Author’s response to reviews

Title: Management of large renal stones: laparoscopic pyelolithotomy versus percutaneous nephrolithotomy

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Author’s response to reviews:

Following are our response about reviewers’ comment to our manuscript.

Reviewer #1:

Minor suggestions:

1. Would consider a sub-group analysis in staghorn calculi. Would be interesting to compare results of LPL and PCNL in this cohort to see if results for stone free rates remain consistent. Would hypothesize that LPL for staghorn calculi may show inferior outcomes compared to PCNL due to lack of access into distant calyces.

——Distribution of stone burden, and total stone burden, is an important predictor of surgical outcome in renal stone diseases. Although included studies comparing PCNL and LPL for multiple complex renal stones, especially for staghorn calculi, have not yet to be done in much detail. Therefore, we did not provided a sub-group analysis due to insufficient data.
2. What percentage of LPL cases are using flexible nephroscopy to assess the entire renal pelvis? Is this routinely done for stone retrieval?

——Only an included study by LEE et al. (Lee JW, Cho SY, Jeong CW, Yu J, Son H, Jeong H, Oh SJ, Kim HH, Lee SB. Comparison of Surgical Outcomes Between Laparoscopic Pyelolithotomy and Percutaneous Nephrolithotomy in Patients with Multiple Renal Stones in Various Parts of the Pelvocalyceal System. J Laparoendosc Adv S, 2014, 24 (9):634-639.) used a flexible nephroscope to overcome difficulties in retrieving calyceal stones, as flexible nephrosopes enable easier approach and assessment of the entire pelvocalyceal system. This procedure is not routinely done.

Reviewer #2: Despite well conducted, I don't believe this study adds anything important to the available literature. Can be interesting for those with specific interest in this field but I think it has too many limitations (mainly heterogeneous CCS studies with small sample sizes and of low to moderate quality included in the meta analysis and, most important of all, the applicability at large of laparoscopic pielolithotomy which requires a long learning curve). Despite this, it's obvious laparoscopic pielolithotomy is feasible (specifically now that also robotic surgery is available) and is indicated in a particular set of patients, as the authors correctly noted, indications given by the surgeon on a single case basis.

——Meta-analysis of observational studies presented particular challenges because of inherent biases that might distort the outcome. However, these studies can be considered as the best available evidence, because no high quality review studies about this topic have been conducted. In addition, we have discussed robotic surgery in the Discussion chapter (para 3) of present study.

Reviewer #3:

The results show better stone free outcome for laparoscopy with less complications as fever, blood loss, despite a longer hospitalization. What I miss in the paper is the dimension of the treated stones and more important the characteristics of stone(single, multiple, stag-horn, pyelic, calicial) that could be an important issue in terms of possible indication of Laparoscopy instead
PCNL and vice versa. Moreover this could lead in a clear indication for Laparoscopy of PCNL for some kind of stone dimensions and characteristic.

I think this is a key point of the paper and when possible this analysis must be made and reported. Moreover the conclusions of the paper should be more strong and effective on indications.

When this will be impossible to obtain, at least it should be clearly and largely discussed.

——We have performed subgroup analyses to assess the effectiveness and safety of LP compared with PCNL in surgical management of solitary renal pelvic calculi larger than 2cm. Most of the outcomes were not greatly affected (Results section, subgroup analyses). The evidence suggests that LP and PCNL are both effective and safe for treatment of solitary renal pelvic calculi larger than 2cm.

We cannot performed subgroup analysis for patients with stag-horn stone due to most of included studies have not reported this information in great detail. However, we have discussed this topic (Discussion section, paragraph 2).

A second important issue is about infective complications. The papers mentions fever but never evaluate the sepsis and septic shock. This should also be evaluated or discussed if not reported by the literature because is a serious possible complication.

——The data of sepsis and septic shock was not reported in the included studies. Therefore, we have discussed this topic (Discussion section, paragraph 4).

Third, laparoscopic approach could be Retro or trans peritoneal. This must be clarified regarding the infective or septic complications because a transperitoneal approach could be more at risk about it.
Retroperitoneal approach is better than transperitoneal for patients with adrenal or renal surgery in terms of operative time, infection, hospital stay and return of bowel function. Therefore, we have discussed this topic (Discussion section, paragraph 4). However, further prospective randomized controlled trials are needed to determine which approach should be favoured.

Last observation. A kidney loss is potential for both the procedure. This should be discussed and when data are available it must be analyzed.

All of the included studies had not reported the major complications (kidney loss). However, we have mentioned this topic in Discussion section, paragraph 5.

All Charts and figures need a better definition of the title in order to be understood.

We have revised the title of figures.

Following I noted some details

1. Pag 3 line 39 and following. The advantages of Laparoscopy are not explained except for the possibility to remove the stone intact. The sentence is about multiples advantages. Please explain more advantages or change the sentence. Moreover, Define 'large renal stones' whit number, measures and characteristic (position and typology) of the stones.

   We adopted reviewer's suggestions and revised the sentence (Introduction, paragraph 2). In addition, the number (single and multiple) and characteristic of stones are presented in Table 1.

2. Pag 3 Line 58 Define 'large renal stones'; Line 60 check the sentence appear not clear nor fluent.

   We have defined 'large renal stones' as the stone diameter \(\geq 2 \text{ cm}\) and rewritten the sentence (Literature search and article selection, para 2).
3. P94 line 17. How complications are evaluated. Was Clavien Dindo classification used in the analyzed literature?

—— Only 6 studies (Basiri et al. 2014; Haggag 2013; Li 2014; Lee 2014; Aminsharifi 2013; Basiri 2014) reported the complications according to Clavien grading system.

4. Page 5 Lines 1 The sentence is unclear. Please rewrite in order to made it more comprehensible and immediate.

—— We have revised the sentence (Results chapter--study characteristics, para 2).

5. Page 5 line 48. Explain and analysis about sepsis.

—— Although none of patients from the included studies encountered sepsis or septic shock after the both procedures, we have added this topic in RESULTS section--Postoperative fever and sepsis.


—— The reasons of conversion to open surgery included injury of renal vein and peritoneum, uncontrolled bleeding, stone migration into the calyx, and perirenal adhesions (RESULTS-Conversion rate and prolonged urine leakage).

7. Page 6 line 58. At this point the authors reveal a previous similar review. That must be mentioned in the introduction chapter of the paper as well.

—— We adopted reviewer's suggestions and added this topic in the introduction chapter of the paper (Introduction, para 3).
8. In the discussion Page 7 lines 13 to 17 the authors report a significative difference in terms of urinary leakage for laparoscopic group. Looking at the result this seems to be in contradiction with them. Please check the result and discussion and clarify which is the truth.

——We have checked and revised this result (Discussion, para 1).

9. Page 7 line 48 and following. The authors discuss about the difficulty to make the suture of the pyelotomy in terms of surgical time and leakage complication. I will discuss the possibility of robotic assistance for this kind of procedure. Moreover I will discuss this topic together with the excellent results of the laparoscopic approach because the only limit seems to be due to the sutures difficulties that are potentially overcome by the robotic dexterity.

——A pure laparoscopic approach is less invasive than an open approach but is technically difficult with longer operative time and leakage complication. The use of the robotic interface has the potential to refine the laparoscopic technique and improve outcomes. Therefore, we adopted reviewer's suggestions and added this topic in the Discussion chapter of the paper (Discussion, para 3).

10. Page 8 line 4. Discuss about stag-horn stones a this time.

——We have discussed in this chapter (Discussion, para 2).

11. Page 8 line 23. Septic complication and risk of kidney loss could be discussed at this time.

——We have discussed in this chapter.(Discussion section, para 4-5.)

12. Page 8 line 5. Also robotic assistance decrease the suture time and related complications. This should be reported.

——We have discussed in this chapter (Discussion, para 3)
13. Page 9, line 9 and following. The authors affirm that ‘LPL can be considered as an alternative approach in patients with a large stone (measure) burden which cannot be removed with a reasonable number of access and sessions of PCNL; for hard stones resistant to fragmentation; patient also requires a concomitant pyeloplasty; or in cases with difficult PCNL access because of kidney and skeletal anomalies.’

My question is why not in almost all cases with one pelvic stone? What about stag-horn stones? When possible after this revision I will better discuss: Laparoscopy could be consider for ALL this cases (explain which) were PCNL is better indicated in this other cases (explain which).

When possible, Revise also the conclusions in consideration of what previously explicated.

——Subgroups analyses by characteristics of stone (solitary or multiple) were performed to explore the potential heterogeneity among the included studies. The results of this meta-analyses were relatively stable. Patients with staghorn stones, laparoscopic surgery can certainly be a reasonable therapeutic option. However, these laparoscopic procedures should only be practiced in centers with expertise in laparoscopy as they are technically challenging. They are also associated with a long learning curve and are somewhat time-consuming.

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——We have provided a completed PRISMA checklist as an additional file.