Clinical study of preoperative fT4/fT3 quotient and thyroid function test in distinguishing benign from malignant thyroid nodules

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ABSTRACT
Objective: To analyze the clinical and pathological characteristics of thyroid nodules and to explore the related risk factors of malignant thyroid nodules. Methods: According to the criteria of inclusion and exclusion, a total of 283 patients with thyroid nodules during January 2015 and December 2017 were divided into benign group (benign nodule, n = 172) and malignant group (malignant nodule, n = 111) based on postoperative histopathological results. The age, sex, serum thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), thyroid stimulating hormone (TSH), free thyroxine (fT4), free three iodine thyroxine (fT3) and fT4/ fT3 ratio were subjected to univariate analysis, and the risk factors of malignant thyroid nodule were screened by multivariate logistic regression analysis. Results: Univariate analysis showed that age, TgAb, fT4 (P < 0.05) and fT4/ fT3 quotient (P < 0.01) were significantly different between the two groups. The fT4/fT3 quotient is a risk factor of malignant nodules. Multivariate logistic regression analysis indicated that the risk factors of malignant thyroid nodule were age (OR: 0.934, 95% CI: 0.911-0.957), TgAb (OR: 2.069, 95% CI: 1.008-4.247) and fT4/ fT3 ratio were subjected to univariate analysis, and the risk factors of malignant thyroid nodule were screened by multivariate logistic regression analysis. Results: Univariate analysis showed that age, TgAb, fT4 (P < 0.05) and fT4/ fT3 quotient (P < 0.01) were significantly different between the two groups. The fT4/fT3 quotient is a risk factor of malignant nodules. Multivariate logistic regression analysis indicated that the risk factors of malignant thyroid nodule were age (OR: 0.934, 95% CI: 0.911-0.957), TgAb (OR: 2.069, 95% CI: 1.008-4.247) and fT4/ fT3 quotient (OR: 1.206, 95% CI: 1.038-1.401). Conclusion: The fT4/fT3 quotient has important diagnostic value in differentiating benign and malignant thyroid nodules. When fT4 / fT3 > 3, it increases the risk of malignancy. The age, TgAb and fT4 are independent risk factors for malignant thyroid nodule, which is of great value in distinguishing benign from malignant thyroid nodules.

1. Introduction

In recent years, the incidence of thyroid nodules has been increasing in China. A meta-analysis including 560877 cases of thyroid nodules revealed that prevalence of thyroid nodules in mainland China was 32%, the prevalence rates of thyroid nodules appeared 26% in male and 39% in female[1]. Thyroid nodules are divided into benign nodules and malignant nodules, of which malignant nodules account for 7%-15%(2]. Age, sex, radiation exposure and family history play an important role in the occurrence of malignant nodules [2]. Thyroglobulin antibodies (TgAb) and peroxidase antibodies (TPOAb) are important anti-thyroid autoantibodies. Abnormal elevations of TgAb and TPOAb are common in autoimmune diseases such as Hashimoto disease (HD). But it can also occur in patients with nodular goiter or thyroid cancer without HD[3]. At present, there is controversy about the relationship between the two antibodies and thyroid cancer[4-6]. In addition, recent studies have shown that serum thyrotropin (TSH) levels in patients with thyroid cancer are higher than those in patients with benign thyroid nodules, and serum free triiodothyronine (fT3) and free thyroxine (fT4) levels are lower than those in patients with benign thyroid nodules. However, this is not consistent with previous studies[7-10]. Moreover, the study of preoperative fT4/fT3 quotient in distinguishing benign from malignant thyroid nodules
has rarely been reported. In this study, we analyzed the relationship between serum TgAb, TPOAb, TSH, fT4, fT3 levels and the ratio of fT4 / fT3 in patients with thyroid nodules who had undergone the first operation in our hospital. We also discussed the value of serum markers to help clinicians distinguish benign and malignant thyroid nodules.

2. Materials and methods

2.1 Subjects

According to the criteria of inclusion and exclusion, a retrospective study was performed to analyze the clinical data of patients with thyroid nodules hospitalized in our hospital from January 2015 to December 2017. Inclusion criteria: 1. Surgery treatment firstly in our hospital; 2. Thyroid function tests a week before operation; 3. Perfect medical records. Exclusion criteria: 1. Past history of thyroid surgery in other hospital; 2. Levothyroxine or hyperthyroidism was administered within 2 weeks before surgery; 3. Lack of postoperative pathological findings; 4. History of head and neck external irradiation and family history of thyroid cancer.

2.2 Methods

Medical records of all patients including age, sex, serum TgAb, TPOAb, TSH, fT4, fT3 levels and pathological reports were collected. Then fT4/fT3 quotient was calculated to each patient. Whether the results of laboratory tests are abnormal or not depends on the reference range of our clinical laboratory. The pathological report was made by two experienced pathologists.

2.3 Statistical analysis

Statistical analyses were performed using SPSS version 25.0. All of the measurement data were analyzed with Student t test and the enumeration data were analyzed with chi-square test. The age, TgAb, TPOAb, TSH, fT4, fT3 and the ratio of fT4 to fT3 were analyzed by univariate analysis. Then the statistically significant indicators of univariate analysis were included in logistic regression analysis to screen the risk factors of thyroid malignant nodules. A $P<0.05$ was considered statistically significant.

3. Results

3.1 Comparison of general data between benign and malignant group

There was no significant difference in gender between the two groups ($P > 0.05$), and there was significant difference in age between the two groups ($P < 0.01$), as shown in Table 1.

3.2 Comparison of positive rates of TgAb and TPOAb in benign and malignant groups

The positive rate of serum TgAb in malignant group was significantly higher than that in benign group ($P < 0.05$), and the positive rate of serum TPOAb in malignant group was also higher than that in benign group, but the difference was not statistically significant ($P > 0.05$), as shown in Table 2. But further analysis revealed that some of these two groups had HD. Generally speaking, the TgAb and TPOAb levels in patients with HD were significantly higher. After removal of patients with HD, TgAb and TPOAb in malignant group were significantly higher than those in benign group, and the difference was statistically significant ($P<0.05$), as shown in Table 3.

3.3 Comparison of TSH, fT4, fT3 and fT4/fT3 quotient between benign and malignant groups

The levels of TSH and fT3 in benign group were slightly higher than those in malignant group ($P > 0.05$), and the levels of fT4 in malignant group were higher than those in benign group ($P < 0.05$),

Table 1.
Comparison of general data between benign and malignant group

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
<th>t/$t^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex(male/female, n/n)</td>
<td>36/136</td>
<td>26/85</td>
<td>0.245</td>
<td>0.621</td>
</tr>
<tr>
<td>Age(年±S)</td>
<td>55.65±12.03</td>
<td>46.59±12.77</td>
<td>6.038</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 2.
Comparison of positive rates of TgAb and TPOAb in benign and malignant groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>TgAb</th>
<th>TPOAb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Positive rate (%)</td>
</tr>
<tr>
<td>Benign</td>
<td>172</td>
<td>24</td>
<td>13.95</td>
</tr>
<tr>
<td>Malignant</td>
<td>111</td>
<td>28</td>
<td>25.23</td>
</tr>
<tr>
<td>$P$</td>
<td>0.017</td>
<td>0.228</td>
<td></td>
</tr>
</tbody>
</table>
as shown in Table 4. The median of fT4/fT3 ratio was used as the cut-off value. The preoperative fT4/fT3 ratio showed significant statistical difference between the two groups (P < 0.01). The fT4/fT3 ratio could be used as a risk factor for malignant nodules (OR: 2.065, 95% CI: 1.270 - 3.357), as shown in Table 5.

3.4 Multivariate logistic regression analysis of risk factors for thyroid nodules

Multivariate logistic regression analysis was performed with benign and malignant thyroid nodules as dependent variables, and the three statistically significant variables (age, TgAb, fT4) in the above univariate analysis were taken as independent variables. The results showed that age, TgAb and fT4 levels were associated with thyroid cancer (P < 0.05), and were independent risk factors of thyroid cancer, as shown in Table 6.

4. Discussion

In recent years, the incidence of thyroid cancer has increased gradually. Compared with 37 200 cases in 2009, there were about 64 300 new cases in the United States in 2016[11]. According to the latest epidemiological survey in South Korea, thyroid cancer has become the most common type of cancer[12]. In addition, according to the epidemiological results of different provinces and cities in China, thyroid cancer is also gradually moving towards the ranks of the most common tumors[13]. However, some scholars have proposed that there are over-diagnosis and over-treatment in the management of thyroid nodules[12]. Some patients even actively request surgical treatment for fear of malignant transformation of nodules, which makes it difficult for clinicians to make appropriate decisions. Therefore, accurate preoperative diagnosis is conducive to timely and effective treatment. The most important significance of thyroid nodule examination is to identify benign and malignant thyroid nodules.

At present, fine needle biopsy (FNA) and TI-RADS grading based on ultrasonography are the most commonly used methods to differentiate benign and malignant thyroid nodules before operation[14]. As an economical and non-invasive examination, ultrasonography is the first choice for thyroid nodules. In 2009, Park, et al[15] proposed a TI-RADS classification system based on 12 ultrasound features to classify the likelihood of thyroid nodule malignancy, which is now widely used. New ultrasound techniques have also been developed and applied to clinical practice, including high-resolution ultrasound (HRUS), real-time elastography (RTE) and contrast-enhanced ultrasound (CEUS)[15-17]. However, the results of ultrasound report largely depend on the advanced equipment and the work experience of doctors, and the TI-RADS classification standards of various hospitals are not uniform. FNA is the gold standard for preoperative evaluation of benign and malignant thyroid nodules, but it is invasive and not accepted by many patients. In addition, many hospitals cannot carry out FNA because of limited conditions, and for the diameter of less than 1 cm nodule is not suitable for FNA, so its application has many limitations[2,18].

Serological examination can be used as a supplementary diagnostic method for ultrasound and FNA. Karatzas, et al[19] showed that TgAb could be used as a potential predictor of papillary thyroid carcinoma when fine needle aspiration biopsy failed to identify benign and malignant thyroid nodules. Moreover, some studies have shown that fT4 and TPOAb can be used as diagnostic markers for thyroid cancer[4,20]. Domestic scholars such as Zhang Wenjing[3], Zhang Yu[21] and Xu W[22] have also shown that fT4, TgAb and TPOAb have certain value in differential diagnosis of thyroid cancer and benign thyroid nodules in Chinese adults, which is consistent with the results of this study. TSH is a major growth factor and regulator of thyroid cells, and many studies have shown that increased risk of thyroid cancer is associated with increased TSH levels[4,5,7]. But some studies have shown there is no correlation...
among them, and some scholars believe that increased TSH levels are negatively correlated with risk of thyroid cancer[23–26]. In light of the inconclusive associations between TSH, thyroid hormones, and thyroid cancer, Huang H et al[27] conducted a nested case-control study to investigate the associations of papillary thyroid cancer (PTC) with TSH and thyroid hormones. The results showed that serum TSH levels below the normal range were associated with a significantly increased risk of PTC; Paradoxically, TSH levels above the normal range were also associated with an increased risk of PTC[27]. They also found that the risk of PTC decreased with increasing TSH levels within the normal ranges, and this discovery has attracted the attention of some scholars[27,28]. In this study, the univariate analysis showed that the levels of TSH and fT3 in benign group were slightly higher than those in malignant group (P > 0.05). This may be due to the fact that most of the cases in this study are within normal TSH levels. Univariate analysis also showed that there were significant differences in serum positive rates of TgAb between benign and malignant thyroid nodules (P < 0.01), and the fT4 and fT4/T3 quotient between the two groups were significantly different (P < 0.05). In addition, we attempted to use 3 as the cut-off value of fT4/fT3 quotient. When ratio of fT4/fT3 > 3, the likelihood of malignancy increased (OR: 2.065, 95% CI: 1.270 - 3.357). This can be considered as a marker for thyroid cancer to further clarify the benign and malignant nodules and guide clinical treatment, especially for patients with TI-RADS 4. Therefore, we believe that thyroid function examination and ultrasonography should be performed before operation in patients with thyroid nodules, and then FNA should be considered according to medical conditions and the patient's personal wishes. For patients who do not undergo FNA or whose FNA results cannot be clearly diagnosed, we should further identify the benign and malignant nodules in combination with the patient's age, sex and serological findings, to provide personalized diagnosis and treatment program.

### References


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