Iranian Journal of Radiology
Volume 20 · Issue 1 · e129454

OPEN PEER REVIEW

Efficacy of Virtual Touch Quantification Technique for Differentiating Patients with Immunoglobulin A Nephropathy (IgAN) from Healthy Controls

Dan Zhang, Ruixing Liu, Beibei Yu, Maosheng Xu, Chunpeng Zou

SUBMITTED	REVISED	ACCEPTED	DOI
1 Jul 2022	14 Jan 2023	17 Jan 2023	10.5812/iranjradiol-129454

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.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Editor-in-Chief 2
2 **Revision 1** Referee 1, Referee 2, Associate Editor, Editor-in-Chief 3
Authors' reply to reviewers 4
Reviewer and editor comments 5
3 **Revision 2** Referee 1, Referee 2, Referee 3, Associate Editor, Editor-in-Chief 8
Authors' reply to reviewers 9
Reviewer and editor comments 18
4 **Revision 3** Associate Editor, Editor-in-Chief 20
Authors' reply to reviewers 21
Reviewer and editor comments 23
5 **Revision 4** Editor-in-Chief 24
Authors' reply to reviewers 25
Reviewer and editor comments 28

1 Original submission

1 comment · 2 Jul 2022

Editor-in-Chief

MINOR REVISION 2 Jul 2022

Dear authors,
Before starting the review process for your article, it is necessary to clarify the following items:

Please mention the ethics code and provide the link. If the web address (link) for the ethics committee approval is not available, please upload the official ethics committee approval document.
Please clarify the funding source and mention the grant number with the link, or upload the official approval document containing the grant number.
Regarding the importance of “conflict of interest” clarification, the corresponding author should fill out the “ICMJE form” and upload it during the submission process. (The form is available in the “conflict of interest” section of the site:
https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).
Regards

2

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.

EIC Decision:

Dear authors,

Before starting the review processing of your article, it is necessary to clarify the following items:

Please mention the ethical code with the link address. If the web address (link) of ethical committee approval is not available, please upload the official approval document ethics committee.

Re: Thank you very much for reminding. We uploaded the ethics committee approval document.

Please clarify the financial resource and mention the grant number with the link address or upload the official approval grant number.

Re: Thanks. The financial resource has been declared at the end of the manuscript with the approval grant number.

Regarding the importance of "conflict of interest" clarification, the corresponding author should fill out the "ICMJE form" form and upload in the submission process. (The form exists in "conflict of interest" section of the site: https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).

Regards

Re: Thanks. I have completed and uploaded the ICMJE form.

2 Revision 1

4 comments · 20 Jul 2022 – 13 Aug 2022

Referee 1 Reviewer

MAJOR REVISION 20 Jul 2022

First of all, thanks to the authors for their submission to the IJR.
Although there are some similar studies on this topic, this manuscript can be useful for further clarifying the diagnostic value of ARFI-VTQ in screening for IgA nephropathy (IgAN).
Generally, the following points must be revised:
1. The scientific writing structure of the manuscript, especially in the method and results sections.
2. English grammar and spelling.
3. The study design is case-control. Therefore, the terms case and control must be used throughout the text rather than other terms.
4. The inclusion and exclusion criteria and sampling methods for each case and control group must be clearly described.
5. In the results section of the abstract, when a variable's value is compared between two groups, the number and p-value must be presented in parentheses.
6. The objective in the full text states that "The purpose of this study was to explore the difference in routine ultrasound parameters and VTQ values between IgAN observation group and normal control group", but in the results section, the comparison was made only for VTQ.
7. The manuscript must be rewritten according to the ATARD guideline, using a similar paper entitled "Acoustic Radiation Force Impulse Imaging for Non-Invasive Assessment of Renal Histopathology in Chronic Kidney Disease" as a template.
8. In the statistical analysis, it must first be clearly stated which test was used for which variable(s). Moreover, one-way ANOWA must be deleted because the outcome here is binary, so ANOWA cannot be used. Also, rather than linear regression, the Pearson correlation coefficient must be used first; then, a multivariate linear regression must be run using all variables that have a p-value less than 0.1 in the univariate analysis (tables 1 &2). Finally, all significant variables from the multivariate regression can be combined into one variable and used in ROC analysis, labeled as the linear regression model.
9. All abbreviations must be defined below the tables.
10. The reporting style of table 2 is incorrect and vague.
11. ROC analysis results must also be reported in a table, along with sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals.
12. The sample size of the study is small, and this must be added as a limitation of the study.
13. The positive predictive value (PPV) of a screening test is a very important index, and it is greatly affected by the prevalence of the intended outcome. For example, if the prevalence of the outcome is 5% or 30%, the PPV becomes 25% and 73%, respectively, using your study's sensitivity (83%) and specificity (87%) values. Therefore, this point must be considered in the conclusion of the study.

Referee 2 Reviewer

MAJOR REVISION 11 Aug 2022

1-The results section of the abstract does not include numerical data. It would be better for the authors to add some numerical data to the abstract.
2-What is the meaning of Depside in the paper? [despite]
3-Please write the paper according to the latest STARD guideline.
4-What is the meaning of “renal calcium deposition wait”?

5-The authors mentioned: “At least 6 valid measurements were collected from each subject, and the average value was taken for statistical analysis.” Which US measurements did the authors repeat 6 times? All conventional US and ARFI-VTQ measurements? Please clarify.
6-How many radiologists performed the measurements, and what was their reliability? [inter-rater and intra-rater reliability]
7-Did the authors check the normality of the data before choosing the statistical tests? Please mention this in the analysis section.
8-Please complete the manufacturer information for SPSS based on the IBM website.
9-Please add the full terms for the abbreviations in the table footnotes.
10-Please follow the journal format for references; for example, journal names should be abbreviated.
11-The authors mentioned in the results: “Furthermore, the histological grading of patients with IgAN was predicted according to H. S. Lee's glomerular grading system [13].” This sentence seems to be appropriate for the discussion and does not belong in the results section. It is not a finding of the current study.
12-It is not clear whether the data in table 2 were obtained using univariate regressions or multivariate regression. Please clarify.
13-Did the authors perform VTQ measurements at the same kidney locations as the Doppler and conventional sonography measurements?
14-Does “VTQ value (m/s)” in table 1 mean ARFI-VTQ measurements?
15-It would be better for the authors to add the 95% CI for the AUC and diagnostic indices [sensitivity and specificity].
16-Please add data on other diagnostic indices to the paper, including PPV, NPV, PLR and NLR.
17-How did the authors choose the cutoff point on the VTQ ROC curve? Did they use the Youden index? Please explain.
18-Please add the cutoff value for the ROC curve to the paper.
19-Based on the ROC curve, it is evident that there are two cutoff points at which the sensitivity or specificity is 1. [At one, the sensitivity is 1, and at the other, the specificity is 1.] It would be very useful if the authors added the data and values for these cutoff points and the diagnostic indices of the curve at these points. [The values of the cutoff points are required too.]
20-What is the diagnostic efficacy of conventional and Doppler US assessments in differentiating IgAN from controls? We should compare the diagnostic performance of VTQ with conventional US and Doppler US to see whether VTQ sonography is better.
21-In a diagnostic test study, the best study design is to recruit subjects clinically suspected of having the disease and then perform the test and the gold standard. Some authors enroll known patients as disease-positive subjects and healthy controls as disease-negative subjects. This study design is not good, as it can falsely increase the diagnostic efficacy and indices [as the disease-positive and disease-negative subjects are selected from two ends of the disease spectrum]. In the current study, the authors have enrolled subjects in this way, and this is a selection fault that can falsely increase the ROC and indices. It would be better for the authors to perform their study using this design. If they cannot change the study, please discuss this in the paper and mention this point as a major limitation.
22-In the discussion, please add the results of similar studies and compare the current study's findings with them. In addition, adding studies on other types of glomerulopathies seems good.
23-Please mention the setting in which healthy controls were selected. How did the authors select the controls? From which clinic or population did the authors select the controls? Did they have any kidney problems? Please explain.
24-Were the patients receiving treatment or not? What was the duration of their disease?

Associate Editor

MAJOR REVISION 13 Aug 2022

Major Revision

Editor-in-Chief

MAJOR REVISION 13 Aug 2022

Dear authors,
Your article needs Major Revision.
Regards

3

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,

Please find our manuscript “Application of Virtual Touch Tissue Quantification Technique in diagnosis of IgA Nephropathy”.

Thank you very much for giving us an opportunity to revise our manuscript. Thank you for your and the reviewers’ comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made corrections which we hope meet with approval. These changes will not influence the content and framework of the paper. We would like to express our appreciation to you and reviewers for comments on our paper.

Looking forward to hearing from you.

Thank you and best regards.

Chunpeng Zou

> Reviewers' Comments:

Reviewer 1:

First of all, thanks to the authors for their submission to the IJR.

Although there are some similar studies on this topic, but this manuscript can be useful for more clarifying of diagnostic value of ARFI-VTQ in screening IgA nephropathy (IgAN).

Generally, the following point must be revised:

1. Scientific writing structure of manuscript, especially in the method and results sections.

Response: Thank you very much for your reminding. The structure of manuscript was revised.

2. English grammar and spelling.

Response: We apologize for English mistakes, which have been corrected. Thank you for your kind concern.

3. The study design is case-control. Therefor, in all part of text must be used of case and control terms rather others idioms.

Response: Thanks for your valuable suggestion. The improper idioms were revised in this manuscript.

4. Inclusion and exclusion criteria and sampling methods of each case and control group must be clearly written.

Response: Thank you for your professional comment. The inclusion and exclusion criteria were provided in the method.

5. In abstract results section, when a variable value compared between two groups, it must be presented the number and p-value in the parenthesis.

Response: Thanks for your reminding. The number and p-value were added to the abstract results section.

6. In full-text objective mentioned that "The purpose of this study was to explore the difference in routine ultrasound parameters and VTQ values between IgAN observation group and normal control group" but in results section the comparison only made by VTQ.

Response: We apologize for the improper presentation. The sentence has been revised. Thanks for reminding us.

7. The manuscript must be re-write according to ATARD guideline and a

similar paper entitled "Acoustic Radiation Force Impulse Imaging for Non-Invasive Assessment of Renal
Histopathology in Chronic Kidney Disease" as template.

Response: Thank you for your valuable comment. We re-wrote the manuscript according to the STARD guideline and the reference you mentioned.

8. In statistical analysis, firstly it must be clearly written that each test used for what variable(s). Moreover, One way ANOWA must be deleted, because here the outcome is binary, and so it cant used of ANOWA. Also, rather than linear regression, at first must be used of Pearson correlation coefficient; and then run a multivariate linear regression using by all variables that have a p-value less than 0.1 in the univariate analysis (tables 1 &2). Finally, all significant variables of multivariate regression can be merged as one variables and use of it ROC analysis entitled as linear regression model.

Response: Thank you very much for your valuable comments. The statistical method was re-written for clear expression. The ANOVA method was deleted. According to your suggestion, the data in Table 2 were firstly calculated with univariate linear regression and the variables that have a p-value less than 0.1 were further calculated with multivariate linear regression. And the indicators (except Lee grade) of significant difference and VTQ were analyzed with a combined ROC curve.

9. All abbreviations must be described in bellow of tables.

Response: Thank you very much for your comment. The abbreviations used in the tables were described according to your suggestion.

10. The reporting style of table 2 is incorrect and vague.

Response: We are sorry for the improper style of table 2. We revised this table based on your advice.

11. Roc analysis results also must be reported in a table align with sensitivity, specificity, positive and negative predictive values with %95 confidence intervals.

Response: Thank you for your professional comment. The information relative to the ROC results you mentioned had been added in Table 3.

12. The sample size of study is small and must be added as limitation of the study.

Response: We have added this limitation to the discussion. Thanks for your reminding.

13. The positive predictive value (PPV) of screening test is very important indices, and it very effected by the prevalence of the intended outcome. For example, if the prevalence of outcome be 5%, or 30%; the PPV becomes 25% and 73% respectively using by your study sensitivity (83%) and specificity (87%) values. Therefore, this point must be considered in conclusion of the study.

Response: Thank you very much for your valuable suggestion. According to your comment, we have learned the importance and method of calculating positive predictive value. We have added this information in Table 3 and the result.

Reviewer 2:

1-the result section of abstract does not have numerical profile. It is better the authors add some data in this format to the abstract.

Response: Thank you very much for your advice. The numerical data were added to the abstract.

2-what is the meaning of Depside in paper? [despite]

Response: We are sorry for the mistake with the word ‘despite’ and we have revised it. Thank you for your nice concern.

3-please write the paper according to the last STARD guideline.

Response: Thank you for your suggestion. We have learned the STARD guideline in diagnostic accuracy tests and revised the manuscript.

4-what is the meaning of “renal calcium deposition wait”?

Response: We apologize for the wrong phrase. We have revised this phrase. Thank you for your reminding.

5-the authors mentioned: “At least 6 valid measurements were collected from each subject, and the average value was taken for statistical analysis.” For which US measurements did the authors repeated assessments in 6 times? For all of conventional US and ARFI-VTQ measurements? Please clarify.

Response: We revised this unclear expression. Each item, including conventional US and VTQ was detected 6 times. We have added this

information to the methods.

6-how many radiologists did perform the measurements and what was their reliability? [inter-rater and intra-rater reliability]

Response: Two radiologists performed the measurements. The inter-operator and intra-operator reliabilities were both fair to good. We have added the relative method to the method part and the results to the result section. Thank you very much for your professional comment.

7-did the authors check the normality of data before choosing the statistical tests? Please mention in analysis section.

Response: Thank you for your helpful comment. The normality of data was checked before being calculated and all continuous variables obeyed normal distribution. We are sorry for this deficiency and the information was added to the analysis section.

8-please complete the manufacturer data of SPSS based on IBM site.

Response: Thank you for your consideration. We completed the manufacturer data of SPSS in the method.

9-please add full term of abbreviations in foot notes in tables.

Response: Thank you for your kind consideration. The abbreviations were detailed in footnotes in tables.

10-please follow journal format in references, for example journal names should be abbreviated.

Response: We appreciate your concern. The format in references was revised according to the request of journal.

11-the authors mentioned in results: “Furthermore, the histological grading of patients with IgAN was predicted according to H. S. Lee's glomerular grading system [13].” This sentence seems to be appropriate for discussion and it does not belong to result section. It is not the finding of the current study.

Response: Thank you for your suggestion. As you mentioned, this sentence was not appropriate for the result section. We moved it to the method to interpret the histological levels.

12-it is not clear if the data in table 2 have been yielded based on univariate regressions or multivariate regression. Please clarify.

Response: Thank you very much for your remark. We have revised table 2

for clear description of results. As in the revised version, both univariate linear regression and multivariate linear regression were used in table 2. The multivariate linear regression was calculated using all variables that have a p-value less than 0.1 in the univariate analysis. All results were shown in table 2.

13-did the authors perform VTQ measurements in the same kidney locations as the measurements of Doppler and conventional sonography?

Response: The VTQ measurements were detected in the same kidney locations as the measurements of Doppler and conventional sonography. We added this information to the method. Thank you for your valuable suggestion.

14-does “VTQ value (m/s)” in table 1 mean ARFI-VTQ measurements?

Response: Yes, the “VTQ value (m/s)” in table 1 was ARFI-VTQ measurements. We are sorry for these unclear abbreviations. We have unified the abbreviation.

15-it is better the authors add 95% CI of AUC and diagnostic indices [Sensitivity and Specificity].

Response: We are thankful for your suggestion. The 95% CI was added to the result.

16-please add other diagnostic indices data to the paper including PPV, NPV, PLR and NLR

Response: The diagnostic data you mentioned were added to the revised Table 3. Thank you for your professional advice.

17-how did the authors choose the cut off point in VTQ ROC curve? Was it Youden index? Please explain.

Response: We choose the cut-off value of the VTQ ROC curve using Youden index. This method was added to the last paragraph of method. The max Youden index was added to the result. We appreciate your valuable question.

18-please add the cut off value of ROC curve in paper.

Response: The cut-off value was added to the result. Thank you for your reminding.

19-based on the ROC curve, it is evident that we have two cutoff points in them the sensitivity and specificity are 1. [in one, the sen. is 1 and in the

other spec is 1] it is very useful if the authors add the data and values of these cutoff points and add the diagnostic indices of curve in them. [the value of cutoff points are required too]

Response: Thank you very much for your professional comment. We totally understand your concern about the determination of the cut-off point. In the present study, the optimal cut-off value was chosen by Youden index (Youden index = sensitivity + specifcity - 1), which was commonly used to select the cutoff points for the markers in clinical trials. The cut-off value of VTQ was 2.47 m/s with a max Youden Index equal to 0.695. We have added this information to the result.

20-what is the diagnostic efficacy of conventional and Doppler US assessments in differentiation of IGAN from controls? we should compare the diagnostic performance of VTQ with conventional US and Doppler US to see if the VTQ sonography is better or not?

Response: Thank you very much for your professional comment. The comparison of diagnostic efficacy of conventional and Doppler US is valuable for this study. However, as a limitation, we did not evaluate the diagnostic efficacy of conventional and Doppler US assessments in the differentiation of IGAN from controls. This limitation was added to the discussion.

21-in a diagnostic test study, the best study design is when we recruit the subjects that are clinically suspicious for the disease; then we perform the test and gold standard. Some authors enroll the known patients as disease positive and their disease negative subjects are healthy controls. This study design is not good as it can increase the diagnostic efficacy and indices falsely [as the disease positive and negative subjects are selected from two ends of disease spectrum]. In the current study, the authors have enrolled subjects in this way and it is a selection fault that can increase falsely the ROC and indices. It is better the authors perform their study in this design. If they can not change the study, Please discuss in this regard in paper and mention this point as a major limitation.

Response: We greatly appreciate your constructive comment. Your viewpoint about the subject collection is valuable and meaningful for our future studies. We are sorry that we could not change this study. This

limitation has been discussed and underlined.

22-in discussion, please add similar studies results and compare the current study findings with them. in addition adding the studies on other types of glumerlopathies seems good.

Response: Thank you for your valuable comment. We have added more similar results and discussion the comparison between them and our findings.

23-please mention the setting of selecting healthy controls. how did the authors select the controls? form which clinic or population did teh authors select the controls? did they have and kidney problem? please explain in this regard.

Response: Thank you for raising your concerns. The healthy controls were randomly selected as control group. All controls were from the same hospital with IgA patients. No one in the control group has any kidney problems. We supplemented this information with the method.

24-did the patients were on treatment or not? and what was the time duration of their disease?

Response: Thanks for your question. In this study, all IgA patients were detected before treatment. These patients were on treatment after being diagnosed. We have added this content to the method.

Reviewer 3:

Considering that in article, there was no evaluation about the difference in the amount of VTQ values in patients with IgA nephropathy and other kidney parenchymal diseases, how did you conclude VTQ values might be used as a predictor of IgAN.

Due to the fact that the amount of VTQ values difference in renal parenchymal diseases has not been evaluated separately, the specificity of VTQ value in IgA nephropathy diagnosis is not certain and is questionable.

Response: We appreciated your valuable comments. In table 1, we listed the difference in VTQ values between different groups. We are sorry for this unclear expression of VTQ values. We also exhibited VTQ values in revised figure 2 on the basis of Table 1. As shown in this figure, the VTQ values in IgAN patients were significantly lessened compared with the control group

($P < 0.001$). The clinical significance of VTQ value in IgAN diagnosis was evaluated based on the VTQ values of all recruiters. Youden index was used to determine the optimal cut-off value. At this point, the cut-off value, AUC (95% CI), sensitivity, and specificity were all provided. The positive predictive value (PPV), negative predictive value (NPV) positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were also added to the manuscript. In addition, we have revised this manuscript carefully and gratefully thank you for your helpful feedback.

3 Revision 2

5 comments · 5 Sep 2022 – 12 Nov 2022

Referee 1 Reviewer

ACCEPT 5 Sep 2022

This manuscript has now been revised well, and it is appropriate from a methodological point of view.

Referee 2 Reviewer

MINOR REVISION 18 Oct 2022

I asked a question about the type of subject selection that could falsely increase the diagnostic indices [reviewer 2, question 21]. Another reviewer has raised a similar point [reviewer 3]. She/he asked how we can conclude [based on the current study] that VTQ is efficient in differentiating IGAN from other renal parenchymal disorders. This point is very important and critical. If we cannot support this point, we cannot write in the title "Application of Virtual Touch Tissue Quantification Technique in diagnosis of Immunoglobulin-A Nephropathy" because here we differentiate IGAN from healthy controls, which is not useful in clinical practice, and, practically, we need a tool for differentiating IGAN from other nephropathies. [My question 21 was about this point too]. [In fact, this paper shows only the difference in VTQ between IGAN patients and healthy controls]. There are some points in this regard that should be addressed:
1-The authors should add to the discussion section the results of studies in which VTQ has been used to differentiate different types of glomerulopathies and parenchymal renal diseases. Then, the authors could more easily suggest that VTQ could be useful in differentiating IGAN from other renal diseases.
2-Based on my request, the authors added the following to the discussion: "The collection of patients diagnosed with IgA and controls is a major limitation of study design, as this design can increase the diagnostic efficacy and indices falsely." This wording does not seem good. They should write instead:
"There is a major limitation in our study. Based on our design, the enrollment in this study is not useful for assessing the efficacy of VTQ in differentiating IGAN from other renal parenchymal disorders, as we compared IGAN patients with healthy subjects. For this reason, a study should be designed in which patients with other glomerular and renal parenchymal diseases are compared with IGAN patients."
3-The title is not appropriate [based on the above-mentioned points]. For example, it could be corrected to:
"Virtual Touch Tissue Quantification Technique in Immunoglobulin-A Nephropathy and its diagnostic efficacy in differentiating this nephropathy from healthy controls" or something like this [the title could give the impression that the study is differentiating IGAN from other parenchymal diseases, and this is wrong.]
4-Please carefully follow this approach in the paper and correct the other parts of the paper based on this approach.

Referee 3 Reviewer

ACCEPT 11 Nov 2022

The authors have improved the paper by addressing the reviewers' comments. The revised version of the paper presents the inclusion and exclusion criteria and the study method more clearly and provides a clearer expression of the VTQ value.

Associate Editor

MINOR REVISION 11 Nov 2022

Minor revision

Editor-in-Chief

MINOR REVISION 12 Nov 2022

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 editor,

Please find our manuscript “Application of Virtual Touch Tissue Quantification Technique in diagnosis of IgA Nephropathy”.

Thank you very much for allowing us to revise our manuscript. Thank you for your and the reviewers’ comments concerning our manuscript. Please find my itemized responses in below and my corrections in the re-submitted files.

Looking forward to hearing from you.

Thank you and best regards.

Yours Sincerely,

CP.Z

Reviewer 1:

The authors have been improved the paper by applying the comments of the reviewers. The revised version of the paper has more clarity in inclusion and exclusion criteria, and also method of study and more clear expression of VTQ value.

Response: We are grateful for your support.

Reviewer 2:

This manuscript currently revised in a good manner; and so, it is appropriate according to methodology point of view.

Response: Thank you very much for taking the time to review this manuscript.

Reviewer 3:

I asked a question about the type of subject selection that could increase falsely the diagnostic indices [reviewer 2, question 21]. Another reviewer has asked similar point [reviewer 3]. She/he asked how can we conclude [based on the current study] that the VTQ is efficient in differentiating IGAN from other renal parenchymal disorders? This point is very important and critical. If we can not support this point, we can not write in title “Application of Virtual Touch Tissue Quantification Technique in diagnosis of Immunoglobulin-A Nephropathy” as here we differentiate the IGAN from healthy controls that is not useful in clinical practice and practically, we need a tools for differentiating IGAN from other nephropaties. [My question 21 was about this point too]. [in fact, this paper shows only the difference of VTQ in IGAN compared to healthy controls]. There are some points in this regards that should be addressed:

Response: We greatly appreciate your valuable and professional comments on this manuscript. According to your following remarks, we revised the title, limitation, and other parts associated with this

problem.

1-The authors should add in discussion section the results of studies in which, they have used VTQ in differentiating different types of glumerolopathgies and parenchymal renal diseases. Then, the authors could easier suggest that the VTQ could be useful in differentiating IGAN from other renal diseases.

Response: Thank you for your professional comment. According to your concern, we have cited related references and discussed them in the discussion section.

2-Based on my request, The authors added in discussion: “The collection of patients diagnosed with IgA and controls is a major limitation of study design, as this design can increase the diagnostic efficacy and indices falsely.” This style does not seem good. They should write instead:

“There is a major limitation in our study. Based on our design, the enrollment of study is not useful for assessment of efficacy of VTQ in differentiating IGAN from other renal parenchymal disorders as we compared the IGAN versus healthy subjects. For this reason, a study should be designed in which other glomerular and renal parenchymal diseases have been compared with IGAN patients.”

Response: Thank you very much for your comment. This content was revised according to your suggestion.

3-The title is not appropriate [based on above mentioned points]. For example, It could be corrected as: “Virtual Touch Tissue Quantification Technique in Immunoglobulin-A Nephropathy and its diagnostic efficacy in differentiating this nephropathy from healthy controls” or something like this [the title could make this impression that the study is differentiating IGAN from other parenchymal diseases and this is wrong.]

Response: We are sorry for this problem with the title. The title was revised based on your advice.

4-Please follow carefully this approach in paper and correct the paper based on this approach in other parts.

Response: We have checked this manuscript carefully and corrected this paper according to your comment.

> Associate Editor's Comments:

Associate Editor 1:

Minor revision

Response: We are thankful for your decision. Thank you for giving us this opportunity to revise. We have revised this manuscript according to all comments given by reviewers.

4 Revision 3

2 comments · 13 Dec 2022 – 31 Dec 2022

Associate Editor

ACCEPT 13 Dec 2022

Accept

Editor-in-Chief

MINOR REVISION 31 Dec 2022

Dear authors,
Your article needs Minor Revision.
Regards

5

Revision 4

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,

Please find our manuscript “Virtual Touch Tissue Quantification Technique in Immunoglobulin-A Nephropathy and Its Diagnostic Efficacy in Differentiating This Nephropathy from Healthy Controls” with ID 129454.

Thank you very much for allowing us to revise our manuscript. Thank you for your and the reviewers’ comments concerning our manuscript. These remarks are valuable and professional. We have revised this manuscript according to these comments. These changes will not influence the content and framework of the paper.

Thank you and best regards.

Yours Sincerely,

> Reviewers' Comments:

Reviewer 1:

a

Reply: Thank you for your feedback.

Reviewer 2:

This paper is suitable for publication in IJR.

Reply: We appreciate your comment.

> Associate Editor's Comments:

Associate Editor 1:

Accept

Reply: We are thankful for your feedback.

Associate Editor 2:

1-please add full term of abbreviations in abstract and in paper [for example ROC, RI,].

Reply: All abbreviations were added in the abstract. Thank you very much for your suggestion.

2-please correct in line 17 and 18 abstract: “ROC curve was used to evaluate diagnostic efficacy of VTQ in differentiating IgAN patients versus healthy people.”

Reply: This sentence was corrected. Thank you for your review.

3-it is better the authors add standard deviations to means in this part [mean±SD]: “2.26 m/s vs 2.61 m/s, 0.68 vs 0.63, 0.56 m/s vs 0.60 m/s”

Reply: The standard deviations were added to the abstract.

4-in line 23, the “diagnostic terms” is better as “diagnostic method”

Reply: This improper word was revised. Thank you for your advice.

5-please change method title to patients and methods

Reply: We have changed the title according to your suggestion.

6-it is better the authirs add sub-title numbers such as: 3.1-Patients and controls ……

Reply: Thank you for your suggestion. The subtitle numbers were supplemented.

7-please correct in line 72: Exclusion criteria were as follows.

Reply: This sentence was corrected. We are thankful for your comment.

8-lines 121-123, please correct the sentence as: “The diagnostic values of VTQ on the diagnosis of patients with IgAN from healthy group were evaluated via the receiver operating characteristic (ROC) curve.”

Reply: The sentence was corrected according to your comment.

9-this sentence seems unclear: “The combined ROC curve was analyzed using VTQ and indicators (except Lee grade) of significant difference in multiple linear regression” please clarify.

Reply: We are sorry for this problem. This sentence was re-written.

10-this part seems unclear: “max Youden index was employed to determine the sensitivity, specificity,” does max mean maximum? Youden index is usually a single value and does not have multiple values. Did you get two or multiple youden indexes? [this part has been mentioned two times in paper lines 124 and 160, please clarify both]

Reply: Thank you for your question. The word “max” means maximum. In this manuscript, we used SPSS to calculate ROC curve, and many pairs of sensitivity and specificity values are generated. The Youden's index was calculated from the sensitivity and specificity values of each of the coordinates obtained in the ROC curve. The Youden Index is calculated as the sum of sensitivity and specificity minus 1. The cut-off value in this manuscript was single and it was defined as the maximum value of the Youden index. We have explained this item in the method.

11-please add numbers to sub-titles of result as: “4.1-The demographic and clinical parameters of patients” ……

Reply: The subtitle numbers were added to the result section.

12-in line 158, please correct: could distinguish

Reply: We corrected this content. Thank you very much for your comment.

13-please clarify the following sentence: “Considering the convenience and two kinds of ROC diagnosis result, using VTQ only might be a proper choice”

Reply: We found this sentence unreasonable and meaningless, so we deleted it. Thank you for pointing out this problem.

14-in lines 167-172, please change inter-operator to inter-observer

Reply: We have replaced “inter-operator” with “inter-observer.”

15-in line 194, the following part is unclear: “..... , while others were undifferentiated.”

Reply: We have corrected this sentence. Thank you for your remark.

16-in line 205; what is β2-MG level?

Reply: β2-MG level means β2-microglobulin level. The combination of value of VTQ and urinary β2-microglobulin level may be a biomarker in patients with gouty kidney damage. We have rewritten this sentence for clarity.

17-this part seems wrong [grammatically]: “..... has made it is possible.....”

Reply: We apologize for this mistake. This sentence was corrected.

18-please change P-values of 0.000 to <0.001.

Reply: The P-values were changed according to your remark.

19-please add full term of ROC to footnote of table 3.

Reply: The full term of ROC was added to the footnote of Table 3.

20-please add the cut off value of ROC curve for calculating diagnostic indices in table 3 to this table.

Reply: The cut-off value of ROC was added to Table 3. Thanks for your comment.

21-the authors mentioned in figure 1 legend the VTQ of normal person in part A but they did not the VTQ value of patient in part B. it is better they mention this value of patient.

Reply: We sorry for this unclear part. We have added the VTQ value to Figure 1B. In addition, we found that the VTQ value in Figure 1A was written incorrectly. We are sorry for this mistake. This problem was corrected in the legend.

22-in figure 3 legend, please change “diagnostic function” to “diagnostic efficacy” or “diagnostic value”.

Reply: We revised this problem in the figure legend. Thank you very much for your careful check and professional remark.

5 Revision 4

1 comment · 17 Jan 2023

Editor-in-Chief

ACCEPT 17 Jan 2023

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