

Response to review for No. Manuscript NO: 40696, Title: Retrograde Intrarenal Surgery versus Miniaturized Percutaneous Nephrolithotomy to Treat Lower Pole Renal Stones 1.5-2.5 cm in Diameter

Dear Editor,

Thank you for your thoughtful review of our manuscript and the opportunity to further improve our work by revision. We have made all the required changes suggested by the editor and the reviewers. Please find our point by point response to all the inquiries below.

Response to the reviewer's comments:

Reviewer #1:

1. Abstract. The authors state in the conclusion section of the abstract that RIRS is superior to mini-PCNL in terms of both duration of the hospitalization stay and costs. I would like to recommend the authors to use a more humble conclusion and not make any statement that their study concludes in favor of the superiority of one method over the other. This is important because it seems that the available data does not allow them to conclude that differences regarding length of hospital stay were due solely to the superiority of RIRS over mini-PCNL, since other confounding factors might have played a role in those differences. Please review the "Core tip" section accordingly and the main text conclusion as well.

Response: The reviewer raised a very valuable point. We have made correction according to the Reviewer's comments. The conclusion was changed as follow.

"RIRS and mini-PCNL are both safe and effective methods for treating LP stones with a diameter of 1.5-2.5 cm. RIRS can be considered as an alternative to PCNL for the treatment for LP stones of 1.5-2.5 cm."

2. Page 4, first paragraph: "Indeed, the European Association of Urology (EAU) guidelines mentioned that RIRS is the first choice of some surgeons for the treatment of larger stones[4]". The reference the authors used to support that statement is a guideline written in German and which reflects the position of the German Academy of Urology and the Austrian Urology Society. It is not a guideline by the European Association of Urology. Moreover, I could not find within the referenced German / Austrian guideline any statement that RIRS is the first choice procedure for the treatment of larger stones. Please, double-check the reference that was intended in that sentence.

Response: The reviewer raised a very valuable point. We have made correction according to the Reviewer's comments. The reference was revised, and the sentence was corrected as follow.

"Indeed, the European Association of Urology (EAU) guidelines mentioned that RIRS is a valid choice of some surgeons for the treatment of larger stones 26304503"

3. The way the mini-PCNL technique was described was not clear enough. For instance: “Localization and proper selection of the puncture sites were aided by the injection of a contrast agent through a 6-F ureteric catheter placed at the beginning of the procedure.” The procedure is performed under fluoroscopy? How were the location of the puncture sites determined?

***Response:** The reviewer raised a very valuable point. We have made correction according to the Reviewer’s comments. The way of mini-PCNL technique was corrected as follow.*

“All procedures were performed with the patient under general anaesthesia. At the beginning of the procedure, placement of a 6 Fch ureteral catheter up to the renal pelvis was performed by means of rigid cystoscopy. Subsequently, patients were placed in the prone position, and percutaneous access was achieved by a urologist under ultrasonography guidance using an 18-gauge needle and guidewire. We used a 0.038-mm J-tipped guidewire to insert through the calyceal puncture into the renal pelvis. The first three Alkan dilators were used to dilatated the tract (8F-14F-16F). Next, we inserted a 16-F sheath And introduced a rigid 10-F ureteroscope. The stone fragmentation was performed using a Ho:YAG laser (365- μ m fibre; energy 2.5 Jd; frequency 20 Hz). A 16-F nephrostomy tube was inserted into the calyceal system at the end of the procedure. Three days after the surgery, the nephrostomy tube was removed. The double J ureteral stent was removed under local anaesthesia 2 weeks later.”

4. Statistical analysis. It is not correct to state that “The χ^2 test was applied to compare non-parametric values and the t-test was used to compare parametric values”. The χ^2 test is appropriate for the comparison of proportions whereas t tests are appropriate for the comparison of means between two groups, when the data follow a normal or nearly normal distribution. If continuous data is found not to follow a nearly normal distribution by visual examination of histograms of the data, then other methods should be used such as the Wilcoxon signed-rank test or bootstrap methods. The authors should also clarify how they assessed the data to decide whether they followed a normal or nearly normal distribution. Textbooks usual recommend against the use of tests such as the Shapiro-Wilk test because of issues related to power.

***Response:** The reviewer raised a very valuable point. We have made correction according to the Reviewer’s comments. The statistical analysis was corrected as follow.*

“The chi-square test was applied to compare the proportions between two groups. Continuous variables are presented as means \pm standard deviations (SD) using student t-test when the data follow a normal distribution. Where the distribution of the continuous variables was not normal, the Wilcoxon signed-rank test was used. The p value was adjusted for gender and BMI. The adjusted calculation was performed using SPSS package with binary logistic regression. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using Statistical product and service solutions (SPSS) 17.0 (SPSS, Inc., Chicago, US).”

5. I would like to recommend the authors to use statistical methods that allow them to adjust for possible confounding. The propensity scores method and generalized linear models could be very useful. This is important because the lack of a statistically significant difference regarding those variables at the baseline does not offer any guarantee that they did not exert any confounding effect concerning the relationship between the outcomes and exposures. Providing statistical analyses with attempt to adjust for confounding would represent a major improvement regarding the overall quality of the study.

Response: The reviewer raised a very valuable point. We have made correction according to the Reviewer's comments. The statistical analysis was corrected as follow and the results were not affected.

“The chi-square test was applied to compare the proportions between two groups. Continuous variables are presented as means \pm standard deviations (SD) using student t-test when the data follow a normal distribution. Where the distribution of the continuous variables was not normal, the Wilcoxon signed-rank test was used. The p value was adjusted for gender and BMI. The adjusted calculation was performed using SPSS package with binary logistic regression. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using Statistical product and service solutions (SPSS) 17.0 (SPSS, Inc., Chicago, US).”

6. Hospitalization times seem quite long when compared with international standards. Please comment why hospitalization times were so long and why patients undergoing RIRS, which is usually an ambulatory procedure, were hospitalized for a mean length of 9 days.

Response: China is a developing country. RIRS has been applied just in some major clinic. Because of the immature community medical system, patients are unwilling to discharge unless they can make a full recovery. What's more important, all preoperative examinations and preparations must be performed in the hospitalization according to the medical insurance system, which spends almost an extra 2-3 days and artificially increases the hospitalization time.

7. The authors should consider the possibility that confounding related to the surgeons' decision to perform RIRS or mini-PCNL influenced their results.

Response: The reviewer raised a very valuable point. All the patients were collected from the same doctor at the Urology Department of Ningbo Urinary Kidney Disease Hospital between December 2015 and April 2017. We have added that in the Patients.

8. In tables 1 and 2, avoid the use of “ \pm ” because it does not inform readers if the information provided refers to Standard Errors or Standard Deviations. The authors should state clearly that those numbers refer to Standard Deviations and provide those number between parentheses. Please see the SAMPL guidelines for Statistical Reporting of Articles published in Biomedical Journals

(<http://www.equator-network.org/wp-content/uploads/2013/07/SAMPL-Guidelines-6-27-13.pdf>)

***Response:** Thank you for your suggestions. We have made correction according to the Reviewer's comments. Detailed information was available in the manuscript.*

Reviewer #2: Review comments for manuscript entitled; Retrograde Intrarenal Surgery versus Miniaturized Percutaneous Nephrolithotomy to Treat Lower Pole Renal Stones 1.5-2.5 cm in Diameter

1. Title: Adequate and clearly reflects Contents 2. The subject fall within the scope of the journal 3. Abstract : well structured 4. Keywords: appropriate 5. Introductions: appropriate. Has summarized relevant studies and explained other authors' findings. 6. Materials and Methods i. EAU should be written in full and abbreviation enclosed in a bracket, thereafter abbreviation can be used. ii. Briefly define the EUA guidelines iii. "Dilation of the tract was performed using the first three Alkan dilators". State the sizes of these dilators. Statistical Analysis i. "The test", write in full before using abbreviation. ii. Also, write SPSS in full and abbreviation in the bracket. Results Information about the hydration status of participants is important in view of the role of adequate hydration in post operative recovery time in stone management.

***Response:** Thank you for your suggestions. We have made correction according to the Reviewer's comments. Detailed information was available in the manuscript.*

Table 2 Below table 2, authors should state what Grade O, I, II, III, IV, V N. oClavien complications represent.

***Response:** Thank you for your suggestions. We have made correction according to the Reviewer's comments.*

"Data presented are as means \pm SD. The p value was adjusted by gender and BMI.

Grade 0: means no complication.

Grade I: Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic and radiographic interventions acceptable therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy.

Grade II: Requiring pharmacologic treatment with drugs other than such allowed for Grade I complications, Blood transfusions and total parenteral nutrition are also included.

Grade III: Requiring surgical, endoscopic, or radiographic intervention.

Grade IV: Life-threatening complication requiring IC / ICU management.

Grade V: Means Death of a patient due to a complication."

Discussion "...RIRs was also a safe and reliable choice for patients with contraindications or preferences for the treatment of treating the single renal stones of 2.0-3.0 cm in diameter" Please reframe this statement.

***Response:** Thank you for your suggestions. We have made correction according to the Reviewer's comments. The sentence was corrected as follow.*

“RIRS was also a safe and reliable choice for patients with single renal stones of 2.0-3.0 cm in diameter.”

References ♣ Reference 1; The first author's name should be written properly. ♣ Reference 4; fur should be written properly. ♣ Alazaby et al [18] is not the same with the reference at position 18 in the reference section, and not found in the ref section. Likewise reference 18 Traxer O in the reference section is not the same with reference 18 in the text.

Response: Thank you for your suggestions. We have made correction according to the Reviewer's comments. Detailed information was available in the manuscript.

Reviewer #3: They have done interesting and useful study.

Response: Thank you for your suggestions.

Edited Manuscript by Editor:

Response: Thank you for your suggestions. We have made correction according to the Reviewer's comments. Detailed information was available in the manuscript.

We tried our best to improve the manuscript by making changes according to the Reviewers' comments. These changes will not influence the content and framework of the paper and we have tracked them in revised paper. Once again, thank you very much for your comments and suggestions, and we really appreciate your suggestions and hope our correction meet with the journal's approval.

Best regards,

Yours sincerely,

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