OPEN PEER REVIEW

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Peer Review Report for "Value of Quantitative Contrast-Enhanced Ultrasonography in Distinguishing Asymptomatic Subacute Thyroiditis from Papillary Thyroid Carcinoma"

Author(s): Na Wang, Hongguang Sun, Tingyue Qi, Haiyan Cao, Nianfen Li, Linhai Zhu, Yongling Ding

Review Timeline:

Submit Date: 6 Jul 2020
Revised Date: 11 Aug 2021
Accepted Date: 15 Aug 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Hashem Sharifian: Reviewer | **Revision** (0) — 24 Jul 2020

Dear AE,
I think the article is a well-structured study, it can be published in IJR.
Thanks.

REFEREE: Reviewer | **Revision** (0) — 4 Aug 2020

Dear AE,
Comments for the authors:
1- English literature should be completely revised.
2- Patients underwent CEUS after pathology result or before that and if that took place after pathology result were operators blind to results or not, these items should be clearly write down in method section.
3- The performed color Doppler exam should be indicated in examination part of the method and images included.
4- Histology micro-graph must be included.

5- The structure of discussion should be completely revised based on known standards.
6- Pathology results obtained from two different methods one after surgery tissue diagnosis and the other after FNA differ from each other, please discuss the problem.
Best Regards

Madjid Shakiba: Reviewer | **Revision (0)** 5 Oct 2020

Dear AE,
Comments for the authors:
1- It is better if the authors add some numerical profile to the result section of abstract. [brief numerical results]
2- some words are chosen inappropriately; for example, security that should be safe, deficiencies that should be shortcomings, etc. please revise the writing style of the whole paper in this regard.
3- please add the objective part to the paper before the method section [according to journal format].
4- In the American College of Rheumatology (ACR) radiology seems correct. Rheumatology is wrong.
5- as the study is retrospective, what was the reason for implementing CEUS for the patients?
6- as the study is retrospective, did all CEUSes perform in a unified and standard method?
7- is FNAB as precise as surgery in the diagnosis of PTC or aSAT?
8- the authors mentioned in inclusion criteria: all lesions were assessed as ≥ TI-RADS IV. Probably this is due the fact that the PTC is malignant and is associated mostly with higher TRIADS scores. In this regard, we can propose some questions:
I- what is routinely the TIRADS score of aSAT? do they present often with TRIADS ≥4? If the answer is no, then the authors have selected special types of aSATs and this could make a selection bias. However, this type of selection makes an underestimation in diagnostic efficacy indices as the more similar aSATs that are more difficult to differentiate from PTC are selected and the indices will be underestimated]. Please explain and discuss if it is needed.
II- How many PTCs are presented with TIRADS scores lower than 4? If most of them show TIRADS 4 or higher, the selection could be acceptable but if a considerable portion of PTCs are lower than 4, the selection could be biased. Please explain.
9- what is the meaning of “fitting degree of quantitative CEUS analysis curve <75%.”?
10- the authors mentioned: “Two trained operators (both with more than 10 years of experience) performed all scans” the study is retrospective and each patient was assessed by one radiologist. Were their expertise for performing a good sonography similar? Did you assess this point?
11- as the study is retrospective, are the images enough for full evaluation of the nodules and thyroid?
12- the main consideration of the study design is that the authors have designed a diagnostic test study as a case-control design that is not appropriate and can make considerable bias. The best design for a diagnostic test study is recruiting the clinically suspicious patients in the study and assessing them by the test and gold standard. The case-control design [enrollment of the known patients with and without the target disease]

can overestimate the diagnostic indices as the patients are selected from two ends of the disease spectrum [obvious positive and negative patients]. Please explain in this regard.
13- the other important consideration of the study is that the authors have recruited the patients with nodules that are diagnosed as the aSAT and PTC based on histopathology; while in daily practice, a patient comes to a clinic with a thyroid nodule and his/her diagnosis could be the other pathologies than aSAT and PTC [for example MTC, FTC,…..]. the results of the study are applicable when we know the only differential diagnoses of a patient with a thyroid nodule is aSAT and PTC [the other diagnoses have been ruled out] and we want to differentiate between only these two diagnoses. In practice, the physician should diagnose among all differential diagnoses and so, the results of the study are not applied for daily practice. Please explain. [in fact, as I mentioned in the previous question, the authors should implement a study on the patient with an unknown thyroid nodule and perform the CEUS and then pathology; then they can assess the diagnostic efficacy of CEUS].
14- the authors mentioned: “Two trained operators (both with more than 10 years of experience) performed all of the above analyses.” were operator radiologist? Or they were sonography technicians?
15- There are some questions on Quantitative CEUS analysis and some parts are unclear. Please respond to the following questions in this regard:
I- what was the interrater reliability of the operator in Quantitative CEUS analysis? [in ROI drawing and other measurements]
II- what was the shape and size of the ROI?
III- the authors mentioned: “Maximum intensity (IMAX, expressed as a percentage)” while they did not mention how did they calculate this percentage?
IV- in figure 1, it is unknown where is whole-ROI, where is the peripheral-ROI, where is the central-ROI and where is control ROI?
V- the authors defined Short RT = rapid wash-in; long RT = slow wash-in. but they did not define what is the criteria for rapid and slow. Please define.
VI- the authors mentioned: “Rise time (RT), compared with the control area” this definition is vague and unclear. is it the time form imaging beginning till the time that the curve is beginning to rise? Or the time denote to the other concept? Please define.
VII- the authors defined: Short TTP=rapid wash-in; long TTP =slow wash-in. but they did not define what is the criteria for rapid and slow. Please define.
VIII- is it possible for sonography to assess simultaneously all the ROIs in the same time by sonography? This is important as the authors want to measure different variables such as RT, TTP, MTT and if the radiologist can not see all the ROIs simultaneously, then he/she can not measure for example the MTT of the central and control area and they inject the contrast one time and it is impossible to measure all variables in one single sonographic view. Please explain.
16- is the accuracy of surgery and fine-needle aspiration similar [as gold standard]? Maybe, the surgery is more accurate. Please explain.
17- in the statistical method section, please answer these questions:
I- for continuous variables with normal distribution, we can use t-test [independent or paired, depending to the type of analysis] but the authors mentioned they used Mann Whitney that is reserved for the ordinal data or continuous data without normality. Please explain in this regard. I think for the continuous variables, the authors should check the normality at the

first time. If the data are normally distributed, they can use parametric tests [instead of non-parametric tests].
II- the authors mentioned: “chi-square test of independence” that is unclear.
III- why the authors did compare the TIRADS scores between aSAT and PTC with two way ANOVA? It seems wrong.
IV- most of AUCs are not enough good. Please add the P values of each ROC to the table 4.
V- one possible assessment could be the comparison between peripheral and central parts of each nodule for “Δ” variables. [for example, the authors could calculate ΔRT4=RT of the peripheral ROI− RT of the central ROI]. It would be interesting if the authors evaluate the goodness of these variables for differentiation. [ΔRT, ΔTTP, ΔmTT]
18- the study is a diagnostic test study, so it should be written as STARD guideline.
Thanks.

REFEREE: Reviewer | **Revision** (0) 23 Oct 2020

Dear AE,
The article is interesting but needs major revision
- Please in inclusion criteria determine if your criteria is a nodule that should be seen in 2 views in ultrasound?
- Your figure1 is unclear. please describe more about central and peripheral located ROI (that I think in figure both smaller ROI are located peripherally)
- Attach more images
and describe more about the 4 types of time-intensity curves, in this manner it is meaningless.
with best regards

REFEREE: Associate Editor | **Revision** (0) 23 Oct 2020

Dear EIC,
The article was reviewed by 4 reviewers and there are major problems.
After revision, it could be re-evaluated.
with best regards

REFEREE: EIC | **Revision** (0) 26 Oct 2020

Dear authors,
Your article needs Major Revision.
Regards

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Editor,

Thank you very much for your letter dated 26th October, and the reviewer's helpful comments for our manuscript 107225. Based on the reviewers' comments and requests, we have made extensive modifications to the original manuscript, and would like to re-submit it for your consideration. The amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers' comments are listed below this letter. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. If there are any other modifications we could make, we would like very much to modify them and we really appreciate your help.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Dr. Ting Yue Qi

Responses to the Reviewer 1:

Comment 1: It is better if the authors add some numerical profile to the result section of abstract. [brief numerical results].

Reply1: Thanks for your advice. We have added the relevant numerical profile to the result section of the abstract in the revised version.

Comment 2: Some words are chosen inappropriately; for example, security that should be safety, deficiencies that should be shortcomings, etc. please revise the writing style of whole paper in this regard.

Reply 2: Thanks for your suggestion. We apologize for the inappropriate words in the article, and the entire manuscript has been revised according to your reminder in the revised version.

Comment 3: Please add objective part to the paper before method section [according to journal format].

Reply3: Thank you for your reminder. We have added the **objectives** part before the method section according to journal format in the revised version.

Comment 4: American College of Rheumatology (ACR) radiology seems correct. Rheumatology is wrong.

Reply4: We sincerely thank the reviewer for careful reading and feel sorry for our carelessness. We have corrected the corresponding error and the original text “American College of Rheumatology (ACR)” has been changed to “American College of Radiology (ACR)” in the revised version.

Comment 5: As the study is retrospective, what was the reason of implementing CEUS for the patients?

Reply5: Routinely, in our hospital, for patients with TIRADS≥4 nodules, CEUS is recommended as a supplemental examination of conventional ultrasound to avoid unnecessary biopsy or surgery.

Comment 6: As the study is retrospective, did all CEUSes perform in a unified and standard method?

Reply 6: Yes. The CEUSes of all patients in this study were performed in a unified and standard way by two experienced doctors, and they all used the same ultrasound machine under the same conditions. Relevant statements have been described in Materials and methods section.

Comment 7: Is FNAB as precise as surgery in diagnosis of PTC or aSAT?

Reply7: Thank you for this comment. In clinic, surgery and subsequent pathology are gold standard for PTC or aSAT diagnosis. Compared to surgery, FNAB also has better sensitivity and specificity in evaluating thyroid tumors (the sensitivity of FNA was 73.53% and specificity of 100%) (*Servilla M, et.al, BolAsoc Med P R. 2016*). Therefore, FNAB has certain reliability as a commonly used clinical method in diagnosis of thyroid diseases.

Comment 8: The authors mentioned in inclusion criteria: all lesions were assessed as ≥ TI-RADS IV. Probably this is due the fact that the PTC is malignant and is associated mostly with higher TIRADS scores. In this regard, we can propose some questions:
I What is routinely the TIRADS score of aSAT? do they present often with TIRADS ≥4? If the answer is no, then the authors have selected special types of aSATs and this could make a selection bias. [however, this type of selection makes an underestimation in diagnostic efficacy indices as the more similar aSATs that are more difficult to differentiate from PTC are selected and the indices will be underestimated]. Please explain and discuss if it is needed.
II How many PTCs are presented with TIRADS scores lower than 4? If most of them show TIRADS 4 or higher, the selection could be acceptable but if a considerable portion of PTCs are lower than 4, the selection could be biased. Please explain.

Reply8: Thank you for this thoughtful comment.

I: According to the ACR classification, aSAT is indeed usually TIRADS ≥ 4 because they are all hypoechoic and solid, and the boundaries of the nodules are blurred.

II: In clinical practice, almost all PTCs present with TIRADS ≥ 4. As we mentioned in the introduction section, although the pain and inflammatory swelling of the acute phase are conducive to a differential diagnosis of SAT, but for asymptomatic patients, it is extremely difficult to distinguish from the PTC.

Comment 9: What is the meaning of “fitting degree of quantitative CEUS analysis curve <75%.”?

Reply9: We feel great thanks for your professional review work. Quantitative CEUS analysis was performed with SonoLiver software version 1.1 (TomTec Imaging Systems, Munich, Germany) which

is an internationally recognized software. The software manual indicates that quality of the fit is the normalized distance between the fitted curve and the raw data (echo-power signal). When the degree of fit is less than 75%, the fitted curve is considered not to represent the original curve. Therefore, it cannot represent the true quantitative analysis result, so it needs to be included in the exclusion criteria.

Comment 10: The authors mentioned: “Two trained operators (both with more than 10 years of experience) performed all scans” the study is retrospective and each patient was assessed by one radiologist. Were their expertise for performing a good sonography similar? Did you assess this point?
Reply10: We are sorry for the unclear expression in the manuscript, and we have made corresponding changes. In China, scanning and evaluation are performed by the same person. For details, please refer to the revised method section.

Comment 11: As the study is retrospective, are the images enough for full evaluation of the nodules and thyroid?
Reply11: Thank you for your careful comment. In our department, each nodule must save images, and we have unified image preservation specifications including longitudinal and transverse 2D images, nodule size measurement images, Color Doppler images and video data. If the patient has undergone CEUS or FNAB examination, it is also necessary to leave relevant video information for later collation and summary.

Comment 12: The main consideration of the study design is that the authors have designed a diagnostic test study as a case control design that is not appropriate and can make considerable bias. The best design for a diagnostic test study is recruiting the clinically suspicious patients in the study and assessing them by the test and gold standard. The case control design [enrollment of the known patients with and without the target disease] can overestimate the diagnostic indices as the patients are selected from two ends of the disease spectrum [obvious positive and negative patients]. Please explain in this regard.
Reply12: Thank you again for your comments to improve the quality of our manuscript. And your valuable suggestions are also issue that we often consider in our research work. Our inclusion criteria indicate that only asymptomatic SAT patients are recruited, because if the patient has symptoms, it is easy for clinicians to distinguish the two diseases. However, as mentioned in our introduction section although the pain and inflammatory swelling of the acute phase are conducive to a differential diagnosis of SAT, hypoechoic and solid characteristics manifest as symptoms subside, making the disease extremely atypical and difficult to distinguish from PTC using conventional US. Even with a CEUS examination, it is still difficult to distinguish these two diseases because they are both hypoenhancement. So our research aims to evaluate the value of quantitative CEUS analysis in discriminating aSAT from PTC nodules.

Comment 13: The other important consideration of the study is that the authors have recruited the patients with nodules that are diagnosed as the aSAT and PTC based on histopathology; while in the daily practice, a patient come to a clinic with a thyroid nodule and his/her diagnosis could be the other pathologies than aSAT and PTC [for example MTC, FTC,…..]. the results of the study are applicable when we know the only differential diagnoses of a patient with a thyroid nodule is aSAT and PTC [the other diagnoses have been ruled out] and we want to differentiate between only these two diagnoses. In

practice, the physician should diagnose among all differential diagnoses and so, the results of the study are not applied for daily practice. Please explain. [in fact, as I mentioned in the previous question, the authors should implement a study on the patient with an unknown thyroid nodule and perform the CEUS and then pathology; then they can assess the diagnostic efficacy of CEUS].

Reply13: Thank you for your suggestion. As you pointed out, we should really distinguish aSAT from all thyroid malignancies such as PTC, MTC, FTC, etc., so as to better prove the value of CEUS quantitative analysis, but we all know that PTC accounts for the largest proportion of all thyroid cancers. To clarify the value of CEUS quantitative analysis in distinguishing aSAT from thyroid cancer, and to obtain more consistent results, we only chose PTC.

Comment 14: The authors mentioned: "Two trained operators (both with more than 10 years of experience) performed all of the above analyses." were operator radiologist? Or they were sonography technicians?

Reply14: No, they are not radiologists. We are sorry for the unclear expression in the manuscript, and we have made corresponding changes. In China, scanning and evaluation are performed by the same person. For details, please refer to the revised method section.

Comment 15: There are some questions on Quantitative CEUS analysis and some parts are unclear. Please respond to the following questions in this regard:

I-what was the intrarater reliability of the operator in Quantitative CEUS analysis? [in ROI drawing and other measurements]

II-what was the shape and size of the ROI?

III-the authors mentioned: "Maximum intensity (IMAX, expressed as a percentage)" while they did not mention how did they calculate this percentage?

IV-in the figure 1, it is unknown where is whole-ROI, where is the peripheral-ROI, where is the central-ROI and where is control ROI?

V-the authors defined Short RT = rapid wash-in; long RT = slow wash-in. but they did not define what is the criteria for rapid and slow. Please define.

VI-the authors mentioned: "Rise time (RT), compared with the control area" this definition is vague and unclear. is it the time form imaging beginning till the time that the curve is beginning to rise? Or the time denote to the other concept? Please define.

VII-the authors defined: Short TTP=rapid wash-in; long TTP =slow wash-in. but they did not define what is the criteria for rapid and slow. Please define.

VIII-is it possible for sonography to assess simultaneously all the ROIs in the same time by sonography? This is important as the authors want to measure different variables such as RT, TTP, MTT and if the radiologist can not see all the ROIs simultaneously, then he/she can not measure for example the MTT of the central and control area and they inject the contrast one time and it is impossible to measure all variables in one single sonographic view. Please explain.

Reply15:

I: Based on your question, can we think that you want to ask about the consistency of Quantitative CEUS analysis results performed by different people? If it is, what we want to say is that our analysis is done by one single person, as mentioned in the article "one operator (with more than 3 years' experience) performed the analysis in order to exclude bias from different operators."

II: Regarding the ROI of different colors, the explanation is as follows (Figure 1):

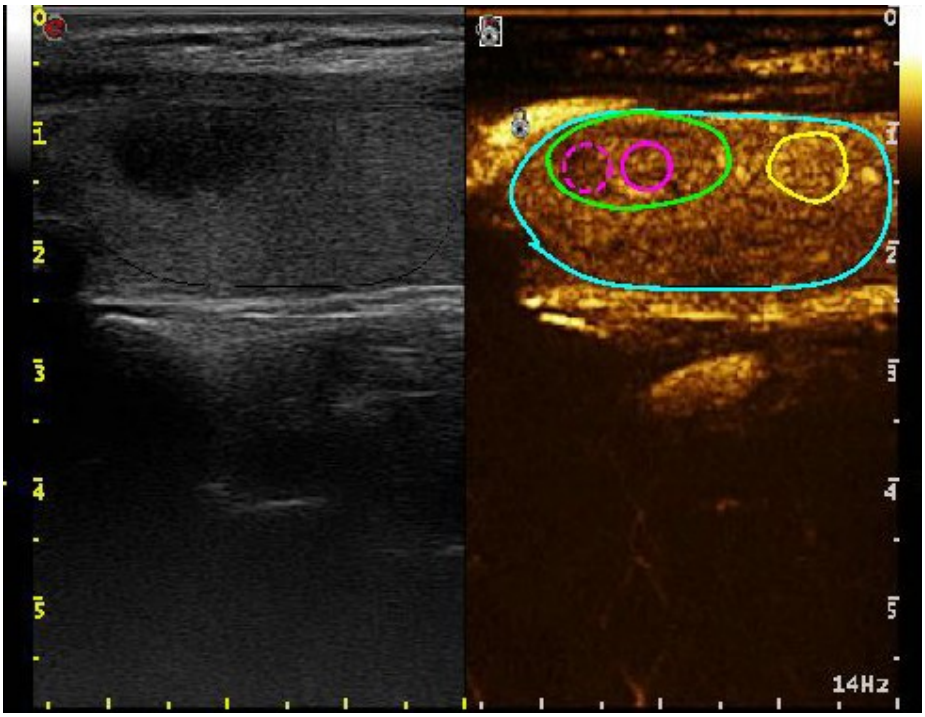


Figure 1

a. The Delimitation ROI (turquoise) outlines the lesion and healthy thyroid parenchyma to be analyzed. It must include ultrasound data only (without any text, label or measurement). As it delimitates the analysis area, you must draw all subsequent regions (reference and parametric) inside the Delimitation ROI.

b. The Analysis ROI (green) outlines the lesion tissue. It also delimitates the visualization of parametric maps.

c. The Reference ROI (yellow) outlines the healthy parenchyma next to the lesion.

d. The Parametric ROI (magenta) outlines 2 circular particular areas inside the Delimitation ROI. The solid line is the central ROI, and the dotted line is the peripheral ROI.

III: IMAX is maximum echo-power with respect to the one in the Reference ROI. We have added it to the revised version.

IV: Sorry for the trouble with your reading, we have added the corresponding arrow in Figure 2, hope it can help your reading.

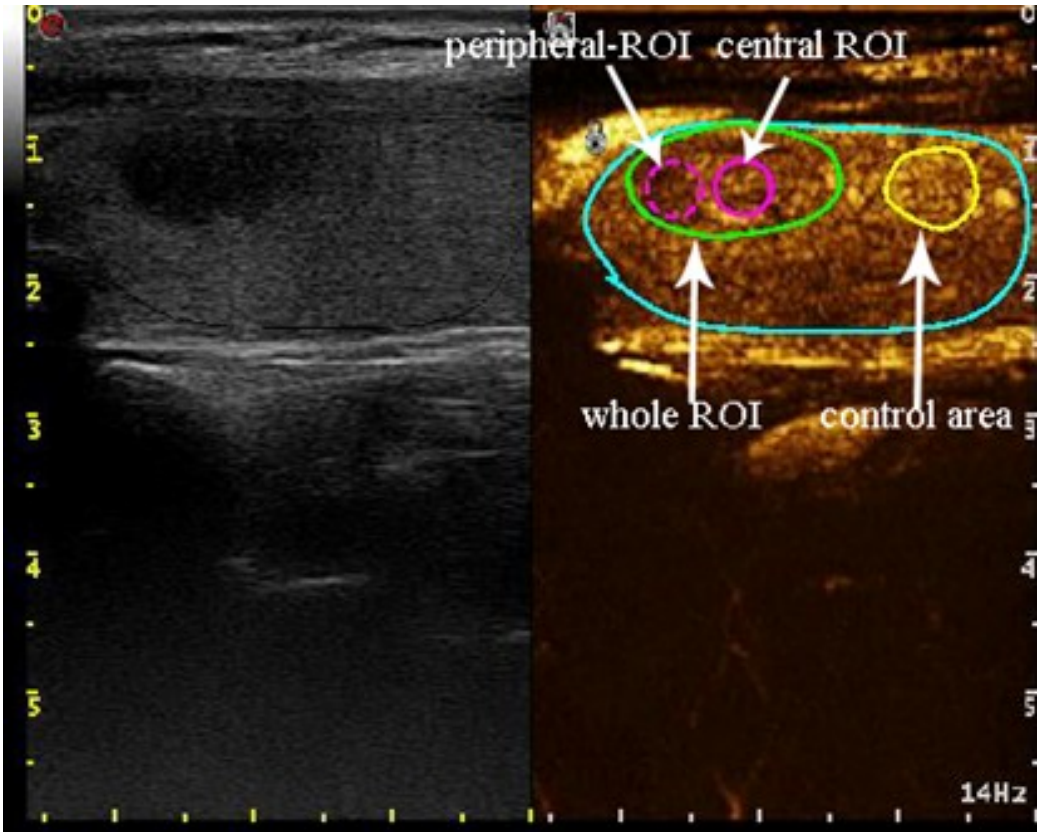


Figure 2

V& VII: We sincerely appreciate your careful comments. As mentioned in the method section the rapid and slow criteria here are relative to the control area, which can reflect to a certain extent the blood supply of the lesion area relative to the surrounding normal tissues.

VI: Rise time is independent of the time origin According to the sonoliver user manual, and this parameter is automatically given by the software.

VIII: As long as we draw the corresponding area of interest on the CEUS video data in sonoliver, these parameters will be automatically given by the software.

Comment 16: Is the accuracy of surgery and fine-needle aspiration similar [as gold standard]? Maybe, the surgery is more accurate. Please explain.

Reply16: Yes, as you said, surgery and subsequent pathology are gold standard for PTC or aSAT diagnosis in clinic. Compared to surgery, FNAB also has better sensitivity and specificity in evaluating thyroid tumors (the sensitivity of FNA was 73.53% and specificity of 100%) (*Servilla M, et.al, BolAsoc Med P R. 2016*). FNAB can also be used as the gold standard and can basically replace surgical pathology.

Comment 17: In the statistical method section, please answer these questions: I-for continuous variables with normal distribution, we can use t test [independent or paired, depending to the type of analysis] but the authors mentioned they used Mann Whitney that is reserved for the ordinal data or continuous data without normality. Please explain in this regard. I think for the continuous variables, the authors should check the normality at the first time. If the data are normally

distributed, they can use parametric tests [instead of non-parametric tests].
II-the authors mentioned: “chi-square test of independence” that is unclear.
III-why the authors did compare the TIRADS scores between aSAT and PTC with two way ANOVA? It seems wrong.
IV-most of AUCs are not enough good. Please add the P values of each ROC to the table 4.
V-one possible assessment could be the comparison between peripheral and central parts of each nodule for “Δ” vriables. [for example, the authors could calculate ΔRT4=RT of the peripheral ROI− RT of the central ROI]. It would be interesting if the authors evaluate the goodness of these variables for differentiation. [ΔRT, ΔTTP, ΔmTT]

Reply17:

I: Thanks for your careful question. We apologize for the mistake in the article. Before we conduct statistical analysis, we usually perform normal distribution test on the data such as K-S test… But in our study, a little part of the data distribution between groups is not normality. Therefore, in order to maintain statistical rigor, we apply both parametric test and non-parametric test in the statistical analysis. And we made corresponding corrections in the original text.

II: We apologize for the mistake in the article. We have made corrections in corresponding positions.

III: In the TIRADS score analysis, comparison between groups covers two factors: **Group** (aSAT and PTC) and **Ti-RADS** (4a, 4b, and 5). Therefore, we used two-way ANOVA analysis to compare the model of the two-factors (Group and Ti-RADS) combine with three types (4a, 4b, and 5).

IV: In Table 4, we have already shown the p-values compared between all the parameters’ AUC.
Since p-value’s acquired from “A vs B” is equivalent to acquire from “B vs A”, Therefore, in the form of the table, we only show the positive triangle to avoid redundancy.

V: Thanks for your advice. In our current study, our aim is to observe and explore the difference in hemodynamics between target diseased nodules and normal thyroid tissue. Therefore, we did not explore the difference in hemodynamics between the central part and the surrounding part of the diseased nodule itself. However, the exploration of nodules in the lesion itself may also provide more information, so we will continue to explore in future research.

Comment 18: The study is a diagnostic test study, so it should be written as STARD guideline.

Reply18: We are sorry that we don’t know much about the STARD guidelines. After careful research based on your suggestions, we believe that diagnostic test research should be conducted strictly in accordance with the STARD guidelines. However, due to our small sample size and retrospective research, it is currently difficult to strictly follow the STARD guidelines for design. Thank you for your careful guidance. If we conduct similar studies in the future, we must strictly follow the STARD guidelines. Special thanks to you for your good comments.

Responses to the Reviewer 2:

Comment: I think the article is a good structured study, it can be published in IJR.

Reply: Thank you for your affirmation of our research, we will work harder in the future.

Responses to the Reviewer 3:

Comment1: English literature should be completely revised.

Reply 1: Thank you for your reminder. We have completely revised the English literature as required by the journal.

Comment2: Patients underwent CEUS after pathology result or before that and if that took place after pathology result were operators blind to results or not, these items should be clearly write down in method section.

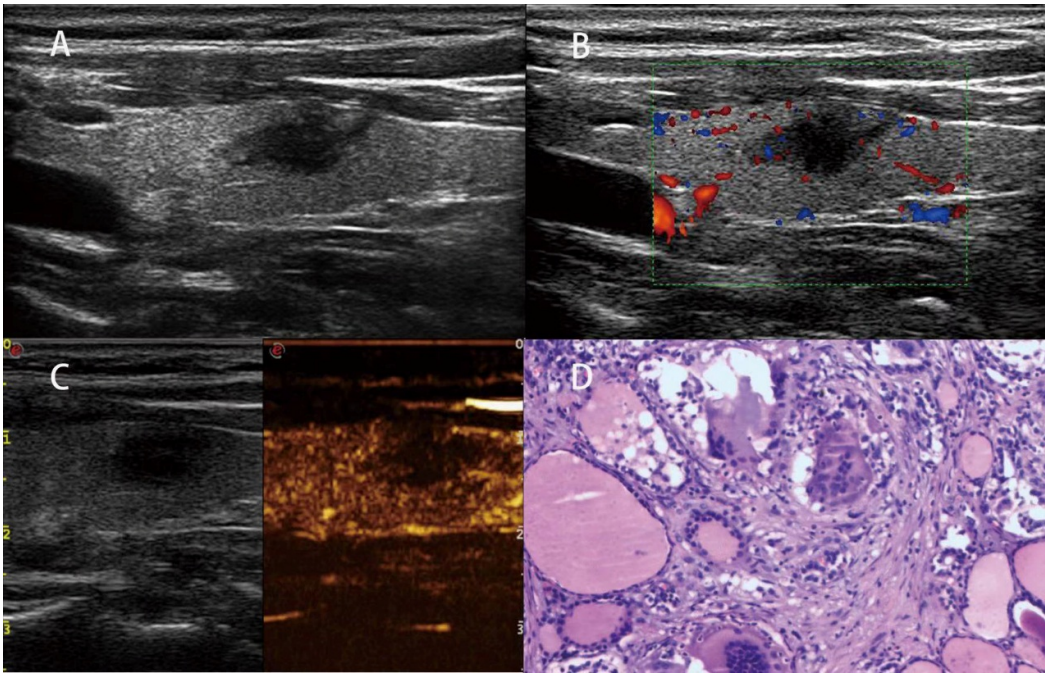
Reply2: Thanks for your advice. We have added relevant content to the method section. Patients who underwent CEUS were all before pathology result.

Comment3: The performed color Doppler exam should be indicated in examination part of the method and images included.

Reply3: Thanks for your advice. We have indicated the implementation conditions for color Doppler inspection in the method section and added corresponding image in the supplementary material.

Comment4: Histology micro-graph must be included.

Reply 4: We have added the histology micro-graphs of PTC and aSAT in the supplementary material (Figure S1, Figure S2).



FigureS1: A, B, C and D are the conventional ultrasound examination two-dimensional image, color Doppler image, CEUS image and Histology micro-graph (HE, ×100) of an aSAT patient in order.

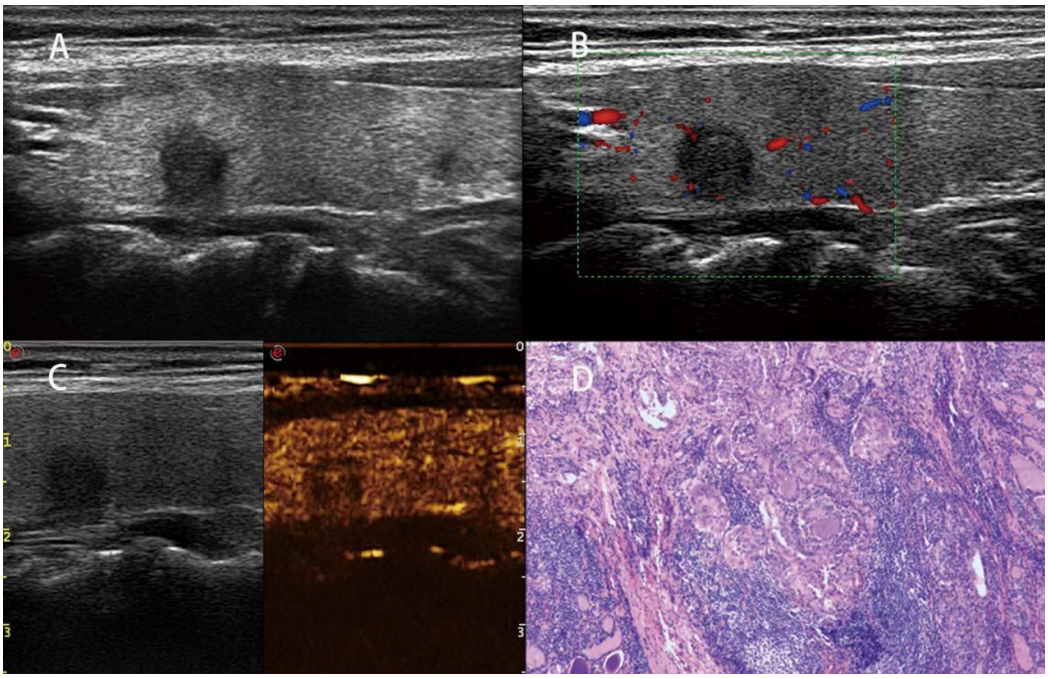


Figure S2: A, B, C and D are the conventional ultrasound examination two-dimensional image, color Doppler image, CEUS image and Histology micro-graph (HE, ×100) of an PTC patient in order.

Comment5: The structure of discussion should be completely revised based on known standards.
Reply5: Thank you for your reminder, we have completely revised the discussion section based on known standards.

Comment6: Pathology results obtained from two different methods one after surgery tissue diagnosis and the other after FNA differ from each other, please discuss the problem.
Reply6: Surgery and subsequent pathology are gold standard for PTC or aSAT diagnosis in clinic. Compared to surgery, FNAB also has better sensitivity and specificity in evaluating thyroid tumors (the sensitivity of FNA was 73.53% and specificity of 100%) (*Servilla M, et.al, BolAsoc Med P R. 2016*). FNAB can also be used as the gold standard in clinical practice and can basically replace surgical pathology.

Responses to the Reviewer 4:

Comment1: Please in inclusion criteria determine is your criteria is a nodule that should be seen in 2 view in ultrasound?
Reply 1: We are very sorry that we did not understand exactly what you mean, in our manuscript, we mean that every nodule can be completely displayed in one single ultrasound view. If a nodule cannot be displayed completely on a single view, complete CEUS information cannot be obtained.

Comment2: Your figure1 are unclear. please describe more about central and peripheral located ROI (that i think in figure both smaller ROI are located peripherally)
Reply2: Thank you for your reminder. It is true that we did not consider comprehensively and did not

clearly indicate every ROI on the image. We have added the corresponding annotations in Figure 2.

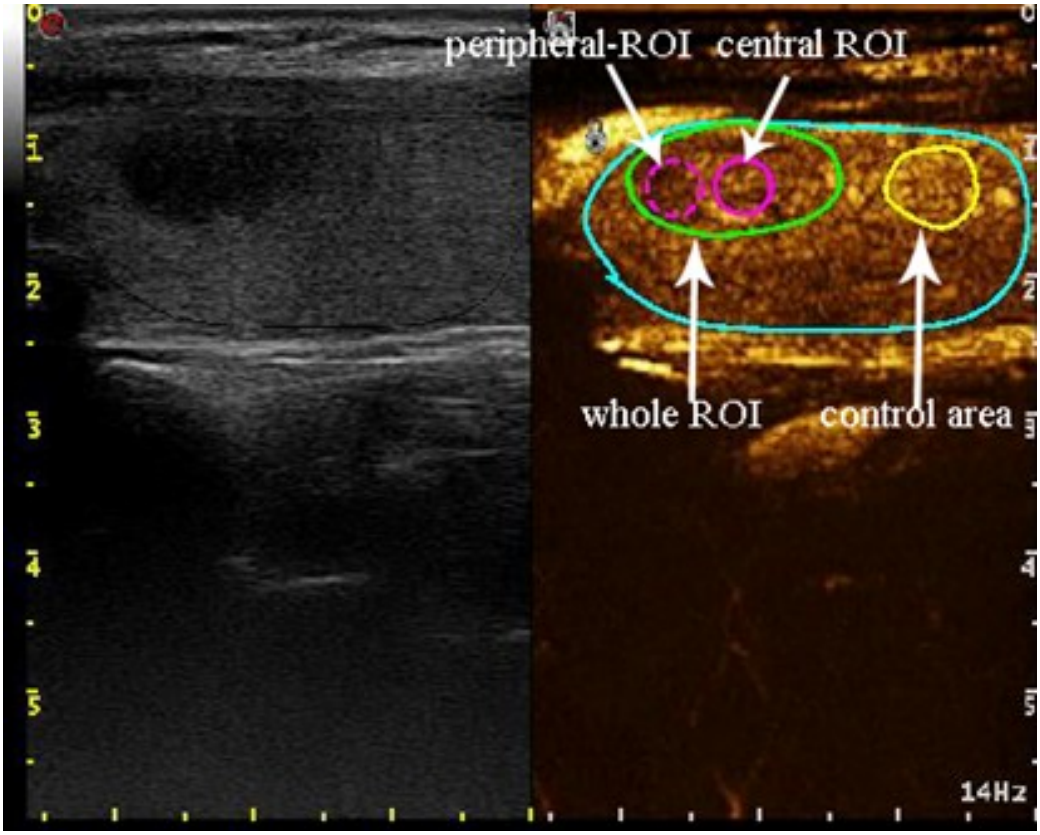


Figure 2

Comment3: Attach more images and describe more about the 4 types time intensity curves, in this manner it is meaningless.

Reply3: Sorry for the trouble with your reading. We have modified Figure 1 in the manuscript according to your requirements, and then made some explanations:

a. The Delimitation ROI (turquoise) outlines the lesion and healthy thyroid parenchyma to be analyzed. As it delimitates the analysis area, you must draw all subsequent regions (reference and parametric) inside the Delimitation ROI. And the turquoise time intensity curve represents the overall time intensity curve of the lesion and healthy thyroid.

b. The Analysis ROI (green) outlines the lesion tissue. It also delimitates the visualization of parametric maps. And the green time intensity curve represents the time intensity curve of the lesion.

c. The Reference ROI (yellow) outlines the healthy parenchyma next to the lesion. And the yellow time intensity curve represents the time intensity curve of the healthy parenchyma next to the lesion.

d. The Parametric ROI (magenta) outlines 2 circular particular areas inside the Delimitation ROI. The solid line is the central ROI, and the dotted line is the peripheral ROI. And the magenta time intensity curve represents the time intensity curve of the 2 circular particular areas inside the Delimitation ROI.

And the following perfusion model curve (Figure 3) can simply explain the relevant parameters.

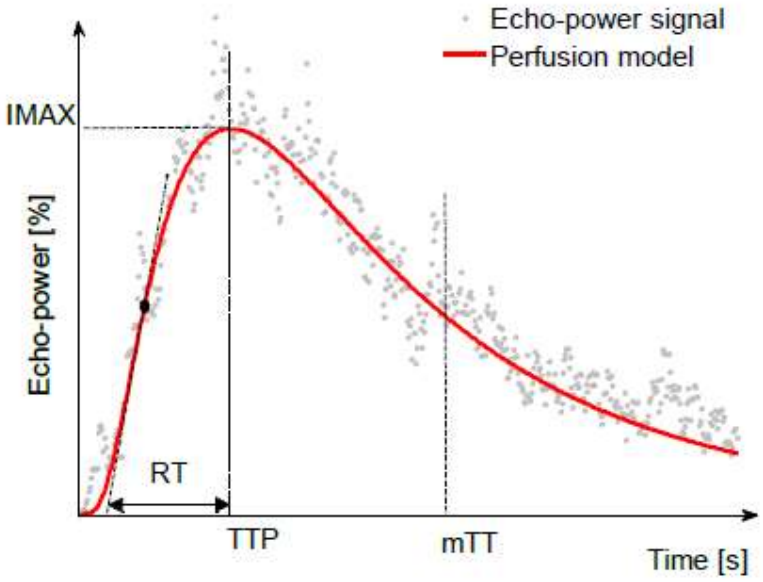

Echo-power signal
Perfusion model
IMAX
Echo-power [%]
RT
TTP
mTT
Time [s]

Figure 3

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 28 Nov 2020

Dear AE,
The corrections are acceptable for publishing the study.
Best Regards

Leila Aghaghazvini: Reviewer | **Revision** (1) 17 Jan 2021

Dear AE,
The article could be accepted.
Only Please add the supplementary diagram about the RT and TTP to the article too.
with best regards

Madjid Shakiba: Reviewer | **Revision** (1) 7 Mar 2021

Dear AE,
Comments for the authors:
1- please add the objective part to the paper before the method section [according to journal format].
2- some points have been mentioned in responses seems to be useful and are better to be added in paper. please add these points mentioned in the responses to the paper appropriately: [questions of reviewer 1] [please add points in the right place of paper in an appropriate writing style]
Reply 5- Routinely, in our hospital, for patients with TIRADS≥4 nodules, CEUS is recommended as a
supplemental examination of conventional ultrasound to avoid unnecessary biopsy or surgery.
Reply 6-The CEUSes of all patients in this study were performed in a unified and standard way
by two experienced doctors, and they all used the same ultrasound machine under the same conditions.
Relevant statements have been described in Materials and methods section.
Reply 8- I: According to the ACR classification, aSAT is indeed usually TIRADS ≥ 4 because they are all hypoechoic and solid, and the boundaries of the nodules are blurred.
II: In clinical practice, almost all PTCs present with TIRADS ≥ 4. As we mentioned in the introduction section, although the pain and inflammatory swelling of the acute phase are

conducive to a differential diagnosis of SAT, but for asymptomatic patients, it is extremely difficult to distinguish from the PTC.

Reply 9-Quantitative CEUS analysis was performed with SonoLiver software version 1.1 (TomTec Imaging Systems, Munich, Germany) which is an internationally recognized software. The software manual indicates that quality of the fit is the normalized distance between the fitted curve and the raw data (echo-power signal). When the degree of fit is less than 75%, the fitted curve is considered not to represent the original curve. Therefore, it cannot represent the true quantitative analysis result, so it needs to be included in the exclusion criteria.

Reply 11- each nodule must save images, and we have unified image preservation specifications including longitudinal and transverse 2D images, nodule size measurement images, Color Doppler images and video data. If the patient has undergone CEUS or FNAB examination, it is also necessary to leave relevant video information for later collation and summary.

Reply 14- No, they are not radiologists. We are sorry for the unclear expression in the manuscript, and we have made corresponding changes. In China, scanning and evaluation are performed by the same person.

Reply 15- please add all relevant and useful points of the response to the paper [I have not paste the points here]. I think all parts [I-VIII] have important points that should be added to the paper properly.

Reply 16- please add relevant explains to the paper appropriately.

3- where is the result of ANOVA analysis in result section?

4- regarding the P value of ROC analysis, I mean the P value for the ROC analysis itself [not the p value for comparing two AUCs]. Each ROC analysis yields a P value showing if the ROC curve have an enough great AUC meaning an efficient differentiating variable under the assessment. Please add p values of ROC analyses itself to the table 4.

5- please add in the discussion the important limitation of the study as the study is retrospective.

6- please add to the paper the points in responses 12 and 13. It is better the authors add the point of reply 12 as a limitation to the discussion too. In addition, the question 13 reply can be addressed in the paper as a limitation too.

Thanks.

Leila Aghaghazvini: Associate Editor | **Revision (1)** 9 Mar 2021

Dear EIC,

The article was reviewed by 3 reviewers and needs some methodological revision and corrections.

With best regards

REFEREE: EIC | **Revision (1)** 9 Mar 2021

Dear authors,

Your article needs Revision.

Regards

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Editor,

Thank you very much for your letter dated 9th March, and the reviewer's helpful comments for our manuscript 107225. Based on the reviewers' comments and requests, we have made extensive modifications to the original manuscript again and would like to re-submit it for your consideration. The amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers' comments are listed below this letter. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. If there are any other modifications we could make, we would like very much to modify them and we really appreciate your help.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Dr. Ting Yue Qi

Responses to the Reviewer 1:

Comment: The article could be accepted. Only please add the supplementary diagram about the RT and TTP to article too.

Reply: Thanks for your advice. We have added the supplementary diagram to our article.

Responses to the Reviewer 2:

Comment 1: please add objective part to the paper before method section [according to journal format].

Reply 1: Thank you for your reminder. We have added the **objective** part to the paper before method section according to journal format in the revised version.

Comment 2: some points has been mentioned in responses seems to be useful and are better to be added in paper. please add these points mentioned in the responses to the paper appropriately: [questions of reviewer 1] [please add points in the right place of paper in an appropriate writing style] Reply 5- Routinely, in our hospital, for patients with TIRADS≥4 nodules, CEUS is recommended as a supplemental examination of conventional ultrasound to avoid unnecessary biopsy or surgery. Reply 6-The CEUSes of all patients in this study were performed in a unified and standard way by two experienced doctors, and they all used the same ultrasound machine under the same conditions.

Relevant statements have been described in Materials and methods section.
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Reply 15- please add all relevant and useful points of the response to the paper [I have not paste the points here]. I think all parts [I-VIII] have important points that should be added to the paper properly.
Reply 16- please add relevant explains to the paper appropriately.
Reply 2: Dear reviewer, sincerely thank you for your careful review, which is particularly helpful to our paper. We have supplemented some of the points we mentioned in our last responses in the appropriate position of the paper according to your suggestions.

Comment 3: where is the result of ANOVA analysis in result section?
Reply 3: Thank you for your careful review. Our **Table 1** contains the F value related to the ANOVA analysis used to compare aSAT and PTC nodules on Ti-RADS grade. We have added the F value of the ANOVA analysis in the results section of the article.

Comment 4: regarding the P value of ROC analysis, I mean the P value for the ROC analysis itself [not p value for comparing two AUCs]. Each ROC analysis yields a P value showing if the ROC curve have an enough great AUC meaning an efficient differentiating variable under the assessment. Please add p values of ROC analyses itself to the table 4.
Reply 4: We feel great thanks for your professional review work. We have added *p* values of ROC analyses itself to the **Table 4**.

Comment 5: please add in discussion the important limitation of the study as the study is retrospective.
Comment 6: please add to the paper the points in the responses 12 and 13. It is better the authors add the point of reply 12 as a limitation to the discussion too. In addition, the question 13 reply can be addressed in the paper as a limitation too.

Reply 5&6: Thank you for your carefully comments. Based on your suggestions, we have made

extensive modifications of limitations in the discussion section.

Responses to the Reviewer 3:

Comment: The corrections are acceptable for publishing the study.

Reply: Thanks reviewer for good comments and hard work.

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (2) — 3 Jun 2021

Dear AE,
The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.
Thanks

REFEREE: Associate Editor | **Revision** (2) — 12 Jun 2021

Dear EIC,
The article can be accepted.
with best regards

REFEREE: Reviewer | **Revision** (2) — 30 Jun 2021

Dear AE,
The authors should explicit abbreviation words In the legend of Figure 1.
Thanks.

REFEREE: Associate Editor | **Revision** (2) — 8 Aug 2021

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

REFEREE: EIC | **Revision** (2) — 9 Aug 2021

Dear authors,
Your article needs Minor Revision.
Regards

OPEN PEER REVIEW

Revision (3)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Editor,

Thank you very much for your letter dated 9th August, and the reviewer's and editor's helpful comments for our manuscript 107225. Based on the comments and requests, we have made extensive modifications to the original manuscript again and would like to re-submit it for your consideration. The amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewer's and editor's comments are listed below this letter. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. If there are any other modifications we could make, we would like very much to modify them and we really appreciate your help.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Dr. Ting Yue Qi

Responses to the Reviewer 2:

Comment: Please explicit abbreviation words In the legend of Figure 1.

Reply: Thank you for your reminder, we have added abbreviation words to the legend of Figure 1 in the revised version.

Responses to the Associate Editor 2:

Comment 1: i think this sentence in abstract could be improved: "Receiver operating characteristic(ROC) curve analysis was used to compare the sensitivity and specificity of each difference variable." We can write the sentence as: "Receiver operating characteristic(ROC) curve analysis was used to assess diagnostic efficacy [and its indices including sensitivity and specificity] for each variable in discriminating aSAT from PTC nodules."

Reply 1: Thank you for this thoughtful suggestion, we have made corresponding changes in the Abstract section in the revised version.

Comment 2: following sentence is somehow unclear: "Although the pain and inflammatory swelling of the acute phase are conducive to a differential diagnosis of SAT, hypoechoic and solid characteristics

manifest (assessed as higher than or equal to Thyroid Imaging Reporting and Data System class IV [TI-RADS IV]) as symptoms subside" I recommend the authors rephrase it.

Reply 2: Thank you for your suggestion. We have rephrased the corresponding sentence in the first section of the Background part of the article in the revised version.

Comment 3: please change materials and methods to patients and method

Reply 3: Thank you for your careful review. Changes have been made as required in the revised version.

Comment 4: it is better the authors add numbers to subtitles such as: 3-1. Subjects, …..

Reply 4: Thank you again for your suggestion. Changes have been made as required in the revised version.

Comment 5: please correct: "all scans and evaluation" to: "all scans and evaluations"

Reply 5: Thank you for your careful review. Corrections have been made as required in the revised version.

Comment 6: in the figure 3 and 4 legends, the authors mentioned TIRADS 6 and 7; are they correct?

Reply 6: We apologize for the mistakes in the original article, thank you very much for your careful review, and we have corrected the mistakes in the figure 3 and 4 legends according to the American College of Radiology (ACR) point system.

Comment 7: Please add abbreviation words In the legend of Figure 1.

Reply 7: Thank you for your reminder, we have added abbreviation words to the legend of Figure 1.

OPEN PEER REVIEW

Revision (3)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (3) 15 Aug 2021

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards

REFEREE: EIC | **Revision** (3) 15 Aug 2021

Dear authors,
Your article is acceptable for the publication in IJR.
Regards