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Thyroid

CD105 (Endoglin) Expression as a Prognostic Marker in Aggressive Papillary Thyroid Carcinoma

İlker Çordan[1] | Tuğba Günler[2]

[1]Internal Medicine Division, Endocrinology Department, Konya City Hospital, University of Health Sciences, Konya, Turkey | [2]Clinic of Pathology, Konya City Hospital, University of Health Sciences, Konya, Turkey

Correspondence: İlker Çordan (dr.ilkercordan@windowslive.com)

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy, with a generally favourable prognosis. However, a subset of PTC cases exhibit aggressive behaviour, including lymph node and distant organ metastases. Identifying biomarkers that can differentiate between benign and malignant lesions, as well as predict tumour aggressiveness, is crucial for improving diagnosis and management. CD105 (endoglin), a marker of neoangiogenesis, has shown promise in various solid tumours as a prognostic factor. Its role in PTC, particularly in distinguishing between metastatic and non-metastatic cases, remains underexplored.

Aims: To investigate the role of CD105 (endoglin) expression in the differential diagnosis and prognostic evaluation of patients with benign thyroid nodules, non-metastatic PTC, and PTC with lymph node metastasis (LNM).

Methods: Thyroid tissues from 148 patients were retrospectively analyzed for CD105 expression, including 49 with thyroid follicular nodular disease (TFND), 48 with PTC without LNM [LNM(−) PTC], and 51 with PTC and LNM [LNM(+) PTC]. Tissues were classified based on CD105 expression, and microvascular density (MVD) scores were calculated using the Weidner method in positive cases. Clinical and pathological features were compared across TFND, LNM(−), and LNM(+) groups.

Results: The rates of CD105 expression significantly differed between the TFND, LNM(−) PTC, and LNM(+) PTC groups (8.2%, 64.6%, and 80.4%, respectively). The CD105 MVD score was significantly higher in the LNM(+) PTC, unifocal LNM(+) PTC, and multifocal LNM(+) PTC groups, in favour of metastasis ($p < 0.001$). CD105 expression was detected in all patients with distant organ metastasis, and these patients also exhibited significantly higher MVD scores ($p < 0.001$).

Conclusion: This study supports the potential use of CD105 expression and its quantitative indicator, the CD105 MVD score, as biomarkers for distinguishing benign thyroid nodules from malignant ones and for evaluating the prognosis of PTC.

1 | Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy, accounting for approximately 80%–85% of all thyroid cancers [1]. While the majority of PTC cases have excellent prognoses due to high survival rates and effective treatment options, a subset of patients experiences aggressive disease characterised by lymph node metastasis (LNM), distant metastasis, and resistance to conventional treatments such as radioactive iodine (RAI) therapy [2, 3]. Identifying reliable biomarkers to distinguish aggressive forms of PTC from indolent ones is critical for improving diagnostic accuracy, risk stratification, and personalised treatment strategies.

Angiogenesis, the formation of new blood vessels, plays a significant role in tumour growth, invasion, and metastasis [4].

CD105, also known as endoglin, is a membrane glycoprotein predominantly expressed in proliferating endothelial cells during angiogenesis [5]. Unlike other endothelial markers, CD105 is specifically associated with the tumour microenvironment and has emerged as a promising biomarker for assessing tumour angiogenesis and progression [6, 7]. Previous studies have demonstrated that high CD105 expression, as identified by CD105 staining, is associated with poor prognosis and an increased risk of metastasis in various solid organ tumours [8–10]. However, its role in thyroid neoplasms, particularly PTC, has not been fully characterised.

The microvascular density (MVD) score, measured using CD105 expression, has been proposed as a convenient marker for angiogenesis and tumour aggressiveness in malignancies [11]. While some studies suggest a strong correlation between CD105 expression and adverse clinical outcomes in thyroid cancers, others report limited or conflicting findings, highlighting the need for further investigation [12, 13]. Furthermore, data on CD105 expression in different PTC risk groups, such as metastatic and non-metastatic cases, remain insufficient.

This study aimed to investigate differences in CD105 expression between PTC and benign thyroid follicular nodular disease (TFND), evaluate the prognostic significance of CD105 MVD scores in patients with PTC, and examine the relationship of this marker with clinical and pathological factors. Furthermore, the study sought to assess the utility of CD105 as a biomarker for distinguishing benign from malignant thyroid lesions and predicting disease progression.

2 | Materials and Methods

2.1 | Patient Selection and Sample Collection

This retrospective study analyzed data from 148 patients who underwent thyroidectomy between August 2020 and January 2024. The patients were divided into three groups: 51 patients with PTC with LNM [LNM(+) PTC], 48 randomly selected patients without LNM [LNM(−) PTC], and 49 patients diagnosed with TFND. All metastatic patients had synchronous metastasis (LNM and distant organ metastases). Patients with thyroid cancer types other than PTC and those with metachronous metastatic recurrences were excluded. In cases with multiple tumours, the largest tumour was considered the index lesion. Demographic and pathological data (age, sex, tumour size, presence and number of lymph node metastases, tumour focus count, capsular invasion, lymphovascular invasion, and distant organ metastasis status) were obtained from the hospital database and analyzed. These data were evaluated in comparison with the 2015 American Thyroid Association (ATA) risk stratification and the 8th edition of the American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM) staging system [14, 15].

2.2 | CD105 (Endoglin) Immunohistochemical Analysis and MVD Scoring

CD105 (endoglin) immunohistochemical analysis was performed on 4-μm-thick sections obtained from thyroidectomy samples, which were fixed in 10% formalin and embedded in paraffin. The sections were routinely stained with hematoxylin-eosin. Histological type, lymphovascular invasion, perineural invasion, and capsule invasion were re-evaluated by two blinded pathologists. Sections obtained from selected paraffin blocks were stained with the CD105 (RB-9291-PO, Thermo Fisher Scientific, Waltham, MA, USA) antibody. Tonsil tissue was used as an external positive control (Figure 1).

Each section was examined under a light microscope (Nikon Eclipse Ci, Nikon Corporation, Tokyo, Japan), and the samples were categorised based on the presence or absence of endoglin expression (endoglin staining characteristics are shown in Figure 2). The presence of brown membranous immunostained blood vessels was considered indicative of positive endoglin expression. For samples with positive endoglin expression, MVD was assessed using the Weidner method [16]. Sections were scanned under low magnification (×4) to identify "hot spot" areas, and the microvessels in the three highest-density areas were individually counted at higher magnification (×20) (area: 0.95 mm^2). MVD was calculated as the average of the three counts and expressed as the mean ± standard deviation in vessels per square millimetre. Any immunostained endothelial cell or cluster of endothelial cells distinct from neighbouring vessels, tumour cells, and connective tissue elements was counted as a single microvessel. Vascular lumen was not required for this definition, and red blood cells were not used to define vessel lumens. Vessels in muscular tissues and areas of necrosis or hemorrhage were excluded from analysis. MVD evaluation was performed without knowledge of the clinicopathological data, ensuring objectivity in the scoring process.

2.3 | Ethical Approval

The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee for Non-Drug and Non-Medical Device Research of a tertiary medical institution (date: May 9, 2024, approval number: 2024/035). Patient approval was not obtained as this study was conducted through the retrospective evaluation of pathology data.

2.4 | Statistical Analysis

Descriptive statistics were used to summarise the data, with numerical variables presented as mean ± standard deviation for normally distributed data or median (Q1–Q3) for non-normally distributed data, and categorical variables expressed as frequencies and percentages. Comparative analyses were conducted using the Chi-square test or Fisher's exact test to assess relationships between categorical variables, while the Wilcoxon rank-sum test or Kruskal–Wallis rank-sum test was used to compare non-normally distributed numerical variables between two or more groups, such as CD105 MVD scores across metastasis statuses. Spearman correlation analysis was performed to explore relationships between continuous variables, such as tumour size, LNM count, and CD105 MVD scores. Receiver operating characteristic (ROC) analysis was employed to evaluate the diagnostic power of the CD105 MVD score in

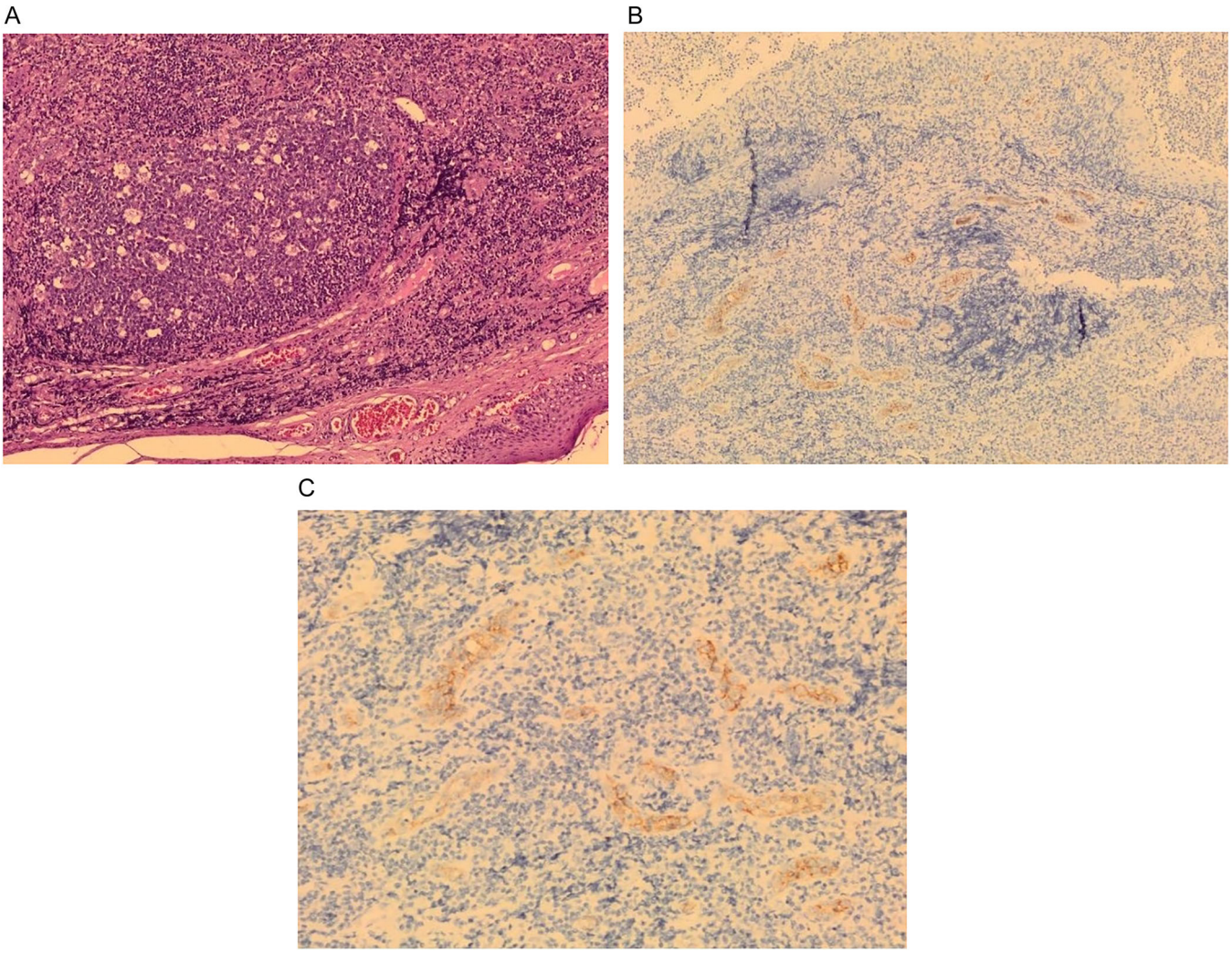

FIGURE 1 | Immunohistochemical analysis of positive control tissue (tonsil): Hematoxylin and eosin staining at ×100 magnification (A), and endoglin staining localised to the membranes of blood vessels (indicated by red arrows) in tonsil tissue at ×100 magnification (B) and at ×200 magnification (C), respectively.

detecting metastasis, calculating the area under the curve (AUC), sensitivity, and specificity. Univariate and multivariate Firth's logistic regression analyses were conducted to identify variables associated with metastasis, with univariate analysis examining individual factors and multivariate analysis adjusting for confounding variables to determine independent predictors. All statistical analyses were performed using R 4.3.2 software, with a $p < 0.05$ considered statistically significant.

3 | Results

Among the 148 patients included in the study, 112 (75.7%) were female, and 36 (24.3%) were male, with a mean age of 48.80 ± 14.29 years. Of the patients, 49 (33.1%) had TFND, while 99 (66.9%) had PTC. In the PTC group, 51 patients (51.5%) had LNM, whereas 48 (48.5%) did not have metastases. Among the patients with LNM, 10 had distant organ metastases (eight to the lungs, one to the bones, and one to the liver).

Tumour size was significantly larger in the benign TFND group compared to the PTC group ($p < 0.001$). Within the PTC group, tumours in LNM(+) patients were significantly larger than those in LNM(−) patients ($p < 0.001$). In addition, tumours in patients with distant metastasis (M1) were larger (30.60 ± 17.57 mm) compared to those without distant metastasis (M0) (16.53 ± 12.39 mm; $p = 0.007$). Tumour sizes and other demographic data are presented in Table 1.

CD105 expression was detected in only four (8.16%) of the 49 patients in the benign group, whereas it was significantly higher (72.73%) in the malignant group ($p < 0.001$). Among the patients with PTC, CD105 expression was higher in those with LNM (80.39%) compared to those without LNM (64.58%), although this difference was not statistically significant ($p = 0.078$). CD105 expression was present in all patients with distant metastasis (M1) (100%) and in 69.66% of those without distant metastasis (M0) ($p = 0.058$).

CD105 MVD scores were higher in patients with either LNM or distant metastasis and varied significantly according to the presence of LNM, the number of metastases, and the presence of distant metastasis ($p < 0.001$ for all). Figure 3 presents the comparison of the percentages of CD105 expression and MVD

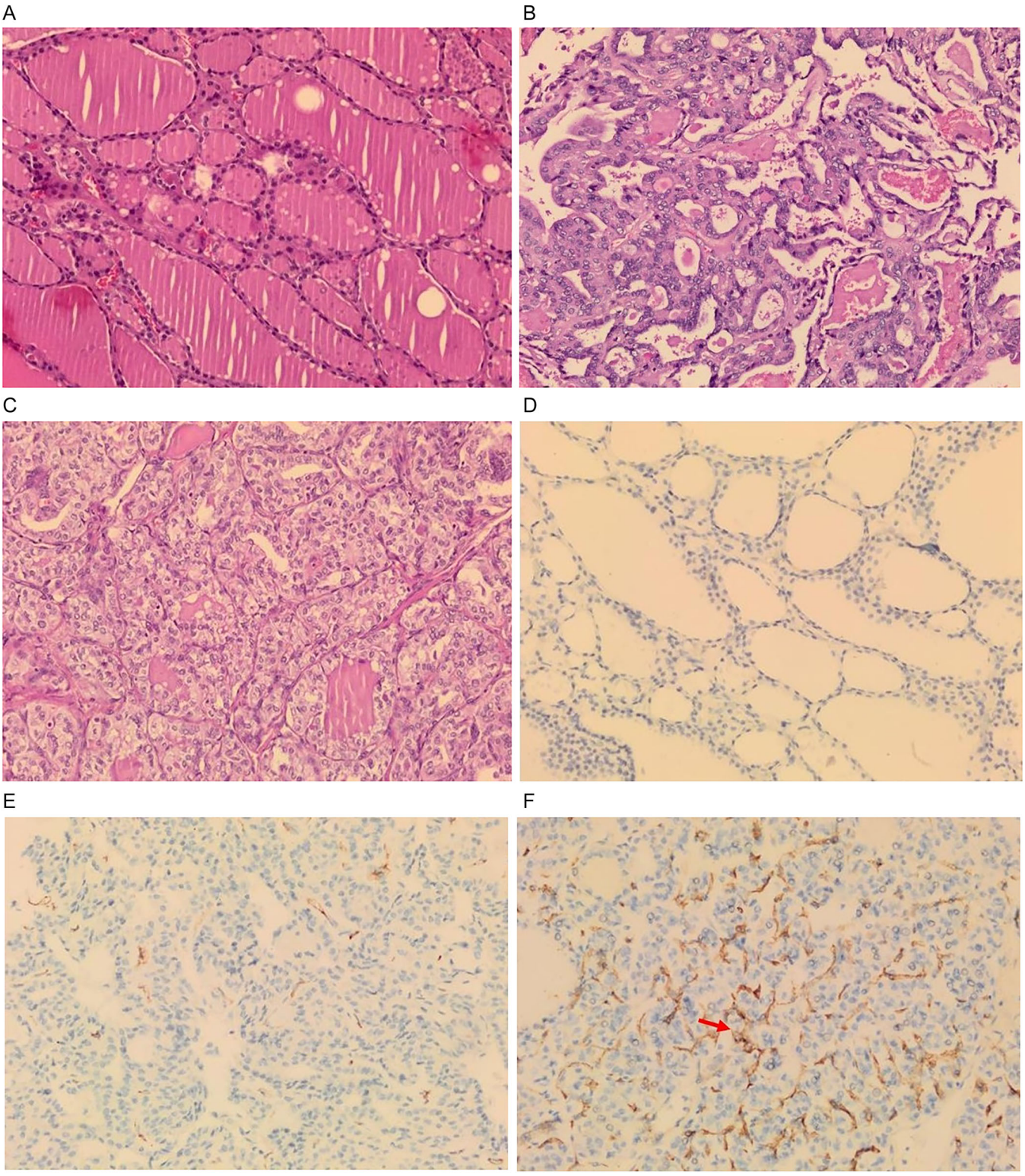

FIGURE 2 | Hematoxylin and eosin-stained sections at ×200 magnification (A–C): Thyroid follicular nodular disease (A), non-metastatic papillary thyroid carcinoma (B), and papillary thyroid carcinoma with metastasis (C). Endoglin-stained sections at ×200 magnification (D–F): Thyroid follicular nodular disease (D) and non-metastatic papillary thyroid carcinoma (E), Dense endoglin-positive blood vessels (indicated by red arrows) observed in the thyroid tissue of a papillary thyroid carcinoma case with lung metastases, shown at ×200 magnification.

scores (vessels/mm^2) among the TFND, LNM(−) PTC, LNM(+) PTC, and distant metastasis groups, and the relationships between CD105 MVD scores, LNM, number of metastases, and distant metastasis status are summarised in Table 2.

The relationships between CD105 MVD scores and factors such as age, sex, 2015 ATA risk scores, AJCC TNM stage, pathological T stage (tumour diameter), thyroid capsule invasion, lymphovascular invasion, perineural invasion, and histological

TABLE 1 | Comparison of demographic and clinical characteristics among study groups.

Variable	TFND ($n = 49$[a])	LNM(−) PTC ($n = 48$[a])	LNM(+) PTC ($n = 51$[a])	p[b]
Sex				
Male	11.00 (22.45%)	9.00 (18.75%)	16.00 (31.37%)	—
Female	38.00 (77.55%)	39.00 (81.25%)	35.00 (68.63%)	—
Tumour size (mm)	32.06 ± 12.58	12.92 ± 8.00	22.69 ± 15.94	< 0.001
LNM count	—	—	5.31 ± 5.13	—
PTC focus count	—	1.50 ± 0.92	2.80 ± 2.33	0.052

Note: Empty cells are indicated with an em dash (—).
Abbreviations: LNM(−) PTC, lymph node metastasis-negative papillary thyroid carcinoma; LNM(+) PTC, lymph node metastasis-positive papillary thyroid carcinoma; TFND, thyroid follicular nodular disease.
[a]n (%), mean ± SD.
[b]Pearson's Chi-squared test, one-way analysis of variance.

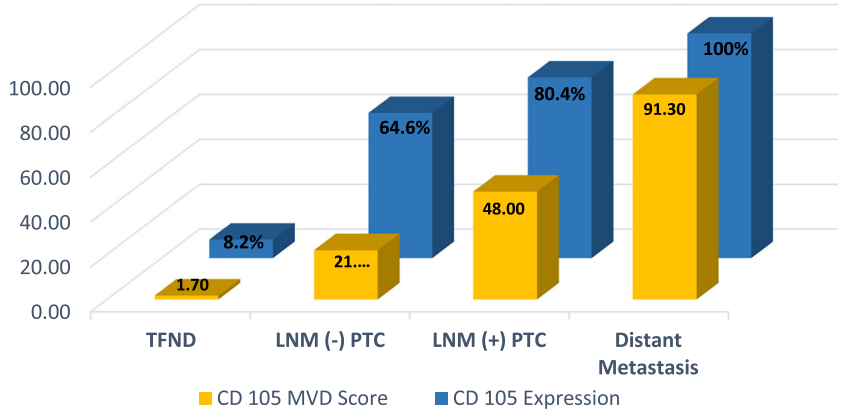

FIGURE 3 | Comparison of CD105 expression and MVD scores among groups.

TABLE 2 | CD105 MVD scores by lymph node and distant metastasis.

Variable	n	CD105 MVD score (median, 25th–75th percentile[a])	p[b]
LNM			**< 0.001**
Absent	48	21.95 (0.00–36.60)	
Present	51	48.00 (19.30–71.30)	
LNM frequency			**< 0.001**
None	48	21.95 (0.00–36.60)	
Unifocal	13	45.30 (0.00–57.30)	
Multifocal	38	49.30 (26.78–81.00)	
Distant metastasis			**< 0.001**
Absent	89	27.30 (0.00–50.60)	
Present	10	91.30 (62.98–124.98)	

Note: Bold values indicate statistical significance at $p < 0.05$.
Abbreviations: LNM, lymph node metastasis; MVD, microvascular density; PTC, papillary thyroid carcinoma.
[a]n (%); median (25th–75th percentile).
[b]Wilcoxon rank-sum test; Kruskal–Wallis rank-sum test; Chi-square test, Fisher's exact test.

subtypes were analyzed. CD105 MVD scores were significantly higher in cases with high 2015 ATA risk, advanced TNM stage, presence of lymphovascular invasion, and higher pathological T stage. The associations between clinicopathological features and CD105 MVD scores in PTC are summarised in Table 3.

Spearman correlation analysis revealed a strong positive correlation between CD105 MVD scores and tumour size, with CD105 MVD scores increasing significantly with tumour size ($r = 0.53$, $p < 0.001$). A positive correlation was also observed between CD105 MVD scores and the number of LNMs ($r = 0.39$, $p < 0.001$). Similarly, there was a strong correlation between tumour size and the number of LNMs ($r = 0.46$, $p < 0.001$). In contrast, there was a weak positive correlation between CD105 MVD scores and the number of primary tumour foci ($r = 0.14$), but this relationship was not statistically significant.

The predictive power of CD105 MVD scores for metastasis in patients with PTC was evaluated using ROC analysis, which yielded an optimal cut-off value of 48 for CD105 MVD, with an AUC of 0.7, a sensitivity of 0.57, and a specificity of 0.81. The ROC curve is illustrated in Figure 4.

To identify factors associated with metastasis in PTC, univariate and multivariate Firth logistic regression analyses were conducted. CD105 MVD scores and tumour diameter were significant in univariate analysis ($p < 0.001$ for both); however, this significance was not retained in multivariate analysis ($p = 0.4$ and $p > 0.9$, respectively). In univariate analysis, the number of tumour foci, capsular invasion, and lymphovascular invasion showed the strongest associations with metastasis. These associations remained significant in multivariate analysis, with tumour foci number ($p = 0.027$), capsular invasion ($p = 0.006$), and lymphovascular invasion ($p = 0.014$) identified as significant factors. Table 4 summarises the results of univariate and

TABLE 3 | Clinicopathological correlates of CD105 MVD in PTC.

Clinicopathological feature	*n*	CD105 MVD score (median, 25th–75th percentile[a])	*p*[b]
Age (years)			0.7
< 55 years	71	32.00 (0.00–54.65)	
≥ 55 years	28	26.60 (0.00–64.00)	
Sex			0.083
Male	25	42.60 (28.00–68.00)	
Female	74	26.60 (0.00–52.98)	
2015 ATA risk score			**< 0.001**
Low risk	55	13.30 (0.00–32.00)	
Intermediate risk	29	50.60 (26.60–74.60)	
High risk	15	68.00 (50.65–118.00)	
AJCC TNM stage*			**0.002**
Stage 1	80	26.95 (0.00–48.65)	
Stage 2	14	66.65 (31.28–121.00)	
Stage 4	5	68.00 (56.00–70.60)	
Pathological (p) T stage			**< 0.001**
pT1	68	21.95 (0.00–48.00)	
pT2-3-4	31	56.00 (37.30–86.00)	
Thyroid capsule invasion			0.08
Absent	65	27.30 (0.00–50.60)	
Present	34	46.65 (18.30–71.65)	
Lymphovascular invasion			**0.004**
Absent	73	26.60 (0.00–48.00)	
Present	26	57.30 (29.00–101.23)	
Perineural invasion			0.91
Absent	95	30.60 (0.00–56.65)	
Present	4	29.30 (19.95–41.33)	
Histological subtype			0.21
Classical type	77	30.60 (0.00–53.00)	
Follicular variant	14	53.30 (6.33–80.63)	

Note: *American Joint Committee on Cancer TNM stage (eighth edition). Bold values indicate statistical significance at $p < 0.05$.
Abbreviations: AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association; MVD, microvascular density; PTC, papillary thyroid carcinoma; TNM, tumour, node, metastasis.
[a]*n* (%); median (25%–75%).
[b]Wilcoxon rank-sum test; Kruskal–Wallis rank-sum test; Chi-Square test; Fisher's exact test.

multivariate Firth's logistic regression analyses, highlighting the variables associated with metastasis in patients with PTC.

4 | Discussion

In this study, we investigated the differences in CD105 expression between PTC and benign TFND while also evaluating the prognostic significance of the CD105 MVD score in patients with PTC. To the best of our knowledge, this is the first study to compare CD105 expression across different risk groups of PTC (metastatic and non-metastatic).

The findings of this study demonstrate that despite smaller tumour sizes, CD105 expression is significantly higher in patients with PTC compared to those with benign TFND. Additionally, CD105 expression was found to increase in high-risk PTC groups, including unifocal and multifocal LNMs and distant organ metastases. Notably, all primary tumour foci exhibiting distant metastases exhibited intense CD105 staining.

The CD105 MVD score also showed strong correlations with various clinicopathological factors indicative of disease prognosis, such as tumour size, the presence and number of LNMs, vascular invasion, distant organ metastases, pathological stage (AJCC TNM), and the 2015 ATA risk score. These findings suggest that CD105 expression could play a critical role in distinguishing benign thyroid nodules from malignant ones during pathological evaluations. Furthermore, the CD105 MVD score,

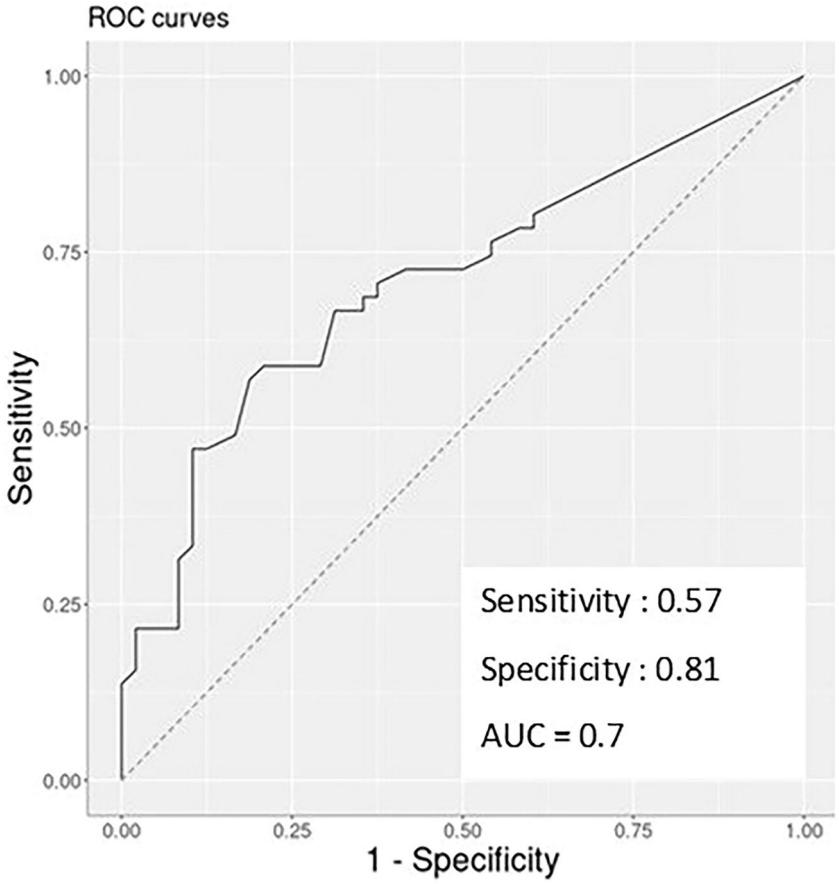

FIGURE 4 | ROC curve analysis for the CD105 MVD score in predicting lymph node metastasis.

TABLE 4 | Logistic regression analyses of variables associated with metastasis.

	Univariate		Multivariate	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
CD105 MVD score	1.02 (1.01–1.04)	**< 0.001**	1.01 (0.99–1.03)	0.4
Age	1.01 (0.99–1.04)	0.36	1.02 (0.98–1.06)	0.4
Sex (female)	0.52 (0.20–1.32)	0.15	0.53 (0.16–1.78)	0.6
Tumour diameter	1.08 (1.03–1.14)	**< 0.001**	1.00 (0.92–1.08)	> 0.9
Number of foci in thyroid cancer	1.24 (0.94–1.64)	**0.035**	1.43 (0.95–2.14)	**0.027**
Capsular invasion	6.21 (2.37–16.2)	**< 0.001**	4.75 (1.55–14.6)	**0.006**
Lymphovascular invasion	10.7 (3.11–37.0)	**< 0.001**	4.99 (1.20–20.7)	**0.014**

Note: Bold values indicate statistical significance at $p < 0.05$.
Abbreviations: CI, confidence interval; MVD, microvascular density; OR, odds ratio.

as a quantitative indicator, holds promise as a biomarker for assessing the malignant potential of PTC.

The role of CD105 in thyroid neoplasms has been the subject of conflicting findings, likely due to the limited sample sizes in earlier studies. Rydlova et al. [12] reported CD105 expression in only a small number of follicular adenomas and carcinomas among thyroid neoplasms. However, subsequent studies revealed that while CD105 expression is rare in benign thyroid tissue, it is prominently expressed in malignant thyroid carcinomas, including papillary, follicular, and medullary subtypes [13, 17]. Our findings align with these later studies, showing significantly higher CD105 expression in patients with PTC compared to those with TFND, despite their smaller tumour sizes. This supports the potential utility of CD105 as a key marker for distinguishing benign thyroid nodules from malignant ones in thyroid pathology.

PTC often spreads locally via lymphatic pathways, with cervical LNM present in 20%–50% of cases at diagnosis. Undetected micrometastases are believed to be more prevalent and clinically significant [18–21]. The CD105 MVD score, as measured in various solid organ malignancies (e.g., breast, endometrial, colorectal, and oral squamous cell carcinomas),

has shown strong correlations with the presence and number of LNMs and is widely recognised as a marker of poor prognosis [22–25]. Our study, consistent with findings in other epithelial tumours, demonstrates a significant relationship between CD105 MVD scores and the presence and frequency of LNM in patients with PTC. These scores were notably higher in the presence of LNM. Higher scores were observed in the presence of lymphatic metastases, which is known to adversely affect survival and increase the frequency of distant organ metastases [26, 27]. The 81% specificity of CD105 in predicting the absence of LNM suggests its potential as a crucial biomarker for identifying low-risk patients and improving risk stratification.

The role of CD105 in promoting tumour vascularisation and facilitating metastasis is well-documented, with higher metastatic rates observed in malignant tumours expressing elevated levels of CD105. In addition, CD105 expression levels in metastatic lesions have been shown to resemble those in primary tumours [28–31]. In the current study, we observed notable CD105 expression in the primary tumours of the PTC group with distant metastases, which exhibited the highest CD105 MVD scores among all groups. Univariate analysis revealed that each unit increase in the CD105 MVD score raised the likelihood of metastasis by 2%, providing significant evidence for the potential role of CD105 in the metastatic process. Furthermore, in our study, the univariate analysis conducted to identify factors associated with metastasis in PTC showed that tumour diameter was significant, and the strong correlation between the CD105 MVD score and tumour size suggested that the effect of CD105 might be mediated through tumour size. However, in the multivariate analysis, both CD105 MVD and tumour diameter lost their significance, while other prognostic factors such as capsular invasion, lymphovascular invasion, and multifocality maintained their significance, suggesting that these two variables may be indirectly related to metastatic potential through these prognostic factors rather than directly. These findings indicate that CD105 expression is not merely a reflection of tumour size and may be associated with more complex mechanisms in tumour biology. Therefore, advanced multivariate models and prospective studies are needed to better understand the precise prognostic role of CD105 in PTC.

Further studies on the role of CD105 in PTC could solidify its utility in differential diagnosis, prognostic assessment, and personalised treatment planning. For instance, CD105 could aid in the differential diagnosis of borderline lesions, such as non-invasive follicular thyroid neoplasm with papillary-like nuclear features. Its potential to predict high-risk PTC early could inform the selection and optimisation of RAI therapy. Evidence suggesting that anti-CD105 monoclonal antibodies inhibit angiogenesis, thereby suppressing tumour growth and metastasis, underscores the therapeutic potential of this biomolecule [32]. In metastatic and RAI-resistant PTC cases, CD105 may serve as a critical target for both localisation and therapeutic strategies.

This study provides a comprehensive analysis by including TFND and various risk groups of PTC. However, its retrospective and single-centre design limits the generalisability of the findings. Pathological data were analyzed at the time of diagnosis, and only synchronous metastases were evaluated, leaving the effect of primary tumours with potential micrometastases unclear. While the data from a small number of patients with distant organ metastases offer valuable insights, the limited sample size may weaken the statistical power of the study. Furthermore, the exclusion of aggressive PTC variants, such as those with BRAF mutations or tall cell and diffuse sclerosing subtypes, represents a significant limitation. Larger-scale and prospective studies are needed to clarify the prognostic value of CD105.

This study provides strong evidence supporting CD105 expression and CD105 MVD score as significant biomarkers in distinguishing PTC from benign TFND and in assessing PTC prognosis. Although CD105 MVD is not an independent risk factor for metastasis, it was found to significantly increase in high-risk PTC groups and exhibit strong correlations with other clinicopathological factors reflecting disease prognosis. Future research may provide greater insights into the practical applications of CD105, contributing to the development of more effective and personalised therapeutic approaches for managing PTC.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.