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A new scoring system for risk stratification of thyroid tumors

Ya Yuan[1†], Hua Shu[1], Lu Li[1], Liuxi Wu[2] and Fei Yu[3*]

Abstract

Objectives To develop an ultrasound feature–based risk stratification system for differentiating benign, low-risk and malignant thyroid tumors and compare it with existing TI-RADS.

Methods The retrospective study included patients who underwent preoperative neck ultrasound examination from January 2018 to June 2023, and their ultrasound characteristics were recorded. According to surgical pathological findings, they were classified into three categories: benign, low-risk, and malignant. Univariable and multivariable logistic regression analyses were used to assess the association of qualitative ultrasound features with different risk stratifications and a new scoring system was established to evaluate its diagnostic efficacy, and to compare it with TI-RADS.

Results Aspect ratio ≥1 was an independent risk factor in the comparison of benign and low-risk thyroid nodules, and in the comparison of benign and malignant nodules, hypoechoic,irregular margin,nodule max diameter ≤1 cm,the aspect ratio ≥1 and elasticity score ≥3 were independent risk factors. According to the multivariate analysis, they were assigned 1, 2, 2, 3, 2/4 points respectively, and we established a new scoring system. According to ROC analysis, the total score of 0–4.5 was considered as benign nodules, 4.5–5.5 was considered as low-risk nodules, and more than 5.5 were considered as malignant nodules. Compared it to ACR-TI-RADS, this scoring system performed better than in differentiating benign and malignant nodules ($P=0.001$, $P=0.018$, respectively).

Conclusion The scoring system based on ultrasound features established in this study can be used for risk stratification of thyroid nodules more efficiently, it has higher sensitivity and specificity for the differentiation of benign and malignant nodules.

Keywords Thyroid tumors, TI-RADS, Risk stratification

Introduction

The thyroid gland tumors give rise to the most common endocrine tumors. In 2022, the World Health Organization (WHO) redefined the categories and subtypes of thyroid tumors according to the cell origin, histological and molecular characteristics, allowing a clearer understanding of thyroid tumors. Of all types, follicular cell-derived tumors are the most common and can be classified into three categories: benign, low-risk, and malignant tumors according to their molecular features and invasive ability [1]. Different from the previous classification of benign and malignant nodules, the new risk stratification

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method can optimize the risk rating of thyroid nodules, make more targeted clinical decisions, avoid unnecessary fine needle aspiration (FNA) or surgical treatment, and reduce the possibility of overtreatment. Among this, low-risk thyroid tumors are borderline tumors that are morphologically and clinically intermediate between benign and malignant tumors. This type of tumor has the potential for metastasis, but the incidence of metastasis is extremely low [1]. Its diagnosis has become a new research hotspot to reduce overtreatment. Jensen CB et.al research indicates the overall prognosis of most thyroid tumors is favorable, especially for low-risk tumors. Early diagnosis does not bring better prognosis [2–5].

However, there is no relevant imaging methods in thyroid tumors risk management. In order to achieve a more standardized diagnosis and treatment of patient, it is imperative to provide effective risk stratification of thyroid nodules as early as possible. At present, the commonly used risk assessment method of thyroid nodules is TI-RADS, which has been published in many countries and regions around the world, and it can be used to assign scores to characteristic variables based on ultrasound to derive the approximate probability of benign and malignant thyroid tumors. However, TI-RADS is mainly based on the ultrasonic characters of papillary thyroid carcinoma, the diagnostic efficacy is not ideal for some specific types of tumors [6–9]. Besides, with the development of medical equipment, multimodal ultrasound technology is widely used in the study of thyroid tumor diagnosis and prognosis evaluation nowadays. The value of multimodal ultrasound in the systematic evaluation of thyroid nodules deserves further discussion.

Above all, this study is attempted to explore and establish a new scoring system of this new risk stratification of thyroid tumors based on multimodal ultrasound technology, which may provide a basis for more accurate risk stratification and clinical decision-making for patients.

Materials and methods

Patients

From January 2018 to June 2023, 367 patients (435 nodules) with thyroid tumors were included in this study, confirmed by histopathological examination of the surgical specimens following thyroidectomy. The exclusion criteria were as follows: not initial surgery or other therapy (I131, ablation) was performed; absence of preoperative thyroid multimodal imaging; conventional pathology was not clear, and immunohistochemistry was lacking. This retrospective study was approved by the Institutional Review Board, and the requirement for informed consent was waived.

Multimodal ultrasound imaging

All the patients underwent preoperative neck ultrasound, and the ultrasound features of the nodules were recorded, including nodule number (single, or multiple), location (left, mid, right, or isthmus), extrathyroidal extension (yes, or no), size (nodule max diameter) (≤1 cm, 1–4 cm, >4 cm), echogenicity (anechoic, hyperechoic, isoechoic, or hypoechoic), composition (cystic, mixed, or solid), aspect ratio (<1, or ≥1), shape (round to oval, or irregular), margin (smooth or irregular), calcifications (absent, microcalcification, macrocalcification, or comet-tail artifacts), halo (absence, regular complete halo, or irregular interrupted halo), blood flow (grade 0 means that no obvious blood flow signal is found; grade 1 means that the nodule with partly clear blood flow signals; grade 2 is the nodules have moderate blood flow signals; grade 3 means that a large number of blood flow signals) [10], elasticity score (1 point means that the lesion was green overall; 2 points mean that the lesion had a mosaic pattern of green and red; 3 points mean that the center of the lesion was red, and the rest of the lesion was green; 4 points mean that the lesion was red overall; and 5 points mean that the lesion and surrounding tissue were red.) [11], suspicious lymph nodes (size ≥1 cm, microcalcifications, cystic aspect, peripheral vascularity, hyperechogenicity, round shape) [12].

Preoperative neck ultrasonography examinations were performed with EPIQ7 (Philips Healthcare) ultrasound instruments equipped with 5–12 MHz linear transducers by a team of operators with more than 5 years of experience in thyroid imaging. Any disagreement between the researchers with respect to these features was resolved by consensus, which were blinded to the clinical information and radiologic report. And then, the results of surgical pathology were followed up.

Statistical analysis

Continuous variables were analyzed in Mann-Whitney U test or t test and presented as means and SDs ($x \pm s$); categorical variables were analyzed using the $\chi 2$ test or Fisher exact test and presented as numbers and percentages (n (%)). Multivariate logistic regression analysis was performed to assess the independent correlation with ultrasonic features. Diagnostic performance of the systems was assessed using receiver operating characteristic (ROC) and area under the ROC curves were calculated with 95% confidence intervals (95% CI). Delong test was used to compare AUCs (area under the curve) of each system. SPSS software (version 26.0, SPSS Inc., Chicago, IL, USA) was applied to analyze the data statistically. Differences were considered statistically significant at $P < 0.05$.

Results

After surgery, in the pathology report of the 367 patients, 435 nodules were identified and classified according to their histologic nature (Table 1), including 119 (27.4%) benign nodules, 121 (27.8%) low-risk nodules and 195 (44.8%) malignant nodules.

Regression analysis of ultrasound features

The recorded ultrasound features (Table 2) were successively included in univariate and multivariate logistic regression analysis to obtain the independent risk factors of thyroid nodules. In the univariate logistic regression analysis, nodule number, location, extrathyroidal extension, nodule max diameter, echogenicity, aspect ratio, composition, calcifications, shape, margin, halo, blood flow, elasticity, suspicious lymph nodes ($P<0.05$) were independent risk factors, and then they were included in the multivariate logistic regression analysis, using the first feature (the benign nodules) as reference category, aspect ratio ≥1 was an independent risk factor in the comparison of benign and low-risk nodules, and in the comparison of benign and malignant nodules, the aspect ratio ≥1, elasticity score ≥3, irregular margin, nodule max diameter ≤1 cm and hypoechoic were independent risk factors.

Establishment of a scoring system based on risk stratification

As shown in Table 3, according to the Odds ratios (EXP(B),ORs) from multivariate logistic regression analysis, the ideal weight was calculated and scored. When the OR value ≤1, this feature was assigned a score of 1, such as hyperechoic; when the OR value was between 1 and 10, the feature was assigned a score of 2, such as the nodule max diameter ≤1 cm, irregular margin and the elasticity score was 3; when the OR value was between 10 and 20, the feature was assigned a score of 3, such as the aspect ratio ≥ 1; and 4 points were assigned to elasticity score was 4, when the OR value > 20. Using this scoring method, all nodules were scored to obtain their respective total score, and then ROC curve analysis (Fig. 1) was performed to obtain the best cut-off value among the three classification nodules. As shown in Fig. 1a, the area under the curve (AUC) was 0.848 (95% confidence interval (CI) 0.811–0.884; $P<0.0001$); the optimal cut-off score was 4.5 with sensitivity of 70.5% and specificity of 92.5% between the comparison in benign and low-risk nodules. Comparison between the low-risk and malignant nodules (Fig. 1b), the optimal cut-off score was 5.5. The AUC was 0.875 (95% CI 0.842–0.908; $P<0.0001$)and the associated sensitivity and specificity were 77.9% and 85%, respectively.

According to the results, we established a new thyroid nodules scoring system based on multiple ultrasound imaging techniques. The total score of 0–4.5 was considered as benign nodules, 4.5–5.5 was considered as low-risk nodules, and more than 5.5 was considered as malignant nodules (The characteristic nodules are shown in Fig. 2).

Table 1 Epidemiologic, and histologic features of the 367 patients (435 nodules) included in the study

Epidemiologic features		
Age	Median (IQR)	45 (12–74)
Histology, n (%)		
Benign (n = 119)	FND	45 (10.3)
	FA	63 (14.5)
	FA–P	11 (2.5)
Low-risk (n = 121)	NIFTP	57 (13.1)
	UMP	64 (14.7)
Malignant (n = 195)	FTC	47 (10.8)
	IEFVPTC	27 (6.2)
	PTC	117 (26.9)
	PDTC	4 (0.9)

FND: Thyroid follicular nodular disease; FA: Follicular adenoma; FA–P: Follicular adenoma with papillary architecture; NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features; UMP: Thyroid tumors of uncertain malignant potential; FTC: Follicular thyroid carcinoma; IEFVPTC: Invasive encapsulated follicular variant papillary carcinoma; PTC: Papillary thyroid carcinoma; PDTC: Poorly diferentiated thyroid carcinoma

Comparison of diagnostic efficacy between benign and malignant nodules

Delong test of ROC analysis was used to compare the diagnostic efficacy of this scoring system and the ACR-TI-RADS. In terms of AUC, this new scoring system performed better than ACR-TI-RADS in differentiating benign and malignant nodules ($P=0.001$, $P=0.018$, respectively). In the diagnosis of benign nodules (Fig. 3a), the AUC of ACR-TI-RADS was 0.767 (95% CI 0.736–0.799); the AUC of the new scoring system was 0.815 (95% CI 0.780–0.849); In the diagnosis of malignant nodules (Fig. 3b), the AUC of ACR-TI-RADS was 0.774 (95% CI 0.734–0.814); the AUC of the new scoring system was 0.815 (95% CI 0.778–0.852).

Discussion

The incidence of thyroid nodules has been increasing in recent years. Only 38% of patients with thyroid tumors will have obvious clinical symptoms, such as neck mass, throat and neck discomfort, and in rare cases, dysphagia, hoarseness and other symptoms. Previous studies have shown that many papillary thyroid microcarcinomas are actually incidentally discovered during postoperative pathological diagnosis [5]. Since thyroid cancer is an indolent tumor, and some subtypes of papillary thyroid carcinoma have been classified as low-risk tumors with a low metastatic rate. Some studies have pointed out that early diagnosis and treatment do not necessarily lead to a better prognosis [5, 13]. Therefore, a growing academic

Table 2 Ultrasound features of thyroid tumors

US features		N (%)
Nodule Number		
	single	352(80.9)
	Multiple	83(19.1)
Location		
	Left	103(23.7)
	mid	104(23.9)
	Right	193(44.4)
	Isthmus	35(8.0)
extrathyroidal extension		
	yes	170(39.1)
	no	265(60.9)
Nodule max diameter		
	≤1 cm	144(33.1)
	1–4 cm	197(45.3)
	>4 cm	94(21.6)
Echogenicity		
	Anechoic	0(0)
	Hypoechoic	274(63.0)
	Isoechoic	158(36.3)
	Hyperechoic	3(0.7)
Aspect Ratio		
	<1	320(73.6)
	≥1	115(26.4)
Composition		
	Cystic	0(0)
	Mixed	117(26.9)
	Solid	318(73.1)
Calcifications		
	Absent	214(49.2)
	Micro	162(37.2)
	Macro	34(7.8)
	comet-tail artifacts	25(5.7)
Shape		
	Round to oval	282(64.8)
	Irregular	153(35.2)
Margin		
	Smooth	216(49.7)
	Irregular	219(50.3)
Halo		
	Absent	341(78.4)
	Regular complete halo	64(14.7)
	Irregular interrupted halo	30(6.9)
Blood Flow		
	0	64(14.7)
	1	121(27.8)
	2	34(7.8)
	3	216(49.7)
Elasticity score		
	1	0(0)
	2	119(27.4)
	3	155(35.6)
	4	161(37.0)
	5	0(0)
Suspicious lymph nodes		
	yes	56(12.9)
	no	379(87.1)

Values are presented as count (%)

discussion has focused on the possibility of overmedication in the diagnosis and treatment of thyroid tumors and some guidelines have begun to suggest that the follow-up and treatment strategies for thyroid tumors can be appropriately relaxed. For some nodules without high-risk factors, even if it is malignant, criteria of active surveillance can also be adopted, which leads to the variety of clinical treatment options. Doctors can make follow-up or surgical plans based on the actual situation of patients to avoid misdiagnosis of malignant nodules and reduce the probability of unnecessary puncture or surgery [14, 15].

Since 2009, many countries and regions, such as the United States, Europe, South Korea and China, have put forward the criteria for the classification of thyroid nodules in line with regional population conditions, aiming to guide ultrasound and clinicians to treat different thyroid nodules more standardized, and to promote and popularize thyroid FNA technology. Despite the existence of many classification methods, ACR-TIRADS classification criteria remains one of the major mathod in the world [16–19]. There are five main characteristics that affect the evaluation of thyroid nodules: 1.solid nodules; 2.hypoechoic or very hypoechoic; 3.irregular margins; 4.micro calcification; 5.aspect ratio ≥1. These systems provide specific recommendations for the sonographic classification of nodules according to their estimated risk of malignancy. However, the existing TI-RADS is mainly based on the ultrasound features of papillary thyroid carcinoma (PTC), attempts to classify the possible malignancy of thyroid tumors and it still has limitations for the diagnosis of some other types of tumors [8]. Therefore, this study included various types of thyroid tumors in the study, because sometimes it is difficult to determine the type of tumor at the time of thyroid ultrasound examination, and screened out independent risk factors according to their risk stratification.

The results of the study showed that hypoechoic, irregular margins, and aspect ratio ≥1 were still independent risk factors for various types of thyroid nodules, which were consistent with the TI-RADS classification criteria. However, solid nodules and microcalcification were excluded from the results of this study. The reason may be that the subjects included in this study were all patients who underwent surgical resection, and solid nodules accounted for the majority of cases, which may have a certain enrollment bias. Similarly, it has been shown that microcalcification is considered a specific

Table 3 Univariate and multivariate logistic regression analysis results

Parameter Estimates

Ya		Sig.	Exp(B)	95% Confidence Interval for Exp(B)			Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
				Lower Bound	Upper Bound				Lower Bound	Upper Bound
1	Intercept	0.992				2	0.125			
	nodule number									
	single	0b					0b			
	multiple	0.491	0.71	0.268	1.881		0.537	0.697	0.222	2.189
	location									
	left	0b					0b			
	mid	0.416	1.707	0.47	6.199		0.857	1.142	0.27	4.825
	right	0.577	1.463	0.384	5.571		0.563	1.56	0.346	7.034
	isthmus	0.337	1.998	0.486	8.209		0.201	2.748	0.583	12.958
	extrathyroidal extension									
	no	0b					0b			
	yes	0.965	1.015	0.527	1.954		0.53	0.775	0.349	1.718
	Nodule max diameter									
	>4 cm	0b					0b			
	1–4 cm	0.661	1.277	0.428	3.81		0.983	0.987	0.293	3.327
	≤1 cm	0.605	0.724	0.213	2.462		0.008	9.274	1.772	48.531
	Echogenicity									
	Hypoechoic	0b					0b			
	Isoechoic	0.991	6.85E-08	0	.c		.	0.071	0.071	0.071
	Hyperechoic	0.991	9.30E-08	0	.c		0.005	0.23	0.082	0.644
	Aspect Ratio									
	<1	0b					0b			
	≥1	0.02	13.401	1.508	119.124		0.007	20.214	2.252	181.427
	composition									
	mixed	0b					0b			
	solid	0.924	0.967	0.487	1.921		0.63	0.787	0.297	2.087
	calcifications									
	absent	0b					0b			
	comet-tail artifacts	0.344	1.65	0.585	4.649		0.169	3.2	0.61	16.781
	macrocalcification	0.435	0.664	0.237	1.856		0.148	2.505	0.723	8.68
	microcalcification	0.323	0.576	0.193	1.72		0.357	1.676	0.558	5.034
	shape									
	round to oval	0b					0b			
	irregular	0.95	1.042	0.288	3.772		0.234	2.162	0.607	7.704
	Margin									
	Smooth	0b					0b			
	Irregular	0.82	1.177	0.287	4.827		0.018	6.199	1.374	27.961
	halo									
	absence	0b					0b			
	regular complete halo	0.329	0.681	0.315	1.473		0.919	0.937	0.268	3.279
	irregular interrupted halo	0.226	1.974	0.656	5.942		0.607	1.441	0.358	5.811
	blood flow									
	3	0b					0b			
	2	0.871	1.098	0.354	3.403		0.328	0.495	0.121	2.026
	1	0.092	2.905	0.84	10.045		0.857	0.883	0.226	3.453
	0	0.181	1.855	0.75	4.589		0.44	0.575	0.141	2.346
	elasticity score									
	2	0b					0b			
	3	0.928	1.034	0.498	2.147		0	9.909	2.898	33.885

Table 3 (continued)

Parameter Estimates								
Ya	Sig.	Exp(B)	95% Confidence Interval for Exp(B)		Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
4	0.151	3.28	0.647	16.621	0	66.815	10.323	432.466
suspicious lymph nodes								
no	0b				0b			
yes	0.969	136359.772	2.95E-253	6.30E + 262	0.968	225600.382	4.89E-253	1.04E + 263

[a]The reference category is: 0

[b]This parameter is set to zero because it is redundant

[c]Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing

Differences were considered statistically significant at $P < 0.05$

indicator of thyroid malignanct tumors, especially for PTC. Although the guidelines have clear diagnostic criteria for different types of calcification, it is still difficult to correctly understand the calcification of thyroid nodules in practice, such as comet-tail artifacts in the solid part of some cystic-solid nodules was not well distinguished from the microcalcification, leading to large bias in this feature [20–22].

In addition to the gray-scale ultrasound features, the new scoring system established in this study incorporates some new technical indicators, such as the elasticity score of nodules. The existing TI-RADS classification incorporates conventional ultrasound features and does not include this type of indicator. Nodules with harder texture are more likely to be malignant, this is also consistent with the results of previous studies [23, 24]. This study showed that the risk of nodules increases when the elasticity score ≥3 points.In addition, the size of the nodules was statistically significant in the results of this study, which was different from previous studies [25]. The results may also be subject to error with respect to nodule size, since many benign nodules should be considered for surgery only if they are large or produce clinical symptoms, whereas malignant nodules are often diagnosed and treated as soon as they are found, which may lead to the selection bias of the study results.

Besides, the study found that the aspect ratio ≥1 was independent risk factor for low-risk nodules, which were assigned 3 points; the aspect ratio ≥1, hypoechoic, irregular margin, nodule max diameter ≤1 cm and elasticity score ≥3 were independent risk factors for malignant nodules, and the scores were 3,1,2,2,2/4 respectively. Different from other TI-RADS classification criteria, this study assigns different scores to different weight features, which can better reflect the importance of this feature in the overall score of thyroid nodules. Using this as a basis for establishing a scoring system, when the nodule score is lower than 4.5, the nodule is mostly considered benign,

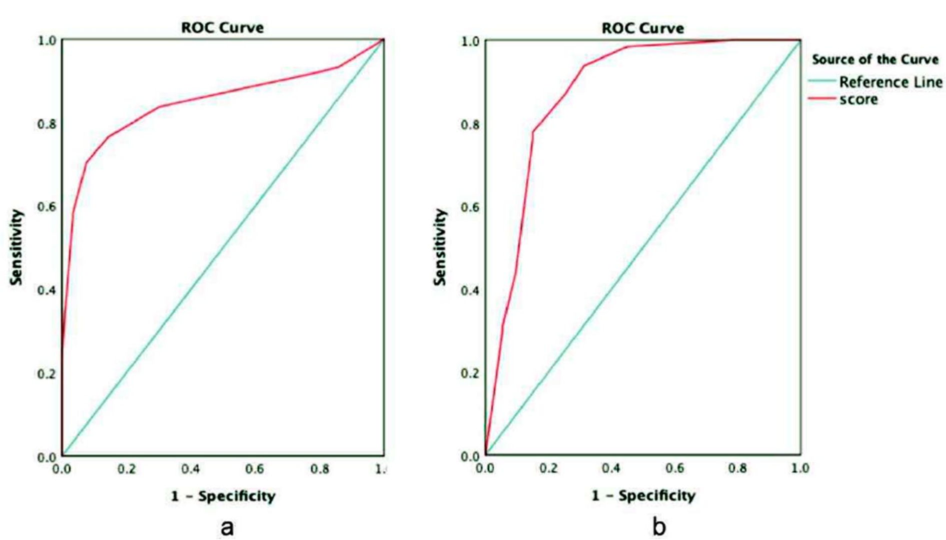

Fig. 1 ROC curve analysis of benign, low-risk and malignant thyroid nodules. **a**: comparison between the benign and low-risk nodules. **b**: comparison between the low-risk and malignant nodules

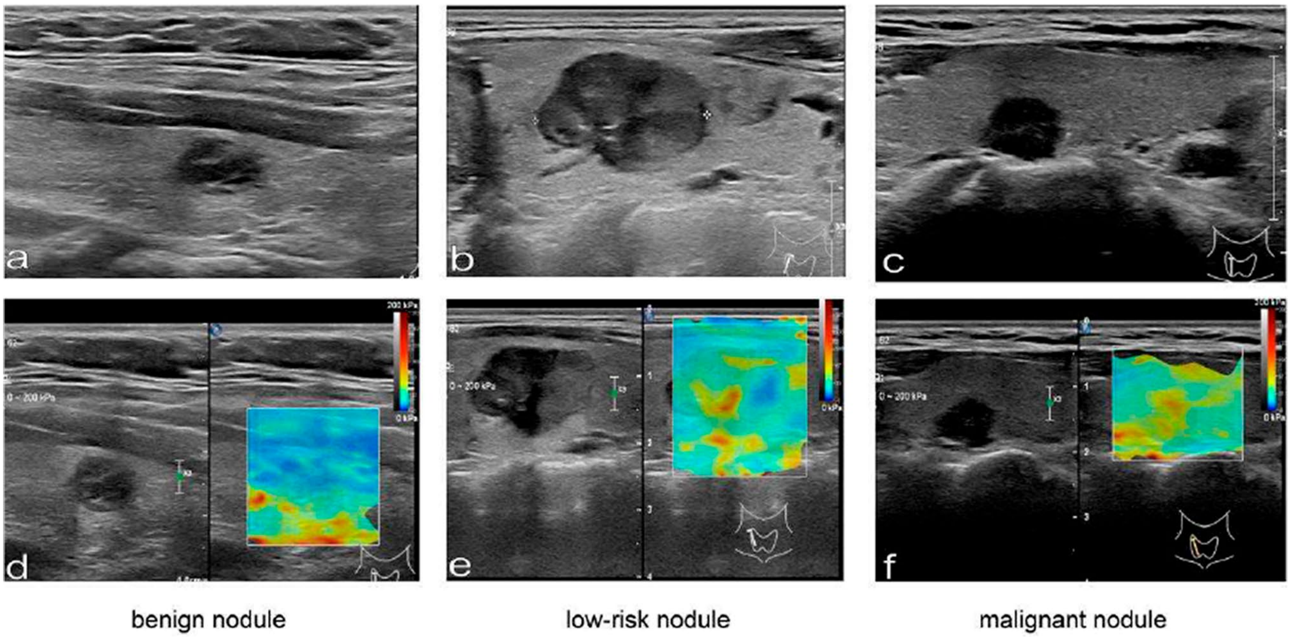

Fig. 2 Characteristic images of benign, low-risk and malignant thyroid nodules. **a** and **d** are the gray-scale and elastography ultrasound images of benign nodule, which do not have malignant features and is scored 0. **b** and **e** are the images of low-risk nodule. Hypoechoic, irregular margin, and elasticity score of 3, so the nodule score is 5. **c** and **f** show the characteristics of malignant nodule. This nodule was scored 12 with hypoechoic, irregular margin, the maximum diameter was 1 cm, the aspect ratio = 1 and elasticity score of 4

and the follow-up period can be extended appropriately if the size of the nodule does not increase significantly. When the score is between 4.5 and 5.5, the nodule is considered to be low-risk, and regular observation can be recommended, or the patient can be treated flexibly according to his/her wishes. When the score is greater than 5.5, malignancy is considered, and the patient can be advised to undergo FNA and further management according to the puncture results. According to this process, it may be possible to standardize the stratified management of thyroid tumors, which helps to optimize the choice of clinical diagnosis and treatment options.

Compared with broadest ACR-TI-RADS, the new scoring system established in this study has better diagnostic efficacy, with higher sensitivity (92.5% vs 38.3%) and lower specificity (70.4% vs 90.7%)in the detection of benign nodules and slightly higher sensitivity and specificity (77.9% vs 72.3%, 85% vs 82.5%,respectively) in the detection of malignant nodules. Notably, this scoring system had lower sensitivity (16.5%) and higher specificity

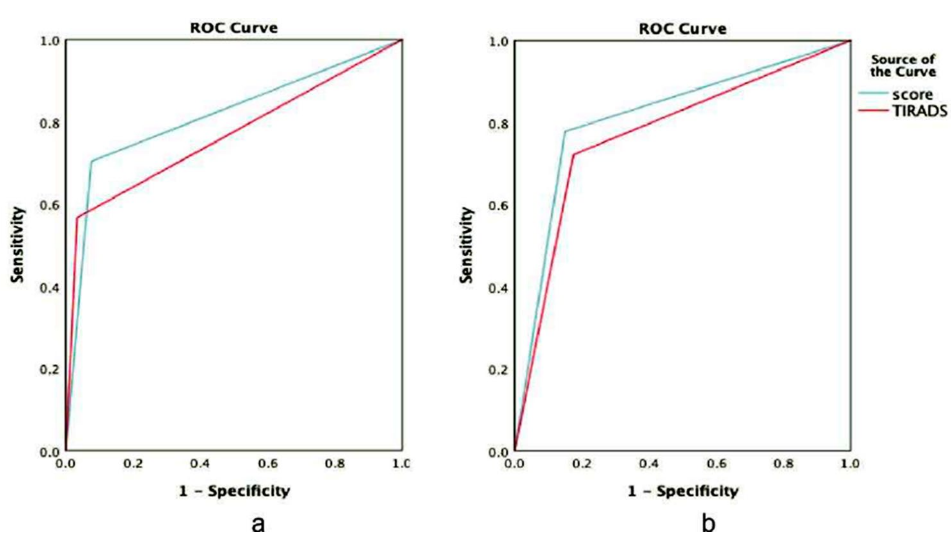

Fig. 3 Delong test of ROC analysis results. **a**: comparison in differentiating benign nodules. **b**: comparison in differentiating malignant nodules

(92.7%) for the diagnosis of low-risk nodules. Low-risk nodules include non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid tumors of uncertain malignant potential (UMP) and hyalinizing trabecular tumor (HTT), it has been shown that the ultrasonographic features of NIFTP and UMP often overlap with those of benign follicular nodules. NIFTP is almost never classified as highly suspicious in the TI-RADS [16, 26, 27]. This is consistent with our findings and may explain why its diagnostic sensitivity is low. Therefore, although the diagnosis of low-risk nodules remains a challenge, it also suggests a possible conservative approach in those with low-suspicious features that can be actively monitored over time. Therefore, it may provide auxiliary information for clinical hierarchical diagnosis and treatment.

There are several limitations of our study. First, this was a single-center retrospective study. Only patients with a confirmed postoperative diagnosis of thyroid follicular cell–derived neoplasms were included. Patients who did not undergo surgery were missed, which may have introduced an element of selection bias.Secondly, the sample size was small and some rare and special types of tumors are not included.Thirdly,many benign nodules should be considered for surgery only if they are large or produce clinical symptoms, whereas malignant nodules are often diagnosed and treated as soon as they are found, which may lead to the bias in the feature of nodule size. This requires further refinement and expand the sample size of future studies to improve the stability and universality of the grading system.

Conclusion

Therefore, the new scoring system established in this study can be used for risk stratification of thyroid nodules more efficiently, and avoid unnecessary puncture and surgery, which provides a strong basis for clinical diagnosis and treatment. Compared with TI-RADS, it has higher sensitivity and specificity for the differentiation of benign and malignant nodules, and also shows high specificity for low-risk nodules.

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Author contributions
Ya Yuan and Hua Shu wrote the main manuscript text. Lu Li and Liuxi Wu prepared the figures and tables. Fei Yu was the corresponding author of the manuscript. All authors reviewed the manuscript.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethical approval
This study was approved by the Ethics Committee of the First Affliated Hospital of Nanjing Medical University (Jiangsu Provincial People's Hospital)on October 25.2023.with the approval no.2023-SR-691.This study complied with the Declaration of Helsinki.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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