Platelet to Lymphocyte Ratio as a Potential Inflammatory Marker Predicting the Effect of Adjuvant Chemotherapy in Stage II Colorectal Cancer Patients

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Abstract

Background: The effect of adjuvant chemotherapy in stage II colorectal cancer (CRC) patients has been in controversy for a long time. Our study aimed to investigate the ability of several common inflammatory markers to predict the effect of chemotherapy in stage II CRC patients, finding an effective method for clinicians to distinguish chemotherapy-effective population.

Methods: A total of 708 stage II CRC patients who underwent radical resection (R0) were included. The Subpopulation Treatment Effect Pattern Plot (STEPP) analysis was used to determine the optimal inflammatory marker and cut-off value. Propensity Score Matching (PSM) was performed to balance discrepancy of the characteristics between the chemotherapy and non-chemotherapy group. Kaplan-Meier method with the log-rank test was used to calculate the restricted mean survival time (RMST) and compare survival difference between chemotherapy and non-chemotherapy patients. Univariate Cox proportional hazard regression analysis was used to calculate Hazard Ratio (HR). Multivariate Cox proportional hazard regression analysis was used to investigate the interaction between the effect of chemotherapy and the clinicopathological characteristics.

Results: Platelet to Lymphocyte Ratio (PLR) was chosen as the predictive marker with a cut-off value of 130 according to STEPP. For all the 708 patients, chemotherapy patients had a better OS than non-chemotherapy patients ($p=0.007$). Besides, the results of subgroup analysis interpreted that PLR was strongly associated with the effect of chemotherapy. In the high-PLR subgroup ($PLR>130$), chemotherapy patients obtained a significantly better survival benefit than non-chemotherapy patients ($p<0.001$). However, in the low PLR subgroup ($PLR\leq 130$), such difference of survival benefit between chemotherapy and non-chemotherapy patients was not found ($p=0.956$). Multivariate Cox survival analysis also found that PLR was the only characteristic associated with the effect of chemotherapy (p interaction= 0.027) among all the 11 clinicopathological characteristics. After PSM, no significant difference in OS was found between the chemotherapy group and the non-chemotherapy group ($p=0.058$). PLR was still the only characteristic associated with the effect of chemotherapy (p interaction= 0.038).

Conclusions: PLR can be used as an effective marker to predict the effect of adjuvant chemotherapy in stage II CRC patients.

Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and ranks second in terms of mortality.[1] Radical resection is the principal curative treatment for nonmetastatic CRC patients. Adjuvant chemotherapy is a crucial means to improve additional survival benefits beyond those from surgery. Remarkably, the efficacy of adjuvant chemotherapy of patients with CRC is very likely to be stage-specific. For stage III CRC patients, adjuvant chemotherapy has already been demonstrated to be of great improvement on survival.[2, 3] However, additional survival benefit from chemotherapy in stage II CRC seems to be unclear. Many studies have been performed to find a significant survival benefit associated with chemotherapy in stage II CRC but failed. In the MOSAIC study and another study based on ACCENT database, oxaliplatin-based chemotherapy does not increase survival in the first 6 to 10 years after surgery.[4, 5] In the QUASAR study, the absolute improvement in survival after chemotherapy with fluorouracil is only 3.6%.[6] However, there is another study demonstrating that treatment with 5-FU/LV following surgery provided significant benefit over surgery alone in stage II CRC.[7] Summarize the above and other studies, both NCCN and ASCO guidelines suggest offering chemotherapy to patients with high-risk stage II CRC.[8–12] Patients are defined as high-risk population if they have T4 depth of invasion, peritumoral lymphatic/venous invasion, histologic grade of 3 or greater, R1-R2 margin status, bowel obstruction or perforation, elevated carcinoembryonic antigen (CEA) more than 5 ng/mL or fewer than 12 nodes were retrieved. However, these high-risk characteristics are determined based on prognosis instead of additional survival benefit from chemotherapy. Guidelines also point out that there are no data that correlate risk features and selection of chemotherapy in high risk stage II patients.[13]

In the process of searching characteristics to predict chemotherapy effects of CRC and other cancers, there were many examples of inflammatory markers being used.[14–16] Inflammatory markers, including platelet to lymphocyte ratio (PLR),

neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), prognostic nutritional index (PNI) and others, have been certificated not only strongly associated with the prognosis of cancer,[17–21] but also with chemo-resistance and chemotherapeutic responses.[22–26] Nevertheless, previous studies of inflammatory markers are focused on advanced cancers which are usually accompanied by metastasis. No studies have been performed in stage II CRC.

In this study, we aimed to investigate the ability of inflammatory markers to predict the effect of chemotherapy in stage II CRC patients and find an effective method for clinicians to distinguish the chemotherapy-effective population.

Methods

Participants and criteria

We retrospectively analyzed stage II CRC patients who received surgical treatment at the Department of Surgical Oncology and General Surgery, the First Affiliated Hospital of China Medical University between August 2010 and August 2015. All the patients enrolled in this study had undergone radical resection (R0) for the first time. Besides, part of them had received adjuvant chemotherapy and the regimen of chemotherapy was single-agent therapy with fluoropyrimidines or combination therapy with fluoropyrimidines and oxaliplatin. All the patients were aged 18 or above and had signed informed consents and agreed to use their personal data for research. The primary inclusion criteria were as follows: (1) adenocarcinoma of colon or rectum diagnosed by histopathology, (2) stage II classified in the light of the eighth edition of the AJCC/UICC TNM classification system, (3) information of patients, including baseline characteristics, follow-up and laboratory data was integral and available. Patients were removed from this study in cases of: (1) had received neoadjuvant chemotherapy, (2) had long-term use of anti-coagulant or anti-inflammatory medicine before surgery, (3) had underwent surgery in emergency circumstances, including obstruction and perforation. As of December 2018, all the patients had been followed up with complete outcomes. The median follow-up period was 49 months. The clinicopathological characteristics, including chemotherapy status, gender, age, tumor localization, tumor size, differentiation, T category, numbers of examined lymph nodes and status of vessel carcinoma embolus and cerebrovascular and cardiovascular diseases (CCVD), and laboratory data were collected using electronic medical records. The neutrophil, platelet and lymphocyte counts were collected using a routine blood test. Albumin level was collected using the hepatic function test. PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. LMR was defined as the absolute lymphocyte count divided by the absolute monocyte count. PNI was defined as $10 \times \text{albumin level (g/dl)} + 0.005 \times \text{lymphocyte count (per mm}^3\text{)}$. [27]

Statistical analysis

The Subpopulation Treatment Effect Pattern Plot (STEPP) analysis was used to determine the optimal predictive inflammatory marker and its cut-off value.[28, 29] Mann-Whitney U test and the Chi-square test were used to compare the differences of the concerned inflammatory markers and the other characteristics, respectively. Our survival analysis was based on overall survival (OS). Kaplan-Meier method with the log-rank test was used to compare survival difference between chemotherapy and non-chemotherapy patients. Univariate Cox proportional hazard regression analysis was used to calculate Hazard Ratio (HR). Multivariate Cox proportional hazard regression analysis was used to assess the interaction between the effect of chemotherapy and the clinicopathological characteristics.

In a survival analysis, it is difficult to calculate the survival probability at a specific time point. The restricted mean survival time (RMST) can be used as an alternative to summarize the profile.[30, 31] The RMST is defined as the mean survival time by the end of a certain time point with clinical meaning in the period of a study. It is equal to the area under the survival curve until the time point. The difference in RMST can be explained as the increase or decrease in survival time caused by a certain treatment. Consequently, the RMST can be regarded as an effective method to measure treatment effects. In our study, the RMST at 60 months calculated by Kaplan-Meier survival analysis was used.

In an observational study, it is impossible for researchers to control the treatment distribution. There may be a great difference on the covariates between treated and non-treated groups, and it is very likely to cause a bias in treatment effect estimates. In our study, propensity Score Matching (PSM) [32-34] was performed to balance the covariates in the two groups and reduce this bias.

Statistical evaluation was performed using SPSS software version 25.0 (IBM Corporation, Armonk, NY, USA) and R software version 3.6.1 (St. Louis, Missouri, USA). All statistical tests were two-sided, and a P-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics

After the selection, a total of 708 stage II CRC patients were included in the study and they were divided into chemotherapy group and non-chemotherapy group. The clinicopathological characteristics of patients were summarized and compared using the Chi-square test in Table 1 and Mann-Whitney U test in Table 2. 447 (63.1%) patients received chemotherapy and 261 (36.9%) patients did not; 431 (60.9%) patients were male and 277 (39.1%) were female; 354 (50.0%) colon cancer patients and 354 (50.0%) rectal cancer patients. The median age of the patients was 63 (range 23-88). According to the Chi-square test and Mann-Whitney U test, there were significant differences in age, differentiation, T category, CCVD, LMR level and PNI level between the chemotherapy group and the non-chemotherapy group. Higher proportions of advanced age (46.7% vs. 11.0%, $p<0.001$), poor differentiation (9.6% vs. 6.0%, $p=0.038$) and positive cardio-cerebrovascular comorbidities (16.9% vs. 10.7%, $p=0.019$) were seen in the non-chemotherapy group, while the chemotherapy group were more often diagnosed with T4 category (67.3% vs. 54.0%, $p<0.001$).

Overall survival analysis

For all the 708 patients with stage II CRC, Kaplan-Meier method with the log-rank test and univariate Cox proportional hazard regression analysis were used to calculate RMST and HR and compare OS between the chemotherapy group and the non-chemotherapy group. The result showed that the chemotherapy group had a better OS than the non-chemotherapy group (Figure 1A, RMST: 56.2 months vs 53.7 months, HR: 0.580, $p=0.007$).

Optimal inflammatory marker

STEPP analysis was performed, taking respectively the level of the four concerned inflammatory markers, including NLR, PLR, LMR and PNI, as x-axis and the cumulate mortality at 60 months measured by Kaplan-Meier method as y-axis to compare the OS between the chemotherapy group and the non-chemotherapy group in different subgroups divided by the level of the inflammatory markers.

In PLR-related STEPP, when $PLR>130$, the cumulate mortality of the non-chemotherapy group was significantly and constantly higher than the cumulate mortality of the chemotherapy group, while the tendency was just on the contrary when $PLR<130$ (Figure 2A). Besides, no such tendency was found in the analyses related with the other inflammatory markers (Figure 2B, 2C and 2D). This result indicated that PLR was closely associated with the survival benefit of chemotherapy. We could further regard the PLR level of 130 as the cut-off value to distinguish chemotherapy-effective patients. Therefore, we divided the patients into high-PLR subgroup ($PLR\geq 130$) and low-PLR subgroup ($PLR<130$) and performed the Chi-square test to compare the PLR level between the chemotherapy group and the non-chemotherapy group (Table 1).

Subgroup survival analysis

Besides the PLR level, we also divided the patients into subgroups by other clinicopathological characteristics, including gender, age, tumor localization, tumor size, differentiation, T category, numbers of examined lymph nodes and the CEA level for further stratified analysis. In each subgroup, Kaplan-Meier method with the log-rank test and univariate Cox proportional

hazard regression analysis were used to calculate RMST and HR and compare OS between chemotherapy and the non-chemotherapy patients. Besides, multivariate Cox proportional hazard regression analysis was used to investigate the interaction between the effect of chemotherapy and the clinicopathological characteristics (Table 3).

The result of Kaplan-Meier survival analysis indicated that the chemotherapy patients with these following conditions had a better OS than the non-chemotherapy patients: male (55.9 months vs. 53.2 months, HR: 0.592, $p=0.035$), rectal cancer (55.6 months vs. 52.2 months, HR: 0.539, $p=0.016$), well or moderate differentiation (56.3 months vs. 53.9 months, HR: 0.569, $p=0.008$), T4 category (55.6 months vs. 51.8 months, HR: 0.501, $p=0.002$), number of examined lymph nodes ≥ 12 (57.1 months vs. 54.5 months, HR: 0.500, $p=0.007$), and the PLR level >130 (Figure 1B and 1C, 56.5 months vs. 51.3 months, HR: 0.371, $p=0.001$). However, according to multivariate Cox survival analysis, PLR was the only characteristic associated with the effect of chemotherapy (p interaction = 0.027).

PSM for chemotherapy patients and non-chemotherapy patients

To minimize the differences in the clinicopathological characteristics, we performed PSM. In total, 166 chemotherapy patients and 166 non-chemotherapy patients were paired with 1:1 on the propensity scores using the nearest-neighbor method with a caliber of 0.02. The clinicopathological characteristics were summarized and compared using the Chi-square test in Table 4. After PSM, the differences in the characteristics between the chemotherapy group and the non-chemotherapy group were acceptable (p value of the Chi-square test >0.05 in all subgroups).

Survival analysis after PSM

The 332 matched patients were also divided into subgroups by the clinicopathological characteristics. In each subgroup, we performed Kaplan-Meier method with the log-rank test and univariate Cox proportional hazard regression analysis to calculate RMST and HR and compare OS between chemotherapy and the non-chemotherapy patients. We also used multivariate Cox survival analysis to assess the interaction between the effect of chemotherapy and the clinicopathological characteristics (Table 5).

However, different from the result before PSM, there was no significant difference in RMST between the chemotherapy patients and the non-chemotherapy patients (Figure 3A, 56.0 months vs. 53.3 months, HR: 0.584, $p=0.058$). Besides, the result of subgroup analysis was also not quite the same as the result before PSM. Kaplan-Meier survival analysis and univariate Cox proportional hazard regression analysis showed that the chemotherapy patients who were male (55.9 months vs. 52.0 months, HR: 0.487, $p=0.042$), T4 category (55.2 months vs. 50.9 months, HR: 0.501, $p=0.027$), number of examined lymph nodes ≥ 12 (57.5 months vs. 54.1 months, HR: 0.404, $p=0.018$), and the PLR level >130 (Figure 3B and 3C, 57.6 months vs. 51.3 months, HR: 0.272, $p=0.005$) had a longer RMST than the non-chemotherapy patients. However, in accordance with the result before PSM, PLR was still the only characteristic associated with the effect of chemotherapy (p interaction = 0.038) according to multivariate Cox proportional hazard regression analysis.

Discussion

Guidelines suggest patients with high-risk stage II CRC should receive adjuvant chemotherapy.[8–12] The NCCN guidelines define patients as high-risk population in the case of: T4 depth of invasion, peritumoral lymphatic/venous invasion, histologic grade of 3 or greater, R1-R2 margin status, bowel obstruction or perforation or fewer than 12 nodes were retrieved. Besides, patients are also defined as high-risk by the ASCO guidelines if they have elevated carcinoembryonic antigen (CEA) (CEA > 5 ng/ml). Although these high-risk characteristics determined by overall survival benefit can distinguish the population with poorer prognosis from all stage II CRC patients, they cannot predict additional survival benefit from chemotherapy of the population. Considering the statistical-significance-lacking difference in survival between the chemotherapy and non-chemotherapy population and the side effects chemotherapy may cause[35, 36], chemotherapy may do more harm than good for certain stage II CRC patients. Given this background, novel biomarkers are required to distinguish chemotherapy-effective population among patients with stage II CRC.

There are substantial evidence showing that the progression of a tumor depends on not only the tumor itself, but also the inflammatory response of the host.[37] The inflammatory response has been proved to lead to an impaired immune function and an anti-tumor immune response of the host. It has been widely accepted as an important stage-independent indicator, especially in renal, gastro–esophageal and colorectal cancers. In fact, inflammatory cells, such as neutrophil, lymphocyte, platelet and monocyte, have already been used in prognostic prediction for CRC patients.[17, 19, 21, 38] Furthermore, some studies also proved the interaction between inflammation and the response and resistance of chemotherapy.[22–26, 39] The results of these studies indicate that predicting the treatment effect of chemotherapy with inflammatory biomarkers is feasible.

As far as we know, our study is the first to predict the effect of chemotherapy in stage II CRC patients by PLR. We found that patients with elevated PLR could obtain a survival benefit from chemotherapy while patients with reduced PLR could not. Furthermore, PLR level was the only characteristic associated with the effect of chemotherapy among all the other characteristics (including other inflammatory markers). There was no change in our result after PSM. The result demonstrated that PLR had the ability to predict the effect of chemotherapy in stage II CRC patients. Besides, we also found something in our results differ from guidelines and previous studies. According to guidelines, stage II CRC patients with poor pathological differentiation or inadequate nodal resection are suggested receive chemotherapy, while this population did not obtain a survival benefit from chemotherapy in our study. The possible reasons of the contradictory results are regarded as follows: Firstly, selection bias caused by the retrospective and single-center nature of our study. Secondly, insufficient sample size of these subgroups. Thirdly, patients with poor pathological differentiation and inadequate nodal resection may not be significantly chemotherapy-effective, even though they are suggested receive chemotherapy. The inability to analyze the role of bowel obstruction and perforation, two known high-risk features, and chemotherapy regimen is also a limitation to our study. Because inflammatory-related indicators, such as neutrophil, platelet and lymphocyte count and albumin level, would largely deviate from the general level in the setting of bowel obstruction or perforation, these patients were excluded before the analysis conducted. Besides, we only compared chemotherapeutic treatment effect between chemotherapy patients and non-chemotherapy patients but further comparison by chemotherapy regimen was not performed because of relatively smaller number of patients received single-agent therapy.

Up to now, many studies have been conducted to explore the role of lymphocyte and platelet in tumor progression. Platelets promote angiogenesis, adhesion, and invasion by secreting angiogenic and tumor growth factors, such as transforming growth factor-beta (TGF β) and vascular epidermal growth factor (VEGF), in a tumor environment.[40–42] Platelets have also been proved to prevent the death of tumor cells by natural killer cells.[43] Besides, platelets can promote other immune cells, such as lymphocytes and neutrophils, to infiltrate into tumor tissues and trigger further inflammatory progress by releasing chemokines and cytokines.[44] Consequently, a high level of platelet can partly reflect systemic inflammation and increased meta-statization of neoplastic cells.[45, 46] Lymphocytes are the main components of the immune defense to malignancy of the host and can induce cytotoxic cell death and inhibit tumor cell proliferation and migration.[47, 48] Therefore, a low level of lymphocyte can partly reflect an impaired activation of adaptive immunity and poor nutritional status.[49, 50] These studies mentioned above did not directly elaborate the mechanisms of lymphocyte and platelet in chemotherapy but truly provided some ideas for our research.

For the significant association between elevated PLR and effective chemotherapy treatment shown in our study, we raised three possible explanations. First, previous clinical studies have proved that CRC patients with elevated PLR may have a poorer prognosis and shorter postoperative survival time than the other patients.[19] Considering high-risk patients usually needed additional therapy, it may be one of the reasons why they can obtain more additional survival benefit from chemotherapy. Second, platelets have been demonstrated to be critical for maintaining tumor vascular generation and integrity.[51] To go a step further, high platelets may be related with a rich network of tumor vessels and increased chemotherapeutic agent transport into the tumor and lead to effective chemotherapy treatment. In fact, improving vascular function has long been discussed as a possibility to improve the treatment effect of chemotherapy.[52] Third, as a common side effect of chemotherapy, myelosuppression is an important factor for the continuation of chemotherapy in clinical practice. In chemotherapy of CRC, both two frequently-used agents, oxaliplatin and capecitabine, have been proved to be

inducers of myelosuppression, including thrombocytopenia.[53–56] Patients with elevated PLR may have greater tolerance against chemotherapy than the other patients so that they can receive longer and large dose of chemotherapy. This can explain association between elevated PLR and effective chemotherapy treatment.

In conclusion, our results indicated a positive association between elevated PLR and effective chemotherapy treatment in stage II CRC patients. PLR showed potential as a practical, inexpensive, highly reliable and easily available marker to predict the effect of chemotherapy and distinguish chemotherapy-effective population. However, the potential mechanisms and the specific predictive capacity of PLR should be validated in further prospective, larger population and multi-center studies.

Conclusions

To summarize, our study found that PLR level was strongly associated with the effect of chemotherapy. Patients with elevated PLR ($PLR > 130$) could obtain great survival benefits from chemotherapy while patients with low PLR ($PLR \leq 130$) could not. It means PLR can be used as an effective marker to predict the effect of chemotherapy and to distinguish the chemotherapy-effective population in stage II CRC patients.

List Of Abbreviations

CRC: colorectal cancer; CEA: carcinoembryonic antigen; CCVD: cerebrovascular and cardiovascular diseases; PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; PNI: prognostic nutritional index; STEPP: Subpopulation Treatment Effect Pattern Plot; OS: overall survival; HR: Hazard Ratio; RMST: restricted mean survival time; PSM: Propensity Score Matching; TGF β : transforming growth factor-beta; VEGF: vascular epidermal growth factor; CI: Confidence interval

Declarations

Ethics approval and consent to participate

The study involving human participants was reviewed and approved by the ethics committees of the First Affiliated Hospital of China Medical University. The patients provided their written informed consent to participate in this study.

Consent to publish

Not applicable

Availability of data and materials

All data generated and analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

PG and ZW formulated the research question. XC and QC collected the bulk of data profiles, YF drafted the full manuscript. YS provided substantial input in planning and revising the manuscript. PG provided statistical support and made revision to the results section of the manuscript. XH and XC contributed revisions to the introduction and the discussion. LX conducted analyses and sorted parts of the methods section. ZW played a crucial role in the design of the research and provided revision to this text. All authors contributed to manuscript revision, read and approved the submitted version.

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Tables

Table 1
Characteristics of non-chemotherapy group and chemotherapy group

Characteristics		Total 708	Non-Chemotherapy 261	Chemotherapy 447	P value ^a
Gender	Male	431 (60.9%)	156 (59.8%)	275 (61.5%)	0.645
	Female	277 (39.1%)	105 (40.2%)	172 (38.5%)	
Age (years)	≤ 55	163 (23.0%)	32 (12.3%)	131 (29.3%)	< 0.001
	56–60	125 (17.7%)	23 (8.8%)	102 (22.8%)	
	61–65	146 (20.6%)	40 (15.3%)	106 (23.7%)	
	66–70	103 (14.5%)	44 (16.9%)	59 (13.2%)	
	> 70	171 (24.2%)	122 (46.7%)	49 (11.0%)	
Location	Rectum	354 (50.0%)	119 (45.6%)	235 (52.6%)	0.073
	Colon	354 (50.0%)	142 (54.4%)	212 (47.4%)	
Size (cm)	≤ 5.0	395 (55.8%)	144 (55.2%)	251 (56.2%)	0.954
	> 5.0	303 (42.8%)	113 (43.3%)	190 (42.5%)	
	Unknown	10 (1.4%)	4 (1.5%)	6 (1.3%)	
Differentiation	Well-moderate	654 (92.4%)	234 (89.7%)	420 (94.0%)	0.038
	Poor	52 (7.3%)	25 (9.6%)	27 (6.0%)	
	Unknown	2 (0.3%)	2 (0.8%)	0 (0)	
T category	3	266 (37.6%)	120 (46.0%)	146 (32.7%)	< 0.001
	4	442 (62.4%)	141 (54.0%)	301 (67.3%)	
CEA ^b (ng/mL)	< 5	388 (54.8%)	135 (51.7%)	253 (56.6%)	0.058
	≥ 5	237 (33.5%)	101 (38.7%)	136 (30.4%)	
	Unknown	83 (11.7%)	25 (9.6%)	58 (13.0%)	
Examined lymph nodes	< 12	186 (26.3%)	75 (28.7%)	111 (24.8%)	0.255
	≥ 12	522 (73.7%)	186 (71.3%)	336 (75.2%)	
Vessel carcinoma embolus	Negative	683 (96.5%)	251 (96.2%)	432 (96.6%)	0.741
	Positive	25 (3.5%)	10 (3.8%)	15 (3.4%)	
CCVD ^c	Negative	616 (87.0%)	217 (83.1%)	399 (89.3%)	0.019
	Positive	92 (13.0%)	44 (16.9%)	48 (10.7%)	

^a P value of the Chi-square test

^b CEA: carcinoembryonic antigen

^c CCVD: cerebrovascular and cardiovascular diseases

^d PLR: platelet to lymphocyte ratio

Characteristics		Total	Non-Chemotherapy	Chemotherapy	P value ^a
		708	261	447	
PLR ^d	≤ 130	371 (52.4%)	134 (51.3%)	237 (53.0%)	0.666
	> 130	337 (47.6%)	127 (48.7%)	210 (47.0%)	
^a P value of the Chi-square test					
^b CEA: carcinoembryonic antigen					
^c CCVD: cerebrovascular and cardiovascular diseases					
^d PLR: platelet to lymphocyte ratio					

Table 2
Inflammatory markers of non-chemotherapy group and chemotherapy group

Marker	Total		Non-chemotherapy		Chemotherapy		P value ^a
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	
PLR ^b	127.60	71.64	128.49	74.81	125.84	69.56	0.562
NLR ^c	1.94	1.28	2.02	1.27	1.88	1.30	0.080
LMR ^d	4.21	2.58	3.91	2.53	4.28	2.56	0.008
PNI ^e	50.28	7.33	48.90	8.05	50.75	6.75	< 0.001
^a P value of Mann-Whitney U test							
^b PLR: platelet to lymphocyte ratio							
^c NLR: neutrophil to lymphocyte ratio							
^d LMR: lymphocyte to monocyte ratio							
^e PNI: prognostic nutritional index							

Table 3
Univariate and multivariate analysis of OS

Characteristics		RMST ^b (95%CI) Non-chemotherapy	RMST (95%CI) Chemotherapy	HR ^c (95%CI)	P value ^a	Interaction p
Total		53.7 (51.9–55.2)	56.2 (55.2–57.0)	0.580 (0.388–0.866)	0.007	-
Gender	Male	53.2 (50.7–55.1)	55.9 (54.4–57.0)	0.592 (0.360–0.971)	0.035	0.751
	Female	54.5 (51.7–56.4)	56.8 (54.8–58.0)	0.560 (0.282–1.112)	0.093	
Age (years)	≤ 55	54.3 (48.0–57.6)	56.3 (53.8–57.8)	0.620 (0.225–1.708)	0.350	0.844
	56–60	55.4 (47.4–58.5)	56.8 (54.4–58.2)	0.725 (0.199–2.634)	0.623	
	61–65	53.3 (46.5–56.9)	55.7 (52.9–57.5)	0.636 (0.240–1.683)	0.357	
	66–70	53.2 (48.1–56.4)	57.3 (53.6–58.8)	0.355 (0.118–1.063)	0.053	
	> 70	53.6 (50.9–55.7)	54.6 (49.5–57.1)	0.834 (0.371–1.875)	0.660	
Location	Rectum	52.2 (49.2–54.5)	55.6 (53.9–56.9)	0.539 (0.323–0.900)	0.016	0.479
	Colon	55.2 (52.8–56.9)	56.9 (55.4–58.1)	0.612 (0.321–1.168)	0.132	
Size (cm)	≤ 5.0	54.0 (51.2–55.8)	56.1 (54.5–57.2)	0.621 (0.361–1.067)	0.081	0.255
	> 5.0	53.7 (50.5–55.8)	56.3 (54.5–57.5)	0.561 (0.306–1.028)	0.058	
Differentiation	Well-moderate	53.9 (52.0–55.4)	56.3 (55.2–57.2)	0.569 (0.373–0.868)	0.008	0.396
	Poor	52.0 (43.2–56.6)	54.7 (46.8–57.8)	0.662 (0.177–2.471)	0.534	
T category	3	56.4 (53.7–58.0)	57.6 (55.5–58.6)	0.654 (0.277–1.543)	0.328	0.382
	4	51.8 (49.2–54.0)	55.6 (54.2–56.8)	0.501 (0.318–0.791)	0.002	
CEA ^d (ng/mL)	< 5	54.6 (51.9–56.4)	56.7 (55.3–57.8)	0.585 (0.323–1.060)	0.073	0.482

^a P value of the log-rank test

^b RMST: the restricted mean survival time

^c HR: Hazard Ratio, chemotherapy patients vs. non-chemotherapy patients

^d CEA: carcinoembryonic antigen

^e PLR: platelet to lymphocyte ratio

Characteristics		RMST ^b (95%CI) Non-chemotherapy	RMST (95%CI) Chemotherapy	HR ^c (95%CI)	P value ^a	Interaction P
	≥ 5	53.5 (50.1–55.7)	55.1 (52.8–56.8)	0.734 (0.384–1.404)	0.348	
Examined lymph nodes	< 12	52.0 (47.5–54.9)	53.6 (50.2–55.6)	0.793 (0.414–1.520)	0.483	0.415
	≥ 12	54.5 (52.3–56.0)	57.1 (55.9–57.9)	0.500 (0.300-0.835)	0.007	
PLR ^e	≤ 130	56.0 (53.6–57.6)	56.0 (54.3–57.2)	0.983 (0.528–1.829)	0.956	0.027
	> 130	51.3 (47.8–53.7)	56.5 (54.8–57.7)	0.371 (0.212–0.649)	< 0.001	
^a P value of the log-rank test						
^b RMST: the restricted mean survival time						
^c HR: Hazard Ratio, chemotherapy patients vs. non-chemotherapy patients						
^d CEA: carcinoembryonic antigen						
^e PLR: platelet to lymphocyte ratio						

Table 4
Characteristics of non-chemotherapy group and chemotherapy group after PSM

Characteristics		Total 332	Non-chemotherapy 166	Chemotherapy 166	P value ^a
Gender	Male	199 (59.9%)	97 (58.4%)	102 (61.4%)	0.575
	Female	133 (40.1%)	69 (41.6%)	64 (38.6%)	
Age (years)	≤ 55	58 (17.4%)	30 (18.1%)	28 (16.9%)	0.879
	56–60	42 (12.7%)	20 (12.0%)	22 (13.2%)	
	61–65	65 (19.6%)	32 (19.3%)	33 (19.9%)	
	66–70	74 (22.3%)	34 (20.5%)	40 (24.1%)	
	> 70	93 (28.0%)	50 (30.1%)	43 (25.9%)	
Location	Rectum	171 (51.5%)	88 (53.0%)	83 (50.0%)	0.583
	Colon	161 (48.5%)	78 (47.0%)	83 (50.0%)	
Size (cm)	≤ 5.0	183 (55.1%)	92 (55.4%)	91 (54.8%)	0.833
	> 5.0	143 (44.0%)	72 (43.4%)	74 (44.6%)	
	Unknown	3 (0.9%)	2 (1.2%)	1 (0.6%)	
Differentiation	Well-moderate	309 (93.1%)	154 (92.8%)	155 (93.4%)	0.829
	Poor	23 (6.9%)	12 (7.2%)	11 (6.6%)	
T category	3	127 (38.3%)	62 (37.3%)	65 (39.2%)	0.735
	4	205 (61.7%)	104 (62.7%)	101 (60.8%)	
CEA ^b (ng/mL)	< 5	175 (52.7%)	88 (53.0%)	87 (52.4%)	0.968
	≥ 5	118 (35.5%)	58 (34.9%)	60 (36.1%)	
	Unknown	39 (11.8%)	20 (12.1%)	19 (11.5%)	
Examined lymph nodes	< 12	84 (25.3%)	41 (24.7%)	43 (25.9%)	0.801
	≥ 12	248 (74.7%)	125 (75.3%)	123 (74.1%)	
Vessel carcinoma embolus	Negative	320 (96.4%)	160 (96.4%)	160 (96.4%)	1.000
	Positive	12 (3.6%)	6 (3.6%)	6 (3.6%)	
CCVD ^c	Negative	287 (86.4%)	147 (88.6%)	140 (84.3%)	0.262
	Positive	45 (13.6%)	19 (11.4%)	26 (15.7%)	
PLR ^d	≤ 130	176 (53.0%)	85 (51.2%)	91 (54.8%)	0.509

^a P value of the Chi-square test

^b CEA: carcinoembryonic antigen

^c CCVD: cerebrovascular and cardiovascular diseases

^d PLR: platelet to lymphocyte ratio

Characteristics	Total	Non-chemotherapy	Chemotherapy	P value ^a
	332	166	166	
> 130	156 (47.0%)	81 (48.8%)	75 (45.2%)	
^a P value of the Chi-square test				
^b CEA: carcinoembryonic antigen				
^c CCVD: cerebrovascular and cardiovascular diseases				
^d PLR: platelet to lymphocyte ratio				

Table 5
Univariate and multivariate analysis of OS after PSM

Characteristics		RMST ^b (95%CI) Non-Chemotherapy	RMST (95%CI) Chemotherapy	HR ^c (95%CI)	P value ^a	Interaction p
Total		53.3 (50.9–55.2)	56.0 (54.0–57.4)	0.584 (0.333–1.025)	0.058	-
Gender	Male	52.0 (48.1–54.6)	55.9 (53.2–57.6)	0.487 (0.240–0.991)	0.042	0.157
	Female	55.0 (50.7–57.2)	56.1 (52.8–58.0)	0.787 (0.310–2.003)	0.615	
Age (years)	≤ 55	53.8 (46.6–57.2)	56.6 (50.7–59.0)	0.536 (0.128–2.251)	0.386	0.574
	56–60	54.6 (45.6–58.2)	57.1 (48.8–59.2)	0.584 (0.097–3.499)	0.551	
	61–65	53.2 (45.7–57.0)	55.6 (49.8–58.3)	0.641 (0.171–2.403)	0.505	
	66–70	54.2 (47.2–57.3)	57.5 (52.6–59.1)	0.392 (0.098–1.576)	0.170	
	> 70	52.0 (46.9–55.2)	53.9 (49.1–56.9)	0.748 (0.305–1.830)	0.522	
Location	Rectum	52.4 (48.6–55.0)	54.6 (51.2–56.8)	0.725 (0.366–1.435)	0.353	0.283
	Colon	54.5 (50.6–56.9)	57.5 (54.9–58.9)	0.428 (0.158–1.163)	0.086	
Size (cm)	≤ 5.0	54.3 (50.8–56.6)	56.7 (54.0–58.1)	0.548 (0.236–1.269)	0.153	0.165
	> 5.0	52.6 (48.6–55.4)	55.1 (51.8–57.3)	0.672 (0.312–1.449)	0.307	
Differentiation	Well-moderate	53.5 (50.8–55.4)	56.1 (54.0–57.5)	0.570 (0.315–1.031)	0.059	0.702
	Poor	50.5 (36.8–56.9)	53.8 (39.9–58.2)	0.711 (0.117–4.339)	0.708	
T category	3	58.1 (54.7–59.3)	57.3 (54.2–58.9)	1.439 (0.342–6.045)	0.618	0.072
	4	50.9 (47.1–53.4)	55.2 (52.1–57.0)	0.501 (0.267–0.939)	0.027	
CEA ^d (ng/mL)	< 5	55.2 (51.8–57.1)	57.3 (54.4–58.7)	0.557 (0.219–1.414)	0.211	0.790

^a P value of the log-rank test

^b RMST: the restricted mean survival time

^c HR: Hazard Ratio, chemotherapy patients vs. non-chemotherapy patients

^d CEA: carcinoembryonic antigen

^e PLR: platelet to lymphocyte ratio

Characteristics		RMST ^b (95%CI)	RMST (95%CI)	HR ^c (95%CI)	P value ^a	Interaction P
		Non-Chemotherapy	Chemotherapy			
	≥ 5	52.4 (46.8–55.7)	55.0 (51.0–57.4)	0.641 (0.265–1.552)	0.320	
Examined lymph nodes	< 12	50.7 (44.5–54.8)	51.7 (46.5–55.1)	0.898 (0.381–2.118)	0.806	0.322
	≥ 12	54.1 (51.4–56.0)	57.5 (55.5–58.7)	0.404 (0.185–0.882)	0.018	
PLR ^e	≤ 130	55.3 (51.8–57.4)	54.9 (52.0–56.8)	1.080 (0.495–2.355)	0.847	0.038
	> 130	51.3 (47.2–54.2)	57.6 (54.2–59.0)	0.272 (0.102–0.726)	0.005	
a P value of the log-rank test						
b RMST: the restricted mean survival time						
c HR: Hazard Ratio, chemotherapy patients vs. non-chemotherapy patients						
d CEA: carcinoembryonic antigen						
e PLR: platelet to lymphocyte ratio						

Figures

Figure 1

Kaplan-Meier survival curve of stage II CRC patients before PSM. (A) The result of total patients. (B) The result of low-PLR subgroup. (C) The result of high-PLR subgroup.

Figure 2

STEPP analysis between the concerned inflammatory markers and the effect of adjuvant chemotherapy. (A) The result of PLR. (B) The result of NLR. (C) The result of LMR. (D) The result of PNI.

Figure 3

Kaplan-Meier survival curve of stage II CRC patients after PSM. (A) The result of total patients. (B) The result of low-PLR subgroup. (C) The result of high-PLR subgroup.

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