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- Peer Review Report -

Reviewer #1: Unassigned

Reviewer #2: A randomized, single-blind clinical trial comparing robotic-assisted fluoroscopic-guided with ultrasound-guided renal access for percutaneous nephrolithotomy. The authors attempt to determine whether robotic-assisted fluoroscopic-guided renal access in mini-PCNL results in better outcomes as compared to conventional ultrasound guided techniques. They conclude that robotic-assisted fluoroscopy-guided PCNL can be performed as safely and effectively as US- guided PCNL, even by novice surgeons using fluoroscopic guidance.

I have the following comments:

1. The paper appears adequately referenced, reads well and the statistical analysis is satisfactory.

2. This is a small study which offers proof of concept, but a larger multi institutional study is needed to offer a meaningful definitive outcome and drive change of practice.

3. The conclusions are satisfactory.

4. Supplementary Figure 1 could perhaps be improved.

Reviewer #3: This paper compares two techniques for gaining percutaneous access for mini-PCNL. One is the often-used ultrasound-guided (US) method which is in common use in many institutions, both academic-based and community-based urologic practice. The novel method involves an artificial intelligence (AI) - guided robotic arm using fluoroscopic guidance (RAF) to make the puncture into the selected calyx for percutaneous stone removal. The study as per the title compares the

two techniques in terms of numerous parameters including time for puncture, number of punctures (including "misses"), complication rate, stone free rate (SFR -- defined as residual stones 4 mm or smaller via KUB imaging at 1 month f/u, and 2 mm or smaller on CT imaging at 3 month f/u), and other data points of interest. The patient population was approximately equal (35/US vs 36/RAF) for the 2 groups and all other parameters were comparable between groups including gender, age, pre-op stone size, etc. Urology residents performed the initial puncture in each group, but in 14% of the US patients, puncture failed initially and it was necessary to switch surgeons to complete the puncture, suggesting US-guidance is more complex and has a more difficult learning curve compared to the RAF technique. This is not surprising, since the AI and robotic arm do the work once the instrument is set up and oriented to the desired calyces target.

Although not readily available in the United States yet, the ANT-X robotic puncture system with programmed AI seems to be a novel way to automate and possibly simplify percutaneous puncture for facilitating PCNL. It was quicker and more accurate, stone-free rates were better in the RAF group, needle puncture required fewer attempts, complications were fewer, and based on this initial study with a minimum number of patients for statistical validity, it would seem the robotic-assisted fluoroscopic method is superior to the traditional ultrasound-guided (US) method. The only advantages I can see for ultrasound-guidance is slightly less fluoroscopy time and the equipment is likely significantly less costly compared to equipment needed for RAF.

The authors should address the question regarding the differences in stone-free rates. Once the puncture is made, and presumably the puncture using each technique was made into the proper calyx, even if US took longer or required more attempts, if patients were truly comparable between groups, then why shouldn't the stone-free rates be similar between groups? Were the surgeons equally distributed between the two techniques? If not, were some surgeons more skilled than others, accounting for the different outcomes in the SFR's? Did the RAF not only

achieve a faster puncture, but was the puncture somehow in a better angle or location to explain the superior SFR's?

Another aspect that one might discuss is somewhat-related to using a robot for radical prostatectomy, nephro-ureterectomy, etc. That aspect has to do with the rare circumstance of the robot malfunctioning such that in the case of no available back-up robot, one must revert to either pure laparoscopy or convert to an open surgical procedure to complete the operation. Even if the RAF procedure becomes widespread and is the standard for PCNL access, robots (like the Da Vinci and ANT-X) are complex and can fail intra-operatively, so urology trainees should still learn other techniques for PCNL puncture including ultrasound-guidance and fluoroscopic guidance, as a back-up. As further experience is gained with this novel system, and cost-benefit analyses are completed, it is possible that the RAF method using the ANT-X or similar robot will become the standard due to the likely advantages as depicted by this early study.

Reviewer #4: The authors present a randomized controlled trial comparing robot controlled renal access to ultrasound guided access. The concept of identifying better ways to obtain real access is laudable, and the authors have designed and executed a very well done clinical study to demonstrate this point. The concept of robot assisted percutaneous surgery is growing in prevalence, and warrants consideration for publication for the Urology audience. In general, the language should be edited for an English speaking audience for style as a couple of phrases could be substituted. For example, in the abstract, "change of puncture surgeon" could be phrased as "the resident was unable to obtain access." These are minor edits and could be readily addressed.

Specific comments:

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1. The authors should specifically define what was meant by successful renal access. Does this mean that a wire could be placed? Was there any objective measure of success?

2. Who was the primary surgeon for all of these cases for the first attempt of renal access? Did they always have a trainee start and only switch to an attending physician after failure? This should be specified.

3. Were patients positioned in the same way for ultrasound access compared to robotic access? What other differences in procedural set up existed between the two study arms? More detail is provided with regard to this dimension of the study for robotic cases as opposed to ultrasound cases.

4. The authors should revise wording for their power calculation which is confusing. How did they come to a total study size of 70 patients? What is meant by a superior margin of -10%?

5. The authors should define what they mean by puncture duration. Did this include imaging time?

Reviewer #5: This is a very interesting study to look at ultrasound guided access vs robotic assisted fluoroscopic guidance.

Line 130: All PCNLs were performed with URS assistance with or without laser lithotomy under
general anesthesia.
* Lithotomy is a position, I think you mean laser lithotripsy.

Line 152: describe how the stones were fragmented. was it laser?

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Did the size of the sheaths make a difference?

Reviewer #6: Unassigned

Reviewer #7: This is a statistical review of this manuscript. The paper is generally well written. I do not have any major concerns about the work. Some minor comments are listed below.

Page 4, line 119-120: The statement "Randomization was performed by adjusting for age, sex, laterality, total stone burden, hydronephrosis grade, and presence of staghorn stones" is unclear to me. In particular, what do you mean by "adjusting for" in a randomization? Doesn't the randomization make all baseline variables, observed or unobserved, balanced in the two arms?

In Statistical Analysis, reasons for doing the further causal evaluation with logistic/linear regressions for this clinical trial data set should be given. I also think the differences in the surgeons, such as their seniority or years of experience in performing the surgery, may confound the effect of RAF vs US. They should be addressed in the paper.

Reported p-values and other numbers in this paper do not quite follow the guidelines. See Section 4.1 in the guidelines for details.

Interpreting the p-values in Table 1 should take the randomization into account. See Section 3.10 in the guidelines for details.

Chief Statistician comments:

Please see *The Journal of Urology* guidelines for reporting statistics: https://www.auajournals.org/doi/10.1097/JU.0000000000000001

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and guidelines for tables and figures: https://www.auajournals.org/doi/full/10.1097/JU.0000000000001096

- P-values should be removed from Table 1, as randomization ensures balance between groups (see guideline 3.10)
- See guideline 2.5 and please clarify in the statistical methods what hypotheses are being addressed by each statistical test. More details about the logistic and linear regression analyses are needed, specifically more detail about what outcomes were assessed, what factors were included in multivariable models, and how those factors were selected for inclusion.
- Please provide justification for the use of multivariable analysis, which is not common in the setting of a randomized trial where confounding factors should be controlled by the randomization process
- The results should better highlight the primary and secondary outcomes as detailed in the methods. As is, the results for the primary outcome are buried in the middle of a paragraph and similarly in the middle of Table 2.

Consultants and Editors contributing to the peer review process for this article were Inderbir S. Gil, Mark Noble, Abhay M. Rane, D. Robert Siemens, and four anonymous reviewers.