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OPEN PEER REVIEW

Thickness of the Hyperechoic Capsule-like Rim Around Pancreatic Lesions Measured by Ultrasound for Differentiating Between Type 1 Autoimmune Pancreatitis and Pancreatic Adenocarcinoma

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

4 comments · 25 Jun 2023 – 3 Jul 2023

Referee 1 Reviewer

MINOR REVISION 25 Jun 2023

Thanks to the authors for considering IJR for their submission.
I read this manuscript and can say that it is relatively appropriate in terms of study design and scientific writing structure; however, the following points need to be considered:
1. Title: It should be written as "Thickness of Capsule-like Hyperecho around Lesions Diagnostic Value for Differential Diagnosis between Type 1 Autoimmune Pancreatitis and Pancreatic Adenocarcinoma"
A. Abstract:
2. Abstract methods:
2.1. The study has a case-control design, with AIP1 cases and PAC controls. This sentence should be added as the first sentence of the abstract methods.
2.2. Inclusion and exclusion criteria for each group should be added.
2.3. What is meant by retrospective measurement and identification? It should be specified: The capsule-like hyperecho around lesions was identified and measured retrospectively.
2.4. A statement that independent variables and outcome(s) were compared between groups should be added.
2.5. Statistical tests and the significance level should be written as the last sentence.
3. Abstract Results:
3.1. First, the means/percentages of important demographic and clinical characteristics of each group should be presented in parentheses along with p-values.
3.2. All values, such as those for mass lesions, should be reported for the case and control groups; moreover, it should be clarified what each value represents: number, count, mean, etc.
3.3. These indices should be reported: cutoff value, sensitivity, specificity, and positive and negative predictive values, along with 95% confidence intervals.
4. According to the sensitivity and positive predictive values in tables 2 and 3, capsule-like hyperecho with a thickness ≥ 0.41 cm has a weak to moderate diagnostic value. Therefore, the conclusion should be edited and written conservatively.
B. Full-Text:
5. 5. Objective: Sentences should be written in the passive voice.
6. Methods
6.1. Patients: Sampling methods, sample size calculation assumptions, and the formula should be added.
6.2. Inclusion and exclusion criteria for each group should be added.
6.3. An ethical considerations section and the ethical approval code should be added.
6.4. Statistical analysis: The first sentence should be edited as follows: For descriptive analysis, numbers and percentages were used for qualitative variables such as..., and means and standard deviations were used for quantitative variables such as ... .
6.5. Statistical analysis: In the second and third sentences, use case and control groups rather than between groups.
7. Results: The area under the ROC curve, sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and odds ratio, along with 95% CIs, should be added to tables 2 & 3.

Referee 2 Reviewer

MAJOR REVISION 2 Jul 2023

Thank you for submitting your manuscript to the Iranian Journal of Radiology.
The main goal of this study was to assess the role of ultrasound examination in the differentiation of autoimmune pancreatitis (AIP) from pancreatic ductal carcinoma (PDA). This study was conducted on 19 patients diagnosed with AIP and 37 patients diagnosed with PDA. Ultrasound images were reviewed retrospectively by one radiologist. After analysis, the authors concluded that the hyperechoic capsule-like rim was thicker in lesions confirmed as AIP by histopathologic examination than in PDA lesions.
Firstly, I would like to say that the main idea of the study is interesting; however, there are major drawbacks in this manuscript as follows:

1. The abstract should be written again. It has major English grammar errors such as 'differential diagnosis between them' or 'showed a significant increasing in the probability'.
2. Most of the time, it is difficult to differentiate between focal mass-like AIP and PDA. Therefore, I would recommend focusing on focal AIP in the manuscript rather than the diffuse type, which is often not so hard to diagnose.
3. The only reference that is related to this study is reference number 14, which is about contrast-enhanced endoscopic US (CE-EUS) in patients with AIP, and it didn't mention anything about the hyperechoic rim of the lesions. More references with related topics are needed. In addition, there is a study by Hoki et al. (Hoki, N.; Mizuno, N.; Sawaki, A.; Tajika, M.; Takayama, R.; Shimizu, Y.; Bhatia, V.; Yamao, K. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. J. Gastroenterol. 2009, 44, 154–159.) which stated that the hypoechoic rim is a feature of focal AIP.
4. The figures are a little vague. Focal lesions of the pancreas are not well visualized. Use better images if available.

Associate Editor

MAJOR REVISION 3 Jul 2023

The manuscript was studied by three expert reviewers and by me. I agree with the reviewers that it can be reconsidered after the suggested revisions. Please:

1- Have the manuscript edited by a professional English editor to restructure and reorganize it and make it more understandable for the reader.

2- I would suggest the following title with minor changes:
"Thickness of capsule-like hyperechoic rim around pancreas for differentiation between Type 1 Autoimmune Pancreatitis and Pancreatic Adenocarcinoma"

Editor-in-Chief

MAJOR REVISION 3 Jul 2023

Dear authors,
Your article needs Major Revision.
Regards

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor and Reviewers,

Thanks very much for taking your time to review this manuscript. I really appreciate all your comments and suggestions! Please find my itemized responses in below and my revisions/corrections in the re-submitted file.

Suggestions From Associate Editor:

1. **Edit the manuscript by a professional English editor to restructure and reorganize it and be more understandable for the reader.**

Response: All authors restructured the manuscript's content and had it reviewed by a professional English writer. Please refer to the re-submitted file for more information on the changes.

2. **I would suggest the following title with minor changes:**

"Thickness of capsule-like hyperechoic rim around pancreas for differentiation between Type 1 Autoimmune Pancreatitis and Pancreatic Adenocarcinoma"

Response: All authors agree that this title accurately captures the entire article and is more concise and understandable than the title we previously proposed, so we decided to use it.

Suggestions From Reviewers:

Reviewer 1:

Response to comment 1: The abstract was revised, and grammar issues were rectified. Please refer to the re-submitted file for more information.

Response to comment 2: This suggestion is highly practical, and we emphasized it in the re-submitted manuscript and added some pertinent content.

Response to comment 3: We added some references related to the topic, and discussed the discrepancy between our findings and those of others. Some studies have claimed that the peripancreatic hypoechoic margin is a characteristic of AIP, which seems to conflict with our findings. The peripancreatic hypoechoic margin, in reality, refers to

the hypoechoic zone between enlarged parenchyma and the well-defined hyperechoic capsule. This sign was so difficult to detect at ultrasonography that it was only found in three AIP1s (15.79%) in our study, which was consistent with the findings of Hoki et al. The well-defined hyperechoic capsule, on the other hand, existed in all cases in this study, which was more universal, and we were concerned about this feature. We compared the thickness of the low-attenuation halo on CT with the peripancreatic hypoechoic margin and the hyperechoic capsule at US, and found that the thickness of the low-attenuation halo on CT was very close to that of the hyperechoic capsule, but differed from that of the peripancreatic hypoechoic margin. Therefore, we believe that the capsule-like hyperechoic rim around pancreas is a more meaningful sign.

Response to comment 4: Unfortunately, autoimmune pancreatitis is rare in our institute. We selected images that are relatively clear, although they are still a little vague. Several ultrasound images were compressed during processing, resulting in a little loss of clarity. We found the original images from our institute's database and replaced them.

Reviewer 2:

Response to comment: The manuscript was revised, and grammar problems were rectified. Limitation number 1 is really an essential problem, but unfortunately, because this is a retrospective study, it is inevitable. In the "Methods" of the manuscript, there is an error in the description of the measuring process. Indeed, we also recognized the significance of precise measurement in the study. Therefore, two doctors with ten-year experience of US examination collaborated on the measuring work to make the results credible. They measured independently and then compared the results. If the part they measured was consistent and the difference was less than 0.05cm, the average value was recorded. Otherwise, they discussed and agreed on the final outcome. The work of defining was also completed by these two doctors together in order to make the

definition as accurate as possible.

Reviewer 3:

Response to comment 1:

The title we previously proposed is really not accurate enough. It has been altered after all authors considered your and the editor's suggestions.

Response to comment 2:

2.1. This sentence clarifies the nature of research and has been added to the re-submitted manuscript.

2.2. We omitted inclusion and exclusion criteria in the initial manuscript, which were added in the re-submitted text. The details are as follows:

Inclusion criteria were: 1) patients diagnosed with AIP1 in accordance with the ICDC criteria; 2) PAC patients who had available histopathologic results. Exclusion criteria were: 1) PAC patients without surgery; 2) patients with multiple site tumors; 3) patients with gastrointestinal perforation, cholecystitis, or bowel blockage; 4) patients who did not have an ultrasound examination or whose image quality was poor.

2.3. The measuring process has been added to the abstract, and it has been specified that this work was conducted retrospectively.

2.4. Independent variable and outcome compared between groups have been added.

2.5. Statistical tests and significant level have been written as last sentence.

Response to comment 3:

3.1. Mean/percentage of important demographical and clinical characteristics of each group in the parenthesis along with p-value have been added to the abstract.

3.2. All values have been written according to case and control group , and the meaning of all values has been clarified.

3.3. Important indicators such as the cut off value have been added.

Response to comment 4:

We revised the conclusion and wrote it in a more conservative style.

Response to comment 5:

The "Objectives" part has been written in passive voice.

Response to comment 6:

6.1. The sample size calculation process and sampling method have been added.

6.2. Inclusion and exclusion criteria have been added.

6.3. Ethical considerations section and ethical approval code have been added.

6.4. & 6.5. The sentences in "Statistical Analysis" have been revised.

Response to comment 7:

These data have been added to Tables 2 & 3.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the purport of the paper. And here we did not list the changes but marked them in yellow fluorescence in the revised paper.

We appreciate the Editor’s and Reviewers’ earnest work and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Yun-Fei Zhang

2 Revision 1

4 comments · 12 Sep 2023 – 26 Sep 2023

Referee 1 Reviewer

MINOR REVISION 12 Sep 2023

Currently, the manuscript has been extensively revised and its quality has improved. However, the following points still need to be considered and the following corrections incorporated.
1. The results in the abstract should be summarized and edited in this manner: "Results: All lesions appeared hypoechoic, and there were no significant differences in gender, age, abdominal pain symptoms, jaundice, or weight loss between the case and control groups ($p > 0.05$). However, there was a significant difference in the pancreatic location involved ($p < 0.05$). Among the lesions, 46 were mass lesions, and the capsule-like hyperechoic rim was thicker in the case group compared to the control group for both all lesions (mean 0.40 ± 0.12 vs. 0.32 ± 0.09 cm, $p = 0.006$) and mass lesions (mean 0.40 ± 0.12 vs. 0.32 ± 0.09 cm, $p = 0.006$). The ROC curve analysis suggested a thickness cut-off level of 0.41 cm for AIP1 in both all lesions and mass lesions. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and odds ratio (OR) for all lesions were 0.58, 0.86, 0.69, 0.80, and 8.80 (95% CI, 2.37–32.64), respectively. In mass lesions, the corresponding values were 0.58, 0.88, 0.64, 0.86, and 10.50 (95% CI, 2.23–49.52)."
2. The abstract conclusion can be edited as follows: "Conclusions: Patients with a capsule-like hyperechoic rim thickness of ≥ 0.41 cm during ultrasonography are more likely to have AIP1. This finding holds valuable clinical significance in differentiating between AIP1 and PAC."
3. The limitations section should contain: 1) Retrospective design: The study relied on images obtained from a workstation rather than direct measurements on the ultrasound machine, which may introduce measurement inaccuracies. 2) Limited sample size: The study may have had a small sample size, which could affect the generalizability of the findings. 3) Classification of lesions: Due to the difficulty in differentiating masses, some lesions were classified as local lesions despite changes observed in follow-up imaging. 4) Exclusion of type 2 AIP: The study only included type 1 AIP cases, potentially limiting the generalizability of the findings to other types of AIP.
4. The full-text conclusion should be edited as: "In conclusion, the presence of a capsule-like hyperechoic rim with a thickness of ≥ 0.41 cm on ultrasonography indicates a higher likelihood of autoimmune pancreatitis type 1 (AIP1) compared to pancreatic adenocarcinoma (PAC). This finding provides valuable information for differentiating between AIP1 and PAC. However, further studies with larger sample sizes and including different types of AIP are needed to validate these results and improve diagnostic accuracy in clinical practice."
5. The complete expansions of all abbreviations need to be provided below the tables.
6. The indices presented in Tables 2 and 3 should include 95% confidence intervals.

Referee 3 Reviewer

ACCEPT 22 Sep 2023

I have received the manuscript entitled (Thickness of Capsule-like Hyperecho around Lesions for Differential Diagnosis between Type 1 Autoimmune Pancreatitis and Pancreatic Adenocarcinoma;) Revision 1:

All of my suggestions have been adequately addressed and acceptably responded to.
I have no further comments to make.

Associate Editor MINOR REVISION 25 Sep 2023

Some concerns raised by one of the reviewers still need to be addressed and corrected.

Editor-in-Chief MINOR REVISION 26 Sep 2023

Dear authors,
Your article needs Minor Revision.
Regards

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor and Reviewers,

Thanks very much for your review! Your suggestions have enabled us to improve our work. Please find my itemized responses in below and my revisions/corrections in the re-submitted file.

Suggestions From Reviewer 1:

Response to comment 1-4: Thank you very much for your careful review. It is not difficult to see that you thoroughly read and revised our article. Your opinions are really pertinent, and your language is succinct and idiomatic. We unanimously agreed to adopt your suggestions and make modifications to the article.

Response to comment 5: The complete expansions of all abbreviations have been provided bellow the tables and figures.

Response to comment 6: The 95% confidence intervals for each index in Tables 2 and 3 have been added.

We have made every effort to improve the manuscript in response to the reviewer's comments, and we hope that this work will be published in the journal.

Thank you once again for your careful work!

Yours sincerely,

Yun-Fei Zhang

3 Revision 2

3 comments · 21 Oct 2023 – 29 Oct 2023

Associate Editor

ACCEPT 21 Oct 2023

Suggested corrections and modifications have been made, and there is no further comment.

Associate Editor

ACCEPT 21 Oct 2023

Dear EIC
I am pleased to inform you that the revised version of the manuscript titled "Thickness of capsule-like hyperechoic rim around pancreas for differentiation between Type 1 Autoimmune Pancreatitis and Pancreatic Adenocarcinoma" is now suitable for publication in the IJR. The authors have effectively addressed the suggestions and comments provided by the reviewers, resulting in significant improvements to the manuscript's quality.

Editor-in-Chief

MINOR REVISION 29 Oct 2023

Dear authors,
Your article needs Minor Revision.
Regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editors and Reviewer,

Thanks very much for your review! Based on your suggestions, we have made further improvements to the manuscript. Please find my itemized responses in below and my revisions/corrections in the re-submitted file.

Suggestions From Associate Editor 3:

Response to comment 0:

All authors agreed with your opinion that the new title is more accurate than what we previously proposed, and the title in the resubmitted manuscript has been revised.

Response to comment 1:

The objective of abstract has been modified.

Response to comment 2:

All “Methods” titles have been changed to “Patients and Methods”.

Response to comment 3:

Thank you so much for your suggestion! The language in this part is not standardized and is too colloquial. The modifications have been made in accordance with the instructions provided in the PASS 2021 software.

Response to comment 4:

Numbers for sub-titles have been added.

Response to comment 5:

The “applied” in line 111 has been changed to “calculated”.

Response to comment 6:

In line 113, this sentence has been modified according to your suggestion.

Response to comment 7 & 9:

Because the full term of OR is mentioned in line 80, this part of line 119 has not been modified, and full terms of other abbreviations have been added.

Response to comment 8:

This sentence has been corrected.

Response to comment 10:

Manufacturer data of SPSS has been added.

Response to comment 11 & 14:

Your opinion is very relevant! Based on your suggestion, we have proposed new subtitles.

Response to comment 12:

Thank you for your help! Our language proficiency is insufficient, and our expression is somewhat confusing. This section has been modified according to your suggestion.

Response to comment 13:

Line 136 has been modified.

Response to comment 15:

Thank you again for your careful review! This is an error. What we want to express is that the AUC is 0.71, and when the cut-off value is 0.41, the Youden index reaches its maximum. This part has been modified.

Response to comment 16:

We have added some content to Discussion to explain that compared to other lesions, AIP and PAC presenting as mass lesions are more difficult to distinguish.

Response to comment 17:

The footnote of Table 1 has been modified.

Response to comment 18:

The display of AUC in Table 2 is indeed inappropriate, and this parameter has been removed.

Response to comment 19:

OR in Table 2 has been deleted.

Response to comment 20:

Table 3 has also been modified similarly to Table 2.

We have made every effort to improve the manuscript in response to the editor's comments, and we hope that this work will be published in the journal.

Thank you once again for your careful work!

Yours sincerely,

Y.-F.Zh.

4 Revision 3

1 comment · 20 Nov 2023

Editor-in-Chief

ACCEPT 20 Nov 2023

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