Impact of preoperative white blood cell count on long-term outcome in patients undergoing surgery for colorectal cancer: a retrospective observational study

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Research Article

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Abstract

Purpose: This study aimed to explore the correlation between preoperative white blood cell (WBC) count and the outcome in patients who underwent surgery for colorectal cancer (CRC) and the potential marker to predict the outcome.

Patients and methods: A total of 8121 Chinese patients at Fudan University Shanghai Cancer Center (FUSCC) undergoing colectomy, Dixon's or Mile's, for CRC from January 2008 to December 2014 were enrolled in present study. Based on that the WBC optimal cut-off value was $7*10^9$, the patients were divided into two groups, the moderate leukocytosis group (the leukocytosis group) and non-leukocytosis group. The impact of preoperative WBC count on disease-free survival (DFS) and overall survival (OS) was investigated using the Kaplan-Meier method and Cox proportional hazard models.

Results: Moderate leukocytosis ($\geq 7*10^9$) was recognized as a prognostic factor for survival independently. Moderate leukocytosis was significantly associated with male sex (P□0.001), advanced T stage (P□0.001), TNM stage (P□0.001), and no preoperative chemotherapy (P□0.001). Moderate leukocytosis group was corelated with poorer overall survival (OS) (P□0.001) and disease-free survival (DFS) (P=0.024) than non-leukocytosis group. In the multivariate analysis, the moderate leukocytosis group had a 19.6% higher risk in OS (HR=1.196, 95CI%:1.088-1.314, P<0.001) and had a 13.1% higher risk in DFS (HR=1.131, 95CI%:1.016-1.259, P=0.024) than the non-leukocytosis group. We found that the association with preoperative moderate leukocytosis and poorer OS (P□0.001) or DFS (P=0.001) in patients with no preoperative chemotherapy in subgroup analysis.

Conclusions: Preoperative moderate leukocytosis is associated with shorter OS, DFS indicating poor outcome in CRC patients after surgery.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer death worldwide, with an emerging trend of the incidence of CRC at younger ages (before age 50 years) rising [1,2].There were 376300 cases and 191000 deaths of CRC in China according to the statistics data in 2015 and there are estimated 592232 cases and 309114 deaths of CRC in China in 2022[3,4]. The global burden of colorectal cancer (CRC) is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 [5]. A study revealed a five-year relative survival of 62% for colon cancer and 65% for rectal cancer in the Netherlands [2]. Reductions in colon and rectal cancer mortality rates are probably due to better accessibility to early detection services and improved specialized care [6]. Colorectal cancer is a life-threatening disease. Although diagnosis, treatment, radiotherapy, and chemotherapy have made great progress, surgery remains the primary treatment of choice. However, there are still many relapses and metastases still occur [7]. We urgently require a diagnostic marker to predict the prognosis of CRC patients after surgery.

Inflammation can be one of the underlying mechanisms linking lifestyle to fatigue in CRC and others cancer patients [8-10]. Despite numerous reports detailing the interplays between cancer and its microenvironment via the inflammatory network, the status of cancer-associated inflammation remains difficult to identify in clinical settings [11]. Systemic inflammation is preoperatively a marker indicating poor prognosis, which is present in approximately 20%-40% of CRC patients [12]. The involvement of neutrophils in cancer initiation and progression could indicate that neutrophils are a potential clinical biomarker and therapeutic target [13]. A study provided insight into the inflammation-related senescence-associated secretory phenotype maintenance by histone modification and the role of senescent cancer-associated fibroblasts in gastric cancer peritoneal dissemination [14]. Emerging evidence indicates that tumors manipulate neutrophils, sometimes early in their differentiation process, to create diverse phenotypes and functional polarization states that are able to alter tumor behavior [13]. A study suggested that the leukocyte and neutrophil count parameters may be clinically relevant biomarkers; therefore, further clinical investigations are required [15].

Recently few studies have demonstrated the relationship of the preoperative peripheral white blood cell (WBC) count and the outcome of CRC; hence, the correlation is unclear. Leukocytosis and neutrophilia are strong prognostic factors for overall survival (OS), progression-free survival (PFS), locoregional-free survival (LFS) and disease-free survival (DFS) in anal cancer treated with chemoradiation [16]. Leukocytosis constitutes an important prognostic marker in anal squamous cell carcinoma patients treated with chemoradiotherapy [17]. Independent impact of leukocytosis and HPV-status on outcome of patients with oropharyngeal cancer (OPC) and the significant impact of leukocytosis on outcome was even more pronounced in HPV-positive patients [18].

Hence, we hypothesized preoperative peripheral WBC count predicts a poorer outcome in patients with CRC undergoing surgical therapy. We designed to investigate the correlation between peripheral WBC count and the outcome in patients with CRC undergoing surgical treatment.

Material And Methods

Study population

This was a retrospective, observational study. The present study was approved by the Ethics Committee of Fudan University Shanghai Cancer (FUSCC) (No. IRB2105235-6), China. 8121 Chinese patients from January 2008 to December 2014 were enrolled as part of the retrospective cohort. Patients who were included underwent surgical therapy for CRC with complete clinical history data, OS records and DFS records. The data were gathered from the database of the FUSCC clinical information system database, including medical history, pathology, operative details, and postoperative outcomes. The eligibility criteria were as follows: complete medical history and follow-up data; no other synchronous malignancy. The exclusion criteria included incomplete data, previous history of cancer, the surgery was emergency, under

14 years of age, and the American Society of Anesthesiologists (ASA) physical status greater than or equal to IV.

The preoperative peripheral WBC count was collected during the routine examination. The WBC optimal cut-off value was 7,000/μL, according to the study performed by Zhang Hao [19]. Based on this WBC cut-off value, the patients were divided into two groups, non-leukocytosis and leukocytosis. The primary outcomes of the study were DFS and OS. DFS was calculated from the time of surgery to the time of the first evidence of tumor recurrence or until December 31,2019. OS was calculated from the time of surgery to the time of death or the last follow-up date.

Statistical analysis

The study was analyzed by SPSS software. All data were expressed as number (percentages). Determination of the optimal cut-off value for preoperative WBC was performed by using X-tile 3.6.1 software (Yale University, New Haven, CT, USA) with the minimum P-values from log-rank×2 statistics for survival, which was $7*10^9$ (7,000/μL)[20]. The relationship between WBC count and the baseline parameters of clinical conditions was analyzed by chi-square tests. We compared survival differences using the log-rank (Mantel-Cox) test. The Kaplan-Meier method was used to generate and evaluate the survival curves for prognosis. We performed the univariate analysis, but if the $P<0.05$, then the multivariate analysis was performed. We used multivariate analyses with a Cox proportional hazards regression model to test independence, significance hazard discrimination and confidence interval. If P value was less than 0.05, a significant difference was considered.

Results

A total of 8121 Chinese patients with CRC undergoing colonic resection or proctectomy were enrolled in this study. The preoperative WBC count appropriate cut-off value was 7,000/μL for prognosis [19]. All the patients were divided into two groups, the leukocytosis group (WBC count ≥7,000/μL) and the non-leukocytosis group (WBC count < 7,000/μL). The leukocytosis group had poorer OS and DFS than the non-leukocytosis group (Figure 1A and 1B; $P<0.001$, $P=0.001$, respectively). The baseline characteristics are shown in Table 1. The incidence of moderate leukocytosis was 23.2% (1,885 out of 8,121 patients). There was no significant difference in treatment year, age, the number of lymph node metastasis, perineural invasion, surgical procedure, the number of cancer node and reoperation within 90 days (P 0.05). There were more male patients in the leukocytosis group than those in the non-leukocytosis group (64.6% vs 57.6%, $P<0.001$). The leukocytosis group had more patients than the non-leukocytosis group with higher T stage (T4, 72.9% vs 65.1%, $P<0.001$), metastasis (16.6% vs 12.2%, $P<0.001$), TNM stage (IV 16.6% vs 12.1%, $P<0.001$), T4/Metastasis (10.4% vs 7.6%, $P<0.001$), liver metastasis (11.1% vs 7.8%, $P<0.001$). Preoperative leukocytosis was also associated with tumor location (colon 51.8% vs 45.8%, $P<0.001$), tumor type (mucoid adenocarcinoma 14.3% vs 11.1%, $P<0.001$), tumor differentiation (poor 24.0% vs 19.7%, $P<0.001$), incisal margin (2.3% vs 1.4%, $P=0.008$), preoperative chemotherapy (5.7% vs

9.1%, P<0.001), postoperative event (32.1% vs 28.6%, P=0.008), the number of lymph nodes (≥12 80.6% vs 77.1%, P=0.001) and blood transfusion (4.0% vs 2.2%, P<0.001).

This implied that patients with preoperative leukocytosis had advanced stage of the CRC.

We used the Univariate Cox regression analysis to analyze the leukocytosis and the others clinical characteristics that were significantly correlated with OS and subsequently in a multivariable Cox regression if the P<0.05 (Table 2 and 3). The leukocytosis was correlated with a hazard ratio of 1.275 (95%CI, 1.162 to 1.400, P<0.001) for OS and a hazard ratio of 1.206 (95%CI, 1.085 to 1.341, P=0.001) for DFS in the univariate analysis. A moderate leukocytosis was associated with a hazard ratio of 1.196 (95%CI, 1.088to 1.314, P<0.001) for OS and a hazard ratio of 1.131 (95%CI, 1.016 to 1.259, P=0.024) for DFS in the multivariate analysis. Age (65-74, ≥75), preoperative chemotherapy, signet cell cancer, relatively poor differentiation, vascular tumor thrombus, perineural invasion, incisal margin, liver metastasis and advanced TNM were associated with a worse impact on OS (Table 2). We also analyzed the associations with DFS (Table 3). The conditions were significantly correlated with worse DFS. Age (65-74, ≥75), preoperative chemotherapy, signet cell cancer, relatively poor differentiation, vascular tumor thrombus, perineural invasion, incisal margin, liver metastasis and advanced TNM were associated with a worse impact on DFS. The leukocytosis was also identified as prognostic factor for OS and DFS independently in the multivariate analysis (P<0.001, P=0.024, respectively).

The Kaplan-Meier survival analysis revealed that OS and DFS were significantly poorer in the leukocytosis group than in the non-leukocytosis group, which are displayed in Figure 1 (Figure 1, P<0.001 and P=0.001, respectively).

We also investigated that the association with preoperative moderate leukocytosis and poorer OS (P 0.001) or DFS (P=0.001) in patients with no preoperative chemotherapy in subgroup analysis (Table 4, Figure 2). However, there was no significant association between preoperative moderate leukocytosis and OS (P=0.088) or DFS (P=0.115) in patients with preoperative chemotherapy (Table 4).

Discussion

As the anesthesiologists in China, we care for the patients not only during the surgery, but also during the preoperative, postoperative, and prognosis stages. We hope that the cancer patients have a comfortable experience perioperatively and better outcome as well. Therefore, we focused on 8121 Chinese CRC patients during a six-year time period. In the present study, the impact of preoperative WBC count as a prognostic factor was investigated to predicting survival in patients with CRC. We confirmed that based on a cut off value of 7,000/μL, patients with moderate leukocytosis had a poorer OS and DFS in this study.

Some studies have demonstrated that peripheral blood leukocytosis and neutrophilia reflected cancer-related inflammation and has been proposed as prognostic immunological biomarkers for various malignancies [10,21]. A study validated leukocytosis as an independent prognostic factor in CRC, which

provided for the first-time vital insight on the correlation of peripheral pretreatment leukocytosis with the tumor-infiltrating cells contexture and might be relevant for future risk stratification[22]. A meta-analysis showed that preoperative leukocytosis was common and correlates with poor pathological and survival outcomes in endometrial carcinoma patients[23]. A study showed that preoperative leukocytosis and the resection severity index were independent risk factors for survival in patients with intrahepatic cholangiocarcinoma [24]. Cancer patients with acute venous thromboembolism and elevated WBC count had an increased incidence of VTE recurrences, major bleeding, or death[25]. In a retrospective analysis concerning cervical cancer, patients with leukocytosis (WBC ≥ 10,000/μL) showed significantly higher treatment failure rate ($P < 0.001$) and shorter OS ($P < 0.001$) than the patients without leukocytosis. In a prospective investigation, patients with leukocytosis exhibited a significantly higher treatment failure rate ($P < 0.001$), shorter PFS ($P < 0.001$) than did the patients without leukocytosis [26]. A study showed that preoperative asymptomatic leukocytosis had a prevalence of 5.6% in CRC resections and carried a significant increased risk of mortality and morbidity [27].An increasing body of evidence supports that visibility of CRC to immune attack is substantial and that it limits disease progression. Analysis of the adaptive immune infiltrate in resected CRC specimens offers prognostic information which is independent of conventionally measured parameters and potentially superior in predictive value [28]. A high WBC and lymphocyte count combined with normal testosterone levels increases the overall mortality of patients treated with radiotherapy for localized prostate cancer within the first 6-7 years post-treatment [29]. Leukocyte and neutrophil count parameters might be clinically relevant biomarkers to be considered for further clinical investigations [15]. Gaining a better mechanistic understanding of the mode of action of anti-inflammatory agents and designing more effective treatment combinations would advance the clinical application of this therapeutic approach [30]. A retrospective cohort study showed that treatment-related leukopenia in anal cancer patients was associated with worse outcome [31]. Further subgroup analysis indicated that preoperative moderate leukocytosis was significantly associated with poorer OS and DFS in patients with no preoperative chemotherapy.

Our study is a large cohort of 8121 patients undergoing colectomy, Dixon's or Mile's, for CRC in China, and our conclusion reliable. However, our study has a few limitations. It was retrospective and was not prospective or randomized. We lacked with relapse-free survival data and disease-specific survival data. Patients were recruited from a single center and were not from a multi-center. Further prospective both clinical studies and laboratory researches are needed to determine the mechanism of relationship between leukocytosis and outcome in patients undergoing surgery for CRC.

In conclusion, the preoperative moderate leukocytosis was significantly associated with survival in CRC negatively.

Declarations

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The first three authors Bei Wang, Lihong Li and Shilai Wang contributed equally to this work.

Author's contributions

Bei Wang, Lihong Li and Shilai Wang contributed equally to this work. Meilin Weng, Zhirong Sun and Changming Zhou contributed to design of the study and data acquisition; Meilin Weng, Changming Zhou and Bei Wang contributed to the data analysis. Bei Wang, Lihong Li and Shilai Wang wrote the manuscript. All authors have reviewed and approved the last manuscript.

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Availability of data and materials

The datasets are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All methods in the study were carried out in accordance with relevant guidelines and regulations of the Declaration of Helsinki. And this study was reviewed and approved by the Ethics Committee of Fudan University Shanghai Cancer (FUSCC) (No. IRB2105235-6), China. The patients have signed informed consent in the study.

Consent for publication

All authors have reviewed and approved the last manuscript.

Competing interests

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

References

1. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol.* 2019;16(12):713-732.
2. Brouwer NPM, Bos A, Lemmens V, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. *Int J Cancer.* 2018;143(11):2758-2766.
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115-132.

4. Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J (Engl).* 2022;135(5):584-590.
5. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683-691.
6. Araghi M, Soerjomataram I, Jenkins M, et al. Global trends in colorectal cancer mortality: projections to the year 2035. *Int J Cancer.* 2019;144(12):2992-3000.
7. Park JH, McMillan DC. Outcome in colorectal cancer-tumour, stroma and so much more. *Ann Oncol.* 2018;29(3):534-535.
8. Wesselink E, van Baar H, van Zutphen M, et al. Inflammation Is a Mediating Factor in the Association between Lifestyle and Fatigue in Colorectal Cancer Patients. *Cancers (Basel).* 2020;12(12).
9. Neufert C, Heichler C, Brabletz T, et al. Inducible mouse models of colon cancer for the analysis of sporadic and inflammation-driven tumor progression and lymph node metastasis. *Nat Protoc.* 2021;16(1):61-85.
10. Ma L, Gonzalez-Junca A, Zheng Y, et al. Inflammation Mediates the Development of Aggressive Breast Cancer Following Radiotherapy. *Clin Cancer Res.* 2021.
11. Kinoshita T, Goto T. Links between Inflammation and Postoperative Cancer Recurrence. *J Clin Med.* 2021;10(2).
12. Tuomisto AE, Mäkinen MJ, Väyrynen JP. Systemic inflammation in colorectal cancer: Underlying factors, effects, and prognostic significance. *World J Gastroenterol.* 2019;25(31):4383-4404.
13. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. *Nat Rev Cancer.* 2016;16(7):431-446.
14. Yasuda T, Koiwa M, Yonemura A, et al. Inflammation-driven senescence-associated secretory phenotype in cancer-associated fibroblasts enhances peritoneal dissemination. *Cell Rep.* 2021;34(8):108779.
15. Schernberg A, Moureau-Zabotto L, Rivin Del Campo E, et al. Leukocytosis and neutrophilia predict outcome in locally advanced esophageal cancer treated with definitive chemoradiation. *Oncotarget.* 2017;8(7):11579-11588.
16. Schernberg A, Escande A, Rivin Del Campo E, et al. Leukocytosis and neutrophilia predicts outcome in anal cancer. *Radiother Oncol.* 2017;122(1):137-145.
17. Martin D, Rödel F, Winkelmann R, Balermpas P, Rödel C, Fokas E. Peripheral Leukocytosis Is Inversely Correlated with Intratumoral CD8+ T-Cell Infiltration and Associated with Worse Outcome after Chemoradiotherapy in Anal Cancer. *Front Immunol.* 2017;8:1225.
18. Gouw ZAR, Paul de Boer J, Navran A, van den Brekel MWM, Sonke JJ, Al-Mamgani A. Baseline peripheral blood leukocytosis: Biological marker predicts outcome in oropharyngeal cancer, regardless of HPV-status. *Oral Oncol.* 2018;78:200-206.
19. Zhang H, Lv H, Weng M, et al. Preoperative leukocytosis is associated with increased tumor-infiltrating neutrophil extracellular traps and worse outcomes in esophageal cancer. *Ann Transl Med.*

2020;8(7):441.
20. Grimm RH, Jr., Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. *Jama.* 1985;254(14):1932-1937.
21. Rimini M, Franco P, De Bari B, et al. The Prognostic Value of the New Combined Hemo-Eosinophil Inflammation Index (HEI Index): A Multicenter Analysis of Anal Cancer Patients Treated with Concurrent Chemo-Radiation. *Cancers (Basel).* 2021;13(4).
22. Hu X, Li YQ, Li QG, Ma YL, Peng JJ, Cai SJ. Baseline Peripheral Blood Leukocytosis Is Negatively Correlated With T-Cell Infiltration Predicting Worse Outcome in Colorectal Cancers. *Front Immunol.* 2018;9:2354.
23. Abu-Zaid A, Alomar O, Baradwan S, et al. Preoperative leukocytosis correlates with unfavorable pathological and survival outcomes in endometrial carcinoma: A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2021;264:88-96.
24. Beetz O, Weigle CA, Cammann S, et al. Preoperative leukocytosis and the resection severity index are independent risk factors for survival in patients with intrahepatic cholangiocarcinoma. *Langenbecks Arch Surg.* 2020;405(7):977-988.
25. Trujillo-Santos J, Di Micco P, Iannuzzo M, et al. Elevated white blood cell count and outcome in cancer patients with venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost.* 2008;100(5):905-911.
26. Mabuchi S, Matsumoto Y, Isohashi F, et al. Pretreatment leukocytosis is an indicator of poor prognosis in patients with cervical cancer. *Gynecol Oncol.* 2011;122(1):25-32.
27. Moghadamyeghaneh Z, Hanna MH, Carmichael JC, Mills SD, Pigazzi A, Stamos MJ. Preoperative Leukocytosis in Colorectal Cancer Patients. *J Am Coll Surg.* 2015;221(1):207-214.
28. Curtis NJ, Primrose JN, Thomas GJ, Mirnezami AH, Ottensmeier CH. The adaptive immune response to colorectal cancer: from the laboratory to clinical practice. *Eur J Surg Oncol.* 2012;38(10):889-896.
29. Taussky D, Souliéres D, Azoulay L, et al. A Combination of Testosterone and White Blood Cell Count as a Predictive Factor of Overall Survival in Localized Prostate Cancer. *Target Oncol.* 2017;12(5):695-701.
30. Hou J, Karin M, Sun B. Targeting cancer-promoting inflammation - have anti-inflammatory therapies come of age? *Nat Rev Clin Oncol.* 2021.
31. Nilsson MP, Scherman J, Gunnlaugsson A, Leon O, Johnsson A, Nilsson ED. Treatment-related leukopenia in anal cancer patients associated with worse outcome: results of a retrospective cohort study. *Acta Oncol.* 2020;59(12):1508-1511.

Tables

Table 1 Baseline clinicopathologic characteristics of 8121 Chinese patients cohort with CRC based on the WBC count

Variables	Cases[number, %]	Preoperative leukocytes [7* 10^9, %]		
		Non-leukocytosis	Leukocytosis	P value
Gender				<0.001
Female	3309[40.7]	2642[42.4]	667[35.4]	
Male	4812[59.3]	3594[57.6]	1218[64.6]	
Treat year				0.916
2008-2012	5084[63]	3902[63]	1182[63]	
2013-2017	3037[37]	2334[37]	703[37]	
Aged[years]				0.446
=<44	1068[13.2]	799[12.8]	269[14.3]	
45-54	1633[20.1]	1247[20.0]	386[20.5]	
55-64	2915[35.9]	2263[36.3]	652[34.6]	
65-74	1746[21.5]	1342[21.5]	404[21.4]	
>=75	759[9.3]	585[9.4]	174[9.2]	
T stage				<0.001
Tx	308[3.8]	259[4.2]	49[2.6]	
Tis	235[2.9]	193[3.1]	42[2.2]	
T1	362[4.5]	303[4.9]	59[3.1]	
T2	1417[17.4]	1152[18.5]	265[14.1]	
T3	362[4.5]	267[4.3]	95[5.0]	
T4	5437[66.9]	4062[65.1]	1375[72.9]	
Lymph node metastasis				0.100
N0	4281[52.7]	3320[53.2]	961[51.0]	
N1	2399[29.5]	1838[29.5]	561[29.8]	
N2	1441[17.7]	1078[17.3]	363[19.3]	
Metastasis				<0.001
M0	7052[86.8]	5480[87.9]	1572[83.4]	
M1	1069[13.2]	756[12.1]	313[16.6]	

TNM stage				<0.001
I	1444[17.8]	1185[19.0]	259[13.7]	
II	2243[27.6]	1665[26.7]	578[30.7]	
III	3152[38.8]	2445[39.2]	707[37.5]	
IV	1069[13.2]	756[12.1]	313[16.6]	
Unknown	213[2.6]	185[3.0]	28[1.5]	
T4/Metastasis				<0.001
Yes	671[8.3]	475[7.6]	196[10.4]	
No	7450[91.7]	5761[92.4]	1689[89.6]	
Liver metastasis				<0.001
Yes	695[8.6]	486[7.8]	209[11.1]	
No	7426[91.4]	5750[92.2]	1676[88.9]	
Tumor location				<0.001
Rectal	4290[52.8]	3381[54.2]	909[48.2]	
Colon	3831[47.2]	2855[45.8]	976[51.8]	
Tumor location				<0.001
Rectal	4290[52.8]	3381[54.2]	909[48.2]	
Left colon	1716[21.1]	1283[20.6]	433[23.0]	
Right colon	1992[24.5]	1483[23.8]	509[27.0]	
Total colon	16[0.2]	12[0.2]	4[0.2]	
Transverse colon	107[1.3]	77[1.2]	30[1.6]	
Tumor type				<0.001
Adenocarcinoma	7030[86.7]	5460[87.6]	1579[83.8]	
Mucoid adenocarcinoma	960[11.8]	690[11.1]	270[14.3]	
Signet cell cancer	122[1.5]	86[1.4]	36[1.9]	
Tumor differentiation				<0.001
Poor	1681[20.7]	1229[19.7]	452[24.0]	
Moderate	5487[67.6]	4233[67.9]	1254[66.5]	
Well	172[2.1]	143[2.3]	29[1.5]	

Unknown	781[9.6]	631[10.1]	150[8.0]	
Vascular tumor thrombus				0.111
Yes	1859[22.9]	1402[22.5]	457[24.2]	
No	6262[77.1]	4834[77.5]	1428[75.8]	
Perineural invasion				0.750
Yes	1552[19.1]	1187[19.0]	365[19.4]	
No	6569[80.9]	5049[81.0]	1520[80.6]	
incisal margin				0.008
Yes	134[1.7]	90[1.4]	44[2.3]	
No	7987[98.3]	6146[98.6]	1841[97.7]	
Surgical procedure				0.757
Open	7467[91.9]	5737[92.0]	1730[91.8]	
Video-assisted	654[8.1]	499[8.0]	155[8.2]	
Preoperative chemotherapy				<0.001
Yes	674[8.3]	566[9.1]	108[5.7]	
No	7447[91.7]	5670[90.9]	1777[94.3]	
Postoperative event				0.008
Yes	2072[70.6]	1568[28.6]	504[32.1]	
No	4980[29.4]	3912[71.4]	1068[67.9]	
The number of lymph node metastasis				0.001
≥12	6325[77.9]	4805[77.1]	1520[80.6]	
<12	1796[22.1]	1431[22.9]	365[19.4]	
Cancer node				0.298
>=1	1249[15.4]	945[15.2]	304[16.1]	
0	6869[84.6]	5290[84.8]	1579[83.9]	
Reoperation within 30 days				0.860
Yes	146[1.8]	113[1.8]	33[1.6]	
No	7975[98.2]	6123[98.2]	1852[98.2]	
Reoperation within 90 days				0.523

0	8091[99.6]	6215[99.7]	1876[99.5]	
1	26[0.3]	18[0.3]	8[0.4]	
2	2[0.0]	2[0.0]	0[0.0]	
3	2[0.0]	1[0.0]	1[0.1]	
Blood transfusion				<0.001
Yes	211[2.6]	135[2.2]	76[4.0]	
No	7910[97.4]	6101[97.8]	1809[96.0]	

Table 2 Univariate analysis and multivariate analysis for overall survival in 8121 patients with CRC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Leukocytosis				
No	1.00		1.00	
Yes	1.275(1.162,1.400)	<0.001	1.196(1.088,1.314)	<0.001
Gender				
Male	1.00			
Female	0.960(0.883,1.044)	0.340	NA	
Age				
≤44	1.00			
45-54	0.944(0.808,1.102)	0.463	1.121(0.959,1.311)	0.153
55-64	0.962(0.836,1.106)	0.586	1.203(1.044,1.388)	0.011
65-74	1.221(1.055,1.414)	0.007	1.665(1.434,1.934)	<0.001
≥75	1.863(1.587,2.187)	<0.001	2.972(2.522,3.503)	<0.001
Preoperative chemotherapy				
No	1.00		1.00	
Yes	1.312(1.15,1.504)	<0.001	1.643(1.408,1.918)	<0.001
Video-assisted surgical procedure				
No	1.00			
Yes	0.945(0.804,1.110)	0.489	NA	
Location				
Rectal	1.00		1.00	
Left colon	0.966(0.866,1.077)	0.532	0.815(0.728,0.911)	<0.001
Right colon	1.166(1.058,1.285)	0.002	0.903(0.814,1.001)	0.052
Total colon	0.325(0.046,2.307)	0.261	0.233(0.033,1.661)	0.146
Transverse colon	1.028(0.707,1.496)	0.885	0.713(0.489,1.042)	0.080
Tumor type				
Adenocarcinoma	1.00		1.00	

Mucoid adenocarcinoma	1.242(1.103,1.400)	<0.001	1.103(0.970,1.253)	0.136
Signet cell cancer	2.548(1.974,3.288)	<0.001	1.568(1.197,2.054)	0.001
Tumor differentiation				
Poor	1.00		1.00	
Moderate	0.516(0.470,0.565)	<0.001	0.746(0.674,0.826)	<0.001
Well	0.296(0.201,0.434)	<0.001	0.721(0.487,1.067)	0.102
Unknown	0.543(0.462,0.639)	<0.001	0.810(0.674,0.974)	0.025
Vascular tumor thrombus				
No	1.00		1.00	
Yes	2.454(2.254,2.672)	<0.001	1.439(1.308,1.583)	<0.001
Perineural invasion				
No	1.00		1.00	
Yes	2.350(2.149,2.568)	<0.001	1.516(1.377,1.669)	<0.001
Incisal margin				
No	1.00		1.00	
Yes	3.408(2.737,4.245)	<0.001	2.047(1.633,2.565)	<0.001
TNM stage				
≤ I	1.00		1.00	
II	1.426(1.185,1.715)	<0.001	1.277(1.058,1.540)	0.011
III	3.173(2.689,3.742)	<0.001	2.392(2.013,2.841)	<0.001
IV	13.016(10.976,15.434)	<0.001	6.655(5.429, 8.158)	<0.001
Unknown	0.915(0.581,1.441)	0.701	0.761(0.472,1.224)	0.260
Liver metastasis				
No	1.00		1.00	
Yes	6.193(6.193,7.567)	<0.001	2.089(1.804,2.420)	<0.001
Reoperation within 30 days				
No	1.00			
Yes	1.139(0.853,1.521)	0.377	NA	

Table 3 Univariate analysis and multivariate analysis for disease-free survival in 8121 patients with CRC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Leukocytosis				
No	1.00		1.00	
Yes	1.206(1.085,1.341)	0.001	1.131(1.016,1.259)	0.024
Gender				
Male	1.00			
Female	0.934(0.850,1.026)	0.156	NA	
Age				
≤44	1.00		1.00	
45-54	0.988(0.826,1.181)	0.893	1.173(0.979,1.405)	0.084
55-64	0.984(0.836,1.157)	0.842	1.150(0,975,1.357)	0.097
65-74	1.337(1.131,1.580)	1.337	1.710(1.442,20.029)	<0.001
≥75	2.061(1.722,2.466)	2.061	2.896(2.409,3.481)	<0.001
Preoperative chemotherapy				
No	1.00		1.00	
Yes	1.427(1.229,1.658)	0.001	1.930(1.625,2.293)	<0.001
Video-assisted surgical procedure				
No	1.00			
Yes	0.860(0.714,1.037)	0.114	NA	
Location				
Rectal	1.00		1.00	
Left colon	0.919(0.813,1.038)	0.175	0.826(0.727,0.937)	0.003
Right colon	1.078(0.966,1.203)	0.182	0.919(0.818,1.034)	0.160
Total colon	0.388(0.055,2.751)	0.343	0.185(0.026,1.320)	0.092
Transverse colon	0.913(0.592,1.406)	0.678	0.785(0507,1.215)	0.277
Tumor type				
Adenocarcinoma	1.00		1.00	

Mucoid adenocarcinoma	1.251(1.095,1.428)	0.001	1.070(0.927,1.235)	0.355
Signet cell cancer	2.609(1.979,3.441)	<0.001	1.470(1.098,1.970)	0.010
Tumor differentiation				
Poor	1.00		1.00	
Moderate	0.529(0.477,0.587)	<0.001	0.792(0.740,0.891)	<0.001
Well	0.323(0.214,0.486)	<0.001	0.779(0.512,1.184)	0.242
Unknown	0.603(0.506,0.719)	<0.001	0.891(0.729,1.089)	0.261
Vascular tumor thrombus				
No	1.00		1.00	
Yes	2.441(2.217,2.688)	<0.001	1.400(1.254,.1563)	<0.001
Perineural invasion				
No	1.00		1.00	
Yes	2.357(2.131,2.608)	<0.001	1.569(1.406,1.750)	<0.001
Incisal margin				
No	1.00		1.00	
Yes	3.444(2.672,4.438)	<0.001	1.774(1.362,2.311)	<0.001
TNM stage				
≤ I	1.00		1.00	
II	1.441(1.198,1.734)	<0.001	1.308(1.083,1.579)	0.005
III	3.286(2.785,3.876)	<0.001	2.502(2.102,2.978)	<0.001
IV	14.661(12.073,17.802)	<0.001	6.285(4.923,8.024)	<0.001
Unknown	0.919(0.584,1.448)	0.716	0.673(0.417,1.088)	0.106
Liver metastasis				
No	1.00		1.00	
Yes	10.245(8.825,11.895)	<0.001	3.280(2.651,4.057)	<0.001
Reoperation within 30 days				
No	1.00			
Yes	1.071(0.767,1.497)	0.687	NA	

Table 4 Subgroup analysis by preoperative white blood cells count for overall survival and disease-free survival in patients with CRC

Prognostic factor	Disease free Survival (Months)		Overall Survival (Months)	
	Mean	P value	Mean	P value
Preoperative chemotherapy				
Yes		0.115		0.088
Leukocytosis	70.746 (61.801,79.692)		71.397 (63.400,79.394)	
Non-leukocytosis	89.256(84.485,94.027)		89.395 (93.632,116.133)	
No		0.001		0.000
Leukocytosis	100.946 (97.875,104.017)		96.588 (93.734,99.443)	
Non-leukocytosis	106.014 (104.356,107.673)		104.537 (102.865,106.210)	

Figures

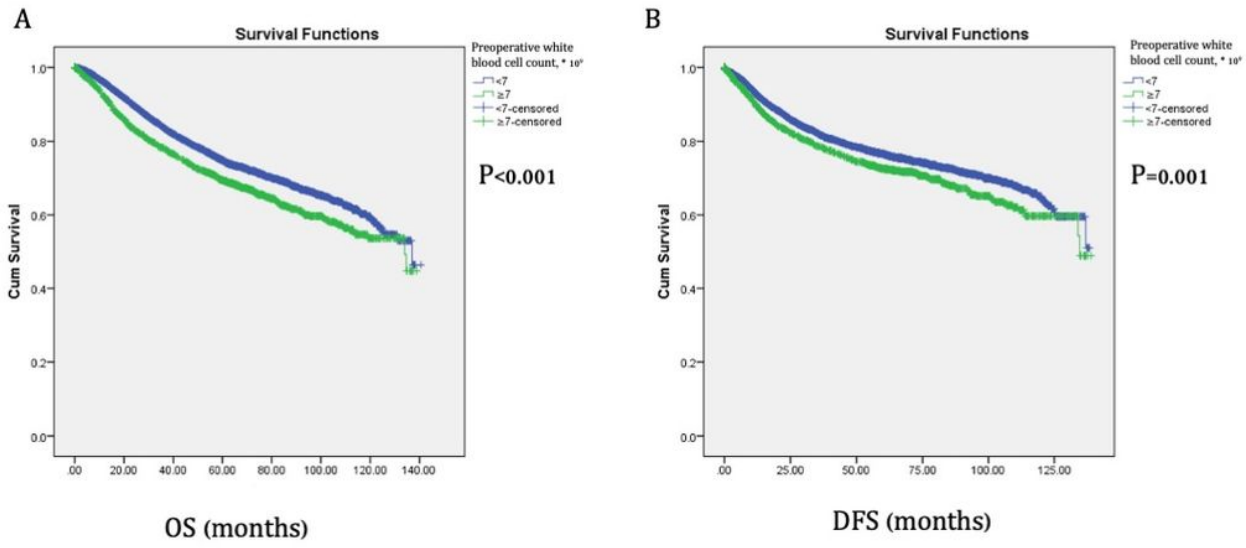

Figure 1

Kaplan-Meier analysis of OS (A) and DFS (B) from 8121 Chinese patients subdivided by preoperative leukocytosis, which was defined as a WBC count over 7,000/μL.

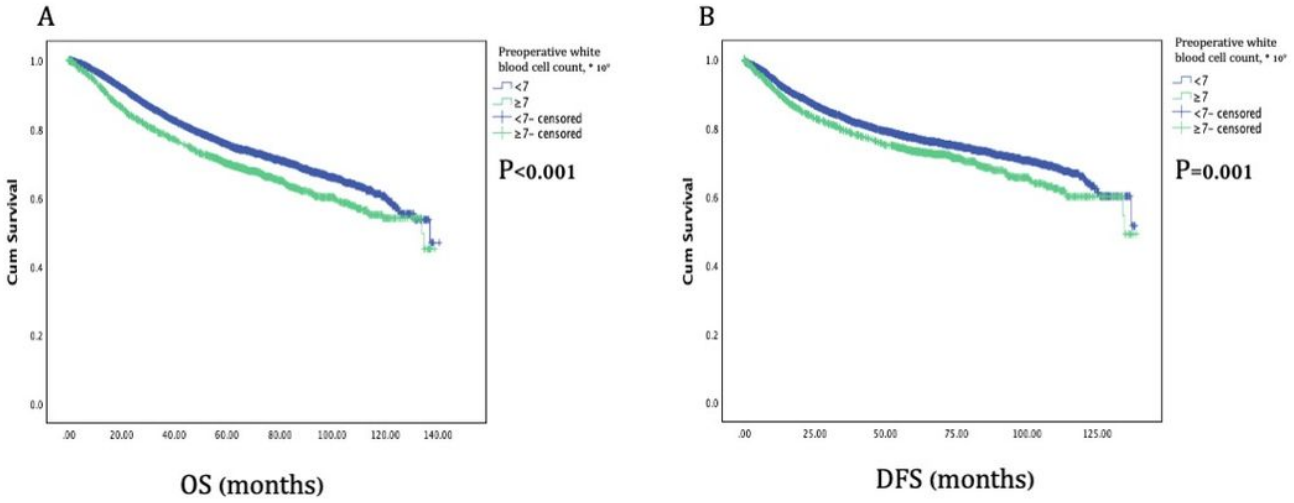

Figure 2

Kaplan-Meier analysis of OS (A) and DFS (B) subdivided by preoperative white blood cells count in patients with no preoperative chemotherapy.