

Retrospective Study

Prognostic significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with stage III and IV colorectal cancer

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Abstract

AIM

To evaluate the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with colorectal cancer (CRC).

METHODS

Between April 1996 and December 2010, medical records from a total of 1868 patients with CRC were retrospectively reviewed. The values of simple inflammatory markers including NLR and PLR in predicting the long-term outcomes of these patients were evaluated using Kaplan-Meier curves and Cox regression models.

RESULTS

The median follow-up duration was 46 mo (interquartile range, 22-73). The estimation of NLR and PLR was based on the time of diagnosis. In multivariate Cox regression analysis, high NLR (≥ 3.0) and high PLR (≥ 160) were independent risk factors predicting poor long-term outcomes in patients with stage III and IV CRC. However, high NLR and high PLR were not prognostic factors in patients with stage I and II CRC.

CONCLUSION

In this study, we identified that high NLR (≥ 3.0) and high PLR (≥ 160) are useful prognostic factors to predict long-term outcomes in patients with stage III and IV CRC.

Key words: Colorectal cancer; Neutrophil; Lymphocyte; Platelet; Prognosis

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Core tip: Recently, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been suggested as important inflammatory markers and potential predictors of long-term outcomes in patients with colorectal cancer (CRC). However, the direct impact of NLR and PLR on long-term outcomes in patients with CRC remains inconclusive. In this study, we identified that high NLR and high PLR are useful independent prognostic factors to predict poor long-term outcomes in patients with stage III and IV CRC. And we propose that initial assessment of NLR and PLR in newly diagnosed stage III and IV CRC patients is important for predicting long-term outcomes.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common tumor in men and the second in women worldwide^[1]. According to the database of GLOBOCAN 2012, 1.4 million new CRC cases and 694000 CRC deaths occurred in 2012 worldwide^[2]. In Eastern Asia, CRC occurs in more than 37.0 per 100000 individuals per year and accounts for approximately 207700 annual deaths^[2]. Although the 5-year relative survival rate of CRC has been increasing over the past few decades, CRC is still the third leading cause of cancer-related death in the world and the median overall survival of patients with metastatic CRC is less than 30 mo^[3,4]. Identification of prognostic markers is an important step for assessing clinical outcome in CRC treatment. In previous studies, tumor stage, histologic grade, number of resected lymph nodes, lymphatic, venous or peri-neural invasion, and carcinoembryonic antigen (CEA) level have been demonstrated as prognostic factors^[5-8]. Recently, a large number of studies have suggested useful biomarkers for predicting clinical outcomes in CRC, however high costs and lack of

standardization limit their application in routine clinical practice^[9,10].

Previous reports have shown that the inflammatory response increases the risk of developing many types of cancer^[11,12]. Some transcription factors including NF- κ B and STAT3 (signal transducer and activator of transcription 3) and several inflammatory cytokines (such as IL-1 β , IL-6, IL-23, and TNF- α) are involved in cancer-related inflammation. Therefore, it has been suggested that the inhibition of these transcription factors and cytokines could decrease the incidence and spread of cancer^[11]. In particular, non-steroidal anti-inflammatory drugs reduce the risk of developing CRC and the mortality of CRC^[13-15]. At this time, it is widely accepted that the inflammatory response has a crucial role in the pathogenesis and progression of cancer. Among the various inflammatory markers, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been shown to influence clinical outcomes in various cancers^[16-19]. NLR and PLR can be easily calculated as the neutrophil count or platelet count divided by the lymphocyte count. Because neutrophil count, platelet count, and lymphocyte count are routinely evaluated, the assessment of NLR and PLR could be routinely used without additional cost in clinical practice. An elevated neutrophil count promotes tumor growth and metastasis by remodeling the extracellular matrix, releasing reactive oxygen species, and suppressing lymphocyte activity^[20]. In addition, the presence of tumor cells affects platelets and causes cancer-induced thrombosis^[21]. As a result of this activation, platelets release a number of growth factors which support tumor growth, angiogenesis, and metastasis^[22]. Recently, NLR and PLR have been suggested as important inflammatory markers and potential predictors of long-term outcomes in patients with CRC^[23-26]. However, because of the diversity in study designs, heterogeneous enrolled patient groups, and different cutoff values, the direct impact of NLR and PLR on long-term outcomes in patients with CRC remains inconclusive. In this study, we aimed to identify the prognostic value of the NLR and PLR in patients with CRC.

MATERIALS AND METHODS

Patients

Between April 1996 and December 2010, the medical records from patients diagnosed with CRC at Kosin University Gospel Hospital (Busan, Korea) were retrospectively reviewed. Patients who were histologically confirmed to have CRC were included. Patients whose medical records did not include complete blood count, and clinicopathological and follow-up data were excluded. Detailed clinical data including patient age, gender, tumor location, histopathology, tumor stage, and use of chemotherapy were collected. This study was approved by the Institutional Review Board of

Table 1 Baseline clinical characteristics of the enrolled patients

Characteristics	Patients (n = 1868)
Mean age (range), yr	65 (28-93)
Gender	
Male	1072 (57.4)
Female	796 (42.6)
Location	
Colon	892 (47.8)
Rectum	957 (51.2)
Unknown	19 (1.0)
Histology	
Well differentiated	484 (25.9)
Moderate differentiated	1066 (57.1)
Poorly differentiated	139 (7.4)
Unknown	179 (9.6)
Tumor stage	
I	281 (15.0)
II	551 (29.5)
III	667 (35.7)
IV	369 (19.8)
Chemotherapy	
No	294 (15.8)
Yes	1574 (84.2)

Values are presented as mean (range) or n (%).

Kosin University Gospel Hospital (KUGH 2016-06-033).

Assessment of NLR and PLR

All blood samples were taken at the time of admission for initial diagnosis and the neutrophil, platelet, and lymphocyte counts identified in these blood samples were used to calculate the NLR and PLR. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. Cutoff values, sensitivity, and specificity of the NLR and PLR were evaluated using receiver operating characteristic (ROC) curves.

Patient follow-up and statistical analysis

The overall survival (OS) was measured from the date of CRC diagnosis to the date of death or final follow-up. The disease free survival (DFS) was measured from the date of CRC diagnosis to the date of recurrence or final follow-up. The recurrence of CRC was diagnosed on radiological and endoscopic histopathological data. Student's *t*-test and χ^2 test were performed for continuous and categorical variables, as appropriate. ROC curves were used to differentiate the ability of the NLR and PLR to predict long-term outcomes in patients with CRC. Kaplan-Meier curves were used to construct survival curves based on cumulative incidences and compared using the Breslow test. Cox proportional hazards regression model was used to assess factors affecting the OS. *P* values less than 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM Co., Armonk, NY).

RESULTS

Baseline characteristics and clinicopathological findings

A total of 1868 patients were included between April 1996 and December 2010. Their mean age was 65 years, and 796 patients (42.6%) were female. The median follow-up duration was 46 mo (interquartile range, 22-73). During the follow-up period, 599 patients (32.1%) died. Baseline characteristics are summarized in Table 1. All patients had data on neutrophil counts, lymphocyte counts, and platelet counts, therefore the NLR and PLR could be calculated for all patients. The mean \pm SD neutrophil count, lymphocyte count, and platelet count were $5.65 \pm 3.14 \times 10^9/L$, $1.86 \pm 0.88 \times 10^9/L$, and $285.25 \pm 98.11 \times 10^9/L$, respectively. And the mean NLR and PLR were 4.54 ± 5.83 and 200.17 ± 168.96 , respectively. On ROC analysis, the NLR and PLR were found to have the largest area under the curve (AUC = 0.569, 95%CI: 0.542-0.597, *P* < 0.001, and AUC = 0.556, 95%CI: 0.528-0.584, *P* < 0.001, respectively) with an optimal NLR cut-off value of 3.0 (sensitivity 51%, specificity 62%) and an optimal PLR cut-off value of 160 (sensitivity 53%, specificity 55%) for predicting OS. Patients were classified into two groups based on the optimal cut-off value of the NLR: high NLR (NLR \geq 3.0) and low NLR (NLR < 3.0). In addition, patients were divided into two groups according to the optimal cut-off value of the PLR: high PLR (PLR \geq 160) and low PLR (PLR < 160).

Clinicopathological findings of the patients according to NLR and PLR are summarized in Table 2. There were statistically significant differences in T stage and peri-neural invasion according to NLR and PLR, however there were not statistically significant differences in N stage and lymphatic invasion according to NLR and PLR.

Overall survival and Disease free survival according to NLR and PLR

Figure 1 shows Kaplan-Meier curves of the OS and the DFS for patients according to NLR and PLR. The OS for patients with low NLR were better than those with high NLR (*P* < 0.001), and the OS for patients with low PLR were also better than those with high PLR (*P* < 0.001) (Figure 1A). The DFS for patients with low NLR were better than those with high NLR (*P* < 0.001), and the DFS for patients with low PLR were also better than those with high PLR (*P* < 0.001) (Figure 1B).

We evaluated the long-term outcomes according to NLR and PLR based on the tumor stage. The 3-year and 5-year OS/DFS rate according to NLR and PLR based on the tumor stage are shown in Table 3. Interestingly, the long-term outcomes according to NLR and PLR were different depending on the tumor stage (Figures 2 and 3). The OS and DFS of patients with stage I and II CRC were not significantly different according to NLR and PLR. However, the OS of patients with stage III and IV CRC were significantly different

Table 2 Clinicopathological findings according to neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio

Variable	NLR < 3.0 (n = 1086)	NLR ≥ 3.0 (n = 782)	P value	PLR < 160 (n = 973)	PLR ≥ 160 (n = 894)	P value
T stage			< 0.001			< 0.001
T1	112	39		112	39	
T2	171	91		159	102	
T3	668	498		579	587	
T4	48	59		41	66	
Unknown	87	95		82	100	
N stage			0.854			0.443
N0	589	434		543	480	
N1	289	201		257	232	
N2	196	138		164	170	
Unknown	12	9		9	12	
Lymphatic invasion			0.421			0.446
Yes	349	253		311	291	
No	587	391		524	453	
Unknown	150	138		138	150	
Vascular invasion			0.243			0.011
Yes	193	149		160	182	
No	742	496		675	562	
Unknown	151	137		138	150	
Peri-neural invasion			0.045			0.004
Yes	168	142		141	169	
No	767	502		693	575	
Unknown	151	138		139	150	

NLR: Neutrophil-to-lymphocyte-ratio; PLR: Platelet-to-lymphocyte-ratio.

Table 3 Overall survival and disease free survival according to neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio

	NLR		PLR	
	Low (< 3.0)	High (≥ 3.0)	Low (< 160)	High (≥ 160)
Overall survival				
Stage I				
3-yr OS rate	97.0%	98.2%	99.3%	94.7%
5-yr OS rate	92.6%	91.9%	94.8%	87.3%
Stage II				
3-yr OS rate	91.2%	89.2%	90.6%	90.1%
5-yr OS rate	86.1%	84.0%	84.3%	86.2%
Stage III				
3-yr OS rate	79.6%	73.4%	82.1%	71.4%
5-yr OS rate	69.3%	60.9%	69.6%	61.9%
Stage IV				
3-yr OS rate	39.8%	21.2%	33.9%	27.4%
5-yr OS rate	34.3%	18.1%	28.6%	23.8%
Disease free survival				
Stage I				
3-yr DFS rate	98.3%	97.4%	98.7%	96.6%
5-yr DFS rate	96.1%	95.6%	97.2%	93.3%
Stage II				
3-yr DFS rate	88.5%	89.3%	87.8%	89.9%
5-yr DFS rate	84.7%	86.5%	83.5%	87.5%
Stage III				
3-yr DFS rate	79.2%	78.1%	79.8%	77.2%
5-yr DFS rate	75.2%	68.6%	74.5%	70.5%
Stage IV				
3-yr DFS rate	42.2%	30.3%	38.5%	34.5%
5-yr DFS rate	37.5%	26.8%	34.3%	30.4%

NLR: Neutrophil-to-lymphocyte-ratio; PLR: Platelet-to-lymphocyte-ratio; OS: Overall survival; DFS: Disease free survival.

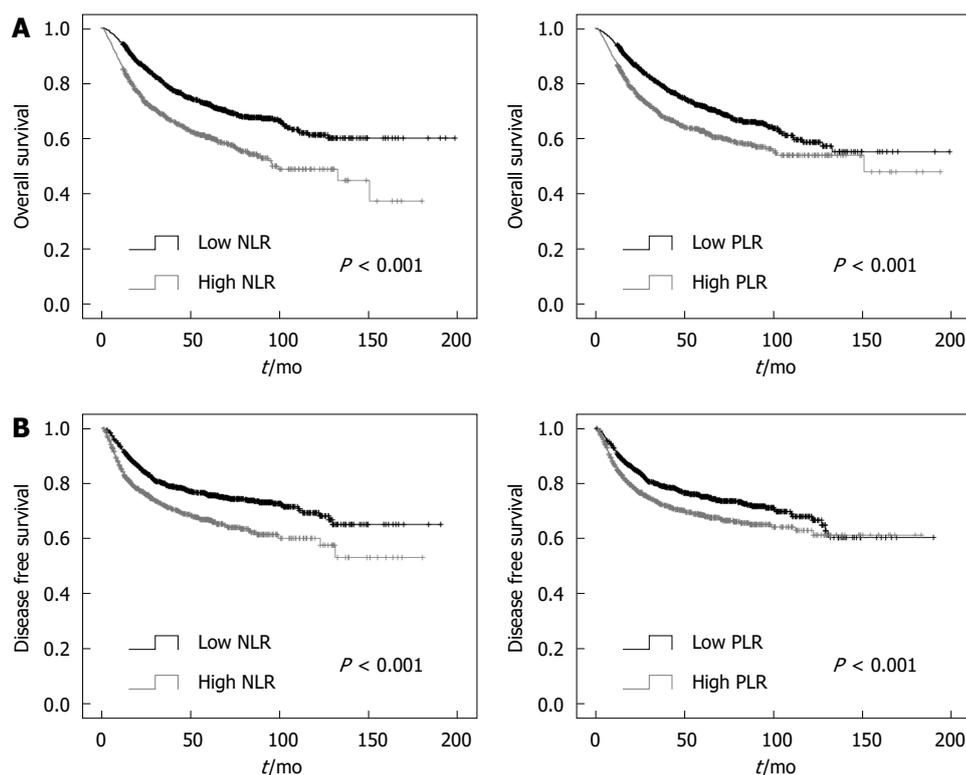


Figure 1 Kaplan-Meier analysis shows the overall survival (A) and disease free survival (B) for patients with colorectal cancer according to neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio.

according to NLR and PLR. And the DFS of patients with stage III and IV CRC were significantly different according to NLR, but not PLR.

Factors affecting long-term outcomes

Multivariate analysis using Cox proportional hazards regression were performed based on the tumor stage. In multivariate analysis in patients with stage I and II CRC, NLR and PLR were not significant factors affecting long-term outcomes (Table 4). However, in patients with stage III and IV CRC, high NLR and PLR were significant prognostic factors affecting long-term outcomes (Table 5). In patients with stage III and IV CRC, high NLR was independent factor affecting OS (HR = 1.44, 95%CI: 1.14-1.83, $P = 0.003$) and DFS (HR = 1.43, 95%CI: 1.11-1.85, $P = 0.005$), and high PLR was also independent factor affecting OS (HR = 1.35, 95%CI: 1.06-1.73, $P = 0.017$) and DFS (HR = 1.32, 95%CI: 1.02-1.69, $P = 0.034$).

DISCUSSION

This study showed that stage III and IV CRC patients with high NLR or high PLR at initial diagnosis had poor prognosis. According to the results of this study, high NLR and high PLR are useful independent prognostic factors to predict poor long-term outcomes in patients with stage III and IV CRC.

The mechanism by which high NLR or high PLR affects poor long-term outcomes in patients with cancer

is not clearly. Recent studies suggested that inflammation and cancer are closely connected by the intrinsic and extrinsic pathways^[11,12]. The intrinsic pathway is activated by genetic alterations resulting in neoplasia, whereas inflammatory conditions increase the risk of developing cancer in the extrinsic pathway. The two pathways result in the activation of transcription factors in tumor cells including NF- κ B, STAT3, and hypoxia-inducible factor 1 α , and these transcription factors produce inflammatory mediators including cytokines and chemokines^[11]. By these processes, the inflammatory response contributes to the pathogenesis and progression of cancer. The relationship between chronic inflammation and CRC has been established by the observations showing the increased risk of CRC in patients with inflammatory bowel disease^[27]. Increased NLR or PLR indicates a relative reduction in lymphocytes and lymphocyte-mediated immune response, which plays a crucial role in cytotoxic cell death. And elevated neutrophils and platelets can cause the synthesis of chemokines, growth factors to promote angiogenesis and tumor progression^[20].

Several studies have reported that some laboratory markers including C-reactive protein and modified Glasgow prognostic score have prognostic value in the cancer population^[28-30]. However, these laboratory markers are not routinely examined as part of the pretreatment assessment of patients with CRC in most hospitals. Whereas, since neutrophil count, platelet count, and lymphocyte count are routinely evaluated,

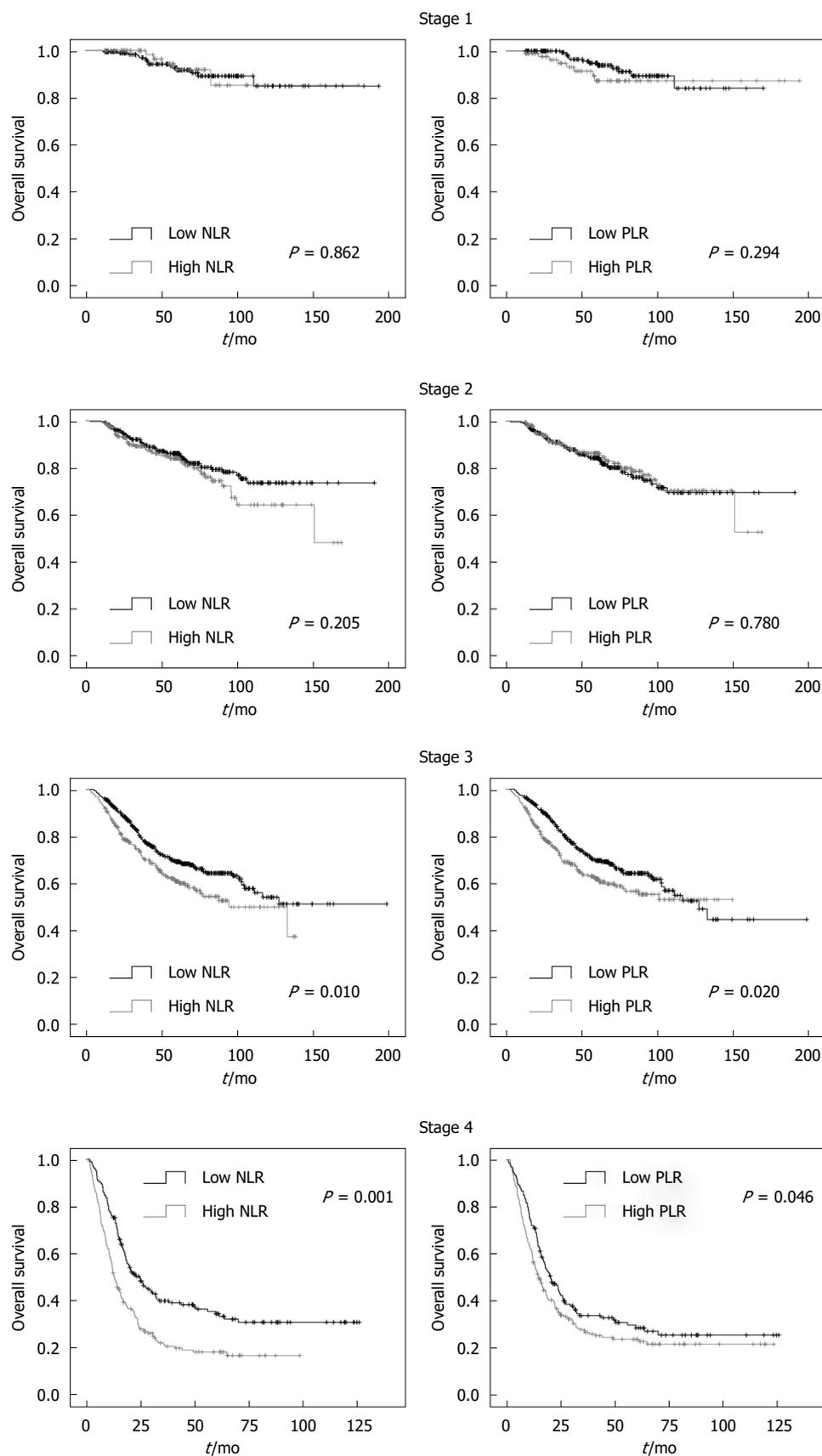


Figure 2 Kaplan-Meier curves show the overall survival of patients with colorectal cancer according to neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio based on tumor stage.

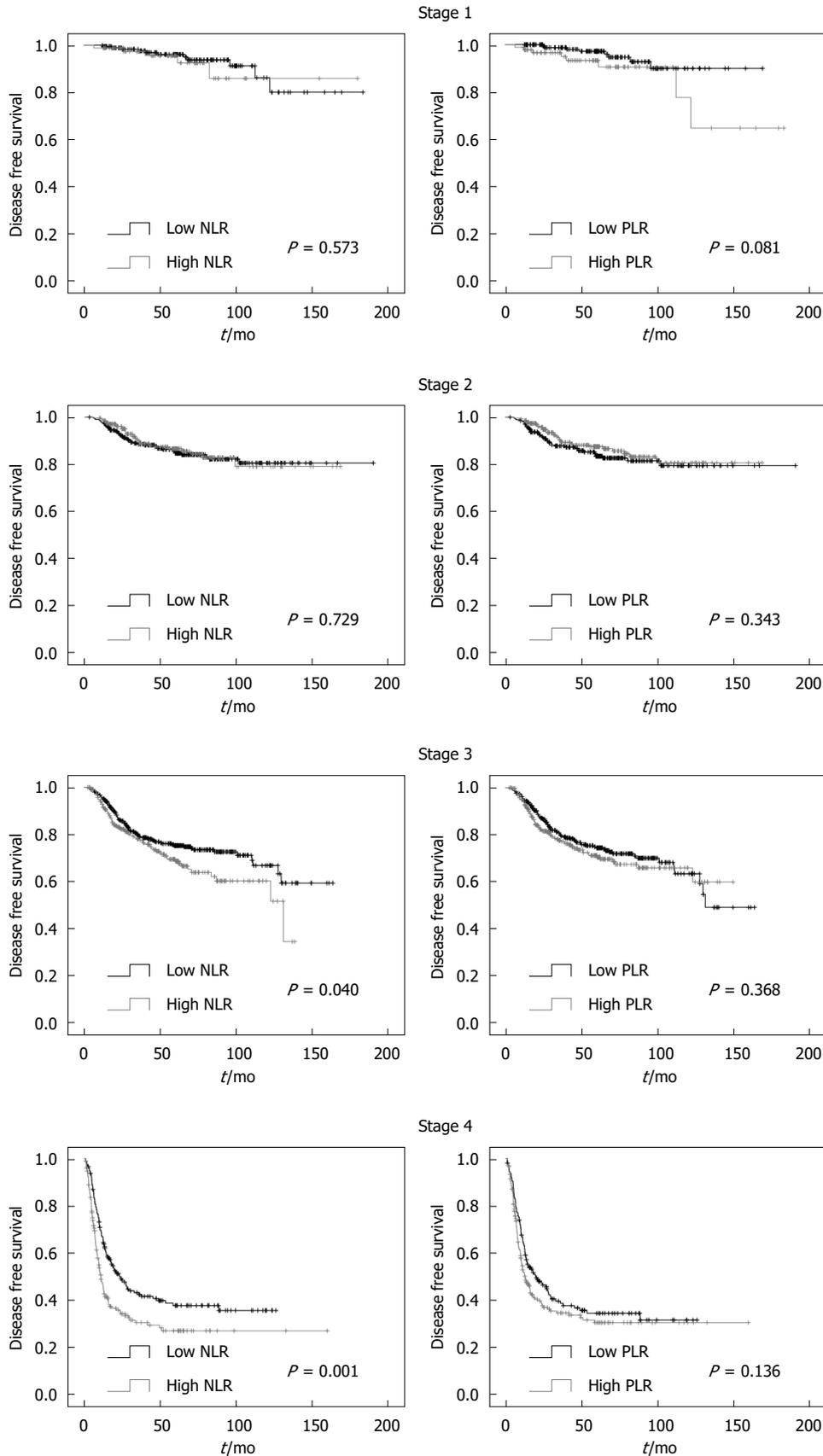


Figure 3 Kaplan-Meier curves show the disease free survival of patients with colorectal cancer according to neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio based on tumor stage.

Table 4 Prognostic factors by multivariate Cox regression analysis (Stage I and II)

Predictor	OS			DFS		
	HR	95%CI	P value	HR	95%CI	P value
Age						
< 60 yr	1.00			1.00		
≥ 60 yr	1.72	1.08-2.76	0.023	1.44	0.91-2.28	0.123
Histology						
Well/moderate differentiated	1.00			1.00		
Poorly differentiated	1.57	0.72-3.47	0.260	2.46	1.25-4.81	0.009
T stage						
T1/T2	1.00			1.00		
T3/T4	1.66	0.95-2.90	0.074	1.62	0.94-2.80	0.084
Lymphatic invasion						
No	1.00			1.00		
Yes	0.77	0.46-1.28	0.306	1.02	0.62-1.68	0.931
Vascular invasion						
No	1.00			1.00		
Yes	2.36	1.46-3.84	< 0.001	1.11	0.64-1.95	0.708
Peri-neural invasion						
No	1.00			1.00		
Yes	2.64	1.59-4.35	< 0.001	3.08	1.86-5.09	< 0.001
NLR						
Low NLR (< 3.0)	1.00			1.00		
High NLR (≥ 3.0)	1.16	0.76-1.76	0.498	1.06	0.69-1.62	0.788
PLR						
Low PLR (< 160)	1.00			1.00		
High PLR (≥ 160)	1.07	0.71-1.62	0.744	0.98	0.64-1.49	0.908

NLR: Neutrophil-to-lymphocyte-ratio; PLR: Platelet-to-lymphocyte-ratio; OS: Overall survival; DFS: Disease free survival.

Table 5 Prognostic factors by multivariate Cox regression analysis (Stage III and IV)

Predictor	OS			DFS		
	HR	95%CI	P value	HR	95%CI	P value
Age						
< 60 yr	1.00			1.00		
≥ 60 yr	1.46	1.13-1.89	0.004	1.10	0.84-1.44	0.479
Histology						
Well/Moderate differentiated	1.00			1.00		
Poorly differentiated	1.90	1.36-2.66	< 0.001	1.46	0.98-2.14	0.058
T stage						
T1/T2	1.00			1.00		
T3/T4	2.61	1.51-4.51	0.001	3.13	1.69-5.78	< 0.001
Lymphatic invasion						
No	1.00			1.00		
Yes	1.19	0.91-1.58	0.199	1.17	0.87-1.57	0.298
Vascular invasion						
No	1.00			1.00		
Yes	1.52	1.15-2.01	0.003	1.39	1.03-1.87	0.031
Peri-neural invasion						
No	1.00			1.00		
Yes	1.45	1.10-1.91	0.008	1.56	1.16-2.08	0.003
NLR						
Low NLR (< 3.0)	1.00			1.00		
High NLR (≥ 3.0)	1.44	1.14-1.83	0.003	1.43	1.11-1.85	0.005
PLR						
Low PLR (< 160)	1.00			1.00		
High PLR (≥ 160)	1.35	1.06-1.73	0.017	1.32	1.02-1.69	0.034

NLR: Neutrophil-to-lymphocyte-ratio; PLR: Platelet-to-lymphocyte-ratio; OS: Overall survival; DFS: Disease free survival.

NLR and PLR could be inexpensive prognostic markers which can easily be assessed in clinical practice.

There has been rapidly growing interest in the association between NLR and long-term outcomes

in patients with CRC^[16,23,24,26,31]. Recently, two meta-analyses showed significant evidence to support the association between high NLR and poor prognosis in patients with CRC^[25,32]. In this study, we aimed

to identify and strengthen the role of NLR and PLR in patients with CRC, therefore we performed the analysis with a large number of CRC patients to determine if these ratios could be useful for predicting long-term outcomes. We identified that patients with low NLR and low PLR showed longer overall survival and disease free survival than those with high NLR and high PLR (Figure 1). Previous studies reported that preoperative NLR may be an independent prognostic marker to predict long-term outcomes in stage II and III CRC^[23,33-35], and also an important predictive marker in stage IV CRC^[36-38]. In our study, we demonstrated that NLR and PLR have predictive values for OS and DFS in patients with stage III and IV CRC. High NLR and high PLR were independent factors affecting OS and DFS in patients with stage III and IV CRC (Table 5). These findings suggest that stage III and IV CRC patients who have high NLR and high PLR should be more carefully managed when establishing a treatment strategy. Whereas, NLR and PLR were not prognostic factors in patients with stage I and II CRC (Table 4). These findings suggest that the assessment of NLR and PLR should be interpreted differently depending on the tumor stage of CRC.

Several studies have proposed various cut-off values of NLR and PLR for OS (for instance, 3 to 5 as a cut-off value of NLR and 150 to 225 as a cut-off value of PLR)^[24,32,35,38-40]. In this study, the cut-off value of NLR was 3.0 (sensitivity 51%, specificity 62%) and the cut-off value of PLR was 160 (sensitivity 53%, specificity 55%). Although the sensitivity and specificity of the cut-off values of NLR and PLR in our results were not high, these values could be relatively reliable due to the large number of patients included in our study.

This study has some limitations. First, this study was retrospectively performed in a single center. Therefore, we could not avoid selection bias when collecting information on patients with CRC. However, we attempted to minimize any bias by repeatedly reviewing the medical records. Second, the NLR and PLR were assessed by single measurements at the time of admission for the initial diagnosis. It would be interesting to examine changes in NLR and PLR during the follow-up period in CRC patients to determine their usefulness as surveillance markers.

In conclusion, our study showed that high NLR and high PLR are useful prognostic factors to predict poor long-term outcomes in patients with stage III and IV CRC. Based on the results of this study, we suggest that initial assessment of NLR and PLR in newly diagnosed stage III and IV CRC patients is important for predicting long-term outcomes.

COMMENTS

Background

Identification of prognostic markers is an important step for assessing clinical outcome in colorectal cancer (CRC) treatment. Recently, a large number of studies have suggested useful biomarkers for predicting clinical outcomes in

CRC, however high costs and lack of standardization limit their application in routine clinical practice. Inflammatory response has a crucial role in the pathogenesis and progression of cancer. Among the various inflammatory markers, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been shown to influence clinical outcomes in various cancers. NLR and PLR can be easily calculated as the neutrophil count or platelet count divided by the lymphocyte count. In this study, we aimed to identify the prognostic value of the NLR and PLR in patients with CRC.

Research frontiers

This study presents that high NLR (≥ 3.0) and high PLR (≥ 160) are useful prognostic factors to predict poor long-term outcomes in patients with stage III and IV CRC.

Innovations and breakthroughs

In this study, a total of 1868 patients were included. The authors used ROC curves to assess optimal cut-off values of the NLR and PLR, and evaluated the roles of the NLR and PLR using Kaplan-Meier curves and Cox regression models in predicting the long-term outcomes in patients with CRC.

Applications

Initial assessment of NLR and PLR in newly diagnosed stage III and IV CRC patients can be helpful to predict long-term outcomes.

Terminology

NLR: calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR: calculated by dividing the absolute platelet count by the absolute lymphocyte count.

Peer-review

This is an interesting retrospective study including a large cohort of CRC patients. Some data are missing and should be supplemented by the authors.

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