Original Article

Diagnostic value of preoperative systemic inflammatory markers and carcinoembryonic antigen in medullary thyroid carcinoma and the risk factors affecting its prognosis

Zhujuan Wu[1#], Yuhan Jiang[1#], Hao Gong[1], Tianyuchen Jiang[1], Anping Su[1], Liangying Yi[2]

[1]Division of Thyroid & Parathyroid Surgery, Department of General Surgery, West China Hospital Sichuan University, Chengdu, China; [2]Department of Sterile Processing Nursing, West China Second University Hospital, Sichuan University, Chengdu, China

Contributions: (I) Conception and design: Z Wu, Y Jiang; (II) Administrative support: All authors; (III) Provision of study materials or patients: Z Wu, Y Jiang, A Su; (IV) Collection and assembly of data: Z Wu, Y Jiang; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Anping Su, MD, PhD. Division of Thyroid & Parathyroid Surgery, Department of General Surgery, West China Hospital, Sichuan University, No. 37 Guoxue Xiang, Chengdu 610041, China. Email: suanping15652@163.com; Liangying Yi, MD, PhD. Department of Sterile Processing Nursing, West China Second University Hospital, Sichuan University, No. 1416 Chenglong Avenue, Chengdu 610041, China. Email: yiliangying2024@163.com.

Background: Medullary thyroid carcinoma (MTC) is a rare malignancy originating from aggressive parafollicular C cells that causes 8–13% of thyroid cancer-related deaths despite its low incidence. Calcitonin and carcinoembryonic antigen (CEA) are considered to be important indicators for the diagnosis of MTC, while serum inflammatory markers have been shown to be valuable in the diagnosis and evaluation of a variety of malignant tumors, but the amount of research literature on MTC is still limited. This article aims to assess the value of serum inflammatory markers, CEA and calcitonin in the differential diagnosis of MTC from papillary thyroid carcinoma (PTC), and to explore the risk factors affecting lateral zone lymph node metastasis of MTC and the clinical features that can be predictive of disease-free survival (DFS).

Methods: We retrospectively analyzed 883 patients with PTC and 128 patients with MTC who received care at West China Hospital Sichuan University. The data of clinical characteristics and follow-up results were collected.

Results: In our cohort, after performing propensity score matching (PSM), there were 117 patients in the MTC group and 436 in the PTC group. Compared with PTC, MTC patients had higher neutrophil-lymphocyte ratio (NLR) (P=0.008), neutrophil-monocyte-platelet-to-lymphocyte ratio (NMPLR) (P=0.03), and CEA values (P<0.001), and no significant differences were found between the remaining baseline characteristics, with CEA having the largest area under the curve (AUC) in the differential diagnosis of PTC and MTC at 0.898 [95% confidence interval (CI): 0.862–0.934, P<0.001]. Univariate and multivariate logistic regression analyses showed that the occurrence of extrathyroidal extension (ETE) [P=0.002, odds ratio (OR): 4.159, 95% CI: 2.734–5.584], calcitonin level >1,000 pg/mL (P=0.002, OR: 4.785, 95% CI: 3.220–6.350) and CEA level (P=0.04, OR: 1.005, 95% CI: 1.000–1.010) were significantly correlated with lateral zone lymph node metastasis in MTC, while platelet-to-lymphocyte ratio (PLR) was a predictor of DFS.

Conclusions: Preoperative blood inflammatory indexes, CEA, and calcitonin level may be able to initially identify MTC and PTC. Meanwhile, ETE, CEA, and calcitonin levels are independent risk factors for lymph node metastasis in the lateral zone of the MTC; therefore, surgeons should consider more carefully planning surgery in conjunction with imaging in patients who have these risk factors at the initial visit.

Keywords: Medullary thyroid carcinoma (MTC); papillary thyroid carcinoma (PTC); differential diagnosis; systemic inflammatory marker; prognosis

Submitted Dec 09, 2024. Accepted for publication Jan 02, 2025. Published online Jan 20, 2025.
doi: 10.21037/gs-24-397
View this article at: https://dx.doi.org/10.21037/gs-24-397

Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor marked by calcitonin (Ctn) production and secretion. Both sporadic and familial cases of MTC can occur, and in families, it may also coexist with multiple endocrine neoplasia type 2A (MEN-2A) or type 2B (MEN-2B) (1). MEN-2A is the most frequent of the MEN type 2 syndromes (95%) and consists of four variants: classical MEN-2A with pheochromocytoma and hyperparathyroidism, MEN-2A with Hirschsprung disease, MEN-2A with cutaneous lichen amyloidosis, and familial MTC. Patients in the remaining 5% of instances (MEN-2B) have MTC, pheochromocytoma, and a unique appearance (2). Sporadic MTC usually appears in the fifth or sixth decade of life; inherited types usually appear earlier (3). Although it is a rare kind of cancer, making up only 1–5% of thyroid cancers overall (4), it is responsible for 8–13% of all thyroid cancer-related deaths (5). Papillary thyroid cancer (PTC) has a 90% 10-year survival rate, while MTC has only 75–85% (6-8).

Parafollicular thyroid cells (C-cells) mainly secrete Ctn and procalcitonin (PCtn). Measurement of serum Ctn concentration at the time a patient is diagnosed with histologic MTC was proposed in the 2015 American Thyroid Association (ATA) guidelines (2). Several studies have found that preoperative measurement of Ctn levels can be used not only at the time of diagnosis for differentiation from other pathologic types of thyroid tumors, but also to better predict the extent of lymph node metastasis in MTC, and can be used postoperatively to assess its treatment outcome (9-15).

Carcinoembryonic antigen (CEA) is a widely used clinical tumor marker that can be present in the serum of patients with colorectal, gastric, pancreatic, lung, and breast cancer. Similarly, it has been found that elevated levels of CEA without other clinical manifestations may be the first and only finding in patients with MTC (1). However, there are fewer studies on the role that CEA plays in the diagnosis, treatment, and prognosis of patients with MTC.

It has been shown that the inflammatory environment promotes tumor angiogenesis, cell mutation and migration, thereby promoting the development of malignant tumors (16,17). Neutrophils are the first cells to reach the site of inflammation, and neutrophils can play a key role in promoting tumor development by releasing cytokines and angiogenic factors. At the same time, lymphocytes secrete abundant cytokines to inhibit the growth of tumor cells. Therefore, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immunoinflammatory index (SII) of preoperative blood markers can reflect tumor outcomes to some extent. Several studies have been conducted to analyze the clinical value of inflammatory indicators such as NLR, PLR, and SII in the diagnosis and prognosis of other cancers (18-26). However, fewer studies have been conducted in MTC.

The purpose of our study is to assess the value of preoperative serum NLR, monocyte-to-lymphocyte ratio (MLR), PLR, SII, neutrophil-monocyte-platelet-to-lymphocyte ratio (NMPLR) and other inflammatory markers, as well as CEA and Ctn levels in the differential diagnosis of MTC and PTC, to further explore the risk factors affecting lymph node metastasis in the lateral zone

Highlight box

Key findings

- We found that preoperative inflammatory indexes, carcinoembryonic antigen (CEA) and calcitonin levels may be able to initially differentiate medullary thyroid carcinoma (MTC) from papillary thyroid carcinoma. Additionally, extrathyroidal extension, CEA and calcitonin levels are independent risk factors for lateral zone lymph node metastasis in MTC.

What is known and what is new?

- Calcitonin is known to be an important tumor marker for MTC, but there are few studies on whether there are changes in blood inflammatory markers in MTC.
- Our study reveals the clinical value of selected blood inflammatory markers, CEA and calcitonin in diagnosing and assessing the prognosis of MTC.

What is the implication, and what should change now?

- The implications of this article are to provide clinicians with new ideas for the diagnosis and prognosis of MTC. In the future, more studies are also needed to further analyze the boundaries between high and low platelet-to-lymphocyte ratio, as well as to more accurately determine whether there is an impact in the prognosis of MTC.

and disease-free survival (DFS) of MTC. We present this article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-397/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was a retrospective clinical diagnostic test, approved by the Ethics Committee of the West China Hospital Sichuan University (No. 20242539). Informed consent was waived because of the retrospective nature of the study. Data were gathered and analyzed for patients with pathologically proven PTC and MTC who underwent thyroid surgery at the Department of Thyroid Surgery, West China Hospital (Chengdu, China) between 2011 and 2021. There were 883 PTC patients and 128 MTC patients who were >18 years old and underwent the first-time thyroidectomy enrolled in the study. Patients who underwent their initial surgery at a different facility or underwent any other form of treatment (such as radiotherapy, chemotherapy, or targeted therapy with tyrosine kinase inhibitors) before the procedure were excluded from the study. Patients with infectious or inflammatory diseases, chronic medical conditions affecting the complete blood count (CBC), history of other active malignancies, acute myocardial infarction within the previous six months, patients receiving immunosuppressive therapy, and patients taking corticosteroids were also excluded. The collected patient data included age, gender, body mass index (BMI), extrathyroidal extension (ETE), tumor-node-metastasis (TNM) stage, multifocality, NLR, MLR, PLR, SII, NMPLR, CEA, Ctn, and so on.

Definition

The tumor stage was precisely established using the eighth edition of the American Joint Cancer Committee's (AJCC) TNM staging system. CBC data were obtained after regular laboratory measurements of leukocytes were made using the SYSMEX XE-2100 automated hematology analyzer (Sysmex, Tokyo, Japan). SII was defined as the absolute neutrophil count multiplied by the absolute platelet count divided by the absolute lymphocyte count. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and PLR and MLR were determined in the same way. NMPLR was determined using the formula: NMPLR = N × M × P/L, where N, M, P, and L represented the absolute neutrophil, monocyte, platelet, and lymphocyte counts, respectively. Local recurrence was defined as the recurrence of the tumor in the surgical area again after the patient's surgery, and the time of locoregional recurrence was recorded as the time when the recurrence was initially detected in the patient. If the patient died during the follow-up period (died from MTC or non-MTC), it was recorded as truncated data, and the recurrence date was recorded as the time of the patient's death. If the patient was lost in the middle of the follow-up period, it was also recorded as truncated data, and the time of recurrence was recorded as the time of the last follow-up period. If the patient did not have any recurrence by the end of the follow-up period, it was also recorded as truncated data, and the date was recorded as the date of the end of the experiment. Tumor spread to distant tissues and organs was referred to as distant metastasis. A biopsy test confirmed locoregional recurrence. Imaging techniques such as computed tomography (CT) and positron emission tomography were used to identify distant metastases. DFS was defined as the time from the patient's initial surgery to the development of locoregional recurrence or distant metastasis. The presence of any locoregional recurrence or distant metastasis recorded as complete data, and loss to visit, death from other causes, or failure to show an event recorded as truncated data.

Statistical analysis

SPSS 26.0 software was applied to the data analysis. The median was used to represent continuous variables having non-normal distributions (confirmed by the Kolmogorov-Smirnov test). Differences between continuous variables were examined using the Mann-Whitney *U* test. Categorical variables were presented as absolute value. Pearson's χ^2 test or Fisher exact test was used to investigate the heterogeneity between categorical variables. Univariate and multivariate logistic regression analyses were used to identify the risk factors for lymph nodes metastasis. Univariate and multivariate Cox regression analyses of predictive survival were performed among the MTC patients. The propensity score matching (PSM) was carried out using R software (R Core Team, Version 4.1.2, Vienna, Austria) with the "matchit" package. The matching procedure made use of the nearest neighbor approach, with the caliper value set to 0.02. To identify the optimal cutoff

values, receiver operating characteristic (ROC) analysis was performed to evaluate the area under the curve (AUC) value, confidence interval (CI), Youden index, sensitivity, and specificity. P value of <0.05 was considered statistically significant.

Results

Demographic and clinicopathologic characteristics of all patients

We recruited a total of 1,011 patients, including 128 patients with MTC and 883 patients with PTC. These 128 patients with MTC were all sporadic cases due to the absence of a family history of the disease. Before PSM performed, fewer patients with MTC were in the age subgroups younger than 55 years (70.3% *vs.* 84.3%) and more patients older than 55 years (29.7% *vs.* 15.7%) compared to patients with PTC (P<0.001). In terms of gender, more female patients accounted for the PTC group than the MTC group (P=0.10), and patients with PTC were also more likely to have multifocal tumors (P=0.02). The blood indicators of NLR (P=0.006), MLR (P=0.02), SII (P=0.02), NMPLR (P=0.01), and CEA (P<0.001) were higher in MTC patients than in PTC patients and the number of patients with Ctn levels greater than 1,000 pg/mL in MTC patients was also significantly higher than that of the PTC group (P<0.001), for which the differences were statistically significant. In addition to this, there was a statistically significant difference in tumor T-stage and N-stage between the two groups (P<0.001). Based on this difference, we used PSM with the caliper value set to 0.02. After PSM performed, there were 117 patients in the MTC group and 436 in the PTC group. After minimizing potential bias using PSM analysis, patients with MTC still had higher NLR (P=0.008), NMPLR (P=0.03), and CEA (P<0.001) values with significant differences compared with PTC, while no significant differences were seen in baseline characteristics for the rest of the data (P>0.05). Additional details between the two groups were shown in *Tables 1*,*2*.

Optimal cutoff values for diagnosis of MTC from PTC

In order to explore whether systemic inflammatory indexes such as NLR and SII have clinical application in the differential diagnosis of MTC and PTC, we hypothesized that systematic inflammatory markers (SIMs) can be used in the differential diagnosis of the above two types of thyroid cancers and plotted ROC curves, and the specific parameters and ROC curve diagrams were shown in *Figure 1* and *Table 3*. The results showed that the AUC of NLR (P=0.008), SII (P=0.01), and NMPLR (P=0.03) are 0.580, 0.575, and 0.567, respectively, while the CEA showed a maximum value of AUC of 0.898 (95% CI: 0.862–0.934, P<0.001), which was characterized by a sensitivity of 0.786, specificity of 0.915, and a Youden Index was 0.701. Meanwhile, we compared the AUCs of NLR, SII, NMPLR and CEA two by two and found that the AUCs between NLR and SII (P=0.81), NLR and NMPLR (P=0.61), SII and NMPLR were not statistically different (P>0.99). However, the AUCs between CEA and NLR, SII, NMPLR showed statistical differences (P<0.001) (Table S1).

Baseline data among MTC patients with or without lateral compartment lymph node metastases

We further divided the MTC patients into groups according to different lymph node stages and compared the baseline data between them in order to be able to initially explore the risk factors affecting lateral compartment lymph node metastasis in MTC patients. As shown in *Table 4*, with no statistically significant difference in the follow-up time between the two groups (P=0.33), patients with lymph node stage later than N1b were more likely to have ETE compared to those with lymph node stage earlier than N1b. Moreover, the number of MTC patients with lateral compartment lymph node metastases with primary tumor staging of T3 and above and Ctn levels greater than 1,000 pg/mL were more prevalent, and they also had larger maximum tumor diameters and higher CEA levels. In addition to this, the number of tumor recurrence and distant metastasis was also significantly higher in MTC patients with lateral compartment lymph node metastasis than in those without lateral compartment lymph node metastasis (P<0.001). The remaining baseline characteristics such as age (P=0.16), gender (P=0.37), and tumor multifocality (P=0.36) were not statistically different between the two groups.

Univariate and multivariate logistic regression analysis of risk factors for lateral compartment lymph node metastasis in MTC

According to the above, we compared the baseline data of MTC patients blow and above N1b, and the differences between the two groups in terms of ETE (P<0.001),

Table 1 Baseline characteristics of PTC and MTC patients (pre-PSM)

Characteristics	MTC (N=128)	PTC (N=883)	P
Age (years)			<0.001
<55	90 (70.3)	744 (84.3)	
≥55	38 (29.7)	139 (15.7)	
BMI (kg/m^2)	22.655 (20.698–24.448)	22.830 (20.550–24.770)	0.57
Sex			0.01
Female	75 (58.6)	617 (69.9)	
Male	53 (41.4)	266 (30.1)	
ETE	52 (40.6)	374 (42.4)	0.22
Multifocality	17 (13.3)	194 (22.0)	0.02
Nodular goiter	65 (50.8)	480 (54.4)	0.45
T stage			<0.001
T1a	42 (32.8)	399 (45.2)	
T1b	27 (21.1)	223 (25.3)	
T2	32 (25.0)	97 (11.0)	
T3a	12 (9.4)	36 (4.1)	
T3b	5 (3.9)	85 (9.6)	
T4a	10 (7.8)	41 (4.6)	
T4b	0	2 (0.2)	
N stage			<0.001
N0	51 (39.8)	407 (46.1)	
N1a	25 (19.5)	290 (32.8)	
N1b	52 (40.6)	186 (21.1)	
M stage			0.89
M1	1 (0.8)	8 (0.9)	
NLR	1.86 (1.44–2.31)	1.68 (1.31–2.11)	0.006
MLR	0.20 (0.16–0.28)	0.19 (0.15–0.24)	0.02
PLR	108.05 (84.40–134.44)	101.46 (78.74–132.46)	0.25
SII	361.55 (270.29–482.60)	322.04 (230.00–452.36)	0.02
NMPLR	136.36 (83.97–210.42)	113.72 (72.26–186.45)	0.01
CEA (ng/mL)	21.22 (4.57–93.93)	1.44 (0.90–2.26)	<0.001
Calcitonin (pg/mL)			<0.001
≤1,000	74 (57.8)	883 (100.0)	
>1,000	54 (42.2)	0	

Data are presented as n (%) or mean (interquartile range). PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; PSM, propensity score matching; BMI, body mass index; ETE, extrathyroidal extension; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immunoinflammatory index; NMPLR, neutrophil-monocyte-platelet-to-lymphocyte ratio; CEA, carcinoembryonic antigen.

Table 2 Baseline characteristics of PTC and MTC patients (after PSM)

Characteristics	MTC (N=117)	PTC (N=436)	P
Age (years)			0.82
<55	86 (73.5)	325 (74.5)	
≥55	31 (26.5)	111 (25.5)	
BMI (kg/m^2)	22.66 (20.72–24.45)	22.83 (20.43–24.72)	0.81
Sex			0.68
Female	70 (59.8)	270 (61.9)	
Male	47 (40.2)	166 (38.1)	
ETE	50 (42.7)	179 (41.1)	0.34
Multifocality	17 (14.5)	57 (13.1)	0.68
Nodular goiter	58 (49.6)	206 (47.2)	0.54
T stage			0.82
T1a	41 (35.0)	166 (38.1)	
T1b	23 (19.7)	97 (22.2)	
T2	28 (23.9)	87 (20.0)	
T3a	10 (8.5)	30 (6.9)	
T3b	5 (4.3)	25 (5.7)	
T4a	10 (8.5)	31 (7.1)	
N stage			0.75
N0	49 (41.9)	190 (43.6)	
N1a	24 (20.5)	98 (22.5)	
N1b	44 (37.6)	148 (33.9)	
M stage			0.95
M1	1 (0.9)	4 (0.9)	
NLR	1.87 (1.45–2.30)	1.67 (1.29–2.14)	0.008
MLR	0.19 (0.15–0.27)	0.19 (0.15–0.24)	0.17
PLR	108.26 (85.26–134.68)	98.35 (77.84–130.96)	0.07
SII	359.53 (270.24–480.35)	313.97 (227.14–439.40)	0.01
NMPLR	132.21 (85.78–209.91)	113.69 (72.77–182.97)	0.03
CEA (ng/mL)	21.00 (4.24–71.20)	1.54 (0.96–2.50)	<0.001
Calcitonin (pg/mL)			<0.001
≤1,000	70 (59.8)	436 (100.0)	
>1,000	47 (40.2)	0	

Data are presented as n (%) or mean (interquartile range). PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; PSM, propensity score matching; BMI, body mass index; ETE, extrathyroidal extension; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immunoinflammatory index; NMPLR, neutrophil-monocyte-platelet-to-lymphocyte ratio; CEA, carcinoembryonic antigen.

largest tumor size (P=0.003), CEA (P<0.001) and Ctn level (P<0.001) were statistically significant. Moreover, although the difference in age between the two groups was not statistically significant, the P value happened to be 0.05, we included the above factors in a univariate logistic regression analysis in the hope of exploring more comprehensively the risk factors affecting lateral lymph node metastasis in patients with MTC (*Table 4*). Among them, the presence of ETE [odds ratio (OR) =6.086, 95% CI: 2.749–13.257, P<0.001], largest tumor diameter (OR =1.354, 95% CI: 1.059–1.731], P=0.02), CEA value (OR =1.010, 95% CI: 1.005–1.016, P<0.001) and Ctn level >1,000 pg/mL (OR =10.179, 95% CI: 4.463–23.212, P<0.001) were associated with lateral compartment lymph node metastasis of MTC, while age was not significantly associated with lateral compartment lymph node metastasis (P=0.05). We also incorporated these variables into a multivariate logistic regression model for analysis, which showed that the presence of ETE (OR =4.159, 95% CI: 2.734–5.584, P=0.002), CEA values (OR =1.005, 95% CI: 1.000–1.010, P=0.04), and Ctn levels >1,000 pg/mL (OR =4.785, 95% CI: 3.220–6.350, P=0.002) were significantly correlated with lateral compartment lymph node metastasis in MTC (*Table 5*).

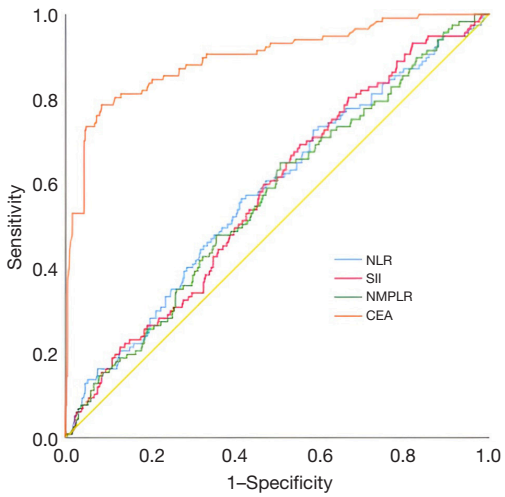

Figure 1 Receiver operating characteristic curve analysis for diagnosis of MTC from PTC. MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immunoinflammatory index; NMPLR, neutrophil-monocyte-platelet-to-lymphocyte ratio; CEA, carcinoembryonic antigen.

Univariate and multivariate Cox regression analysis of risk factors affecting DFS in MTC

We underwent DFS risk factor analysis in MTC patients using univariate and multivariate Cox regression models to identify clinical features influencing structural tumor recurrence. A total of 128 patients with MTC were grouped according to whether they had local recurrence or distant metastasis, and 10 of them showed recurrence or distant metastasis. When comparing the basic clinicopathologic characteristics of these two groups, only PLR showed a statistically significant difference (P<0.05) between the two groups in terms of all inflammatory markers. Based on this, PLR was included in the Cox regression analysis in order to further explore the factors that affect the prognosis of MTC. In the univariate Cox analysis, ETE (P=0.02), clinical AJCC stage of the tumor (P=0.03), PLR (P=0.008), and serum Ctn level (P=0.02) were significant factors. PLR was identified as an independent predictor of DFS when performing multivariate Cox analysis (P=0.03) (*Table 6*).

Table 3 Differentiation of MTC and PTC by blood test indexes (after PSM)

Diagnostic indicators	Cutoff value	AUC (95% CI)	P value	Sensitivity	Specificity	Youden index
NLR	1.797	0.580 (0.522–0.638)	0.008	0.564	0.585	0.149
SII	298.68	0.575 (0.519–0.632)	0.01	0.692	0.447	0.139
NMPLR	111.918	0.567 (0.509–0.624)	0.03	0.65	0.493	0.143
CEA (ng/mL)	3.95	0.898 (0.862–0.934)	<0.001	0.786	0.915	0.701

MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; PSM, propensity score matching; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immunoinflammatory index; NMPLR, neutrophil-monocyte-platelet-to-lymphocyte ratio; CEA, carcinoembryonic antigen; AUC, area under the curve; CI, confidence interval.

Table 4 The baseline data of MTC patients

Characteristic	Blow N1b (N=76)	Above N1b (N=52)	P value
Age (years)	45.72±1.36	50.17±1.87	0.05
<55	57 (75.0)	33 (63.5)	0.16
≥55	19 (25.0)	19 (36.5)	
BMI (kg/m^2)	22.78±0.36	22.22±0.46	0.34
Sex			0.37
Female	47 (61.8)	28 (53.8)	
Male	29 (38.2)	24 (46.2)	
ETE	18 (23.7)	34 (65.4)	<0.001
Multifocality	10 (13.2)	7 (13.5)	0.36
Nodular goiter	35 (46.1)	30 (57.7)	0.20
Primary tumor location			0.62
Left	37 (48.7)	23 (44.2)	
Right	39 (51.3)	29 (55.8)	
Surgical approach of tumor			>0.99
Total thyroidectomy	75 (98.5)	52 (100.0)	
Lobectomy with isthmus resection	1 (1.3)	0	
T stage			0.001
T1a	33 (43.4)	9 (17.3)	
T1b	14 (18.4)	13 (25.0)	
T2	21 (27.6)	11 (21.2)	
T3a	5 (6.6)	7 (13.5)	
T3b	1 (1.3)	4 (7.7)	
T4a	2 (2.6)	8 (15.4)	
N stage			<0.001
N0	51 (67.1)	0	
N1a	25 (32.9)	0	
N1b	0	52 (100.0)	
M stage			0.41
M1	0	1 (1.9)	
AJCC stage			<0.001
I	70 (92.1)	32 (61.5)	
II	6 (7.9)	18 (34.6)	
III	0	2 (3.8)	
Preoperative PTH (pmol/L)	5.91±2.64	5.90±2.32	0.28
Largest tumor size (cm)	1.40 (0.70–3.00)	2.50 (1.28–3.35)	0.003

Table 4 (*continued*)

Table 4 (*continued*)

Characteristic	Blow N1b (N=76)	Above N1b (N=52)	P value
NLR level	1.81 (1.34–2.30)	1.94 (1.51–2.35)	0.29
MLR level	0.19 (0.15–0.26)	0.22 (0.16–0.30)	0.23
PLR level	107.34 (81.33–135.89)	108.83 (88.37–132.62)	0.65
SII level	365.33 (275.49–443.12)	357.34 (259.69–514.62)	0.78
NMPLR level	129.30 (84.12–196.08)	147.23 (82.91–219.61)	0.46
CEA (ng/mL)	8.70 (2.79–36.99)	60.13 (19.10–229.05)	<0.001
Calcitonin (pg/mL)			<0.001
≤1,000	60 (78.9)	14 (26.9)	
>1,000	16 (21.1)	38 (73.1)	
Recurrence & distant metastasis	0	10 (19.23)	<0.001
Follow-up time (months)	45.00 (19.50–96.50)	63.50 (88.00–30.50)	0.33

Data are presented as n (%), mean (interquartile range) or mean ± standard deviation. MTC, medullary thyroid carcinoma; BMI, body mass index; ETE, extrathyroidal extension; AJCC, American Joint Committee on Cancer; PTH, parathyroid hormone; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immunoinflammatory index; NMPLR, neutrophil-monocyte-platelet-to-lymphocyte ratio; CEA, carcinoembryonic antigen.

Table 5 Univariate and multivariate logistic regression analysis of risk factors for lateral compartment lymph node metastasis in MTC

Variables	Univariate				Multivariate			
	Wald	OR	95% CI	P value	Wald	OR	95% CI	P value
Age (years)	3.725	1.029	1.000–1.060	0.05	–	–	–	–
ETE	20.675	6.086	2.749–13.257	<0.001	10.235	4.159	2.734–5.584	0.002
Largest tumor size (cm)	5.853	1.354	1.059–1.731	0.02	–	–	–	–
CEA (ng/mL)	13.094	1.010	1.005–1.016	<0001	5.249	1.005	1.000–1.010	0.04
Calcitonin (>1,000 *vs.* ≤1,000 pg/mL)	30.432	10.179	4.463–23.212	<0.001	12.419	4.785	3.220–6.350	0.002

MTC, medullary thyroid carcinoma; ETE, extrathyroidal extension; CEA, carcinoembryonic antigen; OR, odds ratio; CI, confidence interval.

Discussion

Thyroid medullary carcinoma is a relatively rare malignant tumor originating from the parafollicular cells of the thyroid gland that has a poor prognosis and a high mortality rate despite its low incidence. It has been shown that lymph node metastasis is usually present in 35% of patients with MTC when they are diagnosed, as well as distant metastasis in 13% of patients. The 10-year survival rates for stage I, II, III and IV MTC are 100%, 93%, 71% and 21%, respectively (27). Surgery remains the preferred treatment for locoregional MTC, including at least total thyroidectomy and central lymph node dissection. Early definitive diagnosis and treatment remain central to the management of patients with MTC.

The peptide hormone Ctn secreted by C cells is a very sensitive tumor marker in patients with MTC (16). Despite the fact that serum Ctn-negative MTC patients have been reported in the literature (28), it is still believed that almost all MTCs secrete Ctn. Our study evaluated the correlation between preoperative systemic inflammatory markers, Ctn levels, CEA, and other blood markers and the clinicopathologic features of MTC and PTC. Meanwhile, we further explored the value of these metrics in predicting lateral compartment lymph node metastasis and DFS in MTC.

Table 6 Univariate and multivariate Cox regression analysis of risk factors affecting DFS in MTC patients

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
ETE	11.61	1.47–91.71	0.02	–	–	–
AJCC stage (III *vs.* I & II)	10.8	1.25–93.14	0.03	–	–	–
PLR	1.02	1.00–1.03	0.008	1.01	1.00–1.02	0.03
Calcitonin (>1,000 *vs.* ≤1,000 pg/mL)	12.3	1.56–97.18	0.02	–	–	–

DFS, disease-free survival; MTC, medullary thyroid carcinoma; ETE, extrathyroidal extension; AJCC, American Joint Committee on Cancer; PLR, platelet-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Often blood tests are routine for patients because blood cell data are quick, easy and inexpensive to obtain. The current gold standard for clinical diagnosis of MTC is pathologic examination, but pathologic examination is time-consuming. Therefore, we explored whether systemic inflammatory indicators such as NLR, MLR, PLR, and NMPLR could initially identify PTC and MTC, and whether they could enable clinicians to obtain some clues about the aggressiveness and the prognosis of the disease based on simple and quick blood check indicators before obtaining a pathology report.

Prior to this, the systemic inflammatory response markers SII, NLR, PLR, MLR, and NMPLR in peripheral blood have been extensively studied for their diagnostic and prognostic value in various types of tumors. Prodromidou *et al.* showed that both PLR and NLR can be used for screening and prognostic assessment of ovarian epithelial tumors (29). Song *et al.* showed that derived NLR (dNLR) and MLR play an essential role in the prediction of overall survival in progressive gastric cancer (30). Feng *et al.* found that high NLR, MLR, PLR, neutrophil-to-white blood cell ratio (NWR), monocyte-to-white blood cell ratio (MWR) and low lymphocyte-to-white blood cell ratio (LWR) were associated with poor prognosis of gastric mesenchymal tumors. Combining tumor size with MLR, PLR, and MWR may further improve the value of prognostic prediction for gastric mesenchymal tumors (31). Koh *et al.* found that both NLR and PLR are independently associated with an increased risk of death in breast cancer (32). Zhang *et al.* found that NMPLR can be used to distinguish differentiated thyroid cancer from undifferentiated thyroid cancer and can independently predict overall survival in refractory thyroid cancer (33). In a meta-analysis by Feng *et al.* in 2020, preoperative NLR values were found to serve as a good biomarker in predicting tumor growth, distant metastasis, and disease progression in thyroid cancer (34). Although previous work has identified the diagnostic value of preoperative blood screening indices in several other solid tumors, little attention has been paid to their use in diagnosing and predicting MTCs. Lin *et al.* showed that NLR, MLR, and SII had diagnostic value for MTC, and the diagnostic efficacy of MLR alone and in combination was higher than that of NLR and SII alone for MTC (35). Our findings are consistent with those of Zhang *et al.* and Lin *et al.* that before performing PSM (33,35), preoperative NLR, MLR, SII, and NMPLR were significantly higher in MTC patients than in PTC patients. Further after performing PSM on both groups, NLR, SII, and NMPLR were still significantly higher in the MTC group than PTC group, and the difference was statistically significant. The efficacy of systemic inflammatory markers to identify PTC and MTC after PSM was analyzed using ROC curves and found that the AUCs of NLR, NMPLR, and SII were greater than 0.5 and statistically significant. We further compared the AUCs of NLR, SII, and NMPLR two-by-two which revealed that there was no statistically significant difference between them. Our findings may suggest that NLR, SII, and NMPLR may be available for a simple, fast, and convenient way of preoperative differential diagnosis of MTC and PTC. If NLR, SII, and NMPLR values are significantly elevated in a preoperative blood test, the patient may be more inclined to MTC than to PTC. The diagnostic efficacy among the three of them is very close to each other.

CEA is one of the widely used tumor markers in current clinical practice, and it was originally investigated by Gold *et al.* (36). It is considered to be an oncofetal protein that is normally present in the fetus, but can also be observed in low concentrations in healthy adults (37). CEA concentrations may be significantly elevated in the

serum of many patients with malignant tumors. Although its exact function has not been well investigated, it has been shown to be involved in the cell adhesion process, so it is hypothesized that may have a role in inhibiting apoptosis. As early as 1976, Ishikawa *et al.* were the first to find a correlation between high CEA values and postoperative diagnosis of MTC patients in their study (38). Due to the fact that CEA is more convenient and inexpensive compared to pathologic biopsy, CT and other tests, more and more studies are attempting to apply CEA in the diagnosis of MTC. After Wakabayashi-Nakao *et al.* found that CEACAM4 was specifically expressed only in MTC cell lines, they suggested that CEACAM4 might be able to distinguish MTC from other malignant tumors that also secrete CEA (39). Our study found that CEA levels were significantly higher in MTC than PTC after performing PSM. We analyzed the diagnostic efficacy of CEA in the differential diagnosis of MTC and PTC by plotting the ROC curve and found that the AUC of CEA was the largest compared with the aforementioned inflammatory indicators. Comparing the AUC of CEA with NLR, SII, and NMPLR respectively, we found that the differences were statistically significant, indicating that the diagnostic efficacy of CEA was substantially higher than that of other inflammatory indicators. Thus, CEA can be used in combination with NLR, SII and NMPLR in the differential diagnosis of MTC and PTC in clinical practice.

MTC has a tendency to have higher lymph node metastasis compared to PTC, and Asimakopoulos *et al.* concluded that the tumor cure rate is greatly reduced in MTCs with lateral lymph node metastasis (40). Whether to perform prophylactic lateral zone lymph node dissection for cN0 stage MTC patients is still controversial, and factors such as serum Ctn levels and tumor load in the primary focus need to be considered comprehensively. Niederle *et al.* found that lateral lymph node metastasis in MTC was only seen in patients with desmoplastic stromal reaction (DSR) in intrathyroidal tumors, and they followed up patients with DSR-negative tumors without lateral lymph node dissection and found that none of them had lateral lymph node metastasis or distant metastasis. Therefore, they concluded that prophylactic lateral lymph node dissection could be avoided in DSR-negative patients with MTC (41). However, DSR needs to be identified on intraoperative frozen sections, which is not conducive to early identification of the extent of lymph node metastasis and personalized surgical plans in the preoperative period. Therefore, we grouped 128 MTC patients diagnosed at West China Hospital Sichuan University according to whether they had lateral lymph node metastasis or not and analyzed their baseline data. We found that patients with concomitant lateral lymph node metastasis were significantly larger than MTC patients without lateral lymph node metastasis in terms of age, preoperative CEA, Ctn level, and maximal tumor diameter, and also the number of patients who developed extra-thyroidal invasion in the group with concomitant lateral lymph node metastasis was significantly larger than that in the group without lateral lymph node metastasis, which is in line with the findings of Wu *et al.* (42). We seized these findings to further develop logistic regression models to analyze the risk factors for lymph node metastasis in the lateral zone of the MTC. Univariate analysis identified ETE, maximum tumor diameter, CEA, and Ctn level as strongly associated with lateral zone lymph node metastasis while multivariate analysis identified maximum tumor diameter, CEA, and Ctn level as independent risk factors for lateral zone lymph node metastasis. Therefore, the above risk factors should be actively and adequately evaluated when developing a surgical plan for MTC patients. In particular, in MTC patients with high preoperative CEA and Ctn levels, intraoperative findings of extra-thyroidal invasion, or large tumor diameters, the surgeon should have more careful consideration in deciding the extent of lymph node dissection, and we suggest that this can be done in close conjunction with preoperative lymph node imaging (e.g., ultrasound or CT).

The prognosis of MTC is between papillary carcinoma and undifferentiated carcinoma, which belongs to the moderate malignancy degree, and its prognosis is related to lymph node metastasis, local tumor infiltration, treatment modality, and distant metastases. Structural recurrence is defined as newly detected structural disease or distant metastases in the thyroid bed or cervical lymph nodes. DFS is defined as the time from initial surgery to the first structural recurrence or the last follow-up visit. MTC's 5-, 10-, and 15-year cumulative DFS is 61.8%, 48.6%, and 38.2%, respectively (43). A recent meta-analysis caught our attention and showed no significant correlation between DFS and NLR, MLR, or PLR in patients with DTC, but the original literature included in this meta-analysis was papillary or follicular carcinoma, with no mention of MTC. This also caused us to think about whether or not systemic markers of inflammation were relevant to the prognosis of patients with MTC (44). Wu *et al.* retrospectively analyzed 152 patients with MTC and found that lateral zone lymph

node metastasis and a positive lymph node metastasis rate of greater than 1/3 were independent risk factors for disease progression, and that AJCC stage showed a negative correlation with patients' prognosis, while stage IV patients had a significantly lower survival rate than those at stage III and below (42). Kuo *et al.* found that patients' clinical stage was the strongest factor in disease-specific mortality (DSM) in MTC (45). Kotwal *et al.* found that ETE and preoperative tumor M1 status were independent risk factors for worsening disease-specific survival (DSS) (46). Twito *et al.* also suggested that distant metastasis and the presence of ETE were associated with deterioration of DSS in MTC (47). PLR was found to be an independent predictor of outcome in MTC patients in two studies by Jiang *et al.* Higher preoperative PLR was associated with lymph node metastasis, tumor recurrence, and reduced DFS (48,49). Our findings are consistent with previous studies demonstrating that AJCC stage, presence of ETE and high Ctn levels in MTC patients are strongly associated with worsening DFS, and multifactorial Cox regression analysis found that preoperative PLR levels were significantly associated with DFS. It is worth noting that the range of 95% CIs for ETE, AJCC staging, and Ctn levels was very wide, which led to relative uncertainty in our analysis of the relationship between these three and DFS. This may be due to our small sample size. More multi-center, large-sample clinical studies are also needed in the future to confirm the relationship between these three and the prognosis of MTC. Tumor burden at the time of initial treatment is an important influence on DFS in MTC patients, and it is extremely crucial to perform a thorough and accurate preoperative evaluation and develop a personalized treatment plan for patients.

There are also some limitations in our study. Firstly, our study design was retrospective. Secondly, both our MTC and PTC patients were recruited from the same large tertiary care hospital, so there may be a selection bias. Thirdly, our multivariate analyses after adjusting for significant factors in univariate analyses were limited by the small number of events when examining risk factors affecting DFS in patients with MTC, so the results of our multifactorial analyses still need to be validated in a larger cohort. Due to the relatively low prevalence of MTC, more multicenter and prospective studies are still needed to confirm our findings in the future.

Conclusions

In conclusion, MTC is a more aggressive neuroendocrine tumor than PTC, which has Ctn as a specific tumor marker. In clinical practice, it may be possible to initially differentiate MTC from PTC by preoperative hematologic inflammatory markers, CEA, and Ctn levels. Meanwhile, we found that ETE, high preoperative CEA and Ctn level were independent risk factors for lymph node metastasis in the lateral zone of MTC. Therefore, surgeons should consider more carefully when planning the extent of lymph node dissection in conjunction with imaging in patients with these risk factors at the time of initial consultation. Tumor burden upon initial treatment is an important influence on DFS, so it is extremely crucial to comprehensively and accurately evaluate and develop a personalized treatment plan for patients before operation.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-397/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-397/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-397/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-397/coif). The authors have no conflicts of interest to declare.

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), and was approved by the Ethics Committee of the West China Hospital Sichuan University (No. 20242539). Informed consent was waived because of the retrospective nature of the study.

References

1. Utiger RD. Medullary thyroid carcinoma, genes, and the prevention of cancer. N Engl J Med 1994;331:870-1.
2. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567-610.
3. Tuttle RM, Ball DW, Byrd D, et al. Medullary carcinoma. J Natl Compr Canc Netw 2010;8:512-30.
4. Pitt SC, Moley JF. Medullary, anaplastic, and metastatic cancers of the thyroid. Semin Oncol 2010;37:567-79.
5. Veiga LH, Neta G, Aschebrook-Kilfoy B, et al. Thyroid cancer incidence patterns in Sao Paulo, Brazil, and the U.S. SEER program, 1997-2008. Thyroid 2013;23:748-57.
6. Grozinsky-Glasberg S, Benbassat CA, Tsvetov G, et al. Medullary thyroid cancer: a retrospective analysis of a cohort treated at a single tertiary care center between 1970 and 2005. Thyroid 2007;17:549-56.
7. Sebastian SO, Gonzalez JM, Paricio PP, et al. Papillary thyroid carcinoma: prognostic index for survival including the histological variety. Arch Surg 2000;135:272-7.
8. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer 2006;107:2134-42.
9. Park H, Park J, Choi MS, et al. Preoperative Serum Calcitonin and Its Correlation with Extent of Lymph Node Metastasis in Medullary Thyroid Carcinoma. Cancers (Basel) 2020;12:2894.
10. Miyauchi A, Matsuzuka F, Kuma K, et al. Evaluation of surgical results and prediction of prognosis in patients with medullary thyroid carcinoma by analysis of serum calcitonin levels. World J Surg 1988;12:610-5.
11. Yip DT, Hassan M, Pazaitou-Panayiotou K, et al. Preoperative basal calcitonin and tumor stage correlate with postoperative calcitonin normalization in patients undergoing initial surgical management of medullary thyroid carcinoma. Surgery 2011;150:1168-77.
12. Machens A, Schneyer U, Holzhausen HJ, et al. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab 2005;90:2029-34.
13. Cohen R, Campos JM, Salaün C, et al. Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). J Clin Endocrinol Metab 2000;85:919-22.
14. Cho YY, Jang HW, Jang JY, et al. Clinical outcomes of patients with hypercalcitoninemia after initial treatment for medullary thyroid cancer and postoperative serum calcitonin cutoffs for predicting structural recurrence. Head Neck 2016;38:1501-8.
15. Trivedi S, Salahuddin T, Mithi MT, et al. Medullary Thyroid Carcinoma: A Single Institute Experience. Indian J Otolaryngol Head Neck Surg 2023;75:2884-9.
16. Xu N, Jian Y, Wang Y, et al. Evaluation of neutrophil-to-lymphocyte ratio and calcitonin concentration for predicting lymph node metastasis and distant metastasis in patients with medullary thyroid cancer. Mol Clin Oncol 2018;9:629-34.
17. Febrero B, Ruiz-Manzanera JJ, Ros-Madrid I, et al. Tumor microenvironment in thyroid cancer: Immune cells, patterns, and novel treatments. Head Neck 2024;46:1486-99.
18. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 2013;109:416-21.
19. Xiao WK, Chen D, Li SQ, et al. Prognostic significance of neutrophil-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. BMC Cancer 2014;14:117.
20. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:1204-12.
21. Chen ZY, Raghav K, Lieu CH, et al. Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Cancer 2015;112:1088-97.
22. Wang SC, Chou JF, Strong VE, et al. Pretreatment

Neutrophil to Lymphocyte Ratio Independently Predicts Disease-specific Survival in Resectable Gastroesophageal Junction and Gastric Adenocarcinoma. Ann Surg 2016;263:292-7.
23. Duan H, Zhang X, Wang FX, et al. Prognostic role of neutrophil-lymphocyte ratio in operable esophageal squamous cell carcinoma. World J Gastroenterol 2015;21:5591-7.
24. Zhang WW, Liu KJ, Hu GL, et al. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to other systemic inflammatory response markers in ovarian cancer patients. Tumour Biol 2015;36:8831-7.
25. Takahashi Y, Kawamura M, Hato T, et al. Neutrophil-Lymphocyte Ratio as a Prognostic Marker for Lung Adenocarcinoma After Complete Resection. World J Surg 2016;40:365-72.
26. Smith D, Raices M, Cayol F, et al. Is the neutrophil-to-lymphocyte ratio a prognostic factor in non-small cell lung cancer patients who receive adjuvant chemotherapy? Semin Oncol 2022;49:482-9.
27. Censi S, Manso J, Mian C. Other markers of medullary thyroid cancer, not only calcitonin. Eur J Endocrinol 2023;188:lvac009.
28. Jingzhu Z, Xiangqian Z, Ming G, et al. Clinical challenges with calcitonin-negative medullary thyroid carcinoma: three case reports and a review of the literature. Ann R Coll Surg Engl 2022;104:221-30.
29. Prodromidou A, Andreakos P, Kazakos C, et al. The diagnostic efficacy of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in ovarian cancer. Inflamm Res 2017;66:467-75.
30. Song S, Li C, Li S, et al. Derived neutrophil to lymphocyte ratio and monocyte to lymphocyte ratio may be better biomarkers for predicting overall survival of patients with advanced gastric cancer. Onco Targets Ther 2017;10:3145-54.
31. Feng F, Tian Y, Liu S, et al. Combination of PLR, MLR, MWR, and Tumor Size Could Significantly Increase the Prognostic Value for Gastrointestinal Stromal Tumors. Medicine (Baltimore) 2016;95:e3248.
32. Koh CH, Bhoo-Pathy N, Ng KL, et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer 2015;113:150-8.
33. Zhang L, Luo H, Wang L, et al. Diagnostic and prognostic value of preoperative systemic inflammatory markers in anaplastic thyroid cancer. J Surg Oncol 2020;122:897-905.
34. Feng J, Wang Y, Shan G, et al. Clinical and prognostic value of neutrophil-lymphocyte ratio for patients with thyroid cancer: A meta-analysis. Medicine (Baltimore) 2020;99:e19686.
35. Lin L, Li N, Wu L, et al. Exploration of the application value of peripheral blood NLR, MLR and SII in medullary thyroid carcinoma. Journal of Modern Oncology 2022;30:1753-7.
36. Gold P, Freedman SO. Tests for carcinoembryonic antigen. Role in diagnosis and management of cancer. JAMA 1975;234:190-2.
37. Passos I, Stefanidou E, Meditskou-Eythymiadou S, et al. A Review of the Significance in Measuring Preoperative and Postoperative Carcinoembryonic Antigen (CEA) Values in Patients with Medullary Thyroid Carcinoma (MTC). Medicina (Kaunas) 2021;57:609.
38. Ishikawa N, Hamada S. Association of medullary carcinoma of the thyroid with carcinoembryonic antigen. Br J Cancer 1976;34:111-5.
39. Wakabayashi-Nakao K, Hatakeyama K, Ohshima K, et al. Carcinoembryonic antigen-related cell adhesion molecule 4 (CEACAM4) is specifically expressed in medullary thyroid carcinoma cells. Biomed Res 2014;35:237-42.
40. Asimakopoulos P, Nixon IJ, Shaha AR. Differentiated and Medullary Thyroid Cancer: Surgical Management of Cervical Lymph Nodes. Clin Oncol (R Coll Radiol) 2017;29:283-9.
41. Niederle MB, Riss P, Selberherr A, et al. Omission of lateral lymph node dissection in medullary thyroid cancer without a desmoplastic stromal reaction. Br J Surg 2021;108:174-81.
42. Wu X, Li B, Zheng C. Clinical Characteristics, Surgical Management, and Prognostic Factors of Medullary Thyroid Carcinoma: A Retrospective, Single-Center Study. Technol Cancer Res Treat 2022;21:15330338221078435.
43. Park H, Park SY, Park J, et al. Prognostic Value of Preoperative Serum Calcitonin Levels for Predicting the Recurrence of Medullary Thyroid Carcinoma. Front Endocrinol (Lausanne) 2021;12:749973.
44. Russo E, Guizzardi M, Canali L, et al. Preoperative systemic inflammatory markers as prognostic factors in differentiated thyroid cancer: a systematic review and meta-analysis. Rev Endocr Metab Disord 2023;24:1205-16.
45. Kuo EJ, Sho S, Li N, et al. Risk Factors Associated With Reoperation and Disease-Specific Mortality in Patients With Medullary Thyroid Carcinoma. JAMA Surg 2018;153:52-9.
46. Kotwal A, Erickson D, Geske JR, et al. Predicting Outcomes in Sporadic and Hereditary Medullary Thyroid

Carcinoma over Two Decades. Thyroid 2021;31:616-26.
47. Twito O, Grozinsky-Glasberg S, Levy S, et al. Clinico-pathologic and dynamic prognostic factors in sporadic and familial medullary thyroid carcinoma: an Israeli multi-center study. Eur J Endocrinol 2019;181:13-21.
48. Jiang K, Lei J, Chen W, et al. Association of the preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios with lymph node metastasis and recurrence in patients with medullary thyroid carcinoma. Medicine (Baltimore) 2016;95:e5079.
49. Jiang K, Lei J, Li C, et al. Comparison of the prognostic values of selected inflammation based scores in patients with medullary thyroid carcinoma: A pilot study. J Surg Oncol 2017;116:281-7.

Cite this article as: Wu Z, Jiang Y, Gong H, Jiang T, Su A, Yi L. Diagnostic value of preoperative systemic inflammatory markers and carcinoembryonic antigen in medullary thyroid carcinoma and the risk factors affecting its prognosis. Gland Surg 2025;14(1):13-27. doi: 10.21037/gs-24-397