Does pretreatment elevated calcitonin level cause the poor prognosis in patients with medullary thyroid cancer?

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Background: Medullary thyroid carcinoma (MTC) patients have poor survival, tumor/node/metastasis (TNM) stage and biochemical prognosis are the most important factors. We investigated the clinical significance of calcitonin (Ctn) to assess the biochemical prognosis of MTC.

Methods: This retrospective observational study enrolled 77 MTC patients with complete information and primary surgery at the Department of Thyroid Surgery, China-Japan Union Hospital of Jilin University between 2009 and 2020. Patient and MTC characteristics were recorded. All patients were divided into remission, stable, and progression according to biochemical prognosis. We analyzed the correlation between preoperative serum Ctn, TNM stage and biochemical prognosis.

Results: Elevated preoperative serum Ctn was positively correlated with TNM stage. Patients with higher Ctn, multifocality, and bilateral tumors were associated with a higher TNM stage. Multivariate logistic regression analysis showed that preoperative serum Ctn level was an independent risk factor for TNM stage. Receiver operating characteristic (ROC) analysis found the best Ctn cut-off value for predicting TNM III was 45.88 pg/mL, which had a sensitivity of 87.2% and a specificity of 65.8%. The best Ctn cut-off value for predicting TNM IV was 167.00 pg/mL, with a sensitivity of 92.9% and a specificity of 77.6%. In univariate analysis, patients with higher preoperative serum Ctn, multifocality, bilateral tumors, and higher TNM stage were more likely to progress. The optimal cut-off value for progression was 195.5 pg/mL, which had a sensitivity of 80.0% and a specificity of 70.2%. For every 1-unit increase in preoperative serum Ctn levels, the risk of progression increased by 1.004 times (P=0.008), and patients with TNM stage III [hazard ratio (HR) =9.663; 95% confidence interval (CI): 1.411, 66.156] were nearly 9.7-fold more likely to progress than those in TNM stage I/II.

Conclusions: Elevated preoperative serum Ctn predicted poor clinical outcomes in MTC.

Keywords: Medullary thyroid carcinoma (MTC); calcitonin (Ctn); tumor/node/metastasis stage (TNM stage); biochemical prognosis

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Introduction

Medullary thyroid carcinoma (MTC) is an aggressive tumor originating from the parafollicular C cells and accounts for approximately 5% of all thyroid cancers (1). Although the available screening test and treatment methods reportedly enhance the quality of life for MTC patients, the prognosis of patients with advanced stages or recurrence remains poor (2). Thus, surgery and monitoring biomarkers underlying MTC progression are important. There are many indicators that affect prognosis, including genetics, tumor pathology, etc., but only serological indicators are the easiest and most direct way to monitor and evaluate prognosis.

Calcitonin (Ctn) is a 32 amino acid peptide hormone secreted by parafollicular cells. Ctn is a commonly used biomarker of MTC (3). Routine basal serum Ctn measurement is valuable for detection of MTC in the management of patients with thyroid nodules (4-6). The American Thyroid Association (ATA) guidelines (2) recommend preoperative serum Ctn screening for thyroid malignancies suspected of MTC, and the Chinese MTC guidelines advocate routine preoperative serum Ctn testing for all thyroid malignancies (7). Further, preoperative serum Ctn (8,9) is an important indicator of lymph node metastasis (LNM), which is key for prognosis (10). Thus, the preoperative serum Ctn value is of concern. In clinical practice, postoperative Ctn (11,12), especially the doubling time (13), can be used for postoperative management and prognosis of MTC. The ATA guidelines (2) incorporate postoperative serum Ctn level and its doubling time into the postoperative evaluation and monitoring of MTC. A long-term follow-up study (14) monitored MTC patients for more than 10 years and found that tumor growth was accelerated if the postoperative serum Ctn doubling time was short. Therefore, postoperative serum Ctn could represent a biochemical prognosis for MTC patients. However, there are few studies on preoperative ctn and biochemical prognosis of MTC patients.

In the present study, we aimed to demonstrate the clinical significance of Ctn in patients with MTC and found that increased Ctn levels predicted poor tumor/node/metastasis (TNM) stage and biochemical prognosis of these patients. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2737/rc).

Methods

Design study

This is a retrospective observational study of China-Japan Union Hospital of Jilin University, China, from 2010 to 2020.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of China-Japan Union Hospital (No. 2020010827). Informed consent was taken from all the patients.

MTC diagnosis

Tumor tissue samples collected for histological analysis or surgical resection were obtained from all patients. MTC diagnosis was based on the ATA guidelines (2).

Subjects and data collection

All MTC patient data were collected by thyroid surgery doctors. After exclusion, 77 patients with complete data and follow-up, including serum Ctn levels and clinical and histopathological data, were included in the study (*Figure 1*). The inclusion criteria were as follows: (I) patients consecutively enrolled and diagnosed with primary MTC for the first time; (II) diagnosis confirmed by histological analysis and imaging methods; and (III) follow-up of more than 6 months with complete information.

Measurement of biomarkers and factors

Detection of Ctn and carcinoembryonic antigen (CEA) was performed by chemiluminescence [Ctn (ref.: LKCL1) and CEA (ref.: 7K68-78)] using the IMMULITE 1000 Immunoassay System (Siemens Healthineers, Erlangen, Germany). Normal ranges of Ctn levels were 0.15–6.00 pg/mL for females and 0.15–9.20 pg/mL for males. The upper limit of detection was 585.0 pg/mL. Normal

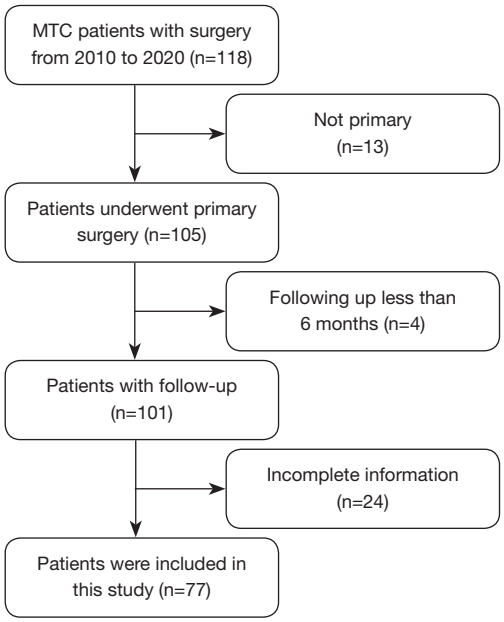

Figure 1 Study cohort with inclusion and exclusion flowchart. MTC, medullary thyroid carcinoma.

range of CEA was 0.5–9.60 ng/mL. Tumor size was the largest diameter of the tumor measured by pathological examination after surgery. Postoperative Ctn assessment was carried out at 1, 3, 6, and 12 months, and annually thereafter. The end of follow-up is December 30, 2020, the follow-up time was 8–128 months, and the median follow-up time was 65 months.

Outcomes measured

As illustrated in Table S1, the patients were divided into three groups based on postoperative serum Ctn level (2,15). Remission: the postoperative Ctn levels of patients fell to normal levels and remained steady. Stable: the postoperative Ctn levels of patients were stable but did not fall to normal levels. Progression: the postoperative Ctn level of patients increased to 150 pg/mL or the doubling time was less than 12 months.

Statistical analysis

SPSS package version 23.0 (IBM Corp., Armonk, NY, USA) was applied to analyze all the data. All results are presented as mean ± standard deviation (SD), median, and interquartile range (IQR) or count (percentage). Fisher's exact test and rank sum test were used to analyze categorical variables. Continuous variables were analyzed with an analysis of variance (ANOVA) test and post-hoc ANOVA was used when appropriate. The Kruskal-Wallis test was used for nonnormal distributions. To predict the biochemical prognosis of MTC, binary logistic regression models were created, and factors contributing to the outcome in the univariate analysis had a $P<0.05$. A $P<0.05$ was considered significant. Receiver operating characteristic (ROC) curves were used to illustrate diagnostic ability.

Results

Characteristics of all patients

Complete data were available for 77 of 101 patients (*Figure 1*). *Table 1* summarizes patient and tumor characteristics. The study included 32 males and 45 females, with a 1:1.4 male-to-female ratio. Mean age at diagnosis was 48.0±12.1 (range, 21–76) years, and 28.6% of patients were aged greater than 55 years. Body mass index (BMI) at diagnosis was 22.80±0.32 kg/m^2. Median follow-up duration was 65 (range, 8–128) months. The median of serum Ctn and CEA before surgery were 145.96 pg/mL and 16.35 μg/L, respectively.

Sixty-one cases (79.2%) underwent total thyroidectomy, and the median of the largest tumor size of the MTC was 1.1 cm. Seventy-six (99%) patients underwent lymph node dissection (LND), among which 25 (32.5%) underwent central LND (CLND), 43 (55.8%) patients underwent CLND + ipsilateral LND, and 8 (10.4%) underwent CLND + bilateral LND. Of the 77 enrolled patients, there were 38 (49.4%) without LNM. Based on the American Joint Committee on Cancer (AJCC) staging system, MTC patients were classified into TNM stage I/II (38, 49.4%), TNM stage III (11, 14.3%), and TNM stage IV (28, 36.4%).

A total of 63 (81.8%) patients had a single tumor, 14 patients (18.2%) showed multifocal tumors, and 8 patients (10.4%) had tumors located in the bilateral thyroid lobes. For cases with unilateral lesions, 31 (40.2%) were identified in the left lobe and 38 (49.4%) in the right lobe. Extrathyroidal extension and Hashimoto's thyroiditis were identified in 6 patients (7.8%) and 4 patients (5.2%), respectively.

Relationship between clinicopathological characteristics and TNM stage

The relationship between clinicopathological characteristics and TNM stage are shown in *Table 2*. Multifocality

Table 1 Characteristics of all patients

Features	N (%)
Total, n	77
Gender	
Men	32 (41.6)
Women	45 (58.4)
Age at diagnosis (years)	
Mean ± SD	48.0±12.1
≤55	55 (71.4)
>55	22 (28.6)
BMI (kg/m^2), mean ± SD	22.80±0.32
Ctn (pg/mL), median (IQR)	145.96 (15.30, 585.00)
CEA (μg/L), median (IQR)	16.35 (5.20, 73.28)
Multifocal MTC	
No	63 (81.8)
Yes	14 (18.2)
Tumor site	
Median (IQR)	1.10 (0.60, 2.40)
Left	31 (40.2)
Right	38 (49.4)
Bilateral	8 (10.4)
Tumor diameter (cm)	
Median (IQR)	1.1 (0.6, 2.4)
≤1	36 (46.8)
1–≤2	19 (28.3)
2–≤4	16 (18.5)
>4	6 (9.8)
N stage	
N0	38 (49.4)
N1a	11 (14.3)
N1b	28 (36.4)
TNM stage	
Stage I/II	38 (49.4)
Stage III	11 (14.3)
Stage IV	28 (36.4)
Extrathyroidal extension	
No	71 (92.2)
Yes	6 (7.8)
Hashimoto's thyroiditis	
No	73 (94.8)
Yes	4 (5.2)
Type of thyroid operation	
Lobectomy	8 (10.4)
Lobectomy + contralateral subtotal	8 (10.4)
Total	61 (79.2)
Type of lymph node operation	
No	1 (1.3)
CLND	25 (32.5)
CLND + ipsilateral LND	43 (55.8)
CLND + bilateral LND	8 (10.4)
Follow-up time (months), median (IQR)	65.0 (34.5, 92.5)

SD, standard deviation; BMI, body mass index; Ctn, calcitonin; IQR, interquartile range; CEA, carcinoembryonic antigen; MTC, medullary thyroid carcinoma; TNM, tumor/node/metastasis; CLND, central lymph node dissection; LND, lymph node dissection.

(P=0.013) and tumor distribution in both thyroid lobes (P=0.042) were associated with a higher stage. No significant association was observed between TNM stage and sex, age, BMI, extrathyroidal extension, and Hashimoto's thyroiditis. Preoperative serum Ctn level was positively associated with the TNM stage. We did not find a correlation between preoperative serum CEA levels and TNM stage. Multivariate logistic regression analysis indicated that preoperative serum Ctn level (P<0.001) was an independent factor for TNM stage (Table S2).

Analysis between the clinicopathological factors and postoperative serum Ctn levels

None of the conventional clinicopathological characteristics, such as sex, age, BMI, extrathyroidal extension, or Hashimoto's thyroiditis were significantly correlated with change in postoperative serum Ctn levels (*Table 3*). Patients with multifocal lesions (P=0.025), bilateral lesions (P=0.008), and high stage (P<0.001) were more likely to have postoperative biochemical progression. Postoperative serum Ctn levels worsened as preoperative serum Ctn (P<0.001) or CEA (P=0.05) levels increased. The extent of resection

Table 2 Relationship between clinicopathological characteristics and TNM stage

Features	Stage I/II	Stage III	Stage IV	χ^2 value	P value
Gender, n (%)				0.487	0.485
Men	17 (44.7)	5 (45.5)	10 (35.7)		
Women	21 (55.3)	6 (54.5)	18 (64.3)		
Age (years), n (%)				0.552	0.457
≤55	28 (73.7)	9 (81.8)	18 (64.3)		
>55	10 (26.3)	2 (18.2)	10 (35.7)		
Age (years), mean ± SD	49.34±10.45	41.64±13.33	48.00±12.09	–	0.166
BMI (kg/m^2), mean ± SD	22.93±0.50	22.31±0.61	22.82±0.53	–	0.818
Multifocal MTC, n (%)				6.225	0.013
No	35 (92.1)	9 (81.8)	19 (67.9)		
Yes	3 (7.9)	2 (18.2)	9 (32.1)		
Tumor site, n (%)				6.354	0.042
Left	16 (42.1)	3 (27.3)	12 (42.9)		
Right	21 (55.3)	7 (63.6)	10 (35.7)		
Bilateral	1 (2.6)	1 (9.1)	6 (21.4)		
Extrathyroidal extension, n (%)				0.098	0.754
No	35 (92.1)	11 (100.0)	25 (89.3)		
Yes	3 (7.9)	0 (0.0)	3 (10.7)		
Hashimoto's thyroiditis, n (%)				0.143	0.705
No	37 (97.4)	9 (81.2)	27 (96.4)		
Yes	1 (2.6)	2 (18.2)	1 (3.6)		
Ctn (pg/mL), median (IQR)	20.79 (2.27, 165.75)	65.99 (16, 114.95)	545.5 (248.64, 585)	28.640	<0.001
CEA (μg/L), median (IQR)	6.35 (4.53, 75.83)	13.90 (5.10, 19.50)	34.40 (8.90, 126.7)	2.903	0.234

TNM, tumor/node/metastasis; SD, standard deviation; BMI, body mass index; MTC, medullary thyroid carcinoma; Ctn, calcitonin; IQR, interquartile range; CEA, carcinoembryonic antigen.

of thyroid lobe had no effect on postoperative Ctn levels. However, less than half of the patients in the remission group underwent CLND + lateral LND (ipsilateral LND or bilateral LND), while 80% of patients in the progression group underwent CLND + lateral LND (P=0.047).

ROC curves for Ctn in predicting TNM stage and progression

Optimal preoperative serum Ctn cut-off value for predicting TNM III was 45.88 pg/mL (P<0.001; *Figure 2A*), with a sensitivity of 87.2%, a specificity of 65.8%, and an area under the curve (AUC) of 0.786. The best Ctn cut-off value for predicting TNM IV was 167.00 pg/mL (P<0.001; *Figure 2B*), with a sensitivity of 92.9%, a specificity of 77.6%, and an AUC of 0.863. Based on the preoperative serum Ctn cut-off values, MTC patients were divided into three groups: <45.88, 45.88–167.00, and >167.00 pg/mL. In order to directly predict the progression of postoperative serum Ctn levels, another ROC curve was drawn. As shown in *Figure 2C*, the best cut-off value was 195.5 pg/mL, with a sensitivity of 80.0%, a specificity of 70.2%, and an AUC of 0.786. Accordingly, the MTC patients were divided into two groups: ≤ 195.5 pg/mL. Consequently, the preoperative serum Ctn level as a continuous variable was changed to a categorical variable. Based on different grouping methods,

Table 3 Analysis between the clinicopathological factors and postoperative serum Ctn levels

Features	Remission	Stable	Progression	χ^2 value	P value
Gender, n (%)				0.041	0.839
Men	21 (42.0)	1 (14.3)	10 (50.0)		
Women	29 (58.0)	6 (85.7)	10 (50.0)		
Age (years), n (%)					
≤55	36 (72.0)	4 (57.1)	15 (75.0)	<0.001	0.984
>55	14 (28.0)	3 (42.9)	5 (25.0)		
Age (years), mean ± SD	48.90±1.524	47.44±5.798	45.95±3.192	0.428	0.654
BMI (kg/m^2), median (IQR)	22.7 (20.8, 24.2)	23.4 (22.5, 24.2)	23.0 (21.2, 24.6)	0.937	0.626
Multifocal MTC, n (%)				7.109	0.025
No	44 (88.0)	3 (42.9)	16 (80.0)		
Yes	6 (12.0)	4 (57.1)	4 (20.0)		
Tumor site, n (%)				12.321	0.008
Left	21 (42.0)	2 (28.6)	8 (40.0)		
Right	27 (54.0)	1 (14.3)	10 (50.0)		
Bilateral	2 (4.0)	4 (57.1)	2 (10.0)		
TNM stage, n (%)				24.830	<0.001
Stage I/II	35 (70.0)	0 (0.0)	3 (15.0)		
Stage III	7 (14.0)	0 (0.0)	4 (20.0)		
Stage IV	8 (16.0)	7 (100.0)	13 (65.0)		
Extrathyroidal extension, n (%)				0.056	0.813
No	46 (92.0)	6 (85.7)	19 (95.0)		
Yes	4 (8.0)	1 (14.3)	1 (5.0)		
Hashimoto's thyroiditis, n (%)				0.107	0.743
No	47 (94.0)	7 (100.0)	19 (95.0)		
Yes	3 (6.0)	0 (0.0)	1 (5.0)		
CEA (μg/L), median (IQR)	7.2 (4.9, 34.4)	190.5 (5.9, 374.2)	39.2 (16.35, 102.1)	6.005	0.05
Ctn (pg/mL), median (IQR)	24.8 (7.3, 178.8)	506.0 (424.0, 585.0)	585.0 (208.0, 585.0)	25.150	<0.001
Type of thyroid operation, n (%)				1.757	0.415
Lobectomy thyroidectomy	5 (10.0)	0 (0.0)	3 (15.0)		
Lobectomy + contralateral subtotal thyroidectomy	7 (14.0)	0 (0.0)	1 (5.0)		
Total thyroidectomy	38 (76.0)	7 (100.0)	16 (80.0)		
Type of lymphnode operation, n (%)				7.951	0.047
No	1 (2.0)	0 (0.0)	0 (0.0)		
CLND	21 (42.0)	0 (0.0)	4 (20.0)		
CLND + ipsilateral LND	26 (52.0)	4 (57.1)	13 (65.0)		
CLND + bilateral LND	2 (4.0)	3 (42.9)	3 (15.0)		

SD, standard deviation; BMI, body mass index; IQR, interquartile range; MTC, medullary thyroid carcinoma; TNM, tumor/node/metastasis; CEA, carcinoembryonic antigen; Ctn, calcitonin; CLND, central lymph node dissection; LND, lymph node dissection.

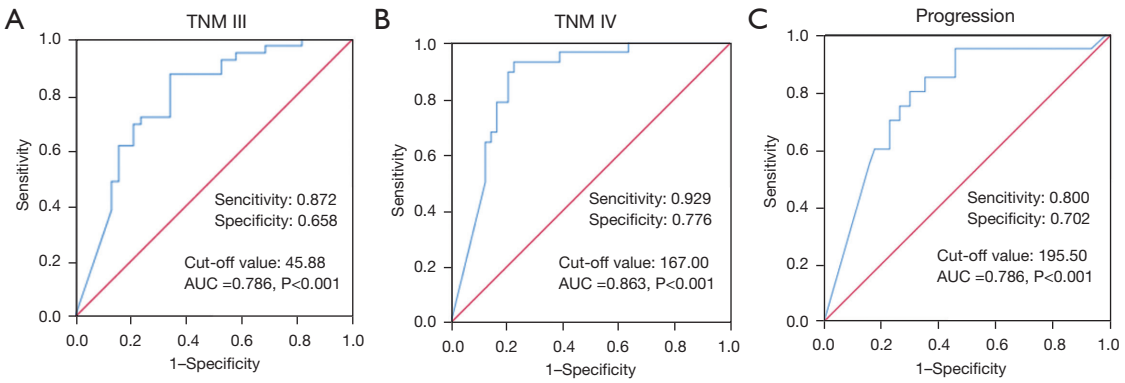

Figure 2 ROC curves for Ctn in predicting TNM stage and progression. (A) ROC curve of preoperative serum Ctn combined detection for stage III; (B) ROC curve of preoperative serum Ctn combined detection for stage IV; (C) ROC curve of preoperative serum Ctn combined detection for progression. TNM, tumor/node/metastasis; AUC, area under the curve; ROC, receiver operating characteristic; Ctn, calcitonin.

we analyzed the correlation between preoperative serum Ctn levels and biochemical prognosis and obtained clinically significant results (Table S3).

Logistic regression analysis

Univariate factors (P<0.05) were considered for the multivariate logistic regression, except for surgical factors and CEA (only 36 patients). Preoperative serum Ctn level and TNM stage were independent biochemical prognostic factors (*Table 4*). For every unit increase in the preoperative serum Ctn level, the risk of postoperative progression increased by 1.004 times (P=0.008), and patients with TNM stage III [hazard ratio (HR) =9.663; 95% confidence interval (CI): 1.411, 66.156] were nearly 9.7-fold more likely to progress than those with TNM stage I/II.

We also established 2 logistic regression models using Ctn as a categorical variable (*Table 4*). Similarly, both preoperative serum Ctn level and TNM stage could independently predict biochemical prognosis. In model 2, patients with higher preoperative Ctn levels (>195.5) were nearly 10.3 times more likely to progress than those with lower preoperative serum Ctn levels (≤195.5 pg/mL) (HR =10.307; 95% CI: 1.792, 59.296). In model 3, compared with the control group (<45.88 pg/mL), patients with preoperative serum Ctn levels of >167.00 pg/mL had a greater risk of progression. However, this phenomenon was not observed in the 45.88–167.00 pg/mL group.

Discussion

In this study, we analyzed the correlation between preoperative serum Ctn levels and change in postoperative serum Ctn levels as well as TNM stage in 77 patients with MTC. In the present observational study, we demonstrated that Ctn was correlated with clinical outcomes and TNM stage in patients with MTC. Preoperative serum Ctn level was an independent factor for postoperative serum Ctn progression as well as for TNM stage. In addition, we found preoperative serum Ctn levels could be potentially used as an important parameter to supplement TNM stage to predict biochemical prognosis. The findings of this study suggest that preoperative serum Ctn level plays a key role in preliminary clinical diagnosis, surgical decision making, and prognosis prediction.

A comprehensive analysis (16) of 72,368 patients with thyroid nodules at 16 institutions verified that if the serum Ctn level was ≥10 pg/mL, the sensitivity for diagnosing MTC was 100% and the specificity was 97.2%. Since serum Ctn levels can be affected by sex, Allelein *et al.* (17) conducted a sex subgroup analysis and found that the best serum Ctn level thresholds for identifying male and female MTC were 46 pg/mL and 35 pg/mL, respectively. In addition, Weber *et al.* (18) reported that the cut-off levels for the diagnosis of MTC were 7.9 pg/mL for females and 15 pg/mL for males. The application of serum Ctn levels has greatly helped in the diagnosis of MTC, especially in

Table 4 Logistic regression analysis

Remission/stable *vs.* progression	B	S.E.	Wald	P value	HR (95% CI)
Model 1					
Multifocal MTC					
No				Ref.	
Yes	0.021	1.109	0.000	0.985	1.022 (0.116, 8.982)
Tumor site					
Bilateral				Ref.	
Left	0.847	1.433	0.349	0.555	2.004 (0.141, 38.667)
Right	0.961	1.374	0.490	0.484	2.520 (0.177, 38.653)
TNM stage					
Stage I/II				Ref.	
Stage III	2.268	0.982	5.341	0.021	9.663 (1.411, 66.156)
Stage IV	1.478	0.831	3.202	0.074	4.424 (0.868, 22.555)
Ctn (pg/mL)	0.004	0.002	7.116	0.008	1.004 (1.001, 1.007)
Model 2					
Multifocal MTC					
No				Ref.	
Yes	0.469	1.149	0.166	0.683	1.598 (0.168, 15.192)
Tumor site					
Bilateral				Ref.	
Left	1.432	1.477	0.941	0.332	4.189 (0.232, 75.711)
Right	1.283	1.406	0.833	0.361	3.609 (0.230, 56.748)
TNM stage					
Stage I/II				Ref.	
Stage III	2.444	1.030	5.632	0.018	11.521 (1.530, 86.729)
Stage IV	1.381	0.840	2.704	0.100	3.980 (0.767, 20.645)
Ctn (pg/mL)					
≤195.5				Ref.	
>195.5	2.333	0.893	6.828	0.009	10.307 (1.792, 59.296)
Model 3					
Multifocal MTC					
No				Ref.	
Yes	–0.024	1.094	0.000	0.983	0.977 (0.114, 8.331)
Tumor site					
Bilateral				Ref.	
Left	1.332	1.402	0.888	0.346	3.749 (0.240, 58.575)
Right	0.955	1.320	0.523	0.469	2.598 (0.196, 34.495)

Table 4 (*continued*)

Table 4 (*continued*)

Remission/stable *vs.* progression	B	S.E.	Wald	P value	HR (95% CI)
TNM stage					
Stage I/II				Ref.	
Stage III	2.646	1.261	4.403	0.036	14.101 (1.191, 167.000)
Stage IV	1.044	0.837	1.556	0.212	2.840 (0.551, 14.636)
Ctn (pg/mL)					
<45.88				Ref.	
45.88–167.00	1.408	1.435	0.963	0.326	4.086 (0.246, 67.988)
>167.00	3.572	1.411	6.412	0.011	35.604 (2.242, 565.476)

MTC, medullary thyroid carcinoma; TNM, tumor/node/metastasis; Ctn, calcitonin; S.E., standard error; HR, hazard ratio; CI, confidence interval.

fine-needle aspiration (FNA) (19). Calcium stimulation (20,21) and pentagastrin (PG) (20,22) can be used to assist Ctn in differentiating C cell proliferation and MTC. Our previous study (23) showed that tumor diameter was strongly correlated with preoperative serum Ctn level (r=0.611) and moderately correlated with preoperative serum CEA level (r=0.482). Yip *et al.* (24) proposed that tumor diameter had strong positive correlations with preoperative serum Ctn level but had moderate positive correlations with preoperative serum CEA level. Preoperative serum Ctn level can be used to evaluate tumor characteristics more accurately than preoperative CEA level can. A previous study (23) analyzed the effect of postoperative serum Ctn levels on disease-free survival in MTC patients. Patients in the progressive group had poorer disease-free survival and postoperative serum Ctn level was more sensitive than postoperative serum CEA level, proving that postoperative serum Ctn level could better reflect the prognosis of patients with MTC.

As both TNM stage and postoperative Ctn levels are prognostic factors, we speculated that preoperative serum Ctn levels could predict prognosis by predicting postoperative serum Ctn levels and TNM stage. In this study, we validated that preoperative serum Ctn level was an independent factor in TNM stage, but no correlation between preoperative serum CEA level and TNM stage was observed. This might be due to the small number of CEA samples. Patients with multifocal lesions, bilateral lesions, high stage, and high preoperative serum Ctn and CEA levels were more likely to have postoperative biochemical progression. Consistent with the results reported by Yip *et al.* (24), only preoperative serum Ctn level and TNM stage were independent factors that affected postoperative serum Ctn levels. Ito *et al.* (25) demonstrated that preoperative Ctn level, preoperative CEA level, and TNM stage were negatively correlated with biochemical cure. This study also found that the larger the range of LND, the worse the biochemical prognosis in patients with MTC. This may because patients with higher preoperative disease burdens might choose more aggressive surgical approaches.

To guide clinical practice and explain the data clearly, cut-off values were obtained by plotting ROC curves. The best cut-off value of preoperative serum Ctn levels for predicting stage III and stage IV were 45.88 and 167.00 pg/mL, respectively, and the optimal cut-off point value for predicting biochemical progression was 195.5 pg/mL. Although the sensitivity and specificity of these cut-off values were slightly lower, the cut-off value for predicting TNM IV was 167 pg/mL with a high sensitivity of 0.929. In patients with TNM IV, lateral LNM always occurs, so the high sensitivity value of 167 pg/mL is essential for guiding surgery. In comparison, Park *et al.* (26) used a cut-off value of 300 pg/mL for ipsilateral LNM with a positive and negative likelihood ratio of 0.18. We believed that the value of 167 pg/mL in our center was more suitable for determining the optimal initial surgical range. In addition, Park *et al.* (27) also indicated that the preoperative serum Ctn cut-off value that predicted structural recurrence was 309 pg/mL. In general, biochemical recurrence tends to occur earlier than structural recurrence. Our results matched it exactly, and the optimal cut-off point value for predicting biochemical progression was 195.5 pg/mL.

As a result, preoperative serum Ctn level was converted from a continuous variable to a categorical variable. Multivariate logistic regression analysis of the progression of postoperative serum Ctn levels was established again. We found that TNM stage IV could not independently predict the biochemical prognosis in these 3 models. However, in model 3, the cut-off value of 167.00 pg/mL made by TNM stage IV became the index for biochemical prognosis, although we did not find this function in the 45.88–167.00 pg/mL group. Therefore, we speculated whether preoperative Ctn level could be included in the TNM stage, especially TNM stage IV. Similarly, Machens and Dralle (10) believed that the number of lymph nodes was an important prognostic classifier that should be incorporated into MTC staging systems. Although the TNM staging system has good predictive performance, it is still insufficient. Park *et al.* (28) found that compared with TNM-7, the 8th TNM edition did not improve predictive performance of MTC patients. Wang *et al.* (29) modified TNM-8 and obtained a more accurate risk stratification. Ye *et al.* (30) reported that serum markers, especially preoperative serum Ctn levels, could be an indicator for guiding clinical strategy in the future. Therefore, based on the above results, we proposed that the inclusion of preoperative serum Ctn level into the TNM stage classification might improve predictive performance in MTC patients.

Postoperative monitoring in MTC patients is crucial due to the poor prognosis and high recurrence rate (2). Our previous study (23) proved that postoperative serum Ctn level could be used to evaluate prognosis. Preoperative serum Ctn level could independently predict the postoperative serum Ctn level, indicating that the preoperative serum Ctn level also had a guiding significance for prognosis. Serum Ctn levels have long been of interest to researchers. Machens *et al.* (31) reported that preoperative serum Ctn levels affected the time that postoperative serum Ctn took to reach normal levels. Chen *et al.* (32) suggested that the postoperative serum Ctn/preoperative serum Ctn ratio was an independent factor influencing the prognosis of patients with MTC. That is to say, in addition to the postoperative serum Ctn level, the preoperative serum Ctn level is also of great significance for evaluating the prognosis of MTC patients. The combination of the 2 levels with assessment of the patients' condition could dynamically provide more accurate diagnosis, treatment, and prognosis in MTC patients.

This study had some limitations. First, this was a retrospective, single-center study. Our data may not necessarily be generalizable to other centers because of the different kits used for serum Ctn level determination. Second, the upper limit of serum Ctn was 585.00 pg/mL. This may lead to some bias, especially in the cut-off value. Finally, the sample size was small, and further studies are required in larger populations to verify our results.

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Footnote

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Ethical Statement: 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of China-Japan Union Hospital (No. 2020010827). Informed consent was taken from all the patients.

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Supplementary

Table S1 Classification based on postoperative Ctn

Group	Definition
Remission	Fall to normal and remain steady
Stable	Not fall to normal but keep steady
Progression	>150 pg/mL or doubling time was <12 months

Ctn, calcitonin.

Table S2 Logistic regression analysis of serum Ctn, tumor site, and multifocal MTC detection to predict TNM stage of MTC patients

Features	B	S.E.	Wald	P value	HR (95% CI)
Multifocal MTC					
No				Ref.	
Yes	1.056	0.990	1.137	0.286	2.874 (0.413, 20.013)
Tumor site					
Bilateral				Ref.	
Left	–0.772	1.508	0.262	0.609	0.462 (0.024, 8.881)
Right	–0.951	1.462	0.423	0.516	0.387 (0.022, 6.791)
Ctn (pg/mL)	0.004	0.001	12.753	<0.001	1.004 (1.002, 1.007)

Ctn, calcitonin; MTC, medullary thyroid carcinoma; TNM, tumor/node/metastasis; S.E., standard error; HR, hazard ratio; CI, confidence interval.

Table S3 Correlation between the preoperative serum Ctn groups and biochemical prognosis of MTC patients

Ctn (classification)	Remission	Stable	Progression	χ^2 value	P value
Ctn1 (pg/mL), n (%)				25.068	<0.001
≤195.5	39 (88.6)	1 (2.3)	4 (9.1)		
>195.5	11 (33.1)	6 (18.2)	16 (48.5)		
Ctn2 (pg/mL), n (%)				26.200	<0.001
<45.88	25(96.2)	0	1(3.8)		
45.88–167.00	8(80.0)	0	2(20.0)		
>167.00	13(35.1)	7(18.9)	17(46.0)		

Ctn, calcitonin; MTC, medullary thyroid carcinoma.

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