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## Reviewer Comments

In this study, a nomogram is being developed that can predict the overall survival of RCC patients. The research method was divided into the development (n=40154) cohort extracted from the SEER database and the validation (n=1188) cohort from the TCGA database, and was analyzed in a considerable number of cases. As a result, ROC curves with appreciable AUC were obtained and nomograms with high predictive accuracy were developed.
However, the prognostic factors extracted by the study were TNM stage, tumor size, tumor grade, and so on. The TMN stage was originally created to predict cancer recurrence and prognosis, and tumor size is a strongly significant factor that defines the stage of RCC. It was considered natural that these factors were extracted as significant factors in this study, and no particularly new findings were obtained from this study. In addition, it is considered clinically meaningless to verify early stage cancer without metastasis and metastatic renal cancer with the same prognostic prediction tool.
Considering these points, the following points should be revised.

Majors:

**1. Regarding prognostic studies in patients with renal cell carcinoma, I think the authors cannot help but mention whether surgery was performed or not and what type of drug treatment was used. In the Discussion, please mention the presence or absence of surgery and drug treatment for advanced metastatic cases.**

Reply 1: We really thank you for your thoroughly review our manuscript. Actually, we have elaborated the surgical modality in the "*Data Source and Patient Selection*" portion. According to the interpretation of the seer database (codes in the following figure), we excluded patients who were not undergoing nephrectomy and those whose surgical modality was unknown (code 00, 10, 11, 12, 13, 14, 15, 16, 20, 21, 22, 23, 24, 25, 26, 27, 90, or 99), and all patients underwent partial nephrectomy or radical nephrectomy. Because there are too many categories of other treatments but only few patients. We add a new sentence in the first paragraph in "Discussion" part to illustrate this point.

For the moment, although surgery remains the mainstay of treatment for renal cell carcinoma, with the development of next-generation VEGF-targeted therapies, immunotherapy agents, and combination regimens, the treatment landscape for advanced and metastatic RCC is changing, Since you mentioned the same problem in the following comment, we give an answer together below, thank you very much.
Changes in the text: Page 5, line 174-175.

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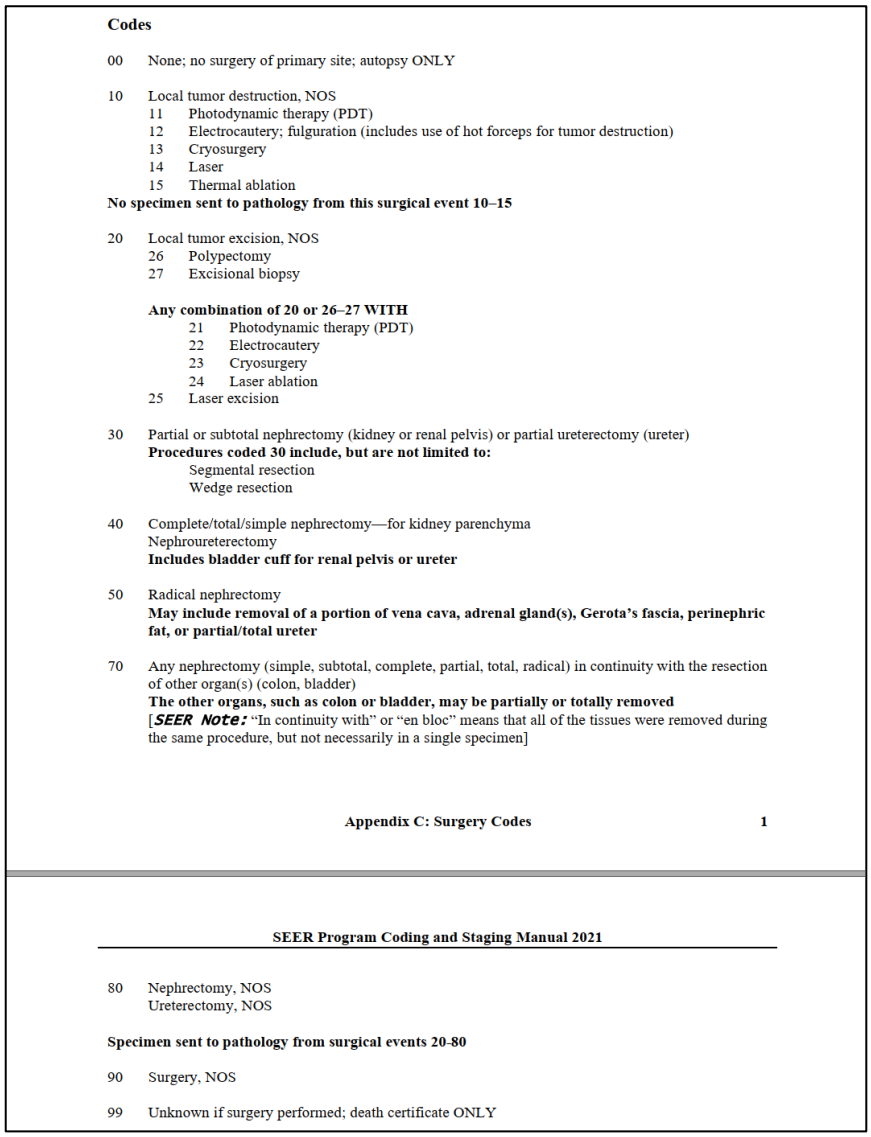
**2. From a similar perspective as above, the SEER database used in this study was from 2010 to 2015. This period was a time of transition to the age of cytokine therapy, the age of molecular-targeted drugs, and the age of immune checkpoint inhibitors as drug therapy for**



**Codes**

00 None; no surgery of primary site; autopsy ONLY

10 Local tumor destruction, NOS
- 11 Photodynamic therapy (PDT)
- 12 Electrocautery; fulguration (includes use of hot forceps for tumor destruction)
- 13 Cryosurgery
- 14 Laser
- 15 Thermal ablation

**No specimen sent to pathology from this surgical event 10–15**

20 Local tumor excision, NOS
- 26 Polypectomy
- 27 Excisional biopsy

**Any combination of 20 or 26–27 WITH**
- 21 Photodynamic therapy (PDT)
- 22 Electrocautery
- 23 Cryosurgery
- 24 Laser ablation

25 Laser excision

30 Partial or subtotal nephrectomy (kidney or renal pelvis) or partial ureterectomy (ureter)
**Procedures coded 30 include, but are not limited to:**
Segmental resection
Wedge resection

40 Complete/total/simple nephrectomy—for kidney parenchyma
Nephroureterectomy
**Includes bladder cuff for renal pelvis or ureter**

50 Radical nephrectomy
**May include removal of a portion of vena cava, adrenal gland(s), Gerota's fascia, perinephric fat, or partial/total ureter**

70 Any nephrectomy (simple, subtotal, complete, partial, total, radical) in continuity with the resection of other organ(s) (colon, bladder)
**The other organs, such as colon or bladder, may be partially or totally removed**
[***SEER Note:*** "In continuity with" or "en bloc" means that all of the tissues were removed during the same procedure, but not necessarily in a single specimen]

**Appendix C: Surgery Codes** **1**

**SEER Program Coding and Staging Manual 2021**

80 Nephrectomy, NOS
Ureterectomy, NOS

**Specimen sent to pathology from surgical events 20-80**

90 Surgery, NOS

99 Unknown if surgery performed; death certificate ONLY

**renal cancer. The prognosis of metastatic renal cancer, in particular, would have been very different depending on which type of drug was primarily used. Is it possible to guess which drug era can prolong the prognosis? Especially in patients with distant metastases, was there a difference in prognosis depending on the time of registration? Please add data or comment on this point in the Discussion.**

Reply 2: We really admire the professionalism of the reviewer. The reason we chose patients from 2010 to 2015 is that all patients used 7th edition of AJCC renal cell carcinoma staging system (reduce the heterogeneity of data). As you said, molecularly targeted drugs as well as immune checkpoint inhibitors can greatly benefit the survival in RCC patients. It is reasonable that we should include the patient drug profile in the prediction model. However, based on the limited nature of the seer database, the information related to drug treatment is missing, we kindly ask your understanding. But we added a new paragraph in the "Discussion" section to talk about this topic, we hope you are satisfied with this.

Changes in the text: page 5, line 190-196.

**3. One of the reasons why age at diagnosis was extracted as a significant factor is that the outcome was the overall survival rate, that is, the event included not only death due to renal cancer but also death due to other causes. Would it be possible for the authors to analyze the cancer-specific survival rate as an outcome?**

Reply 3: Thank you for your reminder. Indeed, cancer-specific survival rates provide a more accurate indication of survival rates in RCC patients. We tried to use cancer-specific survival time in kidney cancer patients in seer database first, but we found that most patients lacked such information, which led to the failure of prognostic model construction. So, we finally chose overall survival as the study endpoint.
Changes in the text: no change in the manuscript.

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**4. We clinicians already know that metastatic cancer has a poor prognosis, and risk classifications such as IMDC have been established. What we need to know most is the overall survival rate in the real world limited to cases without metastasis (M0), and the poor prognostic factors that determine the prognosis. Did the analysis of M0 alone yield any useful findings?**

Reply 4: First of all, we thank the reviewer for reading our article carefully and putting forward very valuable comment. We indeed analyze the M0 patients' prognosis again. The results of the analysis are as follows:
First, we excluded RCC patients with M1 from the original data (2,172). We finally get 37,982 M0 patients from seer database. Then we create a new nomogram (figure C), and we recalculated the AUC curve of the model. We found the 3-year AUC was 0.733 (figure A) and 5-year AUC was 0.728 (figure B), which also shows the good results. However, compared with the initial prognosis model, its performance did not improve significantly (instead, it reduced). Actually, all the patients with M1 were AJCC stage IV. Compared with AJCC stage IV patients with M0, there was only a slight difference in survival, especially the median survival time. In that case, there is little significance in creating a new model for patients with M0. We hope you will be satisfied with our answer, thank you very much.
Changes in the text: no change in the manuscript.

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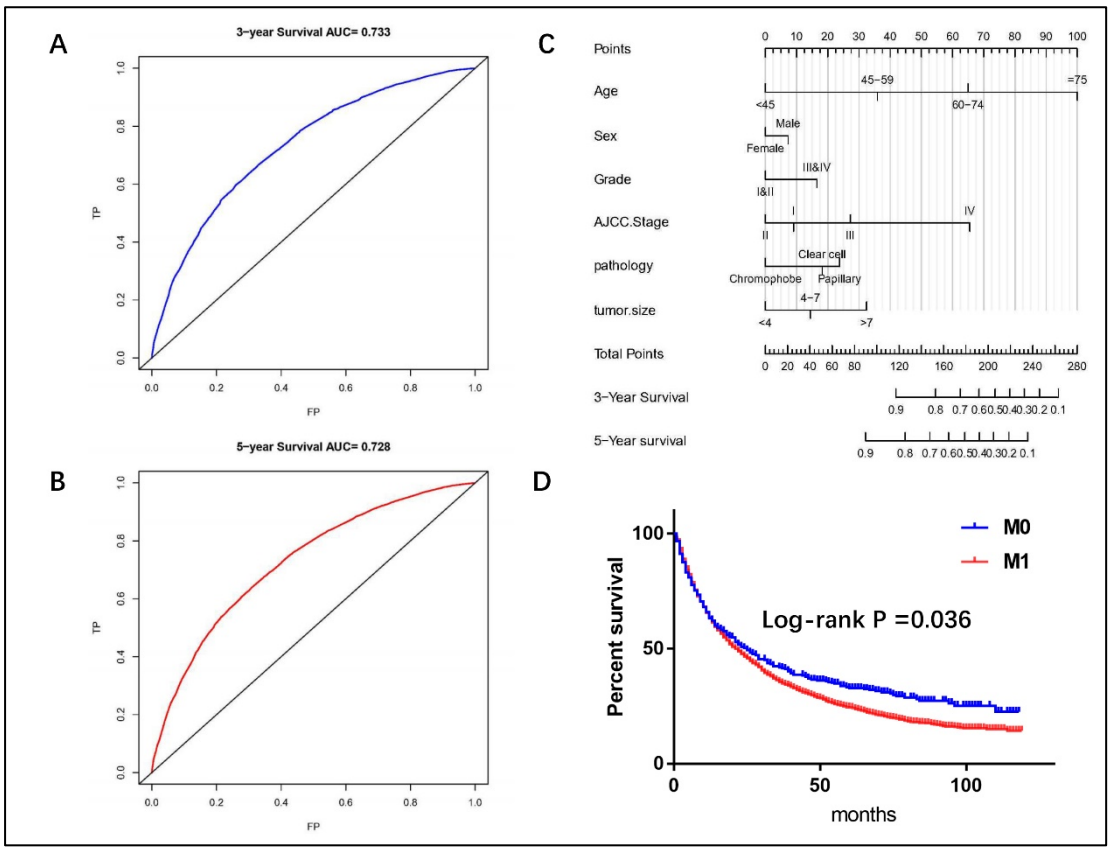
A
3−year Survival AUC= 0.733
TP
FP
B
5−year Survival AUC= 0.728
TP
FP
C
Points
Age
Sex
Grade
AJCC.Stage
pathology
tumor.size
Total Points
3−Year Survival
5−Year survival
45−59
=75
<45
60−74
Male
Female
III&IV
I&II
I
IV
II
III
Clear cell
Chromophobe
Papillary
4−7
<4
>7
D
M0
M1
Log-rank P =0.036
Percent survival
months