
Peer Review File

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Comment 1: - In section 2.1, the authors refer their source database - SEER. I think it would be important for the reader to understand what this database is in more detail. For instance, how were these men diagnosed? How were they treated? Ideally, this should be referenced as well.

Reply 1: *We thank the reviewer for this important comment, and We have added some explanations of SEER database. The cancer was diagnosed normally by prostate puncture or transurethral resection. We included all treatments including surgery, radiation, combined therapies and so on. The modifications can be seen in Page 5. line 111-118.*

Changes in the text: The data of this study were derived from the Surveillance, Epidemiology and End Results (SEER) database. This database is a population-based cancer registry system. At present, it has covered about 29% of cancer patients in the United States, and is one of the most representative large-scale cancer case registration databases in the United States (14). Men with primary PCa diagnosed by prostate puncture or transurethral resection of prostate were retrospectively identified from January 1, 2004, to December 31, 2015.

Comment 2: - In section 2.2, the authors say that primary localised cancer is included, but then they also say (in brackets) that they would consider patients with T4 disease. Many urologists would not consider this to be localised. I think the terminology needs clarification.

Reply 2: *It is highly appreciated that the reviewer give us this important comment. We are sorry for inappropriate use of “localized” and we have replaced it with “non-metastasis” throughout our manuscript (see page 3, line 49; page 4, line 85; page 6, line 121)*

Comment 3: In 2.3, the authors mention documentation and analysis of marital status. This is potentially interesting, however, is not discussed in detail anywhere in the manuscript (or referenced). There may be a psychosocial element to the poor prognosis of unmarried men, as demonstrated previously. (See: <https://www.ncbi.nlm.nih.gov/pubmed/31214808>) I think this should be discussed in more detail.

Reply 3: *It is highly appreciated that the reviewer raised this detailed issue. As the main goal of our manuscript was to analysis the prognosis of men with different risk factors, other factors like marital status were not detailed discussed in our previous manuscript. We have added some discussion on this points in the section of discussion. (see Page 14, line291-302)*

Changes in the text 3: Univariate and multivariate COX analysis showed that age, race, marital status, T stage, PSA level, GS, therapy were the independent risk factors of

high-risk PCa. As for the marital status, some studies(25,26) reported it also affect the prognosis of patients. It was acknowledged that marriage likely serves as a multifaceted proxy for many protective factors including psychosocial support, adherence to follow-up care guidelines along with choice of adjuvant and secondary therapy, healthy lifestyles as so on (27). The nomogram was constructed with risk factors in multivariate COX analyses. This model is an intuitionistic and convenient tool for predicting survival rates. With this predicting model, the 5- and 10-year survival rates of each patient with high-risk PCa can be estimated. The C-index of our nomogram model was 0.773, indicating that the model has good accuracy. The 5- and 10-year calibration curves revealed a good agreement between the actual observation and the nomogram prediction.

Comment 4: I notice that there is no mention of any statistics (e.g. p-values or CIs) in the abstract. I think these should be added.

Reply 4: *We thank the reviewer for this important issue and we are sorry for the lack of p-values in our abstract. The missing statistics have been added as suggested. (see Page3, line 59-69)*

Changes in the text 4:

Abstract

Background: The aim was to evaluate the prognosis of men with all possible high-risk prostate cancers (PCa) stratified by risk factors.

Methods: Within the Surveillance, Epidemiology, and End Results database from 2004 to 2015, men with non-metastasis high-risk PCa were identified. Kaplan–Meier analysis and Cox regressions were adopted to evaluate the overall survival (OS) and prostate cancer-specific survival (PCSS). Nomograms were conducted to build a predictive model. Concordance index (C-index) and calibration curves were used to validate the model.

Results: A total of 151,799 patients were included. Seven risk groups were divided including one high-risk factor of T3-4 (A1), prostate-specific antigen (PSA) >20 ng/ml (A2), and Gleason score (GS) 8-10, two high-risk factors of T3-4 PSA>20 ng/ml (B1), T3-4 GS 8-10 (B2), PSA>20 ng/ml GS 8-10 (B3), and three high-risk factors of T3-4 PSA>20 ng/ml GS 8-10 (C). The survival curves of PCSS showed that A1 was the best among all groups. A2, A3 and B1 had similar results and were all better than B2 [with A2 as reference, A3 HR: 1.09(1.02~1.17), p=0.046; B1 HR: 0.93(0.82~1.05), p=0.103; B2 HR: 1.42(1.32~1.53), p<0.001]. There is no significant difference between B3 and C [HR: 0.94(0.86~1.03), p=0.029] and these two present the worst survival in prognosis. The 10-year PCSS of A1, A2, A3, B1, B2, B3, and C groups were 95.8%, 86.9%, 86.1%, 86.9%, 80.8%, 64.7% and 65.6%, respectively. Three simplified groups were divided including a good prognosis group (A1), an intermediate prognosis group (A2, A3, B1 and B2), and a poor prognosis group (B3 and C). Compared to the good prognosis group, the HR of the intermediate and the poor prognosis group were 4.21(3.96~4.48), p<0.001 and 11.36 (10.59~12.19), p<0.001. A nomogram was built based on these factors. The C-index of the nomogram was 0.772, indicating a good accuracy of the model.

Conclusions: Men with the combination of PSA >20 ng/ml and GS 8-10 had the worst PCSS among all patients. PCa with three high-risk factors was not more aggressive than that with two high-risk factors of GS 8-10 and PSA >20 ng/ml.

Comment 5: Also, I cannot easily find any mention of ethical approval for this study / analysis. This is important, even for retrospective work. If it is not required (e.g. because this is public database work) then this should be stated nonetheless.

Ethics

Reply 5: *We appreciate the reviewer's attention to this meaningful issue. As all data in this study were derived from the public database of SEER, no ethical approval was required. We have stated it at the end of our manuscript. (see Page16, line 338-341)*

Changes in the text 5:

Ethical approval

All data comes from a public database, which removes all patient tags; no ethical approval is required. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Comment 6: In 2.5, the authors refer to "Long Rank P" - I believe this should be Log?

Reply 6: *It is highly appreciated that the reviewer raise this detailed comment. In our analysis, the long rank test was used to calculated the p values of the differences. It is not a misuse of "log".*

Comment 7: In 3.1, it would be better to give the numbers of men as percentages/proportions and then fractions in brackets, as this is clearer to the reader.

Reply 7: *We thank the reviewer pose this important issue. We have added the required percentages in the 3.1 section as suggested. (see Page 8, line 168 and 172)*

Changes in the text 7:

3.1. Patient characteristics

In total, 151,799 patients with a median age of 66 (60-72) years were included. 72143(47.5%), 14979(9.8%) and 30698(20.2%) patients were included in A1, A2, and A3 group. 5121(3.4%), 16589(10.9%), and 7746(5.1%) patients were in B1, B2, and B3 group. 4523 patients were in group C. The baseline characteristics were summarized in Table 1.

Comment 8: In 3.2.1, reference is given to significant difference, but I cannot find any p-values in the text. These should be added.

Reply 8: *It is highly appreciated that the reviewer raise this important issue, and we are sorry for the missing of p values. These values have been added as suggested. (see Page 9, line 181-191)*

Changes in the text 8:

The 5 and 10-year OS and PCSS rates of the overall cohort were 85.5% and 65.4%. For the seven groups, the 10-year OS rate of each group were 82.1%, 55.8%, 57.2%, 64.4%, 60.4%, 35.2% and 44.1%, individually (**Table 2**). Patients in A1 group had the best survival results, followed by men in B1, B2, A3, A2, B3, and C group. Men in B3 group was associated with the worst OS among all groups. Significant differences existed among seven groups ($p<0.001$). With A1 group as the reference, the HR and 95%CI of A2, A3, B1, B2, B3 and C group were 3.2(3.08~3.33), 3.03(2.93~3.14), 2.44(2.29~2.61), 2.64(2.54~2.75), 6.16(5.91~6.43), 4.87(4.61~5.15), respectively. The OS curve and HR results were shown in **Figure 1A** and **Table 3**.

The 5- and 10- year PCSS rate of the overall cohort were 95.3% and 88%. The 10-year PCSS rate of each of these groups were 95.8%, 86.9%, 86.1%, 86.9%, 80.8%, 64.7% and 65.6%, respectively (**Table 2**). Men in A1 group still had the best PCSS, followed by A2, B1, A3, B2, C and B3 group. No significant difference was detected between A2 and B1 group [HR: 1.08, 95%CI (0.95~1.22), $P=0.124$], as well as between B3 and C group [HR: 0.94, 95%CI (0.86~1.03), $P=0.057$]. With men in A1 group as the reference, the HR and 95%CI of A2, A3, B1, B2, B3 and C group were 3.72(3.43~4.03), 4.05(3.78~4.33), 3.44(3.04~3.9), 5.29(4.91~5.7), 11.6(10.74~12.53), 10.95(10~11.99), respectively. These results were presented in **Figure 1B** and **Table 3**.