

## Peer Review File

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### Reviewer A

Considering that the average life expectancy of the population is around 75 years old, it is natural to expect that the 10- or 15-year survival rate of patients over 67 years old would be lower than that of patients under 67 years old. Although the authors calculated the survival rate based on disease-related fatality, there are still various biases that may exist. In particular, the higher prevalence of nodules over 40mm and distant metastases in the group aged 67 and older suggests that significant bias may have already been introduced during the initial diagnostic and therapeutic processes. Therefore, it is unreasonable to predict thyroid cancer death solely based on the cutoff age of 67 using the results analyzed in this study.

#### Reply:

Thank you very much for your comments. We have added this related content in the “limitation” section. The current study suggests that SEER database is an extremely valuable tool for clinical cancer research, but several limitations, like various forms of confounding and selection bias, should be taken into account when interpreting results from a SEER observational study. To adjust for confounding and selection bias that result from non-randomization, one can use a wide variety of techniques, including multi-variate Cox proportional hazards modeling, stratification analysis and so on. In this study, multi-variate Cox proportional hazards modeling was used to minimize confounding and selection bias<sup>1-2</sup>.

#### References

1. Park, H. S., Lloyd, S., Decker, R. H., Wilson, L. D., & Yu, J. B. (2012). *Limitations and biases of the Surveillance, Epidemiology, and End Results database. Current problems in cancer, 36(4), 216–224.* <https://doi.org/10.1016/j.currprobcancer.2012.03.011>
2. Bradburn, M. J., Clark, T. G., Love, S. B., & Altman, D. G. (2003). *Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. British journal of cancer, 89(3), 431–436.* <https://doi.org/10.1038/sj.bjc.6601119>

**Changes in the text:** First, as a retrospective study rather than a prospective cohort study, inherent selection biases cannot be avoided and could limit the external validity of this study. (see Page 11, line 267-269)

### Reviewer B

Using 99,449 patients with differentiated thyroid cancer (DTC) from the SEER database, aim to establish which age-cutoff best predicts cancer specific survival (CSS), and secondly to create a nomogram to predict survival.

After reading the manuscript several important issues remain:

#### 1. General comment

A) In the current study, the authors use the X-tile software to determine the optimal age cutoff. This same kind of analysis was earlier performed by Adam et al (J Clin Oncol 2016) also using

the SEERS database. So might refer to that paper and explore differences. Further, the determined age cutoff could not be compared with TNM system, as data was lacking, which makes the current study less useful. In addition, usually more categories leads to better prediction than just using a single cutoff, so the results of the proposed comparison in Line 233/236 would probably be in favour of the TNM system.

**Reply:**

We sincerely appreciate the valuable comments. We have checked the literature carefully and added it into the “Discussion” part as reference 24 in the revised manuscript. In addition, in order to enroll more suitable patients for this study, we did not select patients with TNM data for analysis, because this type of data was not available for patients before 2004. In the future study, sufficient number of patients including TNM staging information can be extracted in SEER database for validation. Meanwhile, we removed this sentence (Line 233/236) in revised manuscript.

**Changes in the text:** Meanwhile, Adam et al. suggested that patient age is significantly associated with death from PTC in a linear fashion, without an apparent age cut point demarcating survival difference<sup>24</sup>. (see Page 10, line 215-217)

B) In the subgroup analysis for prediction factors, one should not investigate factors that survival is strongly correlated with, because this leads to confounding-by-indication. As this is the case for both lymphadenectomy and surgical treatment, these analyses should not be shown as they are incorrect.

**Reply:**

Thank you very much for the positive feedback and constructive points. To maximize the enrollment of as many patients as possible and to ensure the accuracy of our results, we analyzed data from all patients. In the future, we will continue to collect patients for further verification of the conclusions proposed in this study.

C) The constructed nomogram was not tested regarding its validity, because the whole population was used for constructing it. Usually, one should divide the population into a creation and validation set, so the performance of the nomogram can be validated.

**Reply:**

We totally agree with you that nomogram need to test its validity. However, sufficient sample size can ensure the reliability of the conclusions. In the future, we would pay more attention to improve the validity of nomogram constructed in this study.

D) Please proofread the English sentences, because there are various sentence that are difficult to read.

**Reply:**

Thanks for your suggestion. We have tried our best to polish the language in the revised manuscript.

## 2. Abstract

A) Line 14 ‘impossible to predict’; although several prediction systems exist to predict survival and recurrence, which not all agree on the cutoff age, this doesn’t necessarily mean that these can’t be used.

B) Line 33 ‘thyroid cancer’ also refers to other types of thyroid cancer (e.g. medullary and anaplastic), which has not been covered in the current research. Therefore, please change.

**Reply:**

Thanks for your kind reminder.

**Changes in the text:**

A) However, there are disagreements over the optimal cutoff age among the numerous staging and risk stratification criteria, which make it inconsistent to predict the clinical prognosis of specific DTC patients. (see Page 2, line 17)

B) Accordingly, the optimal cutoff age for predicting death from DTC specifically is 67 years old at the time of the initial diagnosis. (see Page 2, line 39)

### 3. Introduction

A) Line 41 ‘incidence rate’; incidence rate of what?

B) Line 55/56 ‘however.....mortality’. There are more than 15 studies who investigated the change from TNM7 to TNM8, and you might appreciate the meta-analysis of Lechner et al. (Oncologist 2020). So I don’t think this statement is true.

**Reply:**

Thank you for pointing out these problems.

**Changes in the text:**

A) Differentiated thyroid carcinoma (DTC) is made up of the two separate and most common types (papillary thyroid carcinoma [PTC] and follicular thyroid cancer [FTC]) according to histological categorization, and its incidence accounts for 85%-90% of thyroid cancers. (see Page 4, line 46-49)

B) Although a meta-analysis that included six studies and involved 10,850 subjects showed that AJCC-8 revision improved stratification of disease-specific survival among clinical stages of disease compared with AJCC-7. Notably, the clinical characteristics of each study population, including DTC subtype, extent of disease, and treatment, varied significantly among the included reports, and differences between studies were seen with respect to the proportion of patients migrating between stages and disease-specific survival estimates. Therefore, the predictive age need validated in broader populations. (see Page 4, line 63-69)

### 4. Methods

A) Were PTC and FTC also investigated together because earlier research seems that they might have different survival differences. And how many patients with FTC were included in the current study?

**Reply:**

Thank you for pointing out these problems. In this study, there are 91,844 patients with PTC and 7605 with FTC which accounted for 8%. Meanwhile, according to the relevant guidelines and clinical practice, FTC and PTC are consistent in their treatment strategies, so we combined these two pathological subtypes for analysis.

*Reference*

*I. Boucai, L., Zafereo, M., & Cabanillas, M. E. (2024). Thyroid Cancer: A Review. JAMA, 331(5), 425–435. <https://doi.org/10.1001/jama.2023.26348>*

## 5. Discussion

A) Line 167-168; this statement is a bit difficult because it was not tested in the current study.

B) Line 180/181 ‘speculation’ likewise my comment on the abstract, there are >15 studies on this, so I would not call this speculation.

C) Line 243-246 ‘When compared...follow-up’. This is pure speculation, because you did not test this in the manuscript, and earlier studies showed that other age cutoffs were better when using TNM staging. Therefore, please remove the sentence, or change it into that your outcomes should be compared with the TNM staging.

### **Reply:**

Thank you for your insightful comments and kind suggestions.

### **Changes in the text:**

A) Additionally, to estimate the cause-specific mortality of each patient, we created a model that incorporates the ideal cutoff age as well as other common characteristics, which may be helpful to distinguish high-risk patients and follow-up management. (see Page 9, line 193-194)

B) According to the current studies, the median age in numerous earlier investigations was 45<sup>17</sup>, and the increased age threshold for the eighth edition of the TNM system was based on three earlier studies that showed that patients with DTC could have superior DSS predictions with an age cutoff of 55 years<sup>18</sup>. (see Page 9, line 208)

C) Totally agree with you and we removed this sentence in revised manuscript.

## **Reviewer C**

- Material and Methods. Section 2.2. Clinicopathological variable assessment. In tumor characteristics, the tumor type (papillary, follicular) should be included.

### **Reply:**

Thank you for pointing out these problems. In this study, there are 91,844 patients with PTC and 7605 with FTC which accounted for 8%. Meanwhile, according to the relevant guidelines and clinical practice, FTC and PTC are consistent in their treatment strategies, so we combined these two pathological subtypes for analysis.

### *Reference*

*I. Boucai, L., Zafereo, M., & Cabanillas, M. E. (2024). Thyroid Cancer: A Review. JAMA, 331(5), 425–435. <https://doi.org/10.1001/jama.2023.26348>*

- Better than adjuvant therapies after surgery it should be specified whether or not patients have received radioiodine. Other adjuvant therapies should be reserved for systemic (antitumor) treatments or for local radiotherapy.

### **Reply:**

We are sorry for the confusing describe about treatment specifics. We have modified related content in the “Clinicopathological variable assessment” section and the the definition of Radiation therapy was added in the revised manuscript.

**Changes in the text:** treatment specifics (surgeries, radiation therapy [including beam radiation, combination of beam with implants or isotopes, radiation with method or source not specified, radioactive implants, radioisotopes]). (see Page 5, line 93-95)

- The authors should specify if the SEER registry includes the radioiodine activity received or only if radioiodine has been received as a dichotomous variable (no/yes)

**Reply:**

Thank you for pointing out these problems. However, the SEER database does not contain such information. In the further real-world study, we could pay more attention to this factor.

- They should also specify whether data were collected on the primary treatment of the tumor or also on treatments received for a cancer recurrence or other antineoplastic treatments.

**Reply:**

Thank you for pointing out these problems. All data collected in the SEER database refer to the patients' initial treatment. The statement also added in “Clinicopathological variable assessment” section.

**Changes in the text:** The treatment specifics collected in the SEER database refer to the patients' initial treatment. (see Page 5, line 96-97).

- The manuscript does not specify the data regarding the follow-up period of the patients. It should be clarified how long mortality was captured.

**Reply:**

Thanks for your kind reminder and totally agree with you. However, we were unable to extract this data from the SEER database. In the future study, we will specify the data regarding the follow-up period of the patients.

- Authors should also specify whether the follow-up time of their study is sufficient to capture reliable data on mortality. The survival of patients with thyroid cancer is, in general, very long and, for obvious reasons, the latency time between diagnosis and death is always longer in young people than in older people.

**Reply:**

Thank you for your insightful comments and kind suggestions. In the future study, we will focus on these factors.

- Table 1. The expression Radiation therapy is confusing. It must be clarified whether it is a therapeutic dose of radioiodine or another form of radiation.

**Reply:**

We are sorry for the confusing describe about treatment specifics. The definition of Radiation therapy was added in the revised manuscript.

**Changes in the text:** treatment specifics (surgeries, radiation therapy [including beam radiation, combination of beam with implants or isotopes, radiation with method or source not specified, radioactive implants, radioisotopes]). (see Page 5, line 93-95)

- Figure 3. It is probably dispensable. The characters are very small and it includes 9 panels that are difficult to see and analyze in detail.

**Reply:**

Thank you for your kind suggestion. We put Figure3 in the attachment materials as “Supplementary Figure 1”.

- Figure 4. The characters are very small and cannot be read clearly. It is not clear to the reader how the nomogram is used and how the prognosis of 5-year survival and 10-year survival is established. Please, clarify.

**Reply:**

Thank you for pointing out these problems. We have added relevant instructions in “CSS prognostic nomogram” and “Figure legends” sections.

**Changes in the text:**

A) For example, a patient with age >67 years (1: 64 points), male (0: 18 points), tumor size > 20mm, <40mm (1: 32 points), underwent Lymphadenectomy (1: 12 points), without metastasis (0: 0 points), without Surgery (0: 70 points). Thus, the total score is 196 points; the patient’s 5-year survival rate is about 85%, and the 10-year survival rate is about 55%. (see Page 8, line 171-175).

B) Figure 4: A. Nomogram for predicting the 5- and 10-year CSS in DTC patients with a cutoff age of 67 years. (Age, 0: <67 years; 1: >67 years. Gender, 0: male; 1: female. Tumor size: 0: <20mm; 1: > 20mm, <40mm; 2: > 40mm. Lymphadenectomy: 0: no; 1: yes. Metastasis: 0:no; 1: yes. Surgery: 0: no, 1: yes). (see Page 19, line 427-429).

- There are no data on overall survival. It is mentioned in Methods section and, in tables, there is a clear differentiation between mortality from thyroid cancer and other causes, but the risk factors for overall mortality are not defined.

**Reply:**

Thanks for your kind reminder and we delete “overall survival” information in Methods section.

- The management of the nomogram does not seem easy in clinical practice. The authors should specify what advantages this study provides over standard clinical practice procedures.

**Reply:**

we thank the reviewer for the highly valuable comment. We have added this related content in the “discussion” section.

**Changes in the text:**

As a prognostic statistical model, a nomogram can not only visually display the relevant indicators that affect the outcome in multifactor regression analyses but also predict the survival probability through a simple graphical representation, making the prediction simpler and more convenient [39, 40]. Our results show that when predicting the CSS, the model has high degrees of discrimination and calibrated accuracy. Since the model can predict the risk of death well it has a certain value for clinical applications. (see Page 11, line 260-265).