

Peer Review File

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Reviewer A

Comment①:

The authors decided the cut-off value of lumbosacral angle using ROC curve. However, the accuracy was relatively low showing the AUC data (0.674). And there were not significant differences of clinical outcomes except time to reach the stone between $LSA \geq 150^\circ$ and $LSA < 150^\circ$. The author should discuss carefully what this value means. I wonder whether LSA measurement will lead to patient benefit potentially or not.

Reply:

Thank you for your comments and query. In this study, we were able to show a significant association between reachability and LSA, but as you suggested, the AUC was not so high, and the surgical outcome may not have a substantial impact. Although we would have liked to compare total operative time as a more objective endpoint, it was not easy because the present cohort included patients with renal stones. However, there was indeed a significant difference in time to reach the stone, and we consider that this has a positive effect on reducing the risk of infection and ureter injury in URS. Because of the small number of cases, multivariate analysis did not show a significant difference in the incidence of complications between the two groups, which is a limitation of the present study. We want to accumulate cases and search for more evaluable and reasonable outcomes in the future. We added the following sentence as below.

Changes in the text:

(Discussion) The AUC was not so high (0.674, shown in Fig 2), and there were no differences in other perioperative outcomes between the two groups, so the results need to be interpreted carefully. However, we consider that a short time to reach the stone has a positive effect on reducing the risk of infection and a longer time for effective laser-firing in URS. Because of the small number of cases, multivariate analysis did not show a significant difference in the incidence of complications between the two groups, which is a limitation of the present study.

(Limitation) Third, there was a significant difference in time to reach the stone statistically, though it is unclear how clinically beneficial this is to patients.

Comment②

LSA measurement may be subjective and seems to change easily. How much difference of measurements was there between different urologists?

Reply:

Thank you for your comment. We consider that the LSA measurement is straightforward and reproducible. This is the point we would like to emphasize in this study. Even when different

urologists measured it, the error was within about 5 degrees. However, patients with lumbar compression fractures and scoliosis were excluded from the study because they were difficult to evaluate LSA.

Changes in the text:

(Discussion) LSA measurement was straightforward and reproducible. Even when different urologists measured it, the error was within about 5 degrees in the present study.

Comment③

In general, male have a prostate grand and longer urethra than female, and also have a narrower pelvis. Their differences may lead to the results of semi-rigid reachability. The authors should examine the predictors separately by genders.

Reply: Thank you for your critical comments. In the multivariate analysis of reachability, sex was included as an explanatory variable to be adjusted as a confounding factor.

However, when I conducted the multivariate analysis separately by gender, as your suggestion, the results were as follows.

Male

| Male | Odds ratio | 95% CI | P-value |
|---------------------------|------------|-----------|---------|
| LSA | 1.090 | 1.03-1.16 | 0.005 |
| DJ stent | 1.710 | 0.54-5.40 | 0.356 |
| Ureteral orifice stenosis | 0.887 | 0.29-2.70 | 0.832 |

Female

| Female | Odds ratio | 95% CI | P-value |
|---------------------------|------------|-----------|---------|
| LSA | 1.040 | 0.92-1.17 | 0.545 |
| DJ stent | 2.920 | 0.30-28.4 | 0.356 |
| Ureteral orifice stenosis | 0.010 | 0.00-inf | 0.994 |

Multivariate analysis separately by genders showed that LSA was associated with reachability only in males. Based on this result, we created table-2b by sex, as shown above.

Changes in the text:

(Result)In general, males have a prostate grand and longer urethra than females and have a narrower pelvis. Their differences may lead to the results of semi-rigid reachability.

Multivariate analysis separately by genders showed that LSA was associated with reachability only in the male.

(Discussion) we believe that adequate preparation by preoperative LSA measurement will lead to patient benefit potentially **especially in male patients with narrow pelvises.**

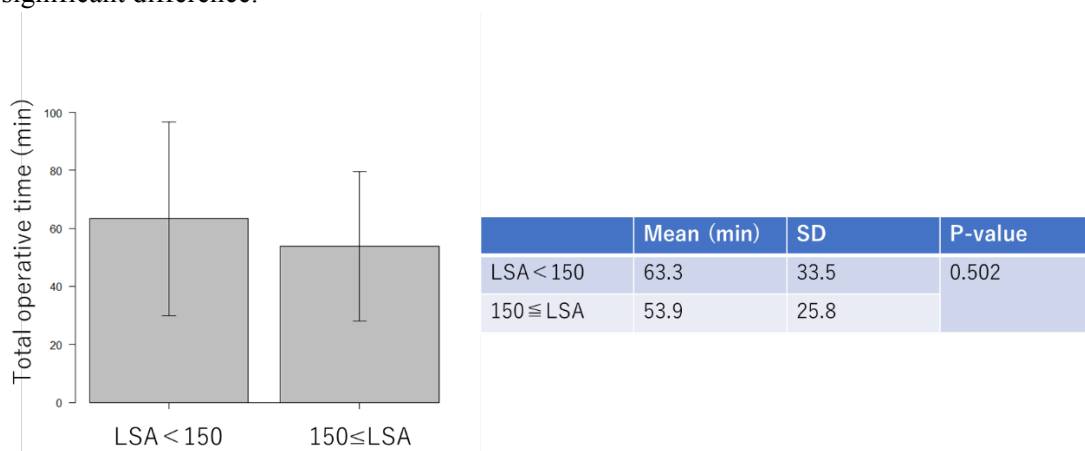
Reviewer B

A few points:

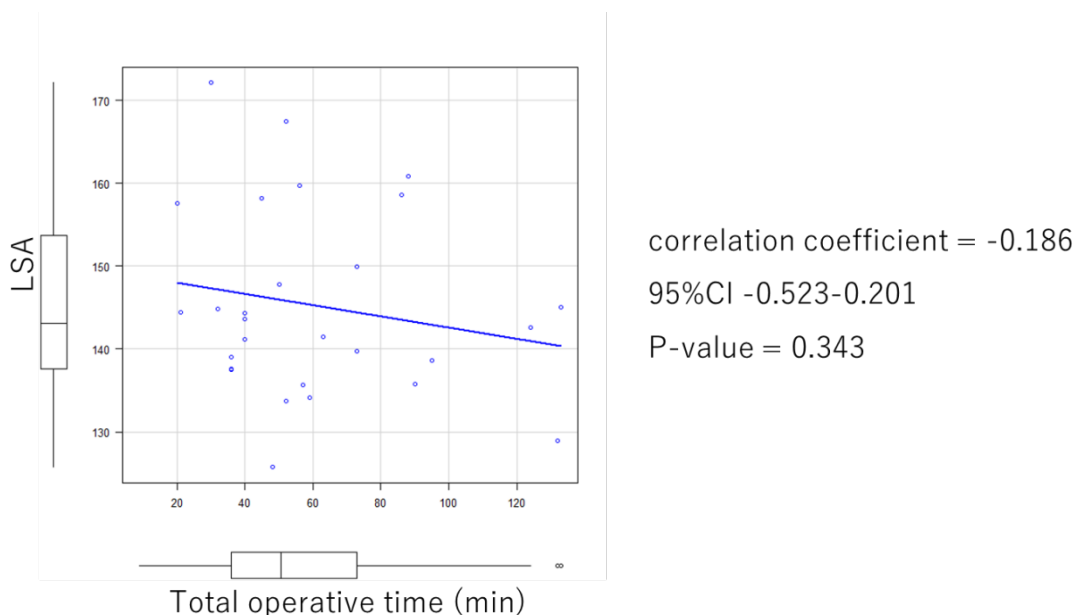
1. I worry that the inclusion of more proximal stones, renal stones, and other additional stones may muddy the results; it would be interesting to see the subset of patients that had only the single ureteral stone being treated.

Reply:

Thank you for your essential query. As the present cohort included patients with renal stones, we couldn't compare the total operative time as the primary endpoint. As your suggestion, there were a total of 36 cases when limited to cases of U2 stones alone. The total operative time was shown as follows when dividing this cohort into two groups according to the LSA cut-off value. Although the operative time was shorter in the large LSA group, there was no significant difference.



We also examined the correlation between operative time and LSA, but we could not find a strong correlation, as shown below. The fact that we could not show a significant difference only for cases with U2 stones alone is a limitation due to the small number of cases in this study.



We added this outcome in the discussion section below.

Changes in the text:

(Discussion) When limited to cases of middle ureteral stones alone, there was a total of 36 cases in this study. However, there was no significant difference in the operative time between the two groups.

2. Similarly, you mention that trainees were involved in many cases, but given that the ease of access and timing for the procedure could be heavily affected by the presence of a trainee or less-skilled surgeon, I would ask that more information on trainee involvement be included as a variable.

Reply:

Thank you for your comments and query. A supervisor supervised all URS, but there may be bias due to the surgeon's skill. Therefore, we conducted an additional study to see a difference between results performed by trainees and results performed by experienced urologists. Urologists with experience of fewer than 100 cases of URS were defined as a trainee. The results are shown below.

Univariate analysis

| | Odds ratio | 95% CI | P-value |
|---------|------------|-----------|---------|
| Trainee | 0.977 | 0.39-2.48 | 0.962 |

Multivariate analysis

| | Odds ratio | 95% CI | P-value |
|---------------------------|------------|-----------|---------|
| Trainee | 0.963 | 0.34-3.04 | 0.948 |
| LSA | 1.060 | 1.00-1.12 | 0.043 |
| Sex (Male) | 6.230 | 1.48-26.3 | 0.012 |
| Ureteral orifice stenosis | 0.629 | 0.07-5.13 | 0.665 |

As shown above, there was no significant difference in the reachability even when the presence of the trainee was included as a variable. We added this finding to the discussion section as below.

Changes in the text:

(Discussion) as trainees were involved in many cases as a surgeon, we conducted an additional study to see if there was a difference between results performed by trainees and results performed by experienced urologists. Urologists with experience of fewer than 100 cases of URS were defined as a trainee. However, there was no significant difference in the reachability even when the presence of trainee was included as a variable (Logistic regression analysis, odds ratio=0.963; 95% confidence interval=0.34–3.04; P=0.948).

3. You do mention that LSA may change from supine to lithotomy - is there any info regarding this? If the preoperative LSA is not relevant to their LSA in lithotomy position, it may decrease the believability of the utility of this measure in practice.

Reply:

Thank you for your essential query. There is no evidence that LSA may change from body position. This information has been removed from the text due to confusing and uncertain information.

Changes in the text:

(Limitation) ~~Fourth, since the effect of the patient's posture on LSA is unknown, LSA may differ between supine and lithotripsy positions.~~

4. My biggest concern is that you comment that this measure makes a large difference on ease of access, although in reality the confidence interval comes VERY close to 1 and the overall timing difference between the <150 and >150 LSA groups was only 2 minutes. I worry that these data, while statistically significant, may not truly be clinically significant. Can you comment?

Reply: Thank you for your comments and query. In this study, as you suggested, the surgical outcome may not have a substantial impact. However, we consider that a short time to reach the stone has a positive effect on reducing the risk of infection and a longer time for effective laser-firing in URS. Because of the small number of cases, multivariate analysis did not show a significant difference in the incidence of complications between the two groups, which is a limitation of the present study. We added the following sentence as below.

Changes in the text:

(Discussion) The AUC was not so high (0.674, shown in Fig 2), and there were no differences in other perioperative outcomes between the two groups, so the results need to be interpreted carefully. However, we consider that a short time to reach the stone has a positive effect on reducing the risk of infection and a longer time for effective laser-firing in URS. Because of the small number of cases, multivariate analysis did not show a significant difference in the incidence of complications between the two groups, which is a limitation of the present study.

Reviewer C

Comment①

There were relatively many unreachable patients in this study cohort (reachable n=77 vs. unreachable n=47). The definition of "reachable" should include the cases in which semi-rigid scope could reach the stone with working guidewire. We can fire the laser with or without working guidewire through two channel.

Reply:

Thank you for your comments and query. As you suggested, there are many cases in which laser-firing is possible using two channels, even with a working guidewire. However, since the main object of this study was to investigate the relationship between pelvic anatomy and ureteral tortuosity, we considered that reaching the stone using an additional guidewire would not be significant. Moreover, we use a 6Fr ureteroscope with the one-working channel in our hospital. We do not use the two working channel URS because it is larger in diameter and increases the risk of ureteral injury. Using two channels may result in ineffective irrigation and poor visualization. We want to perform URS without working guidewires as much as possible to ensure safe laser-firing. We added this finding to the discussion section as below.

Changes in the text:

(Discussion) There are many cases in which laser-firing is possible using two channels, even using a working guidewire. However, since the main object of this study was to investigate the relationship between pelvic anatomy and ureteral tortuosity, we considered that reaching the stone using an additional guidewire would not be significant. More, in our hospital, we use a 6Fr ureteroscope with a one-working channel. We do not use the two working channel URS because it is larger in diameter and increases the risk of ureteral injury

Comment②

In most cases of middle ureteral stone, a UAS is not necessary for fragmenting the stone. A UAS is used for taking out the stone fragments which were pushed back into the upper ureter or renal pelvis. So, the information of the use of UAS is confusing in this study.

Reply:

Thank you for your suggestion. We also considered that the presence or absence of UAS use is not an essential matter in this study. We have removed the rows of "Size of UAS" from Table1-b.

Changes in the text:

(Discussion) ~~76.6% of patients in the reachable group used a UAS, resulting from the aim of an efficient irrigation system not to be of high pressure conditions and ureter friendly stone extraction. In addition, there were many cases in which UAS was used to observe the renal pelvis and treatment of renal stones in the reachable group, so most of the cases of U2 stones could be completed with only a semi-rigid ureteroscope.[1]~~

Comment③

I think the main reason why it is easier for women to insert a semi-rigid scope is the angle or mobility of the bladder and urethra. So, it is difficult for a man with a big body to insert. What do you think about this opinion?

Reply:

Thank you for your critical comments. In addition to what you pointed out, we believed that a male's prostate, urethra, and narrow pelvis reduce reachability. More, well-developed iliopsoas muscles and visceral fat may further reduce reachability. It is challenging to evaluate it objectively, but we agree that it is difficult for a man with a big body to insert.

Changes in the text:

(Discussion) A lower ureteral muscle tone **and mobility of the bladder and urethra** can influence the ease of procedure in the female sex.

Reviewer D

1) Specific comments for revision

a) Major

#1 Hydronephrosis is not included in the patient background. The presence of hydronephrosis might be an important factor for the accessibility of middle ureteral stone. Do you have any data on hydronephrosis?

Reply:

As your suggestion, high-grade hydronephrosis is an important factor affecting ureteral tortuosity. In our institution, all patients with preoperative hydronephrosis undergo ureteral stenting, so basically, the hydronephrosis disappears before surgery. There were 4 cases of patients with grade 3 or higher hydronephrosis who could not be stented. Of these, the reachability of semi-rigid ureteroscope was 50%, and the average time to reach the middle ureteral stone was 152.3 seconds, which was shorter than the overall average. Although the number of cases is small and it is unclear how much hydronephrosis affects the reachability, we believe that patients with severe hydronephrosis will have lower reachability. We added this finding to the discussion section as below.

Changes in the text:

(Discussion) **High-grade hydronephrosis is an important factor as it affects ureteral tortuosity. In our institution, all patients with preoperative hydronephrosis undergo ureteral stenting, so basically, the hydronephrosis disappears before surgery. However, 4 cases of patients with grade 3 or higher hydronephrosis could not be stented. Of these, the reachability of semi-rigid ureteroscope was 50%, and the average time to reach the middle ureteral stone was 152.3 seconds, which was shorter than the overall average.**

b) Minor

#1 p7 line119, "If URS was used", does URS means UAS?

Reply:

Thank you for your query. As you suggested, the sentence seems wrong, so we revised our manuscript below.

Changes in the text:

(Materials and Methods) "If **UAS** was used,"

#2 In Table2, please indicate which sex after the sex in table2.

Reply:

Thank you for your query. As you suggested, we added "Male" to our table2-a like below.

Changes in the table:

(Table2-a, parameter column) "Sex (**Female**)"