

Predictive value of preoperative systemic immune-inflammation index on tumor stage in patients with colorectal cancer

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Abstract: The aim of this study was to demonstrate the clinical significance of the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in association with tumor stage of colorectal cancer (CRC) patients. We undertook a retrospective review of 144 patients with colorectal cancer. Preoperative whole blood counts, serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen (CA-199), and clinicopathologic data were collected. The correlations between laboratory parameters and the tumor, node, and metastasis (TNM) stages were analyzed. ROC analysis indicated that both NLR (0.79) and PLR (0.64) had the comparable predictive powers for the presence of CRC in the general patient group. Kruskal-Wallis analysis revealed that significant elevations of NLR ($P=0.0018$) was firstly detected in all stages and showed a stage-dependent increase following the development of T, M stage (all $P<0.05$), while PLR was only identified as an independent factor for the T stage development ($P<0.05$). Accordingly, NLR and PLR was also identified as an independent factor associated with tumor grade (all $P<0.05$) by the univariate and multivariate regression analysis model. Thus, our data indicated that both neutrophil-and platelet-mediated inflammatory reactions are predominantly involved in the different stages of CRC development. Determination of pretreatment levels of NLR and PLR might provide useful information for the early diagnosis or the therapeutic choices in CRC patients.

Keywords: Colorectal cancer; TNM stage; Neutrophil to lymphocyte ratio; Platelet to lymphocyte ratio

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1. Introduction

Colorectal cancer (CRC) is one of the most leading causes of cancer death in China, because of its recurrence and metastasis[1]. Although there have been remarkable improvements in the treatment and management of CRC, the overall prognosis of advanced CRC is still poor, with a 5-year survival rate less than 12%[2]. The TNM staging system-determined by tumor factors such as tumor depth, lymph node metastasis, and distant metastasis-is the most predictable prognostic factor for colorectal cancer[3]. However, the current system has a drawback that has not able to predict the response and outcome individually, particular for stage II and III CRC patients[4]. Therefore an urgent need remains to identify optimal biomarkers that help the early diagnosis or guide the therapeutic choice, which would be very helpful to predict progression and prognosis of the disease as complementary tools to intervention.

Recently, many randomized trials have provided to evidence in support of the concept that the host inflammatory response is associated with the development and progression of cancer[5,6] and moreover, with a poor outcome independent of the tumor stage[7]. The host-related inflammatory factors such as peripheral blood markers are helpful for determining CRC treatment strategies. Biomarker of neutrophil to lymphocyte ratio (NLR) and platelet to

lymphocyte ratio (PLR) has been reported to be associated with poor prognosis in CRC[8,9]. Nonetheless, rare clinical trials reported the insight into the correlations of the changes of preoperative NLR and PLR levels with CRC tumor stages. The primary objective of this study was to investigate the roles of both neutrophil and platelet-dependent inflammatory response in different tumor stages. And this advantage might be helpful for the therapeutic plan either in the selection of drugs or monitoring the treatment response.

2. Methods and Materials

2.1. Patient and controls selection

We reviewed altogether the records of 144 patients at Zhejiang Chinese Medicine University Affiliated No.3 Hangzhou Hospital during the period from January 2012 to January 2017. Patients were admitted to the hospital for curative resection of primary colorectal adenocarcinomas; no patients received any cancer specific pretreatment. Primary diagnosis included 46 individuals with colon cancer and 98 individuals with rectal cancer. Patients who had evidence of infection, hematological diseases, renal dysfunction, and hyperpyrexia were excluded from the study. As a control group, we reviewed the records of 144 age and gender-matched healthy individuals who performed their annual health check at the hospital. Written informed consent was obtained from all

patients, which have been performed in accordance with the ethical standards of Declaration of Helsinki and its later amendments.

post-hoc test and a multivariate regression model. A two-tailed P value of <0.05 was considered statistically significant.

2.2. Data collection

The clinical-pathological data were collected from medical records at the Department of Hospital Medical Record. The laboratory data including serum CEA, CA199, white blood cell, neutrophil, lymphocyte, platelet counts were collected and detected within 1 week prior to the treatment. For the calculation of the NLR and PLR, NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count and PLR was also conducted by the same way.

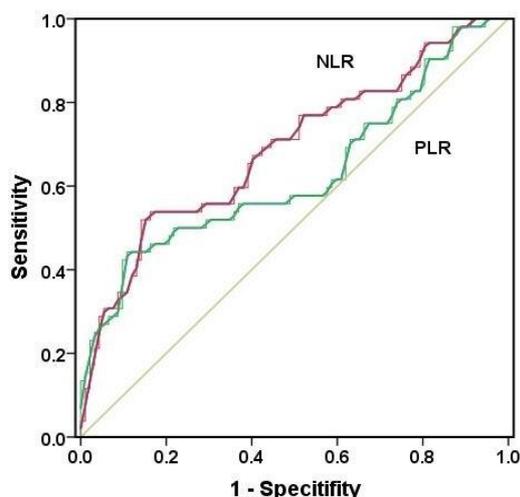


Figure 1. ROC curve analysis for NLR and PLR.

2.3. Statistical analysis

Data were expressed at either median and interquartile range (IQR) or mean and 95% confidence interval (CI), as appropriated. Statistical analyses were carried out by the GraphPad Prism 5 and SPSS version 17 softwares. Values of the area under curve (AUC) obtained from receiver operating characteristic curve (ROC) analysis were used to compare the predictive efficacy of NLR and PLR for presence of CRC. The association of NLR and PLR with TNM stages was evaluated by Kruskal-Wallis test followed by a

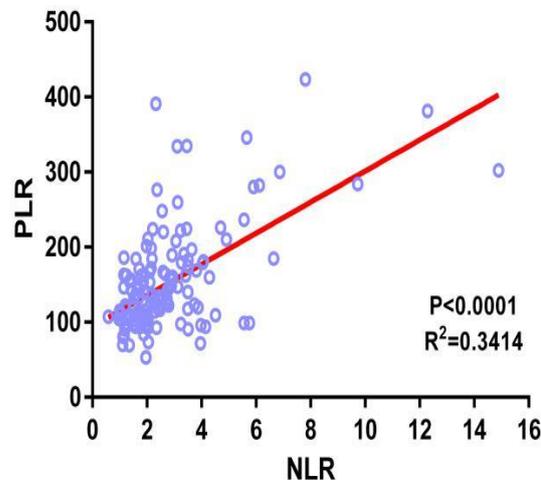


Figure 2. Linear regression of NLR and PLR.

3. Results

3.1. Patient characteristics and comparison in healthy controls

Detailed clinicopathological information of 144 patients are shown in Table 1. CRC patients had higher levels of CEA, CA199, absolute white blood cell (WBC), and neutrophil counts, platelet counts but lower absolute lymphocyte compared to that of controls. ROC analysis indicated that there are no differences between AUC values for NLR (0.79) and PLR (0.64) suggesting that both biomarkers had the comparable predictive powers for the presence of CRC in the general patient group in Figure 1. The optimal cut-off value of NLR was 2.49 and PLR was 182 similarly. Changes in the distribution of the WBC subsets were reflected in higher values of NLR and PLR in the patient group compared in the control group in Figure 2.

Table 1. Demographic information of CRC patients and healthy controls

	CRC patients	Healthy controls	P
Age (years)	61 (50 to 72)	57 (53 to 73)	0.215
Male/Female	85/59	79/65	0.475
CEA (ug/L)	4.7 (1.3 to 11.7)	1.9 (0.8 to 3.1)	<0.001
CA199 (ug/L)	21 (7.9 to 54.2)	5.1 (2.9 to 9.1)	<0.001
WBC (10 ⁹ /L)	6.9 (5.3 to 9.2)	5.5 (4.1 to 7.4)	<0.001
Neutrophil (10 ⁹ /L)	3.7 (2.9 to 4.5)	3.1 (2.4 to 4.3)	<0.001
Lymphocyte (10 ⁹ /L)	1.5 (1.1 to 3.2)	2.0 (1.3 to 2.4)	<0.001
Platelet (10 ⁹ /L)	251 (212 to 286)	211 (176 to 249)	<0.001

Grade	
G1	36 (25.00%)
G2	44 (30.56%)
G3	32 (22.22%)
G4	32 (22.22%)
Stage	
I	20 (13.89%)
II	32 (22.23%)
III	73 (50.69%)
IV	19 (13.19%)
T stage	
T1	5 (3.47%)
T2	44 (30.56%)
T3	69 (47.92%)
T4	26 (18.06%)
N stage	
N0	58 (40.28%)
N1	64 (44.44%)
N2	22 (15.28%)
M stage	
M0	125 (86.81%)
M1	19 (13.19%)
NLR	
<2.49	43 (29.86%)
≥2.49	101 (70.14%)
PLR	
<181	56 (38.89%)
≥181	88 (61.11%)

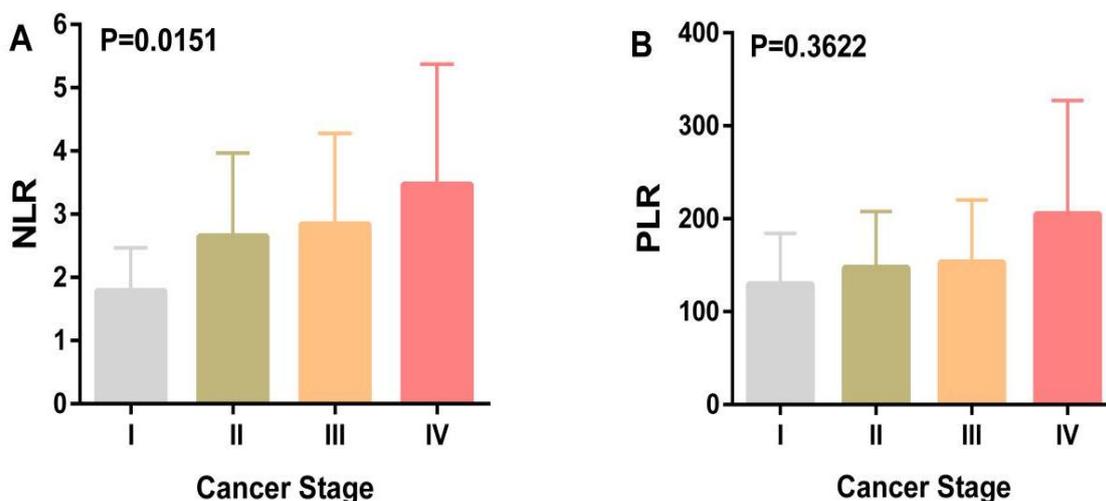


Figure 3. Association of NLR and PLR with cancer stages in CRC patients. (A) For NLR, P=0.0151; (B) For B, p=0.3622.

3.2. Association of NLR and PLR with cancer stages in CRC patients

The associations between NLR and PLR with cancer stage were shown in Figure 3. Analysis of Kruskal-Wallis test indicated that there was significant interactions between tumor stages (I to IV) and NLR ($P=0.0151$) while PLR had no difference ($P=0.3622$). It suggested that NLR maybe superior to the factor of PLR in terms of cancer stage.

3.3. Association of NLR and PLR with independent T, N, and M stages in CRC patients

To focus our interest on the relationship between NLR and PLR with cancer stages, we further analyzed the correlation of both markers with independent T, N, and M stages. Levels of NLR and PLR, classified separately by T, N, and M stages, are shown in Figure 4. Kruskal-Wallis analysis revealed that NLR ($P=0.0057$) and PLR ($P=0.0113$) showed a stage-dependent increase following the development of T stage. Moreover, neither NLR ($P=0.1662$) nor PLR ($P=0.2256$) showed any significant association with the development of N stages. In M stage comparison, only NLR showed significant higher levels in M1 subgroup ($P=0.034$) as compared to M0 subgroup.

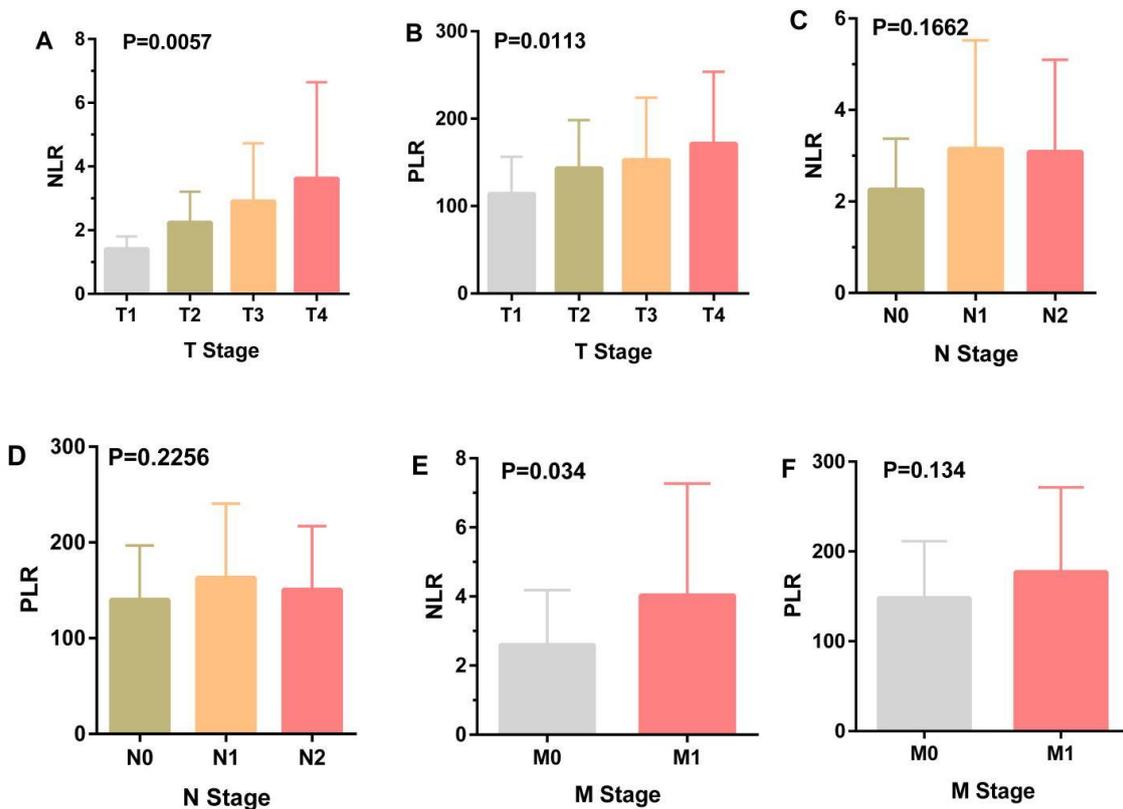


Figure 4. Association of NLP and PLR with independent T, N, and M stages in CRC patients.

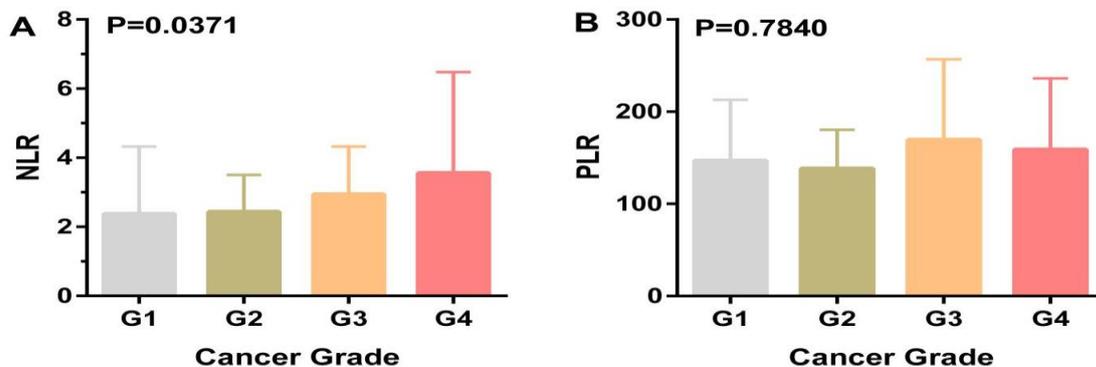


Figure 5. Association of NLP and PLR with cancer grades in CRC patients.

3.4. Association of NLR and PLR with cancer grades in CRC patients

With regard to cancer grade, Figure 5 showed that there was significant interactions between the grade (1 to 4) and NLR ($P=0.0371$), not PLR ($P=0.7840$). In other words, CRC patients with poorer grade had elevated NLR. Using the univariate and multivariate regression analysis model, the NLR was also identified as an independent factor associated with tumor grade ($P<0.05$).

4. Discussion

Links between inflammation and cancer development have garnered much interest in the past few decades[10]. It's well established that hematological markers of systemic inflammation (including NLR and PLR) could help reflect the status of tumor-growth in patients with various types of cancer[11-13]. In this study, we retrospectively examined factors of NLR and PLR in a cohort of CRC patients to provide evidence on the relationships with tumor TNM stages. One of our analysis is that the levels of both markers were significantly higher in CRC patients than in healthy controls. The increase in level of NLR and PLR was all correlated with the development of tumor stage. Further more, NLR showed a significant elevation from stage I to stage IV while analysis of PLR factor indicated no further changes were in the each stage. More importantly, NLR and PLR were also identified as an independent factor associated with tumor grade. Those results suggested that both neutrophil-and platelet-dependent inflammation responses were actively engaged in the different stages of cancer progression. The higher NLR and PLR we observed in the CRC patient are consistent with previous studies[14-15].

The increased levels of both biomarkers would reflect immune cells act closely with tumor development. The following reasons may account for the findings. The neutrophils as a major component of leukocyte population, could be activated and migrated from venous system to tumor cells, releasing large amounts of reactive oxygen species that was capable of inducing cell DNA damage and genetic instability, giving rise to colonic adenomas in cancer microenvironment[16,17]. Furthermore, neutrophil could be triggered by cancer-related inflammatory factors such as interleukin-6, tumor necrosis factor α (TNF- α) and granulocyte colony-stimulating factor, myeloid growth factors produced by cancer cell [18,19]. On the other hand, the lymphocyte is known to play a significant role in defense of tumor cells by inducing cytotoxic cell death and suppressing tumor cell proliferation and migration[20]. Peripheral platelets was thought to be indicators of the inflammatory process induced by cancer cells and a high level of platelets may promote tumor growth by increasing angiogenesis through production of vascular endothelial growth factor[21]. In turn, with this

alteration, the activated platelet favors tumor growth by releasing the granule components such as platelet-derived growth factor (PDGF), and transforming growth factor β (TGF- β)[22]. Therefore, elevated NLR and PLR represent a relative lymphocytopenia and it might affect the immune response to cancer tissues.

Additionally, we are interested in the relationship between the change in NLR, PLR and its relationship with tumor grade. We found it was significantly associated with the degree of tumor cell differentiation. Different grades may lead to different degrees of NLR and PLR. The specific mechanisms by which the PLR and NLR influences the tumor grade for patients with CRC remains incompletely understood. The tumor microenvironment inhabited by inflammatory cells is important in carcinogenesis, promoting cancer growth, invasion, tumor cell proliferation, and migration[23,24]. The difference in tumor grade between both indices should reflect the different pathophysiologic roles of neutrophils and platelets in cancer development.

The present study had the limitation that it was a retrospective, single-center study with a limited number of patients, particularly, only a few stage I and stage IV patients were included. This drawback might lead to an underestimation of the statistical power. Therefore, larger prospective studies will need to be performed to confirm these preliminary results.

In summary, our study demonstrated that the levels of preoperative NLR and PLR are independently correlated with the tumor TNM stages in CRC patients, suggesting the important roles of neutrophils and platelets in bridging the cancer-host interaction during the different steps of cancer development. Both of them have shown the potential values as the markers either in the early diagnosis or tumor T stage evaluation in CRC patients. The utility of them in individual therapy would be an interesting topic in the future study.

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