RESEARCH ARTICLE

Elevated Mean Platelet Volume is Associated with Presence of Colon Cancer

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Abstract

Background: Colon cancer is the second most common cancer in developed countries. Activated platelets play a key role in inflammation and atherothrombosis, with mean platelet volume (MPV) is an early marker of platelet activation. The aim of the study was to clarify the relevance of MPV in patients with colon cancer. Materials and Methods: We measured MPV levels in 128 patients with colon cancer before and after surgery, and 128 controls matched for age, gender, body mass index (BMI) and smoking status. The odds ratios (ORs) and 95% confidence intervals (CIs) for colon cancer were calculated using multivariate logistic regression analyses across MPV quartiles. Results: Patients with colon cancer had higher MPV compared with controls. Surgical tumor resection resulted in a significant decrease in MPV levels (11.4 fL *vs* 10.7 fL; $p<0.001$). A positive correlation between MPV and tumor-nodule-metastases (TNM) stage was found. Furthermore, after adjusting for other risk factors, the ORs (95%CIs) for colon cancer according to MPV quartiles were 1.000, 2.238 (1.014-4.943), 3.410 (1.528-7.613), and 5.379 (2.372-12.198), respectively. Conclusions: The findings show that patients with colon cancer have higher MPV levels compared with controls, and these are reduced after surgery. In addition, MPV was found to be independently associated with the presence of colon cancer. Further studies are warranted to assess the utility of MPV as a novel diagnostic screening tool for colon cancer.

Keywords: Colon cancer - mean platelet volume - platelet activation - diagnostic indicator

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Introduction

Colorectal cancer is the second most common cancer in developed countries and is one of the leading causes of mortality worldwide (Weitz et al., 2005). Deep-vein thrombosis develops in approximately 30% of colorectal cancer surgery patients who do not receive thromboembolic prophylaxis (Lee, 2003). Venous thromboembolism (VTE) is a common complication in patients with cancer. Patients with cancer who develop symptomatic VTE during chemotherapy are at a greater risk of early mortality than those without VTE.

Tumor cells express tissue factor and secrete cytokines that contribute to a prothrombotic microenvironment, which involves activation of platelets. The activated platelets are key players in the thrombotic response and act as the glue that mediates the coagulation cascade. Moreover, platelets represent the link between coagulation and cancer progression (Borsig et al., 2001). A recent study found that activated platelets may contribute to angiogenesis (Italiano et al., 2008). In addition, P-selectin, a marker of platelet hyperactivity, was reported to be higher in patients with cancer (Sierko and Wojtukiewicz, 2004; Connolly and Khorana, 2010).

Mean platelet volume (MPV), a common measure of platelet size, could be used as an index of activated platelet (Park et al., 2002). Furthermore, MPV is an inflammatory indicator in different diseases (Kisacik et al., 2008; Muscari et al., 2009; Yuksel et al., 2009; Berger et al., 2010; Chu et al., 2010; Gasparyan et al., 2010). Some have reported that MPV is increased in cardiovascular disease, peripheral artery disease and cerebrovascular disease (Muscari et al., 2009; Berger et al., 2010; Chu et al., 2010). In contrast, others have demonstrated that MPV is decreased in rheumatoid arthritis and ulcerative colitis (Kisacik et al., 2008; Yuksel et al., 2009; Gasparyan et al., 2010). Recent studies found that MPV could be used to predict the onset of venous thromboembolism and arterial thrombosis (Braekkan et al., 2010). Furthermore, MPV may be a diagnosis marker in hepatocellular carcinoma, pancreatic adenocarcinoma, and gastric cancer (Osada et al., 2010; Karaman et al., 2011; Kurt et al., 2012).

The changes in MPV in patients with colon cancer have not been clearly examined. Clarifying the roles of MPV will have significant clinical implications for the prevention and treatment in colon cancer. Therefore, the aim of the present study is to evaluate MPV levels in patients with colon cancer.

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Materials and Methods

Study population

This study enrolled 256 subjects (149 male and 107 female) at the Second Affiliated Hospital from January 2012 to December 2012. This is a case-control study and there are 128 patients and 128 controls. All cancer patients (mean age 60.2±11.1 years, range 39-77 years) underwent surgery in colorectal cancer surgery department and were identified from the department of pathology in our hospital. None of the patients underwent chemotherapy or radiotherapy before surgery. The clinicopathological parameters were obtained from the pathological reports, including depth of tumor invasion, tumor differentiation, lymph node metastasis, and tumor-nodulus-metastases (TNM) stage, and all of these data were reviewed and confirmed by the experienced pathologists. The controls (mean age 59.2±6.3 years, range 41-70 years) were recruited from the International Physical Examination and Healthy Center of our hospital. They were matched for age, gender, body mass index (BMI), and smoking status. All participants provided written informed consent. The study protocol was approved by the Ethics Committee of the Second Hospital of Harbin Medical University, China.

Clinical examination

All the subjects underwent physical examination, including anthropometric and blood pressure measurements. Blood pressure was determined using a mercury-gravity sphygmomanometer in a sitting position after a 15-min rest. Body weight was measured in light clothing, without shoes, to the nearest 0.5 kg. Height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Biochemical measurements

Clinical data including smoking status, medical history and medication use were recorded for each subject. Venous blood samples were collected from participants after an 8-hour overnight fasting. The values included serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and fasting plasma glucose (FPG). The assays were performed at the Laboratory of Analytical Biochemistry at the Second Hospital of Harbin Medical University, Harbin, using a biochemical analyzer (MODULAR ANALYTICS, Roche, Mannheim, Germany) using standard methods. White blood cell (WBC), haemoglobin, platelet count and MPV were determined with 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%.

Diagnosis and exclusion criteria

Exclusion criteria were hematological disorders, autoimmune 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.

Statistical analyses

All data were presented as means±SD or median (inter-quartile range) for continuous variables and percentage for categorical variables. The between-group differences were determined with Student's t-tests or Mann-Whitney U test or Chi-square test. The differences between pre-operative cancer patients and matched controls were determined using independent sample t-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. A two tailed $p<0.05$ indicated statistical significance. Statistical analyses were conducted with SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

The clinical and laboratory characteristics of subjects with colon cancer and controls are reported in Table 1. The groups were well-matched with respect to age, gender, BMI and smoking status. SBP, DBP, TC, TG, HDL, LDL, FPG, WBC, haemoglobin, and platelet count in two groups had no difference. However, MPV levels in the two groups are significantly different ($p<0.001$).

Correlations between clinicopathological features and MPV in colon cancer are summarized in Table 2. The cancer patients with stage III-IV had significantly higher levels of MPV compared to the patients with stage I-II ($p=0.014$). No correlations were found between MPV and depth of tumor invasion, tumor differentiation, lymph node metastasis, and distant metastasis.

Table 1. Baseline Characteristics of the Participants According to Colon Cancer Status

Variables	With Colon Cancer	Without Colon Cancer	*p* value
N	128	128	
Age (years)	60.2 (11.1)	59.2 (6.3)	0.36
Gender (male, %)	79 (61.7)	70 (54.7)	0.254
BMI (kg/m^2)	23.2 (3.3)	23.1 (3.6)	0.794
Current smoker (n, %)	42 (32.8)	37 (28.9)	0.499
SBP (mmHg)	127.2 (7.9)	126.3 (11.9)	0.487
DBP (mmHg)	77.7 (6.8)	78.1 (7.7)	0.659
TC (mmol/L)	4.70 (1.04)	4.95 (1.13)	0.065
TG (mmol/L)	1.19 (0.94-1.67)	1.19 (0.72-1.76)	0.294
HDL (mmol/L)	1.20 (1.05-1.42)	1.32 (1.05-1.50)	0.167
LDL (mmol/L)	2.86 (0.75)	2.72 (0.92)	0.414
FPG (mmol/L)	5.33 (4.88-6.12)	5.37 (4.91-6.07)	0.911
Haemoglobin (g/dl)	124.2 (11.0)	123.7 (10.9)	0.693
WBC ($\times 10^9$/L)	6.8 (2.3)	6.5 (1.6)	0.237
Platelet ($\times 10^9$/L)	226.6 (87.6)	218.3 (61.4)	0.381
MPV (fL)	11.4 (1.2)	10.7 (1.0)	<0.001

*Values are shown as mean (standard deviation) or median (IQR) or percentage. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; WBC, white blood cell; MPV, mean platelet volume

Table 2. Correlations between Clinicopathological Features and Pre-operative MPV in Colon Cancer

Variables	MPV (fL)	*p* value
Depth of tumor invasion		0.159
≤ Muscular tunic	11.3 (1.1)	
> Muscular tunic	12.2 (2.0)	
Tumor differentiation		0.627
Well-moderate	11.4 (1.2)	
Poor	11.6 (1.5)	
Lymph node metastasis		0.054
Absence	11.2 (1.0)	
Presence	11.6 (1.4)	
Distant metastasis		0.606
Absence	11.5 (1.3)	
Presence	11.3 (0.8)	
TNM stage		0.014
I-II	11.1 (1.0)	
III-IV	11.7 (1.3)	

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

Table 3. Colon Cancer Risk According to Pre-operative MPV Quartiles

Quartiles of MPV	Cases	Controls	OR (95% CI)	*p* value
Q1 (≤10.3)	19	45	1 (reference)	<0.001
Q2 (10.4-11.0)	30	39	2.238 (1.014-4.943)	0.046
Q3 (11.1-11.7)	35	26	3.410 (1.528-7.613)	0.003
Q4 (≥11.8)	44	18	5.379 (2.372-12.198)	<0.001

*Logistic regression analysis adjusted for age, gender, BMI, smoking status, SBP, DBP, FPG, TC, TG, HDL, LDL, and WBC. MPV, mean platelet volume; CI, confidence interval

The risks of colon cancer according to MPV quartiles are shown in Table 3. After adjusting for age, gender, BMI, smoking status, SBP, DBP, FPG, TC, TG, HDL, LDL, and WBC, the prevalence risk of colon cancer for the highest quartile of MPV was 5.379 (2.372-12.198) (p<0.001).

Discussion

The main findings of our study are the following: the patients with colon cancer have higher MPV compared to the controls. Moreover, MPV was found to be independently associated with the presence of colon cancer.

Inflammation is responsible for increased MPV. Chronic inflammation increases the risk of developing colon cancer, acting at different stages of the carcinogenesis process (Rizzo et al., 2011). Pro-inflammatory cytokines such as interleukin-6 (IL-6) were found significantly higher in colon cancer patients. Furthermore, higher IL-6 levels are associated with increasing tumor stages, tumor size, metastasis and decreased survival (Neurath and Finotto, 2011). Recent studies revealed that IL-6 had a direct effect on megakaryocytes and caused platelet activation and aggregation. In addition, various tumor cell-secreted mediators, such as cysteine proteinases or ADP, contribute to platelet activation (Grignani et al., 1988). On the other hand, tumor cells could activate platelets through the production of thrombin triggered by tumor-associated tissue factor (Mueller et al., 1992). Also, activated platelets interact with colon carcinoma cells either via αIIbβ3 structures or via P-selectin (Konstantopoulos and Thomas, 2009). Moreover, activated platelets play a pivotal role in cancer metastasis through the release of cytokines, chemokines and expression of several adhesion receptors (Borsig, 2008). Consistent with this notion, our study revealed that MPV levels were correlated to TNM stage.

Thrombosis is one of the common causes of mortality in patients with colon cancer (Pauwels et al., 1999; Anthonisen et al., 2005). 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 (Gawaz et al., 2005). Therefore, evaluating thrombotic risk in colon cancer applying reliable disease markers is of great clinical importance.

Previous studies have reported that D-dimer, plasminogen activator inhibitor I (PAI-1) and prothrombin fragments are elevated in colorectal cancer (Mytnik and Stasko, 2011). Moreover, P-selectin is involved in colon cancer (Wei et al., 2004). P-selectin reflected activated platelets and mediated interactions between platelets, leukocytes, and endothelial cells (Ferroni et al., 2000). Additionally, P-selectin mediates the formation of platelet-tumor cell emboli and contributes to colonization of distant organs in tumor metastasis (Karpatkin et al., 1988; Borsig et al., 2001). A recent study further showed P-selectin inhibition exerts beneficial effects by attenuating metastasis, inflammation and thrombosis (Kozlowski et al., 2011).

Our study indirectly confirmed the results using a simple marker of platelet activation. The results indicated that the increased thrombotic risk in colon cancer might be induced by the activated platelet. In addition, previous data demonstrated that aspirin could reduce long-term incidence and mortality due to colorectal cancer development (Logan et al., 2008; Rothwell et al., 2010; Christudoss et al., 2013).

The strengths of this analysis are the larger number of patients included, the better matched controls, and direct comparison of MPV at different stages of colon cancer. However, comorbidity is a key factor that influences the changes of MPV (Steiropoulos et al., 2012). Some studies documented that MPV is associated with smoking, obesity, diabetes, coronary artery disease and heart failure (Gasparyan et al., 2010). In our study, we ruled out the influence of comorbidity.

The interpretation of this study has some limitations. Firstly, the study was cross-sectional, and it is difficult to study the direction of causality. A prospective study is needed to clarify this point. Secondly, the study is lacking information about the genetic contributions to colon cancer. The genetic alterations in both dominant oncogenes and tumor suppressor genes are involved in the pathogenesis of human colon cancer (Li et al., 2012).

In conclusion, the findings show that the patients with colon cancer have higher MPV levels compared to the controls. In addition, MPV was found to be independently associated with the presence of colon cancer. Further studies are warranted to assess the exact role of MPV in patients with colon cancer.

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