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Original Article

Mean platelet volume/platelet count ratio is associated with prognosis in patients with pancreatic cancer

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Abstract: An increased mean platelet volume (MPV) is recognized as an early marker of platelet activation. The diagnostic and prognostic impact of the MPV and MPV/platelet count (PC) ratio in some cancers has recently been reported. The aim of this study was to evaluate the prognostic significance of preoperative MPV/PC ratio in pancreatic cancer. A total of 124 pancreatic cancer patients were included in the study and retrospectively reviewed. The preoperative hematological parameters were examined and analyzed along with patient clinicopathological parameters and prognosis. MPV and MPV/PC ratio were significantly increased in the pancreatic cancer group. Patients with pancreatic cancer had a slightly lower platelet count than patients with benign pancreatic tumor or healthy controls. Univariate analysis revealed that overall survival (OS) was significantly shorter in the group with a high MPV/PC ratio than in the other groups (median survival time [MST]: 7.0 months vs. 13.0 months, log-rank, P<0.001). Multivariate analysis confirmed that a high MPV/PC ratio was an independent unfavorable predictive factor for OS (hazard ratio [HR]: 3.726, 95% confidence interval [CI]: 2.018-6.880, P<0.001). A high MPV/PC ratio is closely related with an unfavorable prognosis in patients with pancreatic cancer.

Keywords: MPV, MPV/PC ratio, prognosis, pancreatic cancer

Introduction

Pancreatic cancer is one of the most deadly forms of malignant cancer in the world [1] and has the poorest prognosis among abdominal tumors [2]. Only 20% of pancreatic cancer patients undergo a potentially curable resection at diagnosis [3]. Pancreatic cancer has a median survival of less than 6 months and an overall 5-year survival rate of less than 5% [4]. Surgical resection remains the only curative management option [5]. During the last decade, several tumor markers have been identified for early diagnosis and follow-up of pancreatic cancer [6, 7], but none have proven to be sufficiently effective [8]. The level of serum CA 19-9 is the most widely used marker of pancreatic cancer for diagnosis and prognosis [9]. Previous studies showed CA 19-9 had a sensitivity and specificity of about 70 and 80%, respectively [10]. However, its use as a biomarker is limited as it lacks sensitivity for early or small-diameter pancreatic cancers and can also be increased in patients with benign jaundice, pancreatitis or other gastrointestinal malignancies [11].

Mean platelet volume (MPV) is a platelet volume index. An increased MPV is recognized as an early marker of platelet activation [12]. Large platelets are more reactive than smaller ones as they may be more readily stimulated to produce chemical mediators [13]. Several previous studies have shown increased MPV in gastric cancer [14], lung cancer [15] and hepatocellular carcinoma [16]. In study these preoperative MPV also showed a significant increase in patients with pancreatic cancer.

Recently, the MPV/PC ratio has been reported as a predictor of long-term mortality after non-ST-elevation myocardial infarction [17]. In addition, a previous study suggested that the MPV/PC ratio was increased in patients with hepatocellular carcinoma [16]. The MPV/PC ratio has also been demonstrated to be closely associated with survival in patients with advanced

Table 1. The correlation between MPV/PC ratio and clinicopathological parameters in patients with pancreatic cancer

Characteristics	Total cases (N=124)	MPV/PC ratio ≤0.0567 (N=62)	MPV/PC ratio >0.0567 (N=62)	*P* value
Age (years)				
Median (range)	62 (37-81)	62 (37-78)	61 (41-81)	0.8436
Gender				
Female	61	29	32	0.5900
Male	63	33	30	
Smoking history				
No	90	44	46	0.5783
Yes	34	18	15	
CA19-9 (U/ml)				
<39	23	12	11	0.8173
≥39	101	50	51	
Tumor diameter (cm)				
<3.0	28	13	15	0.6675
≥3.0	96	49	47	
Tumor localization				
Head and neck	83	46	37	0.0858
Body and tail	41	16	25	
Clinical Stage				
I-II	88	42	46	0.4287
III-IV	36	20	16	
Lymphatic metastasis				
No	60	25	35	0.0723
Yes	64	37	27	

Note: N, Number; MPV/PC ratio, mean platelet volume/platelet count ratio.

NSCLC [13]. In this study, we investigated the prognostic significance of preoperative MPV/PC ratio in pancreatic cancer.

Patients and methods

We conducted a retrospective study of patients diagnosed with pancreatic cancer who underwent surgery at the first affiliated hospital of Nanjing Medical University (Nanjing, China), between February 2009 and May 2014. Patients with hypertension, hematological and renal disease, heart failure, chronic infection, hepatic disorder, and other cancers were excluded from the study. For the control groups, 138 age and sex matched healthy controls and 45 patients with benign pancreatic tumor including 36 cases of serous cystadenoma and 9 cases of pancreatic cyst were enrolled in the study. The following clinical characteristics were obtained from the patients' medical records: age, gender, smoking history, pathological lymph node status, clinical staging, tumor diameter, and tumor localization. The preoperative hematological parameters were obtained two days before the surgery. The postoperative hematological parameters were also obtained two weeks after the surgery. Blood samples treated with elhylene diamine tetraacetic acid (EDTA) were tested using an automated hematology analyzer (Sysmex XE-2100, Japan) for measurement of various platelet volume indices. This study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethic Committee of the first affiliated hospital of Nanjing Medical University Written informed consent was obtained from patients before inclusion in the study.

Statistical analysis

All parameters were expressed as means ± standard deviation or median (minimum-maximum), as appropriate. One-way ANOVA was

Table 2. Hematologic parameter of the study groups

Characteristics	Pancreatic cancer (N=124)	Benign pancreatic tumor (N=45)	Healthy Controls (N=138)	*P* value
Age (years)				
Median (range)	62 (37-81)	59 (38-82)	60 (37-81)	0.0744
Gender				
Female	61	28	75	0.3105
Male	63	17	63	
MPV (fl)	10.93 ± 0.12	10.22 ± 0.16	9.52 ± 0.11	<0.0001*
PC ($\times 10^9$/l)	199.3 ± 5.9	218.2 ± 8.2	216.6 ± 3.1	0.0175*
MPV/PC ratio (fl/(10^9/l))	0.062 ± 0.002	0.052 ± 0.003	0.047 ± 0.001	<0.0001*
PDW	14.34 ± 0.18	14.74 ± 0.24	15.10 ± 0.18	0.0124*
Hb (g/dL)	127.3 ± 1.4	133.6 ± 2.4	141.3 ± 1.3	<0.0001*
WBC (10^9/l)	6.4 ± 0.2	5.9 ± 0.3	6.2 ± 0.1	0.4899

Note: Data are presented as means ± standard deviation or median (minimum-maximum). N, Number; MPV, mean platelet volume; PC, platelet count; MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width; Hb, hemoglobin; WBC, white blood cell. *P<0.05.

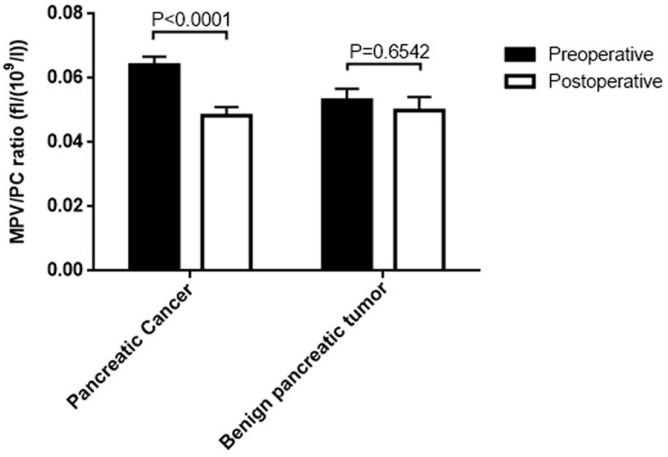

Figure 1. Preoperative and postoperative MPV/PC ratio in patients with pancreatic cancer and benign pancreatic tumor. The postoperative MPV/PC ratio was significantly decreased compared to preoperative MPV/PC ratio in patients with pancreatic cancer (P<0.0001), however, no significant change in patients with benign pancreatic tumor (P=0.6542).

used to compare the parameters of the pancreatic cancer group, benign pancreatic tumor group, and healthy control group. Chi-square test was used to compare the categorical variables. Paired sample t-test was used to compare the parameters of preoperative and postoperative MPV/PC ratio in pancreatic cancer and benign pancreatic tumor group. Overall survival (OS) was measured from the date of surgery to the date of death from any cause or the date the patient was last known to be alive. Univariate and multivariate analyses of OS were performed using the Kaplan-Meier test and the Cox proportional hazards model, respectively. Statistical analyses were performed using IBM SPSS Statistics Ver 2.0 and GraphPad Prism v6. All statistical tests were two-sided and *P*<0.05 was considered to be statistically significant.

Results

The correlation between MPV/PC ratio and clinicopathological parameters in pancreatic cancer

A total of 124 patients with pancreatic cancer were enrolled in this study. The characteristics of these 124 patients are summarized in **Table 1**. Their median age was 62 years (range: 37-81 years) and they included 61 women and 63 men. Thirty-four patients had a history of smoking whereas the remaining 90 patients had never smoked. Sixty-four patients had lymphatic metastasis at diagnosis. The tumor was located in the head or the neck of the pancreas in 83 patients and in the body or the tail of the pancreas in 41 patients. Eighty-eight patients were in stage I-II and 36 cases in stage III-IV. We divided the patients with pancreatic cancer into 2 groups according to the median of the MPV/PC ratio of 0.0567. The characteristics of the 2 groups are shown in **Table 1**. There were no significant differences in age, gender, smoking history, CA19-9 levels, clinical stage, tumor diameter, tumor localization, or lymphatic metastasis between the 2 groups.

Table 3. Univariate analysis of overall survival

Variable	MST (months)	*P* value
Age, <70 years vs. ≥70 years	11.5 vs. 7.0	0.028*
Gender, Female vs. male	12.0 vs. 10.0	0.158
MPV/PC ratio, low vs. high	13.0 vs. 7.0	<0.001*
MPV, low vs. high	11.5 vs. 10.0	0.457
Stage I-II vs. III-IV	13.0 vs. 7.0	0.015*
Lymphatic metastasis, No vs. Yes	14.0 vs. 8.0	<0.001*
Hemoglobin, low vs. high	9.0 vs. 12.0	0.278
Tumor diameter, <3 cm vs. ≥3 cm	12.0 vs. 9.0	0.220
Tumor localization, head and neck vs. body and tail	12.0 vs. 10.0	0.333

Note: MST, median survival time; MPV, mean platelet volume; MPV/PC ratio, mean platelet volume/platelet count ratio. *P<0.05.

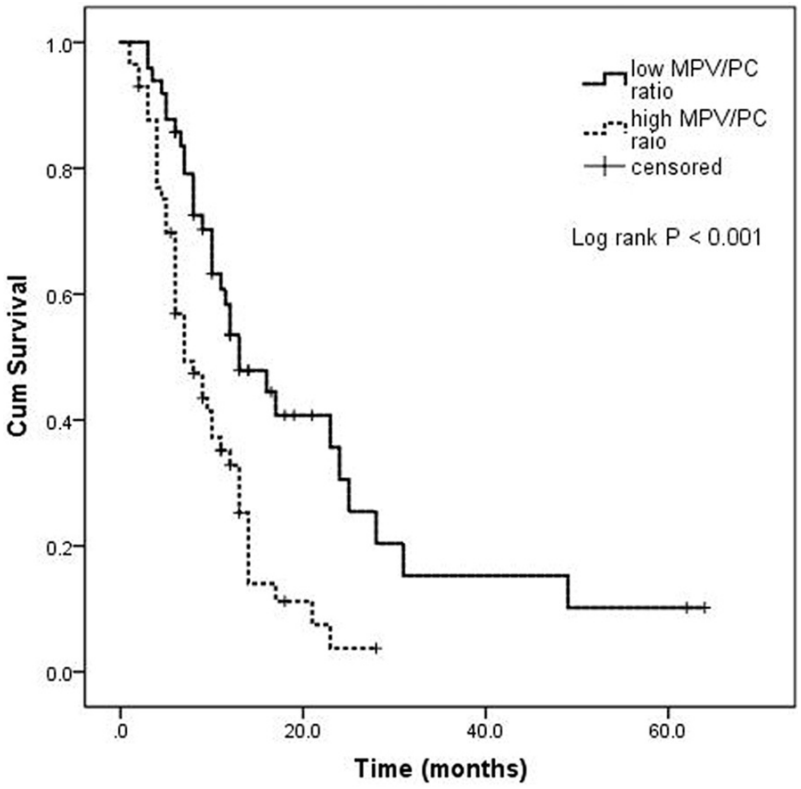

Figure 2. Kaplan-Meier curves for overall survival (OS) of the patients according to the MPV/PC ratio. The median survival times (MSTs) for the group with a high MPV/PC ratio and the group with a low MPV/PC ratio were 7.0 and 13.0 months, respectively (log-rank, P<0.001).

Comparison of hematological parameters among patients with pancreatic cancer, benign pancreatic tumor, and healthy controls

To assess the hematological parameters of patients with pancreatic cancer, 2 comparator groups were considered: 45 patients with benign pancreatic tumor and 138 age- and sex-matched healthy controls. Hematologic parameters of the study groups are given in **Table 2**. There were no statistically significant differences among the groups regarding age, gender, and white blood cells (WBC) (**Table 2**). The platelet count (PC), platelet distribution width (PDW), and hemoglobin levels were lower in patients with pancreatic cancer than in the comparator groups (**Table 2**). In contrast, preoperative MPV levels in patients with pancreatic cancer were found to be significantly higher when compared with benign pancreatic tumor and healthy controls (both P<0.0001, **Table 2**). Interestingly, preoperative MPV/PC ratios in patients with pancreatic cancer were also significantly elevated compared with benign pancreatic tumor and healthy controls (both P<0.0001, **Table 2**). However, MPV/PC ratios in postoperative patients with pancreatic cancer were significantly decreased compared to preoperative values (0.048 ± 0.003 vs. 0.064 ± 0.003, P<0.0001) (**Figure 1**). Furthermore, there were no significant differences in MPV/PC ratios between postoperative pancreatic cancer patients and healthy controls (0.048 ± 0.003 vs. 0.047 ± 0.001, P=0.6606) and between preoperative and postoperative patients with benign pancreatic tumor (0.052 ± 0.003 vs. 0.050 ± 0.004, P=0.6542) (**Figure 1**).

Univariate analyses for overall survival

We conducted a series of survival analyses on July 1, 2015. During this period, 78 patients had died, 28 patients were still alive, and 18 patients were lost in follow-up. Consequently,

Table 4. Multivariate analysis of overall survival

Covariate	HR	95% CI	*P* value
Age, <70 years vs. ≥70 years	1.279	0.747-2.188	0.370
Gender, Female vs. male	0.827	0.575-1.556	0.946
MPV/PC ratio, low vs. high	3.726	2.018-6.880	<0.001*
MPV, low vs. high	0.950	0.570-1.585	0.846
Stage I-II vs. III-IV	1.815	1.049-3.140	0.033*
Lymphatic metastasis, No vs. Yes	3.421	1.960-5.971	<0.001*
Hemoglobin, low vs. high	0.823	0.501-1.353	0.443
Tumor diameter, <3 cm vs. ≥3 cm	1.287	0.794-2.085	0.306
Tumor localization, head and neck vs. body and tail	0.840	0.492-1.434	0.522

Note: MST, median survival time; MPV, mean platelet volume; MPV/PC ratio, mean platelet volume/platelet count ratio.
*P<0.05.

the censoring rate was estimated at 37.1%. In univariate analyses, OS was significantly increased in patients younger than 70 years of age (P=0.028), in early stages of disease (P= 0.015), and patients without lymphatic metastasis (P<0.001). However, gender (P=0.158), MPV levels (P=0.457), tumor diameter (P= 0.220), tumor localization (P=0.333), and hemoglobin levels (P=0.278) were not statistically significant (**Table 3**). We also analyzed the contribution of the MPV/PC ratio to OS. The median survival times (MSTs) were 7.0 months (95% CI: 4.040-9.960) and 13.0 months (95% CI: 8.111-17.889) for patients with high and low MPV/PC ratios, respectively. In univariate analysis, OS was significantly decreased in the patients with a high MPV/PC ratio (P<0.001) (**Figure 2**). We subsequently conducted a multivariate analysis to evaluate the independent survival value of the covariates.

Multivariate analysis for overall survival

Multivariate analysis showed that a high MPV/PC ratio was an independent unfavorable prognostic factor for OS (hazard ratio [HR]: 3.726, 95% CI: 2.018-6.880, P<0.001). In contrast, 2 independent favorable prognostic factors were patients free of lymphatic metastasis (P<0.001) or having an early stage disease (P=0.033) (**Table 4**). However, gender (P=0.946), MPV levels (P=0.846), tumor localization (P=0.522), tumor diameter (P=0.306), and hemoglobin levels (P=0.443) were not significant factors. In contrast to the results of univariate analysis, there was no significant difference in OS between patients younger and older than 70 years of age (P=0.370).

Discussion

Recently, increasing attention has been given to the evaluation of the MPV, which is recognized as an early marker of platelet activation. Previous studies have revealed that an elevation of MPV is involved in the severity and prognosis of cardiovascular disorders [17-20]. Khode *et al.* reported that MPV was significantly higher in patients with acute myocardial infarction than in healthy controls [21]. Elevated MPV levels have been also found in many malignancies, such as hepatocellular carcinoma [16], gastric cancer [14], papillary thyroid carcinoma [22], and colon cancer [23]. Furthermore, Kumagi *et al.* [15] showed that an elevated preoperative MPV value was an independent predictor of shorter disease-free survival and reduced overall survival in patients with non-small-cell lung cancer.

Previous studies reported that MPV was inversely correlated with platelet count in normal populations [24, 25]. Recently, a few studies have suggested that MPV/PC ratio was a better index than MPV in some diseases. MPV/PC ratio has been put forward as a predictor of long-term mortality after myocardial infarction [17]. Moreover, Cho *et al.* reported that the MPV/PC ratio was significantly different between the hepatocellular carcinoma patients and control group, suggesting superior diagnostic value in the receiver operating characteristic curve (ROC curve) than MPV alone [16].

To date, very few studies have examined the relationship between MPV and pancreatic cancer. A study done by Karaman *et al*. evaluated the diagnostic value of MPV for distinguishing

pancreatic neuroendocrine tumors (PNETs) from pancreatic adenocarcinomas and showed lower MPV levels in PNETs compared to pancreatic adenocarcinomas [26]. In yet another study, Aliustaoglu *et al.* assessed the prognostic value of preoperative platelet counts and MPV in patients with pancreatic cancer, but found that MPV was not a prognostic parameter in pancreatic cancer [27]. Our data showed that preoperative MPV was significantly higher in patients with pancreatic cancer when compared to benign pancreatic tumor patients and healthy controls (P<0.001); however, there was a substantial reduction in MPV after surgery. Similar to Aliustaoglu's study, our results also revealed that MPV was not a prognostic factor in pancreatic cancer. In the present study, the correlation between MPV/PC ratio and pancreatic cancer has been evaluated for the first time. Our study demonstrated that MPV/PC ratio was significantly increased preoperatively and decreased postoperatively in patients with pancreatic cancer. In contrast to MPV alone, a high MPV/PC ratio was an independent, unfavorable prognostic factor for overall survival (P<0.001).

In the present study, lower hemoglobin values were also found in patients with pancreatic cancer compared with benign pancreatic tumor or healthy controls (P<0.001). Malignant cells can produce cytokines, such as interleukins (ILs), IFN-γ, and TNF-α, that may induce hemolysis and inhibit erythropoiesis [28]. Prior reports showed that lower hemoglobin levels were a negative prognostic factor in endometrial cancer [29, 30]. Karaman *et al*. also reported that hemoglobin levels have diagnostic value for distinguishing PNETs from pancreatic adenocarcinomas [27]. In the present study, although statistically not significant (MST: 9.0 vs. 12.0, P=0.278), patients with lower hemoglobin levels had shorter MST than those with higher hemoglobin levels.

Platelets play a variety of roles in physiological pathways, including coagulation and inflammation. MPV may be considered an indicator of changes in platelets function and activity [15]. An increased MPV is recognized as an early marker of platelet activation. Activated platelets provide procoagulant surfaces thereby amplifying the coagulation reactions [31]. It has been shown that large platelets are denser and readily stimulated to release thromboxane A2 and inflammatory cytokines (e.g. TNF-α, IL-1, IL-6). Such platelets also have a higher thrombotic and inflammation potential [28]. Previous studies have demonstrated that thrombocytosis and coagulopathy may also influence the prognosis of patients with pancreatic cancer [29]. In addition, our data revealed a reduction of platelet count in patients with pancreatic cancer when compared to benign pancreatic tumor or healthy controls (P=0.0175). Although the mechanism is unclear, it may likely be caused by suppression of bone-marrow or hypersplenism-related portal or splenic vein thrombosis [30]. Consequently, due to elevated MPV and decreased platelet counts, the MPV/PC ratio of circulating platelets would be increased. Pancreatic cancer, especially at an advanced stage, can activate platelets in several ways, such as through tumor necrosis, endotoxin, and cancerous cells, which can in turn induce increased consumption of platelets. Platelet activation may damage endothelium to make cancer cells more prone to invasion and metastasis. Conversely, platelet activation could induce a hypercoagulated state that would result in blood flow carrying fewer immune cells, potentially leading to enhanced cancer cell invasion and metastasis. A possible explanation for the poor prognosis of patients with a high MPV/PC ratio could be due platelet-derived growth factor and vascular endothelial growth factor being released by platelets during blood clotting that may also play important roles in regulating angiogenesis [32].

In conclusion, our results demonstrated that a high MPV/PC ratio was an independent unfavorable prognostic factor for patients with pancreatic cancer. Further study should clarify the etiology by which the amount and volume of platelets modulate mortality in patients with pancreatic cancer.

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Disclosure of conflict of interest

None.

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