Original Article

Red cell distribution width—a potential prognostic indicator for colorectal cancer patients after radical resection in China

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Background: Red cell distribution width (RDW) can signal poor prognosis in inflammatory medical conditions. The purpose of the study was to investigate the relationship between preoperative RDW and colorectal cancer (CRC) in a large cohort of patients.

Methods: A total of 6,224 CRC patients who underwent radical resection at the Fudan University Shanghai Cancer Center were evaluated retrospectively. The prognostic significance of RDW for overall survival (OS) and disease-free survival (DFS) was analyzed using Cox proportional hazards models and Kaplan-Meier method. Propensity score matching (PSM) was used based on survival confounding factors.

Results: The mean age of the study participants was 59.5±12.0 years and the study cohort was 44% female. The overall median and mean RDW values were 13.3% and 14.0%, respectively. Patients were stratified into three groups based on their RDW value (≤13.3%, 13.4–14.0%, and >14.0%). OS and DFS were shown to significantly deteriorate with increasing RDW category. In the PSM population, OS and DFS were significantly lower in the high RDW group compared with matched controls. However, the differences vanished in the comparisons between the middle RDW group and the control group.

Conclusions: Our findings demonstrate that preoperative RDW may represent a simple and powerful prognostic factor for CRC patients after radical resection. Integrating RDW into clinical practice may better inform the prognosis and optimize therapeutic approaches for patients with CRC.

Keywords: Red cell distribution width (RDW); prognostic value; colorectal cancer (CRC); radical surgery; biomarker

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Introduction

Colorectal cancer (CRC) is the second most lethal cancer worldwide (1). Due to the aging population and increasingly westernized lifestyle, the incidence and mortality of colorectal cancer in China have increased rapidly (2). Radical resection is considered a potential curative treatment for CRC. However, 30–50% of CRC patients will experience metastasis and recurrence during follow-up (3). Despite great advances having been made in cancer follow-up and therapy recent years, appropriate tools for the precise identification of subgroups of CRC patients with higher recurrence or mortality risk are scare.

Red blood cell distribution width (RDW) is a quantitative parameter reflecting the volume heterogeneity of peripheral red blood cells. Resulting from impaired erythropoiesis or shortened erythrocyte life span, higher RDW indicates a higher degree of anisocytosis (4). In clinical settings, RDW can be quickly measured using an automated hematology analyzer and reported as a component of the standard complete blood count, with no additional trauma or cost. RDW has been traditionally used for early-stage iron deficiency identification and the differential diagnosis of anemia (5). In recent years, accumulating evidence has investigated that RDW may act as a prognostic factor for various medical conditions, such as renal dysfunction, cardiovascular and pulmonary diseases, several types of cancer, and other inflammatory disorders (6-10). That chronic inflammation is a key determinant of disease progression and survival in various cancers, including CRC, which has been known for several decades (11,12). In addition, chronic blood loss from the gastrointestinal (GI) tract of patients with CRC can result in iron deficiency, with or without anemia (13). Given this clinical scenario, understanding and confirming the relationship between RDW and CRC could be important for patients to receive optimal oncological treatment. To date, the potential prognostic role of RDW with clinical outcomes in CRC patients is still largely unknown. Thus, in the present study, we aimed to investigate whether higher RDW was associated with poorer outcomes in a large cohort of patients undergoing radical resection for CRC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-54/rc).

Highlight box

Key findings

- As an objective, easily obtainable and inexpensive parameter, RDW may be valuable in predicting the survival of CRC patients after radical resection.

What is known and what is new?

- RDW can signal poor prognosis in inflammatory medical conditions.
- OS and DFS were shown to significantly deteriorate with increasing RDW category for CRC patients after radical resection.

What is the implication, and what should change now?

- Preoperative RDW may represent a simple and powerful prognostic factor for CRC patients after radical resection. Integrating RDW into clinical practice may better inform the prognosis and optimize therapeutic approaches for patients with CRC.

Methods

Study population

All consecutive patients undergoing radical surgery for CRC at the Department of Colorectal Surgery, Fudan University Shanghai Cancer Center (FUSCC), between July 1, 2011 and December 31, 2016 were recruited for this retrospective study. The inclusion criteria were as follows: (I) age >18 years; (II) standard open or laparoscopic radical resection for pathology-confirmed CRC; and (III) local disease without distant metastasis. The patients were staged according to the AJCC/UICC-TNM system for CRC (7th ed., 2010). We excluded patients with metastasis, recurrent or other palliative surgery. Furthermore, patients who received operation by surgeons with less than 10 years' surgery experience and patients with inflammatory disorders such as active renal dysfunction, cardiovascular and pulmonary diseases were also excluded (by preoperative creatinine, cardiac ultrasound, and lung function results). Telephone messages and outpatient records were used to follow up patients until death occurred or the end of the study period (November 30, 2019). The primary endpoint was overall survival (OS), which was defined as the period from the date of radical surgery to death or the last follow-up (if death was not determined), and the 5-year OS rates. The secondary endpoints included intensive care unit (ICU) admission, hospital length of stay, disease-free survival (DFS), and the 5-year DFS rates. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review committee of Fudan University Shanghai Cancer Center (No. 050432-4-1911D). Informed consent was waived due to the retrospective nature of the study.

Sociodemographic, clinical, and laboratory measures

Data for CRC patients who had undergone radical surgery, as documented by the tumor registry at our institution, were retrieved for the analysis. Information was obtained from the medical records of the patients, including demographics (age and gender), comorbidities (diabetes mellitus, hypertension, cardiovascular and cerebrovascular disease, chronic obstructive pulmonary disease, and other tumor history), surgical data with pathological examinations [operation mode, tumor site, tumor stage, histological type, external vascular invasion (EMVI), perineural invasion (PNI), circumferential resection margin (CRM), number of lymph nodes dissected), anesthesia parameters (anesthesia type, American Society of Anesthesiologists score (ASA)], laboratory values [white blood cell count, neutrophil count, lymphocyte count, hemoglobin, RDW, platelet count, albumin, aminoleucine transferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase (ALP)], and hospitalization data (hospital length of stay, ICU occupancy rate, hospitalization expenses, drug costs, antibiotic costs). All laboratory parameters were measured within 3 days prior to surgery. The complete blood count testing, including RDW, was performed clinically on Sysmex Hematology Analyzers (Sysmex America) with Sheath Flow Technology in our hospital. Follow-up data included date of relapse and date of death. All data were extracted from the medical data platform of FUSCC by trained staff using standardized data collection and quality-control procedures. The reference range for RDW is approximately 11.6% to 14.4% at our institution.

Statistical analyses

Categorical variables were described as totals and frequencies, and comparisons were made using the chi-squared or Fisher's exact test. Continuous variables were expressed as median ± SD and comparisons were made using Wilcoxon sum rank test or Kruskal-Wallis H test. Medians and means were used to determine the cut-off values for RDW. The Kaplan-Meier method was used to calculate survival rates, and differences between groups were evaluated using the log-rank test. Univariate and multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards models. With the exception of RDW, all other meaningful variables were applied to univariate and multivariable analyses to identify survival confounding factors. Then, propensity score matching (PSM) was utilized between groups to reduce the influence of these confounding factors (6). A two-sided P value <0.05 was considered statistically significant. Standardized mean difference (SMD) was used to evaluate the balance of PS matched groups. PSM was conducted in R (R Core Team, 2014) and the rest of the statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 9,135 patients >18 years of age underwent colorectal resection surgery between 2011 and 2016, and their records were retrieved from the database. Among them, 879 subjects with metastasis, recurrent or other palliative surgery were excluded. The 2,032 CRC patients who underwent operations performed by surgeons less than 10 years' surgery experience were excluded from the study in order to eliminate the influence of surgeon's experience on prognosis. A final sample of 6,224 CRC patients [3,727 (59.9%) male] was eligible for analysis. The study cohort flow diagram is shown in Figure S1.

The histogram of preoperative RDW is shown in Figure S2. The levels of RDW had positively skewed distributions. The mean RDW value (± SD) was 14.0% (±3.2%) and the median value (25–75% IQR) was 13.3% (12.7–14.2%). To test whether high RDW levels are correlated with the clinical outcomes of CRC patients, we stratified the CRC patients into three groups (low, middle, and high) according to the median and mean values of RDW: low group (RDW ≤13.3%), middle group (13.3%< RDW ≤14.0%), and high group (RDW >14.0%). There were 3,294 patients with an RDW value below 13.3% (low RDW group), 1,227 patients with RDW between 13.3% and 14.0% (middle RDW group), and 1,703 patients with an RDW value above 14.0% (high RDW group).

The clinico-pathological characteristics of the study population according to the three groups are given in *Table 1*. There was a greater proportion of female patients with increasing RDW value. Similarly, patients with higher RDW also had significantly higher percentages of right colon cancer and mucinous adenocarcinoma. Furthermore, patients in the group with higher RDW were more likely to

Table 1 Characteristics of patients with different RDW

Characteristics	RDW (%)			Chi^2	F	P
	≤13.3	13.3–14	>14			
Total	3,294 (52.92)	1,227 (19.71)	1,703 (27.36)			
Gender						
Male	2,060 (62.54)	733 (59.74)	934 (54.84)	27.672		<0.001
Female	1,234 (37.46)	494 (40.26)	769 (45.16)			
Age (years)						
<45	388 (11.78)	107 (8.72)	238 (13.98)	114.712		<0.001
45–54	629 (19.10)	213 (17.36)	353 (20.73)			
55–64	1,284 (38.98)	411 (33.50)	476 (27.95)			
65–74	744 (22.59)	330 (26.89)	420 (24.66)			
75+	249 (7.56)	166 (13.53)	216 (12.68)			
Operation						
Open surgery	2,680 (81.36)	988 (80.52)	1,397 (82.03)	1.075		0.584
Laparoscope	614 (18.64)	239 (19.48)	306 (17.97)			
pTNM staging						
I	772 (23.44)	211 (17.20)	242 (14.21)	79.312		<0.001
II	1,057 (32.09)	472 (38.47)	690 (40.52)			
III	1,465 (44.47)	544 (44.34)	771 (45.27)			
Site						
Rectum	1,988 (61.00)	696 (57.81)	873 (52.15)	182.300		<0.001
Left colon	769 (23.60)	272 (22.59)	274 (16.37)			
Right colon	502 (15.40)	236 (19.60)	527 (31.48)			
Histological type						
Adenocarcinoma	2,918 (88.59)	1,080 (88.02)	1,472 (86.44)	12.172		0.016
Mucinous adenocarcinoma	309 (9.38)	129 (10.51)	207 (12.16)			
Signet-ring cell carcinoma	67 (2.03)	18 (1.47)	24 (1.41)			
EMVI						
–	2,561 (77.75)	980 (79.87)	1,383 (81.21)	8.673		0.013
+	733 (22.25)	247 (20.13)	320 (18.79)			
PNI						
–	2,621 (79.57)	986 (80.36)	1,379 (80.97)	1.452		0.484
+	673 (20.43)	241 (19.64)	324 (19.03)			
CRM						
–	3,263 (99.06)	1,216 (99.10)	1,683 (98.83)	0.773		0.679
+	31 (0.94)	11 (0.90)	20 (1.17)			

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	RDW (%)			Chi^2	F	P
	≤13.3	13.3–14	>14			
Anesthesia						
General anesthesia combined with epidural anesthesia	1,984 (60.23)	728 (59.33)	1,013 (59.48)	0.431		0.806
General anesthesia	1,310 (39.77)	499 (40.67)	690 (40.52)			
ASA score						
I	1,206 (36.61)	370 (30.15)	544 (31.94)	41.529		<0.001
II	2,029 (61.60)	814 (66.34)	1,090 (64.00)			
III–V	59 (1.79)	43 (3.50)	69 (4.05)			
Number of lymph nodes examined	16.59±6.23	16.85±6.52	16.70±7.86		0.673	0.510
White blood cell count (10^9/L)	6.29±2.23	6.42±2.26	6.24±2.93		1.743	0.175
Lymphocyte count (10^9/L)	1.76±0.60	1.69±0.65	1.44±0.71		146.922	<0.001
Neutrophil count (10^9/L)	3.96±2.13	4.13±2.10	4.21±2.72		6.942	0.001
Monocyte count (10^9/L)	0.39±0.15	0.41±0.15	0.43±0.18		40.316	<0.001
Neutrophil-lymphocyte ratio	2.77±3.61	2.92±3.04	3.66±3.92		35.457	<0.001
Lymphocyte-monocyte ratio	5.00±2.09	4.47±2.23	3.70±1.94		220.503	<0.001
Hemoglobin (g/L)	135.45±14.85	126.06±16.88	109.17±21.12		1311.268	<0.001
Platelet count (10^9/L)	221.87±61.24	231.21±75.96	249.99±104.68		72.305	<0.001
Albumin (g/L)	42.91±3.46	41.60±3.84	40.62±4.19		212.120	<0.001
Alanine aminotransferase (IU/L)	17.99±12.02	17.09±11.83	18.78±18.71		3.541	0.029
Aspartate aminotransferase (IU/L)	18.33±7.57	18.38±7.30	19.97±11.79		15.709	<0.001
Creatinine (μmol/L)	71.73±16.61	72.12±19.79	69.14±19.70		13.014	<0.001
Alkaline phosphatase (IU/L)	73.36±20.90	74.50±19.94	76.15±33.02		5.508	0.004
Total costs (RMB)	45,323.47±14,323.10	46,442.66±15,528.32	45,887.32±16,405.85		2.619	0.073
Length of stay in hospital (days)	15.51±7.07	15.47±7.52	15.58±6.48		0.098	0.907
Length of stay in ICU (days)	0.15±1.08	0.23±0.90	0.28±1.51		7.176	0.001
Drug costs (RMB)	16,045.78±8,610.42	15,936.78±8,132.17	16,850.07±9,850.19		5.524	0.004
Antibiotic costs (RMB)	995.60±1,065.91	965.96±1,284.38	1,023.90±1,538.25		0.768	0.464

Data are shown as n (%) or mean ± SD. RDW, red cell distribution width; pTNM, pathological tumor-node-metastasis; EMVI, external vascular invasion; PNI, perineural invasion; CRM, circumferential resection margin; ASA, American Society of Anesthesiologists.

have higher tumor-node-metastasis (TNM)-based staging, ASA score, and ICU occupancy rates, whereas patients in the lower RDW group were more likely to have positive EMVI. The mean preoperative levels of lymphocytes, lymphocyte-monocyte ratio, hemoglobin, and albumin were lower, but preoperative values of neutrocytes, monocytes, neutrophil-lymphocyte ratio, PLT, AST, and ALP were higher in groups with higher RDW (P<0.05). In addition, the high RDW group had significantly higher ALT and drug costs, and lower creatinine than the other two groups (P<0.05).

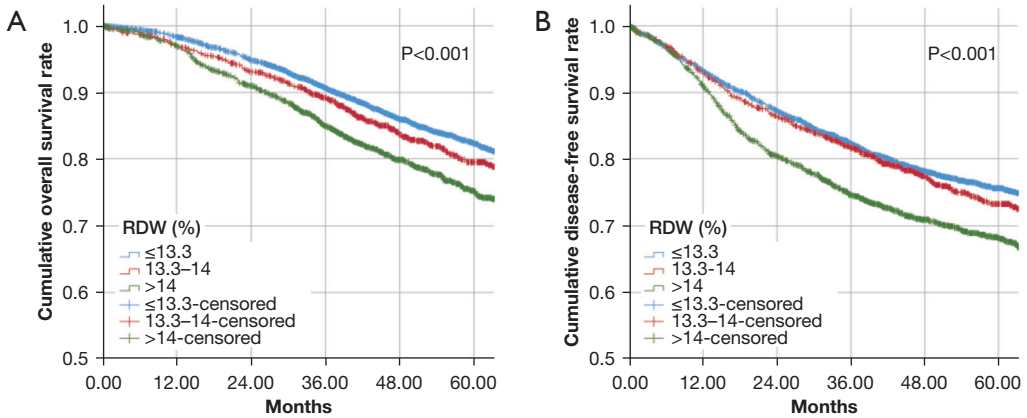

Figure 1 Kaplan-Meier curves of patients with different RDW. (A) Unadjusted overall survival. (B) Unadjusted disease-free survival. RDW, red cell distribution width.

High preoperative RDW is related to poor OS and DFS

During a median longitudinal follow-up period of 56.0 months (95% CI: 55.2–56.9) after the surgery, 1,117 deaths occurred (17.9%) and 1,515 patients (24.3%) had recurred. The Kaplan-Meier cumulative survival curves for OS and DFS according to the three groups of RDW levels are shown in *Figure 1*. The Kaplan-Meier curves showed that patients with high RDW had a worse OS compared with patients with middle or low RDW. The 5-year OS rates for patients in the three RDW groups were as follows: high RDW group (75.1%), middle RDW group (79.5%), and low RDW group (82.3%) (P<0.001; *Figure 1A*). Similarly, the DFS was significantly poorer in the high RDW group *vs.* the other two groups. However, no significant difference in DFS was observed between the middle and low RDW groups. The 5-year DFS rates for patients in the three RDW groups were: high RDW group (68.1%), middle RDW group (73.2%), and low RDW group (75.6%) (P<0.001, *Figure 1B*)

Survival confounding factors other than preoperative RDW

In order to identify the influence of clinico-pathological parameters other than RDW on OS and DFS, univariate and multivariate Cox proportional hazards analyses were performed to select variables for further PSM (*Tables 2,3*). In univariate regression analysis, age, pTNM, tumor site, histological type, EMVI, PNI, CRM, ASA, hemoglobin, neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, albumin, operation duration, and number of lymph nodes extracted were all significantly associated with OS, and with DFS (P<0.001). However, no associations between gender, operation mode, or anesthesia type and survival (OS or DFS) were found. Multivariate regression analysis of prognostic factors affecting survival revealed that gender, age, pTNM, tumor site, histological type, EMVI, PNI, CRM, hemoglobin, lymphocyte-monocyte ratio, albumin, operation duration, and number of lymph nodes examined were significantly associated with OS and DFS. However, no associations between operation mode, anesthesia type, or ASA and survival (OS or DFS) were observed.

Comparisons with propensity score matched controls

As the study was retrospective and observational, we performed PSM analyses adjusted according to the identified survival confounding factors (gender, age, pTNM, tumor site, histological type, EMVI, PNI, CRM, lymphocyte-monocyte ratio, hemoglobin, and albumin) to balance patient characteristics. The CRC patients in the middle RDW group (13.3%< RDW ≤14.0%) and high RDW group (RDW >14.0%) were separately matched (1:1) by propensity score to eligible control patients from the low RDW group ≤13.3% (Figure S3). Finally, PSM was used to create a matched cohort of 1,227 pairs in the middle and low RDW groups (*Table 4*), and another matched cohort of 857 pairs in the high and low RDW groups was generated (*Table 4*). The 11 survival confounding factors were well matched in the two matched cohorts, and none was found to be different between the pairs at baseline. Kaplan-Meier curves showed that there were no significant differences

Table 2 Univariate and multivariate regression of factors affecting OS using Cox regression

Characteristics	Univariate			Multivariate		
	β	P	HR (95% CI)	β	P	HR (95% CI)
Female/Male	–0.103	0.095	0.902 (0.800, 1.018)	–0.145	0.034	0.865 (0.757, 0.989)
Age, years		<0.001			<0.001	
45–54/<45	–0.003	0.979	0.997 (0.785, 1.266)	0.211	0.092	1.235 (0.966, 1.580)
55–64/<45	0.039	0.727	1.039 (0.837, 1.290)	0.300	0.009	1.350 (1.076, 1.694)
65–74/<45	0.274	0.015	1.315 (1.054, 1.641)	0.389	0.001	1.475 (1.165, 1.869)
75+/<45	0.959	<0.001	2.610 (2.074, 3.283)	1.089	<0.001	2.972 (2.319, 3.810)
Laparoscope/open surgery	0.002	0.977	1.002 (0.854, 1.176)			
pTNM		<0.001			<0.001	
II/I	0.528	<0.001	1.695 (1.343, 2.140)	0.428	<0.001	1.535 (1.208, 1.949)
III/I	1.368	<0.001	3.927 (3.171, 4.862)	1.020	<0.001	2.774 (2.210, 3.482)
Site		<0.001			0.013	
Left colon/rectum	–0.159	0.046	0.853 (0.730, 0.997)	–0.238	0.004	0.789 (0.672, 0.925)
Right colon/rectum	–0.010	0.896	0.990 (0.853, 1.149)	–0.104	0.220	0.901 (0.762, 1.064)
Histological type		<0.001			<0.001	
Mucinous adenocarcinoma/adenocarcinoma	0.299	0.001	1.349 (1.131, 1.609)	0.322	<0.001	1.380 (1.153, 1.652)
Signet-ring cell carcinoma/adenocarcinoma	1.138	<0.001	3.121 (2.314, 4.211)	0.668	<0.001	1.950 (1.418, 2.681)
EMVI+/–	0.968	<0.001	2.634 (2.331, 2.975)	0.575	<0.001	1.778 (1.550, 2.039)
PNI+/–	0.860	<0.001	2.363 (2.086, 2.677)	0.516	<0.001	1.675 (1.464, 1.916)
CRM+/–	1.557	<0.001	4.747 (3.389, 6.648)	1.109	<0.001	3.030 (2.138, 4.296)
General anesthesia combined with epidural anesthesia	–0.020	0.755	0.980 (0.866, 1.110)			
ASA score		<0.001				
II/I	0.212	0.001	1.236 (1.086, 1.406)			
III–V/I	0.728	<0.001	2.071 (1.517, 2.828)			
Hemoglobin (g/L)	–0.009	<0.001	0.991 (0.988, 0.993)	–0.007	<0.001	0.993 (0.990, 0.997)
Neutrophil-lymphocyte ratio	0.018	0.003	1.018 (1.006, 1.030)			
Lymphocyte-monocyte ratio	–0.099	<0.001	0.906 (0.878, 0.935)	–0.047	0.006	0.954 (0.922, 0.987)
Albumin (g/L)	–0.070	<0.001	0.933 (0.919, 0.947)	–0.037	<0.001	0.964 (0.946, 0.982)
Operation duration	0.004	<0.001	1.004 (1.002, 1.005)	0.004	<0.001	1.004 (1.003, 1.005)
Number of lymph nodes examined	–0.030	<0.001	0.971 (0.961, 0.980)	–0.036	<0.001	0.965 (0.954, 0.975)

The category after the "/" is the reference category. OS, overall survival; pTNM, pathological tumor-node-metastasis; EMVI, external vascular invasion; PNI, perineural invasion; CRM, circumferential resection margin; ASA, American Society of Anesthesiologists.

Table 3 Univariate and multivariate regression of factors affecting DFS using Cox regression

Characteristics	Univariate			Multivariate		
	β	P	HR (95% CI)	β	P	HR (95% CI)
Female/Male	0.002	0.977	0.918 (0.828, 1.019)	–0.119	0.044	0.888 (0.792, 0.997)
Age, years		<0.001			<0.001	
45–54/<45	–0.035	0.726	0.966 (0.796, 1.173)	0.164	0.107	1.178 (0.965, 1.438)
55–64/<45	–0.021	0.813	0.979 (0.821, 1.167)	0.208	0.027	1.231 (1.024, 1.481)
65–74/<45	0.071	0.448	1.074 (0.894, 1.290)	0.190	0.056	1.210 (0.995, 1.471)
75+/<45	0.558	<0.001	1.748 (1.435, 2.129)	0.684	<0.001	1.982 (1.600, 2.454)
Laparoscope/open surgery	0.002	0.977	1.002 (0.877, 1.145)	–0.213	0.006	0.808 (0.693, 0.942)
pTNM		<0.001			<0.001	
II/I	0.458	<0.001	1.582 (1.310, 1.909)	0.398	<0.001	1.489 (1.227, 1.808)
III/I	1.205	<0.001	3.336 (2.805, 3.966)	0.891	<0.001	2.437 (2.025, 2.933)
Site		0.018			0.005	
Left colon/rectum	–0.195	0.005	0.823 (0.719, 0.942)	–0.225	0.001	0.798 (0.696, 0.916)
Right colon/rectum	–0.039	0.550	0.961 (0.845, 1.093)	–0.069	0.349	0.933 (0.808, 1.079)
Histological type		<0.001			0.003	
Mucinous adenocarcinoma/adenocarcinoma	0.199	0.013	1.220 (1.044, 1.426)	0.200	0.014	1.221 (1.041, 1.432)
Signet-ring cell carcinoma/adenocarcinoma	0.917	<0.001	2.501 (1.905, 3.284)	0.384	0.009	1.467 (1.099, 1.959)
EMVI+/–	0.871	<0.001	2.389 (2.149, 2.657)	0.508	<0.001	1.662 (1.474, 1.874)
PNI+/–	0.810	<0.001	2.249 (2.019, 2.505)	0.489	<0.001	1.631 (1.451, 1.833)
CRM+/–	1.460	<0.001	4.305 (3.177, 5.832)	0.954	<0.001	2.595 (1.898, 3.548)
General anesthesia combined with epidural anesthesia	–0.020	0.708	0.980 (0.883, 1.088)			
ASA score		0.002				
II/I	0.143	0.011	1.153 (1.034, 1.287)			
III–V/I	0.448	0.002	1.565 (1.178, 2.079)			
Neutrophil-lymphocyte ratio	0.018	0.001	1.018 (1.007, 1.029)			
Lymphocyte-monocyte ratio	–0.077	<0.001	0.926 (0.902, 0.950)	–0.041	0.005	0.960 (0.933, 0.987)
Hemoglobin (g/L)	–0.007	<0.001	0.993 (0.991, 0.995)	–0.006	<0.001	0.994 (0.991, 0.997)
Albumin (g/L)	–0.041	<0.001	0.960 (0.948, 0.973)	–0.017	0.040	0.984 (0.968, 0.999)
Operation duration	0.004	<0.001	1.004 (1.003, 1.005)	0.005	<0.001	1.005 (1.003, 1.006)
Number of lymph nodes examined	–0.037	<0.001	0.964 (0.953, 0.974)	–0.031	<0.001	0.970 (0.961, 0.979)

The category after the "/" is the reference category. DFS, disease-free survival; pTNM, pathological tumor-node-metastasis; EMVI, external vascular invasion; PNI, perineural invasion; CRM, circumferential resection margin; ASA, American Society of Anesthesiologists.

Table 4 Baseline characteristics after PSM—1:1 matching in low and middle RDW groups, and in middle and high RDW groups

Characteristics	≤13.3 (N=1,227)	13.3–14 (N=1,227)	Chi^2	t	P	SMD	≤13.3 (N=857)	>14 (N=857)	Chi^2	t	P	SMD
Gender												
Male	759 (49.97)	760 (50.03)	0.311		0.577	0.025	492 (50.00)	492 (50.00)	0		1	<0.001
Female	468 (50.05)	467 (49.95)					365 (50.00)	365 (50.00)				
Age (year)												
<45	128 (47.41)	142 (52.59)	7.929		0.094	0.048	93 (47.69)	102 (52.31)	1.348		0.853	0.056
45–54	218 (48.77)	229 (51.23)					173 (51.49)	163 (48.51)				
55–64	483 (50.74)	469 (49.26)					266 (49.72)	269 (50.28)				
65–74	294 (50.78)	285 (49.22)					214 (49.08)	222 (50.92)				
75+	104 (50.49)	102 (49.51)					111 (52.36)	101 (47.64)				
pTNM staging												
I	271 (51.42)	256 (48.58)	7.888		0.019	0.011	163 (50.31)	161 (49.69)	0.124		0.940	0.017
II	408 (49.16)	422 (50.84)					303 (49.43)	310 (50.57)				
III	548 (49.95)	549 (50.05)					391 (50.32)	386 (49.68)				
Site												
Rectum	722 (50.56)	706 (49.44)	2.171		0.338	0.041	530 (49.95)	531 (50.05)	0.031		0.985	0.013
Left colon	284 (48.55)	301 (51.45)					145 (49.83)	146 (50.17)				
Right colon	205 (50.37)	202 (49.63)					169 (50.45)	166 (49.55)				
Histological type												
Adenocarcinoma	1,062 (49.42)	1,087 (50.58)	2.21		0.331	0.061	751 (49.87)	755 (50.13)	0.092		0.955	0.015
Mucinous adenocarcinoma	145 (54.31)	122 (45.69)					89 (50.86)	86 (49.14)				
Signet-ring cell carcinoma	20 (52.63)	18 (47.37)					17 (51.52)	16 (48.48)				
EMVI												
–	975 (49.97)	976 (50.03)	0.331		0.565	0.002	687 (50.00)	687 (50.00)	0		1	<0.001
+	252 (50.10)	251 (49.90)					170 (50.00)	170 (50.00)				
PNI												
–	978 (49.92)	981 (50.08)	0.279		0.597	0.006	694 (50.11)	691 (49.89)	0.034		0.854	0.009
+	249 (50.30)	246 (49.70)					163 (49.54)	166 (50.46)				
CRM												
–	1,218 (50.02)	1,217 (49.98)	0.202		0.653	0.009	847 (50.09)	844 (49.91)	0.397		0.528	0.030
+	9 (47.37)	10 (52.63)					10 (43.48)	13 (56.52)				
LMR	4.84±2.01	4.89±2.11		–0.611	0.541	0..019	4.03±1.77	4.05±2.21	–0.166		0.868	0.008
Hemoglobin (g/L)	132.70±15.69	132.97±15.67		–0.426	0.67	0.049		122.90±14.27	122.79±16.03	0.147		0.883
Albumin (g/L)	42.40±3.53	42.56±3.67		–1.046	0.296	0.009	41.47±3.63	41.48±3.90	–0.050		0.960	0.002

PSM, propensity score matching; RDW, red blood cell distribution width; SMD, standardized mean difference; pTNM, pathological tumor-node-metastasis; EMVI, external vascular invasion; PNI, perineural invasion; CRM, circumferential resection margin; LMR, lymphocyte to monocyte ratio.

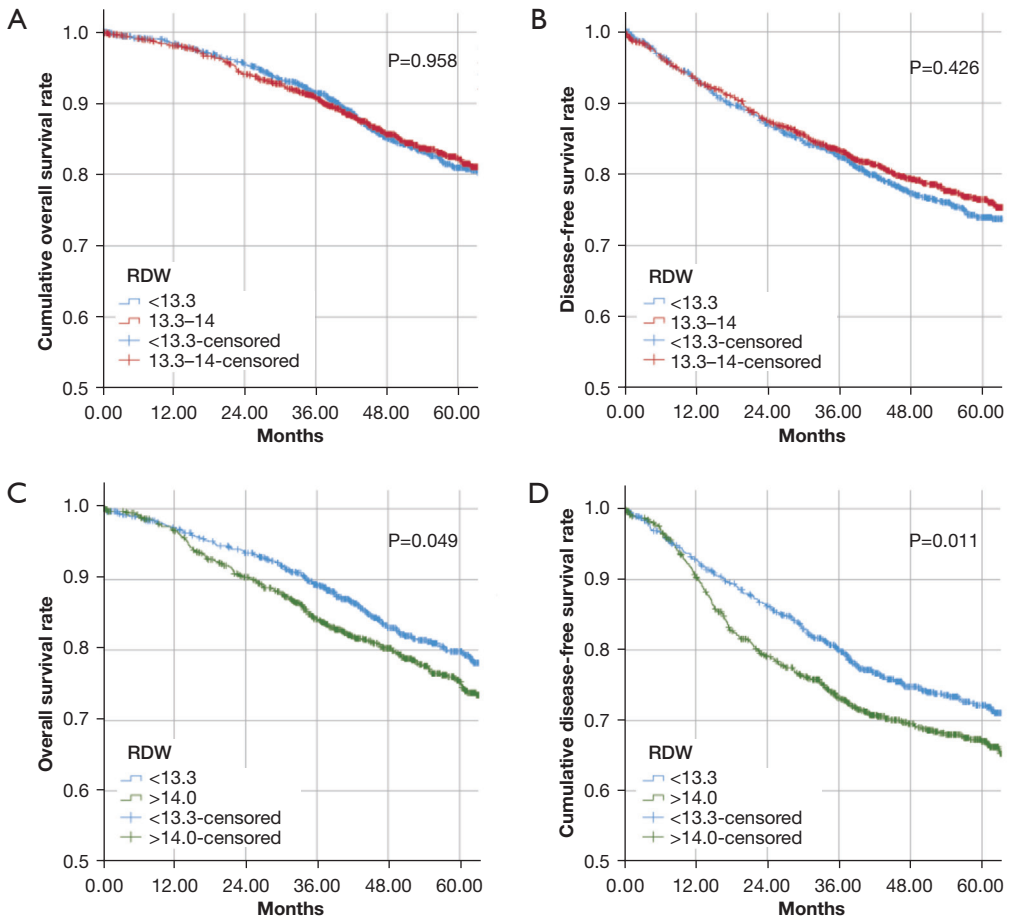

Figure 2 Kaplan-Meier curves of patients with different RDW after PSM. (A) Overall survival in low and middle RDW groups. (B) Disease-free survival in low and middle RDW groups. (C) Overall survival in low and high RDW groups. (D) Disease-free survival in low and high RDW groups. RDW, red blood cell distribution width; PSM, propensity score matching.

in the middle RDW groups compared with PSM controls (P=0.958 *vs.* P=0.426, *Figure 2A*,*2B*). However, an obviously worse OS was observed in the high RDW group in comparison with PSM controls (P=0.049; *Figure 2C*). Moreover, the association between the high RDW group and low RDW group remained significant for DFS after careful PSM (P=0.011; *Figure 2D*).

Discussion

RDW is a routine laboratory parameter, while its value has been generally overlooked in clinical practice. Interestingly, in the present study, we identified that preoperative RDW levels correlate with the main prognostic factors and short-term outcomes in CRC patients undergoing radical resections. In addition, we found that high preoperative RDW was associated with inferior OS and DFS in the cohort of 6,224 CRC patients. The prognostic role of RDW was confirmed after precise PSM in the population. To the best of our knowledge, this is the first large-scale population study to investigate the association between RDW and CRC recurrence and death.

CRC is a growing public health problem with high morbidity and mortality worldwide. As there are different treatment strategies available for different cancer stages, precise stratification of patients using clinical and biological markers is necessary. However, the use of novel molecular bio-markers usually requires complex laboratory tests, which are costly and time-consuming. Therefore, a simple, inexpensive, and readily available bio-marker is needed to aid in the prognostic assessment and decision-making processes for CRC patients after radical surgery.

RDW is part of a routine complete blood count test and is generally utilized for differentiation and classification of anemia. In more recent years, a growing body of evidence has suggested that RDW is a reliable indicator of acute or chronic inflammatory disorders (8,14). Although some authors have reported correlations between high RDW and poor outcomes in lung cancer, esophageal cancer, and hepatocellular carcinoma (8,15), studies evaluating the prognostic role of RDW in CRC have been less extensive. RDW is widely available in the clinical setting at no additional cost and requiring no invasive procedures. This availability is even more important in geographical areas where medical facilities are limited or inaccessible. The popularization of RDW may help minimize the use of invasive and expensive procedures, such as endoscopic biopsy or imaging assessment, to evaluate the prognosis of CRC patients (16). Under this scenario, the clinical significance of RDW in CRC prognosis deserves greater attention.

In the present study, the median and mean values of RDW in the cohort were 13.3% and 14.0%, respectively, which is within the range of RDW cut-off values previously reported in the literature (14,15). It has been established that elderly patients and male patients with CRC are more likely to have a poor prognosis (16-18). Tumor-related features, such as pTNM staging, tumor site, histological type, and EMVI, are all determining factors for the survival of patients with CRC (17,19,20). Host-related parameters, such as lymphocyte counts, neutrophil counts, hemoglobin, platelet counts, albumin, ALT, AST, creatinine, ALP, and ASA have all been reported to be linked with the prognosis of patients with CRC (17,19,21). Our analysis revealed that RDW has a significant association with these proven prognostic indicators for CRC patients. Furthermore, increasing RDW values in patients are correlated with increased ICU days and higher drug costs. On these bases, we analyzed the impact of RDW on long-term outcomes and found that patients with high RDW values had clearly worse OS and DFS. Then, we used PSM to attenuate the impact of confounding factors and still found that patients in the high RDW group had adverse OS and DFS outcomes compared with patients in the low RDW group. Collectively, these results indicate that a high preoperative RDW may be a valuable predictor of poorer outcomes for CRC patients after radical operation.

To date, only eight studies have investigated the potential role of RDW in CRC patients. Three of these studies were conducted to distinguish patients with CRC from healthy controls or patients with colon polyps; in these studies, RDW was used as an early warning biomarker for CRC diagnosis (22-24). The remaining five studies focused on the relationship between RDW and survival in CRC patients. Kust *et al.*, Riedl *et al.*, and Cheng *et al.* found a significant association between high RDW and reduced OS (13,25,26). However, the pronounced prognostic significance vanished in the reports of McSorley *et al.* and Pedrazzani *et al.* (27,28). The patient sample sizes of the four studies were small or intermediate (ranging from 90 to 1,840 patients), the controversial results might be attributed to the population differences thus prompting caution in the interpretation of data. Thus, we investigated the association between RDW and long-term outcomes in a large-scale cohort of 6,224 CRC patients. Additionally, we also investigated the effect of RDW on the short-term outcome of CRC patients and firstly used the PSM analysis to strictly adjust the confounding indicators for CRC prognosis.

The underlying mechanism regarding the relevance of RDW to poor prognosis for patients with CRC has not been elucidated and can be attributed to the following. First, ongoing chronic inflammation can impair iron metabolism, suppress erythropoiesis, and shorten erythrocyte survival in blood. These can lead to an increase in anisocytosis, revealed as increased RDW (6). It is known that prolonged chronic systemic inflammation plays a pivotal role in cancer patients (11,12). Therefore, RDW as an indicator of inflammation is likely to reflect the development and progression of CRC. Second, with the growth of the tumor and chronic bleeding associated with CRC, the deterioration of nutritional status will lead to deficiencies in vitamin B12, iron or folic acid, which could manifest as an increase in RDW (4). These cancer-related malnutrition factors have been found to be one of the causes of increased cancer mortality (13). Therefore, the prognostic ability of RDW may extend beyond systemic inflammation, and may reflect the sub-optimal health status, indicating the decline of system repair, recovery, and defense abilities, which are associated with inferior survival.

Key strengths of our study include the large sample size, adjustment for multiple available confounding factors, and long-term follow-up of the patients' survival. However, there are also some limitations that should be acknowledged when interpreting the results. First of all, the study was retrospectively performed at a single tertiary center, which might raise potential selection bias and limit the generalizability of the results. Second, we evaluated only hemoglobin levels during our study, while factors affecting

the RDW results, such as iron, vitamin B12, and folic acid levels were not assessed. Additionally, the cut-off value for RDW varied between different studies and a standard cut-off value has not been established up to now. Hence, further prospective multi-center studies are necessary to validate the clinical significance of RDW in patients with CRC.

Conclusions

Taken together, as an objective, easily obtainable and inexpensive parameter, RDW may be valuable in predicting the survival of CRC patients after radical resection. Thus, larger, prospective, and randomized investigations are warranted to confirm our findings and stratify CRC patients for personalized therapeutic strategy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-54/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Fudan University Shanghai Cancer Center (No. 050432-4-1911D). Individual consent for this retrospective analysis was waived.

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