Prognostic value of the dynamic change of platelets to lymphocytes ratio and neutrophil to lymphocyte ratio for gastric cancer patients receiving curative surgery.

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Abstract

Background: The inflammatory biomarkers play a prominent role in tumorigenesis and progression of gastric cancer. Inflammatory response has shown to be promising candidate for monitoring the survival prediction in various cancer. Certain percent of cancer related deaths are closely associated with chronic inflammation. Our study aims to focus a precise estimation on the prognostic significance of preoperative Neutrophil to Lymphocyte ratio (NLR), Platelets to Lymphocyte ratio (PLR), derived Neutrophil to Lymphocyte ratio (ΔNLR) and derived Platelet to Lymphocyte ratio (ΔPLR) following gastric cancer.

Methods: A retrospective analysis was conducted in patients with gastric cancer in Shanghai East Hospital affiliated with Tong ji University between December 2012 and June 2015, and total 145 patients were identified eligible. NLR, PLR, Δ NLR and ΔPLR values were calculated from peripheral blood cell count taken before surgery and 6-month post-surgery. Optimal cutoff value was determined by Receiver operating curve (ROC). Kaplan-Meier analysis was used to calculate the overall survival (OS) and Recurrence Free Survival (RFS). Cox regression analysis was performed to assess the prognostic factors. Continuous data with normal distribution was presented as mean ± standard deviation, and non-parametrical data were presented as median with interquartile range (IQR). Categorical data was described by frequency. The Student's t test or one-way ANOVA (Analysis of Variance) was used for comparing continuous variables whereas Fisher's exact test or χ^2 test was used for categorical data

Results: The median follow-up duration was 26 months (IQR, 17–35). Patients were stratified in two groups by NLR (≤ 2.9,>2.9) and PLR (≤ 147,>147).3 years RFS of low ΔNLR and high ΔNLR is 59.0% and 76.7% respectively. Similarly, RFS of low ΔPLR and high ΔPLR group is 58.0% and 76.2%respectively. Multivariate analysis reviled elevated PLR [HR = 1.008,95%CI = 1.002–1.014, P-value = 0.011, for OS and HR = 1.009,95%CI = 1.004–1.014, P-value = 0.001, for RFS] and ΔPLR [HR = .994,95%CI = 0.990–0.999, P-value = 0.016 for OS and HR = 0.991 95%CI = 0.987–0.996 P-value = < 0.001 for RFS] were significantly associated with OS and RFS.

Conclusions: Pre-operative PLR and derived(ΔPLR) are independent prognostic factors of OS and RFS in Gastric Cancer (GC) patients undergoing radical gastrectomy. The reduction of PLR and NLR after surgery might be helpful to predict cancer recurrence in patients who have undergone gastrectomy.

Background

Gastric cancer (GC) is the fourth most common cancer and the third leading cause of cancer-related death worldwide[1]. Despite the advancements in surgical techniques and adjuvant chemotherapies, the overall survival (OS) of GC remains low. The 5-year survival rate of gastric cancer is 20%, this is mainly due to late cancer diagnosis [2, 3]. Along with cancer screening for early detection and finding reliable prognostic factors for the treatment of GC has gained tremendous importance.

In recent years, many studies have found that inflammation and body immune response play an important role in several key steps regarding tumor development, such as tumor initiation, promotion, malignant conversion, invasion and metastasis[4, 5]. There are many biochemical and hematological markers that can be used to evaluate the systemic inflammatory response, such as C-reactive protein (CRP), serum albumin (ALB), white blood cell (WBC), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) [6].These biomarkers are easy to be measured and have been demonstrated to be reliable indicators, providing the clinician a simple way to predict the prognosis of GC patients. However, these biomarkers may have different impacts in respective cancers, which needs further exploration[6].

Preoperative PLR and NLR have been proved to be associated with the prognosis in various solid tumors including colorectal, hepatocellular, gastro-esophageal, ovarian, and pancreatic carcinoma [7, 8]. Many studies have shown that preoperative PLR and NLR are able to predict outcomes of GC [9–13]. Likewise, some meta-analyses have shown that elevated PLR is related with high risk of lymph node metastasis, serosal invasion, and a tendency of advanced stages; similarly NRL showed an identical results [14, 15]. Nevertheless, as for GC patients undergoing radical resection, few studies have investigated post-operative PLR or NLR, none of them have investigated the association between the variation of PLR or NLR before and after surgery and correlating the outcome for GC. Therefore, we conducted a retrospective evaluation to investigate the relationship between the dynamic change of PLR or NLR and the prognosis of patients who underwent radical resection for GC.

Methods

Methods

1. Patient selection

GC patients followed by curative resection and confirmed with surgical pathology between January 2013 and June 2015 at Shanghai East Hospital affiliated with Tongji University were enrolled for the analyses. The exclusion criteria include: 1) infection or inflammatory conditions prior surgery; 2) recurrence tumor; 3) multiple malignant tumor; 4) combined with hematologic or immune system disease; 5) patients receiving pre-operative radiotherapy or chemotherapy. Finally, 145 gastric cancer patients were enrolled in the present study. The written consent from the participants was obtained and the study was approved by the Medical Ethics Committee of Shanghai East Hospital affiliated with Tongji University.

2. Data collection

Data were collected using the medical record system from Shanghai East Hospital. We retrieved the basic demographic information and the clinicopathological variables, including age, sex, tumor differentiation, histological type, cancer embolus status, nerve infiltration status, incisional margin status, regional lymph node metastasis, TNM stage and types of surgery performed. The pathological stage was determined as □, □ or □ according to the American Joint Committee on Cancer tumor-nodes-metastasis (TNM) staging system. The blood parameters before surgery and after complete adjuvant chemotherapy were collected.

We are aware on influence of chemotherapy in inflammatory markers. So, to acquire the reliable value of post-surgery inflammatory markers, we used the blood parameter half month after completing adjuvant chemotherapy. The variation of PLR and NLR before and after surgery was denoted by Δ PLR and ΔNLR, which was calculated as pre-operative PLR and NLR subtracted with post-chemotherapy PLR and NLR respectively.

3. Follow up

After operation, the patients were followed regularly and the last follow-up was till December 2016 or up to death. All patients were followed regularly every 3 months after surgery for the first two years then every 6 months. Physical examination, laboratory tests, dynamic Computed Tomography (CT) of Chest/abdomen/pelvis and gastroscopy were performed to monitor the disease progression at every visit. The median follow-up duration was 26 months (IQR,17-35). Those patients who have withdrawn from the scheduled follow-up, the date of last visit was applied as endpoint. The OS was defined as the time from treatment to death from any cause and RFS was defined as the time from treatment to the first recurrence or death.

4. Statistical method

We used the Microsoft Office Excel 2013 to collect the initial data. The statistical evaluation was conducted using the SPSS program (version 21.0, IBM Corp., USA). Continuous data with normal distribution was presented as mean ± standard deviation, and non-parametrical data were presented as median with interquartile range (IQR). Categorical data was described by frequency. The Student's t test or one-way ANOVA (Analysis of Variance) was used for comparing continuous variables whereas Fisher's exact test or χ^2 test was used for categorical data. Continuous variables were pre-categorized by the optimal cutoff value determined by receiver operating characteristic (ROC) curve analyses. The survival curves were constructed by the Kaplan-Meier test and were compared with log-rank tests. Univariate and multivariate Cox regression models were used to explore the association between the clinicopathological factors and survival data. The P-value <0.05 was considered statistically significant in all tests.

Results

1. Patient characteristics

The demographic and clinical characteristics of the included patients were shown in Table 1. The total number of patients including in the study was 145, and the number of male and female patient's representation was 65.5% and 34.5% respectively. The mean age of the patients was 63.28±11.42 years.

2. Determination of the optimal cutoff value

The cutoff value for PLR was 147 and, 2.9 for NLR (Figure 1), similarly, the cutoff value for ΔPLR was 21.56 and 0.26 for ΔNLR respectively (Figure 2). Besides, the area under the curve (AUC) for PLR was

0.658(0.550-0.766, p=0.005), and the AUC for NLR was 0.581(0.469-0.694, p=0.154); additionally, the AUC for ΔPLR was 0.642(0.498-0.786, p=0.041), and the AUC for ΔNLR was 0.681(0.548-0.814, p=0.009).

3. Relationship between the pre-operative PLR, NLR and the clinical factors

The association between the pre-operative PLR, NLR and the clinical factors are shown in Table 2. Patients with an elevated CEA (>5ng/mL) before surgery was associated with a higher NLR (p=0.008) and elevated CA19-9 (> 27U/mL) before surgery was associated with a higher PLR (p=0.018).

4. Relationship between the pre-operative PLR, NLR and the pathological factors

The association between the PLR, NLR and the pathological factors are listed in Table 3. PLR was significantly higher in patients with cancer embolus (p=0.001), lymphatic metastasis (p=0.006) and higher TNM stage (p=0.008).

5. Relationship between the pre-operative PLR, NLR and the survival

Based on the cut-off value, we divided the patients into two groups PLR≤147 and PLR>147 similarly NLR≤2.9 and NLR>2.9 respectively. According to the Kaplan-Meier analysis, a higher pre-operative PLR was associated with a lower overall survival (OS) (p=0.008) (Figure 3A) and relapse-free survival (RFS) (P=0.014) (Figure 3C), the 3-year OS survival for low-PLR group and high-PLR group is 82.7% and 58.1%, respectively; the 3-year RFS for low-PLR group and high-PLR group is 73.1% and 55.5%, respectively. There were no significant differences observed between pre-operative NLR and OS (p=0.096) (Figure 3B) or RFS(p=0.246) (Figure 3D).

6. Relationship between the ΔPLR, ΔNLR and the survival

According to the Kaplan-Meier curves, patients with lower ΔPLR and ΔNLR exhibited a lower RFS (p=0.036, p=0.024, Figure 4C, 4D), the 3-year RFS of low- ΔPLR group and high- ΔPLR group was 58.0% and 76.2%, respectively and the 3-year RFS of low- ΔNLR group and high- ΔNLR group was 59.0% and 76.7%, respectively. There was no significant difference between ΔPLR and ΔNLR for OS (p=0.125, p=0.137, Figure 4A, 4B).

7. Cox regression analysis

In order to explore the independence prognostic factors, univariate and multivariate Cox regression analysis were applied. The results are illustrated in Table 4 and Table 5. The univariate analysis indicated that high pathological stage (□), lymphatic metastasis, cancer embolus, nerve infiltration, PLR, ΔPLR and ΔNLR were significant for both OS and RFS. Meanwhile, the multivariate analysis showed that the PLR and ΔPLR were independent risk factors for both poor OS and RFS, whereas, TNM stage and Age was the only independent risk factor for poor RFS.

Discussion

Chronic infection contributes to upward malignant tendency, accumulating evidence has indicated that the systemic inflammatory response may be associated with tumor progression, thus may lead to impaired outcome [16-20]. The PLR and NLR are simple and inexpensive markers reflecting the systemic inflammation status [21,22]. In our study, we assessed the prognostic role of PLR and NLR in GC patients undergoing radical surgery. Our results demonstrated that, patients with higher pre-operative PLR and postoperative ΔPLR have a poorer 3-year OS and RFS. The PLR, and ΔPLR were significant prognostic factors for both poor OS and RFS. Furthermore, PLR and ΔPLR were independent risk factors for both OS and RFS, which means a higher pre-operative PLR may contribute poor outcome results for GC, and the lowered value of PLR and NLR after radical surgery might be inversely proportional to the risk of GC recurrence and metastasis.

Several studies have shown that platelets influence the tumor growth via multistep development that nourish proliferative signals by resisting cell death, inducing angiogenesis, evading immune detection and supporting cancer stem cells, indirectly activating peripheral invasion and tumor metastasis sequel [23]. Palumbo et al. introduced the idea of platelet “cloak” which shelters the tumor cells and protects them from immune surveillance [24]. On the other hand, lymphocyte is a major part of the immune system which plays a vital role in anti-tumors immunity [25]. Consistent with our results, PLR is significantly higher in patients with cancer embolus, lymphatic metastasis and higher TNM stage. Thus, PLR can be a dependable prognostic factor.

NLR increases when the neutrophils number increases or the lymphocytes number decreases. The underlying mechanism regarding the association between a high NLR and poor prognosis remains elusive. Some studies had tried to find potential authenticity to reflect the relation of NLR in tumor progression. Initially, the neutrophils were expected to stimulate tumor angiogenesis and an elevated NLR leads to enhance tumor progression [26]. Petrie et al. exhibited that neutrophils can suppress the cytolytic activity of natural killer cells, activate T cells, and lymphocytes[27]. Thus, an elevated NLR might be linked with poor outcome and increased recurrence rate.

We also investigated the change of PLR and NLR after radical resection for GC. We explored that the tumor-associated infection was lowered with tumor resection decreasing the value of PLR and NLR. Some research studies have shown that post-operative inflammatory response was also associated with the prognosis, and post-operative infectious complications may predispose to cancer recurrence [28]. Our results showed that the change of PLR and NLR before and after surgery was positively correlated with RFS for GC patients.

The study was aimed to provide a novel indicator for clinicians to evaluate the prognosis of GC patients undergoing radical resection. The PLR and NLR are easy to obtain from blood routine examination, comparatively cheaper and noninvasive procedure for evaluating patients. Studies have shown that the PLR and NLR can reflect the system inflammatory response [29], and the inflammatory status could contribute to cancer research and reflects the tumor progression [30,17,31]. Based on the results, it has

been concluded that pre-operative PLR and the reduction of PLR and NLR after surgery may be associated with the prognosis of GC patients.

Conclusions

In conclusion, the pre-operative PLR and ΔPLR are independent prognostic factors of OS and RFS in GC patients undergoing radical gastrectomy. Pre-operative PLR might be an economical and reliable prognostic marker in predicting the survival of patients with GC. The decreased value for PLR and NLR after surgery might be helpful to predict cancer recurrence and have survival benefits. Our study was a single institution retrospective study with small sample size. More research needs to be done to define the inflammatory markers as prognostic factor.

List Of Abbreviations

NLR; Neutrophil Lymphocyte Ratio; PLR; Platelets Lymphocyte Ratio; ΔNLR; derived Neutrophil Lymphocyte Ratio; ΔPLR; Derived Platelets Lymphocytes Ratio; RFS; Relapse Free Survival; OS; Overall Survival; GC; Gastric Cancer; CRC; CEA; Carcinoembryonic Antigen; CA; Carbohydrate Antigen; CRP; C-Reactive Protein; ALB; Albumin; WBC; White Blood Cells; TNM; TNM classification of malignant tumor (Tumor; Nodes; Metastasis); AJCC; American Joint Committee on Cancer; IQR; Interquartile Range; CIs; Confidence Interval; AUC; Area Under Curve; SD; Standard Deviation; CT; Computed Tomography; K-M test; Kaplan Meier test

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The approval for this study was obtained from our Ethics committee. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interest

All authors have no conflict of interest to declare.

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Authors Contributions

SB has made substantial contribution to the concept of the study. SB, NL, and HDL were involved in acquisition and analysis. MK, QXJ and NG have drafted the work. HNG revised the manuscript. All the authors read and approved the final manuscript

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Tables

Due to technical limitations the Tables are available as downloads in the Supplementary Files.

Figures

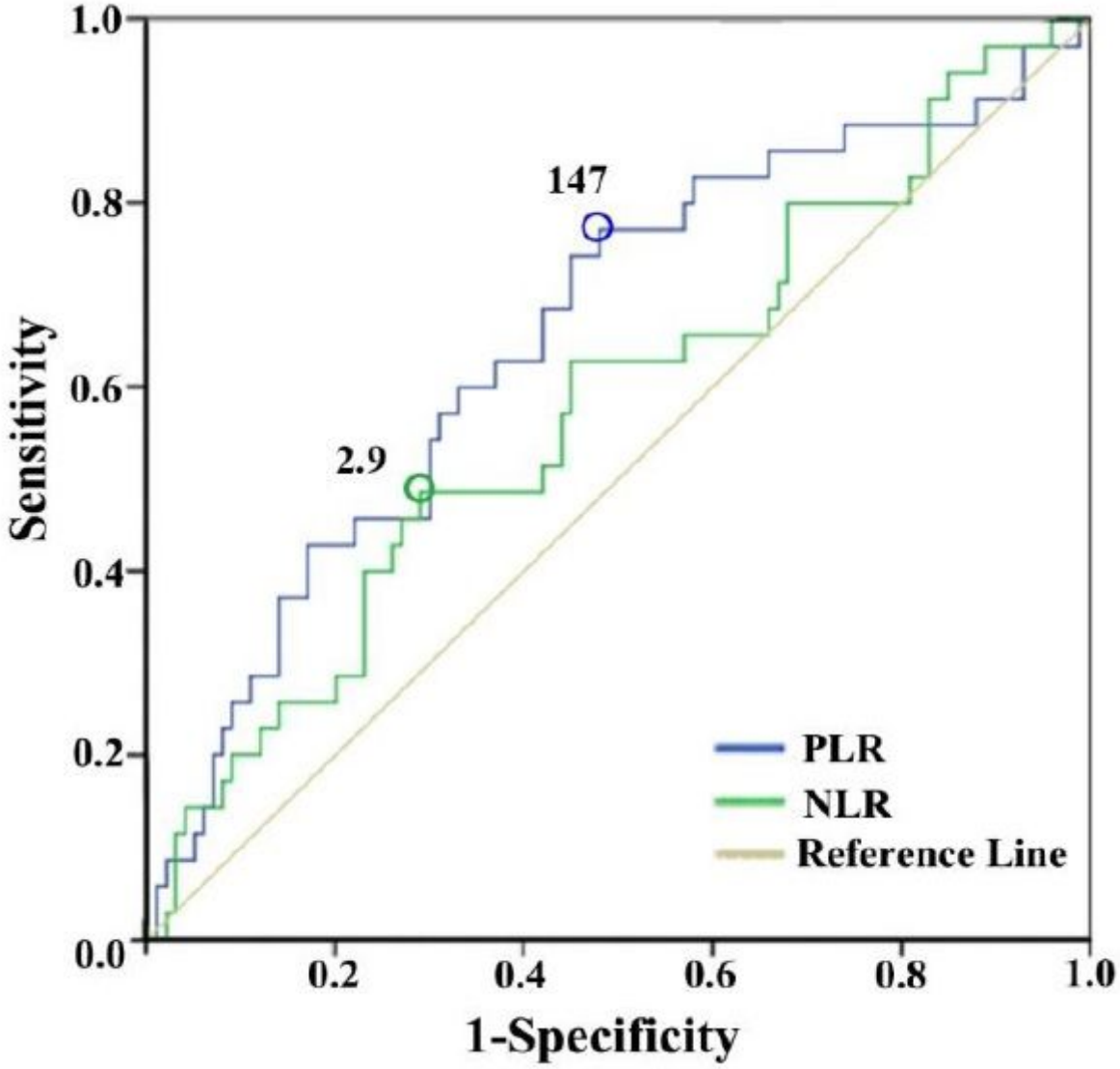

Figure 1

ROC curves for Pre-operative PLR and NLR.

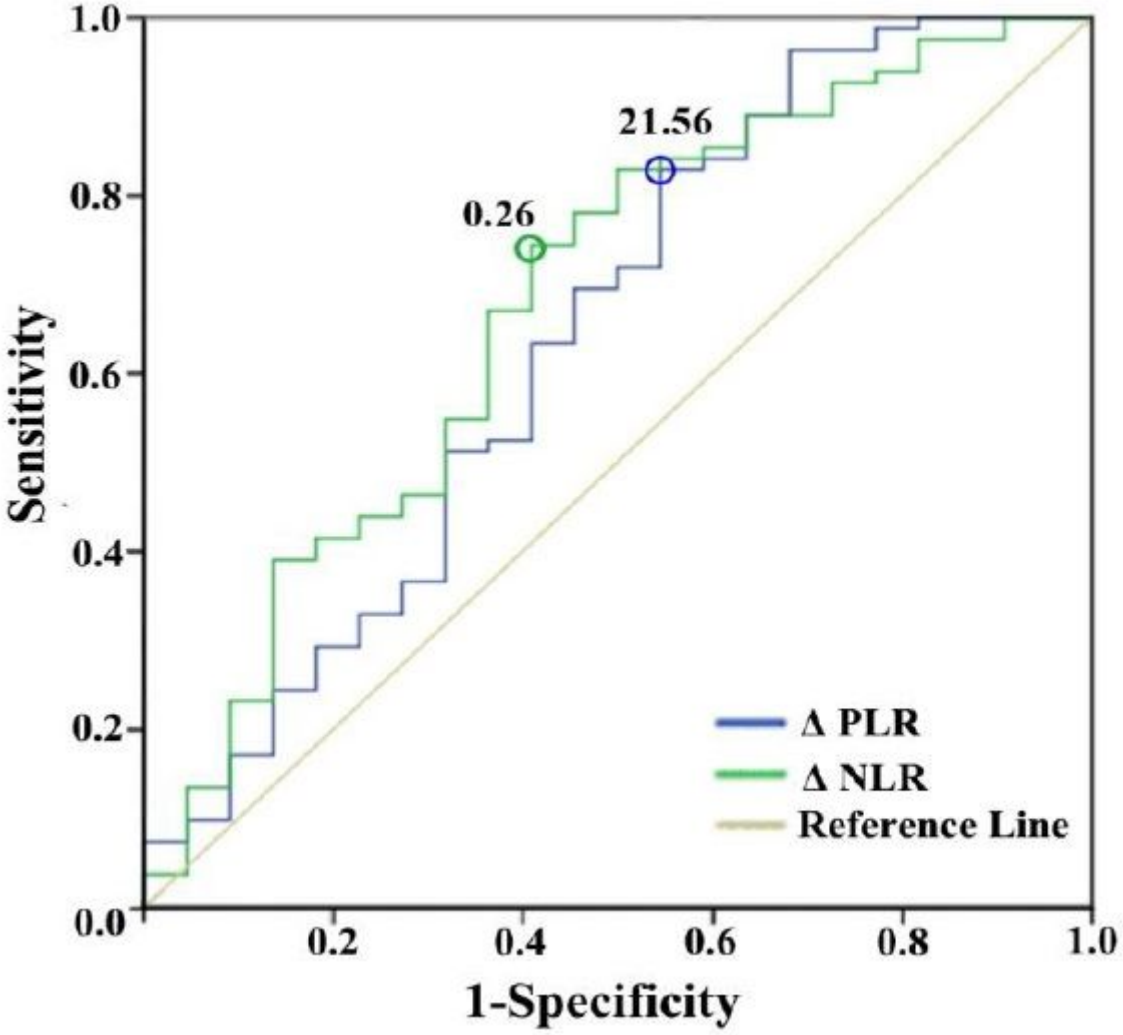

Figure 2

ROC curves for ΔPLR and ΔNLR

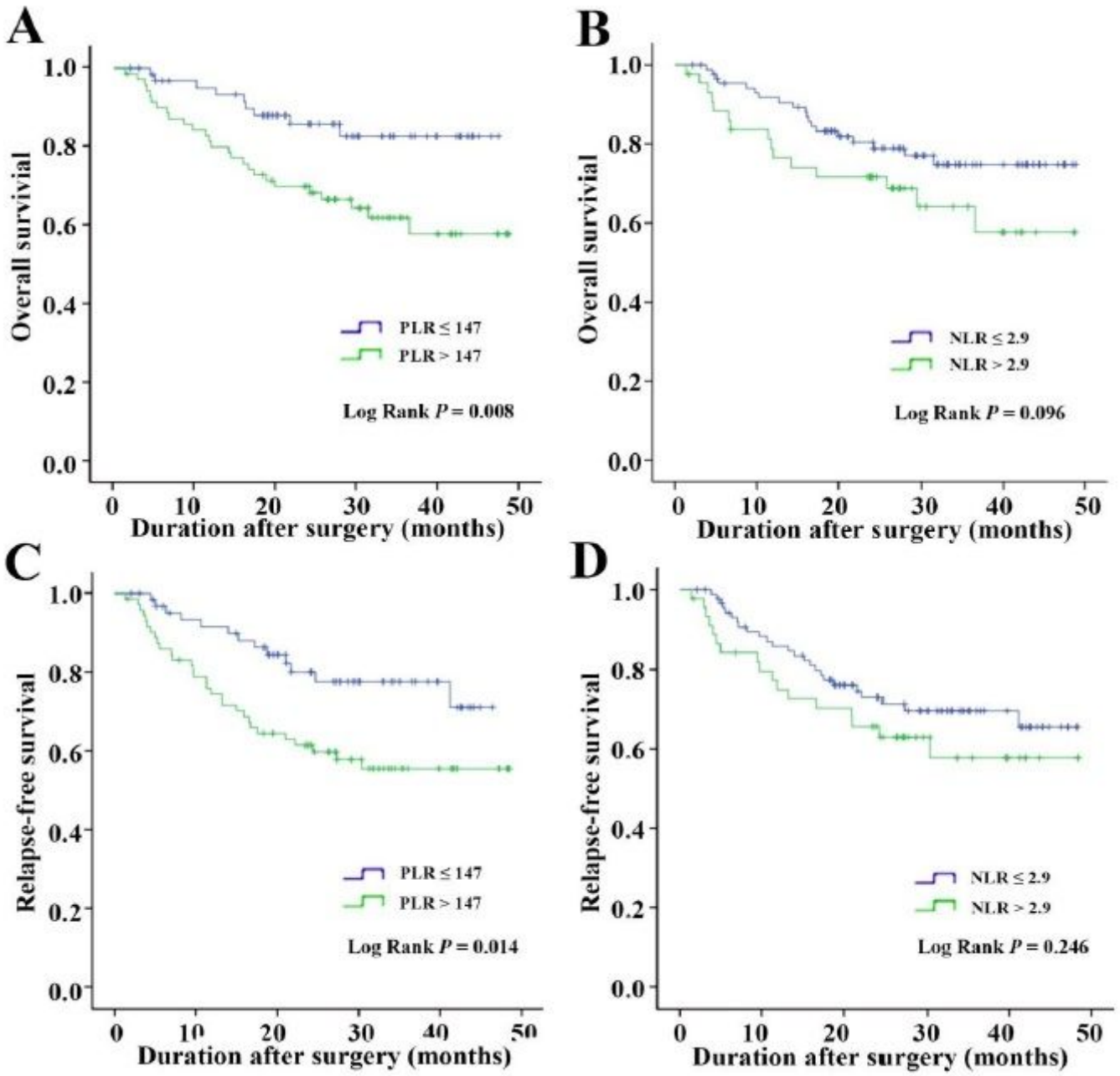

Figure 3

Kaplan-Meier curves for the effect of pre-operative PLR and NLR on OS and RFS of GC patients

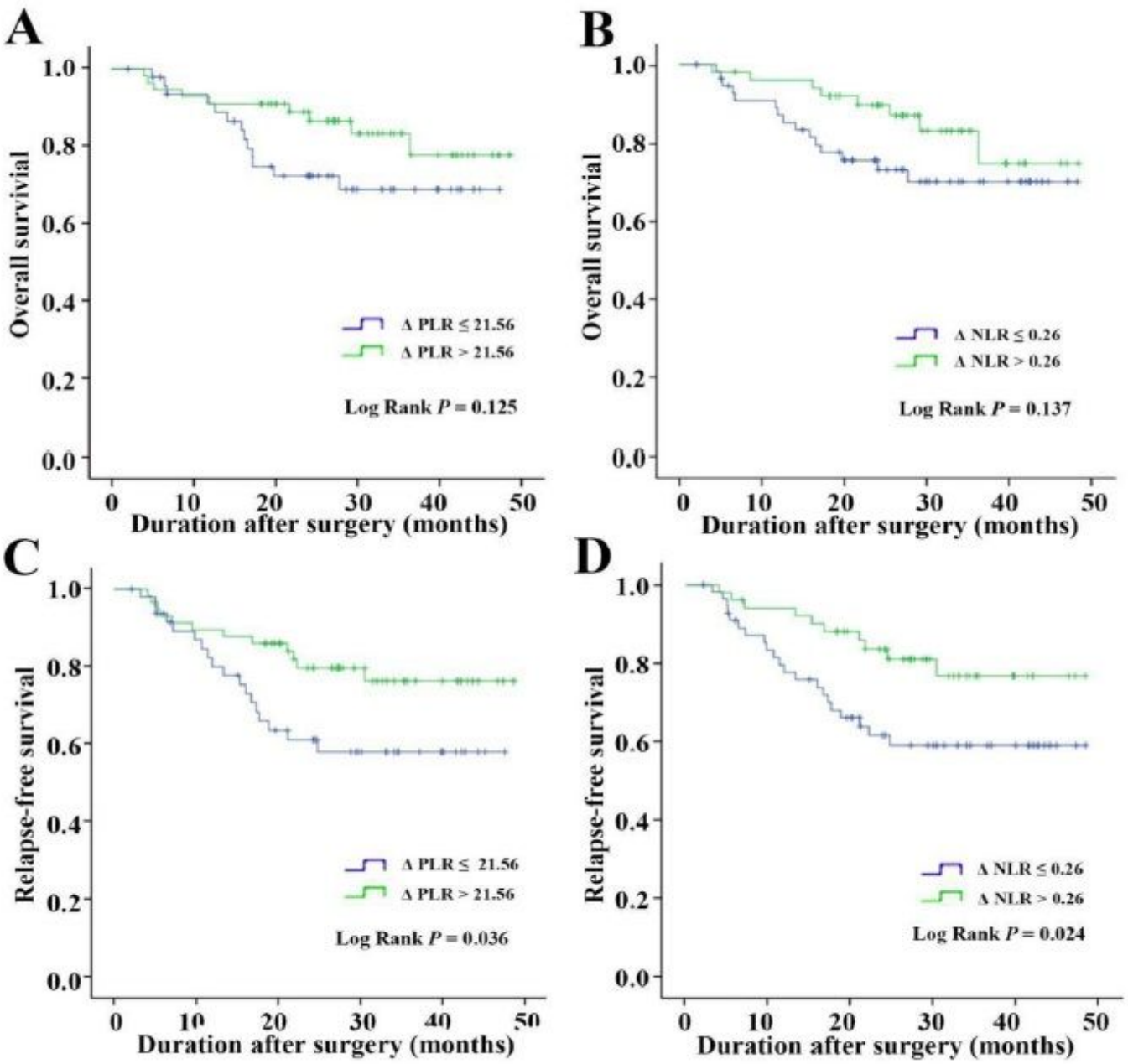

Figure 4

Kaplan-Meier curves for the effect of ΔPLR and ΔNLR on OS and RFS of GC patients.

Supplementary Files

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