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RESEARCH ARTICLE

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Preoperative platelet distribution width-to-platelet ratio combined with serum thyroglobulin may be objective and popularizable indicators in predicting papillary thyroid carcinoma

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Abstract

Objectives: The incidence of papillary thyroid carcinoma (PTC) has increased more rapidly than that of any other cancer type in China. Early indicators with high sensitivity and specificity during diagnosis are required. To date, there has been a paucity of studies investigating the relationship between preoperative platelet distribution width-to-platelet count ratio (PPR) and PTC. This study thus aimed to assess the diagnostic value of PPR combined with serum thyroglobulin (Tg) in patients with PTC.

Methods: A total of 1001 participants were included in our study. 876 patients who underwent surgery for nodular goiter were divided into the PTC group or benign thyroid nodule (BTN) group according to pathology reports, and 125 healthy controls (HCs) were included. Preoperative hemogram parameters and serum Tg levels were compared among three groups. Receiver operating characteristic (ROC) curve was used to evaluate the value of PPR combined with serum Tg for diagnosing PTC.

Results: Platelet distribution width (PDW) and PPR levels were higher in the PTC group than in the BTN and HC groups (both $p < 0.05$) but did not significantly differ between the BTN and HC groups. PDW and PPR levels significantly differed in the presence/absence of lymph node metastasis, the presence/absence of capsule invasion ($p = 0.005$), and TNM stages ($p < 0.001$). Multivariable analyses indicated that high serum Tg levels [adjusted odds ratio (OR), 1.007; 95% confidence interval (CI), 1.004–1.009; $p < 0.001$], high neutrophil-to-lymphocyte ratio (NLR,adjusted OR, 1.928; 95% CI, 1.619–2.295; $p < 0.001$), and high PPR (adjusted OR, 1.378; 95% CI, 1.268–1.497; $p < 0.001$) were independent risk factors for PTC. In ROC analysis, the areas under the curves (AUCs) of serum Tg, PDW, PPR, and NLR for predicting PTC were 0.603, 0.610, 0.706, and 0.685, respectively. PPR combined with serum Tg (PPR + Tg) had a higher diagnostic value (AUC, 0.738; sensitivity, 60%; specificity,

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74.7%) compared with PDW + Tg (AUC, 0.656; sensitivity, 64.4%; specificity, 59.9%) and NLR + Tg (AUC, 0.714; sensitivity, 61.6%; specificity, 71.1%).

Conclusions: Preoperative PPR combined with serum Tg may be objective and popularizable indicators for effective predicting PTC.

KEYWORDS
benign thyroid nodule, papillary thyroid carcinoma, platelet count, platelet distribution width, thyroglobulin

1 | INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common histological subtype of thyroid cancer, accounting for 80%–85% of all thyroid cancers.[1] A multicenter study reported that PTC was the main contributor to overall thyroid cancer in 25 countries and was the only histological subtype that increased systematically in all countries.[2] Lymph metastasis frequently occurs in the early stage of PTC, which affects patient prognosis. As such, early diagnosis of PTC is critical.

Fine needle aspiration cytology (FNAC) is currently considered the main preoperative method for detecting malignancy in thyroid nodules.[3] However, this approach is limited by its invasiveness, cost, inadequate sampling, indeterminate cytology, and operator dependency.[4,5] Accordingly, there is a need to develop novel, convenient, cheap, and objective biomarkers of PTC and to evaluate their potential for predicting PTC.

It is well established that serum thyroglobulin (Tg) can accurately predict thyroid cancer recurrence in postoperative settings. The diagnostic value of serum Tg has recently been highlighted[6,7]; however, one study suggested that several factors affect serum Tg concentration.[8] Therefore, further research is warranted to validate the predictive value of serum Tg. Notably, given that examination of Tg is routinely performed in the clinic, it has high feasibility.

Emerging evidence suggests that platelets, as markers of systemic inflammatory responses, play essential roles in tumorigenesis and progression,[9,10] particularly activated platelets.[11] PDW is an indicator of specific platelet activation and is positively correlated with platelet activation,[12] which reflects platelet volume heterogeneity. The lower the level of PDW, the better the uniformity of platelets. Its increase represents the great disparity of platelet size, which often indicates that the body is in a state of disease. PDW has been shown to be increased in thrombocytopenia from any cause, but PLT level may not be obvious reduced in the early stage of disease, so how PDW changes is unknown. So far, it has been confirmed that chronic consumptive,[13] critical infected,[14–16] and immune-mediated[17] inflammatory condition where PLT indices are distorted, but it is controversial in cancer. Studies have confirmed that PDW may be an indicator in early diagnosis malignancies,[18–21] but there is no research combining PDW with PLT in PTC. Moreover, a single indicator may be susceptible to various factors. Studies combining PDW with PLT have reported that platelet distribution width-to-platelet count ratio (PPR) is closely associated with disease severity and cancer.[22,23] Hence, this study aimed to assess the diagnostic value of preoperative PPR combined with serum Tg for PTC.

2 | METHODS

2.1 | General information

2.1.1 | Participants

This retrospective study included 1001 participants. We selected 875 patients who underwent thyroidectomy or lobectomy and 126 healthy individuals as healthy controls (HCs) between January 1, 2016, and February 30, 2021, at the Affiliated Hospital of Xuzhou Medical University. Patients who underwent thyroidectomy or lobectomy were divided into PTC [500/1001, 109 males and 391 females, the median age was (51.1 ± 13.89) years] and BTN [376/1001, 73 males and 303 females, the median age was (51.37 ± 11.78) years] groups according to postoperative pathology results. HCs (125/1001, 27 males and 98 females, the median age was (50.27 ± 14.89) years] comprised participants without any obvious abnormalities on thyroid ultrasound examination. We retrospectively collected data regarding complete blood counts and clinicopathological data regarding sex, age, height (cm), and weight (kg). Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Data on tumor size, tumor number, type of thyroid disorder (PTC), presence or absence of lymph node metastases, presence or absence of capsule invasion, and TNM stage of patients with PTC were collected. Clinical and pathological TNM staging was performed according to the American Joint Committee on Cancer staging system (8th edition).

The inclusion criteria were as follows: (1) patients with thyroid nodules that were subjected to thyroidectomy (total or subtotal) with lymph node dissection; (2) patients with complete preoperative clinical examination, complete medical history, and definite postoperative pathology; (3) patients with PTC confirmed by postoperative histopathology. Exclusion criteria were as follows: (1) age <18 years; (2) subclinical hypothyroidism or clinical hyperthyroidism (TSH ≥ 4.20 mIU/L or <0.27 mIU/L); (3) diabetes, other cancers, hypercoagulable state diseases, inflammatory diseases, myeloproliferative disorders, and other hematological system diseases, any organ dysfunction, liver or spleen diseases from any case, immunological

diseases, infection or suspicion of infection, or anemia; (4) use of anticoagulants, antiplatelet medicines, and/or alcohol; Given the known effects of thyroglobulin antibody (TgAb) on the measurements of serum Tg levels, patients with detectable TgAb and those that did not undergo measurements of TgAb prior to thyroidectomy were excluded from our study. A final total of 1001 participants (209 men and 792 women) were enrolled in the study. This retrospective study was approved by the Affiliated Hospital of Xuzhou Medical University Research Committee (Approval No. XYFY2021-KL130-01). The need for individual consent was waived due to the retrospective nature of the study. The study conformed to the Declaration of Helsinki.

2.2 | Laboratory assessments

Platelet parameters were measured within 7 days prior to the operation. Venous blood samples were collected after overnight fasting for at least 8–10 h. Serum levels of hemoglobin (Hb, normal range: 130–175 g/L), neutrophil counts (NE, normal range: 1.8–6.3 × 10^9/L), lymphocyte counts (LY, normal range: 1.1–3.2 × 10^9/L), red blood cell distribution width (RDW, normal range: 10.6%–15.0%), mean platelet distribution (MPV, normal range: 6–14 fl), platelet distribution width (PDW, normal range: 9.0%–17.0%), platelet counts (PLT, normal range: 125–350 × 10^9/L), plateletcrit (PCT, normal range: 0.07%–0.33%), red blood counts (RBC, normal range: 3.8–5.1 × 10^{12}/L), white blood counts (WBC, normal range: 3.5–9.5 × 10^9/L), hematocrit (HCT, normal range: 35.0%–45.0%), and platelet-large cell ratio (P-LCR, normal range: 13.0–43.0) were estimated using an AU680 automatic biochemical detector (Beckman Coulter Company). PPR was calculated by dividing the complete PDW by the complete PLT. PLR was calculated by dividing the complete PLT by the complete LN. NLR was calculated by dividing the complete NE by the complete LN. Thyroid stimulating hormone (TSH, normal range: 0.27–4.2 mIU/L) and Tg (normal range: 1.4–78 ng/ml) were assessed with an Access2 automatic immunity analyzer (Beckman Coulter Company). PTC samples were collected by the same pathologist with considerable experience in thyroid carcinoma. Paraffin-embedded specimens were sectioned and stained with hematoxylin and eosin (H&E). H&E data of PTC samples and resected lymph nodes were assessed by a pathologist. Based on postpathology results, tumor size was determined according to the maximum diameter of the lesion. Multifocal tumors were defined as two or more lesions with PTC.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS software (version 26.0). Normality of the distribution was examined by the Shapiro–Wilk test. Descriptive statistics are presented as mean ± SD or median (interquartile range) for continuous variables. Pairwise comparisons were performed using *t* test for data with a normal distribution. Comparisons between multiple groups were performed using one-way ANOVA with Bonferroni correction for normally distributed data, and the Kruskal–Wallis H test was used for non-normally distributed data. Pairwise comparisons were performed using the Nemenyi test. Categorical variables are presented as numbers and percentages, and inter-group differences were assessed for significance using the $\chi 2$ test. Logistic regression was performed to investigate risk factors for PTC. Receiver operating characteristic (ROC) curve were used to evaluate the diagnostic value of indicators. The joint probability of the two indicators is calculated by logistics regression, and the ROC curve is drawn by the joint probability, and the statistical significance of the differences was assessed using the *Z* test. Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Clinical characteristics

The clinical characteristics of the study participants are presented in Table 1. PDW (PTC vs. BTN, $p < 0.05$; PTC vs. HC, $p < 0.05$), serum Tg (PTC vs. BTN, $p = 0.000$; PTC vs. HC, $p = 0.000$), NLR (PTC vs. BTN, $p = 0.000$; PTC vs. HC, $p = 0.000$), and PPR (PTC vs. BTN, $p < 0.05$; PTC vs. HC, $p < 0.05$) were significantly higher in the PTC group than in the BTN and HC groups. However, PLT were significantly lower in the PTC group than in the BTN and HC groups (PTC vs. BTN, $p < 0.05$; PTC vs. HC, $p < 0.05$). PDW and PPR levels in PTC, BTN, and HC groups are presented in Figure 1A,B.

3.2 | Relationship between PDW, PPR, and clinicopathological characteristics in patients with PTC

The correlations between PDW, PPR, and clinicopathologic parameters are summarized in Table 2. As shown in Table 2, PDW and PPR levels did not differ in gender ($p = 0.200$), age ($p = 0.822$), BMI ($p = 0.176$), tumor size ($p = 0.727$), and tumor number ($p = 0.521$). In contrast, PDW and PPR levels significantly differed in the presence/absence of lymph node metastasis, the presence/absence of capsule invasion ($p = 0.005$), and TNM stages ($p < 0.001$).

3.3 | Analysis of PTC risk using univariate and multivariate logistic regression

The logistic regression analysis results for patients with PTC are presented in Table 3. The relationships between independent variables (serum Tg, NLR and PPR) and dependent variables (patients with or without PTC) were analyzed. After correcting for BMI, gender, age, PDW and TSH levels, a binary logistic regression model was established. In univariate logistic regression analyses, PDW (odds ratio [OR], 1.185; 95% confidence interval [CI], 1.117 ~ 1.258; $p < 0.001$), serum Tg (OR, 1.007; 95% CI, 1.004 ~ 1.010; $p < 0.001$), PPR (OR,

TABLE 1 Clinical characteristics of the participants

Parameters	PTC ($n = 500$)	BTN ($n = 376$)	HC ($n = 125$)	F/χ^2	p
Age (years)	51.1 ± 13.89	51.37 ± 11.78	50.27 ± 14.89	0.322	0.725
Gender					
Male	109 (21.8)	73 (19.4)	27 (21.6)	0.784	0.676
Female	391 (78.2)	303 (80.6)	98 (78.4)		
BMI (kg/m^2)	24.65 ± 3.56	24.34 ± 2.81	24.32 ± 2.52	1.174	0.309
TSH (mIU/L)	2.16 ± 0.98	2.12 ± 1.05	2.18 ± 1.04	0.228	0.796
Tg (ng/ml)	42.87 (12.55, 74.09)	33.13 (6.21, 55.58)[a]	14.90 (10.38, 38.25)[a]	32.006	<0.001
WBC (10^9/L)	5.93 ± 1.48	5.85 ± 1.55	5.91 ± 1.37	0.350	0.705
RBC (10^{12}/L)	4.48 ± 0.45	4.51 ± 0.40	4.50 ± 0.49	0.472	0.624
HB (g/L)	133.43 ± 15.56	133.9 ± 14.45	134.14 ± 14.65	0.163	0.850
NE (10^9/L)	3.87 (3.11, 4.79)	3.45 (2.71, 4.19)[a]	3.46 (2.71, 4.12)[a]	43.006	<0.001
LY (10^9/L)	1.70 (1.30, 2.00)	1.90 (1.60, 2.30)[a]	1.90 (1.60, 2.20)[a]	47.702	<0.001
PLT (10^9/L)	200.24 ± 54.12	237.43 ± 58.66[a]	230.99 ± 42.83[a]	120.990	<0.001
HCT (%)	39.93 ± 3.91	40.26 ± 3.83	40.23 ± 4.46	0.857	0.425
RDW (%)	13.13 ± 1.14	13.04 ± 1.28	13.13 ± 1.31	0.688	0.503
PCT (%)	0.26 ± 0.06	0.26 ± 0.06	0.26 ± 0.04	0.039	0.962
PDW (%)	13.83 ± 2.23	13.06 ± 2.24[a]	12.96 ± 1.83[a]	16.813	<0.001
P-LCR	32.34 ± 8.59	32.73 ± 8.95	32.04 ± 7.59	0.387	0.679
NLR	2.35 (1.75, 3.06)	1.82 (1.40, 2.35)[a]	1.78 (1.51, 2.27)[a]	143.823	<0.001
PPR	0.075 ± 0.024	0.059 ± 0.021[a]	0.058 ± 0.014[a]	64.265	<0.001

Notes: (a) compared to papillary thyroid cancer group, both $p < 0.05$.

Abbreviations: BMI, body mass index; BTN, benign thyroid nodule; HC, healthy controls; HGB, hemoglobin; LY, lymphocyte count; MPV, mean platelet volunm; NE, neutrophil count; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PPR, platelet distribution width-to-platelet count ratio; PTC, papillary thyroid cancer; RBC, red blood cell count.

1.424; 95% CI, 1.328 ~ 1.527; $p < 0.001$), and NLR (OR, 2.064; 95% CI, 1.753 ~ 2.431; $p < 0.001$) were correlated with the presence of PTC. In multivariate logistic regression analyses, serum Tg (OR, 1.007; 95% CI, 1.004–1.009; $p < 0.001$), PPR (OR, 1.378; 95% CI, 1.268–1.497; $p < 0.001$), and NLR (OR, 1.928; 95% CI, 1.619–2.295; $p < 0.001$) were independent risk factors for PTC.

3.4 | Diagnostic value of ROC analysis for identifying PTC

The sensitivity, specificity, cutoff value, and AUC values for PDW, PPR, NLR, and the combination of serum Tg are presented in Table 4. The AUC of each indicator for diagnosing PTC was statistically significant (both $p < 0.001$). Based on the Z test results, the AUC was significantly higher for PPR than for PDW, NLR, and Tg. Serum Tg had the highest specificity (79.0%) but low sensitivity (40.8%). When a single inflammatory indicator was combined with serum Tg, PPR combined with serum Tg (PPR + Tg) had a significantly higher diagnostic value (AUC, 0.738; sensitivity, 80%; specificity, 72%) compared with NLR + Tg (AUC, 0.714; sensitivity, 61.6%; specificity, 71.1%, $p < 0.001$) and PDW + Tg (AUC, 0.656; sensitivity, 64.4%; specificity, 59.9%, $p < 0.001$), indicating that the value of PPR combined with serum Tg for diagnosing PTC was the highest (Figure 2).

4 | DISCUSSION

To our knowledge, this is the first report of PPR in patients with PTC. Our analysis indicated that PPR differed quantitatively among PTC, BTN, and HC groups, similar to serum Tg. Multivariate analysis revealed that serum Tg and PPR were independent risk factors for PTC. Furthermore, the high levels of serum Tg and PPR were useful for distinguishing PTC from BTN and HC, and their combination exhibited the best diagnostic efficiency.

Serum Tg is a glycoprotein secreted from follicular cells of the thyroid gland, but its usefulness for preoperative diagnosis remains controversial.[24,25] Previous studies have demonstrated that serum Tg levels are an independent risk factor for PTC,[26] which is consistent with the results of our multivariate logistic regression analysis. A recent prospective study on prediction of malignancy in thyroid nodules indicated that preoperative serum Tg could predict the presence of malignancy.[27] ROC analysis revealed that a serum Tg cutoff value of 53 ng/ml could predict malignant nodules, but our results indicated serum Tg values of up to 59.385 ng/ml. Possible factors underscoring this discrepancy are selection bias in the study population and tumor heterogeneity.[28] Indeed, serum Tg levels are affected by sex and the amount of iodine intake.[8] Kim et al.[24] retrospectively reviewed the clinical records of 4029 differentiated thyroid cancer cases and reported that preoperative Tg levels were

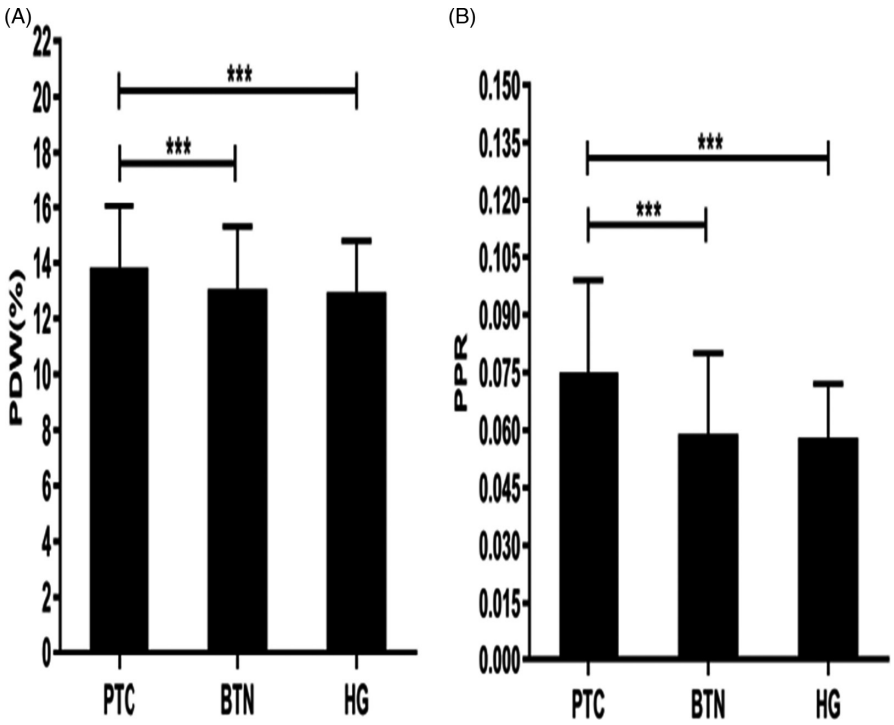

FIGURE 1 Levels of PDW and PPR in PTC group ($n = 500$), BTN group ($n = 376$), and HC group ($n = 125$) were determined by hematology analyzer. (A) PDW in patients with PTC or BTN and healthy controls. (B) PPR in patients with PTC or BTN and healthy controls. BTN, benign thyroid nodule; HC, healthy control; PDW, platelet distribution width; PPR, platelet distribution width-to-platelet count ratio; PTC, papillary thyroid cancer. ***$p < 0.001$

TABLE 2 Correlations between preoperative PDW, PPR levels, and clinicopathological parameters

Parameters	*n*	PDW(%)	*t*	*p*	PPR	*t*	*p*
Age (years)							
<55	332	13.79 ± 2.26	0.623	0.533	0.074 ± 0.026	0.225	0.822
≥55	168	13.92 ± 2.18			0.075 ± 0.021		
Gender							
Male	109	14.05 ± 2.05	1.135	0.257	0.072 ± 0.021	1.285	0.200
Female	391	13.77 ± 2.28			0.075 ± 0.025		
BMI							
<24 kg/m^2	232	13.71 ± 2.18	1.164	0.245	0.073 ± 0.024	1.355	0.176
≥24 kg/m^2	268	13.94 ± 2.27			0.076 ± 0.024		
Tumor size							
<1 cm	297	13.80 ± 2.20	0.392	0.695	0.074 ± 0.024	0.349	0.727
≥1 cm	203	13.88 ± 2.27			0.075 ± 0.025		
tumor number							
<2	303	13.88 ± 2.10	0.581	0.561	0.074 ± 0.023	0.642	0.521
≥2	197	13.76 ± 2.42			0.075 ± 0.026		
Lymph node metastases							
Absent	248	13.46 ± 1.94	3.810	<0.001	0.072 ± 0.023	2.849	0.005
Present	252	14.21 ± 2.43			0.078 ± 0.025		
Capsule invasion							
Absent	286	13.54 ± 1.99	2.720	0.007	0.072 ± 0.021	2.679	0.008
Present	214	14.22 ± 2.46			0.078 ± 0.027		
TNM stage							
I–II	483	13.75 ± 2.09	2.269	0.037	0.074 ± 0.024	3.655	<0.001
III–IV	17	16.10 ± 4.25			0.096 ± 0.024		

Abbreviations: BMI, body mass index; PDW, platelet distribution width; PPR, platelet distribution width-to-platelet count ratio.

TABLE 3 Univariate and multivariate logistic regression analyses

	Univariate			Multivariate		
Variables	**OR (95%CI)**	**Wald χ^2**	***p***	**OR (95%CI)**	***Wald*χ^2**	***p***
Age	1.000 (0.991 ~ 1.009)	<0.001	0.994	0.992 (0.982 ~ 1.002)	2.297	0.130
Gender	0.895 (0.659 ~ 1.214)	0.513	0.474	0.928 (0.657 ~ 1.31)	0.182	0.669
BMI	1.031 (0.991 ~ 1.072)	2.338	0.126	1.044 (0.998 ~ 1.093)	3.560	0.059
TSH	1.024 (0.906 ~ 1.157)	0.142	0.707	1.042 (0.908 ~ 1.196)	0.338	0.561
Tg	1.007 (1.004 ~ 1.010)	27.353	<0.001	1.007 (1.004 ~ 1.009)	22.792	<0.001
PDW	1.185 (1.117 ~ 1.258)	31.083	<0.001	1.016 (0.942 ~ 1.097)	0.173	0.678
NLR	2.064 (1.753 ~ 2.431)	75.537	<0.001	1.928 (1.619 ~ 2.295)	54.491	<0.001
PPR*	1.424 (1.328 ~ 1.527)	98.563	<0.001	1.378 (1.268 ~ 1.497)	57.016	<0.001

Abbreviations: BMI, body mass index; NLR, neutrophil count to lymphocyte count; PDW, platelet distribution width; PPR, platelet distribution width-to-platelet count ratio; Tg, thyroglobulin; TSH, thyroid stimulating hormone. PPR*, PPR was multiplied by 100, and its result were included in regression model.

TABLE 4 Diagnostic performances of PDW, NLR, PPR, and the combination of serum Tg for PTC

Indicators	AUC (95% CI)	*p*	Cutoff values	Sensitivity	Specificity
Tg	0.603 (0.568 ~ 0.638)	<0.001	59.385	40.8	79.0
PDW	0.610 (0.575 ~ 0.645)	<0.001	12.15	76.8	40.1
NLR	0.685 (0.652 ~ 0.717)	<0.001	2.131	58.6	69.7
PPR	0.706 (0.674 ~ 0.738)	<0.001	0.067	55.0	75.4
PDW + Tg	0.656 (0.622 ~ 0.689)	<0.001	0.476 3	64.4	59.9
NLR + Tg	0.714 (0.682 ~ 0.745)	<0.001	0.480 7	61.6	71.1
PPR+Tg	0.738 (0.708 ~ 0.768)	<0.001	0.505 0	60.0	74.7

Abbreviations: NLR, neutrophil-to-lymphocyte count; NLR + Tg, NLR combined with Tg; PDW, platelet distribution width; PDW + Tg, PDW combined with Tg; PTC, papillary thyroid cancer; PPR, platelet distribution width-to-platelet count ratio; PPR + Tg, PPR combined with Tg; Tg, thyroglobulin.

significantly associated with tumor burden and tumor extent. In this study, we observed that serum Tg had very low sensitivity and high specificity, as reported previously.[7] This highlights the limitations of diagnosis based on a single parameter, highlighting the need for a combined diagnosis.

Previous studies on PDW have predominantly focused on cardiovascular disease.[29,30] Cetin et al.[31] ever reported that PDW was a predictor of thrombolysis failure in acute ST-segment elevation myocardial infarction. Subsequently, it was confirmed that both cardiovascular disease and cancer were associated with activated platelets.[32,33] PDW, a marker of platelet morphology and activation, is a coefficient of variation of the platelet volume average. Compared with normal values, high PDW values indicate an unstable volumetric difference and can be a predictor of hepatocellular carcinoma and laryngeal cancer.[34,35] Nevertheless, the molecular mechanisms underlying the association between platelets and tumors remain to be elucidated. It has been suggested that tumors release inflammatory cytokines, including interleukin-6 and tumor necrosis factor-α, which promote platelet activation. Secretion of these factors by growing tumors accelerates heterogenic megakaryocytic maturation,[36] resulting in the production and secretion of immature platelets of various size into the bloodstream, thus leading to an increased PDW. Beksac et al.[37] and Bertol et al.[38] reported that IL-6 levels were higher in patients with PTC than in controls, highlighting the potential role of cytokines in PTC. Yu et al.[39] were the first to investigate PDW in thyroid cancer and reported that PDW was closely associated with the presence of thyroid cancer, which is inconsistent with previous studies. Yildiz et al.[40] retrospectively analyzed 228 patients with PTC and demonstrated that PDW and PLT did not facilitate the distinction between BTN from thyroid cancer. However, these indicators could be effective prognostic factors for PTC. These findings could be due to the small study population and/or susceptibility of single platelet indicators (PDW or PLT) to other factors. A study in patients with breast cancer by Takeuchi et al.[22] demonstrated that an elevated PPR significantly reduced disease-free survival in patients with breast carcinoma and further predicted patient prognosis. We observed an inverse relationship between PDW and PLT in PTC, suggesting the utility of combining these two variables as a ratio. Further, PDW and PPR values were higher in the PTC group than in the BTN and HC groups. Dincel et al.[20] and Sit et al.[41] reported that PLT was lower in patients with PTC than in HC, but there was no significant difference ($p > 0.05$). Of note, we observed that PLT was significantly lower in patients with PTC ($p < 0.05$), in agreement with findings in patients with other cancers, including non-small cell lung

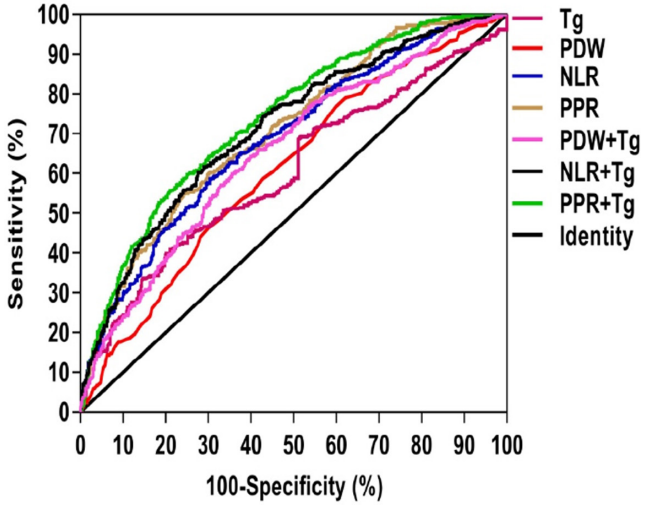

FIGURE 2 Diagnosed value of ROC analysis for identifying PTC. (A) Diagnostic performances of PDW, NLR, PPR, and the combination of serum Tg for distinguishing papillary thyroid cancer from benign thyroid nodule. NLR, neutrophil-to-lymphocyte ratio; NLR + Tg, NLR combined with Tg; PDW, platelet distribution width; PDW + Tg, PDW combined with thyroglobulin; PPR, platelet distribution width-to-platelet count ratio; PPR, PPR combined with Tg; Tg, thyroglobulin

cancer and epithelial ovarian cancer.[42,43] This could be underpinned by the complex role of inflammatory responses in thyroid carcinoma. Therefore, further investigations of this parameter using epidemiological, genetic, and molecular approaches are warranted.

Additionally, we observed that PDW and PPR were associated with capsule invasion, lymph node metastases, and advanced TNM stages (III-IV). In this regard, Machairas et al. reported that platelet indices (PDW) could inform extrathyroidal extension in PTC.[21] Wen et al.[44] retrospectively analyzed 558 patients newly diagnosed with PTC. Of patients, 82 were 55 years of age or older, whereas 476 patients were younger than 55 years of age. Their results demonstrated that preoperative PDW could predict coexistence with pathological features in elderly patients with PTC according to ROC curve. These data indicate that activated platelets are strongly associated with the invasive characteristics of PTC. Studies have demonstrated that P-choice elements, thromboxane A2, platelet-derived growth factor (PDGF), and other active substances are secreted by immature platelets in the tumor microenvironment during platelet activation.[29,45] A research group in Canada examined the association between PDGF (specifically, PDGF-α) signaling and lymph node metastases in PTC, and observed that PDGF-α promoted lymphatic metastases in PTC.[46,47] Moreover, studies have reported that activated platelets create a procoagulant microenvironment that enables tumor cells to cover themselves with platelets and escape from the host immune system,[48] which further promotes cell proliferation and contributes to the invasiveness of PTC.[9] Most tumor metastatic processes seem to be facilitated by the interaction between tumor cells and platelets.[11,49] Nevertheless, more detailed investigations are warranted to confirm their relationship with PTC.

To date, the most well-studied parameter in thyroid cancer is the NLR, but these studies have been restricted to prediction of cancer recurrence and prognosis. Seretis et al.[50] reported higher NLR levels in patients with thyroid cancer than in patients with BTN and suggested that NLR could be useful for distinguishing malignancy from BTN. This view has received support from others in the field.[51,52] Multivariate analyses in this study identified NLR and PPR as independent risk factors for PTC, implicating PPR and NLR in the pathogenesis and progression of PTC. ROC curve analysis revealed that PDW had a certain degree of diagnostic value for PTC (AUC, 0.61; 95% CI, 0.575 ~ 0.645) but low specificity, in accordance with the findings of Yu et al.[39] These findings indicate the limitations of single platelet indicators in the diagnosis of PTC. The combined measure of PPR and serum Tg (PPR + Tg) had a higher diagnostic value (AUC, 0.738; sensitivity, 60%; specificity, 74.7%) compared with PDW + Tg (AUC, 0.656; sensitivity, 64.4%; specificity, 59.9%) and NLR + Tg (AUC, 0.714; sensitivity, 61.6%; specificity, 71.1%). Accordingly, we propose that PPR is superior to NLR and PDW for predicting PTC. This combination may increase diagnostic accuracy and improve cost-effectiveness by reducing the need for repeated the use of high-cost techniques such as FNAC in cases with non-diagnostic test results. Further, our results suggest that the determination of tumor platelet status may facilitate the diagnosis of PTC. Collectively, the evidence reported herein supports the use of PPR as a biomarker for PTC. Considering the wide availability and accessibility of PPR, larger prospective studies verifying the role of PPR in PTC are needed.

This study has several limitations. First, patients who underwent routine blood examination and pathological biopsy were randomly selected as study participants, and patients who did not undergo pathological biopsy were excluded; therefore, the random sample was not included in the target population. Second, given the differences in dietary intake of iodized salt, serum Tg may be different from other countries. Although these results may not be representative of all patients with PTC, our study provide an objective, convenient and easy to popularize method to the differentially diagnosis of PTC, which can reduce unnecessary fine needle biopsy and diagnostic surgery, in order to relieve patients' psychological burden and reduce overdiagnosis. Of course, further prospective randomized controlled studies with large cohorts and multicenter are warranted to investigate the changes in PPR combined with serum Tg in benign and malignant thyroid diseases.

5 | CONCLUSION

To the best of our knowledge, this is the first study to demonstrate the utility of preoperative PPR combined with serum Tg for the diagnosis of PTC. Our findings revealed that the levels of PPR and serum Tg in patients with PTC was significantly higher than that in patients with BTN, and PPR has a higher diagnostic efficacy for PTC than NLR. In addition, the combination of PPR and serum Tg dramatically increased the accuracy of PTC diagnosis.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Changjiang Ying and Jin Jin contributed to conception and design of the research; Changjiang Ying was involved in obtaining financing and critical revision; Jin Jin was involved in preparing and writing the article; Guihua Wu participated in preparation of the article; Hongwei Ling, Chengwei Ruan, Xueman Zheng, and Ying Zhang participated in preparation of the article.

DATA AVAILABILITY STATEMENT

The datasets collected and analyzed during the current study are available from the corresponding author on reasonable request.

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