Original Article

Prognostic value of neutrophil to lymphocyte ratio and platelet counts during chemotherapy in patients with advanced gastric cancer

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ABSTRACT

الأهداف: التحقق من القيمة التنبؤية للتغيرات الديناميكية في نسبة العدلات إلى الخلايا الليمفاوية (NLR) وعدد الصفائح الدموية (PLT) في المرضى الذين يعانون من GC المتقدم أثناء العلاج الكيميائي.

المنهجية: تم تسجيل 259 مريضًا متقدمًا من GC الذين يتلقون العلاج الكيميائي وتجميعهم حسب NLR و PLT المرتفع أو المنخفض، مع صمامات قطع 2.5 و 300×10^9/L/لتر، على التوالي. تم إجراء نموذج البقاء على قيد الحياة Kaplan-Meier واختبار رتبة السجل لمقارنة الاختلافات في نظام التشغيل. تم إجراء تحليلات الانحدار وحيد المتغير ومتعدد المتغيرات من خلال تحليل الانحدار كوكس للتحقيق في عوامل الإنذار المستقلة المحتملة.

النتائج: ارتبط NLR العالي قبل العلاج الكيميائي بنقائل ودرجة عالية من نوع Borrmann على التوالي ، وكان NLR العالي لمرضى GC قبل العلاج الكيميائي أو بعده مرتبطًا بدرجة نوع Borrmann. علاوة على ذلك ، ترتبط معدلات PLT المرتفعة بالدرجات المتقدمة من نوع Borrmann. ومن المثير للاهتمام ، أن المرضى الذين يعانون من انخفاض NLR بعد العلاج الكيميائي أو انخفاض NLR لديهم نسبة ORR و DCR أفضل من أولئك الذين لديهم NLR أعلى أو زيادة NLR. علاوة على ذلك، المرضى الذين يعانون من NLR العالي بعد العلاج الكيميائي وحده أو أعلى بعد العلاج الكيميائي NLR بالإضافة إلى PLT أعلى بعد العلاج الكيميائي كان لها نظام تشغيل ضار.

الخلاصة: اقترحت دراستنا أن NLR العالي بعد العلاج الكيميائي و PLT بعد العلاج الكيميائي قد يكونان علامات تنبؤية سلبية في مرضى GC المتقدمين الذين يخضعون للعلاج الكيميائي.

Objectives: To investigate the predictive significance of dynamic changes in the neutrophil to lymphocyte ratio (NLR) and platelet counts (PLTs) in patients with advanced gastric cancer (GC) during chemotherapy.

Methods: A total of 259 advanced GC patients receiving chemotherapy were enrolled and grouped by high or low NLR with a cut value of 2.5 and PLT with cut value of 300×10^9/L. The Kaplan-Meier survival model and the Log-rank test were carried out to determine the comparison on the overall survival differences. Cox regression analysis was employed to carry out both univariate and multivariate regression studies, aiming to explore potential prognostic factors acting independently.

Results: Higher pre-chemotherapy NLR exhibited an association with metastasis and advanced grade of Borrmann type, and higher NLR of pre- or post-chemotherapy GC patients was related with Borrmann type grade. Moreover, higher PLT counts are associated with advanced grades of Borrmann type. Interestingly, patients with lower post-chemotherapy NLR or decreasing NLR hold better overall response rate and disease control rate than those with higher NLR or increasing NLR. Furthermore, patients with high post-chemotherapy NLR alone or higher post-chemotherapy NLR plus higher post-chemotherapy PLT.

Conclusion: Our study suggested that high post-chemotherapy NLR and post-chemotherapy PLT might be adverse prognostic markers in advanced GC patients undergoing chemotherapy.

Keywords: neutrophils, lymphocytes, platelets (PLTs), stomach neoplasms, chemotherapy.

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Gastric cancer (GC) ranks fourth in incidence of malignant tumors and is the second leading cancer-related death in Asian countries.[1] Inspiring results have been obtained in GC treatments, and a tremendous, prolonged patient survival time has been achieved.[2] However, treatment-related side effects are significant obstacles that cannot be ignored. Therefore, effective biomarkers are urgently needed to accurately predict therapeutic responses and identify those patients who may benefit from recommending therapy.[3,4]

It is widely accepted that several cancers, including GC, are highly associated with inflammation.[5] In addition, inflammation associated with cancer has been implicated as a hallmark of cancer.[6] Much evidence suggests that inflammation is highly associated with malignancy.[7] Abnormal regulation of the immune response can lead to alterations in the immune microenvironment, which can alter the activation of oncogenes and thus induce malignancy.[8] In addition, established malignancies can also affect the body's immune environment through a series of regulatory means, altering immune cell subsets.[9] The inflammatory environment interacts with the tumor microenvironment, resulting in changes in tumor proliferation, metastasis, and recurrence characteristics.[10] Data suggest that microenvironmental inflammatory cells and immunoregulatory medium in microenvironment influence tumor progression and metastasis.[11] Thus, events and molecules associated with this interaction of cancer microenvironment and inflammation processes, which might be outstanding evaluation tools with significant clinical impact in anti-cancer therapeutic interventions.

Current studies illustrated the essential roles of neutrophils in responding to inflammation, lymphocytes in contributing to tumor defense during the immunological response, and platelet in promoting malignance proliferation and metastasis, during tumor progression and cancer development.[12,13] As a result, inflammatory biomarkers like platelet counts (PLTs) with lymphocytes ratio as well as neutrophils-to-lymphocytes ratio (NLR) have been established as prognostic elements in a series of malignancies, such as cervical, lung, breast, and liver malignancies, and more.[14-17] Moreover, scientists have reported that increased NLR and PLR were linked to the poor prognosis in newly diagnosed GC patients.[18] However, whether dynamic change with NLR and PLT in advanced GC following chemotherapy is significant for prognosis remains to be declared.

In the present project, the dynamic change with NLR and PLT in advanced GC following chemotherapy was determined to explore the relationsip with prognosis in GC patients.

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Methods. A total of 897 patients who have been confirmed to diagnose with advanced GC were investigated at the Fourth Hospital of Hebei Medical University, Hebei, China, between February 2010 and February 2015. The inclusion criteria were as follow: I) patients were diagnosed as GC through pathologic means; II) at least 18 years; III) at least one lesion can be measurable; IV) Eastern Cooperative Oncology Group (ECOG) score of 0-1; V) having pre-treatment blood sampling; and VI) no anti-tumor therapy or postoperative adjuvant chemotherapy of ≥6 months. Patients were excluded: I) having fever, systemic inflammatory diseases, hematological diseases, immune disorders, cardiac-cerebral vascular events, and infectious diseases; and II) during the second chemotherapy cycle, the chemotherapy regimen is discontinued or changed. Based on the criteria, 259 matched patients were recruited into this study. All clinical and follow-up records were reviewed retrospectively. Baseline characteristics including age, gender, pathological type, ECOG, and chemotherapy regimen were excerpted. The chemotherapy regimen in this study involved the paclitaxel-based regimen (175 mg/m^2), fluorouracil-based regimen (400 mg/m^2) followed by 2400 mg/m^2 intravenous infusion in 46-48 hours, and fluorouracil plus paclitaxel regimen (intravenous injection [FU] of 500 mg/m^2 for day 1 and 2, 90 mg/m^2 of PTX for day 1). Ethical approval has been obtained from the Fourth Hospital of Hebei Medical University ethics committee, Hebei, China (HYSY-2019031). The informed consents were provided by each patients. This study is according to principles of Helsinki Declaration.

Blood samples were evaluated before initial treatment and after 2 chemotherapy cycles for neutrophil, lymphocyte, and platelet levels. The NLR was determined by dividing the serum neutrophil level by the serum lymphocyte. Pre-chemotherapy NLR and pre-chemotherapy PLT are defined as baseline status, while post-chemotherapy NLR and post-chemotherapy PLT are those values after 2 chemotherapy cycles. The neutrophil, lymphocyte, and platelet level were evaluated by 5-category blood cell analyzer (D11-CRP, Xiyuan Corp, Shanghai, China).

After the pathological diagnosis, thorough patient follow-up was carried out, patients underwent dynamic

computed tomography (CT) scans either every 2 cycles of chemotherapy or at 6-week intervals. Treatment response was assessed following the guidelines of Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response was considered achieved with CR or PR, while disease control encompassed CR, PR, or SD. Survival time was defined as the duration from the commencement of chemotherapy until either the patient's demise or the most recent clinical assessment. The end date of the follow-up was December 2018. The CT was determined by SOMATOM definition (Siemens China Corp., Beijing, China).

Statistical analysis. The Statistical Package for the Social Sciences, version 21.0 software (IBM Corp., Armonk, NY, USA) was carried out for statistics. Based on the literature search, we chose the cut-off value of 2.5 for NLR.[19,20] The count data were as described by numbers and precentages (%), and the Chi-square test carried out the comparison between groups. Overall survival (OS) was defined as from the diagnosis to death date or the final follow-up date. The Kaplan-Meier survival model and the Log-rank test compared OS differences between groups. The overall response rate (ORR) was characterized by the proportion of patients exhibiting a predetermined reduction in disease burden. Disease control rate (DCR) is the sum of the total, partial, and SD rates. Cox regression analysis was employed to carry out both univariate and multivariate regression analyses, aimed at identifying potential independent prognostic factors. Statistical significance was defined as a *p*-value of less than 0.05.

Results. Patient demographic information and clinical characteristics are listed in Table 1. A total of 259 patients with GC following chemotherapy were enrolled in this study, including 196 (75.2%) males and 63 (24.8%) females. There were 129 (49.8%) patients aged >60 years and 130 (50.2%) aged ≤60 years. The chemotherapy regimen mainly consisted of a paclitaxel-based regimen (64.1%), a fluorouracil-based regimen (17.8%), and a fluorouracil plus paclitaxel regimen (16.2%). The tumor sites occurred in the gastric antrum (13.5%), stomach cardia (38.5%), crossing site (19.3%), and gastric body (28.6%). Metastatic foci lied in organs (43.2%), distant lymph nodes (12.4%), peritoneal (22.8%,) and other multi-sites (21.6%). These patients were histologically classified into tubular adenocarcinoma (39.0%), signet ring cell carcinoma (21.2%), mucinous adenocarcinoma (10.4%), papillary carcinoma (22.8%), and other types (6.6%). Bormann type of these GC patients involved with type I (16.6%), type II (29.3%), type III (39.8%), and type IV (14.3%).

The median value of NLR in pre-chemotherapy patients was 2.74 (range: 0.57-3.8) and the median value of NLR in post-chemotherapy patients was 2.00 (range: 0.0-24.0). As illustrated above, the cut-off value was defined as 2.5. As a result, we found that 116 (44.8%) patients had a low pre-chemotherapy NLR level, while 143 (55.2%) patients had a high pre-chemotherapy NLR level (Table 1). On the contrary, 158 (61.0%) patients had a low post-chemotherapy NLR level, while 101 (39.0%) patients had a high post-chemotherapy NLR level. In addition, 89 (34.5%) patients had an increasing NLR level for the dynamic change of NLR, while 170 (65.5%) patients had a decreasing NLR level. No differences existed between any therapeutic regimen, tumor site, and pathological type at pre-chemotherapy NLR, post-chemotherapy NLR, and NLR variation. Interestingly, statistically noteworthy distinctions were observed among pre-chemotherapy NLR and metastatic foci ($p<0.001$), pre-chemotherapy NLR and Bormann type ($p<0.05$), as well as post-chemotherapy NLR and Bormann type ($p<0.001$; Table 1).

Besides, we have found that 58 (22.4%) patients had a low pre-chemotherapy PLT level, while 201 (77.6%) patients had a high pre-chemotherapy PLT level (Table 2). In contrast, 34 (13.1%) patients had a low post-chemotherapy PLT level, while 225 (86.9%) patients had a high post-chemotherapy PLT level. Dynamically, 174 (67.1%) patients had an increasing PLT level, while 85 (32.9%) patients had a decreasing PLT level. There was no significance in gender, age, therapeutic regimen, tumor size, and pathological type of metastatic foci between PLT groups. Nevertheless, statistically significant differences were observed between pre-chemotherapy PLT and Bormann type ($p<0.05$; Table 2).

In the examined cohort, the median OS stood at 14.0 months, while the rate of ORR was 23.16% and the rate of DCR was 80.31% in 259 GC patients treated with chemotherapy. Detailed clinical outcomes corresponding to NLR or PLT levels were summarized in Figure 1 and Table 3. Except for pre-chemotherapy NLR levels, the patients with low post-chemotherapy NLR or decreasing NLR have higher ORR and DCR than those with high NLR or increasing NLR ($p<0.05$). Moreover, the patients with low NLR or decreasing NLR had a slightly longer mOS than those with high NLR or growing NLR. The influence of PLT on OS, ORR, and DCR was similar to NLR.

Table 1 - Relationship between clinicopathological features and neutrophil to lymphocyte ratio levels in patients with advanced gastric cancer following chemotherapy.

Clinical characteristics	Total (n=259)	Pre-treatment			Post-treatment			Dynamic change		
		NLR>2.5	NLR≤2.5	*P*-values	NLR>2.5	NLR≤2.5	*P*-values	Increase	Decrease	*P*-values
Age (years)										
≤60	130 (50.2)	72 (55.4)	58 (44.6)	1.000	51 (39.2)	79 (60.8)	1.0	40 (30.8)	90 (69.2)	0.275
>60	129 (49.8)	71 (55.0)	58 (45.0)		50 (38.8)	79 (61.2)		49 (38.0)	80 (62.0)	
Gender										
Male	196 (75.2)	101 (51.5)	95 (48.5)	0.050	77 (39.3)	119 (60.7)	0.984	70 (35.7)	126 (64.3)	1.0
Female	63 (24.8)	42 (66.7)	21 (33.3)		24 (38.1)	39 (61.9)		19 (30.2)	44 (69.8)	
Regimen										
Paclitaxel-based	166 (64.1)	88 (53.0)	78 (47.0)	0.794	57 (34.3)	109 (65.7)	0.086	59 (35.5)	107 (64.5)	0.849
Fluorouracil-based	46 (17.8)	28 (60.9)	18 (39.1)		21 (45.7)	25 (54.3)		16 (34.8)	30 (65.2)	
Fluorouracil+paclitaxel	42 (16.2)	24 (57.1)	18 (42.9)		19 (45.2)	23 (54.8)		12 (28.6)	30 (71.4)	
Other	5 (1.9)	3 (60.0)	2 (40.0)		4 (80.0)	1 (20.0)		2 (40.0)	3 (60.0)	
Tumor site										
Gastric antrum	35 (13.5)	24 (68.6)	11 (31.4)	0.280	12 (34.3)	23 (65.7)	0.915	12 (34.3)	23 (65.7)	0.896
Stomach cardia	100 (38.6)	55 (55.0)	45 (45.0)		41 (41.0)	59 (59.0)		33 (33.0)	67 (67.0)	
Crossing site	50 (19.3)	28 (56.0)	22 (44.0)		19 (38.0)	31 (62.0)		16 (32.0)	34 (68.0)	
Gastric body	74 (28.6)	36 (48.6)	38 (51.4)		29 (39.2)	45 (60.8)		28 (37.8)	46 (62.2)	
Pathological type										
Tubular adenocarcinoma	101 (39.0)	52 (51.5)	49 (48.5)	0.624	36 (35.6)	65 (64.6)	0.191	31 (30.7)	70 (69.3)	0.585
Signet ring cell carcinoma	55 (21.2)	35 (63.6)	20 (36.4)		29 (52.7)	26 (47.3)		24 (43.6)	31 (56.4)	
Mucinous adenocarcinoma	27 (10.4)	15 (55.6)	12 (44.4)		11 (40.7)	16 (59.3)		9 (33.3)	18 (66.7)	
Papillary carcinoma	59 (22.8)	33 (55.9)	26 (44.1)		19 (32.2)	40 (67.8)		19 (32.2)	40 (67.8)	
Other	17 (6.6)	8 (47.1)	9 (52.9)		6 (35.3)	11 (64.7)		6 (35.3)	11 (64.7)	
Metastasis										
Organ*	112 (43.2)	64 (57.1)	48 (42.9)	0.000**	43 (38.4)	69 (61.6)	0.375	38 (33.9)	74 (66.1)	0.466
Distant lymph node†	32 (12.4)	12 (37.5)	20 (62.5)		10 (31.3)	22 (68.8)		13 (40.6)	19 (59.4)	
Peritoneal	59 (22.8)	23 (39.0)	36 (61.0)		21 (35.6)	38 (64.4)		23 (39.0)	36 (61.0)	
Multi-site‡	56 (21.6)	44 (78.6)	12 (21.4)		27 (48.2)	29 (51.8)		15 (26.8)	41 (73.2)	
Borrmann type										
I	43 (16.6)	21 (48.8)	22 (51.2)	0.024**	11 (25.6)	32 (74.4)	0.007**	14 (32.6)	29 (67.4)	0.968
II	76 (29.3)	34 (44.7)	42 (55.3)		24 (31.6)	52 (68.4)		25 (32.9)	51 (67.1)	
III	103 (39.8)	61 (59.2)	42 (40.8)		44 (42.7)	59 (57.3)		37 (35.9)	66 (64.1)	
IV	37 (14.3)	27 (73.0)	10 (27.0)		22 (59.5)	15 (40.5)		13 (35.1)	24 (64.9)	

Values are presented as numbers and precentages (%). *Include liver, lung, ovary, pancreas, colon, and bone. †Next to the aorta, superior mesenteric, retroperitoneal and supraclavicular lymph nodes. ‡Include distant organ and lymph node metastasis simultaneously; distant organ and peritoneal metastasis simultaneously; distant lymph node and peritoneal metastasis simultaneously; distant organ, distant lymph node and peritoneal metastasis simultaneous. **A *p*-value of <0.05 is statistically significant using Chi-square test.
NLR: neutrophil-to-lymphocyte ratio

Then, we analyzed the correlations between NLR or PLT levels with OS using the Kaplan-Meier methods. As shown in **Figure 2**, we found that patients with high post-chemotherapy NLR levels had significantly shorter mOS than those with low post-chemotherapy NLR (11.0 months versus 15.0 months; hazard ratio [HR]=1.36, 95% confidence interval [CI]: [1.06-1.76]; p=0.014). Afterward, we observed that patients with high post-chemotherapy NLR levels and high PLT levels had significantly shorter mOS than those with low post-chemotherapy NLR and low post-PLR (7.0 months versus 15.0 months; HR=1.73, 95% CI: [2.12-2.74]; p=0.0063). Furthermore, we also find that pathological type (p<0.01) and Bormann type (p<0.0001) have an apparent impact on mOS statistically.

Univariate and multivariate survival analyses were carried out to determine the effects of post-chemotherapeutic NLR and PLT. Based on the univariate analysis results (**Table 4**), favorable prognostic factors for OS were the pathological type of papillary carcinoma (HR=0.36, 95% CI: [0.26-0.49]; p<0.001), adverse prognostic factor for OS included signet ring cell carcinoma (HR=4.77, 95% CI: [3.48-6.54]; p<0.001), mucinous adenocarcinoma (HR=2.20, 95% CI: [1.46-3.31]; p<0.001), Bormann IV type (HR=1.92, 95% CI: [1.34-2.74]; p<0.001), high post-chemotherapy NLR (HR=1.36, 95% CI:

Table 2 - Relationship between clinicopathological features and platelet count levels in patients with advanced gastric cancer following chemotherapy.

Clinical characteristics	Total (n=259)	Pre-treatment PLT			Post-treatment PLT			Dynamic change		
		>300×10⁹/L	≤300×10⁹/L	*P*-values	>300×10⁹/L	≤300×10⁹/L	*P*-values	Increase	Decrease	*P*-values
Age (years)										
>60	130 (50.2)	101 (77.7)	29 (22.3)	1.000	111 (85.4)	19 (14.6)	0.598	92 (70.8)	38 (29.2)	0.270
≤60	129 (49.8)	100 (77.5)	29 (22.5)		114 (88.4)	15 (11.6)		82 (63.6)	47 (36.4)	
Gender										
Male	196 (75.2)	151 (77.0)	45 (23.0)	0.542	168 (85.7)	28 (14.3)	0.123	130 (66.3)	66 (33.7)	1.000
Female	63 (24.8)	50 (79.4)	13 (20.6)		57 (90.5)	6 (9.5)		44 (69.8)	19 (30.2)	
Regimen										
Paclitaxel-based	166 (64.1)	126 (75.9)	40 (24.1)	0.193	146 (88.0)	20 (12.0)	0.529	120 (72.3)	46 (27.7)	0.109
Fluorouracil-based	46 (17.8)	41 (89.1)	5 (10.9)		40 (87.0)	6 (13.0)		25 (54.3)	21 (45.7)	
Fluorouracil and paclitaxel	42 (16.2)	30 (71.4)	12 (28.6)		34 (81.0)	8 (19.0)		26 (61.9)	16 (38.1)	
Other	5 (1.9)	4 (80.0)	1 (20.0)		5 (100.0)	0 (0.0)		3 (60.0)	2 (40.0)	
Tumor site										
Gastric antrum	35 (13.5)	25 (71.4)	10 (28.6)	0.808	28 (80.0)	7 (20.0)	0.455	25 (71.4)	10 (28.6)	0.751
Stomach cardia	100 (38.6)	78 (78.0)	22 (22.0)		87 (87.0)	13 (13.0)		65 (65.0)	35 (35.0)	
Crossing	50 (19.3)	39 (78.0)	11 (22.0)		46 (92.0)	4 (8.0)		36 (72.0)	14 (28.0)	
Gastric body	74 (28.6)	59 (79.7)	15 (20.3)		64 (86.5)	10 (13.5)		48 (64.9)	26 (35.1)	
Pathological type										
Tubular adenocarcinoma	101 (39.0)	75 (74.3)	26 (25.7)	0.661	87 (86.1)	14 (13.9)	0.339	68 (67.3)	33 (32.7)	0.713
Signet ring cell carcinoma	55 (21.2)	41 (74.5)	14 (25.5)		44 (80.0)	11 (20.0)		35 (63.6)	20 (36.4)	
Mucinous adenocarcinoma	27 (10.4)	22 (81.5)	5 (18.5)		24 (88.9)	3 (11.1)		18 (66.7)	9 (33.3)	
Papillary carcinoma	59 (22.8)	49 (83.1)	10 (16.9)		55 (93.2)	4 (6.8)		39 (66.1)	20 (33.9)	
Other	17 (6.6)	14 (82.4)	3 (17.6)		15 (88.2)	2 (11.8)		14 (82.4)	3 (17.6)	
Metastasis										
Organ*	112 (43.2)	88 (78.6)	24 (21.4)	0.809	97 (86.6)	15 (13.4)	0.622	77 (68.8)	35 (31.3)	0.183
Distant lymph node†	32 (12.4)	23 (71.9)	9 (28.1)		30 (93.8)	2 (6.2)		24 (75.0)	8 (25.0)	
Peritoneal	59 (22.8)	45 (76.3)	14 (23.7)		51 (86.4)	8 (13.6)		33 (55.9)	26 (44.1)	
Multi-site‡	56 (21.6)	45 (80.4)	11 (19.6)		47 (83.9)	9 (16.1)		40 (71.4)	16 (28.6)	
Borrmann type										
I	43 (16.6)	27 (62.8)	16 (37.2)	0.035**	41 (95.3)	2 (4.7)	0.065	30 (69.8)	13 (30.2)	0.164
II	76 (29.3)	57 (75.0)	19 (25.0)		67 (88.2)	9 (11.8)		56 (73.7)	20 (26.3)	
III	103 (39.8)	86 (83.5)	17 (16.5)		83 (80.6)	20 (19.4)		61 (59.2)	42 (40.8)	
IV	37 (14.3)	31 (83.8)	6 (16.2)		34 (91.9)	3 (8.1)		27 (73.0)	10 (27.0)	

Values are presented as numbers and precentages (%). *Include liver, lung, ovary, pancreas, colon, and bone. †Next to the aorta, superior mesenteric, retroperitoneal and supraclavicular lymph nodes. ‡Include distant organ and lymph node metastasis simultaneously; distant organ and peritoneal metastasis simultaneously; distant lymph node and peritoneal metastasis simultaneously; distant organ, distant lymph node and peritoneal metastasis simultaneous. **A *p*-value of <0.05 is statistically significant using Chi-square test. PLT: platelet count

[1.06-1.76]; $p<0.05$), and high post-chemotherapy NLR plus high post-chemotherapy PLT (HR=2.02, 95% CI: [1.24-3.27]; $p<0.05$). In the multivariate analysis (Table 4), only the pathological type of papillary carcinoma (HR=0.51, 95% CI: [0.36-0.71]; $p<0.001$), signet ring cell carcinoma (HR=3.88, 95% CI: [2.71-5.42]; $p<0.001$), mucinous adenocarcinoma (HR=2.34, 95% CI: [1.52-3.60]; $p<0.001$) was the independent prognostic factors. However, a notable absence of significant difference was observed between high post-chemotherapy NLR or post-chemotherapy NLR plus post-chemotherapy PLT and shorter OS in multivariate analysis.

Discussion. The human inflammatory response and neoplasia interact with each other and play an essential role in developing a range of cancers.[21] The process of inflammation fosters the growth of tumors, supports the development of new blood vessels (angiogenesis), facilitates the spread of cancer to other parts of the body (metastasis), and strengthens the tumor's ability to resist hormones and chemotherapy treatments by upregulating inflammatory mediators and cytokines, aberrant activation of immunomodulatory cytokines, and inhibiting and DNA damage.[12,13,22] The cancer-associated inflammatory environment assumes a pivotal role in the progression of malignancy, which could explain a range of mechanisms. Inactivation of lymphocytes is involved in the progression and metastasis of cancer. Conversely, pre-treatment levels of neutrophils and lymphocytes can serve as indicators of systemic inflammation or physiological stress.[23,24] In

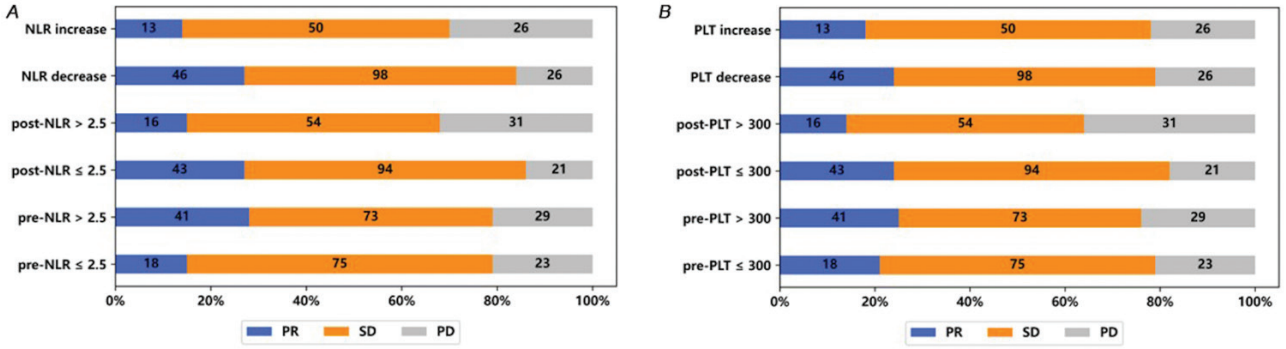

Figure 1 - Clinical outcomes corresponding to: **A)** NLR or **B)** PLT levels in patients with advanced gastric cancer following chemotherapy. NLR: neutrophil-to-lymphocyte ratio, PLR: platelet count, PR: partial response, SD: stable disease, PD: progressive disease

Table 3 - Relationship between clinical outcomes and neutrophil-to-lymphocyte ratio levels in patients with advanced gastric cancer following chemotherapy.

Variables	PR+SD (n=207)	PD (n=52)	*P*-values	PR (n=59)	PD+SD (n=200)	*P*-values	mOS (month)	*P*-values
NLR levels								
Pre-chemotherapy NLR >2.5	114 (55.1)	29 (55.8)	1.000	102 (51.0)	41 (69.5)	0.018*	12.0	0.220
Pre-chemotherapy NLR ≤2.5	93 (44.9)	23 (44.2)		98 (49.0)	18 (30.5)		15.0	
Post-chemotherapy NLR >2.5	70 (33.8)	31 (59.6)	0.001*	85 (42.5)	16 (27.1)	0.048*	11.0	0.0557
Post-chemotherapy NLR ≤2.5	137 (66.2)	21 (40.4)		115 (57.5)	43 (72.9)		15.0	
NLR increase	63 (30.4)	26 50.0)	0.013*	76 (38.0)	13 (22.0)	0.034*	13.0	0.531
NLR decrease	144 (69.6)	26 50.0)		124 (62.0)	46 (78.0)		15.0	
PLT levels								
Pre-chemotherapy PLT >300×10^9/L	45 (21.7)	13 (25.0)	0.75	43 (21.5)	15 (25.4)	0.647	12.0	0.665
Pre-chemotherapy PLT ≤300×10^9/L	162 (78.3)	39 (75.0)		157 (78.5)	44 (74.6)		15.0	
Post-chemotherapy PLT >300×10^9/L	22 (10.6)	12 (23.1)	0.032*	29 (14.5)	5 (8.5)	0.324	11.0	0.867
Post-chemotherapy PLT ≤300×10^9/L	185 (89.4)	40 (76.9)		171 (85.5)	54 (91.5)		15.0	
PLT increase	67 (32.4)	18 (34.6)	0.886	69 (34.5)	16 (27.1)	0.366	13.0	0.875
PLT decrease	140 (67.6)	34 (65.4)		131 (65.5)	43 (72.9)		15.0	

Values are presented as numbers and precentages (%). *A *p*-value of <0.05 is statistically significant using Chi-square test or independent t-test. NLR: neutrophil-to-lymphocyte ratio, PLR: platelet count, PR: partial response, SD: stable disease, PD: progressive disease

addition, neutrophils can catalyze the establishment of an inflammatory microenvironment through the synthesis of cytokines, which are clearly involved at various phases of tumor progression, thus promoting the growth, angiogenesis, and metastasis of cancerous tissue.[25,26] In the case of lymphocytes, their reduction may lead to immune disorders, and elevated concentrations of CD4+ T-lymphocytes at the tumor margin are associated with a potential reduction in the risk of recurrence. Conversely, a decline in lymphocyte subsets (such as CD4+, CD8+, CD3+, and CD56+ T-cells) among patients with advanced tumors can weaken lymphocyte-driven anti-tumor immune responses, and this weakening may contribute to a less favorable prognosis for these patients.[27] However, although the number of lymphocytes is critical, the functional role of lymphocytes in vivo is more important and should be accurately studied in the future.[28] In addition, platelets, as an important factor in thrombosis, can promote tumor proliferation and angiogenesis.[29] Activated platelets could engage with cancer cells within the malignancy microenvironment via paracrine signaling pathways, leading to the development and survival of cancer cells.[30] Therefore, blood inflammatory biomarkers are considered potential prognostic predictors for various cancers.

Moreover, in GC, NLR, and PLR are important prognostic values.[18] Nevertheless, whether dynamic changes in NLR and PLT are valuable biomarkers for prognosis in advanced GC, especially for post-chemotherapy, is unclear. The present study had a significant association between pre-chemotherapy NLR and metastases, pre-chemotherapy NLR or post-chemotherapy NLR and Bormann type, or pre-chemotherapy PLT and Bormann type (p<0.05). Patients in the lower NLR group or the declining NLR group after chemotherapy had better ORR and DCR than those with high NLR or rising NLR (p<0.05).

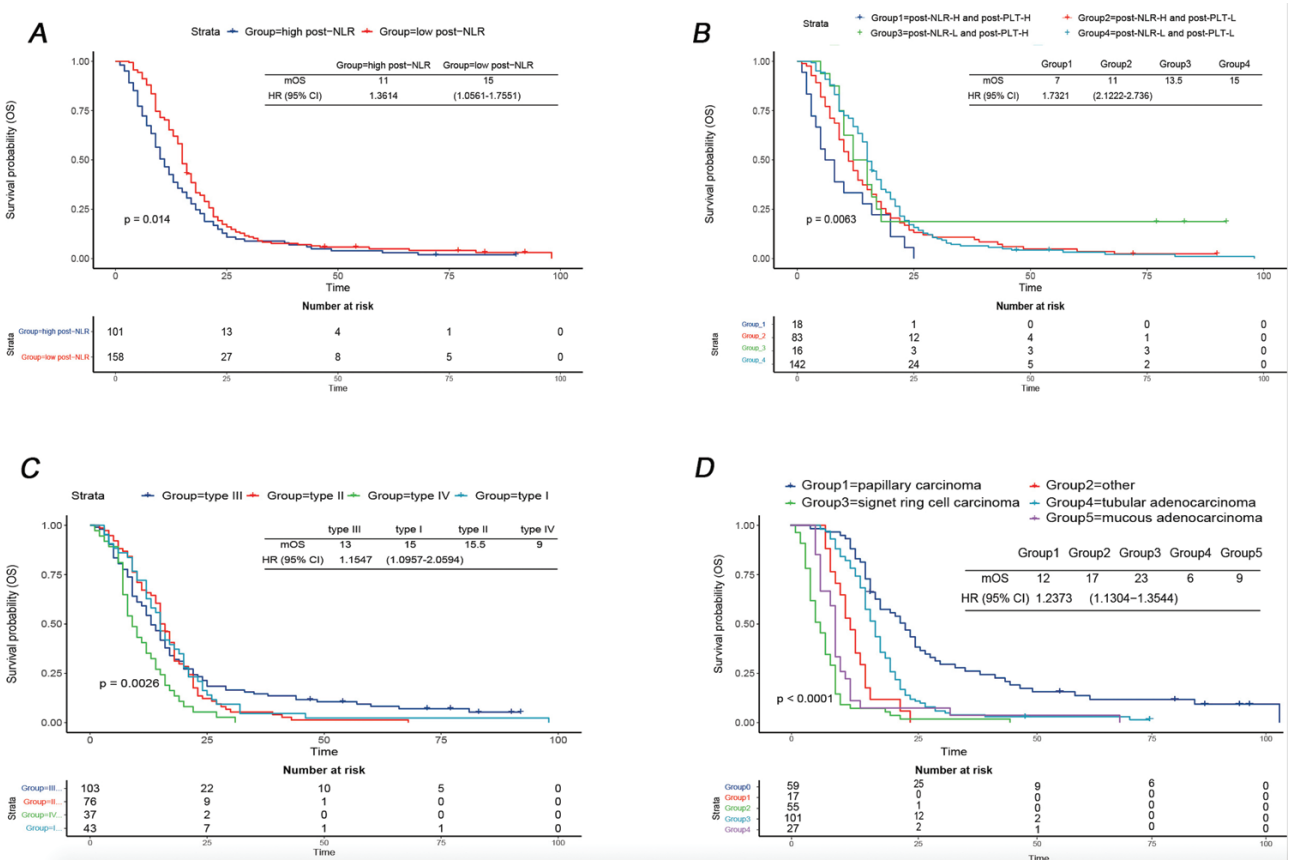

Figure 2 - Kaplan-Meier curves for overall survival in patients with advanced gastric cancer following chemotherapy stratified by: **A)** post-treatment NLR; **B)** postchemotherapy-NLR/postchemotherapy-PLT; **C)** Borrmann type; and **D)** pathological type. NLR: neutrophil to lymphocyte ratio, HR: hazard ratio, CI: confidence interval, PLT: platelet count

Table 4 - Univariate and multivariate analyses of overall survival in patients with advanced gastric cancer following chemotherapy.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-values	HR (95% CI)	*P*-values
Papillary carcinoma	0.36 (0.26-0.49)	<0.0001	0.51 (0.36-0.71)	<0.0001
Signet ring cell carcinoma	4.77 (3.48-6.54)	<0.0001	3.83 (2.71-5.42)	<0.0001
Mucinous adenocarcinoma	2.20 (1.46-3.31)	<0.0001	2.34 (1.52-3.60)	<0.0001
Borramann IV type	1.92 (1.34-2.74)	<0.0001	1.26 (0.86-1.85)	0.232
Post-chemotherapy NLR >2.5	1.36 (1.06-1.76)	0.020	1.11 (0.84-1.46)	0.479
Post-chemotherapy NLR >2.5 + post-chemotherapy PLT >300×10^9/L	2.02 (1.24-3.27)	0.004	1.31 (0.77-2.22)	0.315

Values are presented as hazard ratio (HR) and 95% confidence interval (CI). NLR: neutrophil-to-lymphocyte ratio, PLR: platelet count

More interestingly, we found that patients with low post-chemotherapy NLR levels alone (p<0.05) or low post-chemotherapy NLR plus low post-chemotherapy PLT (p<0.0001) had more favorable OS than high-grade patients.

Several studies have demonstrated that higher NLR levels are significantly associated with poor malignancy prognoses.[12,13,22] For GC, studies have shown that baseline NLR predicts poor prognosis in patients with resectable GC.[31-35] Interestingly, no consistent conclusion was obtained in this study for 2 reasons. First, previous studies included patients treated with targeted therapies, and targeting targeted drugs to specific targets may significantly affect clinical outcomes. Second, different pathological types were integrated into the present study, rather than only one specific

pathological typology. In addition, the different cut-off values may have induced a slight statistical bias. Thus, the role of NLR as a prognostic marker in GC may vary with the treatment of the disease and case classification. Multicenter in-depth clinical investigations are urgently needed to elucidate the role of NLR as a prognostic marker in GC.

Remarkably, more focus has been given to multiple biomarkers and NLR alone. For example, high post-chemotherapy NLR with a low anterior lymphocyte-monocyte ratio was used as a marker of poor prognosis in patients with resectable GC with positive lavage cytology.[35] Similarly, patients with advanced GC and colorectal cancer with low levels of monocyte-to-lymphocyte ratio, NLR, and platelet-to-lymphocyte ratio had significantly higher DCR than those with high levels under anti-PD-1 therapy.[36] Our study found that patients with low post-chemotherapy NLR levels and low post-chemotherapy PLT (p<0.0001) had more favorable OS than those with high levels. Platelets assume a significant and multifaceted role in the progression of cancer and are a potential target and prognostic indicator for cancer treatment.[37,38] Furthermore, the extended utilization of low-dose antiplatelet agents, like aspirin, not only inhibits cancer metastasis but also leads to a notable reduction in cancer incidence.[39] Therefore, this study not only elucidated the effect of NLR on patient prognosis before and after chemotherapy in GC of different pathological subtypes, but also investigated the effect of platelet count on GC prognosis, both NLR and platelet count are data available from clinical blood routine, and the comprehensive evaluation of GC patient prognosis by NLR and platelet count will have a positive guiding effect on the development of chemotherapy regimens for GC.

Given the current phenomenon of high reliance on imaging and molecular imaging combined with some hematological markers for the evaluation of chemotherapy indicators for cancers such as GC,[40] the present study provides another potential option for evaluating the effectiveness of chemotherapy for GC. In clinical practice, we will combine the changes in the indicators elucidated in this study with clinical indicators such as imaging and molecular imaging and molecular biology to evaluate the change or continuation of treatment regimens in an integrated manner.

Study limitations. Although this study yielded relatively promising findings after a well-designed and important sample size analysis, it still has limitations. First, the study adopted a single-institution retrospective design. As a result, complete history data that may affect blood tests, such as NSAIDs, aspirin, and corticosteroids, were lacking. Secondly, chemotherapy regimens differed for each patient. Therefore, the time to assess clinical outcomes may not be constant. Finally, the AUC of survival ROC curves for pre-NLR and post-chemotherapy NLR is not ideal, and we chose the frequently used cut off value of 2.5 in this study. However, we also found divergent outcomes arise from the univariate and multivariate analyses, it is assumed that although the post-chemotherapy NLR or NLR plus PLT is associated with OS in GC patients, it may not be an independent influencing factor. Therefore, further studies must combine with other indicators to further corroborate its role as a prognostic marker. We plan to carry out a large prospective cohort study in the near future to compensate for this study. Also, more mechanisms studies including in vitro and in vivo experiments should be also carried out in the future to further determine the potential effects of peripheral blood cells on GC prognosis.

In conclusion, our study suggests that NLR and PLT levels after chemotherapy may be useful in evaluating the prognosis of patients with advanced GC who are receiving chemotherapy. These noninvasive, convenient, and inexpensive biomarkers would be beneficial for individualized treatment of GC.

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