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***Retrospective Study***

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

Kim JH *et al.* Role of the NLR and PLR in patients with CRC

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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 1,868 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 months (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 100,000 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-kB and STAT3 (signal transducer and activator of transcription 3) and several inflammatory cytokines (such as IL-1β, 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 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 chi-square 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 log-rank 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 1,868 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 months (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 ± SD neutrophil count, lymphocyte count, and platelet count were 5.65 ± 3.14 × 109/L, 1.86 ± 0.88 × 109/L, and 285.25 ± 98.11 × 109/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 ≥ 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 ≥ 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 (Figure 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 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-kB, STAT3, and hypoxia-inducible factor 1α, 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 (CRP) and modified Glasgow prognostic score (mGPS) 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, 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. We 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.

**REFERENCES**

1 **Edwards BK**, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 2010; **116**: 544-573 [PMID: 19998273 DOI: 10.1002/cncr.24760]

2 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

3 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**: 7-30 [PMID: 26742998 DOI: 10.3322/caac.21332]

4 **Loupakis F**, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, Chiara S, Carlomagno C, Boni C, Allegrini G, Boni L, Falcone A. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014; **371**: 1609-1618 [PMID: 25337750 DOI: 10.1056/NEJMoa1403108]

5 **Yamaguchi K**, Ogata Y, Akagi Y, Shirouzu K. Identification of high-risk factors as indicators for adjuvant therapy in stage II colon cancer patients treated at a single institution. *Oncol Lett* 2013; **6**: 659-666 [PMID: 24137386 DOI: 10.3892/ol.2013.1433]

6 **O'Connell JB**, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 2004; **96**: 1420-1425 [PMID: 15467030 DOI: 10.1093/jnci/djh275]

7 **Morris M**, Platell C, de Boer B, McCaul K, Iacopetta B. Population-based study of prognostic factors in stage II colonic cancer. *Br J Surg* 2006; **93**: 866-871 [PMID: 16622901 DOI: 10.1002/bjs.5345]

8 **Le Voyer TE**, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* 2003; **21**: 2912-2919 [PMID: 12885809 DOI: 10.1200/jco.2003.05.062]

9 **Salazar R**, Roepman P, Capella G, Moreno V, Simon I, Dreezen C, Lopez-Doriga A, Santos C, Marijnen C, Westerga J, Bruin S, Kerr D, Kuppen P, van de Velde C, Morreau H, Van Velthuysen L, Glas AM, Van't Veer LJ, Tollenaar R. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. *J Clin Oncol* 2011; **29**: 17-24 [PMID: 21098318 DOI: 10.1200/jco.2010.30.1077]

10 **Roth AD**, Tejpar S, Delorenzi M, Yan P, Fiocca R, Klingbiel D, Dietrich D, Biesmans B, Bodoky G, Barone C, Aranda E, Nordlinger B, Cisar L, Labianca R, Cunningham D, Van Cutsem E, Bosman F. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol* 2010; **28**: 466-474 [PMID: 20008640 DOI: 10.1200/jco.2009.23.3452]

11 **Mantovani A**, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038/nature07205]

12 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867 [PMID: 12490959 DOI: 10.1038/nature01322]

13 **Koehne CH**, Dubois RN. COX-2 inhibition and colorectal cancer. *Semin Oncol* 2004; **31**: 12-21 [PMID: 15252926]

14 **Flossmann E**, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007; **369**: 1603-1613 [PMID: 17499602 DOI: 10.1016/s0140-6736(07)60747-8]

15 **Chan AT**, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007; **356**: 2131-2142 [PMID: 17522398 DOI: 10.1056/NEJMoa067208]

16 **Lee YY**, Choi CH, Kim HJ, Kim TJ, Lee JW, Lee JH, Bae DS, Kim BG. Pretreatment neutrophil: lymphocyte ratio as a prognostic factor in cervical carcinoma. *Anticancer Res* 2012; **32**: 1555-1561 [PMID: 22493401]

17 **Pichler M**, Hutterer GC, Stoeckigt C, Chromecki TF, Stojakovic T, Golbeck S, Eberhard K, Gerger A, Mannweiler S, Pummer K, Zigeuner R. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. *Br J Cancer* 2013; **108**: 901-907 [PMID: 23385728 DOI: 10.1038/bjc.2013.28]

18 **Walsh SR**, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 2005; **91**: 181-184 [PMID: 16118772 DOI: 10.1002/jso.20329]

19 **Sarraf KM**, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2009; **137**: 425-428 [PMID: 19185164 DOI: 10.1016/j.jtcvs.2008.05.046]

20 **Azab B**, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, Habeshy A, Picon A, Bloom S. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. *Med Oncol* 2013; **30**: 432 [PMID: 23283648 DOI: 10.1007/s12032-012-0432-4]

21 **Goubran HA**, Stakiw J, Radosevic M, Burnouf T. Platelet-cancer interactions. *Semin Thromb Hemost* 2014; **40**: 296-305 [PMID: 24590421 DOI: 10.1055/s-0034-1370767]

22 **Goubran HA**, Stakiw J, Radosevic M, Burnouf T. Platelets effects on tumor growth. *Semin Oncol* 2014; **41**: 359-369 [PMID: 25023351 DOI: 10.1053/j.seminoncol.2014.04.006]

23 **Absenger G**, Szkandera J, Pichler M, Stotz M, Arminger F, Weissmueller M, Schaberl-Moser R, Samonigg H, Stojakovic T, Gerger A. A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients. *Br J Cancer* 2013; **109**: 395-400 [PMID: 23820252 DOI: 10.1038/bjc.2013.346]

24 **Mallappa S**, Sinha A, Gupta S, Chadwick SJ. Preoperative neutrophil to lymphocyte ratio & gt; 5 is a prognostic factor for recurrent colorectal cancer. *Colorectal Dis* 2013; **15**: 323-328 [PMID: 22958479 DOI: 10.1111/codi.12008]

25 **Li MX**, Liu XM, Zhang XF, Zhang JF, Wang WL, Zhu Y, Dong J, Cheng JW, Liu ZW, Ma L, Lv Y. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. *Int J Cancer* 2014; **134**: 2403-2413 [PMID: 24122750 DOI: 10.1002/ijc.28536]

26 **Galizia G**, Lieto E, Zamboli A, De Vita F, Castellano P, Romano C, Auricchio A, Cardella F, De Stefano L, Orditura M. Neutrophil to lymphocyte ratio is a strong predictor of tumor recurrence in early colon cancers: A propensity score-matched analysis. *Surgery* 2015; **158**: 112-120 [PMID: 25818659 DOI: 10.1016/j.surg.2015.02.006]

27 **Jess T**, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012; **10**: 639-645 [PMID: 22289873 DOI: 10.1016/j.cgh.2012.01.010]

28 **Pathak S**, Nunes QM, Daniels IR, Smart NJ. Is C-reactive protein useful in prognostication for colorectal cancer? A systematic review. *Colorectal Dis* 2014; **16**: 769-776 [PMID: 25039573 DOI: 10.1111/codi.12700]

29 **Kersten C**, Louhimo J, Ålgars A, Lahdesmaki A, Cvancerova M, Stenstedt K, Haglund C, Gunnarsson U. Increased C-reactive protein implies a poorer stage-specific prognosis in colon cancer. *Acta Oncol* 2013; **52**: 1691-1698 [PMID: 24102179 DOI: 10.3109/0284186x.2013.835494]

30 **Guthrie GJ**, Roxburgh CS, Farhan-Alanie OM, Horgan PG, McMillan DC. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. *Br J Cancer* 2013; **109**: 24-28 [PMID: 23799846 DOI: 10.1038/bjc.2013.330]

31 **Zou ZY**, Liu HL, Ning N, Li SY, DU XH, Li R. Clinical significance of pre-operative neutrophil lymphocyte ratio and platelet lymphocyte ratio as prognostic factors for patients with colorectal cancer. *Oncol Lett* 2016; **11**: 2241-2248 [PMID: 26998156 DOI: 10.3892/ol.2016.4216]

32 **Malietzis G**, Giacometti M, Kennedy RH, Athanasiou T, Aziz O, Jenkins JT. The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. *Ann Surg Oncol* 2014; **21**: 3938-3946 [PMID: 24866438 DOI: 10.1245/s10434-014-3815-2]

33 **Hung HY**, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS, Tasi WS, You JF, You YT, Fan CW, Wang JY, Chiang JM. Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy. *Int J Colorectal Dis* 2011; **26**: 1059-1065 [PMID: 21479566 DOI: 10.1007/s00384-011-1192-x]

34 **Ding PR**, An X, Zhang RX, Fang YJ, Li LR, Chen G, Wu XJ, Lu ZH, Lin JZ, Kong LH, Wan DS, Pan ZZ. Elevated preoperative neutrophil to lymphocyte ratio predicts risk of recurrence following curative resection for stage IIA colon cancer. *Int J Colorectal Dis* 2010; **25**: 1427-1433 [PMID: 20821217 DOI: 10.1007/s00384-010-1052-0]

35 **Absenger G**, Szkandera J, Stotz M, Postlmayr U, Pichler M, Ress AL, Schaberl-Moser R, Loibner H, Samonigg H, Gerger A. Preoperative neutrophil-to-lymphocyte ratio predicts clinical outcome in patients with stage II and III colon cancer. *Anticancer Res* 2013; **33**: 4591-4594 [PMID: 24123035]

36 **Chang Z**, Zheng J, Ma Y, Zhao J, Wang C, Liu Z. The neutrophil-to-lymphocyte ratio as a predictor for recurrence of colorectal liver metastases following radiofrequency ablation. *Med Oncol* 2014; **31**: 855 [PMID: 24477649 DOI: 10.1007/s12032-014-0855-1]

37 **He W**, Yin C, Guo G, Jiang C, Wang F, Qiu H, Chen X, Rong R, Zhang B, Xia L. Initial neutrophil lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. *Med Oncol* 2013; **30**: 439 [PMID: 23307251 DOI: 10.1007/s12032-012-0439-x]

38 **Chua W**, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 2011; **104**: 1288-1295 [PMID: 21448173 DOI: 10.1038/bjc.2011.100]

39 **Szkandera J**, Pichler M, Absenger G, Stotz M, Arminger F, Weissmueller M, Schaberl-Moser R, Samonigg H, Kornprat P, Stojakovic T, Avian A, Gerger A. The elevated preoperative platelet to lymphocyte ratio predicts decreased time to recurrence in colon cancer patients. *Am J Surg* 2014; **208**: 210-214 [PMID: 24581872 DOI: 10.1016/j.amjsurg.2013.10.030]

40 **Neofytou K**, Smyth EC, Giakoustidis A, Khan AZ, Cunningham D, Mudan S. Elevated platelet to lymphocyte ratio predicts poor prognosis after hepatectomy for liver-only colorectal metastases, and it is superior to neutrophil to lymphocyte ratio as an adverse prognostic factor. *Med Oncol* 2014; **31**: 239 [PMID: 25218270 DOI: 10.1007/s12032-014-0239-6]

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



**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 1 Baseline clinical characteristics of the enrolled patients*****n* (%)**

|  |  |
| --- | --- |
| **Characteristics** | **Patients****(*n* = 1, 868)** |
| 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* (%).

**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 |  |  |  |
|  Yes | 168 | 142 |  | 141 | 169 | 0.004 |
|  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 frees survival.

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

|  |  |  |
| --- | --- | --- |
|  | **OS** | **DFS** |
| **Predictor** | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** |
| Age  |  |  |  |  |  |  |
|  < 60 yr | 1 |  |  | 1 |  |  |
|  ≥ 60 yr | 1.72 | 1.08 – 2.76 | 0.023 | 1.44 | 0.91 – 2.28 | 0.123 |
| Histology |  |  |  |  |  |  |
|  Well / Moderate differentiated | 1 |  |  | 1 |  |  |
| Poorly differentiated | 1.57 | 0.72 – 3.47 | 0.260 | 2.46 | 1.25 – 4.81 |  0.009 |
| T stage  |  |  |  |  |  |  |
|  T1 / T2 | 1 |  |  | 1 |  |  |
|  T3 / T4 | 1.66 | 0.95 – 2.90 | 0.074 | 1.62 | 0.94 – 2.80 | 0.084 |
| Lymphatic invasion |  |  |  |  |  |  |
|  No | 1 |  |  | 1 |  |  |
|  Yes | 0.77 | 0.46 – 1.28 | 0.306 | 1.02 | 0.62 – 1.68 | 0.931 |
| Vascular invasion |  |  |  |  |  |  |
|  No | 1 |  |  | 1 |  |  |
|  Yes | 2.36 | 1.46 – 3.84 | < 0.001 | 1.11 | 0.64 – 1.95 | 0.708 |
| Peri-neural invasion |  |  |  |  |  |  |
|  No | 1 |  |  | 1 |  |  |
|  Yes | 2.64 | 1.59 – 4.35 | < 0.001 | 3.08 | 1.86 – 5.09 | < 0.001 |
| NLR |  |  |  |  |  |  |
|  Low NLR (< 3.0) | 1 |  |  | 1 |  |  |
|  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 |  |  | 1 |  |  |
|  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)**

|  |  |  |
| --- | --- | --- |
|  | **OS** | **DFS** |
| **Predictor** | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** |
| Age  |  |  |  |  |  |  |
|  < 60 yr | 1 |  |  | 1 |  |  |
|  ≥ 60 yr | 1.46 | 1.13 – 1.89 | 0.004 | 1.10 | 0.84 – 1.44 | 0.479 |
| Histology |  |  |  |  |  |  |
|  Well / Moderate differentiated | 1 |  |  | 1 |  |  |
| Poorly differentiated | 1.90 | 1.36 – 2.66 | < 0.001 | 1.46 | 0.98 – 2.14 |  0.058 |
| T stage |  |  |  |  |  |  |
|  T1 / T2 | 1 |  |  | 1 |  |  |
|  T3 / T4 | 2.61 | 1.51 – 4.51 | 0.001 | 3.13 | 1.69 – 5.78 | < 0.001 |
| Lymphatic invasion |  |  |  |  |  |  |
|  No | 1 |  |  | 1 |  |  |
|  Yes | 1.19 | 0.91 – 1.58 | 0.199 | 1.17 | 0.87 – 1.57 | 0.298 |
| Vascular invasion |  |  |  |  |  |  |
|  No | 1 |  |  | 1 |  |  |
|  Yes | 1.52 | 1.15 – 2.01 | 0.003 | 1.39 | 1.03 – 1.87 | 0.031 |
| Peri-neural invasion |  |  |  |  |  |  |
|  No | 1 |  |  | 1 |  |  |
|  Yes | 1.45 | 1.10 – 1.91 | 0.008 | 1.56 | 1.16 – 2.08 | 0.003 |
| NLR |  |  |  |  |  |  |
|  Low NLR (< 3.0) | 1 |  |  | 1 |  |  |
|  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 |  |  | 1 |  |  |
|  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.