

Peer Review File

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#Reviewer A

Comment 1: In methods, the author selected some pre-operative factors to analyze. But, did not include the patient status like performance status and ASA etc. I wonder if PS is especially important to judge the pre-operative patient condition.

Reply 1: Thanks for these thoughtful comments. The patient status may have an impact on postoperative recovery. The assessment tools like performance status and ASA are primarily designed to evaluate patient's tolerance to intervention and anesthesia. For ASA score, we reviewed our clinical data sheet and added the statistical results into the manuscript. Two patients (4.7%) in sepsis group and twenty-three patients (3.2%) in non-sepsis group were scored ASA 3. No difference of ASA score was detected in association with sepsis ($P = 0.331$). However, we failed to record performance status in the clinical data sheet. After literature review and rough data analysis, the Eastern Cooperative Oncology Group (ECOG) performance status is not likely to affect postoperative sepsis. Mitsuzuka et al.¹ investigated the factors associated with post-URS febrile urinary tract infection. Ten in one hundred and fifty-three patients had PS 2 or greater that could be thought as "poor PS". There was also no significant difference between febrile UTI group and no febrile UTI group concerning PS score. On the other hand, the PS score has some similarities with the ASA score. PS 2 is described as "Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours"², while ASA 3 is judged by particular diseases: "Patient has severe systemic disease; Substantive functional limitations; One or more moderate to severe diseases"³. The patients with ASA 3 or greater may be roughly regarded as "poor performance status". Based on this, we evaluated the relationship between poor/good performance status and sepsis, then found P -value 0.647. Although it is an estimated result, we expect that more studies could involve the performance status.

Changes in the text: The information related to ASA variable was added in table 1 and line 146. In addition, the percentage of each variable in table 1 were recalculated as the proportion of the number of observation to the number of total patients in sepsis group or non-sepsis group (the original percentage is the proportion of the number of observation in one group to the number of observation in both group, which appears to be confusing).

Reference:

1. Koji Mitsuzuka, Osamu Nakano, Norio Takahashi, et, al. Identification of Factors Associated With Postoperative Febrile Urinary Tract Infection After Ureteroscopy for Urinary Stones. *Urolithiasis*. 2016 Jun;44(3):257-62.
2. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv2nom-4-30-99-final3.pdf
3. <https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system>

Comment 2: In methods, if the patients had acute febrile infection due to stone before fURS, the author ought to manage the infectious status. For this patient, did the author take pre-antibiotic therapy before

fURS? If doing that, you had better include “pre-antibiotic therapy” as item.

Reply 2: Many thanks for this suggestion. The patients with acute febrile infection are more likely to develop sepsis. In our department, all patients will routinely receive at least a dose of prophylactic antibiotics before fURS. If the patients present signs of infection (often positive urine culture, fever or leukocytosis, judged by the urologists), the duration will expand to 7 days. The surgery can be performed until the tests related to infection are negative. In this study, we analyzed the determine factors of “pre-antibiotic therapy” separately: fever, WBC, urine culture, urine WBC, and urine nitrite. The multivariate analysis showed that positive urine culture is a more potent predictor than other factors. So, it may be more precise to analyze individual predictor rather than an integral variable.

Another issue should be also noted. There are two test results for infectious index (fever, urine culture, urine test, and serum WBC). Concerning this issue, we recorded the infectious index in the infectious episode. Besides, other variables close to surgery were recorded.

Changes in the text: The timing of pre-surgery tests were explained in line 120-122 (methods section)

Comment 3: In methods, did you exchange the DJ-stent before fURS for management of the patient who had been already placed the DJ-stent?

Reply 3: Pre-operative DJ-stent insertion is not a routine procedure in our department otherwise the patient had indications (like predicted difficulty in ureteroscope inserting). For patients with DJ-stent, the stent will be removed at the beginning of surgery instead of exchange.

Changes in the text: Only comments as above.

Comment 4: In methods, did you use the ureteral access sheath in all case for management in proximal stone? Or some cases? And then, how length is UAS size?

Reply 4: The 14-Fr ureteral access sheath (Cook Medical, Bloomington, IN) were used for all the patients undergoing fURS. Regarding the length of UAS size, there are 35mm- and 45mm-length sheath in our hospital. The choice of sheath is dependent on patient sex.

Changes in the text: Only comments as above.

Comment 5: In methods, the author used the irrigation pump. Was this pump continuous irrigation machine to maintain the consistency of irrigation pressure? If do so, how did you control in this irrigation pressure because this pressure is related with renal pressure?

Reply 5: The pump is a pressure-sensitive irrigation machine. The intrarenal irrigative pressure is limited to approximate 150 cmH₂O. If the pressure is greater than the rated value, the machine will slow the flow rate to reduce intrarenal pressure automatically.

Changes in the text: Only comments as above.

Comment 6: In result, was there any difference regarding with predictors factor between sepsis and septic shock?

Reply 6: We appreciate the review's important suggestion. It ought to be an interesting comparison between sepsis and septic shock. The results may verify further the predictive value of those predictors. However, there are only 6 patients with septic shock in our study. Statistical analysis by such small samples would produce unreliable results. Thus, we only discussed septic shock by descriptive table. It will be explored in another study in the future with enough patients.

Changes in the text: Only comments as above.

Comment 7: Finally, how will you manage to control the risk for this patient with AGR<1.2 and positive urine from this result in your study?

Reply 7: Thanks for the reviewer's comments. Our study suggested low AGR and positive urine culture as preoperative predictors of sepsis after fURS. Early effective predictors could provide urologists with adequate time to take measures. For patient with AGR < 1.2, the potential diseases should be considered first. If there are no obvious causes, albumin supplement (like protein-rich diet; for low albumin) or treatment to infection (for high globulin) or both could be performed to decrease sepsis probability.

Changes in the text: Only comments as above.

#Reviewer B

We appreciate the review's thoughtful comments. These issues involved the influencing factors that may associated with postoperative sepsis. We mainly focused on preoperative factors in this study, since an early predictive model could be more practical for urologists.

Comment 1: When was the timing of the blood test?

Reply 1: In most cases, the blood tests (including hematological test and liver test) close to the data of surgery were recorded. The timing was often 1~4 days. For patients with signs of infection preoperative, the infection-related blood tests in the infectious episode were recorded. The timing was often within 2 weeks.

Changes in the text: The timing of pre-surgery tests were explained in line 120-122 (methods section).

Comment 2: How about the intrarenal pressure during the operation?

Reply 2: Intrarenal pressure is an important factor that can influence the development of sepsis. In our hospital, we used pressure-sensitive irrigation machine (Shenda Medical, China) to maintain IRP. The intrarenal irrigative pressure is limited to approximate 150 cmH₂O. If the pressure is greater than the rated value, the machine will slow the flow rate to reduce intrarenal pressure automatically.

Changes in the text: Only comments as above.

Comment 3: Were there any associations between stone analysis and postoperative sepsis?

Reply 3: It is a good question since stone composition is a reflection of stone-forming environment. However, the acquisition of stone composition report often delays until the surgery is complete. Though there is probably a relationship between SC and sepsis, the predictive significance of SC is limited for clinical use. Therefore, we did not include such factors in our study. From the literature, some studies have reported the association between infection and SC. Rivera et al.¹ revealed that struvite stone composition is a risk factor for infectious complication in PCNL. Yoshida et al.² also showed that struvite calculi was associated with postoperative SIRS in URS. Struvite stone is accepted as infectious predictor because the infectious environment is needed to form struvite stone.

Changes in the text: Only comments as above.

Reference:

1. Marcelino Rivera, Boyd Viers, Patrick Cockerill, et al. Pre- And Postoperative Predictors of Infection-Related Complications in Patients Undergoing Percutaneous Nephrolithotomy. *J Endourol.* 2016 Sep;30(9):982-6.
2. Satoshi Yoshida, Ryoji Takazawa, Yusuke Uchida, et al. The Significance of Intraoperative Renal Pelvic Urine and Stone Cultures for Patients at a High Risk of Post-Ureteroscopy Systemic Inflammatory Response Syndrome. *Urolithiasis.* 2019 Dec;47(6):533-540.

Comment 4: How about the association between stent indwelling duration and postoperative sepsis?

Reply 4: Preoperative stent indwelling is dependent on predicted difficulty in ureteroscope inserting in our hospital. The timing is no more than 2 weeks before surgery. We included this preoperative factor in our study but no significant difference was detected between sepsis and non-sepsis group. Regarding the duration, the proportion of patients with indwelling stent is low so that we fail to involve the duration variable (six patients in sepsis group and forty-four patients in non-sepsis group).

Changes in the text: Only comments as above.