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Diagnostic value of preoperative hemogram parameters in patients with papillary thyroid cancer: An age- and sex-matched retrospective study

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ABSTRACT

Objective: The aim of this study was to evaluate the diagnostic value of preoperative hemogram parameters —platelet count (PLT), plateletcrit (PCT), platelet distribution width (PDW), mean platelet volume (MPV), and red cell distribution width (RDW)— in differentiating papillary thyroid carcinoma (PTC) from benign thyroid pathology in an age- and sex-matched patient series.

Material and Methods: A total of 2.080 patients who underwent total thyroidectomy at the Gazi University Faculty of Medicine, Department of General Surgery between January 2015 and January 2023 were retrospectively reviewed. After applying exclusion criteria and removing outliers, 1.955 patients were identified. Cases with a histopathological diagnosis of PTC were matched 1:1 with patients with benign thyroid pathology based on sex and 10-year age groups. The final analysis included 348 PTC patients and 348 benign patients (n=696). Preoperative hemogram parameters were compared between the groups using the Mann-Whitney U test, and the diagnostic value was assessed using receiver operating characteristic (ROC) curve analysis.

Results: After matching, no significant difference was found between groups in terms of age (48.0±12.7 vs. 48.3±12.9 years; p=0.754) or sex distribution (p=0.930). None of the parameters —PLT (277.0±70.4 vs. 275.7±69.1 $\times 10^9$/L; p=0.723), PCT (0.270±0.072 vs. 0.270±0.075; p=0.680), PDW (14.1±2.9 vs. 13.8±2.8; p=0.300), MPV (9.54±1.33 vs. 9.42±1.14 fL; p=0.591), or RDW (13.8±1.4 vs. 14.1±1.5; p=0.053)— showed a statistically significant difference between groups. ROC analysis confirmed that none of the parameters demonstrated meaningful diagnostic value (AUC: PLT 0.508, PCT 0.510, PDW 0.473, MPV 0.488, RDW 0.543).

Conclusion: When age- and sex-matching are applied, preoperative PLT, PCT, PDW, MPV, and RDW values do not provide meaningful discrimination between PTC and benign thyroid pathology. Positive findings reported in the literature may be partly attributable to demographic confounding. The potential diagnostic value of combined indices or integration with other complete blood count parameters warrants investigation in prospective studies.

Keywords: Papillary thyroid carcinoma, mean platelet volume, platelet distribution width, plateletcrit, red cell distribution width, hemogram parameters

INTRODUCTION

Thyroid cancer is the most common malignancy of the endocrine system, and its incidence has markedly increased worldwide in recent years. This rise is largely attributed to papillary thyroid carcinoma (PTC), which is both the most common and the least aggressive subtype among all thyroid cancers (1-3). Although fine-needle aspiration biopsy (FNAB) remains the gold standard for preoperative diagnosis of PTC, this method has notable limitations, including inadequate sampling and operator dependency (4). These shortcomings have driven interest in inexpensive and readily accessible complete blood count (CBC) parameters obtainable from routine preoperative blood tests.

The role of chronic inflammation in cancer development, progression, and metastasis is increasingly well understood. Platelets play a pivotal role in this process, actively contributing to tumor angiogenesis, formation of the metastatic niche, and immune evasion (5). The morphological changes induced by platelet activation are reflected in hemogram parameters such as platelet distribution width (PDW), mean platelet volüme (MPV), platelet count (PLT), plateletcrit (PCT) and red cell distribution width (RDW). Among these, MPV and PDW have attracted particular attention; the fact that PDW increases only during pseudopod formation rather than simple platelet swelling makes it a more specific marker of activation compared to MPV (6).

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The results of studies examining these parameters specifically in PTC are conflicting. While some studies have reported significantly elevated MPV in PTC compared to benign nodules and attributed diagnostic value to it (7,8), others have failed to detect any significant intergroup difference (9,10). Studies reporting lower PDW in PTC coexist alongside those reporting higher values (10,11). These contradictory findings point to two main methodological issues: Small sample sizes and lack of age and sex matching. Since PTC is considerably more prevalent in women and middle-aged individuals, unmatched comparisons may mask or exaggerate the true diagnostic value of these parameters due to demographic confounding.

The aim of this study was to evaluate the discriminatory ability of preoperative values of PLT, PCT, PDW, MPV, and RDW to distinguish PTC from benign thyroid disease in a large, age- and sex-matched (1:1) series of patients operated on at Gazi University Faculty of Medicine, Department of General Surgery between January 2015 and January 2023.

MATERIAL and METHODS

Study Design and Patient Selection

This study retrospectively reviewed data from patients who underwent total thyroidectomy at Gazi University Faculty of Medicine, Department of General Surgery, between January 2015 and January 2023. The study protocol was approved by the Gazi University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision number: 598, date: 17.07.2023) and carried out in accordance with the principles of the Declaration of Helsinki. The university hospital obtains general consent from all patients upon admission for the use of anonymized clinical data in scientific research. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria were as follows: (1) Age ≥18 years, (2) total thyroidectomy performed, (3) availability of postoperative histopathological diagnosis, and (4) availability of preoperative complete blood count data. Patients meeting any of the following criteria were excluded: (1) Thyroid dysfunction (TSH <0.27 or >4.2 mIU/L), as both hypothyroidism and hyperthyroidism are known to independently affect platelet indices; (2) history of chronic inflammatory or autoimmune disease such as type 2 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel disease; (3) history of hematological disorders such as thrombocytopenia, thrombocytosis, or myeloproliferative disease; (4) active infection or suspicion of infection within two weeks of admission; (5) use of anticoagulant, antiplatelet, or steroid medications; (6) history of concurrent or prior malignancy; and (7) pregnancy.

Patient selection was carried out in three stages. In the first stage, 2.080 patients who underwent total thyroidectomy within the specified period were screened. In the second stage, the inclusion and exclusion criteria were applied; patients with extreme hemogram values that were deemed clinically implausible were also excluded for data quality reasons. This resulted in the exclusion of 125 patients (6.0%), leaving 1.955 patients (784 PTC, 1.171 benign) eligible for analysis. In the third stage, 1:1 matching based on age and sex was applied to minimize the effect of potential confounders. Matching was performed based on the same sex and 10-year age group (20-29, 30-39, 40-49, 50-59, 60-69, ≥70 years), with one benign patient assigned to each PTC patient. The sample size was determined based on similar studies in the literature. A total of 350 patients were randomly selected from the 784 PTC cases, and matching was applied. As suitable benign matches could not be found for 2 patients, they were excluded. This process yielded two groups of 348 patients each, totaling 696 patients included in the final analysis. The patient selection process is illustrated by a flow diagram in Figure 1.

Hemogram Parameters and Laboratory Method

Preoperative venous blood samples were collected from the antecubital vein the morning before surgery, after at least 8 hours of fasting, and transferred into K_2EDTA tubes (1.8 mg/mL). All hemogram measurements were performed within 2 hours of sample collection using an automated hematology analyzer (Sysmex XN-1000, Sysmex Corporation, Kobe, Japan). To standardize measurements, all samples were analyzed in the same laboratory using the same device.

The parameters included in the study were (PLT, $\times 10^9$/L), (PCT, %), (PDW, %), mean platelet volume (MPV, fL), and red cell distribution width (RDW, %). PLT, MPV, and PCT were measured directly by the analyzer; PDW reflects the breadth of platelet volume distribution and indicates platelet size heterogeneity. RDW is an indicator of anisocytosis, calculated by dividing the standard deviation (SD) of erythrocyte volume by the mean corpuscular volume.

Extreme values considered clinically implausible or attributable to data entry errors were excluded from analysis. For this purpose, measurements falling outside the following reference ranges were excluded: PLT 50-800 $\times 10^9$/L, MPV 5-15 fL, PDW 8-25%, PCT 0.01-1.0%, RDW 10-20%.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD and median (minimum-maximum). Normality of distribution was assessed using the Shapiro-Wilk test; the Mann-Whitney U test was used for intergroup comparisons. Categorical variables were compared using the chi-square test. The diagnostic value of the parameters was evaluated by receiver operating characteristic (ROC) curve analysis; the area under the curve (AUC), cut-off value, sensitivity, and specificity were calculated. A p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 2,080 patients were initially included. After excluding 125 patients who did not meet the inclusion criteria and removing outliers, 1.955 patients remained. Of the 784 patients with a histopathological diagnosis of PTC, 350 were randomly selected; 2 patients could not be matched by age and sex. The final analysis included 348 PTC patients and 348 benign thyroid pathology patients, for a total of 696 patients.

Matching was successful; no statistically significant difference was found between the groups regarding age (benign: 48.0±12.7 years, PTC: 48.3±12.9 years, p=0.754) or sex distribution (p=0.930). Patient demographic characteristics and preoperative hemogram parameters are summarized in Table 1.

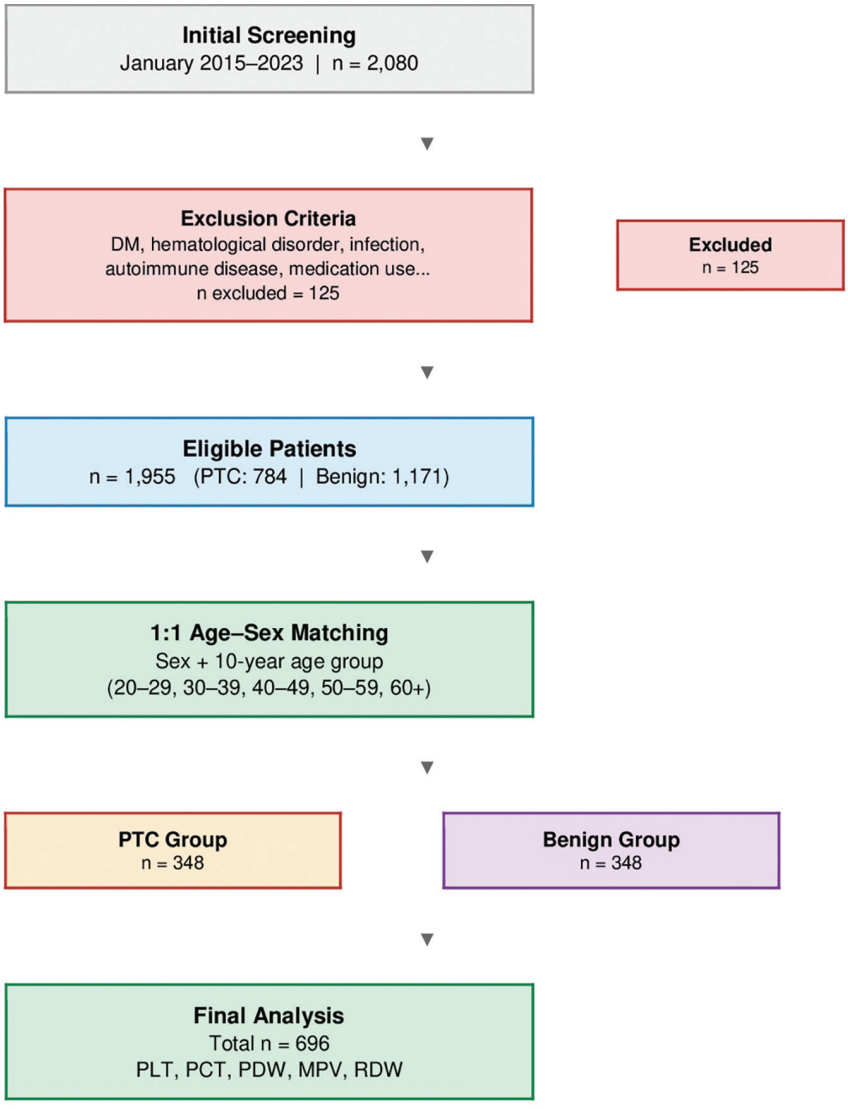

Figure 1. Patient selection flow diagram.

DM: Diabetes mellitus, PTC: Papillary thyroid carcinoma, PLT: Platelet count, PCT: Plateletcrit, PDW: Platelet distribution width, MPV: Mean platelet volume, RDW: Red cell distribution width

Intergroup Comparison of Hemogram Parameters

PLT, PCT, PDW, MPV, and RDW values did not differ significantly between the PTC and benign groups (p>0.05 for all parameters).

PLT values were 277.0±70.4 $\times 10^9$/L in the benign group and 275.7±69.1 $\times 10^9$/L in the PTC group (p=0.723). PCT values were 0.270 in both groups (benign: 0.270±0.072; PTC: 0.270±0.075; p=0.680). PDW was 14.1±2.9 in the benign group and 13.8±2.8 in the PTC group (p=0.300). MPV was 9.54±1.33 fL in the benign group and 9.42±1.14 fL in the PTC group (p=0.591). RDW was 13.8±1.4 in the benign group and 14.1±1.5 in the PTC group; this difference approached but did not reach statistical significance (p=0.053).

ROC Curve Analysis

None of the parameters demonstrated statistically significant diagnostic value in differentiating PTC from benign thyroid pathology. AUC values were 0.508 [95% confidence interval (CI): 0.466-0.550] for PLT, 0.510 (95% CI: 0.468-0.552) for PCT, 0.473 (95% CI: 0.430-0.516) for PDW, 0.488 (95% CI: 0.446-0.530) for MPV, and 0.543 (95% CI: 0.501-0.585) for RDW. All values were close to the reference line (AUC=0.500), indicating no meaningful discriminatory power (Table 2).

DISCUSSION

In a large series comprising 696 age- and sex-matched patients, preoperative PLT, PCT, PDW, MPV, and RDW values did not differ significantly between patients with PTC and those with benign thyroid pathology. ROC curve analysis further confirmed that none of the parameters carried clinically acceptable diagnostic value. This negative result conflicts with the positive findings of previous studies that had methodological limitations such as small sample sizes and lack of matching, and suggests that the true contribution of these parameters to PTC diagnosis warrants reassessment.

Platelets function not as passive bystanders but as active participants in tumor biology. Gkolfinopoulos et al. (5) comprehensively demonstrated that platelets play a critical role in tumor metastasis through three main mechanisms: Preparation of the metastatic niche via extracellular matrix formation and granulocyte recruitment, support of neoangiogenesis through vascular endothelial growth factor and platelet-derived growth factor secretion, and facilitation of immune evasion by suppressing natural killer cells. These biological functions lead to activation of platelets, which interact with tumor cells and in turn cause morphological changes reflected in parameters such as MPV and PDW (6). Vagdatli et al. (6) demonstrated that PDW increases only during pseudopod formation and not with simple platelet swelling, highlighting its greater specificity as an activation marker compared to MPV. Detopoulou et al. (12) reported that hemogram indices are associated with inflammation and tumor progression in many cancer types, but also noted that these associations vary considerably by cancer type and methodology used. This biological basis has accelerated interest in the potential diagnostic value of hemogram parameters in cancer, yet results from PTC-specific studies remain controversial.

Table 1. Comparison of demographic characteristics and hemogram parameters between groups

Parameter	Benign (n=348)	PTC (n=348)	Reference range	p-value
Age (years), mean ± SD	48.0±12.7	48.3±12.9	-	0.754
Sex (F/M), n	264/84	262/86	-	0.930
PLT ($\times 10^9$/L), mean ± SD	277.0±70.4	275.7±69.1	**150-400**	0.723
PCT (%), mean ± SD	0.270±0.072	0.270±0.075	**0.190-0.390**	0.680
PDW (%), mean ± SD	14.1±2.9	13.8±2.8	**9.0-17.0**	0.300
MPV (fL), mean ± SD	9.54±1.33	9.42±1.14	**7.5-12.5**	0.591
RDW (%), mean ± SD	13.8±1.4	14.1±1.5	**11.5-14.5**	0.053

PTC: Papillary thyroid carcinoma, PLT: Platelet count, PCT: Plateletcrit, PDW: Platelet distribution width, MPV: Mean platelet volume, RDW: Red cell distribution width, F: Female, M: Male, SD: Standard deviation. Reference ranges are based on Sysmex XN-1000 analyzer specifications.

Table 2. ROC curve analysis results

Parameter	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)
PLT	0.508 (0.466-0.550)	275.4	48.6	56.3
PCT	0.510 (0.468-0.552)	0.222	69.8	32.9
PDW	0.473 (0.430-0.516)	12.1	73.3	33.0
MPV	0.488 (0.446-0.530)	8.1	85.3	16.2
RDW	0.543 (0.501-0.585)	13.8	50.1	56.5

AUC: Area under the curve, CI: Confidence interval, PLT: Platelet count, PCT: Plateletcrit, PDW: Platelet distribution width, MPV: Mean platelet volume, RDW: Red cell distribution width, ROC: Receiver operating characteristic.

The direction of findings in the literature on MPV in PTC is inconsistent. Baldane et al. (7) found preoperative MPV values to be significantly elevated in PTC patients compared to benign goiter and healthy controls (8.05, 7.57, and 7.36 fL respectively; p=0.001) in a study of 126 patients, and also observed a significant postoperative decrease. These findings suggest that MPV may be a dynamic marker related to tumor burden. Sit et al. (8) reported significantly higher MPV in malignant compared to benign nodules (9.1±1 vs. 7.8±0.8 fL; p<0.001) in a larger series of 199 patients, with an AUC of 0.84 at a cut-off of 8.25 fL.

In contrast, other studies have not supported these findings. Yaylaci et al. (10) found no significant difference in MPV between PTC and benign goiter groups (9.1±1.3 vs. 9.0±1.1 fL; p=0.697) in a series of 79 patients. Similarly, Machairas et al. (9) demonstrated that MPV did not carry discriminatory value between PTC and multinodular hyperplasia (p=0.283) in 228 patients, although MPV was found to be lower in the presence of multifocality. Yildiz et al. (13) showed significantly elevated MPV in PTC cases with tumor diameter greater than 1 cm in a series of 90 patients and interpreted this as a prognostic marker. Yu et al. (14) unexpectedly reported significantly lower MPV in thyroid cancer patients compared to controls (9.1±1.3 vs. 10.0±1.2 fL; p<0.001); this contradictory result may stem from the inclusion of different thyroid cancer histotypes (papillary, follicular, medullary) within the same group. In our study, after age and sex matching, MPV was 9.54±1.33 fL in the benign group and 9.42±1.14 fL in the PTC group, with no significant difference (p=0.591). Given that the majority of studies that reported high AUC values did not perform matching and used healthy control groups, demographic differences may have played a determining role in the reported positive outcomes.

The direction of PDW findings is also inconsistent across studies. Dincel and Bayraktar (11) reported significantly lower PDW in PTC patients compared to benign goiter and healthy controls (18.24±2.34 vs. 19.34±2.24 and 19.33±1.24; p<0.01). Yaylaci et al. (10) similarly found significantly lower PDW in the PTC group compared to the benign group (15.4±1.7 vs. 16.3±1.2; p=0.013). In contrast, Jin et al. (15) demonstrated significantly higher PDW in the PTC group compared to benign nodules and healthy controls in a large series of 1.001 patients, and showed that the combination of PDW/PLT ratio (PPR) with serum thyroglobulin (AUC=0.738) substantially increased the diagnostic value over PDW alone (AUC=0.610). Yu et al. (14) also reported higher PDW in thyroid cancer patients compared to controls (16.5±1.4 vs. 15.1±2.1; p<0.001). Deniz (16) proposed a novel index in a study comparing PTC with benign thyroid nodules and showed that the PLR/PDW ratio (AUC=0.827) had superior diagnostic value compared to PLR (AUC=0.786) or PDW alone. Machairas et al. (9) found lower PDW in T3 tumors but could not detect a significant difference between PTC and benign pathology. Li et al. (17) reported that PDW predicted lateral lymph node metastasis in medullary thyroid carcinoma (AUC=0.645), drawing attention to the prognostic potential of PDW. In our study, PDW was 14.1±2.9 in the benign group and 13.8±2.8 in the PTC group, with no significant difference (p=0.300; AUC=0.473). The contradictory directional findings in the literature indicate that the role of PDW in thyroid cancer has yet to be established, raising the question of whether PDW reflects a genuine biological signal or merely reflects methodological differences.

PCT, calculated from PLT and MPV, is an indicator of platelet mass. Dincel and Bayraktar (11) reported significantly elevated PCT in PTC patients (0.24±0.05 vs. 0.19±0.04; p<0.01). Yaylaci et al. (10) did not find a significant difference in PCT between groups. Machairas et al. (9) found no difference in PCT between PTC and benign groups but demonstrated significantly elevated PCT in tumors with extrathyroidal extension (p=0.012). Yilmaz et al. (18) reported that PCT was associated with clinicopathological features in PTC patients. In our study, PCT was 0.270 in both groups, with no significant difference (p=0.680). This finding supports the hypothesis that PCT may be related not to intergroup differences but to intraoperative tumor characteristics.

RDW is an indicator of heterogeneity in erythrocyte size and is used as a marker of inflammation and malnutrition. Han et al. (19) found significantly higher RDW in the PTC group compared to 400 healthy controls (13.13±0.85 vs. 12.40±0.58; p<0.001) in a study of 780 PTC patients, with an AUC of 0.808. However, the control group in that study consisted of healthy individuals rather than patients with benign thyroid nodules. In our study, RDW was 13.8±1.4 in the benign group and 14.1±1.5 in the PTC group; this difference approached but did not reach statistical significance (p=0.053; AUC=0.543). This borderline result warrants re-examination, particularly with larger sample sizes.

The majority of studies investigating the relationship between PLT and PTC have found no significant difference. Yildiz et al. (13) found no significant difference in PLT between PTC and nodular hyperplasia (265,981±57,340 vs. 241,783±63,289; p=0.062). Dincel and Bayraktar (11) also reported similar PLT values between groups. Machairas et al. (9) showed that PLT was unrelated to tumor size and lymphovascular invasion but was significantly elevated in T3 tumors with extrathyroidal extension. In contrast, Jin et al. (15) found significantly lower PLT in the PTC group compared to the benign group. In our study, PLT was 277.0±70.4 $\times 10^9$/L in the benign group and 275.7±69.1 $\times 10^9$/L in the PTC group, with no significant difference (p=0.723), consistent with the prevailing trend in the literature.

The contradictory findings in the literature are thought to stem largely from methodological differences. Since PTC is considerably more prevalent in women and middle-aged

individuals, demographic factors can introduce significant confounding in unmatched studies. Additionally, the following factors complicate the interpretation of the results: Whether the control group consists of patients with benign thyroid nodules or healthy individuals; the potential effect of analyzer type on MPV and PDW measurements; whether the interval between blood collection and measurement was standardized; and the adequacy of sample size. Vagdatli et al. (6) demonstrated that MPV increases with storage time while PDW decreases, clearly illustrating the extent to which non-standardized preanalytical conditions can affect measurements.

The most fundamental strength of the present study is the application of 1:1 age-sex matching, which minimizes demographic confounding that was overlooked in the majority of previous studies and provides a stronger basis for the validity of our negative finding. Given that FNAB may be inadequate in certain cases, particularly in nodules ≥3 cm (4), routine hemogram parameters appear insufficient to fill this diagnostic gap.

The clinical implications of these findings are noteworthy. The absence of discriminatory power in these widely available and inexpensive parameters suggests that clinicians should not rely on routine hemogram indices as standalone preoperative tools for differentiating PTC from benign thyroid pathology. In clinical practice, normal or elevated MPV, PDW, or RDW values should neither reassure nor alarm the clinician regarding malignancy risk. The diagnostic workup should continue to rely on ultrasonographic evaluation and FNAB as the primary modalities. Nevertheless, these parameters may still be valuable when integrated into multiparametric models or combined with established markers (e.g., thyroglobulin) or with ultrasonographic risk stratification systems. Future research should focus on developing and validating such composite scoring systems in prospective multicenter settings.

As PTC incidence continues to rise (1,3), the need for inexpensive and readily accessible CBC parameters to strengthen preoperative diagnosis persists. However, the present findings indicate that hemogram parameters used individually are insufficient to meet this need. As demonstrated by Deniz (16) with the PLR/PDW combination and by Jin et al. (15) with the PPR plus thyroglobulin combination, indices combining multiple parameters may offer more promising diagnostic performance than single parameters alone. This suggests that future studies should focus on combined indices rather than individual parameters.

Study Limitations

This study has several important limitations. First, its retrospective design carries the risk of selection bias. Second, PCT is not directly measured by some automated analyzers; instead, it is calculated from PLT and MPV, which may limit the reliability of PCT data. Third, although TSH values were used as an exclusion criterion, potential confounders such as thyroid autoantibodies, Hashimoto's thyroiditis, and nodule size were not separately controlled for in the analysis. Fourth, although the study was conducted at a single center, the large sample size partially offsets this limitation. Fifth, neutrophil counts and red blood cell indices were not recorded in this study, precluding the evaluation of combined inflammatory parameters, such as the neutrophil-to-lymphocyte ratio and red blood cell indices. Prospective studies incorporating these parameters alongside platelet indices may provide a more comprehensive assessment of hemogram-based diagnostic tools in PTC.

The study also has important strengths. Unlike most similar studies, 1:1 age-sex matching was applied, thereby systematically controlling for demographic confounding inherent to the epidemiological characteristics of PTC. Furthermore, the sample size of 696 patients substantially exceeds that of most studies in this field. Performing all hemogram measurements on the same analyzer in the same laboratory under standardized conditions minimizes preanalytical variability. Finally, the eight-year study period enables the sample to capture seasonal and annual biological fluctuations.

CONCLUSION

In this study, preoperative PLT, PCT, PDW, MPV, and RDW did not differ significantly between papillary thyroid carcinoma and benign thyroid pathology in a large age- and sex-matched patient series, and none showed clinically acceptable diagnostic value.

Given that a substantial proportion of the positive findings in the literature derive from studies that lack demographic matching, have small sample sizes, and include heterogeneous control groups, the methodological strengths of the present study suggest that this negative result reflects a genuine biological signal. The disappearance of statistically significant differences after matching implies that previously reported positive findings may have been at least partly due to demographic confounding.

These findings indicate that the parameters examined do not provide a meaningful contribution to the preoperative diagnosis of PTC when used individually. Nevertheless, the possibility that novel indices combining multiple parameters or approaches integrating these parameters with other established markers, such as thyroglobulin, may enhance diagnostic value appears to be worth investigating. Future prospective, multicenter studies conducted under standardized preanalytical conditions will more reliably establish the true role of hemogram parameters in thyroid cancer diagnosis.

Ethics

Ethics Committee Approval: The study protocol was approved by the Gazi University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision number: 598, date: 17.07.2023) and carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Footnotes

Author Contributions

Concept - E.G., Y.F.A., Ç.B., M.A.; Design - E.G., Y.F.A., Ç.B., M.A.; Data Collection or Processing - E.G., E.A., Ç.B., M.A.; Analysis or Interpretation - E.G., Y.F.A.; Literature Search - E.G., Y.F.A., E.A.; Writing - E.G.

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