Author's response to reviews

Title: Safety and tissue yield for percutaneous native kidney biopsy according to practitioner and ultrasound technique

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Author's response to reviews: see over
Dear Editor and Reviewers,

Thank you for considering our manuscript for publication. The reviewers’ comments were both insightful and helpful, and, in revising the manuscript, we have incorporated their suggestions and revisions. As per the comments and suggestions made regarding the initial manuscript, we have performed additional experiments, and the revised manuscript includes the results and discussion of these data. A point-by-point response to the reviewers’ concerns follows.

**Reviewer number: 1**

Reviewer: Dr. Pietro Canetta

Reviewer's report:

The authors present a single center series of renal biopsy outcomes, stratified by technique and by provider specialty. The article is written clearly and technically sound, and of interest to the nephrology community. However, there are several points that could improve it. An important general point must be stated: the authors do themselves a disservice by presenting the work as being done for the express purpose of giving "appropriate prominence to the issue that renal biopsy should be performed by nephrologists." While I sympathize with their belief, some of the writing is more appropriate for an opinion piece rather than a research article. This actually weakens their claims, because while they "spin" the interpretation of the
data to suit their bias, they neglect to consider or address an opposite "spin," i.e. a radiologist could easily look at the data in this paper and claim that it wholly supports their equivalence at providing a diagnostic renal biopsy.

Major compulsory revisions:

1. Abstract: in the results section of the abstract, the word "superior" to describe glomerular yield is misleading since it implies better diagnostic yield, which was not demonstrated.

Response: That sentence seemed to be a little over-elusive. This was revised.

2. Methods, 1st para: can the authors explain why patients might end up in each of the three groups? For example, at our institution the only biopsies done by interventional radiology instead of nephrology are those patients that are too obese to be done by ultrasound guidance (a very small percentage.) What factors, at the authors' institution, would cause a patient to undergo blind biopsy vs. real-time vs. being sent to radiology instead? It would seem this is an opportunity for systematic bias between the groups, and should be addressed.

Response: At our institution as a tertiary referral center, it was for attending nephrologists to decide how to perform renal biopsies of their assigned patients in the light of their own preferences for the procedure. This information was added to the 'Methods' section. Uniquely, two attending nephrologists in our division had favored kidney biopsy by radiologists and had referred their own patients to radiologists for the procedure (Group III). Another two attending nephrologists in our division had kept to ultrasound-marked blind renal biopsy and their nephrology fellows in training had also taken the same procedure (Group I). Another one attending nephrologist and his fellows had performed real-time ultrasound-guided renal biopsy (Group II). As shown in Tables 1 and 2, the groups were similar in age, sex, body mass index, blood pressure, the prevalence of hypertension and chronic liver disease,
prebiopsy hemoglobin and hematocrit levels although there some differences regarding the prevalence of diabetes and systemic lupus erythematosus and some laboratory data. We admit that current analysis could hardly be free from selection bias because of the nonrandomization of patients. This point was added to the ‘Discussion’ section.

3. Methods, statistical analysis: the authors describe the logistic regression analysis as including "co-morbid diseases." This is rather vague - what variables exactly were modeled? You may want to consider listing these in a table with the betas or ORs and P-values.

Response: This mistake has been corrected. We examined the association between clinical and laboratory factors and procedural-related complications using multiple logistic regression analysis. The variables included in this analysis were sex, age, body mass index (BMI), presence of diabetes, hypertension, systemic lupus erythematosus (SLE) and chronic liver disease, blood pressure, pre-biopsy haemoglobin, platelet count, proteinuria and estimated glomerular filtration rate (eGFR). When multiple logistic regression analysis was performed to investigate which baseline characteristic factors were associated with the risk of each post-biopsy complication in each group, there was no factor associated with an increased risk of any complication. This content was added to the ‘Results’ section.

4. Discussion, paragraph 3: The following sentence is problematic: "Although the definition of tissue adequacy varies among institutions and investigators, native kidney samples need to have > 20 glomeruli to exclude focal disease processes and enable an accurate assessment of the degree glomerular involvement." The studies cited to support this are hardly definitive, and so the claim of needing >20 gloms should be either qualified (e.g. "we support the threshold of >20 gloms...",") or better supported.
Response: You are absolutely right. Currently, there is no agreement among nephrologists and pathologists on the definition of adequate renal specimen. That sentence was revised.

5. Discussion, final para: the discussion of the limitations of the article is far too brief and glib. You should discuss generalizability, and the opposing interpretation that why should a radiologist stop doing biopsies if they provide equivalent yield? They may even say they provide equal service while letting patients keep more of their precious gloms!
Response: We agree with the reviewer’s comments. The paragraph tended to present a somewhat lopsided view of results. This was revised.

6. Table 2: the +/-SD of creatinine do not seem to correspond to the +/-SD of eGFR -- the SDs of creatinine are all >1mg/dL, while the SDs of eGFR are only ~2 ml/min/1.73m2. This seems to be an error.
Response: Thank you for pointing out our mistakes. This has been corrected.

7. Table 2: proteinuria is notoriously not normally distributed, so it would be more correct to present it as a median (IQR) rather than mean+/-SD.
Response: This mistake has been corrected.

Discretionary revisions:
1. The authors should consider more measured wording in several places, including:
   -Abstract: "many non nephrologists have INVADED the traditional procedure..."
   -Background, 2nd para: "UNFORTUNATELY, in recent times percutaneous...."
   -Background, 3rd para: "give appropriate prominence to the issue that renal biopsy SHOULD
be performed by nephrologists” (after all, the results do not conclusively suggest this and more reasonably can be taken to imply that nephrologists are at least equivalent to radiologists)

-Discussion, 5th para: "The question of why percutaneous renal biopsy should be performed under the aegis of the nephrology community is now answered." (This is FAR too bold a claim.)

Response: As the reviewer recommended, these sentences were revised.

2. Methods, 1st para: in listing the types of patients who "were not considered suitable for biopsy," do the authors mean to say that such patients are NEVER biopsied at the institution, by any provider, or that they excluded such biopsies from the analysis?

Response: At least during the study period, renal biopsies were never performed in the patients with polycystic kidneys, a single kidney, and those who were pregnant. However, the procedure was done even in patients with bleeding disorders if they were indicated for renal biopsy. This sentence was revised.

3. Methods, 1st para: what was the justification for excluding 1-day case biopsies without hospitalization?

Response: As stated in ‘Biopsy safety and yield’ of ‘Methods’ section, close observation for any complication should been performed, and follow-up test for hemoglobin and hematocrit should have been measured 24 hours after renal biopsy. In cases of one-day renal biopsy at our institution, there is no follow-up on the next day after renal biopsy. Therefore, 1-day case biopsies were not considered suitable for this study. We previously reported our experience about adult day-case renal biopsy [Chung S, Shin SJ. Korean J Nephrol 2011].
4. Can the authors discuss the possibility that they may be conflating practitioner with technique? That is to say, the differences between the groups may have less to do with the specialty performing the biopsy and more to do with the biopsy technique being used in each group.

Response: We compared the safety and adequacy of glomerular yield from percutaneous renal biopsy between the biopsy techniques, and the results were as follows.

Supplementary Table 1. Biopsy tissue adequacy between blind biopsy and real-time ultrasound-guided biopsy

<table>
<thead>
<tr>
<th></th>
<th>Blind biopsy (Group I)</th>
<th>Real-time ultrasound-guided biopsy (Group II+III)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of glomeruli</td>
<td>26±17</td>
<td>24±15</td>
<td>0.06</td>
</tr>
<tr>
<td>Failure to diagnosis</td>
<td>5 (1.8)</td>
<td>1 (0.6)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or number (percentage).

Supplementary Table 2. Biopsy-related complications between blind biopsy and real-time ultrasound-guided biopsy

<table>
<thead>
<tr>
<th></th>
<th>Blind biopsy (Group I)</th>
<th>Real-time ultrasound-guided biopsy (Group II+III)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>10 (3.7)</td>
<td>22 (5.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Transfusion</td>
<td>5 (1.9)</td>
<td>7 (1.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Intervention</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>0.98</td>
</tr>
<tr>
<td>Gross haematuria</td>
<td>22 (8.1)</td>
<td>28 (7.3)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
As shown in the above Tables, the adequacy of renal tissue and the frequency of complications were not different between blind biopsy group and real-time ultrasound-guided biopsy group. Since these findings were aside from our purpose of this study, we did not include these in the manuscript.

5. Discussion, 2nd to last para: "According to these results, all biopsies at our institution have been conducted by nephrologists." Do you mean to say "are now conducted"?
Response: According to current results, all biopsies at our institution are now being conducted by nephrologists. Likewise, the sentence has been revised.

6. In table 1, consider removing the "n (%)" after each variable to streamline the look of the table (you clearly state in the legend that values are either mean+/-SD or number (%))
Response: As per the reviewer’s recommendation, the unnecessary repetitions were removed in Tables 1, 3 and 4.

Minor essential revisions:

1. Methods, first para: there appears to be an erroneous number, by "346 cases performed by nephrologists..." I believe they mean 441.
Response: This mistake has been corrected.
Reviewer number: 2

Reviewer: Joji Tokita

Reviewer's report:

Thank you for the opportunity to review this article on operator differences in outcomes (i.e. tissue yield) and safety of ultrasound guided techniques in percutaneous native kidney biopsy. The authors develop a compelling story for further evaluation of modern approaches to obtaining tissue for diagnosis of parenchymal kidney disease. I have followed the framework provided by the journal in providing my commentary.

When assessing the work, please consider the following points:

1. Is the question posed by the authors well defined?

This was a retrospective single center study comparing outcomes of percutaneous native kidney biopsy when performed by nephrologists using an ultrasound guided blind technique, nephrologists using real time ultrasound guidance, and abdominal ultrasound radiologists using real time ultrasound guidance. Biopsies performed by nephrology were conducted by either a first or second year fellow whereas radiology performed biopsies were performed by an attending radiologist with specific expertise in abdominal imaging. The authors state that the aim of the study is to show that renal biopsy should be performed by nephrologists. Presumably this would be evidenced by one or more of the following:

- tissue diagnosis/glomerular yield is superior or improved when performed by nephrology vs radiology
- complication rates were lower when performed by nephrology vs radiology
- other clinical, safety, or procedural risks were minimized when performed by nephrology vs radiology

Response: Thank you for your comments.
2. Are the methods appropriate and well described?

The methods section is reasonably well developed, detailing inclusion and exclusion criteria, time frame of data collection, location of the center, and relevant background information regarding the laboratory and clinical parameter that were measured and reported.

Major Compulsory Revisions:

Of note, on line 9, reference is made to 346 cases performed by nephrologists, however in the previous sentence, the authors state that a total of 441 cases were performed. This needs clarification and may be an error.

Response: This mistake has been corrected.

There was no explanation with regard to how or why patients were stratified to either nephrology or radiology for biopsy. Was this random, sequential, or was there some other underlying pattern or practice in place?

Response: As discussed, one of the major limitations is that this is not randomized study. Consequently, the choice of the procedure was left to the physician. At our institution as a tertiary referral center, it was for attending nephrologists to decide how to perform renal biopsies of their assigned patients in the light of their own preferences for the procedure. This information was added to the ‘Methods’ section. Uniquely, two attending nephrologists in our division had favored kidney biopsy by radiologists and had referred their own patients to radiologists for the procedure (Group III). Another two attending nephrologists in our division had kept to ultrasound-marked blind renal biopsy and their nephrology fellows in training had also taken the same procedure (Group I). Another one attending nephrologist and
his fellows had performed real-time ultrasound-guided renal biopsy (Group II). However, we showed that the groups were relatively well balanced before the comparison of outcome.

The study’s stated aim was to show that biopsy performed by nephrology was superior to biopsy performed by radiology, however, although both groups used real time US guidance, it was not clear whether there were agreed upon standards or targets between the groups. Did radiology know that glomerular yield was essentially the primary endpoint? The number of passes and cores with observable gloms would be an important piece of information to know although one surmises that if the complication rates were similar, the pass and tissue capture rates would also be similar. There is also no mention made of the type of ultrasound device used for image acquisition, specifically whether there was any difference between equipment that used by the nephrology service and that used by radiology. Standardized use of a needle guide and other procedural details remain of critical importance in light of the end point of interest here. (i.e. was this outcome the result of a difference in operator technique or were the nephrologists really superior with regard to localizing the biopsy needle to optimize tissue yield? Or was it both?)

Response: Radiologists have also recognized the importance of glomerular yield as well as postbiopsy complications. As described in ‘Methods’ section, the real-time US-guided renal biopsies were similar between nephrologists and radiologists. With the patient in the prone position on the bed, US images were obtained through the kidney to locate the outer lower pole and measure the depth from the skin to the renal capsule. After administration of local anesthesia under sterile condition, a practitioner advanced the automated biopsy needle to the lower pole of the left kidney capsule under renal-time US guidance, and then the biopsy gun was fired after the needle tip position was confirmed by US. The standard biopsy needle size
in our center was 14 G. All practitioners, both nephrologists and radiologist, have been requested to obtain two specimens of the kidney. In all cases including the biopsies performed by radiologists, a nephrology fellow has checked the obtained specimens with the naked eye. He or she has observed the whole process of the procedure in cases of biopsies performed by radiologists. When the renal specimen was deemed inadequate by gross visual inspection, the nephrology fellow made a request to the radiologist for additional pass. Consequently, the average of two renal specimens was obtained in all biopsies regardless of who performed the procedure. After the procedure, the specimens were hand-delivered by nephrology residents to the department of pathology for histologic evaluation. Some of these were added to the ‘Methods’ section.

One of limitations in this study is that the number of needle passes was not recorded in every case. However, previous studies have reported that number of passes did not affect the rate of complications [Khajehdehi P et al. Am J Kidney Dis 1999; Corapi KM et al. Am J Kidney Dis 2012]. Despite no documentation on the number of needle passes, we also showed that there was no significant difference in overall complications after the biopsy between nephrologists and radiologists. This point was added to the ‘Discussion’ section.

There were some differences in technique and equipment between nephrologists and radiologists. First, nephrologists conducted the biopsy procedure holding the US transducer in the left hand and the biopsy gun in the right hand, while radiologists performed the biopsy with or without using the disinfected biopsy needle bracket that attached to the transducer. Second, the ultrasound machine of radiologists (currently using iU22 ultrasound system, Philips Healthcare, The Netherlands) has usually offered higher image resolution than that of nephrologists (currently using Accuvix V20, Medison Healthcare, Korea), although equipment upgrades including ultrasound machines have occurred. However, there has been
no report to compare the biopsy outcomes according to use of needle bracket or difference in performance of ultrasound machine. It is not clear why the mean number of glomeruli from a renal specimen in the nephrologist-performed real-time ultrasound-guided biopsies was even superior to that in the radiologist-performed real-time ultrasound-guided biopsies in this study. We cautiously speculate that a better understanding of optimal localization of a kidney for biopsy might affect the glomerular yield.

3. Are the data sound?
Table 1 presents the clinical features of the study groups and notes differences between Group 1 and 2 and between 2 and 3 with regard to prevalence of DM and SLE, however, BMI appeared similar across all groups. Presumably the rest of the categories did not have statistically significant differences.

The authors report an average glomerular yield across the board of 25 +/- 16 with a diagnostic failure rate of 1.22%. Although the glomerular yield was superior for procedures performed by nephrologists, the authors note that the proportion of “failure to make a final pathologic diagnosis” was similar among all groups.

The frequency of major bleeding complications such as development of hematoma or requirement for transfusion was 6.8% and there were no cases of death or nephrectomy. There was no statistically significant difference between groups noted.

The data as presented appear sound and the outcomes achieved remain within what would likely be considered within expected variance for this procedure. (i.e. tissue yield rates, complication rates, etc)

Response: Thank you for your comments.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes
Response: Thank you for your comments.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
The authors report similar complication rates and diagnostic failure rates across all three groups. They also note that the glomerular yield was statistically significantly higher for biopsies performed by nephrologists compared to radiologists; however, this did not impact the success of tissue diagnosis. As such, the conclusion in the discussion section that biopsy should definitively be performed by nephrologists on the basis of this and prior background data is rather strong without further qualification of the targets and conditions for both groups. The study conclusion takes a more nuanced approach, suggesting that “current evidence gives preference to nephrologist with respect to percutaneous kidney biopsy.” This should be annotated “ultrasound-guided” as there are other techniques for percutaneous approach to kidney biopsy. We also note that this is a retrospective study.
Response: We agree with the reviewer’s comments. We revised rough and baseless expressions. In this study, the proportion of failure to diagnosis was similar among all groups despite a significant difference in glomerular number between radiologists-performed biopsies and nephrologists-performed biopsies. However, considering the random distribution of focal glomerular diseases, more glomeruli might affect or even change diagnosis as stated in ‘Discussion’ section.

6. Are limitations of the work clearly stated?
Yes
Response: Thank you for your comments.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes
Response: Thank you for your comments.

8. Do the title and abstract accurately convey what has been found?
Yes, but could be a bit clearer. Safety and tissue yield for percutaneous native kidney biopsy according to practitioner and ultrasound technique.
Response: As per the reviewer’s comments, the title was revised.

9. Is the writing acceptable?
The tone of the writing should remain neutral. In the second paragraph of the background section, “Un fortunately” should be deleted and the paragraph should start with “In recent times...” The strongest language should be supported by strong data evident in the study. There were a few other areas that should be reviewed for word choice. Overall, the grammar and syntax otherwise appears acceptable.
Response: We agree with the reviewer’s comments. The overall tone of the writing was revised.

Editorial Comments:
Thank you for submitting the research article entitled 'Safety and outcomes according to practitioners and techniques for percutaneous native renal biopsy' to BMC Nephrology. The
The paper has been peer-reviewed by two experts. You are encouraged to address the comments of the reviewers to resubmit a revised manuscript for reconsideration.

Both reviewers request revision of the overall tone and perspective of the manuscript favoring nephrology performance of native kidney biopsy in the context of results that support equivalence in both complications and glomerular yield. The increase in glomerular yield for nephrologists is not likely to be clinically significant. Also, please consider the concerns of both reviewers, particularly regarding selection bias or non-random allocation of Groups I, II, and III. The authors should explain how patients were selected for each group.

Lastly, Why were patients with right kidney biopsies and 1-day case biopsies excluded?

Response: We agree with your comments. We corrected vague or baseless expressions. In this study, the proportion of failure to diagnosis was similar among all groups despite a significant difference in glomerular number between radiologists-performed biopsies and nephrologists-performed biopsies. However, considering the random distribution of focal glomerular diseases, more glomeruli might affect or even change diagnosis.

As stated in the ‘Discussion’ section, one of the major limitations is that this is not randomized study. Consequently, the choice of the procedure was left to the physician. At our institution as a tertiary referral center, it was for attending nephrologists to decide how to perform renal biopsies of their assigned patients in the light of their own preferences for the procedure. This information was added to the ‘Methods’ section. Uniquely, two attending nephrologists in our division had favored kidney biopsy by radiologists and had referred their own patients to radiologists for the procedure (Group III). Another two attending nephrologists in our division had kept to ultrasound-marked blind renal biopsy and their nephrology fellows in training had also taken the same procedure (Group I). Another one attending nephrologist and his fellows had performed real-time ultrasound-guided renal
biopsy (Group II). However, we showed that the groups were relatively well balanced before the comparison of outcome.

On a few biopsies have been conducted in right kidney. Moreover, almost all cases were done by nephrologists. As stated in ‘Biopsy safety and yield’ of ‘Methods’ section, close observation for any complication should be performed, and follow-up test for hemoglobin and hematocrit should have been measured 24 hours after renal biopsy. In cases of one-day renal biopsy at our institution, there is no follow-up on the next day after renal biopsy. Therefore, biopsies of right kidney and 1-day case biopsies were not considered suitable for this study.

All of the reviewer comments were helpful and provided new insight into our work. We have carefully reviewed and revised the entire manuscript in addition to the recommended changes. Thank you in advance for your consideration of the revised manuscript.

Sungjin Chung, Eun Sil Koh, Sung Jun Kim, Hye Eun Yoon, Cheol Whee Park, Yoon Sik Chang and Seok Joon Shin