Role of ultrasonic Chinese-thyroid imaging reporting and data system classification in interpretating malignant thyroid nodules by different observers

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► ***Original article***

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Received: July 2025
Final revised: November 2025
Accepted: November 2025

Int. J. Radiat. Res., April 2026; 24(2): 411-416

DOI: 10.61186/ijrr.24.2.16

Keywords: *Classification, Doppler ultrasonography, color, malignancy, observation, thyroid gland.*

ABSTRACT

Background: Malignant thyroid nodules are defined as malignancies in the thyroid gland, and usually refer to thyroid cancer. We aimed to retrospectively assess the differences in ultrasonic description and Chinese-Thyroid Imaging Reporting and Data System (C-TIRADS) classification in the interpretation of malignant thyroid nodules by observers (with different years of experience). ***Materials and Methods:*** A total of 119 patients with thyroid nodules (119 nodules, all with postoperative pathological results) treated from January 2020 to January 2023 were selected and subjected to color Doppler ultrasonography. According to the experience of observers (n=4) in thyroid ultrasonography, the subjects were divided into Group A, B, C and D (years of experience: ≤2 years, 3-5 years, 6-10 years, and >10 years). Then the acquired ultrasound images were assessed and classified. ***Results:*** The ultrasound signs of C-TIRADS classification in patients with malignant thyroid nodules, such as degree of enhancement, uniformity of enhancement, mode of enhancement, circular enhancement and mode of washout, were significantly different from those of the subjects with benign thyroid nodules (P<0.05). In Groups A, B, C, and D, the areas under the curves were 0.734, 0.776, 0.823 and 0.885, and the Youden indexes were 0.339, 0.562, 0.630 and 0.835, respectively. The interobserver agreement in the determination of C-TIRADS 4/5/6 of malignant thyroid nodules and the overall agreement were both good (Kappa=0.735, 0.627, 0.651, and 0.765). ***Conclusion:*** The overall interobserver agreement in the selection of C-TIRADS ultrasound descriptors is good.

INTRODUCTION

Malignant thyroid nodules are defined as malignancies in the thyroid gland, and usually refer to thyroid cancer. Thyroid cancer is characterized by slow growth, less obvious symptoms and different epidemiological manifestations due to gender [the incidence rate in females (about 2.70%) is 2-3 times that in males (about 0.70%)] (1), age (prevalent in people aged 20-50 years) (2), region (higher incidence in Mediterranean coastal countries, Japan, *etc*.) (3) and genetic factors (a high risk in relatives with familial thyroid cancer) (4). It is estimated that by 2030, thyroid malignancies will become the fourth major malignancy in the world (5). According to research data in China, although thyroid malignancies are not among the top 10 of more than 100 known cancers so far, their morbidity and mortality are still increasing year by year (6, 7). If not treated promptly, malignant thyroid nodules may spread to surrounding tissues and lymph nodes, or even metastasize to other sites. With early diagnosis and treatment, the 5-year survival rate will exceed 90.00% (8, 9). Chinese-Thyroid Imaging Reporting and Data System (C-TIRADS) is a standardized system for the assessment of thyroid nodules in adults, designed to assist physicians in the classification, assessment, and management of thyroid nodules. Studies have verified that C-TIRADS has good diagnostic efficacy and serves as one of the effective supplementary means for the diagnosis of benign and malignant thyroid nodules. Due to the different development standards of C-TIRADS in different countries and regions, however, its sensitivity slightly varies, but its accuracy is mostly over 85.00% (10). As shown by data from previous studies, the area under the curve (AUC) of diagnostic efficacy of C-TIRADS is larger than those of ACR-TIRADS and EU-TIRADS, but no similar large-scale studies are available, so research is needed.

We aimed to evaluate the interobserver diagnostic efficacy of C-TIRADS for malignant thyroid nodules and to compare its performance with other widely used stratification systems. The findings are expected to support clinicians in more accurately estimating malignancy risk and formulating appropriate diagnostic and therapeutic strategies.

MATERIALS AND METHODS

General data

A total of 119 patients with malignant thyroid

[DOI: 10.61186/ijrr.24.2.16]

nodules (119 nodules, all with postoperative pathological results) treated in our hospital from January 2020 to January 2023 were selected. The inclusion criteria were as follows: 1) patients with thyroid nodules of 1-5 cm in size, 2) those with malignant nodules detected by ultrasound or other imaging and biopsy examinations, with an irregular shape, blurred margin and uneven internal echo, and 3) those who signed the informed consent form and had complete and valid clinical data.

The exclusion criteria were as follows: 1) patients aged <18 years or >85 years, 2) those with abnormal symptoms such as hyperthyroidism or hypothyroidism, 3) those with benign thyroid nodules detected by imaging and fine needle aspiration biopsy, 4) those with other serious diseases, such as various malignancies or severe cardiovascular diseases, or 5) pregnant or lactating women. Among the patients enrolled, there were 26 benign cases, including 7 males and 19 females aged 18-85 (51.25±4.67) years, and the maximum diameter of mass was 4.50-66 (20.27±10.63) mm. There were 93 malignant cases, including 29 males and 64 females aged 18-85 (51.34±4.52) years, and the maximum diameter of mass was 4.50-66 (20.21±10.37) mm. Age, gender, and maximum diameter of mass had no significant differences and were comparable between the two groups (P>0.05). This study complied with the medical research principles specified in the *Declaration of Helsinki* [11] and was approved by the ethics committee of our hospital (approval No. NFH202001005on January 8th, 2020).

Ultrasonography

ACUSON OXANA2 ultrasonic diagnostic equipment (Siemens AG, Germany; probe frequency: 4-15 MHz) was set to a thyroid testing mode. The patient was instructed to take a supine position with pillows placed under the shoulder to fully expose the neck. The routine ultrasound signs of malignant nodules in each group such as location, size, shape, boundary and echo were conventionally detected. The probe was adjusted to make it on the body surface of the thyroid gland, and the maximum longitudinal section of malignant nodules was selected (make sure that there is a mass in the center of the sampling frame), followed by detection. The image was frozen after stabilization (lasting for 3 s under a breath-holding state) and preserved, and then the shear wave elastography value was measured. Each malignant nodule was detected 3 times, and the average value was taken.

Image interpretation

The image was interpreted by two radiologists (≥5 years of experience in thyroid ultrasonography). With reference to a previous literature [12], the ultrasonic features (shape, location, echo type, posterior echo, margin, calcification, *etc*.) and C-TIRADS classification (scored based on the ultrasonic features including solid nature, vertical position, microcalcification, very low echo, blurred/irregular margin or presence of lesion invasion, with 1 point for each item, and cystic component with comet tail sign indicated benign nodules scored -1 point) of malignant nodules of all subjects were recorded. Then the malignant risk was stratified according to the total score: C-TIRADS2 (type 2, completely benign, -1 point, malignant rate=0, no further examination required), C-TIRADS3 [type 3-4A, possibly benign (0 points <malignant rate <2.00%) or low suspicion of malignancy (10.00% <malignant rate <50.00%), 0-1 point, long-term follow-up required], C-TIRADS4 (type 4B, intermediate suspicion of malignancy, 2 points, 10.00% <malignant rate <50.00%, further examinations such as fine needle aspiration biopsy required), C-TIRADS5 (type 4C, high suspicion of malignancy, 3-4 points, 50.00% <malignant rate ≤90.00%, surgical resection or other treatment required), and C-TIRADS6 (type 5, highly malignant, 5 points, malignant rate >90.00%, surgical resection or other treatment required). All observers received training regarding thyroid ultrasonography before enrollment of subjects, and were not aware of the clinical data, imaging test or pathological diagnosis results of all patients with malignant thyroid nodules before evaluation and classification of ultrasound images (signs).

Statistical analysis

An Excel database (Microsoft, USA) was established, and all baseline data and study data were subjected to processing with SPSS21.0 software (IBM, USA). The measurement data were described by ($\bar{x}$±*s*), and the *t*-test was used for comparison of sample means and the χ^2 test was employed for intergroup comparison. With pathological results as the gold standard, the area under receiver operating characteristic curve (AUC) and Youden index were calculated, based on which the optimal cut-off point of C-TIRADS classification was obtained. The paired χ^2 test was used for the diagnostic efficacy (sensitivity, specificity, *etc*.) for malignant thyroid nodules, and the Kappa test was utilized for the interobserver agreement (selection of ultrasound descriptors and C-TIRADS classification). P<0.05 was considered a statistically significant difference.

RESULTS

Pathological results

Among the 119 thyroid nodules, there were 26 (21.85%) benign nodules and 93 (78.15%) malignant nodules, including 83 cases of papillary thyroid carcinoma (89.25%), 7 cases of medullary carcinoma (7.53%), and 3 cases of lymphoma (3.23%).

Ultrasound signs of benign and malignant thyroid nodules

The ultrasound signs of C-TIRADS classification such as degree of enhancement, uniformity of enhancement, mode of enhancement, circular enhancement and mode of washout in patients with malignant thyroid nodules were significantly different from those with benign thyroid nodules (P<0.05) (table 1 and figure 1).

Table 1. Ultrasound signs of benign and malignant thyroid nodules.

Indicator and classification		Group		χ^2	*P*
Indicator	Classification	Benign (*n*=26)	Malignant (*n*=93)		
Degree of enhancement	Hyperenhancement	5	16	29.168	<0.001
	Hypoenhancement	9	72		
	Isoenhancement	12	5		
Uniformity of enhancement	Homogeneous	11	62	5.084	0.024
	Heterogeneous	15	31		
Mode of enhancement	Concentric	5	32	6.126	0.047
	Eccentric	8	11		
	Diffuse	13	50		
Circular enhancement	Yes	10	2	33.511	<0.001
	No	16	91		
Mode of washout	Rapid	4	47	14.139	<0.001
	Slow	15	21		
	Synchronous	7	25		

Figure 1. Ultrasound images of **(A)** benign, **(B)** suspiciously malignant, and **(C)** malignant thyroid nodules.

C-TIRADS classification results and pathological results of thyroid nodules

C-TIRADS4, C-TIRADS5 and C-TIRADS6 cases accounted for 29.03%, 44.09% and 13.98%, respectively, in Group A, 31.18%, 47.31% and 7.53%, respectively, in Group B, 33.33%, 46.24% and 5.38%, respectively, in Group C, and 34.41%, 56.99% and 8.60%, respectively, in Group D. The malignant rate was 78.49%, 84.95%, 88.17% and 95.70%, respectively, in Groups A, B, C and D (table 2).

Table 2. C-TIRADS classification results and pathological results of thyroid nodules.

Group	Classification	C-TIRADS risk stratification					Pathology	
		2	3	4	5	6	Benign	Malignant
A	Benign	1	3	7	13	1	16	16
	Malignant	0	12	27	41	13	14	73
B	Benign	0	2	9	15	0	19	8
	Malignant	0	13	29	44	7	13	79
C	Benign	0	1	10	13	2	22	5
	Malignant	0	14	31	43	5	10	82
D	Benign	0	0	9	16	1	24	2
	Malignant	0	0	32	53	8	4	89

C-TIRADS: Chinese-Thyroid Imaging Reporting and Data System. Group A, B, C and D: years of experience: ≤2 years, 3-5 years, 6-10 years, and >10 years.

Diagnostic efficacy for benign and malignant thyroid nodules

The accuracy and sensitivity in Groups A and B were lower than those in Group D (χ^2= 15.846, 7.905; 11.610, 8.473, P<0.05) (Table 3). In Groups A, B, C, and D, the AUC value was 0.734, 0.776, 0.823 and 0.885, and the Youden index was 0.339, 0.562, 0.630 and 0.835, respectively, and the cut-off point of C-TIRADS classification for diagnosing benign and malignant thyroid nodules was between C-TIRADS4 and C-TIRADS5 (figure 2).

Table 3. Diagnostic efficacy for benign and malignant thyroid nodules.

Group	Accuracy	Sensitivity	Specificity	Predictive value	
				Positive	Negative
A	74.79	83.91	50.00	82.02	53.33
B	82.35	85.87	70.37	90.80	59.38
C	87.39	94.25	68.75	89.13	81.48
D	94.96	97.80	85.71	95.70	92.31

Group A, B, C and D: years of experience: ≤2 years, 3-5 years, 6-10 years, and >10 years.

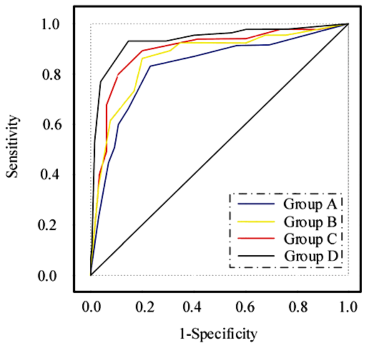

Figure 2. Receiver operating characteristic curves for diagnosis of benign and malignant thyroid nodules (four groups).

[DOI: 10.61186/ijrr.24.2.16]

Interobserver agreement

According to Kappa agreement analysis, the interobserver agreement in the judgement of shape, location and echo type of malignant thyroid nodules was good (Kappa=0.622, 0.553, 0.554), the interobserver agreement in the judgement of posterior echo and calcification was moderate (Kappa=0.449, 0.426), and the interobserver agreement in the judgement of margin and classification was fine (Kappa=0.227, 0.271) (table 4 and figure 3).

Table 4. Interobserver agreement in selection of ultrasound descriptors for malignant thyroid nodules.

Ultrasound sign	Kappa	Standard error	95% confidence interval		*P*
			Lower limit	Upper limit	
Shape	0.622	0.031	0.551	0.679	<0.001
Location	0.553	0.032	0.487	0.602	<0.001
Margin	0.227	0.024	0.172	0.255	<0.001
Echo type	0.554	0.035	0.491	0.613	<0.001
Posterior echo	0.449	0.033	0.372	0.498	<0.001
Calcification	0.426	0.034	0.392	0.517	<0.001
Classification	0.271	0.023	0.235	0.318	<0.001

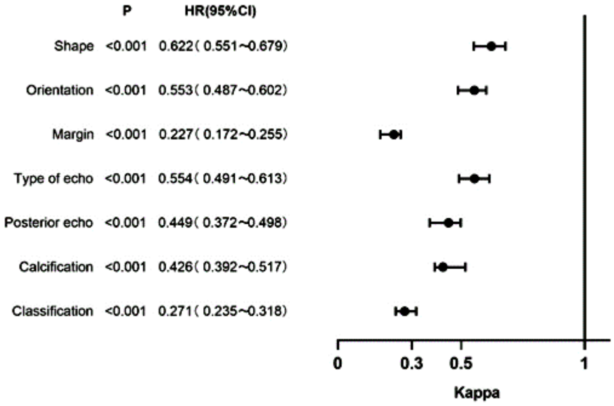

Figure 3. Interobserver agreement in selection of ultrasound descriptors for malignant thyroid nodules. CI: Confidence interval; HR: hazard ratio.

Interobserver agreement in C-TIRADS classification of malignant thyroid nodules

The interobserver agreement in the judgement of C-TIRADS 4/5/6 of malignant thyroid nodules and the overall agreement were both good (Kappa=0.735, 0.627, 0.651, and 0.765) (table 5 and figure 4).

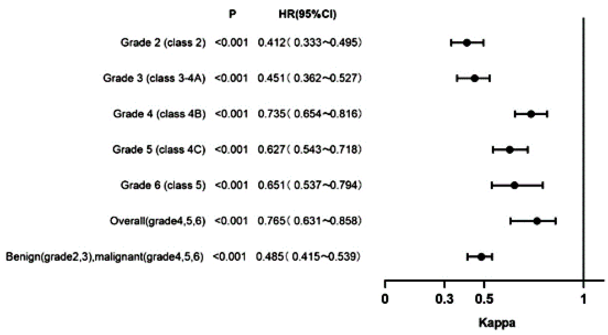

Figure 4. Interobserver agreement in C-TIRADS classification of malignant thyroid nodules. C-TIRADS: Chinese-Thyroid Imaging Reporting and Data System; CI: confidence interval; HR: hazard ratio.

Table 5. Interobserver agreement in C-TIRADS classification of malignant thyroid nodules.

C-TIRADS classification	Kappa	Standard error	95% confidence interval		*P*
			Lower limit	Upper limit	
C-TIRADS2 (type 2)	0.412	0.045	0.333	0.495	<0.001
C-TIRADS3 (type 3-4A)	0.451	0.043	0.362	0.527	<0.001
C-TIRADS4 (type 4B)	0.735	0.044	0.654	0.816	<0.001
C-TIRADS5 (type 4C)	0.627	0.048	0.543	0.718	<0.001
C-TIRADS6 (type 5)	0.651	0.049	0.537	0.794	<0.001
Overall (type 4/5/6)	0.765	0.034	0.631	0.858	<0.001
Benign (type 2/3), Malignant (type 4/5/6)	0.485	0.038	0.415	0.539	<0.001

DISCUSSION

In recent years, the research on the use of TIRADS classification for thyroid nodules has attracted much attention. The diagnostic efficacy of TIRADS is good, but TIRADS has slight differences in the risk stratification of malignant thyroid nodules among countries and regions. With pathological results as the gold standard, the AUC value of C-TIRADS is larger than that of ACR-TIRADS, EU-TIRADS, ATA Guidelines and Kwak-TIRADS (0.913 *vs*. 0.890, 0.868, 0.880, and 0.901), but the diagnostic accuracy of the five methods all exceeds 85.00% [13]. This is consistent with recent findings showing that ultrasound-based TI-RADS systems generally achieve high diagnostic accuracy in predicting thyroid malignancy, typically above 85-90% [14]. It has been confirmed that C-TIRADS has comparable efficacy to ACR-TIRADS but higher specificity in the diagnosis of benign and malignant thyroid nodules, which can help reduce puncture [12]. Similar conclusions were also reported in a systematic analysis that emphasized the value of TI-RADS in reducing unnecessary biopsy while maintaining sensitivity [15].

Kwak-TIRADS is more similar to C-TIRADS in the diagnosis of malignant thyroid nodules because they both conduct ultrasonic differentiation and stratification of malignant thyroid nodules from the solid nature, microcalcification, aspect ratio (>1) and irregular margin, but the former is based on a small sample size, while the latter is based on multiple centers (131 hospitals) and a large sample size. Combining these ultrasound features with structured TI-RADS categories can improve the predictive ability for more aggressive biological behavior, such as central lymph node metastasis in papillary thyroid carcinoma [16]. C-TIRADS based on the malignant risk of thyroid nodules (type 2-5, malignant rate: 0-100%) is more suitable for the clinical practice of diagnosis and treatment of thyroid nodules in China, so it is superior to the other several versions of TIRADS.

In this study, the accuracy, sensitivity, AUC value and Youden index were 74.79%, 83.91%, 0.734 and 0.339, respectively, in Group A, 82.35%, 85.87%, 0.776 and 0.562, respectively, in Group B, 87.39%,

[DOI: 10.61186/ijrr.24.2.16]

94.25%, 0.823 and 0.630, respectively, in Group C, 94.96%, 97.80%, 0.885 and 0.835, respectively, in Group D. The cut-off points of C-TIRADS classification for diagnosing benign and malignant thyroid nodules was between C-TIRADS4 and C-TIRADS5. This threshold agrees with recent multicenter validations of TI-RADS-based stratification [15], and the highest accuracy and sensitivity (89.60%, 92.40%) were similar to those in the clinical study [13], suggesting that C-TIRADS classification has good diagnostic efficacy for malignant thyroid nodules, but its efficacy is also affected by the diagnostic skills of observers.

According to the ultrasound signs (such as degree of enhancement, uniformity of enhancement, mode of enhancement, circular enhancement, and mode of washout) and risk stratification results of malignant thyroid nodules, the judgment basis and cut-off point of C-TIRADS classification for diagnosing benign and malignant thyroid nodules were between C-TIRADS4 and C-TIRADS5. The reason is that there are some differences in histopathological structure and hemodynamics between benign and malignant thyroid nodules as shown from ultrasound signs, and the higher the C-TIRADS classification, the higher the malignant rate. Collectively, C-TIRADS classification is effective in evaluating malignant thyroid nodules and has certain clinical reference value. Multimodal ultrasound studies, including CEUS-based and microvascular-based diagnostic approaches, have also supported the value of enhancement patterns and perfusion characteristics in differentiating benign from malignant nodules [17].

There were no significant differences in the degree of enhancement, uniformity of enhancement, and mode of washout between benign and malignant thyroid nodules [18]. We herein found that the subjective factors of the observer obviously affected the efficacy of C-TIRADS classification in the diagnosis of benign and malignant thyroid nodules. Therefore, it is necessary to study the interobserver agreement in the diagnosis of malignant thyroid nodules. Shape, calcification, aspect ratio, echo, blood flow distribution, hardness and margin are all important reference bases for the evaluation of benign and malignant thyroid nodules.

It was found that the interobserver agreement in the judgement of the shape, location and echo type of malignant thyroid nodules was good (Kappa=0.622, 0.553, and 0.554), suggesting that the observers in Groups A, B, C and D had basically the same understanding of the shape, location and echo type of malignant thyroid nodules, independent of their working years and working experience. The shape, location and echo type of malignant thyroid nodules are important indicators for determining whether they are benign or malignant. As compared to benign nodules, malignant thyroid nodules are more irregular in shape, with blurred margin, usually located in the peripheral area of the thyroid gland, and mostly display hypoechoes or mixed echoes [19]. Hypoechoes indicate more parenchyma within the nodule, and mixed echoes indicate a mixture of parenchyma and fluid within the nodule. However, it should be noted that these three indicators cannot differentiate the benign and malignant thyroid nodules, but can only be used as evaluation indicators, and contrast-enhanced ultrasound is required for diagnosis. Similarly, Chen *et al.* emphasized the complementary value of CEUS and microvascular imaging in improving TI-RADS-based risk stratification [20].

In this study, the ultrasound signs of C-TIRADS classification such as degree of enhancement, uniformity of enhancement, mode of enhancement, circular enhancement and mode of washout in patients with malignant thyroid nodules were significantly different from those with benign thyroid nodules ($P<0.05$), and the former was dominated by inhomogeneous and low enhancement and rapid washout, while the latter was dominated by diffuse, homogeneous and circular enhancement. The possible reasons include invasive growth of malignant thyroid nodules, rapid neovascularization and presence of arteriovenous fistula [21]. The interobserver agreement in the judgement of posterior echo and calcification was moderate (Kappa=0.449, 0.426), suggesting that observers in Groups A, B, C and D need to improve their understanding and mastery of posterior echo and calcification of malignant thyroid nodules. Similar challenges with interobserver variability have been highlighted in recent literatures [15, 16].

Malignant thyroid nodules usually present inhomogeneous or unclear posterior echo or hypoechoic areas and they are less prone to calcification. Previous studies have confirmed [22, 23] that benign thyroid nodules are more likely to have different types of calcifications than malignant nodules, such as spotted, circular, arc-shaped and granular calcification. It is of certain reference value to use blurred margin, hypoechoic nodules, microcalcification and aspect ratio ≥1 as predictive features of malignant thyroid nodules.

Besides, the interobserver agreement in the judgement of margin and classification was fine (Kappa=0.227, 0.271), suggesting that the observers in Groups A, B, C and D need to improve their understanding and mastery of margin and classification of malignant thyroid nodules. Malignant nodules usually show irregular or jagged margin, while benign nodules usually display smooth or regular margin. Radzina *et al.* [24] confirmed that the peak intensity inside benign or malignant thyroid nodules is lower than that in the marginal region, wherein the peak intensity in benign nodules is higher than that in malignant nodules, and the time to peak is shorter than that of malignant nodules and longer inside the nodules than that in the marginal

[DOI: 10.61186/ijrr.24.2.16]

region.

In addition, there were fewer C-TIRADS4/5/6 cases in Groups A and B than Groups C and D, and the malignant rates in Groups A and B (78.49% and 84.95%) were also lower than those in Groups C and D (88.17% and 95.70%). The overall interobserver agreement in the C-TIRADS classification of malignant thyroid nodules was good (Kappa=0.765). This is supported by a recent study that observer experience played a key role in the stability of TI-RADS-based classification [16].

Nevertheless, this study still has several limitations. First, this was a single-center retrospective study, and the sample size of each observer group was relatively limited, which may affect the generalizability of the results. Second, although all observers received standardized training before evaluation, differences in clinical experience and recognition of ultrasound descriptors may still lead to biased classification results. These limitations should be addressed in future multicenter studies with larger sample sizes and more standardized ultrasonographic protocols.

In conclusion, C-TIRADS classification has high clinical value for the diagnosis of malignant thyroid nodules. The overall interobserver agreement in the selection of C-TIRADS ultrasound descriptors is generally good, suggesting that it is necessary to enhance the training on the use of some ultrasound descriptors regardless of the physician's working experience.

Acknowledgments: *This study was not financially supported.*

Conflict of interest: The authors declare no conflict of interest.

Funding: No funds received for this work.

Ethical consideration: This study complied with the medical research principles specified in the *Declaration of Helsinki* and was approved by the ethics committee of our hospital (approval No. NFH202001005on January 8th, 2020).

Author contributions: J.L. and J.W. contributed equally to this work and should be considered co-first authors. They conducted the data analysis, performed ultrasonographic assessments, and wrote the initial draft. X.L. and X.Z. jointly supervised the project and provided critical revisions; both should be regarded as co-corresponding authors. J.Q. contributed to data interpretation and assisted with statistical processing. All authors reviewed and approved the final manuscript.

Possible AI usage for manuscript preparation: The authors did not use AI for manuscript preparation.

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[DOI: 10.61186/ijrr.24.2.16]