

Peer Review File

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Bladder cancer is the most common cancer of the urinary system (1), with greater than 90% of pathological types being urothelial carcinoma (2). Primary Adenocarcinoma of the Bladder (ACB) is a rare form of tumor with a high degree of malignancy, late staging and poor prognosis. In the manuscript “Development and Validation of a Nomogram for Predicting Survival in Patients with Non-metastatic Primary Adenocarcinoma of the Bladder”, authors developed a nomogram for predicting cancer-specific survival of patients with non-metastatic primary adenocarcinoma of the bladder (NMACB).

General response to the comments

We thank the reviewers for the valuable suggestions to improve our manuscript. We have carefully revised the manuscript according to these suggestions and believe that it has been significantly improved. The following are our point-by-point responses to the specific comments.

Comment 1: There was similar report (Clin Cancer Res. 2017 Nov 15;23(22):6904-6911) and (Medicine (Baltimore). 2019 Nov;98(44): e17725) in the PubMed. What is the novel idea in the paper? Please elaborate in the introduction.

Reply 1: Thank you for your useful comment. Some of the text was ambiguous, and we have modified the text to be more clearly.

Changes in the text: we have modified our text as advised (see page 3 line 58-64) Multiple nomograms have been established to inform clinical practice in bladder cancer (1-3). The majority of nomograms focus on urothelial carcinoma of the bladder. There are significant differences in etiology, treatment, and prognosis between primary bladder adenocarcinoma and urothelial cancer. Nomograms developed for use with bladder urothelial carcinoma are not suitable for patients with ACB. However no predictive nomograms have been developed for ACB due to its low incidence rate.

1. Wu S, Zheng J, Li Y, et al. A Radiomics Nomogram for the Preoperative Prediction of Lymph Node Metastasis in Bladder Cancer. Clin Cancer Res 2017;23:6904-11.
2. Zhang Y, Hong Y-k, Zhuang D-w, et al. Bladder cancer survival nomogram. Medicine 2019;98.
3. Tang F, He Z, Lu Z, et al. Application of nomograms in the prediction of overall

survival and cancer-specific survival in patients with T1 high-grade bladder cancer. *Exp Ther Med* 2019;18:3405-14.

Comment 2: ACB is a rare form of tumor. Why to focus on NMACB in the paper? Please elucidate detailed in the introduction.

Reply 2: Thank you for your question. As prognosis and therapeutic options for metastatic versus non-metastatic primary bladder adenocarcinoma vary widely. A cohort from localized disease to metastatic disease may have great heterogeneity, which may weaken our clinically applicable to real life practice (4-5). So we focus on NMACB in the paper.

4. Danby RD, Zhang W, Medd P, et al. High proportions of regulatory T cells in PBSC grafts predict improved survival after allogeneic haematopoietic SCT. *Bone Marrow Transplant* 2016;51:110-8.

5. Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *The Lancet* 2016;387:239-50.

Changes in the text: we have modified our text as advised (see page 3, line 64-66) Prognosis and therapeutic options for non-metastatic versus metastatic ACB vary widely. The present study focused on non-metastatic primary adenocarcinoma of the bladder (NMACB).

Comment 3: How to randomly grouping? How to reduce selection bias?

Reply 3: A Simple random sampling process was administered using computer-generated numbers, with an allocation ratio of 3 : 1 (training cohort : validation cohort). We use the following methods to control selection bias: firstly, we have clear inclusion and exclusion criteria, as shown in figure 1. Secondly, we constructed and validated the nomogram by bootstrap sampling which could be used to generate 95% confidence intervals of Harrell's concordance index (C-index) and area under the receiver operating characteristic (ROC) curve (AUC) (6).

6. Ayala-Peacock DN, Peiffer AM, Lucas JT, et al. A nomogram for predicting distant brain failure in patients treated with gamma knife stereotactic radiosurgery without whole brain radiotherapy. *Neuro Oncol* 2014;16:1283-8.

Comment 4: The figure 4 was not clear enough. Please replace it with a new. In the figure 3 legend, (a)-(f) was showed. But a-f was not marked in the figure 3.

Reply 4: We appreciate the reviewer's attention to detail. We have re-uploaded figure 4 and we have marked (a)-(f) in the figure 3.

Changes in the text: we have modified our figures as advised (see Figure 3-4).

Fig.3 ROC curves. The ability of the Nomogram to be measured by the AUC. 1- year (A), 3- year (B) and 5- year (C) ROC curves in the training cohort; 1- year (D), 3- year (E) and 5- year (F) ROC curves in the validation cohort. ROC: receiver operating characteristics curve; AUC: the area under the receiver operating characteristics curve.

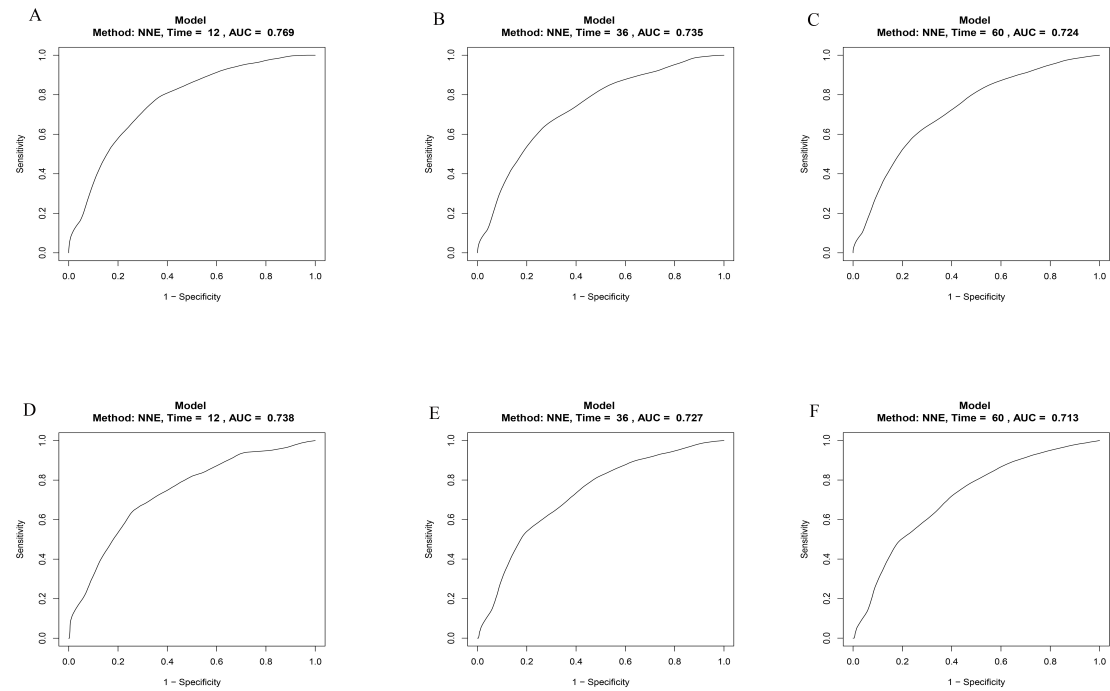
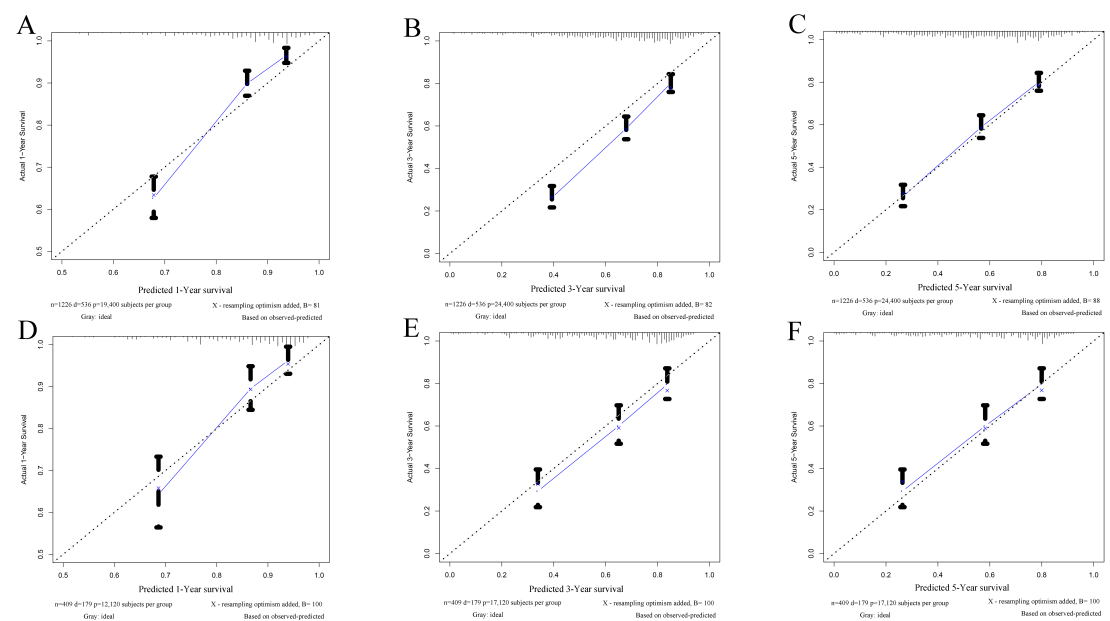


Fig.4 Cancer-specific survival calibration plots. The relationship between the predicted survival probabilities and actual values. 1-year (A), 3-year (B) and 5-year (C) calibration plots in the training cohort; 1-year (D), 3- year (E) and 5-year (F) calibration plots in the validation cohort.



Comment 5: In the limitations, the additional bias includes?

Reply 5: Thank you for your question. The SEER database lacks information about treatment strategies, tumor markers or biochemical or immunological factors, which may significantly correlate with prognosis. Lack of those information may lead to confounding bias. The SEER database also lacks detailed information regarding patient-level characteristics, such as comorbid conditions. And there may have been selection bias where patients who received only chemotherapy or radiotherapy may have been too sick to undergo surgery (7).

7. Yang CF, Chan DY, Speicher PJ, et al. Role of Adjuvant Therapy in a Population-Based Cohort of Patients With Early-Stage Small-Cell Lung Cancer. *J Clin Oncol* 2016;34:1057-64.

Changes in the text: we have modified our text as advised (see Page 10-11, line 224-226).

Thirdly, the SEER database lacks information about treatment strategies, family history, occupation, comorbid conditions, tumor markers or biochemical or immunological factors, which may cause confounding or selection bias.

Comment 6: Please enrich the progress of the treatment for ACB in the discussion.

Reply 6: The reviewer has made a very good point here. The suggestion would provide valuable information to our study. We have added the following in discussion: “Surgery with or without adjuvant radiation or chemotherapy is the principal form of treatment for patients with ACB. The most commonly used surgical procedure is radical or partial cystectomy with or without node dissection (8). The role of chemotherapy and radiotherapy in primary adenocarcinoma of the bladder is controversial. No specific recommendations exist for the use or type of chemotherapy or radiotherapy (9,10).”

8. Porten SP, Willis D, Kamat AM. Variant histology: role in management and prognosis of nonmuscle invasive bladder cancer. *Current Opinion in Urology* 2014;24:517-23.

9. Alanee S, Alvarado-Cabrero I, Murugan P, et al. Update of the International Consultation on Urological Diseases on bladder cancer 2018: non-urothelial cancers of the urinary bladder. *World J Urol* 2019;37:107-14.

10. Tsironis G, Bamias A. Treating bladder adenocarcinoma. *Transl Androl Urol* 2018;7:S699-S701.

Changes in the text: we have modified our text as advised (see Page 9, line 194-198).

Surgery with or without adjuvant radiation or chemotherapy is the main stay of treatment for the patients with ACB. The most used surgical procedure is radical or partial cystectomy with or without node dissection. The role of chemotherapy and

radiotherapy in primary adenocarcinoma of the bladder is controversial. There are no specific recommendations exist for the use and type of chemotherapy and radiotherapy. Szarvas et al. (22) and Tatli et al. (21) believed that chemotherapy regimens containing 5-FU can improve the prognosis of ACB, while others have indicated that radiotherapy, or neo-adjuvant or adjuvant chemotherapy have not proved efficacious in adenocarcinoma of the bladder (23,24). Conversely, in this study, chemotherapy or radiotherapy were found not to be independent prognostic factors.

Comment 7: Why not to validate the nomogram based on the real data in your hospital? Why chemotherapy and radiotherapy was not independent prognostic factors?

Reply 7: We thank the reviewer for this insightful comment. The external validation suggested by the reviewer is interesting and would help to establish the accuracy and clinical utility of our model. However, primary adenocarcinoma of the bladder (ACB) is a rare form of tumor, and we don't have enough samples in our own hospital to validate the nomogram. We consider this external validation outside the scope of the current study. Now, we are working with other organizations to build a multicenter sample bank and we wish to finish it in our continued study.

Chemotherapy and radiotherapy are often considered when treating primary adenocarcinoma of the bladder (ACB). Szarvas et al. (11) and Tatli et al. (12) believed that chemotherapy regimens containing 5-FU can improve the prognosis of ACB, However, the role of chemotherapy and radiotherapy in primary adenocarcinoma of the bladder is controversial. No specific recommendations exist with respect to the use and type of chemotherapy and radiotherapy (13,14). Considering that the current study was based on a large, nationwide, population-based database, we assumed that patients' chemotherapy and radiotherapy regimen may vary depending on the hospital they visit. Therefore, the prognostic effect might be decreased.

11. Alanee S, Alvarado-Cabrero I, Murugan P, et al. Update of the International Consultation on Urological Diseases on bladder cancer 2018: non-urothelial cancers of the urinary bladder. *World J Urol* 2019;37:107-14.
12. Tsironis G, Bamias A. Treating bladder adenocarcinoma. *Transl Androl Urol* 2018;7:S699-S701.
13. Szarvas T, Modos O, Niedworok C, et al. Clinical, prognostic, and therapeutic aspects of urachal carcinoma-A comprehensive review with meta-analysis of 1,010 cases. *Urol Oncol* 2016;34:388-98.
14. Tatli AM, Uysal M, Goksu SS, et al. Complete response of primary bladder adenocarcinoma with the FOLFOX4 regimen. *Urol Int* 2015;94:363-5.