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*Original Article*

# A new proposed tumor-node-metastasis-age staging system for stage IV medullary thyroid carcinoma based on the SEER database

Man Li[1*], Yihui Huang[1*], Min Wang[1*], Wen Zeng[3], Sichao Chen[1], Wei Zhou[1], Wei Wei[4], Chao Zhang[5], Di Hu[1], Jianglong Huang[1], Zeming Liu[2#], Liang Guo[1#]

*Departments of [1]Plastic Surgery, [3]Ophthalmology, Zhongnan Hospital of Wuhan University, Wuhan 430071, Hubei Province, China; [2]Department of Plastic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China; [4]Department of Pediatrics, St. John Hospital and Medical Center, Detroit, MI, USA; [5]Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China. [*]Equal contributors. [#]Equal contributors.*

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**Abstract:** Medullary thyroid carcinoma (MTC) is a rare and lethal cancer. There are currently controversies regarding its staging. This study aimed to verify the significance of the patient's age in the prognosis of MTC and propose its addition to the current staging system. Data on cancer-specific survival (CSS) from the Surveillance, Epidemiology, and End Results database between 2010 and 2015 were used. X-Tile, nomograms, Cox proportional hazards regression analysis, Kaplan-Meier curves, and log-rank tests were used to evaluate mortality rates to create a new staging system. A total of 849 patients were included. Patients were divided into three categories based on their ages at diagnosis: ≤41 years, n = 224 (26.4%); 42-71 years, n = 516 (60.8%); and ≥72 years, n = 109 (12.8%). Independent factors for survival in the multivariate analysis included age (42-71 years, hazard ratio [HR], 2.81, 95% confidence interval [CI], 1.07-7.42; ≥72 years, HR, 8.71, 95% CI, 2.88-26.34), T stage (T2, HR, 3.60, 95% CI, 1.31-9.88), and M stage (M1, HR, 8.43, 95% CI, 4.40-16.16), with P<0.05. The Harrell's concordance index for tumor node metastasis (TNM) nomogram and TNM-age nomogram was 0.904 and 0.908, respectively. The areas under the curve (AUCs) for a 3-year CSS were 0.88 and 0.873, respectively. The corresponding AUCs for a 5-year CSS were 0.892 and 0.888, respectively. A new TNM-age staging system based on cancer-specific mortality rate analysis is proposed. This system provides a more accurate risk stratification and ensures more rational treatment measures for patients with stage IV MTC.

**Keywords:** Medullary thyroid carcinoma, SEER, TNM staging system, age, nomogram

## Introduction

Thyroid cancer is a malignant tumor with a high global incidence. Medullary thyroid carcinoma (MTC), one of the four common pathological types of thyroid cancer, is a neuroendocrine tumor arising from calcitonin-secreting parafollicular C cells [1, 2]. MTC's highly variable biological behavior ranges from indolent to very aggressive [3, 4]. It accounts for 1-2% of thyroid cancers but >10% of thyroid cancer-related deaths [5, 6].

The American Joint Committee on Cancer (AJCC) for International Cancer Control tumor-node-metastasis (TNM) staging system provides the most important criterion for clinical diagnosis and treatment [7]. The revised TNM staging system for MTC published in 2017 was extrapolated from that of differentiated thyroid cancer (DTC) [8, 9]. However, MTC is inherently different from DTC in terms of clinical presentation, treatment recommendations, and prognosis. Although the eighth edition of the TNM staging system made substantial improvements in thyroid cancer staging, it remains controversial for predicting the survival of patients with MTC [3, 10].

Age was shown to be an important independent prognostic factor in patients with MTC, and relevant age cutoff values were studied [11]. Previous research has found a significant difference between the mean ages of patients with

**Table 1.** Basic characteristics of patients with medullary thyroid carcinoma (n = 849)

| Covariate | Number | % |
|---|---|---|
| Race | | |
| White | 699 | 83.2 |
| Black | 73 | 8.7 |
| Other | 68 | 8.1 |
| Sex | | |
| Female | 512 | 60.3 |
| Male | 337 | 39.7 |
| Age | 51.61±17.92 | |
| Stage | | |
| I | 322 | 38.0 |
| II | 164 | 19.3 |
| III | 87 | 10.2 |
| IVa | 190 | 22.4 |
| IVb | 22 | 2.6 |
| IVc | 64 | 7.5 |
| T-stage | | |
| T1 | 394 | 46.4 |
| T2 | 202 | 23.8 |
| T3 | 174 | 20.5 |
| T4a | 44 | 5.2 |
| T4b | 35 | 4.1 |
| N-stage | | |
| N0 | 503 | 59.2 |
| N1a | 105 | 12.4 |
| N1b | 241 | 28.4 |
| M-stage | | |
| M0 | 785 | 92.5 |
| M1 | 64 | 7.5 |
| Extension | | |
| No | 703 | 82.8 |
| Yes | 146 | 17.2 |
| Number of tumor foci | | |
| 1 | 570 | 68.1 |
| ≥2 | 267 | 31.9 |
| Surgical Procedure | | |
| Biopsy | 38 | 4.5 |
| Lobectomy | 54 | 6.4 |
| Subtotal or near-total thyroidectomy | 11 | 1.3 |
| Total thyroidectomy | 738 | 87.8 |
| CSS | | |
| Alive | 789 | 92.9 |
| Death | 60 | 7.1 |

Abbreviations: CSS, cancer-specific survival.

familial MTC (32 years old) and those with sporadic cases (53 years old) [12]. To optimize the AJCC staging system for MTC, we developed a new nomogram prognostic model generated using age and TNM stages, and evaluated its performance compared with the current TNM staging system. Furthermore, based on the new nomogram model, a new proposed staging system was also generated.

## Materials and methods

### *Patient data and ethics statement*

For this study, we retrieved the data of patients with medullary carcinoma (code: 8510/3) for the period 2010-2015 from the Surveillance, Epidemiology, and End Results (SEER) program 18. The SEER data are anonymous and publicly accessible; hence, global cancer researchers can obtain data through application, and ethical review was not required. Data on each patient's race, sex, age at diagnosis, T stage, N stage, M stage, tumor extension, number of tumor foci, surgical method, survival months, and cancer-specific survival (CSS) were acquired. To obtain more accurate and effective results, 623 patients with unknown data on survival months or TNM stage were excluded.

### *Clinicopathological variable assessment*

The cutoff points for age at diagnosis were calculated using the X-Tile software program (Yale University, New Haven, CT, USA), with CSS as the primary outcome. Univariate and multivariate Cox proportional hazards models were then used to assess the risk factors associated with the prognosis of patients with MTC. To determine the association between age group and prognosis using the new cutoff point, multivariate Cox proportional hazards models were generated using a three-step adjustment. The first step adjusted demographics, while the second step adjusted demographics, TNM stage, extension, and number of tumor foci. Finally, the third step adjusted the factors in the second step plus the surgical method.

### *Construction and validation of the nomograms*

The nomogram was developed using the data of 849 patients diagnosed during 2010-2015. The primary outcome of the study was

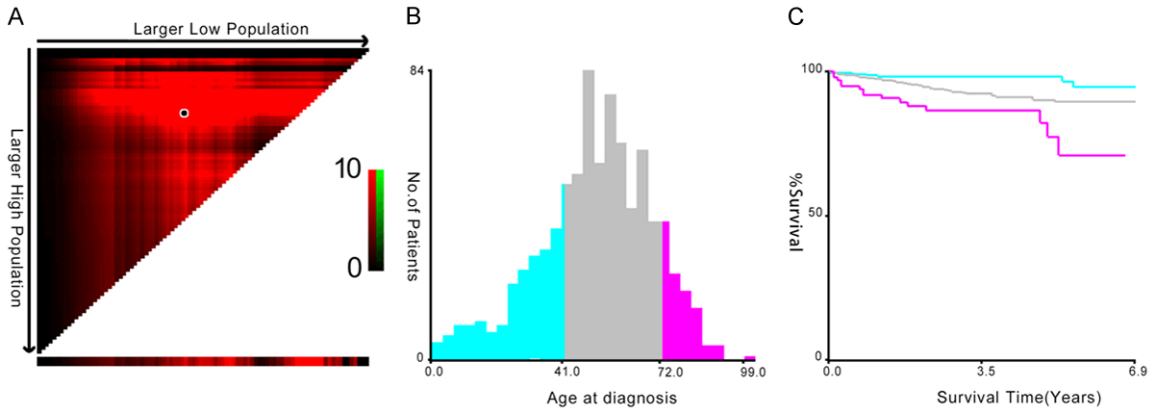


**Figure 1.** Identification of optimal cutoff points of age at diagnosis using the X-tile program. (A) The cutoff points of age at diagnosis were determined using the software with the black dots. Histograms (B) and Kaplan-Meier curves (C) were established based on the cutoff points determined. Optimal cutoff points of age at diagnosis were 41 and 72 years.

**Table 2.** Univariate and multivariate Cox regression analysis based on age at diagnose for 849 patients with MTC

| Cox Regression Analysis | Parameters | | HR | 95% CI | | *p* value |
|---|---|---|---|---|---|---|
| Univariate | Age | ≤41 | ref | | | |
| | | 42-71 | 2.84 | 1.203 | 6.709 | 0.017 |
| | | ≥72 | 5.999 | 2.324 | 15.486 | <0.001 |
| Multivariate Adjust[1] | Age | ≤41 | ref | | | |
| | | 42-71 | 2.786 | 1.179 | 6.584 | 0.02 |
| | | ≥72 | 5.909 | 2.287 | 15.266 | <0.001 |
| Multivariate Adjust[2] | Age | ≤41 | ref | | | |
| | | 42-71 | 2.814 | 1.068 | 7.419 | 0.036 |
| | | ≥72 | 8.952 | 3.017 | 26.565 | <0.001 |
| Multivariate Adjust[3] | Age | ≤41 | ref | | | |
| | | 42-71 | 2.47 | 0.921 | 6.625 | 0.073 |
| | | ≥72 | 8.705 | 2.876 | 26.343 | <0.001 |

Adjust[1] included race, sex, age; Adjust[2] included race, sex, age, T category, N category, M category, extension, number of tumor foci; Adjust[3] included factors in adjust[2] and surgical methods. Abbreviations: HR, hazard ratio; CI, confidence interval.

CSS [13, 14]. The nomogram was validated using the 3-year and 5-year CSS rates based on significant prognostic factors identified in the multivariate analysis. The validation was carried out using the rms package in R, version 3.5.3 (http://www.r-project.org/). Receiver operating characteristic (ROC) curves and Harrell's concordance index (C-index) were applied to measure the performance of the nomograms. Calibration curves were also plotted to compare the outcomes predicted by the nomograms and the actual survival outcomes.

### *Statistical analyses*

A new staging system was proposed and further generated based on the new nomogram model. Survival curves were generated using the Kaplan-Meier method and analyzed using the log-rank test to compare differences in survival predicted by the new and the current staging systems.

SPSS version 23.0 (IBM Corp, Armonk, NY), GraphPad Prism version 6 (GraphPad Software Inc., La Jolla, CA, USA), and Stata version 12 (StataCorp, College Station, TX, USA) were used for data analysis. P<0.05 was considered to indicate statistical significance.

## Results

### *Demographic and clinical features*

A total of 849 patients with pathologically confirmed MTC were identified from the SEER database. As shown in **Table 1**, the cohort comprised 699 white patients (83.2%), 73 black patients (8.7%), and 68 patients of other races (8.1%). The female:male ratio was 1.52. There were 394 (46.4%), 202 (23.8%), 174 (20.5%), 44 (5.2%), and 35 (4.1%) patients with T1, T2, T3, T4a, and T4b stage, respectively;

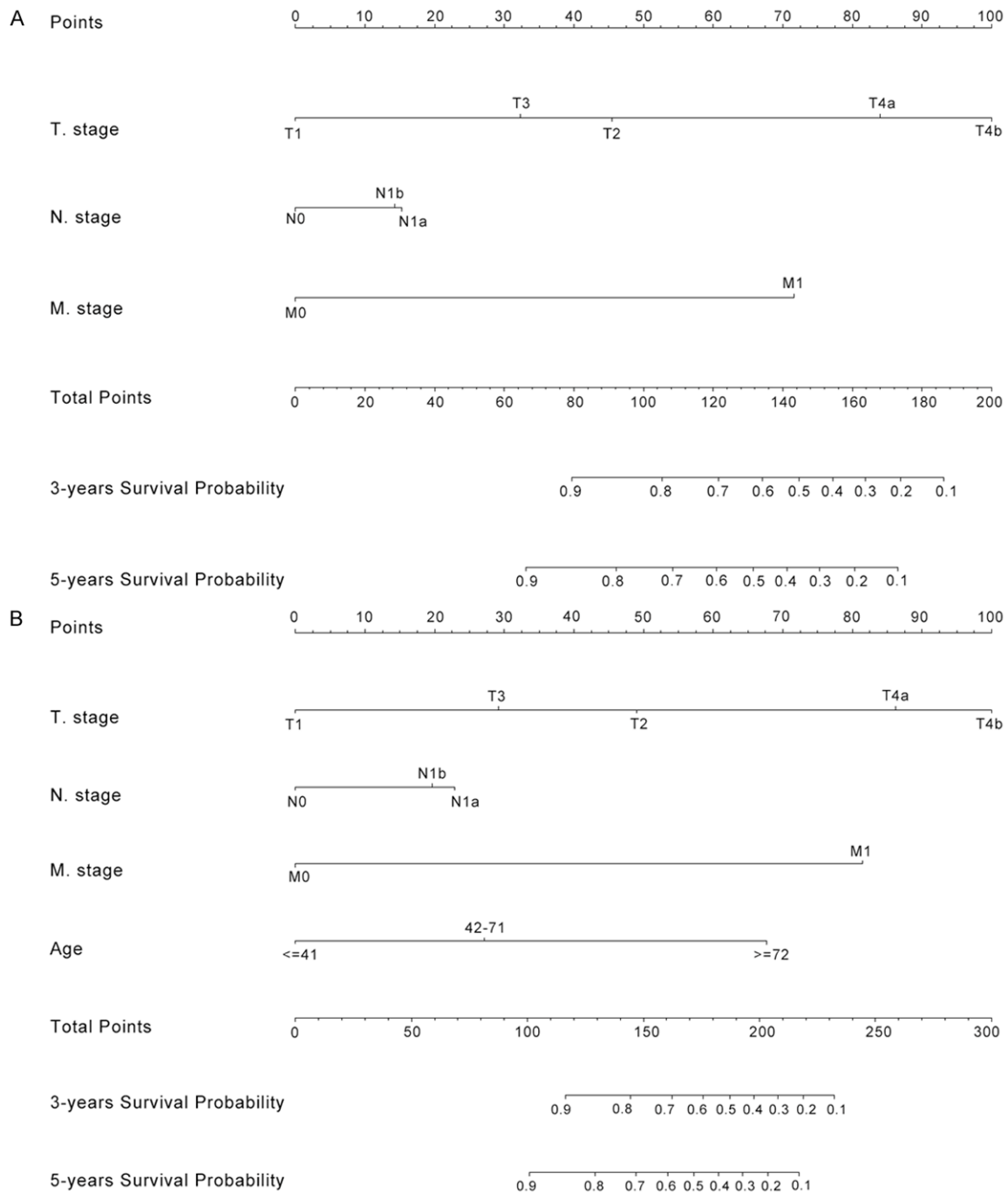


**Figure 2.** Nomograms predicting 3-year and 5-year cancer-specific survival (CSS) of patients. A. Prognostic factors of tumor-node-metastasis (TNM) nomogram including T stage, N stage, and M stage; B. TNM-age nomogram including T stage, N stage, M stage and age at diagnosis.

503 (59.2%), 105 (12.4%), and 241 (28.4%) patients with N0, N1a, and N1b stage, respectively; 785 (92.5%) and 64 (7.5%) patients with M0 and M1 stage, respectively; and 146 (17.2%) patients with extension.

*Identification of cutoff values of age*

We used the X-tile program to analyze the data of patients with MTC from the SEER database. The results showed that 41 years and 72 years

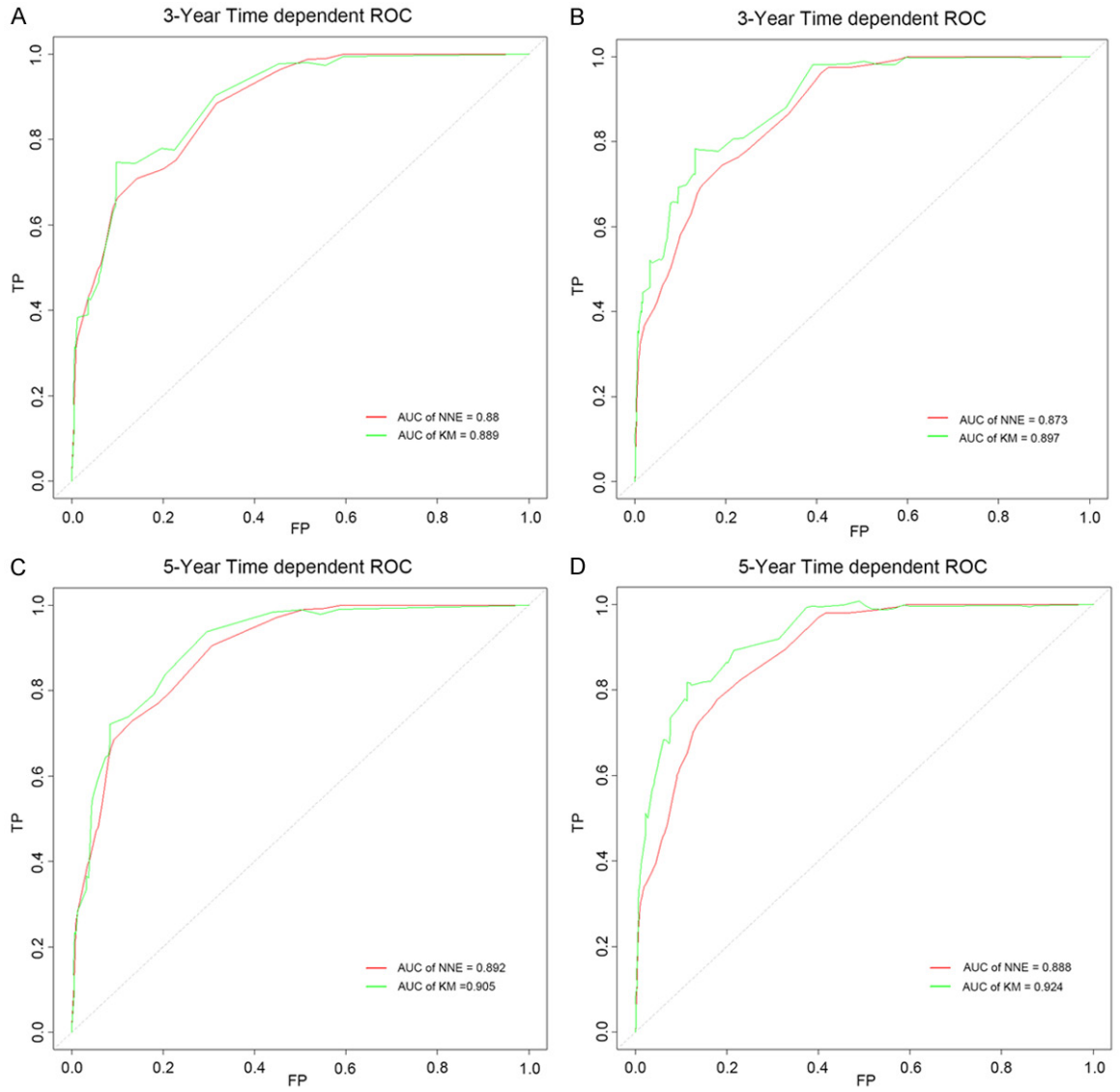


**Figure 3.** The areas under the curve (AUC) of the two nomograms. A. AUC of the TNM nomogram for 3-year CSS; B. AUC of the TNM-age nomogram for 3-year CSS; C. AUC of the TNM nomogram for 5-year CSS; D. AUC of the TNM-age nomogram for 5-year CSS.

were the best cutoff values of age at diagnosis (**Figure 1**). Therefore, the patients were assigned to three categories as shown in Table S1: age ≤41 years, n = 224 (26.4%); age 42-71 years, n = 516 (60.8%); and age ≥72 years, n = 109 (12.8%).

*Univariate and multivariate analyses of MTC risk factors*

The prognostic factors for CSS in patients with MTC are presented in **Table 2**. In the univariate analysis, the age at diagnosis was significantly associated with CSS (P<0.05). On multivariate analysis, independent factors for survival included age (42-71 years, hazard ratio [HR], 2.81, 95% confidence interval [CI], 1.07-7.42; ≥72 years, HR, 8.71, 95% CI, 2.88-26.34), T stage (T2, HR, 3.60, 95% CI, 1.31-9.88), and M stage (M1, HR, 8.43, 95% CI, 4.40-16.16), with all p<0.05. After adjusting race, sex, T stage, N stage, M stage, extension, number of tumor foci, and surgical method, patients ≥72 years of age still had a higher risk for worse CSS than patients ≤41 years of age (P<0.001).

*Development and validation of the nomograms*

Nomograms integrating statistically significant prognostic factors of CSS were established

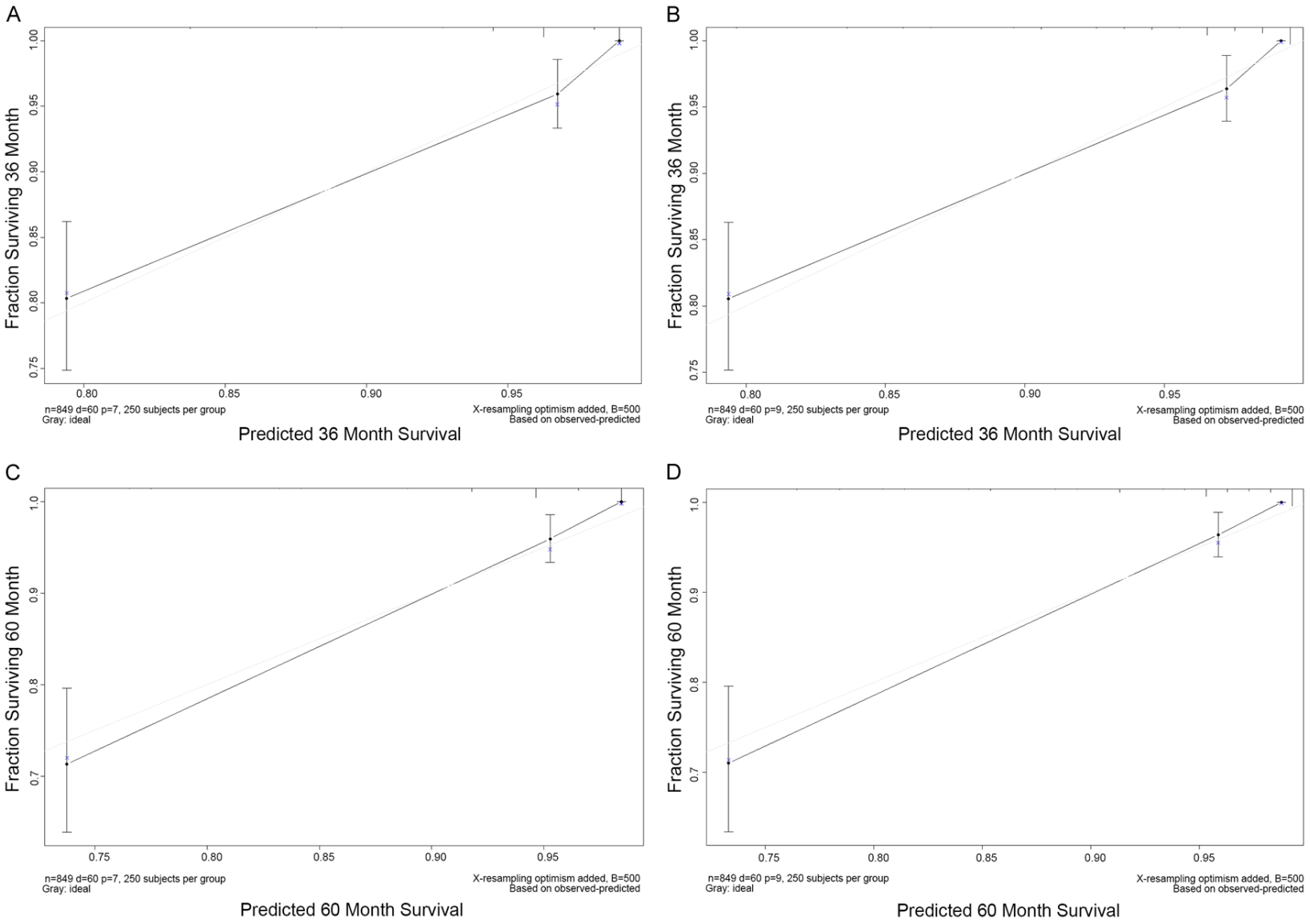


**Figure 4.** The calibration plots of the two nomograms. A. The calibration plots of TNM nomogram for 3-year CSS; B. The calibration plots of the TNM-age nomogram for 3-year CSS; C. The calibration plots of the TNM nomogram for 5-year CSS; D. The calibration plots of the TNM-age nomogram for 5- year CSS.

**Table 3.** New proposed stage for medullary thyroidcarcinoma

| Current Stage | New Proposed | |
|---|---|---|
| IVa | IVa' | ≤41 IVa |
| IVb | IVb' | ≤41 IVb, c >41 IVa, b |
| IVc | IVc' | >41 IVc |

(**Figure 2**). Each point on the horizontal line of a prognostic factor, including age at diagnosis, T stage, N stage, and M stage, had a corresponding score in the nomograms. All the points were converted and added to get the final score. To validate the predictive value of age, we constructed a TNM nomogram (including TNM stage) and a TNM-age nomogram (including TNM stage and age) and compared the 3-year and 5-year survival probabilities. The nomograms were evaluated using discrimination and calibration curves. As illustrated in **Figure 3**, the ROC curves of the nomograms demonstrated an excellent discrimination for the prediction of the survival rate, and the areas under the curve (AUCs) of the TNM and TNM-age nomograms for 3-year CSS were 0.88 and 0.873, respectively. The corresponding AUCs for 5-year CSS were 0.892 and 0.888, respectively. Calibration plots suggested that the TNM-age nomogram had better concordance with actual survival data than the TNM nomogram (**Figure 4**). The C-indexes for the TNM nomogram and the TNM-age nomogram were 0.904 and 0.908, respectively.

*Proposed TNM staging system based on age at diagnosis*

Based on the nomogram evaluations, the difference between combining the age and TNM stage and TNM stage alone was not large when all the stages were combined. However, after we generated the Kaplan-Meier survival curves for each TNM stage separately, we found significantly large differences in the age groups of patients with stage IV MTC alone. With the aim to better distinguish the prognosis of patients with stage IV disease, we further used age as a prognostic factor in the staging system and assigned a new proposed system with stages IVa', IVb', and IVc' (**Table 3**). Compared with the current staging system, the new proposed staging system showed better distinguishability in the survival of patients with stage IV MTC (**Figure 5**).

## Discussion

A cohort of 849 patients with accurate clinical information was screened from SEER [15]. We evaluated appropriate cutoff values of age at diagnosis and incorporated this variable into a nomogram with TNM stage as a promising prognostic factor. Univariate and multivariate analyses of MTC risk factors confirmed the significance of age. We found no significant difference between the two nomogram models (TNM nomogram C-index = 0.904 and TNM-age nomogram C-index = 0.908). Therefore, further subgroup analysis for each stage was performed to investigate any differences among the three age groups. The results showed that the difference was significant in patients with stage IV disease alone.

Because of the rarity of MTC and the lack of relevant clinical data, the current staging system is still based on the classification structure of DTC, which is not accurate. To improve the situation, previous studies have proposed new staging systems [10, 16-18]. For instance, Adam et al. determined that the current AJCC TNM staging system for MTC upstaged a significant number of patients to stage IV and proposed a new TNM grouping that was better at discriminating survival [10]. Yang et al. also put forward an anatomical staging system with a postoperative calcitonin measurement [18].

Our results are consistent with the results of previous studies which demonstrated that age is an important prognostic factor for patients with MTC. Kebebew et al. found that age and TNM stage alone were independent predictors of survival [19], and Qu et al. confirmed the prognostic significance and optimal cutoff of age in MTC [11]. Therefore, we incorporated age as a prognostic factor into the assessment system and evaluated its effectiveness. This study confirmed that the new staging system, which incorporated age, is more accurate than the current staging system in predicting the survival period, especially for patients with stage IV disease.

Based on the findings from our study and previous works, we propose to add age to the TNM staging system for MTC, as shown in **Table 3**. Patients ≤41 years of age with stage IVa disease are categorized as having stage IVa', patients >41 years of age with stage IVc dis-

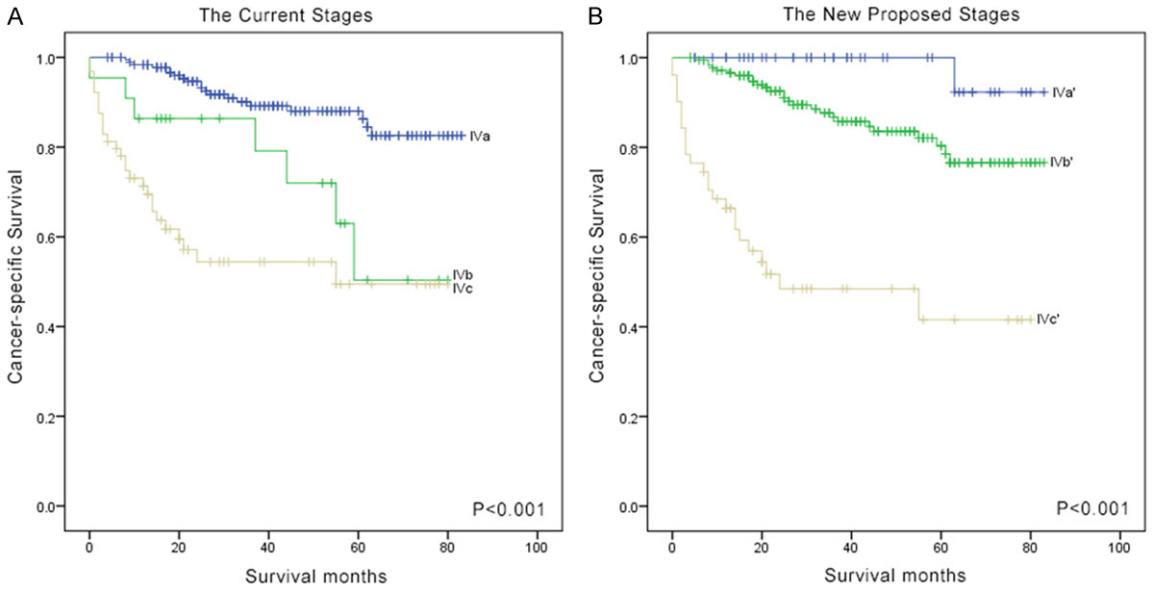


**Figure 5.** Kaplan Meier curves for the two stage systems. A. Kaplan Meier curves for the current Iva, IVb, IVc stages of medullary thyroid carcinoma; B. Kaplan Meier curves for the new proposed IVa', IVb', IVc' stages of medullary thyroid carcinoma.

ease are categorized as having stage IVc', and the remaining patients (patients ≤41 years of age with stage IVb or IVc and those >41 years of age with stage IVa or IVb) are classified as having stage IVb'. For the practicality of the proposed new system, patients ≥72 years of age were not included. The new proposed staging system, which included age as a prognosis factor, can better distinguish the survival time of patients with stage IV MTC, in contrast to the current staging system.

Age is an independent risk factor for the disease-specific mortality (HR, 1.36 per decade; 95% CI, 1.17-1.59) of MTC [20], which is consistent with the results of this study. With increasing age, the prevalence and severity of many diseases increase. Subsequently, the ability to tolerate treatment decreases, affecting the treatment effect, increasing complications, and ultimately affecting CSS. Papillary thyroid carcinoma (PTC) often occurs concurrently with MTC, and the rate of simultaneous MTC and PTC ranges from 2.6% to 19% [6]. A previous study also identified age as an independent factor in the PTC staging system. Rondi et al. found that patients ≥60 years of age had worse disease-specific survival and disease-free survival after a diagnosis of PTC across all stages of disease. They proposed three categories instead of the single cutoff of 45 years of age [21]. There are also studies showing that patients with sporadic MTC tend to be older than those with familial MTC [22]. Patients with sporadic MTC tended to have systemic symptoms (diarrhea, bone pain, or flushing) and were more likely to have widely metastatic MTC. Moreover, the disease outcome is worse in sporadic MTC than familial MTC, with up to 33.3% of patients dying within 5 years [19].

There are some limitations in this study. First, Because the nomograms were established based on retrospective data from the SEER database, errors and biases occurred. Second, the sample size was relatively small. Additionally, cytokines, especially serum calcitonin, were also proven to be relevant to the prognosis of MTC in the recent years [11, 22]. However, because of the lack of data in the SEER database, these factors were not evaluated in this research. Patient management should be adjusted for these factors after their impact on MTC is clarified.

In conclusion, our results indicated that incorporating age into the TNM staging system improved the accuracy of the system. The inclusion of age for patients with stage IV MTC provided a more accurate risk stratification and potential treatment selection than the current AJCC TNM staging system.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Liang Guo, Department of Plastic Surgery, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, China. E-mail: guoliangwhzn@163.com; Zeming Liu, Department of Plastic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China. E-mail: 6myt@163.com

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**Table S1.** The distribution of patients in different age group after applying the cut-off values generated by X-tile

| Covariate | Level | Number | % |
|---|---|---|---|
| Age | ≤41 | 224 | 26.4 |
| | 42-71 | 516 | 60.8 |
| | ≥72 | 109 | 12.8 |