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Preoperative mean platelet volume and platelet distribution associated with thyroid cancer

Y. J. YU[1,‡], N. LI[2,‡], Z. Y. YUN[2], Y. NIU[3], J. J. XU[4], Z. P. LIU[5], T. LIU[6], R. T. WANG[2,*], K. J. YU[4,*]

[1]Medical College of Yangzhou Polytechnic College, Yangzhou, Jiangsu, 225009, China; [2]Department of Internal Medicine, the Third Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, 150081, China; [3]Department of Geriatrics, the Second Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, 150086, China; [4]Department of Intensive Care Unit, the Third Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, 150081, China; [5]Departments of Internal Medicine and Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]Division of Hypothalamic Research, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, 75390, USA

**Correspondence: ruitaowang@126.com, kaijiang_yu@yeah.net*
[‡]Contributed equally to this work.

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Thyroid cancer is the most frequent cancer of the endocrine glands and the fifth most frequent cancer in women. Activated platelets play a crucial role in thrombosis, inflammation, and cancer. Mean platelet volume (MPV) and platelet distribution width (PDW) are early index of platelet activation. The purpose of this study is to investigate platelet indices levels in thyroid cancer. The study enrolled 280 patients with thyroid cancer and 280 control subjects. Patients' characteristics and hematologic tests data were collected at the time of diagnosis. Correlations between platelet indices and clinical characteristics were analyzed. The odds ratios (ORs) and 95% confidence intervals (CIs) for thyroid cancer were calculated using multivariate logistic regression analyses across MPV and PDW quartiles. The patients with thyroid cancer had lower MPV and higher PDW compared with control subjects. MPV was correlated with tumor-nodus-metastases (TNM) stage and lymph node metastasis. Moreover, after adjusting for other risk factors, the prevalence risk of thyroid cancer for the lowest quartile of MPV was 7.242 (4.069-12.887) ($P < 0.001$) and for the highest quartile of PDW was 6.065 (3.321-11.076) ($P < 0.001$), respectively. The study showed that the patients with thyroid cancer have lower MPV and higher PDW compared to control subjects. Moreover, MPV and PDW were independently associated with the presence of thyroid cancer. Further studies are needed to evaluate the utility of MPV and PDW as novel diagnostic screening tools for thyroid cancer.

Key words: thyroid cancer, mean platelet volume, platelet distribution width, platelet activation

Thyroid cancer is the most frequent cancer of the endocrine glands and the fifth most frequent cancer in women, with an increasing incidence [1]. Although many advancements achieved in diagnosis and treatment, the precise mechanisms promoting the development and progression of the disease are only partially known. Activated platelets play a key role in cancer progression and metastases [2, 3]. A recent study found that activated platelets may contribute to angiogenesis [4]. Aberrant expression of receptors for platelet-derived growth factor was observed in an anaplastic thyroid carcinoma cell line [5]. Furthermore, platelet-derived growth factor receptor-α promotes lymphatic metastases in papillary thyroid cancer [6]. Gene expression profiling identifies platelet-derived growth factor as a diagnostic molecular marker for papillary thyroid carcinoma and follicular carcinoma [7].

Mean platelet volume (MPV) is an indicator of activated platelets and is associated with gastric cancer, ovarian cancer, lung cancer, colon cancer, and breast cancer [8-12]. Platelet distribution width (PDW), another platelet parameter, indicates variation in platelet size and differentially diagnoses thrombocytopenia [13]. Some reports found that MPV was higher in patients with thyroid malignancies than in patients with benign thyroid diseases and control subjects [14, 15]. However, these studies were the small number of patients and did not to rule out confounding factors such as body mass index, smoking status, fasting plasma glucose, and medica-

tion use. The aim of the present study is to evaluate platelet indices in patients with thyroid cancer.

Patients and methods

Patients. Data from 280 patients diagnosed with thyroid carcinoma at the department of thyroid surgery, the Third Affiliated Hospital, Harbin Medical University (Harbin, China) between January 2013 and June 2013 were retrospectively reviewed. All cancer patients (mean age 45.7 ± 10.6 years, range 18-78 years) underwent surgery and were identified from the department of pathology in our hospital. None of the patients underwent chemotherapy or radiotherapy before surgery. 280 control subjects (mean age 46.5 ± 8.4 years, range 28-62 years) were recruited and they were matched for age, gender, body mass index (BMI), and smoking status. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Third Hospital of Harbin Medical University, China. Informed consent was obtained from each of the patients.

Clinical examination and biochemical measurements. The preoperative work-up included a general clinical examination, a complete blood count, a blood chemistry profile, thyroid ultrasound, and a chest x-ray. BMI was calculated as weight (kg) divided by height squared (m^2). Clinical data included smoking status, medical history and medication use. The whole blood samples were drawn after an 8-h overnight fasting and all samples were processed within 30 min after blood collection. White blood cell (WBC), haemoglobin, and platelet indices were determined with an autoanalyzer (Sysmex XE-2100, Kobe, Japan). The inter- and intra-assays coefficients of variation (CVs) of all these assays were below 5%.

Statistical analyses. All statistical analyses were performed using SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, USA). The descriptive statistics are presented as means ± SD or medians (interquartile range) for continuous variables and percentages of the number for categorical variables. The between-group differences were determined with Student's *t*-tests or Mann-Whitney *U* test or Chi-square test. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for colon cancer were calculated after adjusting for confounding variables across MPV quartiles using multivariate logistic regression analysis. All tests were 2-tailed with a p-value of <0.05 considered statistically significant.

Table 1. The characteristics of the participants according to thyroid carcinoma status.

Variables	With thyroid carcinoma	Without thyroid carcinoma	P value
N	280	280	
Age (years)	45.7 (10.6)	46.5 (8.4)	0.301
Gender (male, %)	40 (14.3)	49 (17.5)	0.298
BMI (kg/m^2)	23.6 (3.2)	24.0 (3.3)	0.156
Current smoker (%)	18 (6.4)	28 (10.0)	0.124
TC (mmol/L)	4.51 (0.94)	4.74 (0.93)	0.004
TG (mmol/L)	1.08 (0.75-1.59)	1.09 (0.68-1.75)	0.971
FPG (mmol/L)	5.00 (4.70-5.40)	4.83 (4.46-5.47)	0.017
WBC (×10^9/L)	6.1 (1.5)	6.4 (1.7)	0.083
Haemoglobin (g/dl)	135.4 (16.8)	145.7 (13.8)	<0.001
Platelet (×10^9/L)	229.1 (54.8)	256.3 (59.5)	<0.001
MPV (fL)	9.1 (1.3)	10.0 (1.2)	<0.001
PDW (%)	16.5 (1.4)	15.1 (2.1)	<0.001

Values are shown as mean (standard deviation) or median (IQR) or percentage. BMI, body mass index; TC, total cholesterol; TG, triglyceride; FPG, fasting plasma glucose; WBC, white blood cell; MPV, mean platelet volume; PDW, platelet distribution width.

Results

The clinical and laboratory characteristics of patients with colon cancer and control subjects are documented

Table 2. The characteristics of the patients according to thyroid carcinoma histology.

Variables	Papillary carcinoma	Follicular carcinoma	Medullary carcinoma	P value
N	158	53	69	
Age (years)	44.5 (8.8)	47.1 (10.9)	47.6 (10.1)	0.072
Gender (male, %)	8 (5.1)	11 (20.8)	21 (30.4)	<0.001
BMI (kg/m2)	23.8 (3.0)	22.8 (3.6)	23.8 (3.3)	0.113
Current smoker (%)	0 (0)	9 (17.0)	9 (13.0)	<0.001
TC (mmol/L)	4.53 (0.88)	4.48 (1.19)	4.90 (0.89)	0.937
TG (mmol/L)	1.03 (0.68-1.43)	1.09 (0.70-1.77)	1.20 (0.81-1.68)	0.104
FPG (mmol/L)	4.80 (4.60-5.30)	5.10 (4.81-5.43)	5.10 (4.80-5.45)	0.004
Haemoglobin (g/dl)	132.3 (13.4)	135.4 (13.9)	142.5 (22.9)	<0.001
WBC (×10^9/L)	6.2 (1.5)	6.0 (1.5)	6.0 (1.5)	0.433
Platelet (×10^9/L)	227.0 (51.3)	233.6 (61.9)	230.5 (57.3)	0.731
MPV (fL)	9.1 (1.2)	8.9 (1.0)	9.3 (1.5)	0.298
PDW (%)	16.7 (1.1)	16.4 (1.9)	16.1 (1.7)	0.015

Values are shown as mean (standard deviation) or median (IQR) or percentage. BMI, body mass index; TC, total cholesterol; TG, triglyceride; FPG, fasting plasma glucose; WBC, white blood cell; MPV, mean platelet volume; PDW, platelet distribution width.

Table 3. Correlations between clinicopathological features and pre-operative MPV and PDW in thyroid carcinoma.

Variables	Papillary carcinoma	P	Follicular carcinoma	P	Medullary carcinoma	P
MPV (fL)						
TNM classification						
T1+T2	9.1 (1.2)		9.8 (0.7)		9.3 (1.5)	
T3+T4	-	-	8.8 (0.9)	0.006	-	-
Lymph node metastasis						
Absence	9.1 (1.2)		9.4 (1.3)		9.0 (1.3)	
Presence	7.9 (0.5)	0.155	7.9 (0.6)	0.002	9.7 (1.7)	0.082
Distant metastasis						
Absence	9.1 (1.2)		9.2 (1.3)		9.3 (1.5)	
Presence	-	-	7.5 (0)	0.068	9.8 (1.6)	0.556
Stage						
I – II	9.1 (1.2)		8.9 (0.8)		9.0 (1.3)	
III – IV	-	-	9.0 (1.4)	0.871	9.7 (1.7)	0.082
PDW (%)						
TNM classification						
T1+T2	16.7 (1.1)		16.3 (1.8)		16.1 (1.7)	
T3+T4	-	-	17.2 (2.2)	0.183	-	-
Lymph node metastasis						
Absence	16.7 (0.3)		16.3 (2.0)		16.0 (1.5)	
Presence	16.7 (1.1)	0.99	17.1 (0.3)	0.27	16.2 (1.9)	0.57
Distant metastasis						
Absence	16.7 (1.1)		16.4 (1.9)		15.6 (0.4)	
Presence	-	-	16.8 (0)	0.769	16.1 (1.7)	0.603
Stage						
I – II	16.7 (1.1)		16.2 (1.8)		16.0 (1.5)	
III – IV	-	-	17.2 (1.8)	0.104	16.2 (1.9)	0.57

Values are shown as mean (standard deviation). MPV, mean platelet volume; PDW, platelet distribution width; TNM, tumor-nodulus-metastases.

in Table 1. The groups were well-matched with respect to age, gender, BMI and smoking status. TG and WBC in two groups had no difference. However, TC, FPG, haemoglobin, platelet count, MPV, and PDW in two groups are prominently different.

Table 4. Thyroid carcinoma risk according to pre-operative MPV and PDW quartiles.

Quartiles	Cases	Controls	OR (95% CI)	P value
MPV (fL)				
Q1 (≤8.6)	110	34	7.242 (4.069-12.887)	< 0.001
Q2 (8.7-9.5)	89	52	3.953 (2.281-6.852)	< 0.001
Q3 (9.6-10.4)	40	102	0.912 (0.523-1.590)	0.744
Q4 (≥10.5)	41	92	1 (reference)	
PDW (%)				
Q1 (≤14.6)	22	118	1 (reference)	
Q2 (14.7-16.4)	91	51	9.954 (5.406-18.329)	< 0.001
Q3 (16.5-17.0)	89	53	7.591 (4.145-13.900)	< 0.001
Q4 (≥17.1)	78	58	6.065 (3.321-11.076)	< 0.001

Logistic regression analysis adjusted for age, gender, BMI, smoking status, FPG, TC, TG, haemoglobin and WBC. MPV, mean platelet volume; PDW, platelet distribution width; CI, confidence interval.

The characteristics of the patients according to thyroid carcinoma histology are shown in Table 2. There were no significantly different in age, BMI, TC, TG, WBC, platelet count and MPV among three groups. However, male sex and smoking had a higher prevalence in patients with medullary carcinoma. In addition, FPG and haemoglobin increased, and PDW reduced in medullary carcinoma compared with those in papillary carcinoma.

Correlations between clinicopathological features and MPV and PDW in thyroid cancer are presented in Table 3. No correlations were found between MPV and PDW and TNM stage, TNM classification, lymph node metastasis, and distant metastasis both in papillary carcinoma and in medullary carcinoma. However, the follicular carcinoma patients with T3+T4 and lymph node metastasis had significantly lower levels of MPV compared to the patients with T1+T2 (p = 0.006). In addition, the follicular carcinoma patients with lymph node metastasis had markedly reduced MPV compared to those without lymph node metastasis (p = 0.002). MPV did not show significant difference in TNM stage and distant metastasis in papillary carcinoma.

The risks of thyroid cancer according to MPV and PDW quartiles are reported in Table 4. After adjusting for age, gen-

der, BMI, smoking status, FPG, TC, TG, haemoglobin and WBC, the prevalence risk of thyroid cancer for the lowest quartile of MPV was 7.242 (4.069-12.887) ($P < 0.001$) and for the highest quartile of PDW was 6.065 (3.321-11.076) ($P < 0.001$), respectively.

Discussion

The main findings of our study are the following: the patients with thyroid cancer have lower MPV and higher PDW compared to control subjects. Furthermore, MPV and PDW were found to be independently associated with the presence of thyroid cancer.

Accumulating experimental and clinical evidences support the hypothesis that platelet activation during cancer promotes disease progression[16]. We found that reduced MPV and increased PDW in patients with thyroid cancer. The mechanism is unclear. Bone marrow cells (including megakaryocytes) dys-regulation may contribute to changed MPV and PDW. Platelet volume is determined both during megakaryopoiesis and during thrombopoiesis. Megakaryocytic maturation, platelet production and platelet size could be modulated by cytokines, such as interleukin-6 (IL-6), granulocytes colony stimulating factor (G-CSF) and macrophage colony stimulating factor (M-CSF) [17]. Furthermore, Megakaryopoiesis and subsequent thrombopoiesis in cancer may be stimulated by the cytokines G-CSF and M-CSF, which could be secreted by tumor cells [18]. MPV and PDW was an early indicator of activated platelets. Reduced MPV was regarded as an enhanced consumption of large platelets in inflammatory states [19]. In addition, MPV has been shown to be positively associated with levels of thrombopoietin and interleukin-6, cytokines that regulate megakaryocyte ploidy [20, 21]. Platelet distribution width is a measure of platelet heterogeneity. The heterogeneity in platelet volume is caused by heterogeneous demarcation of megakarocytes [22].

Aberrant expression of receptors for platelet-derived growth factor receptors and B-like protein were observed in thyroid carcinoma cell line [5, 23]. In addition, platelet-derived growth factor receptor-α promotes lymphatic metastases in papillary thyroid cancer [6]. However, our study revealed that MPV levels were correlated to TNM stage and lymph node metastasis in follicular thyroid cancer. Therefore, the changes of MPV levels in follicular carcinoma and papillary carcinoma suggest that platelets may exert a different effect in different pathological types of thyroid cancers.

Thrombosis is one of the common cause of mortality in cancer. Activated platelets provide procoagulant surface amplifying the coagulation process. Multifactorial complex interactions between platelets, endothelial cells and leukocytes further stimulate production of proinflammatory cytokines and lead to thrombosis [24]. Therefore, evaluating thrombotic risk in thyroid cancer is of great clinical importance. In this study, we provided evidence that activated platelets in thyroid cancer using a simple, relatively inexpensive, almost universally obtained test. This result is in agreement with other reports that the aspirin-mediated inactivation of platelets may restore antitumor reactivity [25].

The strengths of this study are the large number of patients, the well-matched controls, and consideration of comorbidities. Previous studies reported that increased MPV is associated with smoking, obesity, diabetes, coronary artery disease and medication use [26]. Although some studies showed that MPV was higher in patients with thyroid malignancies than in patients with benign thyroid disease and control subjects, these studies included small number of patients and failed to rule out the influence of comorbidities and some drugs. This study has limitations: (1) the study was cross-sectional, and this type of study fails to indicate a causal relationshipis. A prospective study is needed to clarify this point. (2) the study is lacking information about the genetic contributions to thyroid cancer.

In conclusion, the study showed that the patients with thyroid cancer have lower MPV and higher PDW compared to control subjects. Moreover, MPV and PDW were independently associated with the presence of thyroid cancer. Further studies are needed.

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