Mean platelet volume predicts chemotherapy response and prognosis in patients with unresectable gastric cancer

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Abstract. Gastric cancer is the fourth most frequent cancer and the second cause of cancer-related mortalities worldwide. Platelets play an important and multifaceted role in cancer progression. Elevated mean platelet volume (MPV) detected in peripheral blood has been identified in various types of cancer. In the present study, we investigated the application value of MPV in the prediction of chemotherapy response and prognosis in patients with unresectable gastric cancer. A total of 128 patients with unresectable gastric cancer were included and divided according to the median values of baseline MPV (low MPV: <11.65 or high MPV: ≥11.65). A low baseline MPV level was correlated with reduced metastasis. The results showed that patients with a low baseline level of MPV improved response to chemotherapy. Changes in MPV were associated with therapeutic efficacy. Patients who remained in or were transferred into the low MPV level subgroup following first-line chemotherapy had improved response, compared to those remaining in or being transferred into the high MPV level group. The patients with a higher baseline MPV had decreased progression-free and overall survival ratios. Univariate and multivariate analyses revealed that baseline MPV was a prognostic factor affecting progression-free survival. In conclusion, the results showed that MPV measurements can provide important prognostic information for gastric cancer patients.

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Introduction

Gastric cancer is the fourth most common malignant disease worldwide and the second most common cause of mortality from cancer (1). Countries in East Asia have a higher incidence of gastric cancer (i.e., >40 cases per 100,000). Data for individual countries have shown that gastric cancer is the most common cancer in Japan and the second most common in China and Korea (2). Although early diagnosis and treatment of gastric cancer can significantly improve prognosis, the 5-year survival rate is only 10-15% in individuals with advanced disease (3). This poor outcome may be due to the high incidence of serosal invasion, direct invasion into the adjacent organs and early metastasis (4,5). Biomarkers, such as carbohydrate antigen 19-9 and carcinoembryonic antigen are unsatisfactory due to their low sensitivity (5,6). Therefore, identification of novel biomarkers for the diagnosis and follow up of gastric cancer is essential.

Platelets (PLTs) play an important and multifaceted role in cancer progression (7). Firstly, PLTs facilitate metastasis (8). During hematogenous dissemination, the interaction between circulating tumor cells and PLTs is believed to promote tumor cell survival within the circulation (9) and increase the arrest of tumor cell emboli within the microcirculation (10). Secondly, various studies demonstrated that the release of pro-inflammatory cytokines by cancer, such as interleukin (IL)-1, IL-3, and IL-6, promotes the proliferation of megakaryocytes, leading to the gradual establishment of thrombocytosis (11). Considering the close relationship between PLTs and cancer, biomarkers derived from PLTs are important. Elevated mean platelet volume (MPV) detected in peripheral blood has been identified in various types of cancer, including hepatocellular

carcinoma (12), ovarian cancer (13), colon cancer (14), lung cancer and breast cancer (15), suggesting that PLT-associated markers serve as potential candidates for the diagnosis and follow up of gastric cancer.

In the present study, we investigated whether MPV provided beneficial diagnostic and prognostic information for patients with unresectable gastric cancer.

Materials and methods

Subjects and inclusion criteria. The study was conducted as a retrospective investigation of gastric cancer patients who had been referred to the First Affiliated Hospital of Soochow University (Suzhou, China) between June 2010 and June 2011. Approval for the study was granted by the Medical Ethics Committees of the First Affiliated Hospital of Soochow University.

In total, 128 inoperable gastric cancer patients were recruited in this study. Of the 128 patients, 53 patients were locally advanced and the remaining 75 patients were relapsed or metastastic. Patient characteristics are detailed in Table I. The mean age of the 128 patients was 68 years (range, 32-82 years). The inclusion criteria were as follows: a) those with histologically or cytologically confirmed recurrent or metastatic gastric cancer; b) age >18 years; c) Karnofsky performance status score of ≥70; d) those with a predicted survival of ≥3 months; e) either naive to antitumor treatment or the postoperative adjuvant chemotherapy was performed ≥6 months after the last dose of chemotherapy; f) in case of patients who were scheduled for radiotherapy on the target lesion, radiotherapy was required to have been finished for ≥3 months; g) those with ≥1 measurable lesion [minimum 10x10 mm on computed tomography (CT) or magnetic resonance imaging]; and h) those who met the following laboratory criteria: white blood cells (WBC) ≥4.0x10^9/l; absolute neutrophil count ≥1.5x10^9/l; PLT ≥100x10^9/l; serum bilirubin ≤ upper limit of normal (ULN); alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase ≤ ULNx2.5 (if without liver metastasis) or ≤ ULNx5 (if with liver metastasis); urea nitrogen ≤ ULNx1.25; and creatinine ≤ ULNx1.25.

Blood samples. Blood (5-7 ml) was collected in a sterile ethylenediamime-N,N,N´,N´-tetraacetic acid tube. The blood samples were obtained between 06:30 a.m. and 07:30 a.m. to standardize the known impact of circulating hormones (circadian rhythm) on the number and subtype distribution of the various WBC indices. Hematological parameters were analyzed within 30 min after collection using a hematology analyzer (XE2100; Sysmex Corp., Kobe, Japan) and MPV levels were recorded.

Chemotherapy and evaluation. Patients were administered first-line chemotherapy according to the clinical practice guideline for gastric cancer (2006, the first edition) of National Comprehensive Cancer Network. 5-Fluorouracil (5-FU)/leucovorin, 5-FU-based, cisplatin-based, oxaliplatin-based, taxane-based, and irinotecan-based, epirubicin, cisplatin and fluorouracil were recommended. CT scanning was performed for the assessment of response every 2 months and evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria (16).

Table I. Relationship between MPV and clinicopathological characteristics.

Clinicopathological characteristics	No.	MPV High (no.)	MPV Low (no.)	χ^2 test	P-value
Gender				0.298	0.585
Male	79	41	38		
Female	49	23	26		
Age, years					
<65	72	38	34	0.508	0.476
≥65	56	26	30		
Tumor size, cm				1.276	0.259
<5	86	40	46		
≥5	42	24	18		
Lauren type				0.508	0.476
Intestinal	72	34	38		
Diffuse	56	30	26		
Distant metastasis				20.802	<0.0001[a]
No	35	6	29		
Yes	93	58	35		
Degree of differentiation				1.3474	0.2457
Highly differentiated	38	16	22		
Moderately and poorly differentiated	90	48	42		
HER-2				0.1357	0.7126
++ - +++	46	22	24		
0 - +	82	42	40		
Ki-67				0.011	0.918
≥15%	57	29	28		
<15%	71	35	36		

MPV, mean platelet volume; HER-2, human epidermal growth factor receptor 2. [a]Statistical significance at P<0.05.

Table II. Association between the MPV baseline levels and chemotherapeutic efficacy.

MPV levels	PR+SD (n=81)	PD (n=47)	χ^2 test	P-value
Low, n=60	47	17	5.6822	0.0171[a]
High, n=60	34	30		

MPV, mean platelet volume; PR, partial response; SD, stable disease; PD, progressive disease. [a]Statistical significance at P<0.05.

Follow up. The responses to chemoradiotherapy including complete remission, regression, stable disease, and disease progression, and overall and disease-free survival (DFS) were recorded. Survival time was measured from the date of chemo-

Table III. Association between changes in the MPV level and chemotherapeutic efficacy.

Pre-chemotherapy	Post-chemotherapy	PR+SD (n=81)	PD (n=47)	χ^2 test	P-value
Low (n=64)	Low (n=51)	44	7	13.1977	0.0003[a]
	High (n=13)	5	8		
High (n=64)	Low (n=25)	18	7	7.9426	0.0048[a]
	High (n=39)	14	25		

MPV, mean platelet volume; PR, partial response; SD, stable disease; PD, progressive disease. [a]Statistical significance at P<0.05.

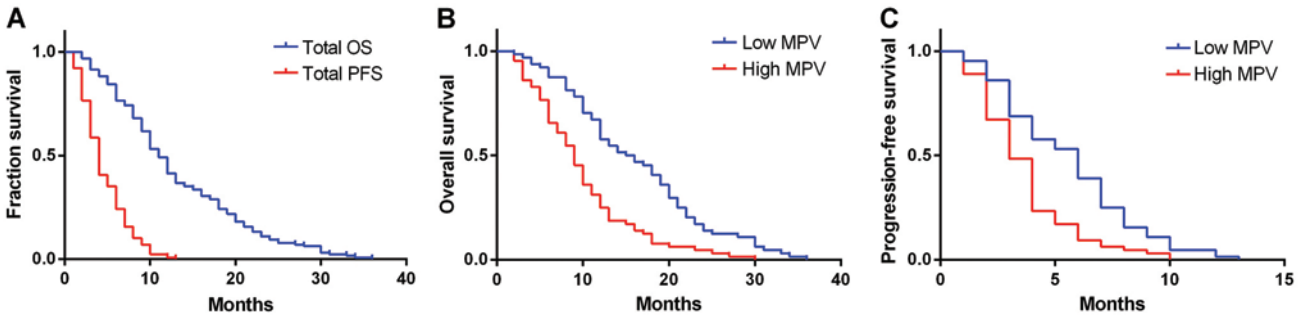

Figure 1. Association between the mean platelet volume (MPV) level and the outcomes. (A) Predicted probability of progression-free survival (PFS) and overall survival (OS). (B) OS and (C) PFS according to MPV.

radiotherapy until death or last clinical evaluation. Following first-line chemotherapy, disease progression after chemoradiotherapy was defined as lack of response to chemoradiotherapy. By contrast, stable disease, complete response or disease regression after chemoradiotherapy was defined as response to chemoradiotherapy. Patients were regularly followed up for 36 months. The prognostic analyses were performed based on progression-free survival (PFS) and overall survival (OS).

Statistical analysis. Statistical analyses were performed using SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA). Multivariate Cox regression was performed for each outcome parameter, using a backwards elimination technique to derive a potentially suitable set of predictors. The association between the MPV level and clinicopathological characteristics or chemotherapeutic efficacy was examined and assessed by the χ^2 tests. For analysis of survival data, Kaplan-Meier curves were constructed, and statistical analysis was carried out using the log-rank test. OS was defined as the time from the initiation of chemotherapy to the patient succumbing due to any cause. P<0.05 was considered to indicate a statistically significant difference.

Results

Relationship between the baseline MPV level and clinicopathological characteristics. Patients were divided according to the median value of baseline MPV (MPV low: <11.65 or MPV high: ≥11.65). The relationships between the baseline MPV level and clinicopathological characteristics were examined and assessed by the χ^2 tests. The results showed that a low baseline MPV level was only correlated with reduced metastasis, but not with other clinicopathological characteristics (Table I).

Baseline MPV level predicts the chemotherapeutic efficacy. The association between the baseline MPV level and chemotherapeutic efficacy is provided in Table II. Patients with low baseline level of MPV had an improved response to chemotherapy, suggesting that the baseline MPV level did not predict chemotherapeutic efficacy.

Changes in MPV levels are associated with the chemotherapeutic efficacy. To define the association between changes in the MPV level with chemotherapeutic efficacy, blood samples were collected at the same time the CT evaluation was performed after first-line chemotherapy. The results showed that 51 patients with a low baseline MPV level, remained in this group after first-line chemotherapy (Table III). By contrast, 13 patients from this group were transferred into the high MPV level group. A total of 39 patients with a high baseline MPV level retained a high MPV level following first-line chemotherapy. By contrast, 25 patients with a high baseline MPV level were transferred into the low MPV level group. Patients remaining in or transferring into the low MPV level subgroup after first-line chemotherapy had an improved chemotherapy response, compared to those remaining in or transferring into the high level group.

MPV levels predict the outcomes. The median OS for all the patients was 11 months with a median PFS of 4 months (Fig. 1A). Follow up for survivors was 36 months. Kaplan-Meier plots showing the influence of MPV status on OS and PFS are shown in Fig. 1B and C. The median OS and PFS of the high MPV level group were 9 and 3 months, respectively, whereas that for the low MPV level group were 15.5 and 6 months, respectively. Significant differences

Table IV. Univariate and multivariate analyses of risk factors for the overall and disease-free survival.

	Overall survival				Progression- free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Risk factor	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender								
Male or female	1.21 (0.65-1.92)	0.793	-	-	1.18 (0.69-1.92)	0.887	-	-
Age								
<65 or ≥65 years	1.19 (0.58-2.60)	0.798	-	-	1.17 (0.68-1.94)	0.848	-	-
Tumor size								
<5 or ≥5 cm	1.22 (0.69-2.34)	0.305	-	-	1.34 (0.89-2.58)	0.276	-	-
Lauren type								
Intestinal or diffuse type	1.37 (0.83-2.16)	0.697	-	-	1.35 (0.52-2.59)	0.784	-	-
Distant metastasis								
No or yes	1.92 (1.29-3.36)	0.025[a]	1.93 (1.28-3.41)	0.022[a]	1.72 (1.41-2.96)	0.028[a]	-	-
Degree of differentiation								
Highly or moderately + poorly	1.21 (0.77-1.91)	0.856	-	-	1.19 (0.68-1.87)	0.832	-	-
HER-2								
++ - +++ or 0 - +	1.25 (0.78-2.10)	0.694	-	-	1.28 (0.78-2.35)	0.722	-	
Ki-67								
(≥15 or <15%)	1.12 (0.71-1.62)	0.847	-	-	1.21 (0.55-1.58)	0.395	-	-
Chemotherapeutic efficacy								
PR+SD or PD	1.98 (1.31-3.30)	0.021[a]	-	-	2.03 (1.62-3.05)	0.041[a]	2.16 (1.69-3.37)	0.039[a]
MPV								
Low or high	2.68 (1.70-3.48)	0.001[b]	-	-	2.64 (1.52-3.34)	0.001[b]	2.52 (1.39-3.50)	0.001[b]

MPV, mean platelet volume; HER-2, human epidermal growth factor receptor 2; OR, odds ratio; CI, confidence interval; PR, partial response; SD, stable disease; PD, progressive disease. [a,b]Statistical significance at $P<0.05$.

were identified between the OS and PFS of the two groups (P<0.001). Thus, the patients with a higher MPV level had decreased survival.

Univariate and multivariate analyses of risk factors for OS and DFS. Univariate and multivariate analyses were performed to identify the risk factors associated with OS and PFS. As shown in Table IV, the univariate analysis revealed that 3 of the 10 risk factors affected OS and PFS, including distant metastasis, chemotherapeutic efficacy and MPV. The multivariate analysis confirmed that distant metastasis was the prognostic factor affecting OS. By contrast, the chemotherapeutic efficacy and MPV were prognostic factors affecting PFS.

Discussion

PLT activation is of paramount importance in the progression of malignancy. Previous findings have shown that the risk of cancer diagnosis is elevated after primary deep vein thrombosis or pulmonary embolism (17). Additionally, experimental and clinical data suggest that the activation of PLTs is a hallmark in the natural course of cancer, by promoting neoangiogenesis, degradation of the extracellular matrix, release of adhesion molecules, and growth factors, all of which are essential components for further tumor growth and metastatic spread (11).

Besides the impact that PLT activation has on cancer, an elevated PLT count in combination with other abnormal test results seems to be predictive for an underlying malignant disease (18), suggesting the potential of using PLT-associated factors as biomarkers for cancer diagnosis and treatment.

Evidence has shown that the larger PLTs are more reactive than the smaller ones and are more likely to aggregate, leading to thrombosis. Large PLTs (LPLTs) are independent risk factors for myocardial infarction, and PLT size is one predictor of recurrent myocardial infarction and death (19). A high level of MPV, a marker of PLT size, may indicate tendency towards thrombosis, and has been demonstrated in the case of myocardial infarction and cerebrovascular embolus (20). In cancer, an increase in the percentage of large PLTs has been observed, and because young, metabolically active PLTs appear in the circulation, this may lead to an increase in MPV (21). Recent findings have suggested that the MPV is a valuable biomarker for the diagnosis and follow up of various types of cancer (12-15).

The association between PLT and cancer may be linked by systemic inflammatory response (SIR) (22), which seems to play a critical role in the development and progression of various types of cancer by promoting cancer cell proliferation and survival, angiogenesis, tumor metastasis and impacting tumor response to systemic therapies (7). The mechanism involved in the effect on PLT by inflammation may be due to the release of pro-inflammatory cytokines, such as IL-1, IL-3 and IL-6, in many types of cancer. These cytokines have been proven to be able to promote the proliferation of megakaryocytes, resulting in PLT activation and aggregation, which potentially lead to the gradual establishment of thrombocytosis (11). This exact stimulation inevitably leads to an increased detection of more primitive types of circulating PLTs (11). This accelerated coagulation of PLTs may promote the metastasis of cancer cells. When covered with PLTs, cancer cells can overcome the stress in the bloodstream, including attacks by the immune system and physical factors (i.e., shear force and mechanical trauma due to passage through the microvasculature) (8,23). Thus, the alliance of PLTs and cancer united by inflammation presents a positive feedback in the progression of malignancy.

Gastric cancer is usually located in the pyloric antrum and in the pylorus, but in 25% of cases in the body (corpus) and fundus of the stomach. Chronic inflammation of the stomach caused by *Helicobacter pylori* often leads to neoplastic transformation (21). Clinical and epidemiological studies have shown that gastric cancer is an inflammation-driven malignancy (24-26). Elevated serum concentrations of pro-inflammatory cytokines such as IL-6 were observed to be significantly higher in individuals with gastric cancer, as well as in patients with other inflammation-associated cancer types, such as colon and prostate cancers (27,28). Therefore, we speculated that the elevated MPV level in gastric cancer patients may be due to a consequence of SIR. In patients with better chemotherapeutic efficacy, decreased MPV level may be due to remission of SIR, leading to a more favorable prognosis. By contrast, non-decreasing MPV may reflect persistent SIR and worse outcomes.

The results of the present study indicate that MPV may be used in the prediction of chemotherapy response and the follow up of gastric cancer. Considering the high gastric cancer morbidity and less developed economic conditions in China, this non-invasive, convenient and cost-effective biomarker may be beneficial in the treatment of gastric cancer.

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