RESEARCH ARTICLE

Decreased Mean Platelet Volume is Associated with Cervical Cancer Development

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Abstract

Background: Cervical cancer is the most common gynecological malignant disorder worldwide. Activated platelets play a key role in cancer development and progression. Mean platelet volume (MPV) is an early indicator of platelet activation. The aim of the present study was to evaluate MPV levels in patients with cervical cancer. **Materials and methods:** A total of 181 patients with cervical cancer and 181 controls between January 2015 and June 2015 were included in the study. Patient characteristics and hematologic test data at initial diagnosis were collected and odds ratios (ORs) and 95% confidence intervals (CIs) for risk of cervical cancer were calculated using multivariate logistic regression analyses across MPV quartiles. **Results:** MPV levels were decreased in patients with cervical cancer compared with control subjects. A significant correlation between MPV and FIGO stage was found. Moreover, after adjusting for other risk factors, the ORs (95%CIs) for cervical cancer according to MPV quartiles were 4.450 (1.975-10.026), 2.505 (1.206-5.202), 0.573 (0.261-1.259), and 1.000, respectively. **Conclusions:** MPV was found to be independently associated with the presence of cervical cancer. Our results suggest that MPV could be potential diagnostic screening tool.

Keywords: Cervical cancer- Mean platelet volume- diagnosis

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Introduction

Cervical cancer is the most common gynecological malignant disorder worldwide. Although cervical cancer screening is a frequently used method for early evaluation, there are still large numbers of cases in advanced stage in the developing countries. Therefore, identification of novel markers to find patients with cervical cancer is warranted.

Platelets play a multifaceted role in cancer progression and metastases. Complex interactions between platelets and tumor cells result in tumor growth, aberrant angiogenesis, invasion, and metastasis(Bambace and Holmes, 2011; Goubran et al., 2014). Several studies have reported that elevated platelets are associated with a poor prognosis in various types of cancer, including pancreatic cancer, gastric cancer, colorectal cancer, endometrial cancer, and ovarian cancer (Chadha et al., 2015; Feng et al.,2016; Heng and Benjapibal, 2014; Josa et al., 2015; Li et al., 2014). However, total platelet count is determined by the balance between the rate of production and consumption of platelets. A normal platelet count could conceal the presence of highly hypercoagulative and pro-inflammatory cancer phenotypes in the presence of efficient compensatory mechanisms (Seretis,et al., 2015). Mean platelet volume (MPV) is an index of activated platelets and is linked to different inflammatory conditions(Gasparyan et al., 2011). Many research studies found that MPV changed in gastric cancer, ovarian cancer, lung cancer, colon cancer, and breast cancer (Gu et al., 2015; Kemalet al., 2014; Kilincalp et al.,2014; Kumagai et al., 2015; Li et al., 2014).

To the best of our knowledge, the relationship between MPV and cervical cancer has not yet been reported. Therefore, the aim of the present study is to evaluate MPV levels in patients with cervical cancer.

Materials and Methods

The study included 181 patients with cervical cancer (mean age 46.9 ± 7.4 years, range 27-67 years) who were admitted to the Third Affiliated Hospital, Harbin Medical University between January 2015 and June 2015. Patients meeting all of the following requirements were eligible for enrollment: (1) undergone complete surgical resection and diagnosis of cervical cancer was confirmed by histology; (2) without distant metastasis at diagnosis; (3) untreated before diagnosis. Exclusion criteria included: hematological disorders, autoimmune

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diseases, systemic inflammatory diseases, coronary artery disease, hypertension, diabetes mellitus, thyroid disease, renal disease, hepatic disorder and other cancer, and medical treatment with anticoagulant, statins, and acetylic salicylic acid. 181 control subjects (mean age 46.6 ± 4.8 years, range 28-62 years) were recruited from the Third Affiliated Hospital, Harbin Medical University. They were matched for age, gender, body mass index (BMI), and smoking status.

Informed consent was obtained from all individual participants included in the study. This study was approved by the Institutional Review Board of the 3rd Affiliated Hospital of Harbin Medical University.

Clinical examination and biochemical measurements

All the subjects underwent physical examination. BMI was calculated as the ratio of weight (kg) to height squared (m^2). Clinical data including smoking status, medical history and medication use were recorded for each subject. Venous blood samples after a 10-hour overnight fasting were collected from the individuals within 1 week prior to surgery. The values included serum total cholesterol (TC), triglyceride (TG), and fasting plasma glucose (FPG). The assays were performed at the Laboratory of Analytical Biochemistry at the Third Hospital of Harbin Medical University on the biochemical analyzer (MODULAR ANALYTICS, Roche, Mannheim, Germany). White blood cell (WBC), haemoglobin, and platelet indices were measured by an autoanalyzer (Sysmex XE-2100, Kobe, Japan). The whole blood samples were collected in EDTA-containing tubes, and all samples were processed within 30 minutes after blood collection. The inter- and intra-assays coefficients of variation (CVs) of all these assays were below 5%.

Statistics

The descriptive statistics are presented as means ± SD or medians (interquartile range) for continuous variables and percentages of the number for categorical variables. When baseline characteristics between two groups were compared, normally distributed continuous variables were compared with the Student t test and skewed-distributed with the Mann-Whitney U test. The Chi-square test was used for categorical variables. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for cervical 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. All statistical analyses were performed using SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, USA).

Table 1. The Characteristics of the Participants According to Cervical Cancer Status

Variables	Without cervical cancer	With cervical cancer	P value
N	181	181	
Age (years)	46.6±4.8	46.9±7.4	0.577
BMI (kg/m^2)	23.7±3.2	23.4±2.7	0.388
TC (mmol/L)	4.73±0.92	4.56±0.96	0.081
TG (mmol/L)	0.98 (0.61-1.72)	0.92 (0.59-1.37)	0.069
FPG (mmol/L)	4.83 (4.38-5.39)	5.04 (4.70-5.30)	0.006
WBC (×109/L)	6.0±1.7	5.8±1.8	0.321
Haemoglobin (g/dl)	140.3±13.8	124.0± 13.6	<0.001
Platelet (×109/L)	246.3±58.9	234.2±61.5	0.057
MPV (fL)	9.2±0.9	8.6±1.3	<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.

Results

The clinical and laboratory characteristics of subjects with cervical cancer and control subjects are reported in Table 1. The groups were well-matched with respect to age and BMI. TC, TG, WBC, and platelet count in two groups had no difference. However, FPG, haemoglobin, and MPV in two groups are markedly different ($p < 0.001$). The MPV values in patients with cervical cancer and control subjects were 8.6 ± 1.3 and 9.2 ± 0.9 fl, respectively.

Correlations between clinicopathological features and platelet and MPV in cervical cancer are presented in Table 2. There were no correlations between platelet count and MPV and depth of tumor histology, tumor differentiation, and tumor size. The cervical cancer patients with stage IIb had significantly higher platelet count and MPV compared to the patients with stage I-IIa.

The risks of cervical cancer according to MPV quartiles are summarized in Table 3. After adjusting for age, BMI, FPG, TC, TG, haemoglobin and WBC, the prevalence risk of cervical cancer for the lowest quartile of MPV was 4.450 (1.975-10.026) ($p < 0.001$).

Table 2. Correlations between Clinicopathological Features and Pre-Operative Platelet and MPV in Cervical Cancer

Variables	N	Platelet (×10^9/L)	P	MPV (fL)	P
Tumor histology			0.761		0.158
Squamous	162	235.3±59.1		8.6±1.3	
Adenocarcinoma	15	226.3±87.2		8.8±1.3	
Other	4	218.8±60.6		7.5±0.6	
Grade			0.331		0.155
Well-differentiated	25	217.2±69.3		8.4±1.5	
Moderately-differentiated	100	236.7±63.0		8.5±1.2	
Poorly/undifferentiated	56	237.3±54.7		8.9±1.3	
FIGO stage			0.012		0.039
Ia	22	225.5±58.8		9.0±1.6	
Ib	77	244.8±65.2		8.8±1.2	
IIa	44	243.1±57.3		8.6±1.3	
IIb	38	207.6±53.0		8.1±1.1	
Size of primary tumor			0.265		0.474
≤4 cm	151	231.9±62.5		8.6±1.3	
>4 cm	30	245.7±56.1		8.5±1.2	

Values are shown as mean (standard deviation); MPV, mean platelet volume.

Table 3. Cervical Cancer Risk According to Pre-Operative MPV Quartiles

Variables	OR (95% CI)	p value
TC (mmol/L)	0.748 (0.549–1.020)	0.066
TG (mmol/L)	0.794 (0.534–1.180)	0.253
FPG (mmol/L)	0.830 (0.529–1.304)	0.42
Platelet (×109/L)	0.996 (0.991–1.001)	0.081
Haemoglobin (g/dl)	0.916 (0.896–0.937)	< 0.001
MPV (fL)		< 0.001
Q1 (≤8.1)	4.179 (1.884-9.272)	< 0.001
Q2 (8.2-9.1)	2.551 (1.228-5.300)	0.012
Q3 (9.2-9.8)	0.575 (0.264-1.251)	0.163
Q4 (≥9.9)	1 (reference)	

Logistic regression analysis adjusted for age, BMI, FPG, TC, TG, haemoglobin and WBC. CI, confidence interval.

Discussion

In this study, we provided evidence that platelets are activated in cervical cancer using a simple, relatively inexpensive, almost universally obtained test. The patients with cervical cancer have reduced MPV compared to the controls. Furthermore, we found that MPV was found to be independently associated with the presence of cervical cancer.

Literature comparisons

More and more attention is being paid to activated platelet, a paramount mediator in tumor development, tumor cell growth, angiogenesis, and metastasis. Some studies suggested that thrombocytosis is associated with poor prognosis in patients with various tumor types, including cancer of the lung, ovary, endometrium, rectum, kidney, stomach, pancreas, brain, and breast. Several clinical studies have observed the changed biomarkers of platelet activation, such as soluble P-selectin, CD40 ligand, and β-thromboglobulin (β-TG) in patients with cancer (Al-Mondhiry, 1983; Ay et al., 2008; Huang et al., 2012). However, these markers for measuring activated platelets were not routinely evaluated in clinical practice. MPV levels are routinely recorded in the clinical setting and can be easily estimated prior to treatment. Thus, MPV might be useful in early detection and in helping clinicians to adopt rational treatment programs.

Mechanistic considerations

At present, the molecular mechanism underlying the association of reduced MPV with cervical cancer is unknown. 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) (Kaushansky, 1998). Increased interleukin-6 (IL-6) has been verified in almost all types of tumors acting as a major cytokine in the tumour microenvironment (Lippitz and Harris,2016). An increasing body of evidence validated that IL-6 promotes tumorigenesis by regulating apoptosis, survival, proliferation, angiogenesis, metastasis and metabolism (Kumariet al., 2016). 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 (Kowanetz et al., 2010). MPV was an early indicator of activated platelets. Reduced MPV was regarded as an enhanced consumption of large platelets in inflammatory states (Gasparyan et al., 2011). Furthermore, MPV has been found to be positively associated with levels of thrombopoietin and interleukin-6, cytokines that regulate megakaryocyte ploidy (Brown et al.,1997; Martin et al., 1983).

Another possible mechanism is that platelets play a crucial role in promoting the hypercoagulable state in cancer. Activated platelets create a procoagulant micro-environment that enables the tumor cells to cover themselves with platelets and evade the host immune system (Mezouar et al.,2016). Multifactorial complex interactions between platelets, endothelial cells and leukocytes further stimulate production of proinflammatory cytokines and lead to thrombosis (Gawaz et al., 2005). The mentioned above were just suggested based on theory. More experiments need to be carried out to explore the molecular mechanism for the change of MPV in cervical cancer.

Study limitations

The present study has some limitations. Firstly, based on the cross-sectional study design, the present findings are inherently limited in the ability to eliminate causal relationship between MPV and cervical cancer. Secondly, because some inflammatory markers, such as IL-6, are not routinely measured in our hospital, we could not analyze their association with cervical cancer.

In conclusion, the study showed that MPV was independently associated with the presence of cervical cancer. Our results suggest that MPV could be potential diagnostic screening tool for cervical cancer.

Conflict of Interest

None.

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