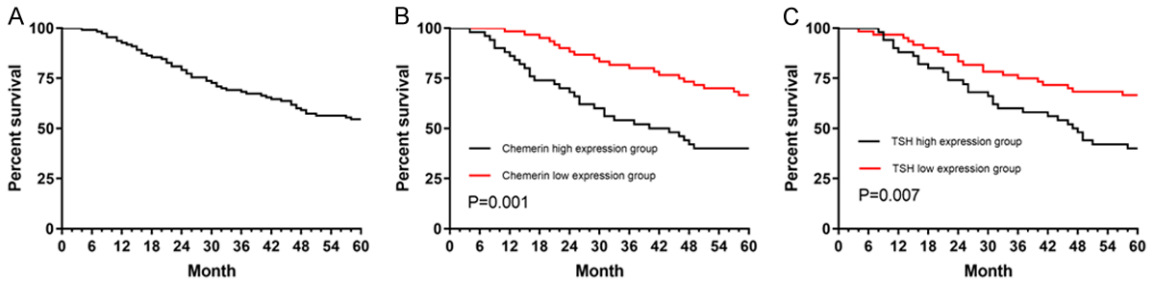


**Figure 2.** Survivorship curve. A. The 5-year overall survival rate; B. The 5-year survival rate of the Chemerin high expression group and low expression group; C.The 5-year survival rate in the TSH high expression group and in the TSH low expression group.

tial diagnostic indicators in distinguishing thyroid cancer from thyroid benign tumors. To this end, ROC curves were used to analyze the diagnostic value of the two indicators in patients with thyroid cancer and benign thyroid disease. ROC curves can easily detect the ability to recognize diseases at any threshold. When the area under the curve is greater than 0.5, this is an indicator of diagnostic value for the detection of diseases [25]. Drawing ROC curves, results showed that the area under Chemerin curve was 0.854, while that under TSH curve was only 0.701. The area under the curve was 0.880 through joint detection, significantly higher than the two indexes separately. This suggests that Chemerin combined with TSH is of high clinical value in the diagnosis of thyroid carcinoma and benign thyroid lesions.

Cancer is difficult to cure relative to other diseases. Clinically, 5-year survival rates are used to evaluate treatment effects of patient surgery or other treatment methods. If the patient survives for more than 5 years after surgery or other treatments, the patient's tumor cure possibility can be considered [26]. Therefore, 5-year follow-ups were conducted for thyroid cancer patients. Results showed that the 5-year overall survival rate of 110 patients was 54.55%. This was lower than that of foreign studies [27]. Further analysis revealed that the 5-year survival rate of Chemerin and TSH group was significantly lower than that of the Chemerin and TSH group, suggesting that Chemerin and TSH expression can be used as a potential prognostic indicator of patient survival. Therefore, this study preliminarily proves that Chemerin and TSH have certain diagnostic value in thyroid cancer and benign thyroid lesions. They can be used as potential observation indexes for prognosis, observing their expression levels.

However, there were several limitations to the current study. First, this study was carried out in a single center. This study did not collect samples together with other centers. Whether these two indicators can be used as potential prognostic indicators for thyroid cancer remains unclear. Second, it is not clear how differential expression of Chemerin affects lymph node metastasis of thyroid carcinoma. Therefore, sample sizes should be increased in future research, further exploring the relationship between Chemerin and thyroid cancer and verifying present results.

In summary, Chemerin and TSH have certain diagnostic value in thyroid cancer and benign thyroid lesions. They should be considered potential predictors of prognosis, observing their expression levels.

## Disclosure of conflict of interest

None.

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