Establishing a diagnostic scale of subacute thyroiditis without radioisotope scanning

Zhouyi Xiong
  Yuebei People's Hospital

Chunying Luo
  Yuebei People's Hospital

Li Wang
  Yuebei People's Hospital

Bin Xiong
  Yuebei People's Hospital

Jianneng Wu
  Yuebei People's Hospital

Research article

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Abstract

Background: Radioisotope scanning is important to diagnose subacute thyroiditis(SAT),but it's not always available.So we aim to establish a diagnostic scale for SAT without radioisotope scanning.

Methods: The suspected SAT patients hospitalized in Yuebei people's Hospital from January 2012 to December 2016 were selected and divided into study group and control group according to whether they were diagnosed as SAT. The clinical indexes of two groups were collected and the diagnostic scale of SAT was established by using binary logistic regression analysis.The effectiveness of the scale was evaluated by ROC curve.

Results: Of 261 patients,69% of patients were confirmed with SAT and the remaining 31% of patients were not diagnosed with SAT. After univariate analysis,variables which were considered statistically different(P <0.05) between the two groups were selected as independent variables and the diagnosis of SAT was taken as dependent variable in the binary logistic regression model. The logistic regression model consisted of 4 variables, each was thyroid tenderness,firm on palpation, increased ESR and hyperthyroidism.The P value of Omnibus tests was ≤0.001 and the Nagelkerke R Square was 0.894. The diagnostic scoring scale was established with these four variables according to their regression coeffient.The area under the ROC curve for this diagnostic scale was 0.989(95% confidence interval, 0.978-1.0).The highest Youden index was 0.908,the corresponding cut-off point was 5.5.Internally validation shows a sensitivity of 93.33% and a specificity of 97.53% of our scale.

Conclusions: We established and validated a diagnostic scale for SAT without the need for radioisotope scanning for the first time.It has good application in institutions that do not have radioisotope machines or among pregnant and lactating women.

Background

Subacute thyroiditis(SAT), also known as de Quervain's thyroiditis, is a self-limited disease of the thyroid gland.It is the most common disease with thyroid pain and the incidence is reported to be 3.6 cases in every 100000 people[1],but it is elevated in China as we have observed. The diagnosis of SAT is mainly based on thyroid pain,increased erythrocyte sedimentation rate(ESR) or C-reactive protein(CRP),and most importantly, high serum thyroid hormone concentrations while the uptake of radioactive iodine or technetium is low(because of the destruction of thyrocytes).However, the radioisotope scanning is not always available in primary care institutions,and sometimes it is contraindicated in specific situations such as in pregnant or lactating women.Thus,some patients might be misdiagnosed as Graves' disease[2], upper respiratory infection,dental problem[3],pharyngitis or abscess.Wrong diagnoses seriously affect the treatment and prognosis of this disease. An alternative method for diagnosing SAT is needed in clinical practice.Thus,the purpose of this study is to establish a SAT diagnostic scale without radioisotope scanning and using simple clinical indicators.

Methods

We performed a retrospective study among adult patients who were suspected to have SAT and were also accepted 99 m-Tc thyroid static imaging in Yuebei People's Hospital. Inclusion criteria: Patients with anterior neck pain,enlarged thyroid or hyperthyroidism as the chief complaint for the first time and were admitted to hospital between January 2012 to December 2016.All patients received no treatment before and each one of them have accepted 99 m-Tc thyroid static imaging for diagnosing after being admitted.Exclusion criteria:Patients who were previously confirmed Graves' disease,thyroid tumor,suppurative thyroidits, autoimmune thyroiditis or any other confirmed thyroid diseases.We also excluded confirmed upper respiratory infection,dental disease,pregnancy or recurrent SAT.The medical records of all patients were thoroughly examined,and the final diagnoses were reassessed by endocrinologists.Diagnosis of SAT were based on clinical manifestations and laboratory test results,including one or both side neck pain, thyroid swelling and/or thyroid tenderness,increased ESR and/or CRP,elevated serum thyroid hormone concentrations and suppressed uptake of Technetium-99m[4].Sometimes not every patient could meet all the above standard, the final diagnosis was made by at least two endocrinologists under these circumstances. Patients who were confirmed with SAT formed the case group and those who were confirmed with not SAT formed the control group. The study was approved by the hospital Ethics Review Committee.

All variables were extracted from the database of the hospital.We collected the vital signs and physical examination results of all patients during the period of first evaluation. We also collected the results of laboratory tests,thyroid ultrasound and 99 m-Tc scan results of patients before diagnosing and treatment. Missing values were also counted. Descriptive data were shown as mean ± SD(for parametric tests) or frequencies(for nonparametric tests). We performed univariate analysis of all variables between groups. Student's t test was used if continuous variables were subject to normal distribution or satisfing homogeneity of variance.If not,Wilcoxon's rank sum test was used.For dichotomous variables,Chi-square test was used.For categorical variables, Wilcoxon's rank sum test was used.All variables with P⬚0.05 in the univariate analysis were considered statistically different and were selected as covariates in the full multivariable logistic regression model with the diagnosis of SAT as the dependent variable.

We used the forward:likelihood ratio method to generate the statistically optimal logistic regression model(with entry as P ≤ 0.05 and removal as P⬚0.10).Meanwhile,we carried out the omnibus tests of model coefficients and calculated the Nagelkerke R Square.Then,for clinical use,we developed a diagnostic scale with the use of variables in the regression model,with weighting based on each regression coefficient. According the our clinical scale,each patients was assigned a score.We used these scores to draw a receiver operating characteristic(ROC) curve to evaluate the diagnostic performance of our scale.The optimal cut-off point was determined by Youden index(Youden index equals to sensitivity plus specificity minus 100%).All patients were once again diagnosed using our diagnostic scale,and were compared with former diagnosis to evaluate the diagnostic test characteristics (sensitivity, specificity, positive and negative predictive values, false positive rate,false negative rate and accuracy) using 2 by 2 tables.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). P⬚0.05 was considered statistically significant.

Results

We included 261 inpatients in our study.Among them,180 patients (68.97%)were confirmed with SAT and 81 patients(31.03%) were diagnosed with other diseases such as nodular goiter(51 patients),Graves' disease(6 patients),thyroid tumor(7 atients),hashimoto thyroiditis(8 patients),upper respiratory infection(1 pateint) and other diseases(8 patients). The mean age of the SAT group was 46.77 ± 10.30,and 82.2% were females.The mean age of the control group was 48.32 ± 13.408,and 81.5% were females. For 89.1% patients of the SAT group,the thyroid was not visualized or was visualized poorly on 99 m-Tc thyroid static imaging.Table 1 shows the descriptive statistics and univariate analysis of clinical variables between the two groups.

Table 1
Descriptive statistics and univariate analysis of clinical variables between the two groups.

variables	case group	control group	P value
Male sex,No.(%)	32(17.8)	15(18.5)	0.085
Age(years)	46.77 ± 10.301	48.32 ± 13.408	0.157
Systolic pressure(mmHg)	118.689 ± 13.399	123.259 ± 16.505	0.025
Diastolic pressure(mmHg)	76.072 ± 9.520	80.605 ± 10.003	0.001
Heart rate(bpm)	87.42 ± 12.896	80.52 ± 10.932	≤ 0.001
Elevated heart rate,No.(%)	21(11.7)	2(2.5)	0.015
Prior upper respiratory infection,No.(%)	26(14.4)	4(4.9)	0.026
Fever,No.(%)	60(33.3)	0	≤ 0.001
Neck pain,No.(%)	174(96.7)	21(25.9)	≤ 0.001
Thyroid tenderness,No.(%)	176(97.8)	9(11.1)	≤ 0.001
Odynophagia,No.(%)	135(75)	6(7.4)	≤ 0.001
Radiating pain,No.(%)	89(49.4)	5(6.2)	≤ 0.001
Palpitation,No.(%)	41(22.8)	6(7.4)	0.003
Hands tremble,No.(%)	10(5.6)	2(2.5)	0.352
Weight loss,No.(%)	26(14.4)	1(1.2)	0.001
Thyroid swelling,No.(%)	168(93.3)	71(87.7)	0.127
Firm on palpation,No.(%)	148(82.2)	6(7.4)	≤ 0.001
Elevated white blood cell,No.(%)	45(25)	3(3.7)	≤ 0.001
White blood cell count($\times 10^9$/L)	8.41 ± 2.906	6.61 ± 2.879	≤ 0.001
Elevated neutrophil,No.(%)	65(36.1)	7(8.6)	≤ 0.001
Neutrophil count($\times 10^9$/L)	6.01 ± 2.596	4.13 ± 2.866	≤ 0.001
Neutrophil percentage(%)	69.45 ± 12.342	58.63 ± 11.519	≤ 0.001
Increased ESR,No.(%)	140(77.8)	3(3.7)	≤ 0.001

Descriptive data was shown as mean ± SD or frequencies.Abbreviations:ESR, erythrocyte sedimentation rate;CRP, C-reactive protein;TT3, total triiodothyronine;TT4,total thyroxine;FT3,free triiodothyronine;FT4,free thyroxine;TSH, thyroid stimulating hormone;TPOAb, thyroid peroxidase antibodies;TgAb, thyroglobulin antibodies.

variables	case group	control group	P value
ESR(mm/h)	44.52 ± 24.528	14.64 ± 8.303	≤ 0.001
Elevated CRP,No.(%)	127(70.6)	7(8.6)	≤ 0.001
CRP(mg/dl)	8.03 ± 9.799	1.53 ± 1.702	≤ 0.001
Hyperthyroidism,No.(%)	106(58.9)	13(16)	≤ 0.001
TT3(nmol/L)	2.689 ± 1.376	1.814 ± 0.702	≤ 0.001
TT4(nmol/L)	165.269 ± 61.090	107.673 ± 44.966	≤ 0.001
FT3(pmol/L)	9.338 ± 8.943	6.205 ± 5.747	≤ 0.001
FT4(pmol/L)	31.013 ± 19.379	20.388 ± 15.724	≤ 0.001
TSH(µIU/ml)	0.505 ± 1.402	4.564 ± 15.498	≤ 0.001
TPOAb(IU/ml)	34.556 ± 67.144	59.267 ± 130.235	0.198
TgAb(IU/ml)	283.146 ± 534.564	214.571 ± 598.836	≤ 0.001
Suppressed uptake of Technetium-99 m,No.(%) FT3/FT4	156(89.1) 0.307 ± 0.195	19(23.5) 0.311 ± 0.102	≤ 0.001 0.472
Descriptive data was shown as mean ± SD or frequencies.Abbreviations:ESR, erythrocyte sedimentation rate;CRP, C-reactive protein;TT3, total triiodothyronine;TT4,total thyroxine;FT3,free triiodothyronine;FT4,free thyroxine;TSH, thyroid stimulating hormone;TPOAb, thyroid peroxidase antibodies;TgAb, thyroglobulin antibodies.			

After univariate analysis, systolic pressure, diastolic pressure,heart rate,elevated heart rate, prior upper respiratory infection,fever,neck pain,thyroid tenderness,odynophagia,radiating pain,palpitation,weight loss,firm on palpation,elevated white blood cell,white blood cell count,elevated neutrophi,neutrophil count,neutrophil percentage, increased ESR,ESR, elevated CRP, CRP, hyperthyroidism, total triiodothyronine(TT3),total thyroxine(TT4),free triiodothyronine(FT3),free thyroxine(FT4), thyroid stimulating hormone(TSH), thyroglobulin antibodies(TgAb) and suppressed uptake of Technetium-99m were considered significantly different between the two groups and were selected as covariates in the full multivariable logistic regression model. Because the suppressed uptake of Technetium-99m was the diagnostic method our study wanted to exclude, this variable was eliminated in the full multivariable logistic regression model artificial. The logistic regression model finally consisted of 4 variables that were independently predictive factors (as shown in Table 2) with the diagnosis of SAT as the dependent variable.The equation for the logistic model was as follows:

P=-4.994(constant)+(5.271*thyroid tenderness)+(2.315*firm on palpation)+(2.682*increased ESR)+(2.910* hyperthyroidism).

Variables of the final logistic regression model and clinical scores of the diagnostic scale.

Variable	Regression coeffient	OR(95%CI)	P value	Clinical score
Thyroid tenderness	5.271	194.577(23.184-1633.048)	≤ 0.001	5
Firm on palpation	2.315	10.125(2.092–48.996)	0.004	2
Increased ESR	2.682	14.613(2.099-101.715)	0.007	3
Hyperthyroidism	2.910	18.364(1.881-179.305)	0.012	3
Maximum score				13

The P value of Omnibus tests was ≤ 0.001 and the Nagelkerke R Square was 0.894.

The regression coefficients of these 4 variables were then rescaled to easy-to-use scores(as shown in Table 2),with the total points being 13. Then we performed ROC curve analysis of the diagnostic scale. The area under the ROC curve was 0.989(95% confidence interval, 0.978-1.0) as shown in Fig. 1.The highest Youden index was 0.908,while the corresponding cut-off point was 5.5. With the optimal cut-off point,all patients were once again diagnosed and compared with former diagnosis to evaluate the diagnostic test characteristics using 2 by 2 tables(as shown in Table 3).Our scale has a sensitivity of 93.33% and a specificity of 97.53%. Positive and negative predictive values were 98.82% and 86.81%,respectively. False positive and false negative rates were 2.47% and 6.67% respectively.The accuracy of our diagnostic scale was 94.64%.

Table 3

Diagnostic test results compared with former diagnosis(reference test) using 2 by 2 tables.

		Reference test		
		SAT	No SAT	
Test results	SAT	a 168	b 2	a + b = 170
	No SAT	c 12	d 79	c + d = 91
		a + c = 180	b + d = 81	
a,true positive;b,false positive;c,false negative;d,true negative.				

Sensitivity = a/(a + c) × 100%=93.33%; specificity = d/(b + d) × 100%=97.53%;PPV = a/(a + b) × 100%=98.82%;NPV = d/(c + d) × 100%=86.81%; False positive rate = b/(b + d) × 100%=2.47%; false negative rates = c/(a + c) × 100%=6.67%;accuracy=(a + d)/n × 100%=94.64%

Disccusion

Subacute thyroiditis is a non-bacterial inflammatory disease of the thyroid gland. It comprises nearly 3%-6% of all thyroid lesions[5].The diagnosis is made by a combination of clinical manifestations, physical examinations and laboratory tests[6].Tissue diagnosis is not a routine,but only necessary in rare cases such as in differential diagnosis of thyroid cancer[7].Usually,the typical SAT has three stages:hyperthyroidism stage,hypothyroidism stage and normal thyroid function stage. However, patients may come to hospital at any stage, and the clinical manifestations may not show in a typical way, which makes the diagnosis more difficult. Furthermore,a study showed most laboratory results associated with thyrotoxicosis have reached abnormal levels within 3 weeks after onset.But longer time-lags could existed between the onset of clinical symptoms and the appearance of abnormal laboratory findings in patients with SAT[9].Therefore,hyperthyroidism and suppressed uptake of Technetium-99 m (99 m-Tc) or 131I at the same time play a significant role in diagnosing. However, the radioisotope scanning is not always available in every hospital and sometimes it is contraindicated in specific situations such as in pregnant or lactating women. So we developed and internally validated a diagnostic model for SAT without the need for radioisotope scanning.

Our model contained a limited number of signs and symptoms and 2 laboratory tests,which were easy to perform in primary care institutions.Thyroid tenderness will appear almost 100% due to the inflammatory destruction of thyrocytes.In our diagnostic model,the regression coefficient of this variable was 5.271 with a clinical score of 5,demonstrating the importance of thyroid tenderness in diagnosing SAT.Follicular epithelial cells and multinuclear giant cells against a dirty background is the pathological characteristics of SAT,resulting in feeling firm on thyroid palpation[10].The variable of "firm on palpation" obtained a clinical score of 2 according to the regression coefficient in our model. Different degrees of inflammatory cell infiltration can lead to different levels of firmness, and in some cases,the gland felt no firm on palpation.This partly explained the cause of the relatively low score. ESR is a sensitive indicator of acute inflammation and always elevated in SAT patients[4, 6].But ESR is not a special feature to some certain diseases,so it earned only 3 scores in our model.In the first stage of SAT,all patients are hyperthyroidism,which is defined by elevated FT3 and/or FT4 concentrations and suppressed TSH level in our study, whether they have symptoms or not.However,patients may be at other stages when they come to hospital.Their thyroid function may be normal or even decreased.So the variable of hyperthyroidism was assigned 3 scores in our model. The P value of Omnibus tests of our model was ≤ 0.001 and the Nagelkerke R Square was 0.894,demonstrating that our model has statistically significant differences and better goodness of fit.According to the ROC curve analysis,the optimal cut-off point was 5.5.At this point, our model has high sensitivity(93.33%) and specificity(97.53%) in our patients. The accuracy of our diagnostic model was also high(94.64%).To our knowledge, this diagnostic study is the first one to develop a clinical prediction model for the diagnosis of SAT.

A lot of studies have shown that the etiology of SAT was related to viral infection such as coxsackievirus, echovirus, mumps, measles, influenza and other viruses[11, 12] because there was a flu-like syndrome before the disease onset.In our study,only 14.4% patients had upper respiratory infection before SAT,maybe due to the blurry memory of patients and the inapparent infections.Espinoza et al[13] have compared the diagnostic value of radioactive iodine uptake, 99 m-Tc thyroid static imaging and thyroid

ultrasonography.They found both radioisotope scanning had a better correlation with the clinical diagnosis of SAT than that with thyroid ultrasonography. In our study,we used the 99 m-Tc thyroid static imaging to evaluate the thyroid uptake function instead of radioactive iodine uptake because radioactive iodine uptake needs more time(24hours) and is more complicated to operate.As reported by Frates et al[14] ,the typical appearance of sonography of SAT was a patchy, poorly defined hypoechoic process that could affect a portion of one or both lobes, an entire lobe, or the entire gland.However,they also found that the sonographic findings of SAT could mimic a large nodule replacing the lobe,the changes of lymphocytic,Hashimoto thyroiditis,thyroid carcinoma or thyroid lymphoma, leading to the differential diagnosis became more difficult.Furthermore,sonography is a relatively subjective examination and requires experienced doctors to get analysable results.So we excluded sonography as a variable from our model. Fever is also a clinical presentation of SAT.Sometimes fever was the only clinical manifestation as reported by Dalugama[15].But this situation is rare and fever can present in many diseases.So fever, though there was significant difference between the two groups,was not included in our regression model. It is important to differentiate SAT from Graves' disease(GD) because they have similar clinical features and thyroid hormone concentrations but have different treatments and prognosis.Some studies have demonstrated that a higher ratio of FT3 to FT4 supported a diagnosis of GD and a very low ratio supported a diagnosis of SAT[16, 17].However in our study,the ratio of FT3 to FT4 showed no significant difference between the two groups,mainly because GD only occupied a small portion in our patients.The sample size was not large enough to make statistical difference.

Our study has some limitations. First, it was a retrospective study. We could only collected data from the hospital system other than examining the patients by ourselves,which may cause the inconsistency.Second,we have excluded patients who did not perform radioisotope scanning or in pregnant or lactating women,which might lead to a selection bias.Third, our patients were all at their first attack and first visit to hospital.We were not sure if our diagnostic model was suitable for recurrent patients or treated patients. The last but not the least, the specificity and sensitivity of our diagnostic model were really high because we only did internal validation and obtained overoptimistic results.Therefore,external validation is needed before wider application.

Conclusions

In conclusion, we established a diagnostic scale for SAT without the need for radioisotope scanning for the first time.It is an excellent and easy way to diagnose SAT.Although it cannot fully replace radioisotope scanning,it has good application in institutions that have no access to radioisotope machines or in pregnant and lactating women.

Abbreviations

SAT
subacute thyroiditis
ESR

erythrocyte sedimentation rate

CRP

C-reactive protein

ROC

receiver operating characteristic

TT3

total triiodothyronine

TT4

total thyroxine

FT3

free triiodothyronine

FT4

free thyroxine

TSH

thyroid stimulating hormone

TgAb

thyroglobulin antibodies

99 m-Tc

Technetium-99 m

GD

Graves' disease

TPOAb

thyroid peroxidase antibodies

Declarations

Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
The study was approved by the Ethics Review Committee of Yuebei People's Hospital.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

JNW oversaw the entire project and revised the manuscript. ZYX analyzed the data and drafted the article. CYL, LW and BZ contributed to the collection of datas and revised the article. All authors gave their final approval of the version to be published.

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Figures
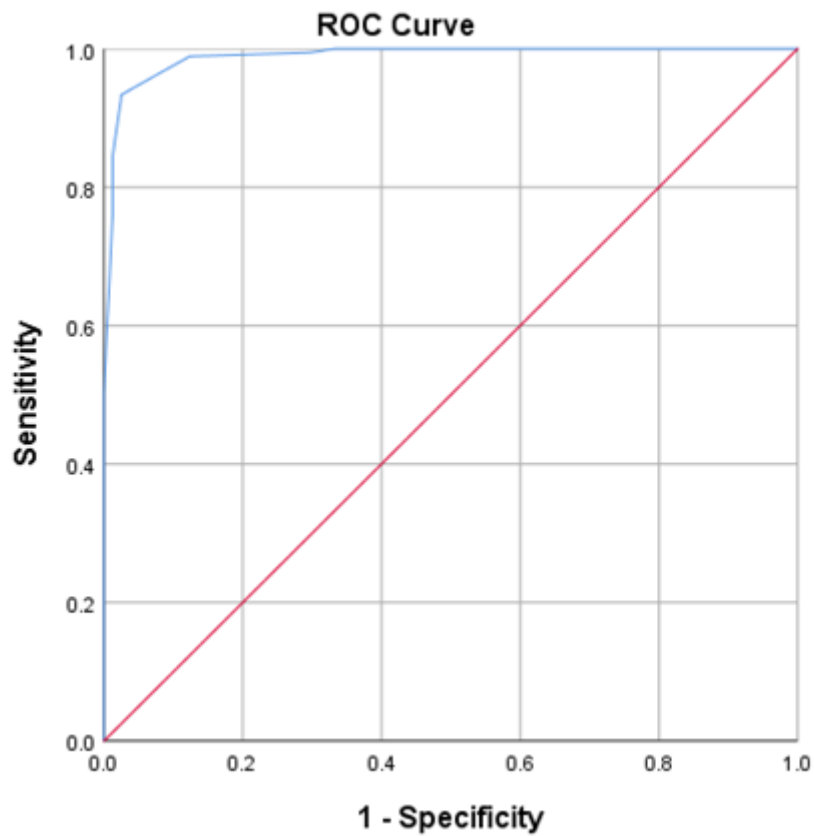
Figure 1

Area under the receiver operating characteristic (ROC) curve for the diagnostic scale(Sensitivity vs. 1-Specificity). The diagonal line indicates the curve for a virtual model without predicting value (ROC of 0.5).