Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-1192

Reviewer A: This is a interesting paper on a novel prediction tool for survival in sarcomatoid renal cell carcinoma, the paper is well written a could be considered for publication after some adaptations:

Comment 1: page 3 line 1 - you state "laterality was assessed but no trace of it is found in the paper

Reply 1: Initially, we downloaded information such as “laterality” and “marital status”, but after we checked the relevant information, we found that these factors had no statistical significance for OS and CSS. Therefore, “laterality” was not included in the model construction at the beginning and was revised. In the process, we also deleted individual factors such as marital status. We have deleted the relevant description in Patient variables.

Changes in the text: We deleted “laterality” “stage” “grade” in the passage, please see page 5, line 7-8.

Comment 2: page 3 "nomogram construction" - you only state a multivariate analysis, where is the mandatory univariate analysis that leeds to multivariate analysis?

Reply 2: During the single factor cox regression analysis of all factors, we found that all factors except race are statistically significant for OS, CSS ($P<0.1$), race ($P=0.4$), but we consider in multivariate analysis, the results may be different, so we noticed that race has statistical significance for OS during multivariate analysis.

Changes in the text: Please see Table 2 and page 9, line 12-16 in the text.

Comment 3: page 3 "web construction" - add years and centimeters to age and size

Reply 3: Agree and thanks to your suggestion.

Changes in the text: The age and tumor unit have been added to the calculator web page according to your requirements. (Please see the web in the web construction, Page 12, Line 10-11)

Comment 4: page 4 "results data" to avoid confusion - present results as : overall 3670 RCC of which 1894 SRCC and 1776 conventional RCC

Reply 4: Agree and thanks to your suggestion. We have changed the expression

in the text to avoid confusion.
Changes in the text: Please see details in page 9, line 1-2 in the text.

Comment 5: page 4 "prognostic nomograms and validation" - add 95% confidence intervals for reported values
Reply 5: Agree and thank you for your suggestions. We recalculated the in-dex values of the two models and their 95% confidence intervals. The OS and CSS of the two models are significantly different, and the p values are both less than 0.01.
Changes in the text: Please see page 10, line 14-18 in the text.

Comment 6: page 5 "web-based survival calculator" - I used the calculator and it is possible to enter contradictory values : e.G. tumor size >13.5cm ant T-stage 1 : this should be corrected
Reply 6: Thanks to your suggestion. We have noticed this problem, but it is technically difficult to implement. We use the Dynamic package in Rstudio to upload data to the web page to make a survival time calculator. DynNom is a generic function to display the results of statistical model objects as a dynamic nomogram in an 'RStudio' panel or web browser. DynNom supports a large number of model objects from a variety of packages. So when T staging and tumor size are used as two independent variable factors, Therefore, we can only use this R package to display the results without restricting certain conditions of the selection. However, as a clinician, these two conditions cannot be met at the same time. Therefore, we have to pay attention to the actual situation of the patient when choosing.
Changes in the text: the new website please follow the link in page 12, line 10-11.

Comment 7: page 6 "discussion" line 7 - add more recent research to referrences 7 and 8 e.g. Holz et al. Urol Oncol 2020 Sep 6;S1078-1439(20)30383-5.doi: 10.1016/j.urolonc.2020.08.017.
Reply 7: We have read your recommended literature in detail and found that it has a high reference significance, and added it to the cited literature.
Changes in the text: Please see the reference of No.10.

Comment 8: page 6 line 38 - rephrase For example, a 56-year-old Asian woman with pathological stage T3aN0M0 and a tumor diameter of 8cm has a 3-year CSS of 56.0% (95% CI 3948.0%−65.0%) if she undergoes surgery, whereas her 3-

year CSS is only 22.5% (95% CI 13.6%−37.0%) if she can't undergo surgery.
Reply 8: Thank you for your suggestion. Based on your and other reviewers' comments, we have deleted the examples in the discussion section. A discussion about the pathology of sarcoma-type renal cancer and the significance of model construction have been added to make it more in-depth and representative.
Changes in the text: Please see more details in page 13, line 1-8/line18 -22; page 15, line 5-11/line 15-18.

Comment 9: Table 2 - p values should not be indicated as "0" but <0.001
Reply 9: Agree and thanks to your suggestion.
Changes in the test: The corresponding P value has been modified. (Please see table 2)

Reviewer B: This is an interesting paper on a huge cohort of patients with sarcomatoid RCC (sRCC). The authors developed an OS and a CSS nomogram and a web-based survival rate calculator predicting the OS and CSS of sRCC patients. Several points should be considered:

Comment 1: Abstract and conconculsion: Despite the fact that these new nomograms present better discrimination than previous ones, I would not claim c-indicies of about 75% as good. They are rather fair or moderate as still a quarter of patients is inaccurately counseled. This needs to be changed.
Reply 1: Agree and thanks for your suggestion. We have change the expression in the text and make it more suitable.
Changes in the text: Please see page 3, line 1-2.

Comment 2: Intro/Discussion: It should be clarified what type nomogram this is: a pre- or post treatment nomogram. This should also be included to the title.
Reply 2: Agree and thanks for your suggestion. This model includes both pre-treatment and post-treatment patients. Some patients have undergone surgery while some patients have not undergone surgery, and some patients only survive for a short time after diagnosis. The model obtained by summarizing all the data together predicts the clinical prognosis for a specific patient with different characteristics.
Changes in the text: Please see the title in page 1 and page 16, line 5.

Comment 3: Material and methods: What type of stage was used? Clinical or pathological? Please explain and add to the manuscript. Both can not be mixed as

the accuracy of data is completely different.
Reply 3: The stage we used refers to the clinical stage, but one of the reviewers pointed out that our clinical stage has a high correlation with the TNM staging in the article, so in the cox multivariate regression analysis, it may affect each other. Therefore, in the revised manuscript, we retained the more accurate T/N/M of stage and deleted the clinical stage, and deleted the patients with incomplete information in the T/N/M stage to make the results more accurate.
Changes in the text: We have modified the model and please see table 1 and table 2.

Comment 4: Material and methods: If patients did not undergo surgery: how was the histological subtype identified?
Reply 4: For patients who have not undergone surgery, pathological tissues can be obtained through needle biopsy for diagnosis.
Changes in the text: We have notice the source of the pathology. Please see page 4, line 20-21.

Comment 5: Material and methods: It would be of greatest value adding the extent of sarcomatoid component to the nomogram, as this does impact course of disease and outcomes.
Reply 5: Agree and thanks to your opinion. Unfortunately, the information obtained through the SEER database is limited, and the specific sarcoma-like percentage in the pathological tissues is not included. It may be because the patient's pathological report information was not uploaded to the seer database in detail, or we were unable to download it. This is the limitation of this article.
Changes in the text: Please see the page 14, line 5-6.

Comment 6: Material and methods: Please include margin status to the nomogram
Reply 6: Thanks for your suggestion. Similarly, the resection margin status is not included in the downloadable patient information. There is no doubt that this data can significantly affect the patient's prognostic survival time and tumor recurrence and progression.
Changes in the text: Please see page 14, line 9-10.

Comment 7: Material and methods: Which type of additional or subsequent treatment did patients receive? This is of utmost importance as treatment in the metastatic setting is a major driver for outcomes, especially since introduction of

Checkpoint-inhibitor therapies.
Reply 7: Agree and thanks to your suggestion. Unfortunately, we cannot download specific information about patient treatment from the database. But this is really important for prognostic analysis. Regarding the treatment of checkpoint inhibitor therapy, such as the application of PD-1, it has been approved by the US FDA for clinical use since 2015. Our data is downloaded from patients with sarcoma-type renal cancer during 2004-2015, so these patients did not apply relevant treatments.
Changes in the text: Please see page 14, line 16-18.

Comment 8: Material and methods: If this is a pre-treatment nomogram (what I assume), please include the variable synchronous metastasis
Reply 8: The nomogram is based on the patients both pre- and post-treatment. We cannot get all the distant metastasis positions and numbers from the seer database. We have added more detailed explanation in the discussion section.
Changes in the text: Please see page 14, line 9-15 in the text.

Comment 9: Material and methods: To improve validity of the nomogram, I recommend excluding patients with missing information on nodal or metastasis status. Since the nomogram has a variable "X", it seems, not all patients were completely staged.
Reply 9: Agree and thanks for your advice. We have deleted the unknown patient information in T/N/M according to your opinion and re-included it in the analysis and modeling. The model results are more optimized than before.
Changes in the text: Please see figure 1, table 1, table 2, and page 9, line 1-7 in the text.

Comment 10: Discussion: A one page discussion of a complex statistical method including nomogram construction and decision curve analysis is absolutely insufficient. The value of this newly developed nomogram remains mainly uncommented and is not adequately discussed in the context of literature. An entire paragraph of a case example discussion is a no brainer in this context.
Reply 10: Agree and thanks for your suggestion. We have deleted the examples in the discussion section and discussed in detail the value and significance of the prognostic model in this article, also added relevant opinions to the rare pathology in the discussion section.
Changes in the text: Please see more details in page 13, line 1-8/line18 -22; page 15, line 5-11/line 15-18.

Comment 11: Table 2: A p-value can not be zero.
Reply 11: Agree and thanks for your suggestion. The corresponding P value has been modified.
Changes in the text: Please see table 2.

Reviewer C: Authors created nomograms for predicting 3- and 5-year OS and CSS rates in patients diagnosed with sarcomatoid RCC within the SEER database (2004-2015).
Several major and minor revisions are required:

Comment 1: Major limit is the definition of sarcomatoid RCC. Specifically sarcomatoid variant is a de-differentiation of clear cell or non-clear cell RCC and not a properly histologic variant. Authors should intensively discuss this point
Reply 1: Agree and thanks for your suggestion. We have discussed in detail the value and significance of the prognostic model in this article, also added relevant opinions to the rare pathology in the discussion section as well as add more relevant explanations in the discussion section.
Changes in the text: Please see page 12, line 21-22 and page 13, line 1-8.

Comment 2: Authors should more intensively explain how they selected cases for development and validation: SEER registries?? Other explanations? Otherwise authors could use bootstrap resamples
Reply 2: Agree and thanks to your suggestion. As some reviewers suggested that Stage and TNM staging are highly correlated, which will affect the results of multi-factor cox regression analysis, we have retained the more accurate TNM staging and deleted the stage. At the same time, we checked the relevant literature and deleted the positions and marital status that were of little clinical significance. Since pathology now classifies sarcoma-type renal cancer as a high grade, we also delete grade.
Changes in the text: According to your opinion, we have made the specific inclusion and screening criteria into a flowchart, as shown in figure 1, also modified in page 9, line 1-8.

Comment 3: I believe these nomogram are not useful in clinical practice. Why authors include both metastatic and non metastatic tumors? Why both surgically and non surgically treated? It should be better to focus on a specific setting
Reply 3: Thanks for your advice. The nomogram we designed is to summarize

the information characteristics of common clinical patients, such as age, gender, T/N/M staging, etc. We take surgery or not as one of the options, and the estimated survival time results can be better guide the patient's next treatment. Because in clinical work, when a patient suffers from cancer, it is often accompanied by metastasis and later staging. Therefore, the patient and doctors are concerned about how long the survival difference can be caused by surgery or not and different metastatic stage. Therefore, we will compare the different prognosis with surgery or not by using the model, the purpose is to specify the survival benefits of a patient with a specific characteristic.

Comment 4: Information about systemic therapies are lacking
Reply 4: Thanks for your suggestion. Unfortunately, we cannot download specific information about patient treatment from the database. But this is really important for prognostic analysis. Regarding the treatment of checkpoint inhibitor therapy, such as the application of PD-1, it has been approved by the US FDA for clinical use since 2015. Our data is downloaded from patients with sarcoma-type renal cancer during 2004-2015, so these patients did not apply relevant treatments.
Changes in the text: Please see page 14, line 9-18 in the text.

Comment 5: The paragraph about AUC (explanation of AUC) is not useful and could be deleted
Reply 5: Agree and thanks to your suggestion. We have delete the explanation of AUC according to your suggestion.
Changes in the text: Please see page 6, line 10-18.

Comment 6: Why did authors used the following strata for age: <62, 62-76 and >76? Please create more clinically useful strata (for example <60 vs 60-75 vs >75). Moreover this categorial data should be reported in table 1. Moreover, why did authors use decades in Cox models? Please be consistent throughout the manuscript
Reply 6: Agree and thanks to your suggestion. In most cases of clinical research, the relationship between continuous indicators and outcomes is not linear. For example, the relationship between age and tumor occurrence may suddenly increase after the age rises to a certain value. In addition, continuous indicators are used in clinical applications. It is not as convenient as classification index, so when clinical application of relevant index always find a way to find a normal range or cut-off value. We use x-tile software to divide according to the cutoff

value, which maximizes the statistical significance. It is concluded that the two values of 62 and 76 are the best and have the greatest statistical significance. In addition, the age in Table 1 is divided by x-tile, and we have changed the application synchronously.
Changes in the text: Please see table 1and table 2.

Comment 7: Why did authors used the following strata for size: <5.5, 5.5-13.5 and >13.5? Please create more clinically useful strata (for example <5 vs 5-10 vs >10). Moreover this categorial data should be reported in table 1. Moreover, why did authors use another categorization in Cox models? Please be consistent throughout the manuscript
Reply 7: Similarly, when applying X-tile analysis, we found that the two values of 5.5 and 13.5 are statistically significant. In clinical work, the size of the patient's tumor is often estimated by CT, and the scan level of CT is 5 mm each, which can meet the purpose of clinical decision-making. We also modify the classification in the cox model simultaneously.
Changes in the text: Please see table 1 and table 2.

Comment 8: Authors could create a consort diagram with inclusion and exclusion criteria with numbers
Reply 8: Agree and thanks to your suggestion. The detailed inclusion and exclusion criteria are made into a flowchart, as shown in Figure 1.
Changes in the text: Please see figure 1 and page 9, line 1-8 in the text.

Comment 9: Please report p-values in Table 1
Reply 9: Agree and thanks to your suggestion. The corresponding P value has been modified. Figure 1 only shows the number and percentage of classifications in the training set and validation set. The training set and the validation set are divided according to 7:3.
Changes in the text: Please see table 1.

Comment 10: Please report crude numbers of deaths for OM and CSM
Reply 10: Agree and thanks for your suggestion. We have add the death numbers in detail of overall and SRCC specifically.
Changes in the text: Please see page 9, line 21-22.

Comment 11: The part about DCA could be removed or simplified. Moreover, it has to be moved to materials and methods

Reply 11: Agree and thanks to your suggestion. We have moved DCA to materials and methods and also make it simplified.
Changes in the text: Please see page 7, line 1-10 and page 11, line 3-9.

Comment 12: I believe authors could remove tumor grade from their analysis, since sarcomatoid dedifferentiation means a “high grade” tumor
Reply 12: Considering that sarcoma-like differentiated renal cell carcinoma is of high grade, we have deleted grade according to your suggestion.
Changes in the text: Please see table 1, table 2 and page 5,line 7-8 in the text.

Comment 13: I think authors could re-calculate tumor stages since there are a lot of missing data
Reply 13: We followed your opinion of question No.15, so we deleted the Stage, kept the more accurate T/N/M staging and deleted the patients with missing data and then re-analyzed.
Changes in the text: Please see figure 1, table 1, table 2 and page 9, line 1-8 in the text.

Comment 14: Authors could simplify their T stage categories: T1 vs T2 vs T3 vs T4 vs Tx
Reply 14: Thank you for the suggestion. In accordance with the opinions of you and other reviewers, patients with missing information were deleted and re-included in the analysis. The results were more accurate than before. However, in the classification of T3, because T3a/T3b/T3c respectively refer to tumor thrombi located in the renal vein/inferior vena cava below the diaphragm/inferior vena cava above the diaphragm, patients with different clinical characteristics have obvious prognostic differences, so we don’t merged together.
Changes in the text: Please see Table 1 ,Table 2 and website from the link in page 12, line 10-11 .

Comment 15: Is not correct to fit Cox models with both stage and TNM, since these variables are highly correlated. I suggest to remove staging
Reply 15: Agree and thanks to your suggestion. We have deleted the unknown patient information in T/N/M and Stage of patients according to your opinion and re-included it in the analysis and modeling. The model results are more optimized than before.
Changes in the text: Please see table 1 and table 2 and statement in page 5, line

7.

Comment 16: How is possible that T3c is associated with higher OM rates, relative to T4? Please recode T stage

Reply 16: Thanks for your suggestion. We consider that there are only 40 patients in T3c stage and 373 patients in T4 stage. Therefore, insufficient sample size may cause statistical errors. On the other hand, after read the relevant literature, we found it is possible that patients in T3c stage will survive less than T4 stage. In the T stage of renal cell carcinoma: T3c stage refers to the presence of tumor thrombi in renal blood vessels, and the tumor thrombus exceeds the diaphragm. T4 stage refers to tumor metastasis to other organs, such as lung metastasis, liver metastasis, etc. Taken together, because the T3 stage tumor thrombus tissue is closer to the heart, and the tumor thrombus can fall off and cause pulmonary embolism and other conditions that may lead to sudden death or cardiac accidents, although T4 stage patients have distant metastases, the number is not defined. Both prognosis survival time is poor, but patients in T3c stage may have a shorter survival time.

Changes in the text: We have discussed through the point in page 15, line 5-11.