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ORIGINAL RESEARCH

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Clinical detection of "extremely low-risk" follicular thyroid carcinoma: A population-based study of 7304 patients

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Abstract

Background: Previous studies have not been consistent in the risk of metastasis in follicular thyroid carcinoma (FTC). Therefore, we conducted a large population study to stratify the risk of distant metastasis in FTC patients using only clinical parameters.

Methods: We extracted FTC patients from The Surveillance, Epidemiology, and End Results (SEER) database and divided them into training and validation cohorts.

Results: The two cohorts consisted of 4913 and 2391 patients, respectively. We developed a nomogram and risk table based on a logistic regression model using algorithm-selected variables. Receiver Operating Characteristic (ROC) analyses showed high discriminatory power in the training and validation cohorts (Area under the curve [AUC] of 0.85 and 0.84, respectively). Extremely low, low, intermediate, and high-risk groups had 0.3%, 1%, 3.5%, and 16.7% risk of distant metastasis, respectively.

Conclusions: Our risk scoring table can separates patients into four risk groups and efficiently detect patients with almost no risk of metastasis.

KEYWORDS

follicular carcinoma, low-risk, risk stratification, SEER, thyroid, thyroiddistant metastasis

1 | INTRODUCTION

Follicular thyroid carcinoma (FTC) is a malignant thyroid tumor derived from the monoclonal proliferation of thyroid follicular cells.[1] FTC is well known for its tendency to disseminate hematogenously.[1] Lymph node metastasis (LNM) of FTC is less frequent than distant metastasis.[1,2]

Distant metastasis, regardless of the metastatic location, is a significant indicator of poorer prognosis in FTC patients compared to FTC patients without metastasis.[3–5] However, studies showed various results in the frequency of metastasis in FTC patients.[4,6,7] Therefore, it is important to evaluate and stratify the risk of metastasis in FTC patients more definitively.

Although detecting high-risk factors of metastasis is crucial, it is also important to detect FTC cases with a low risk of metastasis. However, most studies have attempted only to determine FTC patients with high metastatic risk[8,9] and poorer outcomes.[4,5,10] Very few studies have focused on how to stratify FTC patients with low metastatic risk.[11]

Several studies were conducted harnessing clinical, imaging, and pathological aspects, to estimate the metastatic risk and prognosis of FTC patients.[6,12,13] In 2014, the Armed Forces Institute of Pathology (AFIP) developed a prognostic category based on vascular invasion in histology.[14] Another study established a predictive method of FTC metastasis using ultrasonography.[6] Overall, these predictive systems

focused on the detection of high-risk FTC patients. Clinical characteristics were obviously related to the risk of metastasis.[8,9] Quantitative interpretation of these parameters could be a more objective screening tool for distant metastasis in FTC patients.

The present study used a large sample size and combined many clinical parameters to construct a risk scoring table that stratifies the metastatic risk of FTC patients at initial presentation. We especially focused on classifying different groups with low to intermediate metastatic risks. We collected data for this study from the Surveillance, Epidemiology, and End Results (SEER) project.

2 | MATERIALS AND METHODS

2.1 | Case selection

We accessed and extracted FTC patients from the SEER 18 registry database in the 2004–2015 period. Variables such as age, race, gender, marital status, tumor size, extrathyroidal extension (ETE), lymph node metastasis (LNM), distant metastasis, survival time, and vital status were included. ETE was defined as tumor invasion beyond the thyroid capsule: stage T4, extension into muscles, pericapsular soft tissue, major blood vessels, trachea, and cartilages. The ETE is, by our definition, both microscopic and macroscopic ETE. The delineation between microscopic and macroscopic ETE is not clear if we use the categories in the SEER database. We excluded patients whose information did not include age, tumor size, race, LNM, and distant metastasis. Cases without histological confirmation were also excluded. The patients were then randomly divided into training and validation cohorts with a training: validation ratio of 2:1.

2.2 | Construction of the model

In the training cohort, we employed univariate logistic regression models to evaluate each variable's capacity to estimae metastasis.

TABLE 1 Patient characteristics in the training, validation, and combined cohorts

Variables	Total ($n = 7304$)	Training ($n = 4913$)	Validation ($n = 2391$)	p
Age[a] (years)	52 (38–64)	52 (38–64)	52 (39–65)	.606
Gender				.167
Male	2211 (29.7%)	1522 (30.4%)	689 (28.3%)	
Female	5222 (70.3%)	3477 (69.6%)	1745 (71.7%)	
Race				.874
White	5760 (78.9%)	3863 (78.6%)	1897 (79.3%)	
Black	912 (12.5%)	628 (12.8%)	284 (11.9%)	
API	632 (8.7%)	422 (8.6%)	210 (8.8%)	
Size[a] (cm)	3.3 (2.1–4.8)	3.4 (2.1–4.8)	3.2 (2.2–4.5)	.732
ETE				.922
No	6778 (92.8%)	4555 (92.7%)	2223 (93%)	
Yes	526 (8.6%)	358 (7.3%)	168 (7%)	
LNM				.863
No	7063 (96.7%)	4747 (96.6%)	2316 (96.9%)	
Yes	241 (3.3%)	166 (3.4%)	75 (3.1%)	
Distant metastasis				.418
No	7009 (96%)	4725 (96.2%)	2284 (95.6%)	
Yes	295 (4%)	188 (3.8%)	107 (4.4%)	
Surgery				.999
No/unknown	142 (1.9%)	97 (2%)	45 (1.9%)	
Yes	7162 (98.1%)	4816 (98%)	2346 (98.1%)	
Radiation				.906
No/unknown	3322 (45.5%)	2253 (45.9%)	1069 (44.7%)	
Radioisotopes	3797 (54.5%)	2539 (54.1%)	1258 (55.3%)	
Others	185 (2.5%)	121 (2.5%)	64 (2.7%)	
Chemotherapy				.519
No/unknown	7256 (99.3%)	4877 (99.3%)	2379 (99.5%)	
Yes	48 (0.7%)	36 (0.7%)	12 (0.5%)	

Abbreviations: API, Asian or Pacific Islander; ETE, extrathyroidal extension; LNM, lymph node metastasis.
[a]Age and tumor size numbers refer to the median and interquartile range.

Next, the stepwise algorithm based on the Akaike Information Criterion (AIC) and the Bayesian Model Averaging (BMA) procedure were performed to select the optimal model by omitting uninformative variables.[15]

2.3 | Construction of risk scoring table

Based on the optimal model, we constructed the nomogram and risk scoring table. The Receiver Operating Characteristic (ROC) analysis was performed to evaluate the model. The area under the curve (AUC) and 95% confidence interval (95% CI) were calculated using 1000 bootstrap samples.

2.4 | Validation of the model and the risk scoring table

In the validation phase, we used the model to calculate the linear predictor indices (LPI) for all patients in the validation cohort. Regression on the LPI of the validation dataset was performed to evaluate the slope, and ROC analysis on the LPI was employed to evaluate the trained model. To prevent overfitting, we used 1000 bootstrap samples to calculate the AUC and 95% CI. Calibration plots in both cohorts were constructed to examine the model's goodness-of-fit (GOF). To examine the validity of our risk scoring table, we established a frequency table to compare the risk of FTC metastasis among risk groups in the validation, training, and combined cohorts.

2.5 | Statistical analysis

The median and interquartile range (IQR) are descriptive statistics of continuous variables, and the frequency is the descriptive statistic of categorical variables. We compared continuous variables between the cohorts using Kruskal-Wallis significant test and categorical variables with Chi-square significant test. Univariate and multivariate logistic regression models were employed to calculate the odds ratio (OR) of metastasis between patients. All the tests were considered significant at a $p < .05$. All the analyses were performed using R software version 4.1.0 (the R Foundation, Vienna, Austria).

3 | RESULTS

3.1 | Case selection

We extracted 10 280 cases with the diagnosis of FTC in the thyroid gland from the database and selected 7304 cases as per our criteria for the study. The patients were randomly grouped into training and validation cohorts. The training and validation cohorts included 4913 and 2391 patients, respectively.

3.2 | Patient characteristics

Table 1 summarizes the patient characteristics of the training, validation, and combined cohorts. Overall, there were no differences between cohorts. The patient's age IQR was from 38 to 64 years old

TABLE 2 Univariate and multivariate analysis of variables with distant metastasis in the training cohort

	Univariate		Multivariate	
Variables	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	1.07 (1.05–1.08)	<.001	4.67 (3.47–6.29)	<.001
Gender				
Female	1		1	
Male	1.39 (1.03–1.88)	.032	1.04 (0.74–1.44)	.835
Race				
White	1		1	
Black	1.55 (1.03–2.34)	.035	1.95 (1.25–3.06)	.004
API	2.97 (2.03–4.36)	<.001	3.07 (2.0–4.72)	<.001
Size	1.14 (1.09–1.19)	<.001	1.18 (1.06–1.32)	.004
ETE				
No	1		1	
Yes	7.4 (5.31–10.2)	<.001	3.31 (2.26–4.86)	<.001
LNM				
No	1		1	
Yes	14.4 (9.92–20.9)	<.001	7.8 (5.05–12.03)	<.001

Abbreviations: API, Asian or Pacific Islander; 95% CI, 95% confidence interval; ETE, extrathyroidal extension; LNM, lymph node metastasis; OR, odds ratio.

with a median age of 52 years old. The tumor was more common in females than males, and the most frequent race represented in the dataset was White, followed by Black (12.3%), and Asian and Pacific Islander (8.5%).

The median tumor size was 3.3 cm (IQR: 2.1–4.8 cm). The probability of ETE was 8.6%. LNM was found in 3.3% of FTC patients and the risk of metastasis was 4%. The most common treatment option was surgery (98.1%). By contrast, only 0.6% of patients received chemotherapy.

3.3 | Construction of the model

In the training cohort, univariate multivariate logistic regression analyses were performed to evaluate each potential variable: age, gender, race, tumor size, ETE, and LNM (Table 2). Older patients had a higher risk of metastasis (OR = 1.07; 95% CI = 1.05–1.08; $p < .001$). For race, Asian or Pacific Islander (API) with FTC had the highest probability of metastasis (OR = 2.97; 95% CI = 2.03–4.36; $p < .001$) compared to Black (OR = 1.94; 95% CI = 1.24–3.03; $p = .035$) and White patients. Patients with larger tumor sizes also had a higher risk of metastasis (OR = 1.14; 95% CI = 1.09–1.19; $p < .001$). The presence of ETE (OR = 6.44; 95% CI = 4.69–8.85; $p < .001$) or LNM (OR = 14.4; 95% CI = 9.92–20.9; $p < .001$) were positive predictors of metastasis. Gender appeared to be a weak indicator of metastasis: univariate analysis showed statistical significance (OR = 1.39; 95% CI = 1.03–1.88; $p = .032$), but multivariate regression analysis yielded no difference (OR = 1.05; 95% CI = 0.75–1.46; $p = .782$). Based on regression analyses, we performed analyses on age, gender, race, tumor size, ETE, and LNM by applying stepwise algorithm and BMA

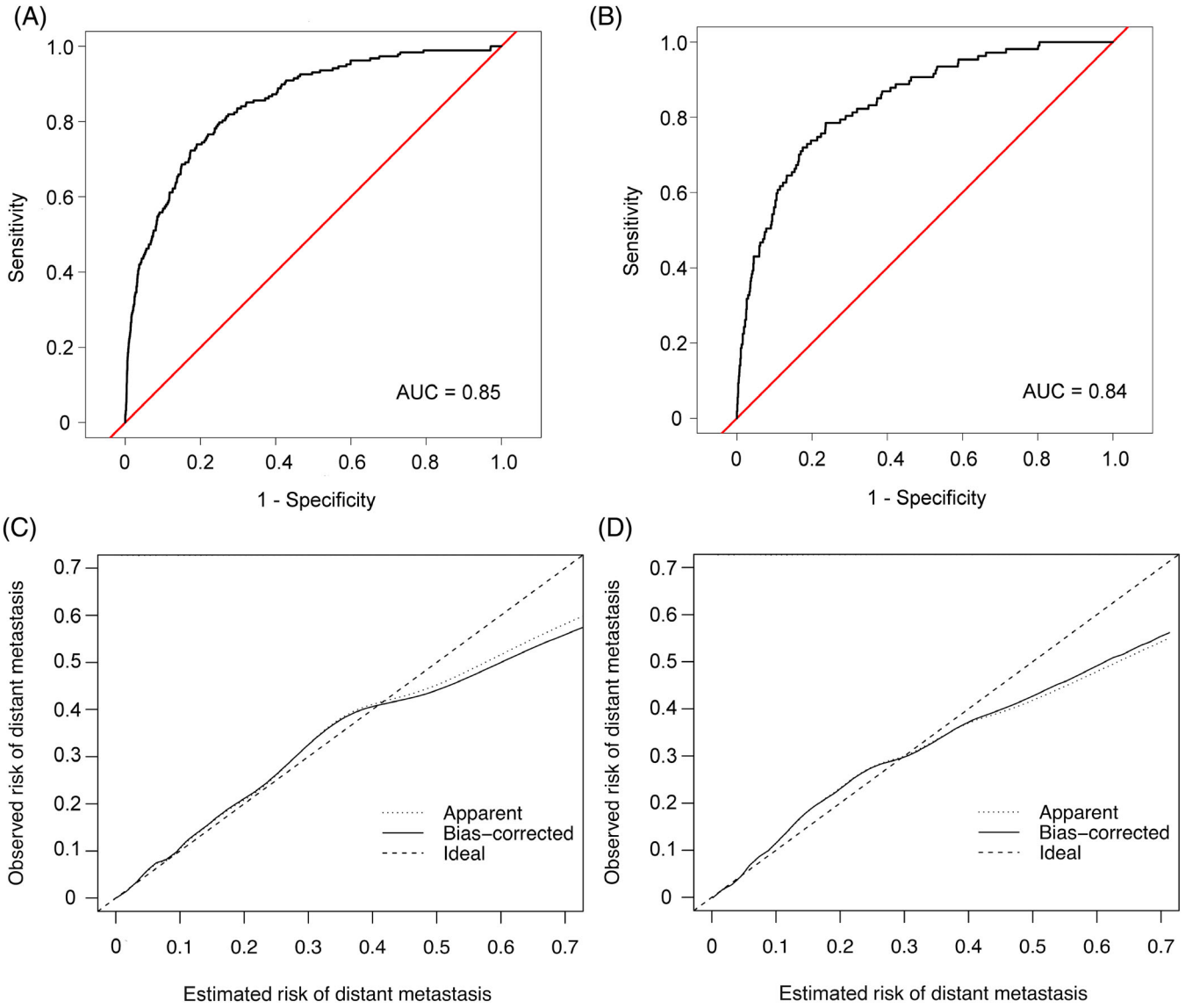

FIGURE 1 The receiver operating characteristic (ROC) curves showing a high area under the curve (AUC) in the training (A) and validation (B) cohort. The calibration plots showing the fitness of the model with observed values, using bootstrap-predicted values, in the training (C) and validation (D) cohorts.

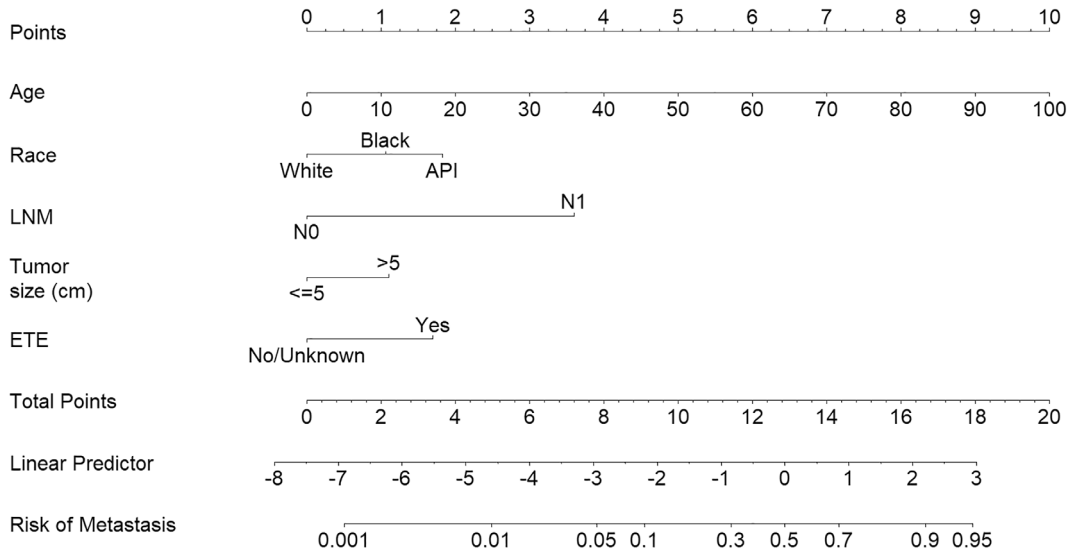

FIGURE 2 The nomogram to estimate the risk of distant metastasis in follicular thyroid carcinoma patients. The total points are vertically related to the corresponding linear predictor indexes; API, Asian or Pacific Islander.

procedure. Finally, age, race, tumor size, ETE, and LNM were included in the optimal model.

3.4 | Examining the linearity of continuous variables: age and tumor size

To examine the linear relationship between continuous variables and metastatic risk, we performed subgroup logistic regression analyses to see how significant these variables are in predicting metastatic risk within each subgroup of the training cohort. We divided age subgroups into <55 and ≥55 years old in accordance with the AJCC staging system.[16] We found that age was still of predictive value when the patient was <55 years old (Table S1). To determine an optimal cut-off of tumor size, we categorized size into many subgroups and performed analysis within each group. We found that a tumor size from 0 to 5 cm was not related to metastatic risk (Table S1). Therefore, we retained age as the continuous variable and changed the size into a categorical variable: ≤ 5 cm and >5 cm.

3.5 | Construction of the risk scoring table

The ROC analysis was performed to evaluate the model (Figure 1A). The AUC was 0.85 (95% CI = 0.82–0.88), indicating the high discriminatory power of the model in the training cohort.

We established a nomogram to calculate the risk of distant metastasis at diagnosis was established (Figure 2). The distribution of the model's LPI was constructed (Figure S1A). A risk scoring table was then constructed based on LPI and nomogram (Table 3). In the table, the score of each variable was approximated based on the variable score in the nomogram. To determine cut-off points for stratification, we performed K-means clustering on the LPI. The elbow method illustrated a significant reduction of variation when $k \leq 4$ (Figure S2A). Therefore, we selected $k = 4$ and calculated the LPI of each clusters (Figure S2B). We selected cut-off LPI values based on the corresponding maximal and minimal points in each groups. The cut-off scores were approximated, using the cut-off LPI values in the nomogram.

TABLE 3 Risk table of distant metastasis in follicular thyroid carcinoma patients

Variables	Score
Age (years)	0.1 point per 1 year
Tumor size >5 cm	1
Race	
White	0
Black	1
Asian or Pacific Islander	2
Extrathyroidal Extension	2
Lymph node metastasis	3.5
Total score	
0–4 points	Extremely low
>4 to 6 points	Low
>6 to <9 points	Intermediate
≥9 points	High

3.6 | Validation of the model and risk scoring table

Using the trained model, we calculated the LPI for each patient in the validation cohort and found its distribution was preserved compared to the training cohort (Figure S1B). Next, regression on the LPI revealed a slope of 0.98 (95% CI = 0.85–1.15) which is equivalent to

TABLE 4 Risk of distant metastasis at diagnosis among risk groups

	Risk of distant metastasis (95% CI)[a]					
Risk group	Total		Training		Validation	
Extremely low	$n = 1513$	0.3% (0.07–0.53%)	$n = 1028$	0.19% (0.0–0.49%)	$n = 485$	0.41% (0.0–1%)
Low	$n = 2514$	1% (0.6–1.3%)	$n = 1673$	0.83% (0.42–1.3%)	$n = 841$	1.2% (0.6–1.9%)
Intermediate	$n = 2116$	3.5% (2.7–4.3%)	$n = 1422$	3.4% (2.6–4.4%)	$n = 694$	3.6% (2.3–4.9%)
High	$n = 1161$	16.7% (14.5–19%)	$n = 790$	15.6% (13.2–18.1%)	$n = 371$	18.8% (14.8–22.9%)

[a]95% confidence interval (95%CI) calculated using 1000 bootstrap samples in each cohort. A chi-squared significant test showed no differences in the risk group distribution of metastatic cases in all cohorts ($p = .975$).

1 ($p = .596$). Therefore, the discrimination of the model on the validation dataset was preserved.

We performed ROC analysis was used to evaluate the performance of the model on the validation cohort (Figure 1B). AUC was 0.84 (95% CI = 0.8–0.88), using 1000 bootstrap samples, indicating a high discriminatory power.

We created calibration plots to evaluate the accuracy of the model's estimation (Figure 1C,D). In these plots, the estimated probability of distant metastasis was calculated using 100 bootstrap samples. The model can accurately estimate metastatic risk at diagnosis when the metastatic risk was lower than 40%. However, the model became miscalibrated when metastatic risk was higher than 40%. The results of a Hosmer–Lemeshow significant test with 10th percentile divisions was done in the training ($p = .528$) and validation ($p = .65$) cohorts. The results illustrated the preserved GOF of the model in both cohorts.

3.7 | The probability of distant metastasis among risk groups

Using the risk table, we stratified patients into four groups each within the training, validation, and combined cohorts. Table 4 shows the probability of distant metastasis at diagnosis within each group and cohort. There were no differences between the three cohorts in the distribution of patients within each risk group between the three cohorts ($p = .975$). Overall, there were 20.7%, 34.4%, 29%, and 15.9% of FTC patients within the extremely low, low, intermediate, and high-risk groups, respectively.

Almost no patients in the extremely low-risk group had any risk of metastasis (0.3%; 95% CI = 0.07–0.53%). In the combined cohort, the low-risk group had a probability of metastasis of about 1% (95% CI = 0.6–1.3%). In contrast, the intermediate-risk group had a 3.5% risk of metastasis (95% CI = 2.7–4.3%) and the high-risk group had a striking propensity for metastasis at diagnosis with 16.7% (95% CI = 14.5–19%) of patients developing metastatic disease.

4 | DISCUSSION

Since our risk scoring table stratifies a large number of patients into only four risk groups, it has the potential to be highly productive and useful. The risk stratification would not be nearly as meaningful if the table classified only a few patients into each risk group. As to the risk scoring itself, extremely low-risk patients had almost no risk of metastasis at the time of diagnosis, and low-risk patients had only about 1% risk of metastasis. Whereas, patients with intermediate-risk had about a 3.5% chance of having metastatic disease while high-risk patients had a significant tendency for distant metastasis. In clinical practice, this table could be a useful adjunctive tool for interpretation along with other investigations. Furthermore, not all medical systems are equipped to perform a comprehensive investigation for distant metastasis in FTC patients due to the lack of facilities. In such cases, our risk scoring table can be a helpful tool. It is noteworthy that our risk table works well for detecting patients with almost no risk of metastasis, which may help alleviate clinical concerns of metastasis in some circumstances. In the combined cohort, 99.7% of FTC patients with extremely low risk had not developed the metastatic disease at the time of diagnosis.

Previous studies developed many methods for determining prognosis and metastatic risk of FTC.[6] A well-known prognostic category established by the AFIP in 2014 is based on the presence of vascular invasion.[14] However, the AFIP classification is not appropriate for screening FTC patients with a low risk of distant metastasis since the AFIP system is purposed to detect patients with prognoses that are worse than the general population of FTC patients.[12,14] Another study established a prognostic model using ultrasonographical features of FTC to predict the risk of metastasis.[6] Despite its high performance, their model was not available to quantify the parameters and stratify the risk of metastasis. It is not clear whether their model's estimation capability worked well in patients with extremely low risk of metastasis.

Age is considered a crucial risk factor in patients with differentiated thyroid carcinoma.[17] Studies showed that patients with metastatic FTC were generally older than nonmetastatic FTC patients.[6,18] Age is also incorporated into the American Joint Committee on Cancer (AJCC) tumor staging for differentiated thyroid carcinoma. However, AJCC classification is not specifically purposed to estimate the risk of metastasis.[19] Although gender is a prognostic factor of thyroid cancers,[20] we did not find a clear association between gender and distant metastasis in the present study, which was consistent with other studies.[6,18]

Race was a strong factor in the training model of the present study. The explanations for the significant effect of race on metastatic risk are quite complicated. First, a SEER-based study by Kristin et al.

showed that many demographic characteristics differed significantly among races.[21] Therefore, the demographic features can serve as confounders of race in the present model. However, race may still affect the tumor characteristics after controlling for age, gender, tumor stage, and demographic factors. Non-white ethnicity was associated with a tumor size ≥4 cm,[21] and the genetic background of FTC is different among races. In a systematic review, we illustrated that there were differences in the genetic background of FTC patients between Asian countries and Western countries.[22] *RAS* mutations were found to be associated with distant metastasis of FTC in another study.[23] Conversely, it is not clear whether the presence of *PAX8/PPARγ* fusion leads to a poorer or more favorable outcome in FTC patients.[24–27] Therefore, although a comprehensive description of the genetic discrepancies among races has not been established, although our results concluded that race was related to the risk of distant metastasis in FTC patients.

Tumor size, ETE, and LNM are prognostic factors of FTC.[28,29] These tumor characteristics were also included in the present model. Large tumor size was associated with a higher risk of metastasis although the effect size was relatively low compared to race, ETE, and LNM (Table 3). Although LNM and ETE were uncommon in the present study, the presence of these factors significantly increased the risk of distant metastasis, and our findings were therefore consistent with previous studies.[28,29] Although the AJCC tumor staging system can be used to replace these factors,[16] this can cause a loss of information. In tumor-node-metastasis (TNM) grading, size is used as a category, but an increase in tumor size does not change the T3a grades unless there is accompanied by ETE.[16] As a result, the significance of tumor size beyond 4 cm is lost. In our study, both size and ETE can contribute to distant metastasis separately.

However, there are limitations to the study. First, the information obtained from the SEER database itself is heterogeneous and may be confounded by unobserved factors. LNM may be affected by the fact that lymph nodes are not often examined at the time of FTC resection. We attempted to reduce this bias by excluding cases with unknown lymph node status. Nevertheless, external validation is needed to examine our model outside of the SEER database before it can be used in clinical practice. Second, our calibration plots illustrated that the model became less accurate when the probability of distant metastasis was >40%. This limitation of the present model, however, was not crucial to our results since our focus was on separating patients with extremely low, low, and intermediate FTC metastatic risk (<40%), which we were able to calibrate precisely. Finally, noninvasive follicular neoplasms with papillary thyroid carcinoma-like nuclear features (NIFTP) and follicular variant of papillary thyroid carcinoma were potentially misclassified as FTC in the SEER database. The distinction between these tumors can only be made by histology.

5 | CONCLUSION

In conclusion, our risk table is a productive means for clarifying four risk groups of patients with distinct probabilities of metastasis. This table can be referenced in conjunction with imaging, histopathologic, and molecular investigations for a more accurate estimation of FTC metastatic risk.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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