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Original Article

Prognostic significance of preoperative platelet-lymphocyte ratio in a Chinese cohort patient with colorectal cancer

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Abstract: Cancer-related systemic inflammation affects many aspects of malignancy. The platelet-to-lymphocyte ratio (PLR), an easily applicable inflammatory marker based on platelet and lymphocyte counts, is associated with the clinical outcome of some cancers. The present study aimed to investigate the prognostic significance of the preoperative PLR in a cohort of colorectal cancer (CRC) patients. A total of 138 patients with CRC were enrolled in this retrospective study. The optimal cutoff value for the PLR was calculated using receiver operating curve (ROC) analysis. The correlation of PLR with the clinicopathological characteristics of patients was explored. Cox proportional hazard analysis was applied to determine the independent prognostic effect of PLR. PLR of 248 yielded the most optimal predictive value for the prognosis of CRC [area under the curve (AUC) = 0.820]. High level of PLR was significantly associated with lymph node and distance metastasis (P<0.001 and = 0.003, respectively), vascular and perinural invasion (P<0.001), advanced TNM stage (P<0.001), and poor differentiation (P = 0.037). Furthermore, the univariable analysis showed a significant impact of increased PLR on OS (HR = 4.326, 95% CI: 2.903-6.445, P<0.001), while this association remained significant in multivariable analysis (adjusted HR = 4.605, 95% CI: 2.786-7.611, P<0.001). Our findings indicated that elevated preoperative PLR might have potential value in predicting poor outcome in patients with CRC.

Keywords: Platelet-lymphocyte ratio, colorectal cancer, prognosis, inflammation, thrombocytosis

Introduction

Colorectal cancer (CRC) is the third leading cancer and is one of the common causes of cancer-related death worldwide [1]. With the economic development, lifestyle changes, and population aging, CRC has continued to show an increasing trend in incidence in China [2]. The prognosis of CRC has improved dramatically within the last decade, with a median survival time of 24-30 months, due to the development of systemic algorithms including chemotherapeutic and molecular targeting agents [3-5]. However, the patients with advanced CRC still have poor outcome. The prognosis of cancer patients is usually determined by the use of clinical or histopathological factors, especially TNM stage system. However, different patients with same stage usually have different outcome. It's very important to discriminate different risk groups, which may help determine right therapeutic regimens for these patients. Therefore, the intrinsic genetic background of the CRC such as microsatellite instability and KRAS mutation were explored [6-8]. Some researchers suggested that cancer progression and survival rates were not determined based on the local characteristics of the tumor, but also by the host-response factors such as performance status, weight loss, and systemic inflammatory response [9]. In addition, the method to detect molecular parameters is still under investigation and its clinical applications are limited by high costs and nonconvenient. Therefore, recently the clinical role of easy available inflammation related markers in cancer has gained widely concerned.

Pre-therapeutic elevated systemic inflammation response has been considered to associ-

ate with a poor outcome independent of the tumor stage [10, 11]. Several inflammation indices including the serum white blood cells, acute phase proteins and the combined parameters such as Glasgow prognostic score (GPS), neutrophil lymphocyte ratio (NLR), lymphocyte monocyte ratio (LMR), and Onodera's prognostic nutritional index (PNI) have been consistently studied for potential application in cancer prognosis [12-14]. Platelets are also part of the inflammatory response and the link between thrombocytosis and shorter survival time has been established in several types of solid tumors including breast, lung, colon, gastric and ovarian cancers [15-18], with the recognition that low lymphocyte counts may also be associated with poor prognosis [19]. The platelet to lymphocyte ratio (PLR) has been hypothesized and studied as a prognostic biomarker in various cancers including CRC [20-22].

Since the complete blood count (CBC) is a simple, low cost, and routine preoperative testing, no extra cost would be incurred for the use of PLR. In this study, we investigated the association between the preoperative PLR and prognosis of CRC patients, and aimed to find a new easy accessible and reliable prognostic marker complementing the TNM stage system in clinical practice and then for the stratification of patients in further treatment.

Materials and methods

Study subjects

We performed a retrospective chart review of 138 patients who underwent colonoectomy for CRC at Taizhou People's Hospital, Jiangsu Province, China between 2005 and 2009 to collect their clinical characteristics and demographic data. None of these cases had received preoperative chemotherapy or irradiation. Patients who had incomplete laboratory data particularly preoperative CBC and had no available medical records or surgical pathological reports were excluded. Patients who had any conditions that may affect the number of leukocytes or proportion of differential count (e.g., immediate past or current history or signs or symptoms of infection, hematologic diseases, steroid intake or receiving blood transfusion) were also excluded. The histological subtype of CRC was determined according to the 1997 UICC classification. The pathological staging was determined according to the 2002 TNM classification. Routine laboratory measurements including CBC, and automated differential counts were carried out on the day of admission in order to exclude any effects attributable to inflammation associated with sequential preoperative examinations. The ethical committee of the Taizhou People's Hospital approved the study. Written informed consents were obtained from all patients according to the guidelines approved by the Institutional Research Board.

Two millimeters of peripheral blood was collected from patients, and was sent to the laboratory center to be assessed within one hour after venipuncture. A complete blood profile, including total and differential leukocyte counts, was measured using the COULTER LH 750 Hematology Analyzer (Beckman Coulter Inc., Brea, CA, USA). The intra-assay coefficient of variation for white blood cell was 2.5%, and the standard error of differential count was less than 3%. The PLR was calculated by dividing the platelet count by the lymphocyte count.

Follow-up

Overall survival (OS) was defined as the time from the first day of treatment to the time of death from any cause. When the patient was lost to follow-up or the death was not recorded, the patient was censored. The survival time of censored patients was defined by the period from the initiation of treatment to the last day of follow up or to December 31, 2014, the date on which the survival was investigated. Patients were followed every 3 months for the first 2 years after treatment, then every 6 months for the subsequent 3 years. Follow-up information, including death cause, was obtained through reviewing clinical information and direct contact with family. The designed during of follow-up was 5 years.

Statistical analyses

The cutoff value for the PLR was determined applying receiver operating curve (ROC) analysis. The relationship between the PLR and other clinicopathological features was analyzed by Student *t*-test or one way ANOVA test. Patients' clinical end points (5-year OS) were calculated using the Kaplan-Meier method and compared by the log-rank test. Univariable and multivariable Cox proportion analysis were performed to

Table 1. Baseline characteristics of CRC patients according to the PLR value

Variables		Total (n = 138)	PLR	*P* value
Age (year)	≥61	84	231.02 ± 81.31	0.548
	<61	54	228.33 ± 90.22	
Sex	Male	78	233.72 ± 80.54	0.677
	Female	60	227.62 ± 91.03	
LNM	Positive	58	269.07 ± 90.60	<0.001
	Negative	80	203.51 ± 69.11	
Distance metastasis	Positive	5	340.00 ± 91.90	0.003
	Negative	133	226.97 ± 82.31	
Vascular invasion	Positive	22	293.18 ± 90.56	<0.001
	Negative	116	219.28 ± 78.93	
Perinural invasion	Positive	24	294.79 ± 86.75	<0.001
	Negative	114	217.65 ± 78.63	
Histologic grade	Well	55	243.85 ± 94.67	0.037
	Moderate	61	234.44 ± 84.26	
	Poor	22	189.73 ± 39.27	
TNM stages	I	2	142.50 ± 21.92	<0.001
	II	34	192.47 ± 44.18	
	III	97	240.80 ± 88.75	
	IV	5	340.00 ± 91.90	

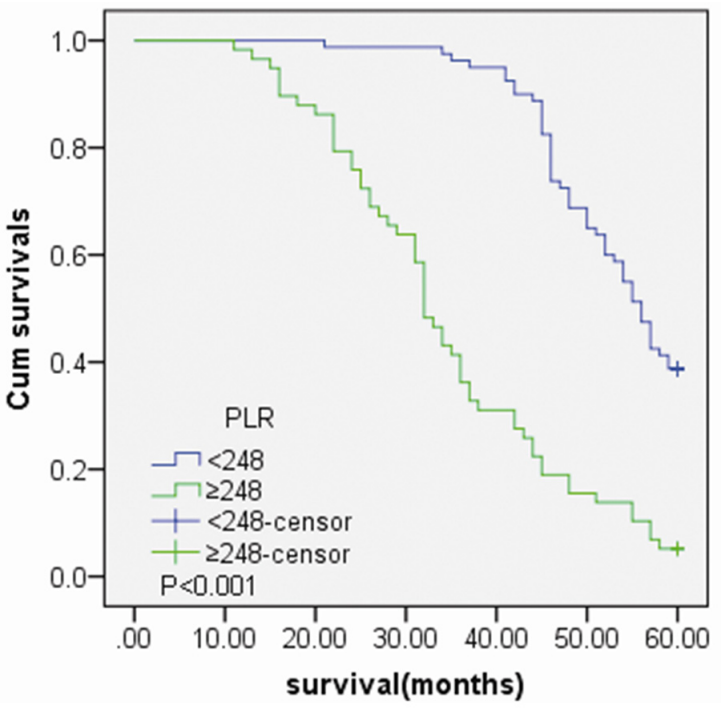

Figure 1. Kaplan-Meier (KM) survival curve of CRC patients was stratified by the preoperative PLR. The 5-year survival rate of patients with high level of PLR was 5.20% whereas 38.80% in patients with low level of PLR (*P*<0.001).

determine the influence of potential confounders such as age, gender, pathologic tumor stage, grade, lymph node metastasis (LNM), distance metastasis, vascular and perineural invasion on OS. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 (IBM Co., Armonk, NY, USA). A two sided *P*<0.05 was considered statistically significant.

Results

Patients' characteristics

Between January 2005 and December 2009, 150 patients with CRC in our hospital were recruited. Twelve patients were excluded because of incomplete clinical data. As a result, a total of 138 patients in this cohort met all inclusion criteria and were included in the study. The baseline clinicopathological parameters of 138 patients were listed in **Table 1**. The mean age of the patients was 61.38 ± 11.35 years (range, 33 to 82 years). A minor dominance of male cases (n = 78) was observed compared with their female counterparts (n = 60). In addition, most of the patients were classified as stage III, followed by stage II, and only five patients with stage IV and two with stage I. Fifty eight patients exhibited regional lymph node involvement. There were only five patients with distance metastasis who received palliative resection, of which all cases had significantly high levels of PLR.

Clinicopathological significance of PLR

The mean PLR of these patients was 231.07 ± 84.99. PLR of 248 yielded the most optimal predictive value for distinguishing death from survival according to ROC curves. Therefore, we determined a cutoff value of PLR

Table 2. Univariate and multivariate analysis of factors associated with the overall survival in patients with CRC

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.009 (0.997-1.027)	0.335		
Gender	0.761 (0.513-1.128)	0.174		
PLR	4.326 (2.903-6.445)	<0.001	4.605 (2.786-7.611)	<0.001
LNM	2.356 (1.594-3.482)	<0.001	0.574 (0.333-0.989)	0.046
Distance metastasis	4.428 (1.381-14.292)	<0.001	7.591 (2.090-27.569)	0.002
Vascular involvement	6.145 (3.697-10.213)	<0.001	0.466 (0.101-2.156)	0.329
Perineural invasion	6.741 (4.102-11.077)	<0.001	13.20 (2.799-62.241)	0.001
Histology grades	0.782 (0.597-1.024)	0.073		
TNM stages	3.072 (1.868-5.051)	<0.001	1.487 (0.886-2.496)	0.033

to divide patients into high (PLR≥248) and low (PLR<248) PLR groups [area under the curve (AUC) = 0.820]. Overall, there were 80 patients with low level of PLR and 58 patients with high level of PLR. The clinicopathological characteristics of the patients according to PLR level were shown in **Table 1**. High level of PLR was significantly correlated with LNM (*P*<0.001), vascular (*P*<0.001) and perinural involvement (*P*<0.001), distance metastasis (*P* = 0.003), high tumor grade (*P* = 0.037) as well as advanced TNM stage (*P*<0.001). There were no significant differences in age and sex between high and low levels of PLR groups.

Survival

During the total follow-up time of 5 years, 104 patients (75%) were dead, 34 patients (25%) were still alive. Patients with high PLR had a median OS of 35 months, whereas those with low PLR had a median OS of 53 months (*P*<0.001, log-rank test; **Figure 1**). Furthermore, the results of univariate and multivariate analyses were showed in **Table 2**. In present study, 9 factors including age, gender, PLR, LNM, distance metastasis, vascular and perineural involvement, histological grades, and TNM stages were included in the univariate analysis. In univariable analysis, high PLR (HR = 4.326, 95% CI: 2.903-6.445, *P*<0.001), LNM (HR = 2.356, 95% CI: 1.594-3.482, *P*<0.001), distance metastasis (HR = 4.428, 95% CI: 1.381-14.292, *P*<0.001), vascular (HR = 6.145, 95% CI: 3.697-10.213, *P*<0.001) and perineural involvement (HR = 6.741, 95% CI: 4.102-11.077, *P*<0.001), and advanced TNM stage (HR = 3.072, 95% CI: 1.868-5.051, *P*<0.001) were associated with shorter OS. In further multivariate analyses, PLR (HR = 4.605, 95% CI: 2.786-7.611, *P*<0.001), along with the others factors such as distance metastasis (HR = 7.591, 95% CI: 2.090-27.569, *P* = 0.002), perineural involvement (HR = 13.20, 95% CI: 2.799-62.241, *P* = 0.001), and TNM stage (HR = 1.487, 95% CI: 1.086-2.496, *P* = 0.033), were still identified as independent prognostic factors (**Table 2**).

Discussion

Systemic inflammation, recognized as the 'seventh hallmark of cancer', has been reported to contribute to cancer proliferation, migration, angiogenesis, resistance to hormonal and chemotherapy, as well as the suppression of antitumor immunity through the release of chemokines, especially regulatory T cells, and therefore to affect their outcome [23-26]. A wide spectrum of hematological and biochemical markers including the levels of blood white blood cells, platelets and acute-phase proteins such as C-reactive protein (CRP) and albumin can reflect the systemic inflammatory state [27, 28]. Actually, studies on inflammation markers and host inflammatory responses in cancers have been actively carried out since 2000 [29]. Previous studies has reported that elevated WBC count and reactive thrombocytosis were predictive of outcome in addition to histological subtype, age and sex in the situation before any staging procedure to evaluate the patient for surgery [17, 30]. In addition to elevated neutrophil and platelet count reflecting systemic inflammation, decreased lymphocyte count is associated with immune suppression and may

also be associated with the shorter survival in cancers [31]. Therefore, the neutrophil to lymphocyte ratio (NLR) and PLR which combine both inflammatory and immunosuppressive indices might be better biomarkers than WBC count or platelet count alone. Increased NLR and PLR levels have already been shown to be correlated with the increase in cancer-associated system inflammation, and indicated advanced stage and predict poor outcomes in several types of malignancy including CRC [32]. Our current study mainly aimed to evaluate the role of PLR in a cohort of Chinese patient with CRC in our hospital. We found that there was no significant association of PLR with the patient's age and gender. However, it was encouraging that PLR were notably increased in cases with LNM or distance metastasis, vascular or perineural involvement, high grade as well as advanced TNM stages. Therefore, we could speculate that PLR might correlate closely with the progression of CRC and increased platelet count and decrease of lymphocyte might promote CRC cells local invasion as well as distance shift. In addition, in this study, patients with PLR over 248 were found to have relatively poorer 5-year survival compared with those with low level of PLR, indicated that PLR was an independent prognosticator of OS in CRC. The results of our study were consistent with other previous studies which found that high level of PLR appeared to be a poor prognostic factor [22, 33].

Although there is growing interest in a clinical interpretation of these interactions, the exact mechanisms underlying the association between an elevated level of PLR and the biological behavior of cancer cells remain unclear till now. High level of PLR may reflect relatively elevated plate count and/or depleted lymphocytes. Recent studies have demonstrated that reactive thrombocytosis was associated with survival after surgery for several types of cancer [17, 34]. Firstly, the release of inflammatory mediators (e.g. interleukin (IL)-1, IL-3, and IL-6) through tumor-host interaction can stimulate the proliferation of megakaryocytes, the platelet progenitor cells and then leading to reactive thrombocytosis [35]. Among these inflammatory cytokines, IL-6 has an important role in this reaction [36], as it is a multifunctional cytokine with a number of physiological actions. Secondly, thrombocytosis can also be induced from the tumor itself as a variety of neoplastic cells can stimulate platelet activation [37]. Recent experimental and clinical data indicated that the activation of platelets was crucial for cancer progression by promoting angiogenesis, degradation of the extracellular matrix, and release of adhesion molecules and growth factors [38]. In addition, tumor cell-induced platelet aggregation results in platelet coating of the tumor cells display co-expression of platelet markers which protects them from natural killer (NK) cells. These consequent may attenuating the ability of NK cells to shield circulating cancer cells against the immune system and inducing epithelial- mesenchymal transition, which leading to tumor metastasis [39-41]. Therefore, these results indicated platelets might contribute to accelerated tumor metastasis and progression. On the other hand, lymphocytes, usually $CD3^+$T cells and NK cells, can participate in cancer immuno-surveillance and then inhibit cancer cell proliferation and metastasis [42]. The number of lymphocytes is an undisputed prognostic marker in surgical oncology, reflecting the endogenous anticancer ability of the immune system [43, 44]. Lymphocytopeniais frequently observed in advanced cancer patients, and low lymphocyte count is strongly associated with a poor prognosis in advanced cancer patients [45]. Tumor-infiltrating lymphocytes in particular have been extensively studied, and appear to have an anti-tumorigenic role in CRC [46-48]. Taken together, it is likely that a high level of PLR may reflect the combined effects of thrombosis and lymphocytopenia, and may be a more meaningful prognostic factor for survival than either alone. Theoretically, direct measurement of the serum IL-6 level is the best way to estimate system inflammation based on tumor-host interaction. However, there are many unsolved problems associated with the routine measurement of IL-6 in cancer patients. Although a recent study has revealed that the serum level of IL-6 is associated with the postoperative survival of patients with gastric cancer [49], routine measurement of IL-6 is difficult in a clinical setting because of its high cost and inconvenience. On the contrary, PLR is easy to measure routinely because of its low cost and convenience. Therefore, this parameter has been investigated as prognostic indicator for different cancer entities in recent 2-3 years.

Since high level of preoperative PLR was confirmed to indicate poor prognosis in CRC, it might be very significant for cancer prevention and treatment. Therefore, the effects of anti-inflammatory drugs on tumor occurrence and development have already been investigated extensively. There was an increasing body of evidence that supports the use of anti-inflammatory agents to decrease recurrence rates and improve survival in some cancers including CRC. Anti-platelet drugs, being widely used to prevent cardiovascular disease, have additionally been found to reduce the incidence of colorectal adenomas and the rates of overall cancer deaths. The prophylactic application of non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the incidence of colon cancer by 40% to 50% [50-53]. Therefore, patients with high preoperative PLR, which indicating the system inflammation in patients with CRC could be considered as relatively high-risk patients who should be integrated with multi-mode anti-tumor therapies, such as chemotherapy, radiotherapy as well as the attempting to anti-inflammation method.

Although our study revealed an unfavorable outcome in the CRC patients with high level of PLR, some limitations of our study were inherent to its design including the retrospective data collection. First, sample size was small and only 138 patients were recruited. Second, the cancer progression and survival are determined according to the local characteristics of the cancer and the host response. We did not include the intrinsic genetic background in this study. The application of a combination of these parameters reflecting both the tumor characteristics and host systemic inflammatory status is important for predicting patient survival more precisely and selecting the optimal treatment in patients with CRC. Moreover, the cutoff value of PLR in previous studies varied partially attributing to different characteristic of subjects and various methods used in different studies [21-33]. Meanwhile, the relatively small sample size in our study could not allow determination of the most appropriate cutoff value for PLR. Therefore, our data have to be regarded as preliminary and should be validated and confirmed by additional more large and prospect studies.

In conclusion, we hereby showed that PLR could be a simple and useful system for predicting the prognosis of CRC patients. Further study should be carried out to confirm the role of this scoring system and then to optimize treatment strategy.

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Disclosure of conflict of interest

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