

Peer Review File

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Reviewer A

This paper looks at creation of a nomogram to predict OS in a surgical cohort undergoing nephrectomy and venous thrombectomy.

I will suggest the following edits

(i) with the evolution systemic therapy options especially in the immuno-oncology era, how will that affect the OS measurements in this nomogram? This should be discussed by the authors as it will affect the applicability of this nomogram in contemporary practice

Reply 1: Dear reviewer, we have summarized the systemic treatment received by the patients, of which 58 (50.8%) received targeted therapy and 56 (49.2%) did not receive targeted therapy. Unfortunately, our results did not suggest a survival benefit from targeted therapy in this patient population. (The term "targeted therapy" used in this article refers to postoperative targeted therapy.)

In recent years, the application of tyrosine kinase inhibitors such as sunitinib and sorafenib has significantly improved the prognosis of metastatic renal cell carcinoma [1]. There is currently controversy over whether to use TKI-type targeted drugs after surgery for high-risk non-metastatic renal cancer. Although some studies have found that using sunitinib after surgery for high-risk non-metastatic renal cancer is beneficial [2], multiple clinical trials on adjuvant therapy for high-risk non-metastatic renal cancer have been conducted worldwide, including several studies on targeted therapy that have yielded few positive results [3].

Changes in the text:

we have modified our text as advised (see Page 3, line 53-59) ; we added some data we added some data (see Table 1 and Table 2)

(ii) the majority of patients are node negative - how will this affect the nomogram performance in a case with node metastasis? In node negative patients, is this classified as pathological N0 or clinical N0- this is not clear in the manuscript and will impact the utility of the nomogram

Reply 2: Thank you for the detailed review of this article. Our center performs lymph node dissection only when there is evidence of lymph node enlargement on preoperative imaging. Patients are classified as N1 only if tumor cells are present in the lymph nodes removed during surgery. According to these criteria, our study found no significant correlation between lymph node metastasis and patient survival. The Cox univariate analysis included postoperative lymph node involvement, but it was found to be unrelated to patient survival and therefore was not included in the nomogram. The value of lymph node dissection in radical nephrectomy for kidney cancer has been a subject of controversy. Some

researchers believe that lymph node dissection offers no survival benefit for kidney cancer patients [4]. Clinical regional lymph node dissection is often performed to determine the local stage of the tumor and may guide decisions regarding adjuvant therapy, but it is unclear whether it provides survival benefits on its own [5, 6]. Karmali et al. [7] analyzed sentinel lymph nodes in kidney cancer patients and found that renal cell carcinoma is more prone to hematogenous metastasis rather than lymphatic spread. Patients with regional lymph node metastasis often have distant metastasis already, and only 2% to 5% of patients have lymph node metastasis without distant spread. Therefore, lymph node metastasis may not be an independent risk factor for patient prognosis.

Changes in the text:

we have modified our text as advised (see Page 16-17, line 340-367)

(iii) length of stay was significant in the multivariate analysis - what is the prognostic impact of this factor? and how does it affect the nomogram development?

Reply 3: Firstly, I would like to express my gratitude for the expert's advice. There is a significant difference in hospitalization time between the survival group and the deceased group. The generation of this difference is associated with factors such as the patient's preoperative condition (such as age, presence of diabetes or hypertension), postoperative complication severity and recovery, hospital nursing level, and patient subjective preferences. Considering these factors, we did not include hospitalization time as a variable in our analysis of prognostic factors.

(iv) this nomogram should ideally be validated in a population if possible

Reply 4: Thank you for your valuable feedback. In fact, the validation of the nomogram in the population is a goal that the authors strive to achieve. However, due to the rarity of cases of renal cancer with tumor thrombus, conducting multicenter, large-sample studies poses significant challenges at present. Our study has comprehensively analyzed non-metastatic patients from our center between 2011 and 2022. Unfortunately, the patients from 2023, with a shorter follow-up time, may introduce bias. Therefore, it is regrettable that we were unable to validate this offline chart in the population. We will acknowledge this limitation and, as soon as the conditions are overcome, the authors will make immediate efforts to conduct multicenter validation studies.

Reviewer B

This is a paper on prognostic factors for renal cancer with tumor thrombus, which I found very interesting. However, I have several concerns, and I kindly request you to clarify the following.

There are numerous laparoscopic cases. Are grade 0 tumors those in which the tumor thrombus has only advanced into the renal vein?

Reply 1: First and foremost, I express my gratitude to the knowledgeable experts for their valuable input and assistance in enhancing the text for the purpose of

plagiarism checking. Yes, there are several methods for grading venous tumor thrombus, and common grading systems include the Mayo classification, renal cell carcinoma TNM staging, and the 301 grading system. Among them, the grading system proposed by Mayo Clinic is the most commonly used and clinically practical. In the Mayo classification, Grade 0 tumor thrombus refers to a thrombus confined to the renal vein. The surgical approach involves complete removal of the affected kidney and the renal vein containing the thrombus, similar to radical nephrectomy. In this study, there were a total of 48 patients with Grade 0 tumor thrombus, accounting for 42% of the cases.

Changes in the text:

we have modified our text as advised (see Page 8, line 169)

Were there no cases that transitioned from laparoscopic to open surgery mid-procedure?

Reply 2: Many thanks to the experts for their careful reading. There are no such patients.

It seems that whether there was infiltration into the venous wall or how much the tumor was in contact with the venous wall could influence the difficulty of the operation more than the tumor size. Please consider examining this further.

Reply 3: We appreciate the expert review. This aspect was taken into consideration during the initial design of the study. The pathological reports of the patients were reviewed, and only 5 patients were found to have evidence of tumor thrombus infiltrating the vein wall. Due to the small number of patients, they were not included in the study. However, we have briefly reviewed relevant literature and conducted discussions as follows:

In recent years, the significance of infiltrating the inferior vena cava (IVC) wall in patients with renal cell carcinoma and IVC tumor thrombus has gained recognition. Studies have demonstrated that patients with tumor thrombus invading the IVC wall and not undergoing resection have a 5-year survival rate of 26%, whereas those who undergo resection can achieve a 5-year survival rate of 57% [8] [9]. Consequently, resecting the invaded vessel wall becomes imperative for patients with IVC wall invasion. However, it is important to acknowledge that radical nephrectomy + IVC tumor thrombectomy + segmental resection of the IVC carries a higher surgical risk, necessitating careful consideration of postoperative complications. Therefore, accurate assessment of invasion is of utmost importance, and MRI of the IVC serves as a valuable tool for determining both the length of the tumor thrombus and its invasion of the IVC wall. Notably, MRI exhibits a reported sensitivity, specificity, and accuracy of 100%, 89%, and 92%, respectively, in diagnosing tumor thrombus infiltration of the IVC wall [10]. In a retrospective analysis by GOHJI et al. [11], data from 18 patients who underwent IVC tumor thrombectomy revealed that an IVC diameter greater than 40 mm on preoperative abdominal CT constitutes a risk factor for IVC wall invasion by the tumor thrombus. While preoperative imaging examinations offer some insight into the extent of IVC wall invasion by the tumor thrombus,

intraoperative visual inspection remains a reliable and effective method. Intraoperative indicators of tumor thrombus invading the IVC wall include a rough and non-smooth appearance of the vessel wall after incision, whitening of color, harder texture upon palpation, and poor vascular elasticity. In conclusion, a comprehensive approach incorporating preoperative imaging and intraoperative assessment is pivotal for tailoring individualized treatment plans and selecting appropriate surgical approaches for patients.

The explanation of the DCA curve in Figure 5 is very unclear. Could you add annotations or provide a detailed explanation in the main text?"

Reply 4: I would like to sincerely express my gratitude and appreciation towards the knowledgeable experts who have generously contributed their valuable insights and assistance in enhancing the text for the specific purpose of plagiarism checking. I am truly grateful for their expertise and guidance in ensuring the integrity of the content.

We have added more detailed explanations in the Methods section, as follows:

Decision curve analysis (DCA) is a statistical method used to evaluate and compare the clinical utility of different prediction models or diagnostic tests. It provides a framework for assessing the net benefit of using a particular model or test in clinical decision-making. In DCA, a set of threshold probabilities is defined, representing the clinician's willingness to treat or intervene based on the predicted probability of an outcome. The net benefit is calculated by weighing the benefits and harms at each threshold probability. By plotting the net benefit against the threshold probability, the performance of different models or tests can be compared. A model or test with higher net benefit over a wide range of threshold probabilities indicates superior clinical utility. In addition, calibration curve, also known as a calibration plot or reliability diagram, is a graphical representation that assesses the performance and calibration of a predictive model, was adopted to evaluate how well the predicted probabilities from our risk score system with the actual observed outcomes and determine whether our model is overconfident or underconfident in its predictions.

We have added more detailed explanations in the Results section, as follows:

In the bootstrapped DCA analysis conducted on patients with thrombus, the risk score exhibited a significantly higher net benefit in accurately predicting OS, particularly in the 5-year period. This was in comparison to preoperative LDH, neutrophil count, tumor thrombus grading, and tumor diameter (Figure 4A). Moreover, when examining the bootstrapped calibration plots of the risk score, it can be observed that there were no adverse deviations between the predicted risk and observed risk for 1-, 2-, 3-, and 5-year OS across the entire range (Figure 4B).

Changes in the text:

we have modified our text as advised (see Page 6,7,10, line 134-156, line 203-211)

Reviewer C

The manuscript is systematically organized, focusing on evaluating factors that impact the prognosis of non-metastatic renal carcinoma patients with VTT. It aims to equip clinicians with a research-based framework for prognosis prediction in this demographic. The importance of this study, especially considering the intricacies of RCC with VTT treatment, is evident.

Introduction:

Lines 45-64: This segment effectively gives an overview, emphasizing the importance of the vein system invasion in renal carcinoma and its challenges. It would be beneficial to expand on the "considerable challenges and risks associated with surgery" and elucidate why it's the preferred treatment. The authors should consider also discussing the possible role of systemic immunotherapy in this particular setting.

Reply 1: Dear reviewer, we added some discussion about significant challenges and risks associated with surgery: Renal cell carcinoma with venous tumor thrombus is a disease in the urological system that is associated with poor prognosis and significant treatment challenges. Patients with renal cell carcinoma and tumor thrombus who do not undergo surgical treatment have an extremely poor prognosis, with an average survival period of 4-6 months and a 5-year overall survival rate of 0-10% [12, 13]. A study analyzed data from 390 untreated patients with renal cell carcinoma and tumor thrombus using the SEER database. Among these patients, 278 died during the follow-up period, with 243 deaths attributed to renal cell carcinoma. The median survival period for these patients was only 5 months, and the one-year survival rate was only 29% [14]. Review of a large series of patients treated with systemic targeted therapy with in situ RCC tumor thrombi revealed minimal clinical effect on the tumor thrombus level and failed to demonstrate a significant impact on the surgical approach in those proceeding to thrombectomy[15, 16]. Most studies have confirmed that for patients with renal cell carcinoma who have venous tumor thrombus without distant metastasis, surgical treatment is still the primary treatment modality and has shown good efficacy, with a five-year disease-free survival (DFS) rate ranging from 39% to 60% [17, 18]. However, surgical treatment for patients with renal cell carcinoma and tumor thrombus is relatively challenging, with higher surgical risks. Intraoperative tumor thrombus detachment may lead to pulmonary embolism and patient mortality. Therefore, careful evaluation of patients is necessary before selecting a treatment approach.

Changes in the text:

we have modified our text as advised (see Page 3-4, line 53-69)

Patients and Methods:

Lines 66-111: This part is systematically laid out. Adding exclusion criteria would help clarify which patients were deemed unsuitable for the research.

Reply 2: We have included exclusion criteria in the manuscript as follows:

Exclusion criteria: ①Patients with preoperative imaging suggesting the presence of metastasis. ②Patients who underwent incomplete surgical procedures, such as exploratory laparotomy without tumor resection. ③Patients who were lost to follow-up.

Changes in the text:

we have modified our text as advised (see Page 5, line 98-102)

Lines 81-84: How was a patient's "passing" verified during the monitoring period?

Reply 3: Dear reviewer, "passing" means all patients are followed up via telephone or outpatient visits, and there are no patients lost.

Changes in the text:

we have modified our text as advised (see Page 5, line 106-107)

Lines 86-110: The statistical approaches are detailed comprehensively. Delving into the reasons for choosing specific tests over others could be informative for those less versed in statistical methodologies.

Reply 4: We add more detailed explanations in the Methods section as follows:

Decision curve analysis (DCA) is a statistical method used to evaluate and compare the clinical utility of different prediction models or diagnostic tests. It provides a framework for assessing the net benefit of using a particular model or test in clinical decision-making. In DCA, a set of threshold probabilities is defined, representing the clinician's willingness to treat or intervene based on the predicted probability of an outcome. The net benefit is calculated by weighing the benefits and harms at each threshold probability. By plotting the net benefit against the threshold probability, the performance of different models or tests can be compared. A model or test with higher net benefit over a wide range of threshold probabilities indicates superior clinical utility. DCA enables the identification of models that provide added value beyond traditional approaches or existing standards of care. It helps clinicians make informed decisions about the adoption and implementation of prediction models or tests in real-world scenarios. To compare the clinical benefit of applying novel risk score system in clinical practice when comparing with other parameters, including LDH, neutrophil, thrombus grading and tumor diameter, we applied DCA curve to assess prognostic benefit of risk score system, which was illustrated by R package ggDCA. In addition, calibration curve, also known as a calibration plot or reliability diagram, is a graphical representation that assesses the performance and calibration of a predictive model, was adopted to evaluate how well the predicted probabilities from our risk score system with the actual observed outcomes and determine whether our model is overconfident or underconfident in its predictions. In essence, it measures the agreement between predicted probabilities and the true probabilities of an event occurring. Ideally, a well-calibrated model will have

points on the calibration curve that lie close to the diagonal line ($y = x$). This indicates that the predicted probabilities closely match the actual probabilities.

Changes in the text:

we have modified our text as advised (see Page 6-7, line 122-156)

Results:

Lines 112-157: An inconsistency is present in the count of male vs. female participants. The combined sum should be 114, but it totals 144. Please address this.

Reply 5: Thank you for your careful reading. We have identified the error and made the necessary corrections.

Changes in the text:

we have modified our text as advised (see Page 8, line 160)

Lines 115-124: Adding more baseline characteristics from the table to the text would enhance readability and understanding of the manuscript.

Reply 6: Thank you for your careful reading. We have made additional descriptions in the article to address the manuscript.

Changes in the text:

we have modified our text as advised (see Page 8, line 170-174)

Lines 131-141: In the table showcasing both univariate and multivariate analyses, confidence intervals are missing.

Reply 7: Thank you for your suggestion. We have analyzed it and incorporated it into the table as per your recommendation.

Changes in the text:

we added some data we added some data (see Table 2)

Discussion:

Lines 158-247: This section is pivotal and comprehensively tackles numerous pertinent aspects. Contemplate reorganizing to initially discuss your study's outcomes before contrasting them with prior literature.

Emphasizing novel insights or discrepancies between your research and previous studies would be valuable. Reflect on the practical implications of these results and how they could influence prevailing protocols.

Reply 8: After modifications, we first present our research findings and analyze the relationships between tumor diameter, preoperative LDH, preoperative neutrophil count, and prognosis. We then discuss the practical significance of these findings and their impact on current treatment plans.

Changes in the text:

we have modified our text as advised (see Page 11, line223-237; Page 12, line256-264; Page 13, line271-281; Page 15, line329-338; Page 17, line340-382)

Your discussion on VTT grading's relevance and its ongoing debate is enlightening. Expanding on this and presenting a more definitive viewpoint could strengthen this segment.

Reply 9: In the realm of tumor thrombus and its impact on patient prognosis, an ongoing debate persists.

This phenomenon may be because the sample numbers were relatively small and grade 0 VTT accounts for a relatively large proportion and the differences in the backgrounds of the investigated patients among institutions, progress in the operative technique, mean follow-up duration, and the particular clinicopathologic factors investigated together with the levels of tumor thrombus. Furthermore, significant factors predicting OS may change according to the follow-up duration, and these differences may result in controversy in terms of the impact of tumor thrombus extension on survival.[8]

Changes in the text:

we have modified our text as advised (see Page 11, line271-281)

General Recommendations and Minor Edits:

The manuscript could benefit from minor grammatical and syntactical enhancements to improve readability.

Lines 48-49: The sentence "Vein system invasion is a major feature of local progression of renal carcinoma accounting for 4%-10% in all the renal cancer patients" is somewhat intricate. A revision for simplicity would help.

Reply 10: Thank you for your careful reading. We have made the necessary corrections.

Changes in the text:

we have modified our text as advised (see Page 3, line47-50)

Line 115: The statement, "The tumors were situated on the left in 69 instances and left in 91 instances", appears to be a mistake.

Reply 11: Thank you for your careful reading. We have identified the error and made the necessary corrections.

Changes in the text:

we have modified our text as advised (see Page 8, line162)

Contemplating the addition of a section addressing the study's constraints would aid readers in discerning potential biases or impacting factors.

Reply 12: Thank you for your suggestion. We have added a new section to address the limitations of the research, as per your recommendation.

Changes in the text:

we have modified our text as advised (see Page 19, line399-413)

A conclusion segment that encapsulates primary insights and their potential clinical ramifications would be a worthy addition.

Reply 13: Thank you for your suggestion. We have supplemented the content of the summary section as per your recommendation

Changes in the text:

we have modified our text as advised (see Page 19-20, line415-435)