

Predictive Value of Postoperative Peripheral CD4+ T Cells Percentage in Stage I–III Colorectal Cancer: A Retrospective Multicenter Cohort Study of 1028 Subjects

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Objective: Association of postoperative peripheral CD4+ T cells percentage and recurrence in colorectal cancer (CRC) remains to be explored. Therefore, we aimed to investigate the association between the postoperative peripheral CD4+ T cells percentage and recurrence in CRC patients.

Patients and Methods: Consecutive stage I–III CRC patients without neoadjuvant treatment undergoing curative resection from January 2010 to July 2016 were identified in two Chinese centers. The association between the postoperative CD4+ T cells percentage, measured within 12 weeks after surgery, and recurrence-free survival (RFS) was analyzed.

Results: A total of 1028 patients were identified (training set: 913 patients, validation set: 115 patients). In the training set, the 5-year RFS rate of the 441 patients with abnormal postoperative CD4+ T cells percentage was significantly lower than that of those with normal percentage (70.3% [95% CI 65.7–75.2%] vs 77.6% [95% CI 73.7–81.7%] and unadjusted hazard ratio [HR] 1.36 [95% CI 1.04–1.78], $P=0.02$). The result was confirmed in the validation set. Multivariable Cox regression analysis demonstrated that the association of postoperative CD4+ T cells percentage with 5-year RFS was independent both in the training and validation sets. In propensity score matching analysis, patients with normal postoperative CD4+ T cells percentage were found to have a favourable response to adjuvant chemotherapy (HR 0.29 [95% CI 0.12–0.72], $P=0.008$).

Conclusion: Postoperative peripheral CD4+ T cells percentage is a predictive biomarker for RFS in patients with CRC, which can identify those who will benefit from adjuvant chemotherapy.

Keywords: recurrence, peripheral CD4+ T cells, colorectal cancer, adjuvant chemotherapy, propensity score matching analysis

Introduction

Among men and women across the world, colorectal cancer (CRC) is the fourth and third leading cause of cancer-related death, respectively,¹ even though the survival rate has improved with early diagnosis and multiple therapies.² For the standard treatment of CRC, adjuvant chemotherapy after surgery may be required depending on the tumor stage.^{3,4} However, the TNM stage fails to provide complete prognostic information, and clinical outcomes vary significantly among patients with the same tumor stage.⁵ Thus, there is an urgent need for a new prognostic tool to determine

the risk of CRC recurrence and develop personalized treatments for patients with a high probability of recovery, such as intensified local or systemic treatment.

The host local and systemic immunity is significantly associated with tumor response to treatment and prognosis.^{6–13} The local tumor-infiltrating lymphocytes (TILs) represent the local immunity in the tumor micro-environment. Multiple studies confirmed that TILs in the tumor played a prominent role in the prognosis of patients with CRC, and some investigators suggested that the immunoscore should be a new component in the classification of colon cancer according to the TNM classification system.^{6–9} However, these studies focused only on local immunity and ignored the systemic immunity.

The systemic immunity is constituted by the immune cells in the peripheral blood except for the spleen, lymph node, and bone marrow.¹² Some studies suggested that the peripheral subsets of immune cells may play a more important and effective antitumour role than that of TILs in the tumor region.^{12,14} For example, anti-PD-1 therapy in patients with basal or squamous cell carcinoma mainly relied on recruitment of novel T cells from peripheral sources rather than on reinvigorating pre-existing intratumoural TILs.¹⁴ There is a strong evidence from murine studies that an emergent population of peripheral CD4⁺ T cells primed by a subtype of conventional dendritic cells, cDC2, contribute to the systemic immunity with effective antitumour capabilities, as a difference to CD8⁺ T cells.^{10,12} Additionally, peripheral CD4⁺ T cells were significantly expanded in patients responding to immunotherapy.¹² Hence, peripheral CD4⁺ T cells may be a marker for predicting treatment response and prognosis in cancer; however, there is controversy in this regard.^{15–18} One study stated that peripheral CD4⁺ T cells percentage had a predictive value of anti-PD-L1/PD-1 immunotherapy response in lung cancer patients,¹⁵ while another study reported no significant predictive value for progression-free survival (PFS) in metastatic breast cancer and prostate cancer with metastatic bone lesions.¹⁶ For CRC, one study of a small cohort (N = 40) with advanced stages stated that the counts of peripheral CD4⁺ T cells ≥ 300 cells/ul before surgery had a beneficial effect on overall survival (OS) by using an univariate analysis,¹⁷ while another study reported that the preoperative peripheral CD4⁺ T cell counts did not have prognostic value on OS.¹⁸

Hence, the value of peripheral CD4⁺ T cells on the clinical outcome is not clear in cancer. Thus, the current study aims to analyse the influence of postoperative

peripheral CD4⁺ T cells on the recurrence in patients with CRC in a retrospective multicenter cohort.

Patients and Methods

This retrospective study was approved by the institutional review boards of Yunnan Cancer Hospital and the First Affiliated Hospital of Kunming Medical University. The requirement for informed consent was waived by the board, due to the nature of the retrospective study. All of the patient data in the survey was anonymized.

Patients

We retrospectively identified 1028 consecutive patients who underwent surgical resection for stage I to III colorectal adenocarcinoma between January 2010 and July 2016 at 2 centers of Yunnan Province in China. [Figure 1](#) demonstrates the study flowchart, which includes the inclusion and exclusion criteria. The patients were grouped into two sets: one training set (n=913 from center 1) and one validation set (n=115 from center 2).

Specimen Collection

After admission, the patients who met the inclusion criteria were collected 2 mL of fasting venous blood with heparin anticoagulant tube at 6:00–8:00 in the morning. The blood was mixed upside down, and sent for examination within 2 hrs.

Postoperative Peripheral CD4⁺ T Cells Determination

Postoperative CD4⁺ T cells were defined as the circulating CD4⁺ T cells, including absolute count and percentage value, and were measured within 12 weeks after surgery by using flow cytometry-based method. Detailed description of the CD4⁺ T cell absolute count and percentage determination procedure by flow cytometry, and the formulation method of the reference range are shown in the [Supplementary Methods](#) text sections and [Table S1](#). Patients were grouped by CD4⁺ T cells percentage status compared to healthy Yunnan population as follows: patients with normal postoperative CD4⁺ T cells percentage (31.4% to 43.8%) and patients with abnormal postoperative CD4⁺ T cells percentage (>43.8% or <31.3%), while patients were also grouped by CD4⁺ T cells count status compared to healthy Yunnan population as follows: patients with normal postoperative CD4⁺ T cells count (345 to 1402 cells/ul) and patients with abnormal postoperative CD4⁺ T cells count (>1402 cells/ul or <345 cells/ul).¹⁹

Adjuvant Chemotherapy Protocol

Partial patient with stage II–III CRC received the adjuvant chemotherapy according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in the CRC.^{3,4} Adjuvant chemotherapy protocol included FOLFOX, CapeOX, Capecitabine, or 5-FU/leucovorin.

Surveillance Protocol

The clinical evaluation included physical examination, measurement of serum carcinoembryonic antigen (CEA) level, imaging, and colonoscopy. CEA levels were tested at 3- to 6-month intervals for the first 2 years and at 6-month intervals for >2–5 years. Imaging, including contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis was performed at a minimum of every 12 months for at least 3 years. Colonoscopy was performed 1 year after surgery and then repeated every 2–5 years unless advanced adenomas were identified. All recurrent cases were confirmed via histology or imaging.

Outcomes

The recurrence-free survival (RFS) time was calculated from the date of surgery to the date of recurrence, death, or the last follow-up. Patients who were alive without recurrence or died before the last follow-up were censored.

Statistical Analysis

All statistical analyses were done with the R software (version 3.4.0; <http://www.R-project.org>). The statistical significance levels reported in the findings were all two-sided, with statistical significance set at a *P*-value <0.05. Mean values ± standard deviations (SD) (normal distribution) or median (quartile) (skewed distribution) were provided for continuous variables, whereas frequencies and percentages were provided for categorical variables. Assessment of the correlation between the CD4+ T cells percentage and different clinicopathologic parameters was analysed using the Mann–Whitney *U*-test or chi-square test.

Kaplan–Meier method was used to analyse the correlation between variables and RFS, and the Log-rank test (univariate analysis) to compare survival curves.

Univariate and multivariable Cox regression model evaluated the associations of CD4+ T cells percentage and count with RFS, and the hazard ratios (HR) and 95% confidence interval (CI) were calculated.⁶ The multivariable Cox regression model was re-developed with the significant variables, and all predictors still contributed significantly to the reduced model.²⁰

To confirm the predictive contribution of postoperative CD4+ T cells percentage to RFS with adjuvant chemotherapy, propensity score matching was used to select the cases for further analysis because the baseline characteristics were

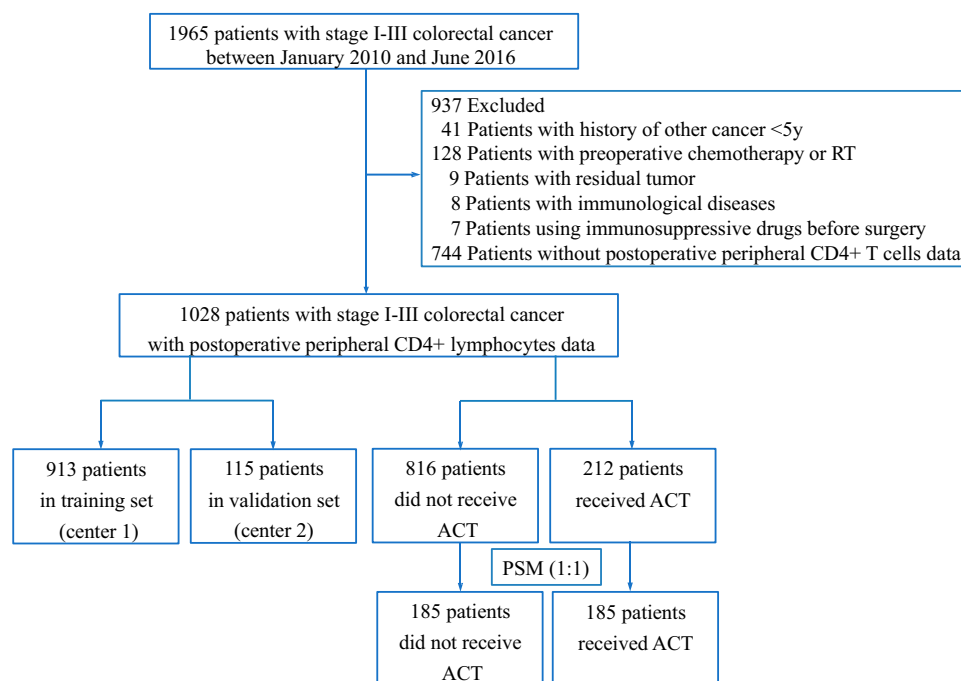


Figure 1 Study flow chart.

Table I Correlation Between Postoperative CD4+ T Cells Percentage and Clinicopathologic Features in Colorectal Cancer Patients

Clinicopathologic	Normal CD4+ (n=496)		Abnormal CD4+ (n=496)		P-value
Feature	No.	%	No.	%	
Sex					0.02
Male	295	55.45	312	62.90	
Female	237	44.55	184	37.10	
Age, years					0.02
<65	380	71.43	319	64.31	
≥65	152	28.57	177	35.69	
BMI					0.76
<24	361	67.86	341	68.75	
≥24	171	32.14	155	31.25	
Surgical approach					0.85
OR	407	76.50	382	77.02	
LR	125	23.50	114	22.98	
Primary site					0.86
Colon	256	48.12	236	47.58	
Rectal	276	51.88	260	52.42	
Tumor differentiation					0.58
Well	54	10.15	47	9.48	
Moderate	279	52.44	266	53.63	
Poor-undifferentiated	171	32.14	148	29.84	
Unknown	28	5.26	35	7.06	
Histological type					0.96
Adenocarcinomas	517	97.18	483	97.38	
Mucinous adenocarcinomas	12	2.26	10	2.02	
Signet-ring cell carcinomas	3	0.56	3	0.60	
T stage					0.67
T1	23	4.32	24	4.84	
T2	85	15.98	87	17.54	
T3	383	71.99	355	71.57	
T4	41	7.71	30	6.05	
N stage					0.31
N0	297	55.83	269	54.23	
N1	152	28.57	161	32.46	
N2	83	15.60	66	13.31	
AJCC 7th ed. stage					0.61
Stage I	88	16.54	88	17.74	
Stage II	212	39.85	183	36.90	
Stage III	232	43.61	225	45.36	
Tumor deposit					0.75
Yes	37	6.95	37	7.46	
No	495	93.05	459	92.54	
Postoperative CD4+ T cells count					<0.001

(Continued)

Table I (Continued).

Clinicopathologic	Normal CD4+ (n=496)		Abnormal CD4+ (n=496)		P-value
Feature	No.	%	No.	%	
Normal	513	96.43	420	84.85	
Abnormal	19	3.57	75	15.15	
Adjuvant chemotherapy					0.84
Yes	421	79.14	395	79.64	
No	111	20.86	101	20.36	

Abbreviations: BMI, body mass index; LR, laparoscopic resection; OR, open resection.

significantly different between the patients who received adjuvant chemotherapy and the patients who did not receive the adjuvant chemotherapy. The propensity score model was used to minimize the potential bias caused by confounding covariates.²¹ A multivariable logistic regression model was constructed to generate propensity scores. The clinicopathologic factors included in the model were age at diagnosis, sex, body mass index (BMI), pathological T stage, pathological N stage, histologic grade (high, moderate, poor differentiation, or undifferentiated), and Histological type (mucinous type, yes or no). Patients who received adjuvant chemotherapy were matched to those who did not receive adjuvant chemotherapy at a 1:1 using a greedy nearest neighbor matching algorithm with no replacement. A caliper width equal to 0.1 of the standard deviation was used as the logit of the propensity score.²² Patient characteristics between the propensity score-matched groups were compared using Mann–Whitney *U*-test or chi-square test. Further details on the PSM methods can be found in the [Supplementary Table S1](#).

Results

Patient Characteristics

The cohort of 1028 patients (607 men and 421 women with a mean age of 57.64 years) was followed-up for a long term (median intervals: 52 months, interquartile range [IQR]: 40–70 months). Tumors were located in the colon in 492 patients (47.86%) and in the rectum in 536 patients (52.14%). All patients had undergone surgical resection with histological negative resection margins, and 816 (79.38%) were treated with adjuvant chemotherapy. A total of 258 patients experienced tumor recurrence. [Supplementary Table S2](#) shows detailed clinicopathological characteristics of the training and validation sets. There were significant

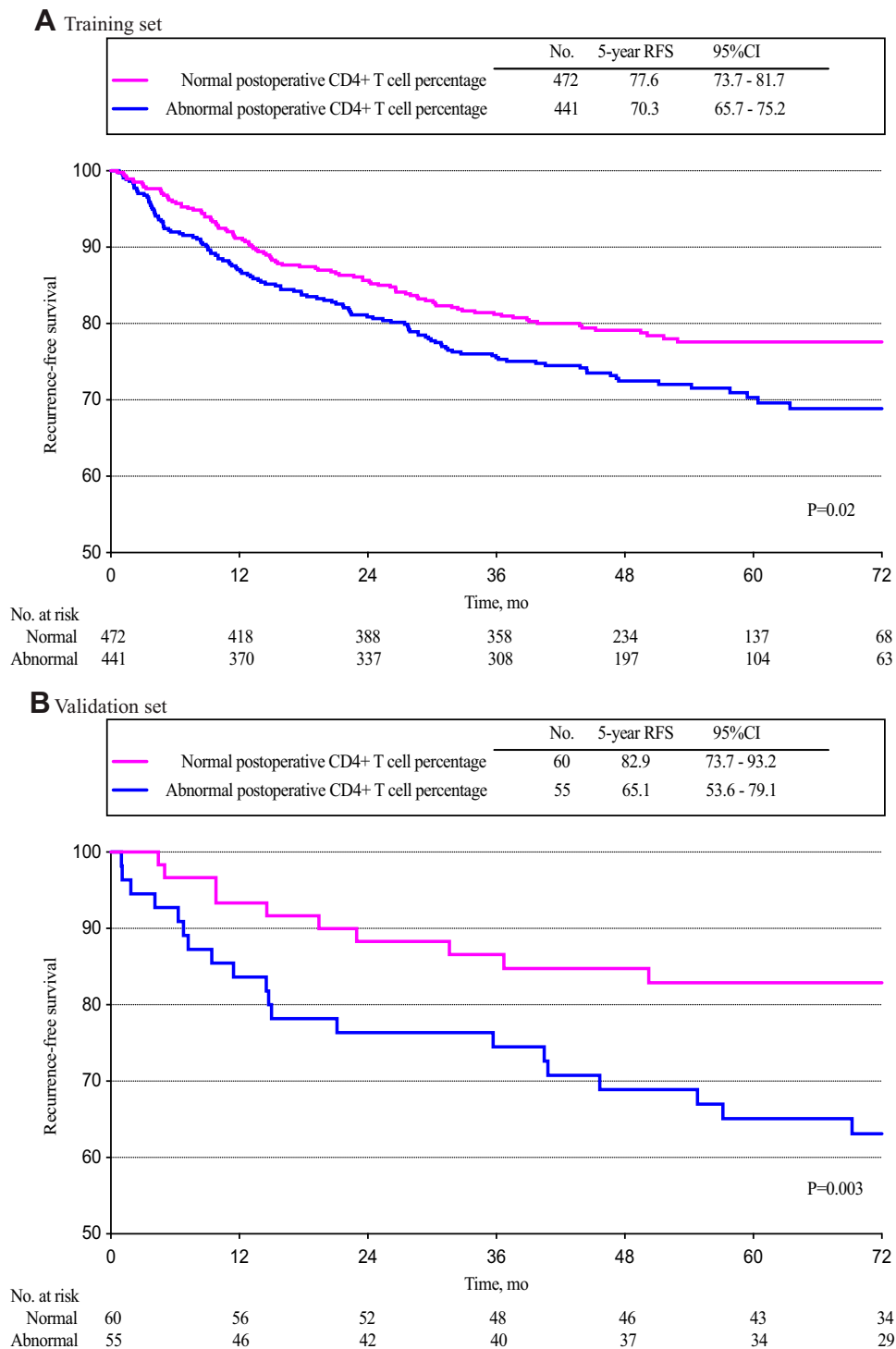


Figure 2 Kaplan-Meier estimates of recurrence-free survival according to the postoperative CD4+ T cells percentage. **(A)** In the training set. **(B)** In the validation set.

differences in the clinical characteristics including age, tumor differentiation, T stage, and tumor deposit between the training and the validation sets ([Table S2](#)). Median intervals

(IQR) of the follow-up of the training and validation sets were 53 months (IQR: 42–71 months) and 51 months (IQR: 39–70 months), respectively.

Association of Postoperative CD4+ T Cells Percentage with Clinicopathologic Characteristics

Table 1 shows the clinicopathological characteristics of patients with normal, or abnormal postoperative CD4+ T cells percentages. The postoperative CD4+ T cells percentages were correlated with sex, age, and the postoperative CD4+ T cells count. No association was noted between postoperative CD4+ T cells percentages and other clinicopathological characteristics including BMI, surgical approach, primary site, tumor differentiation, histologic type, T stage, N stage, and tumor deposit.

Association of Postoperative CD4+ T Cells Percentage with 5-Year RFS

The 5-year RFS rate of the 441 patients with abnormal postoperative CD4+ T cells percentage was 70.3% (95% CI, 65.7–75.2%), which was significantly lower than the 77.6% (95% CI, 73.7–81.7%) 5-year RFS in the 472 patients with normal postoperative CD4+ T cells percentage

(unadjusted HR, 1.36; 95% CI, 1.04–1.78; $P = 0.02$) in the training set (Figure 2A). The result was confirmed in the validation set (Figure 2B). The 55 patients with the abnormal postoperative CD4+ T cells percentage had the lower 5-year RFS rate than that of 60 patients with the normal postoperative CD4+ T cells percentage (unadjusted HR, 2.27; 95% CI, 1.06–4.89; $P = 0.04$) in the validation set (Figure 2B).

Applying univariate Cox regression analysis to the training set, the abnormal postoperative peripheral CD4+ T cells percentage was associated with significantly shorter RFS, while the postoperative peripheral CD4+ T cells count was not significantly associated with RFS. Multivariate analysis in the training set showed that the abnormal postoperative peripheral CD4+ T cells percentage was independently associated with shorter RFS (HR, 1.35; 95% CI, 1.03–1.77; $P = 0.03$; Table 2) as well as with higher TNM stage in a model that included sex, age, BMI, surgical approach, primary site, tumor differentiation, histologic type, TNM stage, the postoperative CD4+ T cells count, and tumor deposit. Similar results were obtained in the validation set (Table 2).

Table 2 Cox Proportional Hazard Model Showing Hazard Ratios for 5-Year Recurrence-Free Survival by Variables

	Training Set			Validation Set		
	HR	95% CI	P-value	HR	95% CI	P-value
Univariable Cox model						
Postoperative CD4+ T cells percentage						
Normal	1.0 (reference)			1.0 (reference)		
Abnormal	1.36	1.04, 1.78	0.02	2.27	1.06, 4.89	0.04
Postoperative CD4+ T cells count						
Normal	1.0 (reference)			1.0 (reference)		
Abnormal	1.19	0.77, 1.83	0.44	1.17	0.36, 3.88	0.79
Multivariable Cox model						
Postoperative CD4+ T cells percentage						
Normal	1.0 (reference)			1.0 (reference)		
Abnormal	1.35	1.03, 1.77	0.03	2.56	1.19, 5.51	0.02
AJCC 7th ed. stage						
Stage I	1.0 (reference)			1.0 (reference)		
Stage II	1.47	0.88, 2.47	0.15	4.26	0.54, 33.62	0.17
Stage III	3.23	2.00, 5.21	<0.001	11.12	1.48, 83.30	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio.

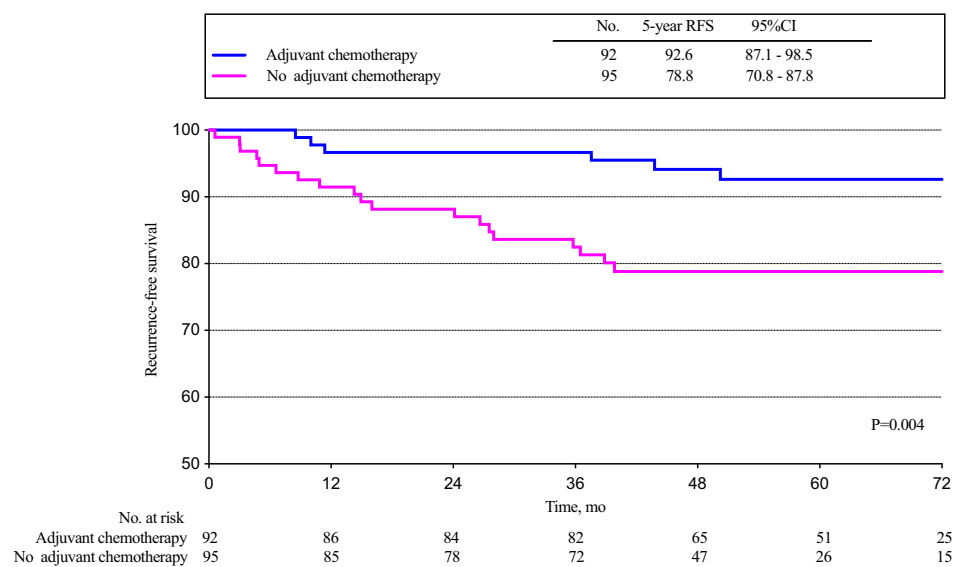
Propensity Score Matching of Adjuvant Chemotherapy

In total, 816 patients receiving adjuvant chemotherapy were matched to 212 patients who did not receive adjuvant chemotherapy. After propensity score matching, 185 pairs of patients were 1:1 matched in the two groups, and all baseline characteristics were well balanced ([Supplementary Table S3](#)).

Predictive Contribution of Postoperative CD4+ T Cells Percentage to RFS with Adjuvant Chemotherapy

In the matched population, adjuvant chemotherapy significantly enhanced 5-year RFS relative to no adjuvant chemotherapy (HR 0.29, 95% CI 0.12–0.72; $P = 0.008$; [Figure 3A](#)) in patients with normal postoperative CD4+ T cells percentage, but did not provide a statistically significant

A Normal postoperative CD4+ T cell percentage group



B Abnormal postoperative CD4+ T cell percentage group

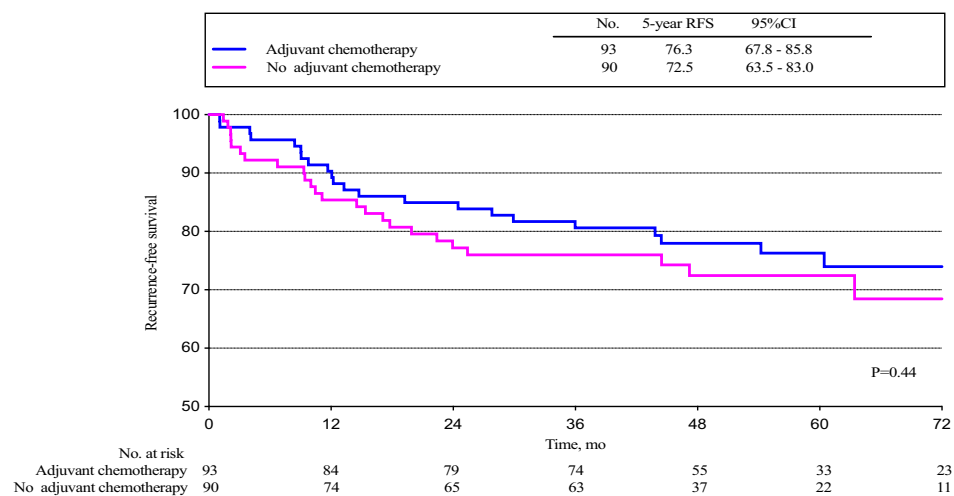


Figure 3 Kaplan-Meier estimates of recurrence-free survival according to the postoperative CD4+ T cells percentage and treatment arm. **(A)** In normal postoperative CD4+ T cells percentage group. **(B)** In abnormal postoperative CD4+ T cells percentage group.

benefit in patients with abnormal postoperative CD4+ T cells percentage (HR 0.81, 95% CI 0.39–1.43; $P = 0.47$; Figure 3B).

Discussion

Our study evidenced that the postoperative peripheral CD4+ T cells percentage was predictive for RFS with adjuvant chemotherapy after propensity score-matched analysis in a large cohort of CRC patients. To our knowledge, no large cohort studies previously investigated the predictive value of peripheral CD4+ T cells in CRC. Our results suggested that the postoperative peripheral CD4+ T cells constitute a predictive biomarker in CRC, unlike the tumor-infiltrating CD3+ and CD8+ T cells as prognostic biomarkers described in the previous studies.^{6–9}

Our result was different from the previous studies.^{17,18} We systematically reviewed the published literature and performed database queries between 2005 and July 2019 with a focus on the effect of T cells on the prognosis in CRC (Table S4). We observed that the majority of these studies evaluated the prognostic impact of TILs, while only two studies focused on the peripheral T cells in a CRC setting. However, these two studies were performed with relatively small sample sizes and did not indicate the peripheral CD4+ T cells percentage as a predictive biomarker.^{17,18}

Our study findings have important clinical value. Whether chemotherapy is needed for CRC patients is mainly based on TNM staging according to the current guidelines.^{3,4} But adjuvant chemotherapy had different effect on the CRC patient with the same tumor stage.⁵ This means administration of adjuvant chemotherapy to all patients with the same tumor stage is unnecessary for partial patients who are cured with surgery alone.²³ Hence, it is important to find a predictive biomarker identifying those CRC patients who are more likely to benefit from adjuvant chemotherapy. Our result showed that adjuvant chemotherapy provided a survival benefit to patients with normal postoperative CD4+ T cells percentage, but did not show a statistically significant benefit to patients with abnormal postoperative CD4+ T cells percentage. Therefore, postoperative CD4+ T cells percentage for CRC patients is a predictive biomarker rather than a prognostic biomarker,²⁴ and might allow for better identification of patients who are most likely to benefit from adjuvant chemotherapy.^{23,24}

The present study confirmed prior controversy over the prognostic or predictive value of peripheral CD4+ T cells in cancer patients, as stated in the “Introduction” section. This may be related to the research design. In our research design, all patients were divided into normal and abnormal groups by two cut-off values, which is different from the research

design of previous studies that only divided the peripheral CD4+ T cells percentage into two groups by one cut-off value in lung cancer,¹⁵ or into three groups according to the linear relationship between peripheral CD4+ T cells percentage and PFS in metastatic breast cancer, and prostate cancer patients with metastatic bone lesions.¹⁶

This study has two main limitations. Firstly, our study did not include TIL as an adjust parameter which may affect the independent prognostic effect of the peripheral CD4+ T cells percentage in CRC. However, one study confirmed that the prevalence of some T cell subsets in the tumor was not associated with their frequency in peripheral blood.²⁵ Secondly, genomic characteristics including microsatellite instability, KRAS, NRAS, and BRAF, which are proposed as predictors of CRC patient outcomes,²⁶ were not considered in this study due to the lack of identification method for these characteristics in the hospitals before 2016.

In conclusion, our study demonstrates that postoperative peripheral CD4+ T cells percentage is a predictive biomarker for RFS in patients with CRC, which can identify the patients who will benefit from adjuvant chemotherapy.

Data Sharing Statement

After de-identification, individual participant data will be made available to investigators who provide a methodologically sound proposal for meta-analyses. Proposals should be directed to Dingyun You (youdingyun@qq.com).

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Disclosure

The authors declare that they have no potential conflicts of interest.

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