Role of hematological and platelet parameters in diagnosis of papillary thyroid carcinoma

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Abstract

Objective

Thyroid cancer is the most common cancer of the endocrine and is apparent in about 5 percent of thyroid nodules. Platelets have been shown to play an important role in chronic inflammation, cancer progression, and metastases. Recent research has been done on the correlation between platelet factor and many other types of cancer. This study aimed to investigate the diagnostic accuracy of platelet factor and other CBC parameters in papillary thyroid carcinoma.

Material and Methods

Thirty hundred and fifty patients were divided into two groups retrospectively. Group 1: papillary thyroid carcinoma patients (n = 150). Group 2: normal healthy subjects (n = 200). PLT, MPV, PDW, and CBC parameters were compared between groups, and $p < 0.05$ was accepted as significant

Results

The neutrophil count and NLR (neutrophil to lymphocyte ratio) were significantly higher, while the Hb, PLT, MPV, RDW, lymphocyte, and monocyte count, were significantly lower in patients compared with the control group. These parameters scored low in all parameters of diagnostic accuracy, with overall accuracy ranging between 41 and 66%.

Conclusions

NLR, MPV, and PLT are relatively inexpensive and widely available from routine blood tests. Although we found higher NLR values and lower PLT and MPV values in patients with papillary thyroid carcinoma, these factors cannot effectively diagnose thyroid cancer.

Introduction

The most common endocrine malignancy is thyroid cancer and is found in approximately 5% of thyroid nodules[1,2]. There are four main types of thyroid cancer: papillary, follicular, medullary (solid amyloid), and anaplastic[3–5]. Over the past few decades, the prevalence of thyroid cancer (mainly papillary carcinomas) has increased rapidly [6,7].

The most prominent primary thyroid malignancy is papillary thyroid carcinoma (PTC), which accounts for 85–90% of all thyroid cancers[8]. Papillary thyroid microcarcinoma (PTMC) is a PTC with a diameter of less than 10 mm and is often multifocal[9,10].

In most malignancies, early diagnosis is the only chance for cure. For this main reason, physicians have made great strides over the years to develop screening approaches that would allow early cancer diagnosis. Although some markers for certain types of cancer have been identified, a suitable method of diagnosis has yet to be discovered. For routine use, this diagnostic method must be available, cheap, and easy to interpret.

Platelets play an important role during chronic inflammation, cancer development, and metastasis through their secretions of pro-inflammatory factors, chemokines, and growth factors [11]. The majority of malignant patients are vulnerable to hypercoagulability. Platelets release angiogenic growth factors in these patients and by adhering to tumor capillaries potentially leads to thrombosis[12].

PLT, MPV, and PDW are three CBC platelet-related parameters[11]. In recent years, studies have shown that PLT and its indices can be used as inflammatory markers in cancer cases [13,14]. MPV is a correlated marker with functional shifts in platelets but does not represent microscopic changes and can be easily measured with commonly used hemocytometers [15,16]. Larger platelets are more involved in metabolism and enzymes than smaller platelets[17]. PDW is determined as the coefficient of variance of the mean platelet volume. High PDW values indicate that the change in mean platelet volume is more than average. Previously, the association between MPV and many other types of cancer was studied[18–21].

Based on the assumption that tumors induce a systemic inflammatory reaction that can be reflected by the neutrophil-to-lymphocyte ratio (NLR), Seretis et al. were among the first groups to study the potential association between papillary thyroid carcinoma and NLR and suggested that NLR could predict occult PTMC in otherwise benign goiters[22].

There are very few studies evaluating the supporting role of platelet function parameters in PTC cases, and the findings of these tests are highly controversial.

The purpose of this study is to investigate whether hematological and platelet factors would be valuable inflammatory markers in the differential diagnosis of benign and malignant thyroid disorders.

Material And Method

2.1. patients

This retrospective case-control study analysis was performed in Imam Reza Hospital, Kermanshah between October 2018 and June 2019. The research design was approved by the ethical committee and institutional review board of Kermanshah (university of m Medical Sciences (IR.KUMS.REC.1397.698 (where the study was conducted.

We reviewed the medical records of 152 patient who had a total thyroidectomy which selected by random sampling Patients who have had acute or chronic infection, hypertension, renal failure, nutritional anemia or iron deficiency diabetes mellitus, chronic inflammatory disease or autoimmune disease, heart failure,

myeloproliferative disorders, other known malignancy, hepatic or renal disorders, taking anticoagulation medicine and thyroid-stimulating hormone (TSH) outside the normal range were excluded from the study. Patients with lobectomy and the pathology of patients with medullary thyroid cancer were also excluded from the study.

A simple random sampling method was used to select 200 healthy individuals with normal TSH and thyroid autoantibodies and their regular thyroid ultrasound test findings as a healthy control group. As a consequence, all patients were classified into three groups: PTC patients in Group 1 (n = 150), and healthy controls in Group 2 (n = 200).

Pathology reports were checked separately by two authors to determine final diagnosis and ensure that exclusion criteria were correctly met in any applicant for enrollment in our study2.2. Data collection and test

Patients were assessed for age, gender, white blood cell count (WBC), lymphocyte count, neutrophil count, monocyte count, PLT, PDW, MPV, RDW, NLR and PLR (Platelet to lymphocyte ratio). All blood samples were obtained from the venous system between 7:30 AM and 9:00 AM, collected through the cephalic vein in potassium ethylenediaminetetraacetate tubes, and measured using an automated counter of blood cells (Sysmex XT 1800 I, Japan).

2.3. Sensitivity and specificity value:

Sensitivity, specificity of positive predictive value (PPV), and negative predictive value (NPV) of these tests were also identified.. The area under the receiver operating characteristic (ROC) curve was used to calculate the sensitivity and specificity of cut-off points, predictive positive and negative values, and likelihood ratios. The confidence interval (CI) was set at 95% and the P-value < 0.05 was found statistically significant. The cutoff point for the MPV in our analysis was 7.6 FL. The reference values were (4–10) 1 000 / mm3 for WBC, (12–18) g / dL for hemoglobin (Hb), 40% -70% for neutrophils, (140–440) 1 000 / mm3 for PLT, 11% -16% for RDW, 8.5–12.5 FL for MPV, 10–17 FL for PDW, 17% -45% for platelet larger cell ratio 36% -50% for hematocrits.

2.4. Statistical analysis

All analyses were performed using SPSS, version 20. Descriptive qualitative data were presented as numbers and percentage values, while all quantitative parameters were presented as mean scores, standard deviations, interquartile ranges (IQR) ranges, and medians. To evaluate normal distribution, the Kolmogorov-Smirnov test was implemented. al, the Chi-square method was performed to compare qualitative data followed by an independent t-test. Nonparametric results were compared using the Mann-Whitney method.

Results

A total of 150 patients (papillary and follicular) with a preoperative diagnosis of thyroid cancer were included in the current study. Of these 47 (31,3%) were males and 103 (68,7%) females, with a male to female ratio of1:2,19. Their age ranged from 21 to 86 years with a mean of 41,84 ± 14,06. The comparisons of demographic and laboratory values between the groups are shown in Tables 1 and 2.

There were statistically significant differences between patients and control groups regarding all the studied parameters except the mean WBC, RBC, PDW, PLCR, and PLR.

The neutrophil count and NLR (neutrophil to lymphocyte ratio) were significantly higher, while the Hb, PLT, MPV, RDW, lymphocyte, and monocyte count, were significantly lower in patients compared with control group. Higher PLT of the patients ($p = .001$) and RDW ($p = .005$), were found in patients with papillary thyroid carcinoma when compared with follicular thyroid carcinoma.

In the ROC curve analysis, both NLR and PLR fared poorly. For the NLR, neutrophil count, Hb, PLT, MPV, RDW, lymphocyte and monocyte count the area under the ROC curve (AUC) was 0.41, 0.63, 0.58, 0.61, 0.57, 0.66, 0.58 and 0.57 (Fig. 3).

Data on the predictive power of variables in cases of thyroid cancer and ROC analysis are provided in Table 3 and Fig. 1.

Table 1
The main characteristic and CBC data of patients with thyroid cancer and controls

Parameter	Statistical Information	Thyroid cancer (n = 150)	Controls (n = 200)	p_value
Age (years)	Mean ± SD	41.84 ± 14.06	39.06 ± 18.204	0.208£
	Range	21–86	1–85	
Gender	Male (%)	47 (31.3%)	86 (43%)	0.029¥
	Female (%)	103 (68.7%)	114 (57%)	
WBC count (x 10^9 /L)	Mean ± SD	8.28 ± 2.71	8.34 ± 3.51	0.196±
	Range	1.50 ± 20.20	3.72 ± 23.60	
RBC (x 10^6/µL)	Mean ± SD	4.68 ± .61950	4.7 ± .51316	0.140£
	Range	3.41–7.13	2,56 – 6,24	
Hb	Mean ± SD	13.34 ± 1.89	13.81 ± 2.36	0.010±
	Range	9.30 ± 19.80	7,20–37,90	
PLT	Mean ± SD	233.06 ± 66.45	257.17 ± 58.14	0.000±
	Range	67–471	151–439	
MPV	Mean ± SD	9.70 ± 1.30	9.87 ± 0.81	0.016±
	Range	7.30–15.50	8-14.40	
PDW	Mean ± SD	12.15 ± 2.15	11.81 ± 1.81	0.450±
	Range	8.4–20.10	1.7–22,30	
PLCR	Mean ± SD	23.06 ± 7.49	24.06 ± 5.54	0.099±
	Range	7.8–45.80	3.18-56,70	
RDW	Mean ± SD	13.45 ± 2.39	13.93 ± 1.35	0.000±
	Range	4.2–31.7	11,5–23,90	
Neutr	Mean ± SD	63,53 ± 12.20	57.51 ± 14.10	0.000±
	Range	34–92	6,34–91,1	
Lymph	Mean ± SD	28.37 ± 11.96	31.76 ± 12.62	0.015±
	Range	4–88	5.7–72	
Mono	Mean ± SD	7.35 ± 2,22	7.86 ± 2,18	0.016±
	Range	1–15	2.9–11,70	

Parameter	Statistical Information	Thyroid cancer (n = 150)	Controls (n = 200)	p_value
NLR	Mean ± SD	3.31 ± 3.48	2.62 ± 2.76	.002±
	Range	0.61–22.25	0.29–15.98	
PLR	Mean ± SD	10.65 ± 8.12	10.40 ± 8.29	.782±
	Range	1.66-58	2.63–58.14	

¥ Chi-square test, £ independent t-test, ± Mann-Whitney, WBC: white blood cell; RBC; red blood cell; Hct; hematocrit; Hb: hemoglobin; PLT: platelet; MPV: mean platelet volume; PDW: platelet distribution width;

PLRC: Platelet large cell ratio; RDW: red blood cell distribution width; Mono: monocyte; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

Table 2
The main characteristic and CBC data of papillary and follicular cancer

Parameter	Statistical Information	papillary (n = 129)	follicular (n = 17)	Controls (n = 200)	p_1	p_2	p_3
Age (years)	Mean ± SD Range	40□75 ± 13,47 21–86	47,47 ± 16,81 24–79	39.06 ± 18.204 1–85	0.508	.081	.111£
Gender	Male (%) Female (%)	41 (31.8%) 88 (68.2%)	5 (29.4%) 12 (70.6%)	86 (43%) 114 (57%)	p > 0.05	p > 0.05	p > 0.05¥
WBC count (x 10^9 /L)	Median (IQR) Range	8,20 ± 2,69 1,50 – 20,20	8,28 ± 2,37 3,9–13,90	8.34 ± 3.51 3.72 ± 23.60	.0.357	.283	.451±
RBC (x 10^6/µL)	Mean ± SD Range	4,66 ± 0.58 3,41-6.22	4,82 ± 0.87 4,06–7,13	4.7 ± .51316 2,56 – 6,24	0.148	.466	.914£
Hb	Median (IQR) Range	13.35 ± 1,86 9,30 – 19	13,54 ± 2,28 11,10–19,80	13.81 ± 2.36 7,20–37,90	0.022	.187	.867±
PLT	Median (IQR) Range	233,65 ± 63,34 67–471	197,82 ± 72,3 81–332	257.17 ± 58.14 151–439	.004	.001	.020±
MPV	Median (IQR) Range	9.62 ± 1,22 7,30 – 15	10,37 ± 1,79 7,8–15,50	9.87 ± 0.81 8–14,40	0.003	.217	.054±
PDW	Median (IQR) Range	12,06 ± 2,12 8,40 – 20,10	12,80 ± 2,34 9,5–17,10	11.81 ± 1.81 1.7–22,30	0.803	.098	.213±
PLCR	Median (IQR) Range	22,69 ± 7,45 7.8–45,80	25,94 ± 7,71 11,6–38,20	24.06 ± 5.54 3.18-56,70	.023	.141	.068±
RDW	Median (IQR) Range	13,48 ± 2,50 4,20–31,70	13,41 ± 1,78 11,8–19,5	13.93 ± 1.35 11,5–23,90	.000	.005	.531±

Parameter	Statistical Information	papillary (n = 129)	follicular (n = 17)	Controls (n = 200)	p_1	p_2	p_3
Neutr	Median (IQR)	63,39 ± 11,64	62,91 ± 14,92	57.51 ± 14.10	.000	.111	.937±
	Range	40,80–92	34–83	6,34–91,1			
Lymph	Median (IQR)	28,62 ± 11,59	28,32 ± 13,65	31.76 ± 12.62	0.028	.288	.886±
	Range	4–88	10–56	5.7–72			
Mono	Median (IQR)	7,30 ± 2 ,29	7,46 ± 1,83	7.86 ± 2,18	0.015	.521	.590±
	Range	1–15	5–10,50	2.9–11,70			
NLR	Mean ± SD	3.16 ± 1.98	3.26 ± 2.57	2.62 ± 2.76	.004	.204	.855±
	Range	.84-22.52	.61 – 8.30	0.29–15.98			
PLR	Mean ± SD	10.53 ± 7.88	8.61 ± 4.32	10.40 ± 8.29	.831	.679	.608±
	Range	1.66-58	2.01–14.50	2.63–58.14			

¥ Chi-square test, £ independent t-test, ± Mann-Whitney, WBC: white blood cell; RBC; red blood cell; Hct; hematocrit; Hb: hemoglobin; PLT: platelet; MPV: mean platelet volume; PDW: platelet distribution width;

PLRC: Platelet large cell ratio; RDW: red blood cell distribution width; Mono: monocyte; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

P_1: compare papillary and control group, P2: compare follicular and control group, P3: compare papillary and follicular group

Table 3
Diagnostic value analysis for significant different data between thyroid cancers compared to Control group

Parameter	AUC	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
MPV	0.57	8.9500	71.3	55.2	36.7	25.9	1.32	0.61
PLT	0.61	247.500	62.2	65.4	53.49	67.42	1.8	0.58
RDW	0.66	13.4500	62.7	68.1	62.5	66.39	1.97	0.57
Hb	0.58	11.2500	88	47.6	41.5	21.8	1.2	0.43
Neutrophil	0.63	59.1000	61.3	60	50.82	65.87	1.53	0.65
Lymphocyte	0.58	32.000	63.3	50.1	45.73	59.67	1.27	0.73
Monocyte	0.57	7.9500	56.3	50.3	48.39	61.34	1.13	0.87
NLR	0.41	1.0055	96.1	72.1	44.58	77.8	2.1	0.92

Discussion

This study suggested that MPV and PLT measurements and other CBC parameters were not significantly different from controls in PTC patients.

Giardi et al. [23] retrospectively evaluated 517 patients submitted to thyroidectomy. Of their patient, 83.2% of 95 patients with PTC were females, which is in good agreement with the results of the present study.

In the history of infection and inflammation, there are many types of cancer. Inflammation is an essential and critical phase in the production and progression of cancer[24]. Tumor cells release cytokines such as IL-1, IL 6, and other growth factors that promote platelet production, and activated platelets are involved in each cancer development step. Platelets also play a significant metabolic function in cancer pathogenesis through their angiogenic, metastatic, and proteolytic activity in the context of inflammation [25]. Platelets provide the production and release of VEGF, which plays a role in tumor angiogenesis and inflammation[26]. Furthermore, elevated platelet levels have been observed in several types of cancers in association with increased risk of recurrence, later stages, and metastasis [27].

PTC analyses a persistent inflammation-related disease. Beksac et al [28]found that IL-6 in presurgical samples was higher in PTC and returned to normal after surgery in PTC patients. Similarly, in patients with PTC, Kobawala et al. [29] demonstrated that IL-6 rates were significantly higher in patients with mild thyroid disease and that its levels were strongly associated with tumor intensity, extrathyroid expansion, and distant metastasis. enhanced generation of platelets may contribute to the occurrence of large thrombocytes, resulting in elevated PDW rates [30]

The number of platelets has been investigated in several different studies in organ cancer. For instance, in cases of non-small cell lung cancer and epithelial ovarian cancer, PLT levels were shown to be significantly lower, but there was no difference in breast and colon cancer[27,31–34]. Balden et al. [35] demonstrated that there was no significant difference between PCT and control groups regarding PLT. In this study, the PTC patient had a lower PLT count compared to the control group. However, analysis of the ROC curve shows that this factor obtained a poor AUC score (AUC tests ≤ 0.75 are generally considered not to be clinically useful).

MPV has been reported for many types of cancer. Preferably, MPV rates in endometrial cancer[21], ovarian cancer[19], colorectal cancer[20], and gastric cancer [36] be significantly increased relative to healthy controls. Larger platelets are more involved in metabolism and enzymes than smaller platelets. MPV is a repressive platelet function, and substantial evidence demonstrates that MPV is an important biological variable[17].

Baldane et al. [35] found that MPV in PTC cases was significantly higher than benign goiters and healthy controls and MPV values returned to normal postoperatively. However, in our analysis, we found a significant difference in MPV rates among the groups. However, due to the low AUC score, it cannot be used as a diagnostic factor. One possible explanation for this may be that during the inflammatory response, platelets are recruited to the region of inflammation where they are damaged and their volume is reduced[15,37]. Based on this, it has been suggested that large platelet production boosts in bone marrow in patients with PTC, but platelet consumption and conversion of large platelets to small platelets also increase in the inflammatory area; therefore, platelet counts and MPV may probably remain unchanged [38].

The factors that stimulate platelet production often increase the width of the platelet distribution.PDW illustrates the increase in platelet size and indicates rapid platelet release[39,40]. Dincel and Bayraktar [39] observed that relative to multinodular goiter patients and normal healthy participants, PDW decreased in patients with PTC. Yaylaci et al [41] found that PDW in the papillary cancer group was significantly lower than in healthy goiters. In contrast, Li et al. [42] observed that PDW was higher than normal in patients with thyroid cancer and higher in patients with papillary carcinoma compared to follicular and medullary carcinoma. This study was unable to demonstrate any significant differences in PDW between groups.

The basic hematological function of parameters such as the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio was also analyzed [22,43,44]. High NLR levels are attributed to either neutrophilia or lymphopenia. Neutrophilia affects the immune system by eliminating the cytolytic ability of lymphocytes, activated T cells, and natural killer cells[45]. Common factors in neutrophilia or lymphopenia are dysregulation of the release of cytokines, chemokines, and growth factors produced by both tumor cells and related tumor microenvironment host cells[46]. In another study, a specific increase in NLR was found in papillary and micropapillary carcinomas compared to benign goiters and controls, although no cut-off was suggested[22]. However, the findings of the current study do not support previous research. We

observed significantly higher NLR values in patients with PTC, which was also not known for PLR. In addition, analysis of the ROC curve revealed that both variables achieved lower AUC scores. These results are in agreement with the findings of other studies in which no differences between PTC and control groups were found in NLR, PLR [6, 9, 10].

These results may be explained by the fact that in thyroid carcinogenesis, chronic inflammation may be less important[46,47]. Moreover, these indices are mainly unspecified and require careful screening of patients with strict exclusion criteria because they are affected by a multitude of medical conditions, illnesses, and medicines [47]. In addition, constitutional differences between individuals, such as different subtypes of HLA, may lead to differential systemic inflammatory responses to various exogenous and endogenous stimuli [17,22].

Our study has a number of limitations. Our analysis is a retrospective review in a single institution and the sample size was relatively small. More prospective largescale research is necessary to evaluate shifts in platelet indices in benign and malignant thyroid diseases.

Conclusion

Virulent tumors induce a generalized inflammatory reaction that can be described and quantified by indices such as PLT factors and the neutrophil-to-lymphocyte ratio. While NLR, PLR, and MPV were found to be significantly different in patients with papillary carcinomas compared to the control group, these biomarkers performed poorly in the analysis of diagnostic accuracy and could not effectively diagnose thyroid cancer.

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Figures

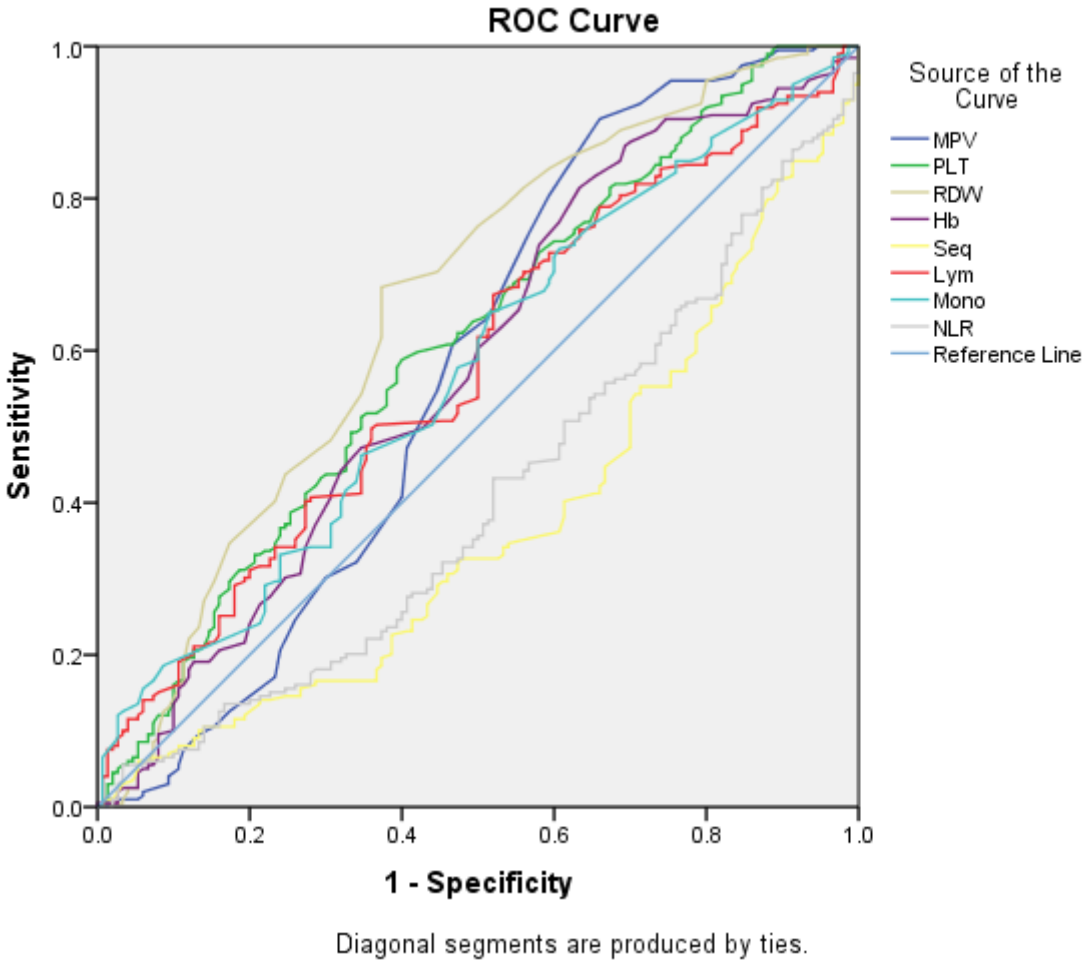

Figure 1

Receiver operating characteristic curve for predictors of cases of thyroid cancer.. MPV: mean platelet volumr;PLT: Platelet count; RDW: Red blood cell distribution width, seq: Neutrophil count; Lym: lymphocyte count; Mono: Monocyte count; NLR: Neutrophil to lymphocyte ratio.