ORIGINAL RESEARCH

Improving Diagnostic Coincidence Rate of Graves' Disease by Ultrasound Examination with Clinical Symptoms

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Objective: Combining ultrasound parameters with patient's clinical symptoms to explore the feasibility of improving the diagnostic coincidence rate of hyperthyroidism.

Methods: A total of 179 untreated patients with diffuse echogenic changes of the thyroid on ultrasound and abnormal laboratory examinations were enrolled this study. There were 119 cases of hyperthyroidism, 29 cases of subclinical hyperthyroidism, 26 cases of subclinical hypothyroidism, and 5 cases of Hashimoto's thyroiditis with clinically confirmed diagnosis. The thyroid volume, blood supply grade, peak velocity of the superior thyroid artery (STA) by ultrasound, heart rate (HR), and clinical symptoms was used to determine the optimal indicators for the diagnosis of hyperthyroidism, and to compare these indicators (study group) with the previous ultrasound criteria reported in the literature (control group).

Results: According to logistic regression analysis, from all the factors studied, hyperthyroidism symptoms had the most significant correlation with the diagnosis of hyperthyroidism (P = 0.001), followed by STA peak velocity (P = 0.005), HR (P = 0.009), echogenicity(P = 0.015)and blood flow Grade III (P = 0.041) in order of importance, the other factors include thyroid volume, blood flow Grade I and II were not correlated with the diagnosis of hyperthyroidism (P > 0.05). The diagnostic coincidence rate of hyperthyroidism by increased STA peak velocity was 85.7% (102/119), while the hyperthyroidism symptoms significantly increased the diagnostic coincidence rate to 95.8% (114/119). Comparing the study group to the control group, the area under the receiver operating curve (ROC) was 0.993 vs 0.899 (Z = 3.868, P = 0.001). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 89.92% vs. 68.91%, 96.67% vs. 96.67%, 92.18% vs. 78.21%, 98.17% vs. 97.62%, and 82.80% vs. 61.05%, respectively.

Conclusions: The optimal indicators for the diagnosis of hyperthyroidism is the presence of hyperthyroidism symptoms in untreated patients with diffuse echogenic changes of the thyroid, followed by increased STA peak velocity. This suggests that ultrasound doctors should carefully considerate clinical information and instead of just limited to ultrasound itself. By combining ultrasound parameters with the clinical manifestations of patients, the diagnostic coincidence rate can be truly improved.

Key words: Hyperthyroidism; Clinical symptoms; Blood flow velocity; Superior thyroid artery; Ultrasound

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Clinically, diffuse thyroid diseases include hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, subclinical hypothyroidism, and Hashimoto's thyroiditis. Hyperthyroidism not only has the highest incidence rate (about 85% is Graves' disease), but also has great impact on entire body systems. Therefore, it has been drawn an attention for ultrasound research. The ultrasound imaging of diffuse thyroid

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disease mainly show the changes of diffuse thyroid parenchyma echogenicity and increased blood flow. Over the years, research on the diagnosis of hyperthyroidism by ultrasound has made considerable progress. However, some shortcomings still exist in the application of current protocol and criteria for clinical practice.

Some investigators only studied the sonographic characteristics (such as thyroid volume, blood supply, blood velocity of thyroid artery, etc.) of hyperthyroidism [1-3], while others studied the differential diagnosis between hyperthyroidism and one of the above diffuse diseases [4,5]. Some research just studied the influence of one factor on the diagnosis of hyperthyroidism, such as the heart rate, the blood flow velocity of thyroid artery [6]. Only three literatures have studied the influence of two factors on the diagnosis of hyperthyroidism, i.e., the heart rate and peak flow rate of superior thyroid artery (STA) [7-9]. Most literatures had shortcomings in research methods: (1) the selection of cases was not rigorous, such as not distinguished patients with newly diagnosed and those had received treatment; (2) the precise measurement site of the thyroid artery was not clear. Sometimes, the measurement site was randomly selected or just selected the lower segment of the STA where close to the gland; (3) the research design methods were retrospectively analyzed, and no blind control was used.

In fact, thyroid volume, STA peak velocity, and HR are factors that can be directly obtained by ultrasound. Until now, the diagnosis of hyperthyroidism by ultrasound has been limited to ultrasound itself without input of clinical symptoms. However, in view of the advantages of ultrasound, imaging doctors can fully communicate with patients during entire examination, and it is easy to obtain a reliable medical history. Therefore, clinical symptoms could be included as the study factor. The typical clinical symptoms of hyperthyroidism including excessive sweating, heat intolerance, increased bowel movements, tremor, nervousness, agitation, rapid heart rate, weight loss, fatigue, decreased concentration, irregular and scant menstrual flow and proximal limb muscle atrophy and so on. However, a small number of patients, contrary to the typical symptoms of general hyperthyroidism, are indifferent hyperthyroidism, characterized by emotional indifference, not easily excited, daze, lethargy, depression, emaciation, fatigue, haggard face, dry skin, sweaty, lower eyelid edema, can also be complicated by anemia, stomach disease, hypertension, hyperlipidemia, high blood viscosity and immune disorders. The clinical manifestations of hyperthyroidism are very complex and careful patient consultation is necessary. In this study, we attempted to analyze combining thyroid volume, STA peak velocity, blood supply grade, HR on ultrasound imaging and clinical symptoms in patients with diffuse echogenic changes of the thyroid gland, and to use double-blind control with clinical diagnosis including biochemical test to explore the possibility of improving diagnostic rate of hyperthyroidism than that stated in previous literatures.

Patients and Methods

Patients

A total of 179 patients, aged from 9 to 82 years, were enrolled, with an average age of 37.9±15.2 years, including 47 males and 132 females. Inclusion criteria: (1) untreated diffuse thyroid lesions; (2) patients with no more than two masses in each thyroid lobe and each tumor's diameter ≦1.0 cm; (3) patients having an interval between laboratory examination and ultrasonic examination of no more than 3 days. The laboratory examination included routine bloods, and seven items of thyroid function (TT3: Total triiodothyronine; TT4: Total thyroid hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Hypersensitivity thyroid stimulating hormone; TPO: Thyroid peroxidase antibody; TGAb: Thyroglobulin antibody). Exclusion criteria: (1) neonatal hyperthyroidism; (2) autonomous hyperfunctional thyroid adenoma; (3) drug-induced hyperthyroidism; (4) secondary hyperthyroidism; (5) allogenic hyperthyroidism; (6) postoperative hyperthyroidism; (7) history of radioiodine treatment for hyperthyroidism; (8) patients with the largest diameter of a single thyroid tumor was ⩾1.5 cm (because relatively large tumors have an impact on hemodynamics); (9) patients with more than three masses in each thyroid lobe and tumor diameter >1.0 cm; (10) patients convalescing from serious disease or destructive thyroiditis (including subacute thyroiditis and postpartum thyroiditis); (11) untreated primary adrenal dysfunction; (12) patients with malignant tumor lesions in any system of the body; (13) patients who received cardiovascular drug intervention before a color Doppler ultrasound examination; (14) and patients with STA anatomical variations (such as being too small or hard to find the starting point).

Ultrasound evaluation

High-resolution ultrasound systems, including Aixplorer (Supersonic Imaging, France) and Aloka a-10 (Japan) machines, with transducer frequency of 4–15 MHz were utilized in this study.

Before ultrasound examination, we instructed every patient to rest for 10 min and relax their body to avoid inaccurate measurements of HR or blood flow velocity. The thyroid gland was scanned in the transverse, sagittal, and oblique sections by experienced ultrasound practitioners. The size of the thyroid was measured on grayscale imaging. Color Doppler velocity was uniformly lowered to 4.0–4.5 cm/s during the grading of thyroid blood supply. Blood flow grading of the thyroid was used based on previous study [10]: Grade 0: no increased in blood supply; Grade I: blood flow increased in a star-spot pattern, and thyroid background echo in the color window is still dominated by a large area of glandular substance; Grade II: blood flow increased as a bulky dot and branch pattern, and thyroid glandular parenchyma and blood flow signal in the color window are 50 vs. 50; Grade III: known as "fire-sea sign", the thyroid is dominantly covered by a diffuse blood flow signal, making it almost impossible to show the glandular parenchyma. STA peak velocity was measured according to our previous study [6], that is, sampling and measurement are conducted at the brightest part of color blood flow imaging of the STA on both sides. The value of the STA peak velocity ≥70 cm/s was considered as increase value [11]. HR values were obtained from pulse Doppler ultrasound.

In this study, we evaluated the diagnostic value of the following 6 sonographic features to differentiate hyperthyroidism and non-hyperthyroidism. Sonographic parameters included STA peak velocity (X1), heart rate (X2), thyroid volume (X3), thyroid blood supply(X4), clinical symptoms (X5), and echogenicity (X6). Clinical diagnosis was used as a reference standard. A double-blind control was used, in which neither sonographic doctor nor the patient was aware of the laboratory results or clinical diagnosis before the procedure.

Statistical Analysis

We refer to the research method in this paper as the study group, and refer to the method described in the literatures to diagnose hyperthyroidism by combining heart rate and maximum flow velocity of the STA as the control group, and conduct a comparative study of the two. Statistical analyses were performed by SPSS 21.0. The logistic regression was used to simulate a model to differentiate hyperthyroidism from non-hyperthyroidism. A P value < 0.05 was considered statistically significant. The statistically significant features were encapsulated in this model. This model's performance was conducted by crossing validation, including sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. The receiver operator characteristic curves (ROC) of multivariate observations between study group and control group were drawn, which can assess the logistic regression model's prediction performance. Z test was used to differentiate the significance of the area under the ROC curve between the two groups.

Results

Of the 179 patients, 119 (66.48%) were diagnosed with hyperthyroidism after a double-blind control process. Among the remaining 60 patients, 24 (13.41%) were subclinical hyperthyroidism, 26 (14.53%) were subclinical hypothyroidism and 10 (5.58%) were Hashimoto's thyroiditis. Clinical data for patients and sonographic characteristics for thyroid were presented in Table 1.

According to the patients' STA peak velocity, HR and corresponding clinical symptoms, 119 patients with hyperthyroidism were classified, as shown in Table 2. Type A was characterized by either high peak velocity or fast HR, Type B was characterized by high peak velocity and slow heart rate, Type C presented normal peak velocity and fast HR, Type D presented normal peak velocity and normal HR. Ultrasound imaging of all types were shown in Figure 1.

In order to explore which parameters were closely related to the diagnosis of hyperthyroidism, the study analysis considered "Whether or not hyperthyroidism" as the dependent variable (y = 0,1) and thyroid volume, STA peak velocity, blood supply grade, HR, clinical symptoms and echogenicity as covariables in logistic regression analysis (Table 3).

From summary of logistic regression analysis, the adjusted R square of goodness and fit test was 0.919. The sonographic parameters and clinical symptoms were detailed in Table 2. The age, thyroid volume and thyroid blood supply (Grade I, Grade II) were not found to have significantly difference between hyperthyroidism and non-hyperthyroidism (P > 0.05). Among these sonographic parameters, STA peak velocity, HR, thyroid blood supply (Grade III), echogenicity and clinical symptoms had statistically significance between hyperthyroidism and non-hyperthyroidism; especially for the clinical symptoms, in which its regression coefficient value (B) was 6.617, and the P (Sig.) value showed a significance of 0.001 level and its OR value was 747.822. The clinical symptoms had the most positive influence on the determination of hyperthyroidism.

After cross validation, the ROC curve was obtained (Fig 2). The area under the ROC curve (AUC) in study group for using this formula to differentiate hyperthyroidism and non-hyperthyroidism was 0.993. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 89.92%, 96.67%, 92.18%, 98.17%, and 82.80%, respectively while the AUC in control group was 0.899. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 68.91%, 96.67%, 78.21%, 97.62%, and 61.05%, respectively. Using Z test to differentiate the significance of the AUC between the study group and the control group, there was a significant difference in diagnostic coincidence rate between the two groups ($Z = 3.868$, $P < 0.001$).

Table 1 Ultrasound and clinical data of the patients

Characteristic	Definition	Total	Hyperthyroidism	Non-hyperthyroidism
Echogenicity				
No hypoechogenicity	0	49	21 (17.65%)	28 (46.67%)
Hypoechogenicity	1	130	98 (82.35%)	32 (53.33%)
Thyroid volume				
Normal	0	53	23 (19.33%)	33 (55.00%)
Large	1	122	96 (80.67%)	23 (38.33%)
Small	2	4	0 (0.00%)	4 (6.67%)
Peak velocity of STA				
< 70 cm/s	0	66	17 (14.29%)	44 (73.33%)
≧ 70 cm/s	1	113	102 (85.71%)	16 (26.67%)
Heart rate				
< 100 bpm	0	90	36 (30.25%)	54 (90.00%)
≧ 100 bpm	1	89	83 (69.75%)	6 (10.00%)
Blood supply grade				
Normal	0	17	0 (0.00%)	17 (28.33%)
Grade I	1	40	10 (8.41%)	34 (56.67%)
Grade II	2	87	70 (58.82%)	6 (10.00%)
Grade III	3	35	39 (32.77%)	3 (5.00%)
Clinical symptoms				
No hyperthyroidism symptoms	0	71	12 (10.08%)	58 (96.67%)
Hyperthyroidism symptoms	1	108	107 (89.92%)	2 (3.33%)

Table 2 Types and main characteristics by ultrasound in hyperthyroidism

Types	Cases	STA peak velocity		Heart rate		Hyperthyroidism symptoms	
		High	Normal	Quickened	Normal	Yes	No
Type A	72	72	0	72	0	70	2
Type B	30	30	0	0	30	28	2
Type C	11	0	11	11	0	10	1
Type D	6	0	6	0	6	6	0
Total	119	102	17	83	36	114	5

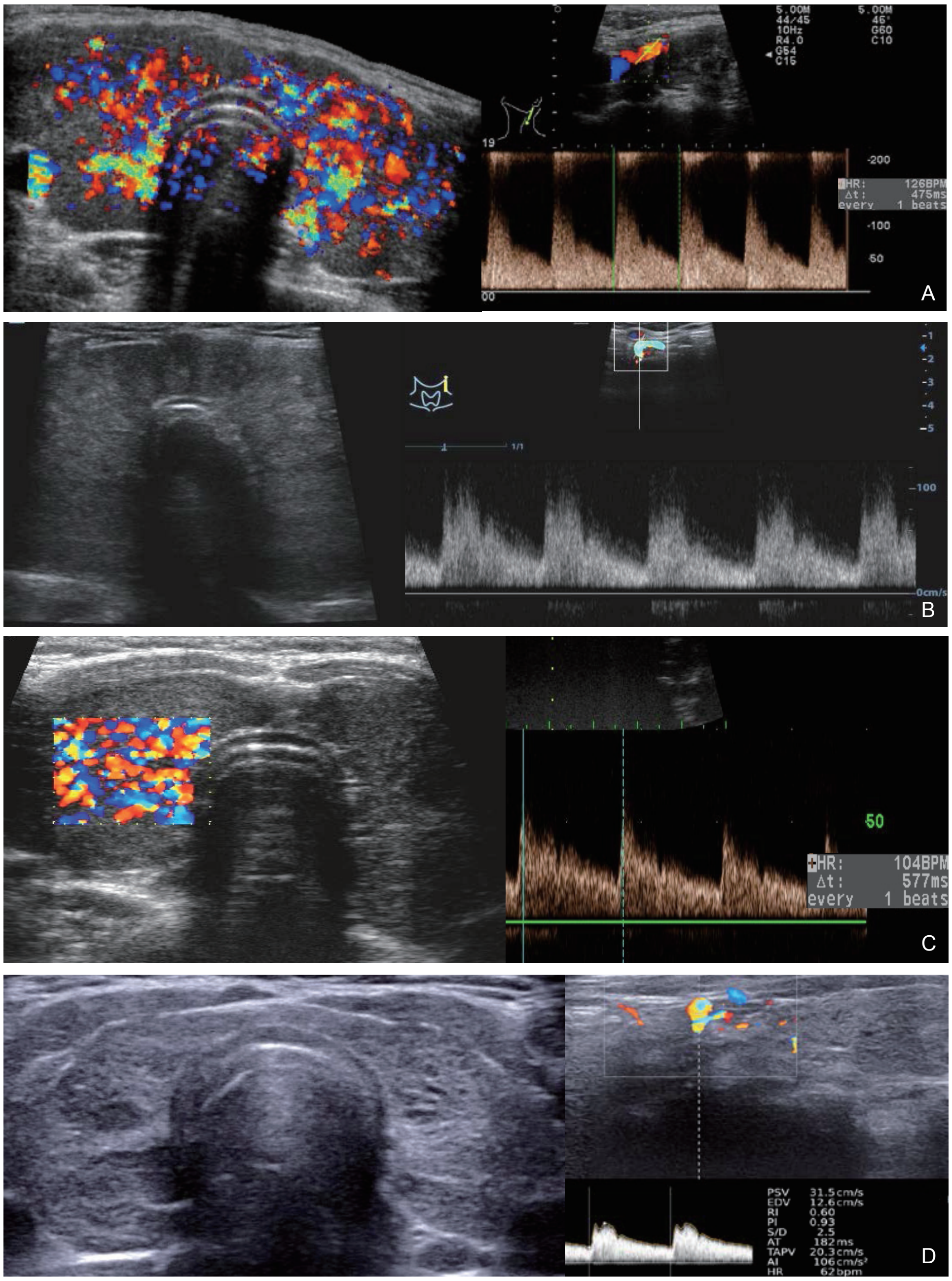

Figure 1 (A) Ultrasound imaging showing the Type A with high peak velocity of STA and fast HR. (B) Ultrasound imaging showing the Type B with high peak velocity of STA and normal HR. (C) Ultrasound imaging showing the Type C with normal peak velocity of STA and fast HR. (D) Ultrasound imaging showing the Type D with normal peak velocity and normal HR.

Discussion

Hyperthyroidism is a medical condition that results from an excess of thyroid hormone in the blood. Thyroid hormones control most metabolic processes in the body. In cases of hyperthyroidism, these processes are often sped up causing symptoms of hyperthyroidism, such as increased excitability and hypermetabolism of the nervous, circulatory, digestive system and so on. However, some middle-aged and elderly patients show indifferent symptoms [12,13] which was contrary to the typical hyperthyroidism, such as lethargy, anorexia, and apathy. By means of magnetic resonance imaging, Zhi et al. [14] pointed out that abnormal brain spontaneous activity was mainly in default mode network (DMN), and this implicated that hyperthyroid patients were with neuro-pathological substrate of relevant emotional and cognitive dysfunction, yet they didn't point out what the neuro-pathological substrate was.

Due to the variety of clinical manifestations of hyperthyroidism, the consultation should be as detailed as possible. For example, the acceleration of HR caused by increased excitability due to hyperthyroidism should be differentiated from cardiovascular disease.

All of thyroid enlargement, rich blood supply, and high velocity of STA can be measured by ultrasound in patients with hyperthyroidism. These ultrasound features can also be found in subclinical hyperthyroidism, subclinical hypothyroidism and Hashimoto's thyroiditis, which increased the difficulty of making a diagnosis and differential diagnosis among them. In the current literatures on ultrasound examination, peak velocity was the most studied factor [6,15,16], followed by thyroid volume and HR. In the majority of the studies [11-13], thyroid volume, peak velocity, and HR were considered single independent factor to explore their relationship with hyperthyroidism. These above factors were statistically different from their control group, but overlapping data between groups made it difficult to give an exact diagnosis, and result in a high false positive rate. From the literatures, only three studies [7-9] were found to investigate dual factors, all of which reported the application of the product of STA peak velocity and HR to diagnose hyperthyroidism. However, in clinical practice, it was no better than the use of a single factor.

Table 3 The "Coefficients" results of logistic regression analysis

Model	Variables	*β*	OR	Wald	*P* value
Constant		−4.999	0.007	5.994	0.014
Age		0.007	1.008	0.049	0.825
STA peak velocity	X1	4.322	75.368	7.966	0.005
HR	X2	3.935	51.175	6.888	0.009
Thyroid volume	X3			0.224	0.894
Normal	X3(1)	12.274	213 487.844	0.000	0.999
Enlarged	X3(2)	12.841	377 499.544	0.000	0.999
Thyroid blood supply	X4			4.972	0.174
Grade I	X4(1)	−17.284	0.000	0.000	0.998
Grade II	X4(2)	1.862	6.436	1.254	0.263
Grade III	X4(3)	3.662	38.920	4.193	0.041
Clinical symptoms	X5	6.617	747.822	12.893	0.001
Echogenicity	X6	−3.159	0.042	5.898	0.015

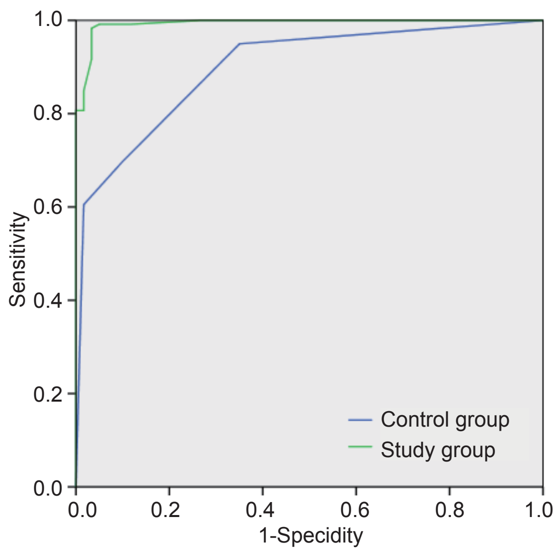

Figure 2 The ROC curve of logistic analysis.

In this study, the patients were divided into four types according to the ultrasonic parameters of peak velocity and heart rate, and compared with clinical symptoms (Table 2). All cases in Type A had high peak velocity and fast heart rate, and 97.2% (70/72) had hyperthyroidism symptoms. In most patients with type B, C and D had normal thyroid volume, fast or slow heart rate, and high or low peak velocity; however, most of them had hyperthyroidism symptoms, and the symptoms of type C and type D are mostly indifferent and the sympathetic nerve excitement was rare. We also can see from Table 2 that for patients with hyperthyroidism, clinical symptoms are the important determinant regardless of the type of ultrasound features.

Our current study suggested that neither patients' age (P = 0.825) nor thyroid volume (P_{x3} = 0.894) was correlation with the diagnosis of hyperthyroidism

(Table 3). In general, thyroid blood supply grade had no statistical significance (P_{x4} = 0.174), in which both Grade I (*P* = 0.998) and Grade II (*P* = 0.263) had no statistical significance, while only Grade III (*P* = 0.041) was statistically significant, that its *P* value was close to 0.05, indicating that increased blood supply in the glands was a secondary reference factor for the diagnosis of hyperthyroidism. Increased blood flow with Grade II and Grade III in the thyroid parenchyma was more common in patients with type A and type B, and increased thyroid volume in these two types accounted for a larger proportion of overall patients. Vita [17] et al. proved that thyroid vascularization correlated directly with thyroid volume and that larger thyroids tended to be more vascularized. Uchida et al. [18] also assessed the frequency and sonographic and laboratory characteristics of Graves' disease with intrathyroid hypo-vascularity, and they found that the thyroid volume and thyrotropin receptor antibody level were significantly lower in patients with Graves' disease and hypovascular thyroid pattern than those with hyper-vascular thyroid pattern. Another 4 factors in Table 3 were statistically significant with the clinical symptoms (*P* = 0.001) while STA peak velocity (*P* = 0.005), HR (*P* = 0.009), and echogenicity (*P* = 0.015) were ranked in order of their contribution to the diagnosis of hyperthyroidism. The clinical symptom was absolutely superior to any other parameter obtained by ultrasound. Goichot et al. [19] thought that positive diagnosis of Graves' disease after biological confirmation of thyrotoxicosis does not always require complementary etiological examinations if clinical presentation is unambiguous, notably including extra-thyroid signs.

As shown in Figure 1 and Table 4, the area under the ROC (AUC) curve indicates that the research method in this paper was significantly better than those described in the past literatures (*P* = 0.001).

All of these statistical results above further indicated that during the examination of diffuse thyroid disease, in addition to accurate acquisition of relevant parameters by ultrasound, it is more important to pay attention to medical history, and clinical symptom is the best factor to improve the diagnostic coincidence rate of hyperthyroidism.

The sonographic manifestations of hyperthyroidism, subclinical hyperthyroidism, subclinical hypothyroidism and Hashimoto's thyroiditis are similar to each other, all of which can be manifested as increased thyroid volume, increased blood supply, and increased STA peak velocity. In the differential diagnosis, hyperthyroidism can be distinguished initially from others with the information of clinical symptoms.

The presence of hyperthyroidism symptoms is a highly specific factor for the diagnosis of hyperthyroidism. Before obtaining laboratory examination results, the presence of hyperthyroidism symptoms is the only reliable diagnostic factors. In our study, there were still five patients with hyperthyroidism who were not asked about their specific symptoms, which may be related to the fact that hyperthyroidism involves many organs and systems, that the individual clinical manifestations of hyperthyroidism are different, or sometimes, when hyperthyroidism is mild, patients may not experience any symptoms.

One might ask a question: since clinical symptoms are so accurate in diagnosing hyperthyroidism, should ultrasound be needed? The answer is positive. First, we can use ultrasound to image structure quantification to differentiate normal from pathological thyroid parenchyma in patients with diffuse autoimmune thyroid disease, including hyperthyroidism [20]. Secondly, we can distinguish hyperthyroidism from other autoimmune thyroid disease by clinical symptoms and laboratory examinations. Ultimately, treatment options are determined by ultrasound evaluation of the presence and malignancy of nodules in the thyroid [21]. Thus, Ultrasound imaging could play a key role for the diagnosis and treatment of hyperthyroidism in clinical settings.

There are some shortcomings of this study. Because subclinical hyperthyroidism and subclinical hypothyroidism cases were few, the differential diagnosis of hyperthyroidism, subclinical hyperthyroidism, subclinical hypothyroidism and Hashimoto's thyroiditis could not analyzed. Further research with larger sample size is still needed.

Conclusion

For patients with finding diffuse echogenicity changes in thyroid gland by ultrasound, further combination of STA peak velocity, HR and thyroid blood supply with clinical symptoms could significantly improve the diagnostic coincidence rate of hyperthyroidism.

Conflict of Interest

Authors declared that there is no conflict of interest for this study.

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