Author’s response to reviews

Title: Prognosis and risk factors of patients with upper urinary tract urothelial carcinoma and postoperative recurrence of bladder cancer in central China

Authors:
Qingwei Wang (qwwang@zzu.edu.cn)
Tao Zhang (1027953585@qq.com)
Junwei Wu (wujunweichom@126.com)
Jianguo Wen (jgwen@hotmail.com)
Deshang Tao (1024324125@qq.com)
Tingxiang Wan (wtxzzu2016@163.com)
Wen Zhu (1227693022@qq.com)

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Author’s response to reviews:

Dear editors and Reviewers,

Thank you for your excellent suggestions and comments concerning our manuscript entitled “Prognosis and risk factors of patients with upper urinary tract urothelial carcinoma and postoperative recurrence of bladder cancer in central China” (manuscript ID: BURO-D-18-00354). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in yellow in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Responds to the reviewer’s comments:

#1 reviewer: Rebecca O'Malley.

The authors query a retrospective database of patients surgically treated with radical nephroureterectomy for upper tract urothelial carcinoma (UTUC) in order to determine the overall survival (OS) and bladder cancer (BC) recurrence as well as risk factors for each in
central China. The analysis includes 439 patients. There are unfortunately several issues with both the methodology and the presentation of the results. The conclusions drawn are also not clearly supported by the included data. Please see my comments below to this effect.

Comment 1: - Beginning around line 41 of the background section what is listed is should be in the methods section not the background. Should rather have a statement of hypothesis here. The last line "Our findings will provide a scientific basis for the effective prevention and treatment of UTUCs." Is much too strong a conclusion and not part of the background. Again should be just the hypothesis i.e. in order to investigate risk factors and prognosis of UTUC in central China we developed a database…etc.

Response: Thanks for your good suggestion. The part you mentioned is “In this study, UTUC patients were primarily from central China, and some risk factors (such as diabetes mellitus (DM) with or without metformin use) were …… and survival analysis to analyze the risk factors and prognosis of BC recurrence. Our findings will provide a scientific basis for the effective prevention and treatment of UTUCs.” It is not really suitable for writing in background. At your suggestion, we have deleted it. And we added the following words “Since the epidemiology and disease characteristics of UTUCs may be related to different areas and the relationship between some debatable risk factors and UTUCs is unclear, we developed a database of UTUC in our region to investigate the risk factors of prognosis of UTUC and BC recurrence in central China. We hope that our research will contribute to the treatment of UTUCs and reduce the risk of recurrence of bladder tumors after RNU.” in the end of background. All the above added contents were showed on page 2, line 66-71. Besides, we also added those words “Currently, It is still controversial that the relationship between some risk factors and UTUCs, such as diabetes mellitus (DM) with or without history of metformin medication, preoperative ureteroscopy, the low location of UTUC.” in the second paragraph of Background, which was showed on page 2, line 53-56.

Comment 2: - Authors state in section 2.1 that "All patients had complete clinical and follow-up data". Seems unlikely with > 400 patients.

Response: Thank you for your suggestion. We are sorry that we didn’t present the inclusion and exclusion criteria in this manuscript. We have rewrite the methods part. We deleted the following content: “All patients had complete clinical and follow-up data. Among them, 236 were male (53.7%) and 203 were female (46.3%) (male-to-female ratio, 1:1.16). The age range was 32–85 years old (average, 66.7 years); 132 cases were <50 years old, and 307 were >50 years old”. Besides, we added the following sentences: “Data of patients with upper urinary tract tumors (UUTTs) from the Department of Urology of our hospital (the largest hospital in China, located
in central China) were collected from March 2011 to February 2017. The inclusion criteria were as follows: 1. patients with unilateral UTUCs; 2. those who underwent RNU; 3. those with postoperative pathological confirmation of UTUC; 4. those with complete clinical data and follow-up. The exclusion criteria were as follows: 1. patients with bilateral UTUC patients; 2. those with a history of UTUC awaiting renal transplantation; 3. those who received conservative treatment or simple nephrectomy; and 4. those with incomplete or missing clinical data.

Finally, 481 patients with UUTT were selected. Among them, 12 patients did not undergo RNU, 8 had incomplete clinical data, 11 were lost to follow-up, 5 had squamous cell carcinoma, 4 had adenocarcinoma and 2 were diagnosed with sarcoma. Finally, 439 patients with UTUC were included in this study. All patients underwent RNU with bladder cuff resection, and each patient was confirmed as UTUC by pathological reports.”

The new added content were show on page 3, 2.1 section, line 85-98.

Comments 3:- In section 2.3 states "Overall survival time was monitored by telephone." This requires clarification—were family members asked or physicians? How was cause of death determined?

Response: It’s a quite good question. Under your proposal, we have rewritten this part, which were showed as below: “All the patients were followed up regularly by telephone or internet contact which was recorded in the Electronic Medical Records (EMR) System of our hospital. Full-time urologists were responsible for following up the patients according to the UTUC guidelines, and the patients were urged to undergo their medical examinations on time. All examination results during the follow up period were recorded in detail. Postoperatively, cystoscopy was performed every 3 months within 2 years to assess for recurrence, then once every 6 months in the 3rd–4th year, and then once a year thereafter. During the follow-up time, other routine examinations were performed including: blood routine tests, liver and kidney function tests, abdominal B-scan ultrasonography, chest X-ray every 6 months, and abdominal computed tomography (CT) once a year. Based on the treatment guidelines for UTUCs and patients' wishes, bladder perfusion chemotherapy following RNU for patients with UTUC was not a compulsory treatment. Depending on whether bladder instillation was performed after the operation, patients were divided into two groups: the perfusion group and the non-perfusion group. Perfusion was performed once a week for a maximum of 8 weeks, then once a month for one year following the operation. All data were recorded and monitored using Jiahe Electronic Medical Record System. The survival rate, BC recurrence rate, and risk factors of BC recurrence were analyzed. The mortality and cause of death at the follow-up period was calculated based on
data obtained from the family members and the remaining data was obtained from the EMR system or the primary care physician.” The new added contents was showed in page 4, line 125-145.

Comment 4: - Last 2 lines of section 2.3 are describing the outcomes of interest not the "Follow-up" as the section is named. There should be a separate section describing the outcomes of interest (including how they were determined as above comment about OS) and what factors were examined specifically as risk factors for which outcome.

Response: Thank you very much for your advice. The sentence you mentioned is “Focusing on tumor-associated death and BC recurrence rate, the survival rate, risk factors of UTUCs and BC recurrence were analyzed to predict the prognosis of UTUC patients”. Indeed, as you said, this sentence really shouldn't be included in the follow-up paragraph. It is about the result of this study. So we moved these words to the results section. And the following 3 parts 3.1, 3.2 and 3.3 were modified as well and showed the detailed results on the survival rate, risk factors of UTUCs and BC recurrence, respectively. So we hope this modification could satisfied your request.

Comment 5: - Definitions of risk factors also need to be included somewhere, e.g. Smoking yes or no—does that mean current smoking, or any past smoking or a specific amount of past smoking, For "Taking Chinese herbs…” does this include any amount/duration of ingestion? Etc.

Response: This suggestion is of great significance. A person's smoking history is determined by his smoking index, which is Number of cigarettes per day×Years of smoking. If smoking index is above 200, the subject was considered to have a history of smoking. No matter current smoking, or past smoking history.

The next is the question that “Taking Chinese herbs… does this include any amount/duration of ingestion?” The history of taking Chinese medicine containing aristolochic acid was considered if the following criterion was met: 1) taking Chinese herbal medicine or Chinese patent medicine containing caulis aristolochiae manshuriensis. And the duration of ingestion included the continuous use of caulis aristolochiae manshuriensis > 15 days, or discontinuous use for more than 2 months; 2) Continuous or intermittent use of other types of Chinese herbal or proprietary medicines containing aristolochic acid ingredients for more than 6 months.

Besides, we defined those two cases as diabetes. 1) Diabetes mellitus history diagnosed before; 2) The subjects’ fasting blood glucose (FBG) were ≥7mmol/L (at least 2 times), or random blood
glucose levels were >11.1mmol/L. And those more than 50 years old was considered as old age. Low tumor location means ureteral urothelial carcinoma(UUC). The tumor clinical staging was performed according to the American Joint Committee on Cancer (AJCC) 2002; the tumor grading was assessed based on the WHO pathological grading system of malignant urothelial cancer 2004.

Comment 6: Table 1 needs to be tidied up to reflect the characteristics in the correct columns.

Response: Thank you so much for your good suggestion. We tidied up Table 1 renewedly. We change the title “Clinical data of patients with UTUCs” into “The related influencing factors of UTUCs and the risk factors of bladder cancer recurrence in this study”. And we reorganized the column of recurrence of bladder cancer to make it more orderly. And we added 2 influencing factors: age and sex. Please check it.

Comment 7: 1) Description of results needs to be more detailed. It is not clear how the risk factors interact with the outcome of interest.

2) The headings on Table 2 and 3 are not clear—what does "B" "Wald" and "Exp(B)" mean for example?

3) I cannot tell from either the table or the test whether increasing age is associated with increased BC recurrence or is it decreasing? Is DM without metformin use associated with increasing or decreasing risk? The tables are totally unclear and the fact that there is no corresponding text makes it impossible to decipher which way factors are associated and the magnitude of that association. There is some mention in the discussion but again this is not enough to understand the interactions and is further confusing.

Response: It’s a quite good suggestion for this manuscript. We are very sorry for making you feel confused by our negligence and mistakes.

(1) We have rewritten the results part. We added the following sentences: “Overall, 439 patients were included in the final statistical analysis. Among the 439 patients, 236 were males(53.7%) and 203 were females(46.3%). The follow-up period ranged from 18 to 84 months, with an average of 62.5 months. Factors included in the analysis were showed in Table 1. Tumor-associated death and BC recurrence rate, the survival rate, risk factors for UTUCs and BC recurrence were analyzed to predict the prognosis of patients with UTUC”. These words were showed in Results part, page 4, line161-166.
(2) “B”=Partial regression coefficient, which means the variable quantity of dependent variable with the change of independent variable per unit on the premise of controlling other variables. “SE” means standard error. “Wald” means chi-square, a test index similar to t test or F test. "Exp(B)" means OR(odds ratio). OR > 1 indicates that the greater the value of this factor, the greater the probability of events, also known as risk factors. OR < 1 indicates that the greater the value of this factor, the smaller the probability of occurrence of events, also known as protective factors.

(3) In the results part, 3.2 section, we have add the following contents which is “This suggested that smoking, taking Chinese medicine containing aristolochic acid, history of BC, older age, advanced tumor stage and high-grade tumor, larger tumors and presence of LNM were the risk factors of UTUC patients with poor prognosis.” to explain the table 2. The added words were show on page 5, line 178-181.

In the results part, 3.3 section, we deleted the words “The factors related to postoperative BC recurrence were tumor stage, tumor grade, preoperative ureteroscopy, postoperative bladder perfusion chemotherapy, low tumor staging, and diabetes”, and add the new content “We found that advanced tumor stage and high-grade tumor, preoperative ureteroscopy, DM without metformin use and UUC were risk factors of postoperative BC recurrence. Patients with 1 or more than 1 of the risk factors were more likely to experience BC recurrence. And regular postoperative bladder perfusion chemotherapy was a protective factor for recurrent BC.”. Those added sentences were showed on page 5, line 187-191.

Comment 8:- Since there were only 89 patients with recurrent BC analyzing 11 variables in the multivariable logistical regression analysis is not statistically sound.

Response: Thank you so much for your advice. After discussion with the statistics professional, we have different opinions on this issue. The question of how many samples are needed for logistic multivariate regression analysis has been controversial. Traditionally, in logistic regression, the ratio of variables to sample size is at least five times. In this study, table 3 showed the results of a binary logistic regression model of BC recurrence in UTUC patients. The 439 cases of UTUC patients were the samples size, not the 89 cases of recurrent bladder cancer patients. Whether or not BC recurrence is the dependent variable (Y variable) and the outcome of the study, and the 11 influencing factors are the independent variables. The independent variables of this study are 11 and the sample size is 439, and the ratio of variables to sample size is about 40 (it’s more than 5 times), so the sample size should be enough.
Comment 9:- First sentence of discussion is not correct. The factors listed were associated with worse survival, not worse "pathological outcomes" of UTUC.

Response: Thanks a lot for pointing out the error. We have corrected this mistake by changing "pathological outcomes" into “survival”.

Comment 10:- The conclusions mentioned in the discussion and conclusions sections are not original in that the recommendations for close follow -up and minimizing risk factors like smoking are not new and are already known to most urologists. Associations of high grade/stage and increasing age with poor outcomes, for example, are well known. The statement that ureteroscopy should NOT be used in diagnosis of UTUC on the other hand is much too strong and not supported by the data presented.

Response: Thank you for your pertinent advice. The conclusion is to summarize the results of our research, and each study could have original and non-original conclusions. The problem of our conclusion you mentioned is that we didn’t highlight the characteristics of our research. This problem does exist. So we rewrote the conclusion. The renewed words were showed on page 8, line 333-341.

We have changed the statement that “ureteroscopy should not the primary method for diagnosing UTUCs” into “preoperative ureteroscopy should not be the primary and routine method for diagnosing UTUCs if the imaging diagnosis is relatively clear”(the change was shown on page 7, line 293-294). The logistic regression analysis of risk factors of postoperative BC recurrence showed preoperative ureteroscopy was related with bladder cancer recurrence statistically (P=0.003). (Results 3.3 section and table 3 presented this result). We thought the result should be able to support the above conclusion.

Special thanks to you for your good comments.

#2 reviewer : Jamil Ghahhari.

The study in question is a retrospective analysis that presents, in my opinion, some important limitations, to be reported.
Comment 1: The manuscript was certainly well structured in the different parts (background / methods / Results / Discussion) although in the "background" section the authors mentioned too many data related to the methods. This aspect is to be reviewed.

Response: Thank you very much for your quite useful suggestion. The other reviewer also put forward the similar question. We have made correction carefully according to your comments. The sentences that you mentioned is “In this study, UTUC patients ……for the effective prevention and treatment of UTUCs.” It is not really suitable for writing in background. We have deleted it at your suggestion. Furthermore we added the following words “Since the epidemiology and disease characteristics of UTUCs may be related to different areas and the relationship between some debatable risk factors and UTUCs is unclear, we developed a database of UTUC in our region to investigate the risk factors of prognosis of UTUC and BC recurrence in central China. We hope that our research will contribute to the treatment of UTUCs and reduce the risk of recurrence of bladder tumors after RNU.” in the end of background. All the above added contents were showed on page 2, line 66-71. Besides, we also added those words “Currently, It is still controversial that the influence of some risk factors on UTUCs, such as diabetes mellitus (DM) with or without history of metformin medication, preoperative ureteroscopy, the low location of UTUC.” in the second paragraph of Background, which was showed on page 2, line 53-56. Thanks again.

Comment 2: Moreover, the risk factors proposed and analyzed (some well known and therefore not original, such as cigarette smoking, age, tumor characteristics) have not been well analyzed all adequately (for smoking, for example, had to be evaluated the number of cigarettes per day, years of exposure to cigarette smoke and passive smoking).

The study, although not original, remains a good analysis with a good sample of patients involved in a retrospective way.

Response: Thank you so much for this excellent suggestion. Since our preliminary negligence, we didn’t realize that those vague could make the readers so confused.

(1) The risk factors were well known and not original. Although, many influencing factors adopted in this study were not the first put forward by us, our study still presented the meaningful characteristics. 1. The data were mainly obtained from the population of the central areas of China, and the sample size is relatively large. 2. Besides, It is still controversial that the influence of some risk factors on UTUCs, such as DM with or without history of metformin medication, preoperative ureteroscopy, the low location of UTUC. The results of our study were on the basis of the large sample size, so the conclusion were more convincing. Since the epidemiology and disease characteristics of UTUCs may be related to
different areas and the relationship between the controversial risk factors and UTUCs is unclear, we developed a database of UTUC in our region to investigate the risk factors of prognosis of UTUC and BC recurrence in central China. We hope that our research will contribute to the treatment of UTUCs and reduce the risk of recurrence of bladder tumors after RNU. As your advice, we rewrote the conclusion as following: “In this study, the 5-year survival rate of UTUC patients from central China was not high compared to other regions, which deserved more attention. We found the advanced tumor stage and high-grade tumor were not only the risk factors for poor UTUC prognosis, but also for BC recurrence. Besides, preoperative ureteroscopy, DM without metformin use were high risk factors of BC recurrence and postoperative bladder perfusion chemotherapy was a protective factor. So we suggested that UTUC patients with the above risk factors of BC recurrence should be compulsively implemented with bladder perfusion chemotherapy regularly. In addition, we suggest that preoperative ureteroscopy should not be exercised except when the preoperative imaging diagnosis is difficult.” Those sentences were showed in page 8, line 333-341.

(2) How to define some influencing factors, for example smoking, taking Chinese medicine containing aristolochic acid, DM, etc. The following 3 paragraphs are the detailed explanation for the confused places.

A person's smoking history is determined by his smoking index, which is Number of cigarettes per day×Years of smoking. If smoking index is above 200, the subject was considered to have a history of smoking. No matter current smoking, or past smoking history.

The next is the question that “Taking Chinese herbs… does this include any amount/duration of ingestion?” The history of taking Chinese medicine containing aristolochic acid was considered if the following criterion was met: 1) taking Chinese herbal medicine or Chinese patent medicine containing caulis aristolochiae manshuriensis. And the duration of ingestion included the continuous use of caulis aristolochiae manshuriensis > 15 days, or discontinuous use for more than 2 months; 2) Continuous or intermittent use of other types of Chinese herbal or proprietary medicines containing aristolochic acid ingredients for more than 6 months.

Besides, we defined those two cases as diabetes. 1) Diabetes mellitus history diagnosed before; 2) The subjects’ fasting blood glucose (FBG) were ≥7mmol/L (at least 2 times), or random blood glucose levels were >11.1mmol/L. And those more than 50 years old was considered as old age. Low tumor location means ureteral urothelial carcinoma(UUC). The tumor clinical staging was performed according to the American Joint Committee on Cancer (AJCC) 2002; the tumor
grading was assessed based on the WHO pathological grading system of malignant urothelial cancer 2004.

Thanks again for your quite helpful advices.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in yellow in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.