

## Peer Review File

Article information: <https://dx.doi.org/10.21037/tcr-22-2478>

### Reviewer Comments

Using 652 patients, the authors constructed a nomogram to predict the presence of papillary thyroid carcinoma (PTC) in thyroid nodules, and afterwards validated it. Main result is that based on age, TSH, inflammatory markers and ultrasound features, a nomogram can be constructed which performed well.

After reading the manuscript several important issues remain:

#### 1. General comment

Comment 1: More accurately than what? As no other methods were evaluated. E.g. one could compare the nomogram with the TI-RADS classification.

Reply: We are very grateful for the Reviewer's comments. We collected the TI-RADS classification information of the patients again and analyzed this information to obtain the ROC curve as well as the AUC. A comparison of the diagnostic efficacy of the diagnostic model and the TI-RADS showed that the former was superior to the latter. This indicates that the diagnostic model we constructed may possess better accuracy.

Changes in the text: We have modified our text as advised (see Page 5, line 3-4, Page 8, line 8-9, Page 10, line 12-16, Page11, line 17-18, Page 15, line 17-18, and Figure 4B)

Comment 2: If the nomogram predicts a nodule as non-PTC, this still means it can be another type of thyroid cancer (TC). Therefore, why not comparing TC with non-TC.

Reply: We thank the Reviewer for carefully evaluating our work. At the outset of the study design, it was considered that PTC accounts for a large proportion of all thyroid cancers and that the ultrasound presentation of other types of thyroid cancer may differ from that of PTC (1-2). If PTC and other types of thyroid cancer are combined to compare with benign thyroid nodules, the diagnostic efficacy may not be satisfactory. The Reviewer's comments also made us realize that this is a shortcoming of our study, so we wrote this part in the limitation. We will also go further to construct diagnostic models to accurately distinguish other types of thyroid cancer from benign thyroid nodules.

Changes in the text: We have added the relevant content to the discussion (see Page 16, line 7-10)

Comment 3: Could the authors speculate in which way the nomogram can be used; do the results of the external validation give a suggestion in what way it can be used?

Reply: We are very grateful for the Reviewer's comments. We have added how to use the nomogram and suggestions for using it according to the Reviewer's

comments.

Changes in the text: We have added the relevant content to the discussion (see Page 11, line 20-22 and Page 16, line 14-16)

## 2. Regarding the Abstract

Comment 1: Page 2, Line 4 'to estimate TPC before surgery when treating thyroid nodules'; this statement is very vague; please rephrase.

Reply: We appreciate the Reviewer for carefully estimating our work. We have re-written this statement according to the Reviewer's suggestion

Changes in the text: We have modified our text as advised (see Page 2, line 4-5)

Comment 2: Page 2, Line 12 'tall-than-wide'; this should be 'taller-than-wide'. Please also correct in the text, because this is frequently mistaken.

Reply: We are very sorry that we misspelled "taller-than-wide" as "tall-than-wide".

Changes in the text: We have modified our text as advised (see Page 2, line 13)

Comment 3: Page 2, Line 17. One should mention the accuracy, sensitivity and specificity of the external validation, because that says something about the performance of the created nomogram.

Reply: We are very grateful for the Reviewer's comments. We have added external validation for accuracy, sensitivity and specificity according to the Reviewer's suggestion.

Changes in the text: We have modified our text as advised (see Page 2, line 19-20)

## 3. Regarding the Introduction

Comment 1: Page 4, Line 17 'Therefore, it is used in the evaluation of thyroid nodules'. TSH is measured to assess whether a nodule is hyperfunctioning, because in that case the chance that it is malignant is very low. Therefore, the statement is not true.

Reply: We are very grateful for the Reviewer's comments. We have re-written this statement according to the Reviewer's suggestion.

Changes in the text: We have modified our text as advised (see Page 4, line 18-19)

## 4. Regarding the Methods

Comment 1: Page 5, Study population. The primary and validation cohort are taken from different time periods. This might introduce bias as difference might occur that you cannot control for. Therefore, one should include patients from the full time period, and thereafter randomize patients in either the primary or validation cohort.

Reply: We thank the Reviewer for carefully evaluating our work. In our study, to demonstrate that the model we constructed can be used for datasets other than the model data, we selected patients from different time periods as the validation cohort for external validation. The same approach was used for the external validation of many studies (3-7). The existence of bias in this is a flaw in our study,

so this flaw is also written into the limitation, and in the future, we will also perform external validation based on Spatio-temporal to reduce the bias.

Changes in the text: We have added the relevant content to the discussion (see Page 16, line 5-7)

Comment 2: Why was tumor size not investigated as a potential factor?

Reply: We appreciate the Reviewer for carefully estimating our work. At the beginning of our study design, we reviewed a lot of literature on ultrasound manifestations of thyroid cancer. Studies suggest that a correlation between nodule size and risk of malignancy remain controversial (8-11). However, rapid growth of solid nodules may be a clinical manifestation of high-grade malignancy. Therefore, we used the size of tumor growth instead of tumor size but removed this variable due to excessive missing values.

Changes in the text: None

Comment 3: Page 7, Line 8 'variation'; this should be variables.

Reply: We are very sorry that we misspelled " variables " as " variation ".

Changes in the text: We have modified our text as advised (see Page 7, line 10)

Comment 4: Page 7, Line 9/10 'stepwise regression'; when starting with the full model and thereafter omitting variables which are not significant is called 'backward selection'.

Reply: We thank the Reviewer for attentively evaluating our work. We have made correction according to the Reviewer's comments.

Changes in the text: We have modified our text as advised (see Page 7, line 11)

## 5. Regarding the Discussion

Comment 1: Page 11, Line 13 'excellent'; which of the results is excellent?

Reply: We appreciate the Reviewer for attentively estimating our work. We have revised the article to make it more understandable according to the Reviewer's suggestion.

Changes in the text: We have modified our text as advised (see Page 11, line 18-19)

Comment 2: Page 12, Line 15-17; please add an appropriate reference.

Reply: We have added an appropriate reference according to the Reviewer's comments.

Changes in the text: We have modified our text as advised (see Page 13, line 4)

Comment 3: Page 15, Line 9/10; one should mention the results of the external validation, because that says something about the performance of the created nomogram.

Reply: We are very grateful for the Reviewer's comments. We have added external validation for accuracy, sensitivity and specificity.

Changes in the text: We have modified our text as advised (see Page 15, line 19-20)

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3. Huang C, Cong S, Liang T, et al. Development and validation of an ultrasound-based nomogram for preoperative prediction of cervical central lymph node metastasis in papillary thyroid carcinoma. *Gland Surg*. 2020 Aug;9(4):956-967.
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5. Wang X, Mao M, He Z, et al. Development and Validation of a Prognostic Nomogram in AFP-negative hepatocellular carcinoma. *Int J Biol Sci*. 2019 Jan 1;15(1):221-228.
6. Hu HT, Wang Z, Huang XW, et al. Ultrasound-based radiomics score: a potential biomarker for the prediction of microvascular invasion in hepatocellular carcinoma. *Eur Radiol*. 2019 Jun;29(6):2890-2901.
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8. Jinih M, Faisal F, Abdalla K, et al. Association between thyroid nodule size and malignancy rate. *Ann R Coll Surg Engl*. 2020 Jan;102(1):43-48.
9. Cavallo A, Johnson DN, White MG, et al. Thyroid Nodule Size at Ultrasound as a Predictor of Malignancy and Final Pathologic Size. *Thyroid*. 2017 May;27(5):641-650.
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