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Clinicopathologic and epidemiological characteristics of prognostic factors in post-surgical survival of colorectal cancer patients in Jiangsu Province, China

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ABSTRACT

Poor survival among colorectal cancer (CRC) patients has been widely associated with clinico-epidemiological features and treatment regimen. In Jiangsu (China), however, it is not known which one of the prognostic factors explains the survival disparities among patients with CRC. This prospective study using 1078 patients (stages I-IV) that underwent surgery at Jiangsu Hospital, explored the relevant factors affecting the prognoses of right-side colon cancer (RCC), left-side colon cancer (LCC) and rectal cancer (ReC) patients. Of these cases, 234 (21.7%), 241 (22.4%) and 603 (55.9%) were found to have RCC, LCC and ReC respectively. Compared to LCC, RCC exhibited a greater proportion of older patients, poorly differentiated carcinomas, higher T-stage and higher TNM-stage. The overall survival (OS) for RCC was 60 *vs.*78 or 77 months for LCC or ReC respectively ($P = 0.030$). There were no significant differences in OS between LCC and ReC across the subgroups ($P = 0.633$). In multivariate analysis, RCC patients had age (> 60 *vs.* ≤ 60 years, HR = 1.529, $P = 0.019$), N-stage (N1 *vs.* N0, HR = 4.056, $P = 0.012$) and M-stage (M1 *vs.* M0, HR = 3.442, $P < 0.0001$) as independent prognostic factors, whereas smoking status was found to be a predictor of mortality (smoker *vs.* nonsmoker, HR = 2.343, $P = 0.017$) for LCC. In addition, age (> 60 *vs.* ≤ 60 years, HR = 2.199, $P < 0.0001$), alcohol consumption (drinker *vs.* nondrinker, HR = 0.510, $P = 0.034$), tumor grade (Poor *vs.* well/moderate, HR = 2.759, $P = 0.031$) and T-stage (T3-4 *vs.* T1-2, HR = 1.742, $P < 0.0001$) were found to be predictors of mortality for ReC. There were significant pairwise interactions across subgroups. Furthermore, significant differences were observed for LCC *vs.* RCC (OS, HR = 0.783, $P = 0.039$), but no statistically significant differences for ReC *vs.* RCC ($P = 0.149$) and LCC *vs.* ReC ($P = 0.355$). Nevertheless, significant differences remained between ReC *vs.* RCC for male (HR = 0.591, $P = 0.009$), drinker (HR = 0.396, $P = 0.005$), rural resident (HR = 0.437,$P = 0.022$), tumor grade (well/moderate, HR = 0.475, $P = 0.022$), T-stage (T1-2, HR = 0.362, $P = 0.001$), N-stage (N0, HR = 0.604, $P = 0.011$), M-stage(M0, HR = 0.401, $P = 0.006$) and TNM-stage (I-II, HR = 0.567, $P = 0.005$). Statistically significant differences were observed for LCC *vs.* RCC for gender (female, HR = 0.495, $P = 0.003$) and T-stage (T1-2, HR = 0.417, $P = 0.010$) as well as for LCC *vs.* ReC in patients with smoking habits (HR = 1.951, $P = 0.002$) and M-stage (M0, HR = 2.291, $P = 0.003$). These findings suggest that the variations in CRC post-surgical survival in China may be primarily explained with the clinicopathologic features and epidemiological characteristic of the patients. Patients with RCC had significantly worse OS compared to both LCC and ReC in several subgroups.

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1. Introduction

Colorectal cancer (CRC) is one of the leading causes of morbidity and mortality in both Western and Asian countries [1–3]. In China, the incidence of CRC is increasing rapidly, and it is now ranked fifth in terms of morbidity and mortality among all malignancies [1]. With the increased adoption of western lifestyle including *inter alia* dietary patterns and sedentary habits in China, in 2015 CRC accounted for approximately 376,300 new diagnosed cases and 191,000 deaths [1,4,5].

Findings from population-based studies have revealed marked disparities in the prognosis of CRC incidence and survival in populations of different socio-demographic, including differences in age composition [6], gender [7,8], residence [9], alcohol consumption and tobacco use [4,10–12]. In 2015 for example, age-standardized 5-year relative survival of all cancers combined in China was only 40.5% and it was 56.9% for CRC; with great difference between urban patients (59.3%) and rural patients (52.6%) [13]. Several studies have also investigated survival patterns by tumor location [14–16], stage at diagnosis [17–19], tumor grade [20,21], depth of invasion [22–24] and treatment regimen [25–27]. Liu Fangqi et al [17] revealed that patients with right-sided colon cancer (RCC) had a worse prognostic overall survival (OS) compared to those with left-sided colon cancer (LCC) and rectal cancer (ReC).

Understanding the relevant prognostic factors for survival after CRC surgery remains an active area of investigation in China. To the best of our knowledge this is the first prospective analysis that provides the most comprehensive and up-to-date assessment of the prognostic factors of Post-surgical survival of colorectal cancer in Jiangsu province, China. In our present study, we have explored the relevant factors affecting the prognoses between RCC, LCC and ReC. We have also characterized the survival differences among Chinese patients with CRC based on epidemiological and clinopathological features, as well as treatment regimen.

2. Materials and methods

2.1. Study population

Between January 2007 and October 2011, a total of 1078 newly diagnosed and histologically confirmed patients with CRC were consecutively recruited from the Jiangsu Hospital Cancer Center in China. The enrolled patients had to match the following criteria (1) histologically confirmed with primary colorectal adenocarcinoma and no history of other cancers; (2) received curative surgical resection treatment, but without any preoperative anticancer treatment; and (3) with complete clinical and follow-up data as well as common epidemiological data. The sixth edition of the American Joint Committee on Cancer (AJCC)'s TNM classification was used to assess the clinicopathological features of the patients. The following variables were analyzed for all patients: (1) epidemiological characteristics, including age at diagnosis ($\leq$60, > 60years), sex (male, female), smoking status (nonsmoker, smoker), drinking status (nondrinker, drinker), residence (rural, urban); (2) clinicopathological features: subsite tumor location (RCC, LCC and ReC); tumor grade (well/moderately differentiated and poorly differentiated);T-Stage (depth of invasion) (T1-2, T3-4) ; N-Stage (lymph metastasis) (N0, N1), M-Stage (distant metastasis) (M0, M1) and TNM-Stage (I-II, III-IV); and (3) treatment regimens including lack of chemotherapy for patients at stages I and II, and chemotherapy for those at stages III and IV. Patients receiving chemotherapy were categorized into two subgroups, namely those treated with Folinic acid, fluorouracil and oxaliplatin (FOLFOX) and another adjuvant chemotherapy, including Folinic acid-fluorouracil-irinotecan (FOLFIRI).

2.2. Data collection and measurement

A face-to-face interview was administered by trained physicians and nurses. Information on the participants' demographic characteristics (age, sex, resident) and lifestyles (smoking, drinking) was recorded in a structured questionnaire. Smoking status was categorized as smoker *vs*. nonsmoker. Smokers (current smokers) were defined as persons who smoked at least one cigarette a day or any other product (pipe/cigars). We did not take into account the differences in the types of product (cigarettes and pipe/cigars) and quantity taken per day (light, moderate or heavy cigarette) during the study. Nonsmokers, however, were subjects who reported never to have smoked any product (cigarettes and pipe/cigars) during their entire lives or smoked one or more products but had stopped smoking at least six months before the baseline survey. The overall prevalence of tobacco smoking was 50.38% (332/659) in men and 18.83% (77/409) in women. Similarly, alcohol drinking status was categorized as drinker *vs*. nondrinker and drinker was defined as drinking alcohol on at least 12 occasions during the past 12 months prior to interview. Nondrinkers, however, were subjects who reported to have never drank alcohol or drank alcohol mostly six occasions per year. Differences in the type of alcohol (beer, wine, distilled spirit) and the quantity taken daily (moderate or heavy drinker) were not accounted for due to lack of information. Overall, the prevalence of alcohol drinking was 40.21% (265/659) in men and 18.83% (77/409) in women, respectively.

All clinical and pathological information were reviewed retrospectively and assessed according to the sixth edition of AJCC. The cases with cancer in the proximal two-thirds of the transverse colon, ascending colon, hepatic flexure and cecum were considered RCC while those cases with cancer in the distal third of the transverse colon, splenic flexure, descending colon, and sigmoid colon were considered LCC. Of the 1078 subjects, 234 (21.7%), 241 (22.4%) and 603 (55.9%) were identified to have RCC, LCC and ReC respectively. All patients at stage III-IV underwent curative resection. Adjuvant chemotherapy was carried out either with FOLFOX or another adjuvant including FOLFIRI, based on the China guideline for diagnosis and comprehensive treatment of CRC [28,29]. Briefly, FOLFOX regimen is based on at least 6 cycles of monthly bolus intravenous administration of 5-fluorouracil (400–425 mg/m2/day) and leucovorin (20 mg/m2/day) for 1–5 days.

Informed consent was obtained from each enrolled subject before the recruitment. The institutional review boards (IRB) of the Southeast University (Nanjing China) approved this study under the approval ethical reference code 2017ZDKYSB165.

2.3. Follow-up

All patients were followed-up by a trained clinical specialist from Jiangsu Hospital Cancer Center through on personal or family contacts from the time of diagnosis to death or the last follow-up (cutoff in June 2016). The median follow-up duration was 68.62 months (range of 0–112.70 months), during which time 644 (59.74%) patients (165 (70.51%) RCC, 140 (58.09%) LCC and 339 (56.22%) ReC) died (the detailed data has been described elsewhere) [30]. Due to the lack of information in assessing cause-specific mortality, some authorities including the Food and Drug Administration (FDA) and the European Medicine Agency have advocated overall survival as a more appropriate endpoint for such studies [31]. Overall survival (OS) was defined as the time from initial surgical resection until death due to any cause. Patients alive or lost to follow-up are censored.

2.4. Statistics analysis

Frequency distribution of epidemiology, clinicopathological features and treatment regimens for RCC, LCC and ReC were summarized using both Chi-square test ($\chi 2$ tests) for categorical variables and Kruskal Wallis test for continuous variables. The prognostic effect of each subsite location on overall survival (OS) was first evaluated with the Kaplan-Meier method. Differences between survival curves for RCC, LCC and ReC were compared with the log-rank test. Secondly, Cox

proportional hazards regression models were used for the unadjusted univariate and adjusted multivariate survival analyses. Proportionality assumptions for the Cox regression models were tested, as well as Schoenfeld residuals plots for each subsite location over time. Variables and pairwise interactions included in the full Cox models are covariates that have been reported previously to have associations with CRC cancer mortality. For the prognostic significance of variables, the Cox regression was performed to obtain the unadjusted and adjusted hazards ratios (HRs) at 95% confidence intervals (CIs) in OS for RCC, LCC and ReC patients within each subgroup, controlling for all other variables. Entry and removal probabilities for stepwise-regression were 0.05 and 0.10, respectively. In addition, Lakatos method was used to determine the power of the study. Most of statistical analyses were performed with SPSS software (SPSS Inc., Chicago, IL), using two-sided testing with a significance level at p-value of 0.05. SAS version 9.1.3 (SAS Institute), was used to determine the power of the study.

3. Results

3.1. Patients' characteristics by epidemiological and clinicopathological features

Table 1 shows the epidemiological and clinico-pathological characteristics of patients with CRC by subsite tumor location for the 1078 cases analyzed. Of these cases, 234 (21.71%), 241 (22.36%) and 603 (55.93%) had respectively RCC, LCC and ReC. The cases were most commonly diagnosed between the age range of up 60 years (63.0%) than over 60 years (37.0%), with a greater proportion of males 61.1%. Among patients older than 60 years, 20.30% of the patients had RCC compared to 20.05% with LCC. A small proportion of cases were smoker (37.9%) and drinker (31.7%), but among those cases respectively, there were 42.54% and 38.30% with ReC. Moreover, the 51.84% of smoker and 56.14% of drinker patients are from rural area. Furthermore, LCC was most likely for patients with smoker (32.03%) and drinker (33.63%) compared respectively to 25.43% and 28.07% for RCC.

With respect to the clinico-pathological features of the cases, the histologic grade was consistent across each subsite location, with only 4.4% of tumors being poorly differentiated. A greater proportion of cases had a higher level of tumor depth of invasion (T3-4 = 74.1%) with no regional lymph node metastasis (N0 = 57.6%) and no distant metastasis (M0 = 88.9%). When stratified by tumor node metastasis stage, more than 55.4% of all cases were at stage I-II in each of the subsite locations of CRC. In TNM stage III-IV, patients with LCC (23.08%) were slightly frequently higher compared to RCC (20.58%), but no statistical significant (P = 0.693). In addition, patients with RCC exhibited a higher frequency of distant metastasis M1(36.67%) compared to only 28.33% and 35.0% for LCC and ReC respectively.

There were significant differences between subsite location regarding smoking status, drinking status, tumor grade, T-stage, M-stage (all, $P < 0.05$). Concerning the treatment regimens, more than half of all cases did not have chemotherapy (55.4%) and they were either at stage I-II. In contrast, patients from stage III-IV received either FOLFOX or FOLFIRI.

3.2. Survival outcomes after CRC diagnosis

Median follow-up duration was 68.62 months (range, 0–112.70 months). Unadjusted Kaplan Meier survival curves based on subsite location revealed significantly better overall median survival (OS)

Table 1
Epidemiological and Clinicopathological Characteristics of post-surgical patients with colorectal cancer (CRC).

Characteristics	CRC	RCC	LCC	ReC	P-value
Variables	(N = 1078) (%)	(n = 234) (%)	(n = 241) (%)	(n = 603) (%)	
Age (Mean ± SD) years	(55.79 ± 12.39)	(54.96 ± 13.39)	(53.93 ± 12.68)	(56.86 ± 11.77)	0.162
≤60	679 (63.0)	153(65.4)	161(66.8)	365(60.5)	
> 60	399 (37.0)	81(34.6)	80(33.2)	238(39.5)	
Gender					0.999
Male	659 (61.1)	143(61.1)	147 (61)	369(61.2)	
Female	419 (38.9)	91(38.9)	94(39)	234(38.8)	
Smoking					< 0.0001
Nonsmoker	669 (62.1)	130 (55.6)	110 (45.6)	429(71.1)	
Smoker	409 (37.9)	104 (44.4)	131(54.4)	174(28.9)	
Drinking					< 0.0001
Nondrinker	736 (68.3)	138 (59)	126 (52.3)	472(78.3)	
Drinker	342 (31.7)	96 (41)	115 (47.7)	131(21.7)	
Residence					0.556
Rural	552 (51.2)	122 (52.1)	116 (48.1)	314 (52.3)	
Urban	526 (48.8)	112 (47.9)	125 (51.9)	289 (47.7)	
Tumor Grade					0.925
Well/Moderate	1031(95.6)	223(95.3)	230(95.4)	578(95.9)	
Poor	47(4.4)	11(4.7)	11(4.6)	25(4.1)	
T-Stage					< 0.0001
T1-2	279(25.9)	27(11.5)	48(19.9)	204(33.8)	
T3-4	799(74.1)	207(88.5)	193(80.1)	399(66.2)	
N-Stage					0.495
N0	621 (57.6)	142 (60.7)	140 (58.1)	339 (56.2)	
N1	457(42.4)	92 (39.3)	101(41.9)	264 (43.8)	
M-Stage					< 0.0001
M0	958 (88.9)	190 (81.2)	207(85.9)	561(93)	
M1	120 (11.1)	44 (18.8)	34 (14.1)	42(7)	
TNM-Stage					0.693
I/II	597(55.4)	135(57.7)	130(53.9)	332(55.1)	
III/IV	481(44.6)	99(42.3)	111(46.1)	271(44.9)	
Adjuvant[a] chemotherapy					0.231
FOLFOX	343(31.8)	67(28.6)	77(32.0)	199(33.0)	
FOLFIRI	138(12.8)	32(13.7)	34(14.1)	72(11.9)	

Abbreviation: CRC-colorectal cancer, RCC-right colon cancer, LCC-left colon cancer, ReC-rectum cancer,:TNM-tumor-node-metastasis, FOLFOX-Folinic acid Fluorouracil Oxaliplatin, FOLFIRI-Folinic acid Fluorouracil Irinotecan. a: Only patients with TNM III/IV have received a chemotherapy regimen.

Table 2
Univariate and Multivariate analysis of the risk of mortality among colorectal cancer subsite location by epidemiological and clinico-pathological characteristics.

	RCC (n = 234) OS (months, 95%CI) = 60.17(45.42-74.92)				LCC(n = 241) OS (months, 95%CI) = 78.03(64.62-91.44)				ReC(n = 603) OS (months, 95%CI) = 76.57(66.04-87.10)			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	Pvalue	HR (95%CI)	P value	HR (95%CI)	P value
Age (> 60 *vs*. ≤ 60) years	1.275(0.928-1.752)	0.135	1.529(1.072-2.183)	0.019	1.258(0.890-1.779)	0.193	1.344(0.879-2.057)	0.173	1.170(0.943-1.452)	0.154	2.199(1.674-2.889)	< 0.0001
Sex (Female *vs*. Male)	0.838(0.610-1.150)	0.274	0.695(0.388-1.244)	0.221	0.662(0.465-0.943)	0.022	0.755(0.435-1.311)	0.318	0.935(0.751-1.165)	0.549	0.960(0.747-1.235)	0.752
Smoker *vs*. nonsmoker	1.394(1.027-1.892)	0.033	1.119(0.691-1.813)	0.647	1.193(0.853-1.667)	0.302	2.343(1.168-4.700)	0.017	1.081(0.857-1.365)	0.511	0.913(0.602-1.383)	0.667
Drinker *vs*. nondrinker	1.543(1.135-2.097)	0.006	1.286(0.793-2.087)	0.308	1.450(1.039-2.023)	0.029	1.027(0.582-1.812)	0.926	1.129(0.876-1.456)	0.348	0.510(0.274-0.949)	0.034
Urban *vs*. Rural	0.873(0.643-1.187)	0.387	1.082(0.765-1.529)	0.656	0.596(0.426-0.833)	0.002	1.151(0.666-1.988)	0.614	0.979(0.791-1.212)	0.845	0.934(0.752-1.159)	0.533
Poor *vs*. Well/Moderate	1.201(0.613-2.352)	0.594	1.579(0.767-3.250)	0.215	0.497(0.184-1.343)	0.168	0.727(0.255-2.073)	0.551	1.074(0.640-1.802)	0.787	2.759(1.100-6.921)	0.031
T-stage (T3-4 *vs*. T1-2)	1.052(0.659-1.679)	0.832	0.883(0.530-1.470)	0.631	1.342(0.871-2.069)	0.182	0.976(0.612-1.556)	0.919	2.416(1.870-3.121)	< 0.0001	1.742(1.332-2.277)	< 0.0001
N-Stage (N1 *vs*. N0)	5.226(3.770-7.246)	< 0.0001	4.056(1.364-12.060)	0.012	3.618(2.558-5.116)	< 0.0001	2.548(0.939-6.919)	0.066	5.635(4.470-7.103)	< 0.0001	0.814(0.337-1.966)	0.647
M-Stage (M1 *vs*. M0)	4.174(2.879-6.051)	< 0.0001	3.442(1.901-6.232)	< 0.0001	3.906(2.599-5.869)	< 0.0001	0.743(0.339-1.627)	0.457	4.686(3.314-6.625)	< 0.0001	1.482(0.980-2.241)	0.067
TNM (III-IV *vs*. I-II)	5.197(3.753-7.196)	< 0.0001			4.556(3.181-6.527)	< 0.0001			6.148(4.861-7.777)	< 0.0001		
FOLFIRI *vs*. FOLFOX	1.437(0.924-2.235)	0.108	1.426(0.866-2.348)	0.164	0.666(0.419-1.057)	0.084	0.725(0.444-1.184)	0.198	0.713(0.526-0.967)	0.030	0.694(0.507-0.951)	0.023
Age*Smoking	1.398(0.835-2.343)	0.203			1.842(1.201-2.825)	0.005			0.972(0.691-1.367)	0.869	0.488(0.299-0.798)	0.004
Age*Tumor grade	1.895(0.701-5.122)	0.208			0.749(0.277-2.025)	0.569			0.920(0.490-1.726)	0.795	0.295(0.095-0.910)	0.034
Age*M-stage	4.578(2.707-7.740)	< 0.0001			5.764(3.111-10.68)	< 0.0001	2.881(1.172-7.083)	0.021	6.093(3.595-10.329)	< 0.0001		
Sex*Smoking	1.571(1.033-2.390)	0.035			0.515(0.296-0.894)	0.018	0.064(0.017-0.235)	< 0.0001	1.483(0.765-2.877)	0.244		
Sex*Drinking	1.645(1.095-2.473)	0.017	2.058(1.053-4.024)	0.035	0.761(0.458-1.264)	0.291	8.882(2.471-31.923)	0.001	1.757(0.936-3.298)	0.080		
Sex*M-stage	2.328(1.258-4.309)	0.007	0.182(0.069-0.481)	0.001	2.249(1.239-4.082)	0.008			5.166(3.174-8.407)	< 0.0001		
Sex*TNM-stage	3.302(2.201-4.954)	< 0.0001	2.663(1.227-5.778)	0.013	1.508(1.004-2.265)	0.048			2.922(2.265-3.770)	< 0.0001		
Smoking*Drinking	1.520(1.113-2.075)	0.008			1.321(0.948-1.842)	0.100			1.144(0.872-1.502)	0.332	3.328(1.574-7.035)	0.002
Smoking*Residence	1.181(0.799-1.746)	0.404			0.548(0.364-0.825)	0.004	0.306(0.147-0.637)	0.002	1.043(0.774-1.405)	0.782		
Smoking*M-stage	4.054(2.579-6.371)	< 0.0001			6.892(4.021-11.81)	< 0.0001	6.480(2.259-18.588)	0.001	3.217(1.432-7.231)	0.005		
Drinking*M-stage	5.095(3.139-8.270)	< 0.0001			5.918(3.403-10.29)	< 0.0001			7.596(3.723-15.496)	< 0.0001	2.846(1.150-7.043)	0.024

Abbreviation: CRC-colorectal cancer, RCC-right colon cancer, LCC-left colon cancer, ReC-rectum cancer, TNM-tumor-node-metastasis, FOLFOX-Folinic acid Fluorouracil Oxaliplatin, FOLFIRI-Folinic acid Fluorouracil Irinotecan, OS-Overall survival, HR-Hazard ratio, 95%CI-95%confidence interval.

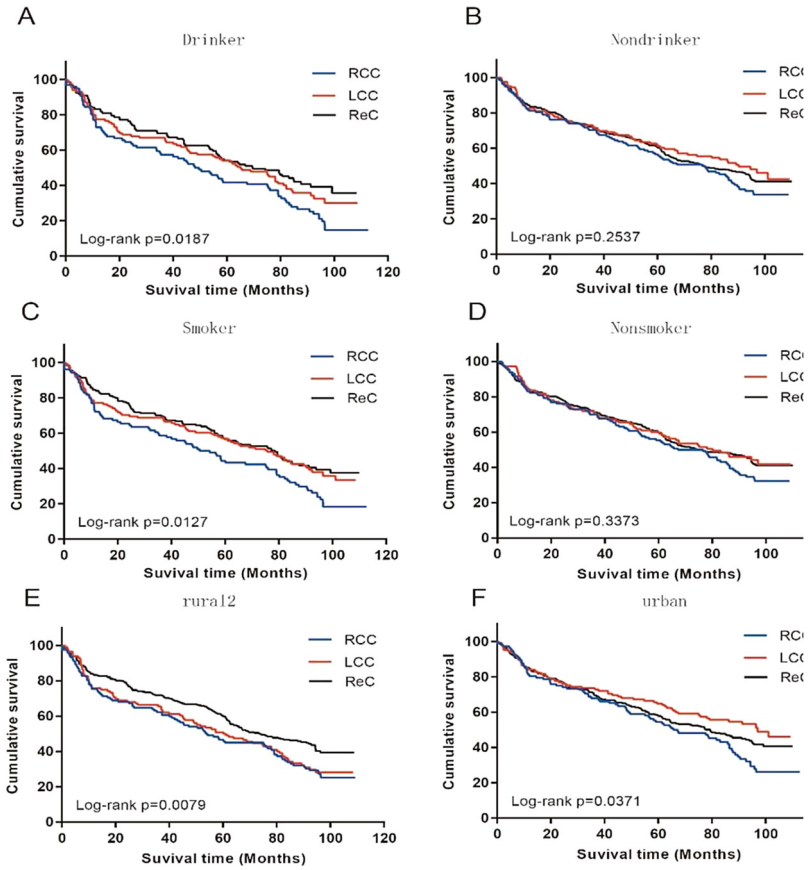

Fig. 1. Survival disparities of CRC patients related to tumor location and epidemiological characteristics, (A)Drinker, (B) Nondrinker, (C) Smoker, (D) Nonsmoker, (E) Rural patients (F) Urban patients.

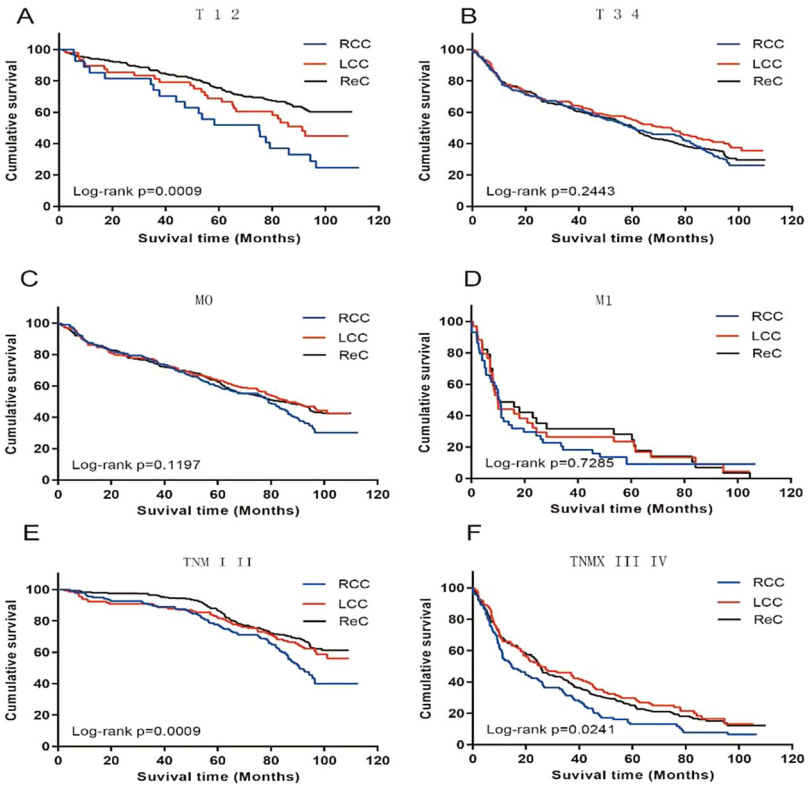

Fig. 2. Survival disparities of CRC patients related to tumor location and Clinico-pathological characteristics, (A) patients with T-stage I-II, (B)patients with T-stage III-IV, (C) patients without metastasis, (D)patients with metastasis, (E) patients with TNM stage I-II, (F) patients with TNM stage III-IV.

Table 3
Comparison of risk mortality among colorectal cancer subsite location by epidemiological and clinico-pathological characteristics.

	LCC *vs.* RCC				Rec *vs.* RCC				LCC *vs.* ReC			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Overall	0.779(0.622-0.976)	0.030	0.783(0.620-0.988)	0.039	0.743(0.617-0.895)	0.002	0.864(0.708-1.054)	0.149	1.049(0.861-1.277)	0.637	0.906(0.735-1.117)	0.355
Age (years)												
≤60	0.780(0.589-1.034)	0.084	0.811(0.559-1.175)	0.268	0.753(0.594-0.955)	0.019	0.763(0.546-1.067)	0.114	1.036(0.807-1.330)	0.780	1.062(0.765-1.475)	0.718
> 60	0.782(0.537-1.139)	0.200	0.760(0.453-1.276)	0.299	0.699(0.517-0.946)	0.020	1.189(0.815-1.734)	0.369	1.118(0.810-1.544)	0.496	0.639(0.403-1.013)	0.057
Gender												
Male	0.854(0.646-1.128)	0.266	0.761(0.486-1.193)	0.234	0.716(0.566-0.905)	0.005	0.591(0.398-0.878)	0.009	1.393(0.936-1.521)	0.155	1.288(0.846-1.959)	0.238
Female	0.668(0.455-0.981)	0.040	0.495(0.313-0.782)	0.003	0.790(0.581-1.074)	0.133	0.691(0.477-1.003)	0.052	0.846(0.604-1.185)	0.330	0.716(0.466-1.100)	0.128
Smoking												
Nonsmoker	0.821(0.589-1.143)	0.242	0.815(0.580-1.145)	0.238	0.842(0.656-1.079)	0.174	0.989(0.760-1.286)	0.933	0.975 (0.735-1.294)	0.861	0.824(0.615-1.105)	0.196
Smoker	0.705 (0.517-0.960)	0.027	1.583(0.996-2.517)	0.052	0.658 (0.491-0.882)	0.005	0.811(0.509-1.294)	0.380	1.071 (0.798-1.436)	0.648	1.951(1.281-2.971)	0.002
Drinking												
Nondrinker	0.771 (0.560-1.063)	0.112	0.766(0.552-1.062)	0.110	0.858 (0.674-1.092)	0.214	0.972(0.756-1.251)	0.828	0.899 (0.685-1.180)	0.442	0.787(0.595-1.042)	0.095
Drinker	0.743 (0.541-1.022)	0.067	1.223(0.649-2.306)	0.533	0.642 (0.468-0.880)	0.006	0.396(0.207-0.761)	0.005	1.158 (0.843-1.592)	0.366	1.130(0.792-1.613)	0.501
Residence												
Rural	0.938 (0.694-1.270)	0.680	0.570(0.256-1.271)	0.169	0.702 (0.544-0.905)	0.006	0.437(0.216-0.886)	0.022	1.338 (1.027-1.742)	0.031	1.304(0.706-2.411)	0.396
Urban	0.646 (0.461-0.907)	0.012	1.432(0.817-2.510)	0.209	0.790 (0.601-1.038)	0.090	1.308(0.834-2.052)	0.242	0.818 (0.608-1.101)	0.185	1.095(0.662-1.812)	0.724
Tumor Grade												
Well/Mod.	0.810(0.644-1.019)	0.073	0.781(0.404-1.510)	0.462	0.747(0.617-0.905)	0.003	0.475(0.272-0.830)	0.009	1.084(0.887-1.324)	0.430	1.645(0.994-2.722)	0.053
Poorly	0.314(0.096-1.022)	0.054	0.0001(0.000-1.41)	0.931	0.714(0.312-1.637)	0.426	1.404(0.136-14.53)	0.776	0.440(0.145-1.336)	0.147	0.0001(0.000-1.00)	0.929
T-Stage												
T1-2	0.621(0.345-1.118)	0.112	0.417(0.214-0.811)	0.010	0.408(0.249-0.669)	< 0.0001	0.362(0.199-0.658)	0.001	1.520(0.967-2.388)	0.070	1.152(0.693-1.913)	0.586
T3-4	0.824(0.645-1.052)	0.121	0.966(0.715-1.305)	0.822	0.974(0.795-1.193)	0.798	0.863(0.666-1.118)	0.265	0.846(0.679-1.053)	0.135	1.119(0.852-1.471)	0.418
N-Stage												
N0	0.751(0.537-1.051)	0.095	0.836(0.545-1.282)	0.411	0.588 (0.443-0.781)	< 0.0001	0.604(0.410-0.890)	0.011	1.277 (0.938-1.740)	0.121	1.384(0.927-2.068)	0.112
N1	0.633 (0.466-0.860)	0.003	0.830(0.601-1.147)	0.260	0.717 (0.558-0.921)	0.009	0.994(0.753-1.313)	0.967	0.884 (0.684-1.142)	0.344	0.835(0.633-1.102)	0.203
M-Stage												
M0	0.790 (0.611-1.022)	0.072	0.919(0.435-1.941)	0.824	0.824 (0.669-1.015)	0.069	0.401(0.210-0.766)	0.006	0.959 (0.770-1.194)	0.708	2.291(1.329-3.952)	0.003
M1	0868 (0542-1.390)	0.555	1.074(0.644-1.793)	0.784	1.018 (0.652-1.590)	0.937	1.326(0.806-2.180)	0.267	0.852 (0.528-1.376)	0.513	0.810(0.486-1.351)	0.420
TNM Stage												
I-II	0.664(0.464-0.951)	0.025	0.725(0.463-1.136)	0.161	0.578(0.432-0.774)	< 0.0001	0.567(0.383-0.840)	0.005	1.149(0.824-1.601)	0.413	1.279(0.839-1.949)	0.253
III-IV	0.687(0.513-0.920)	0.012	0.814(0.599-1.106)	0.188	0.754(0.590-0.962)	0.023	0.960(0.733-1.258)	0.767	0.911(0.713-1.164)	0.457	0.848(0.648-1.110)	0.229
Adjuvant												
FOLFOX	0.843 (0.594-1.196)	0.338	0.958(0.666-1.376)	0.814	0.880 (0.656-1.180)	0.392	1.114(0.808-1.535)	0.510	0.958 (0.719-1.276)	0.769	0.860(0.624-1.183)	0.354
FOLFIRI	0.427 (0.249-0.733)	0.002	0.411(0.221-0.767)	0.005	0.506 (0.321-0.798)	0.003	0.563(0.325-0.975)	0.040	0.843 (0.526-1.354)	0.480	0.732(0.444-1.206)	0.220

Abbreviation: CRC-colorectal cancer, RCC-right colon cancer, LCC-left colon cancer, ReC-rectum cancer, TNM-tumor-node-metastasis, FOLFOX-Folinic acid Fluorouracil Oxaliplatin, FOLFIRI-Folinic acid Fluorouracil Irinotecan, OS-Overall survival, HR-Hazard Ratio, 95%CI-95%confidence interval.

among LCC patients (OS = 78.033 months, 95% confidence interval (CI) (64.623–91.444)) and ReC patients (OS = 76.567 months, 95% CI (66.036–87.097)) compared with RCC patients (OS = 60.167 months, 95%CI (45.418–74.915)). However, there was no significant difference between LCC and ReC patients (P < 0.633) (Table 2). Similarly, analogous results of survival disparities by subsite location were observed in each subgroup of epidemiological and pathological features, as well as treatment regimens (Figs.1 and 2). For instance, RCC or LCC patients with healthy behavior (nonsmoker, nondrinker) are more likely to enjoy higher OS as compared with unhealthy behavior. OS for patients with RCC (76.633 months for nondrinker *vs*. 48.133 months for drinker) and for patients with LCC (90.333 months for nondrinker *vs*. 65.133 months for drinker) (Fig. 1). Similar trend was also observed for the clinicopathological features and tumor location (Fig. 2).

In addition, the unadjusted Cox regression analysis showed that patients with LCC (HR = 0.779, 95%CI (0.622–0.976), P = 0.030) and ReC (HR = 0.743, 95%CI (0.617–0.895), P = 0.002) had significantly decreased risk of mortality compared with RCC patients, and with no statistically significant differences between LCC and ReC (P = 0.635) (Table 3). Meanwhile, LCC patients showed statistical differences between sex (female *vs*. male, HR = 0.662, P = 0.022), drinking habits (drinker *vs*. nondrinker, HR = 1.450, P = 0.029) and Residence (urban *vs*. rural, HR = 0.596, P = 0.002). However, no significant differences in risk of mortality were observed for older *vs*. younger patients when stratified by each subsite location (All P > 0.05) (Table 2).

Meanwhile, there were statistically significant differences between ReC *vs*. RCC within age group. For instance, patients with ReC *vs*. RCC had decreased risk of mortality in the both age group (HR = 0.753, P = 0.019 for ≤ 60 years and HR = 0.699, P = 0.020 for > 60 years), as shown in Tables 3.

Women patients from all combined subsite location showed a significant decrease in the risk for mortality compared to men (HR = 0.844, 95%CI (0.719-0.991), P = 0.039) (Supplementary Materials-Table S1). However, no statistically significant differences for gender were observed between these two subsite groups RCC and ReC. Instead, there were statistically significant differences in prognoses for women patients with LCC *vs*. RCC (HR = 0.668, 95%CI (0.455-0.981), P = 0.040) and for men patients with ReC *vs*. RCC (HR = 0.716 (0.566-0.905), P = 0.005). All smoker or drinker patients had significant increased risk of mortality (HR = 1.204, 95%CI (1.029–1.409), P = 0.021 and HR = 1.342, 95%CI (1.142–1.577), P < 0.0001 respectively) compared with nonsmoker or nondrinker. However, no significant differences in risk of mortality were observed for smoker *vs*. nonsmoker patients when stratified by LCC or ReC (All P > 0.05). In addition, patients with ReC revealed no significant risk of mortality between drinker *vs*. nondrinker (P = 0.348). (Tables 2 & S1)

In contrast, there were statistically significant differences for smoker patients with LCC *vs*. RCC (HR = 0.705, 95%CI (0.517-0.960), P = 0.027) and ReC *vs*. RCC (HR = 0.658, 95%CI (0.491-0.882), P = 0.005). Combining all subsites location, patients from urban areas had decreased risk of mortality (HR = 0.851, 95%CI (0.729-0.993), P = 0.041) compared with those living in rural areas. However, patients with RCC or ReC showed no significant differences between urban *vs*. rural residence. Nevertheless, there were statistically significant differences in prognoses for urban patients with LCC *vs*. RCC (HR = 0.646, 95%CI (0.461-0.907), P = 0.012) and rural patients with ReC *vs*. RCC (HR = 0.702, 95%CI (0.544-0.905), P = 0.006). In comparison with tumor grade (Poor *vs*. well/moderate), no significant differences in prognoses have been observed for all subsite location. Meanwhile, tumor grade (well/moderate) patients with ReC *vs*. RCC had a decreased risk of mortality (HR = 0.747, 95%CI (0.617–0.905), P = 0.003).

And regarding the depth of invasion, there were no statistically significant differences between (T3-4 *vs*. T1-2) for patients with both RCC and LCC, but statistically significant differences were observed for patients with ReC (HR = 2.416 95%CI (1.870–3.121); P < 0.0001). Additionally, there were statistically significant differences in prognosis for T1-2 stage with ReC *vs*. RCC patients (HR = 0.408, 95%CI (0.249-0.669), P < 0.0001). Furthermore, an increased risk of mortality was observed for both patients with higher lymph node (N1 *vs*. N0) and higher distant metastasis (M1 *vs*. M0) for all subsite location (All P < 0.0001). However, there were no statistically significant differences for both (LCC *vs*. RCC) and (LCC *vs*. ReC) patients without lymph node (N0) but statistically significant was observed for Rec *vs*. RCC (HR = 0.588, 95%CI (0.443-0.781); P < 0.0001). In addition, there were statistically significant differences in prognoses for higher lymph node patients with LCC *vs*. RCC (HR = 0.633, 95%CI (0.466-0.860), P = 0.003) and ReC *vs*. RCC (HR = 0.717, 95%CI (0.558-0.921), P = 0.009), but no significant for ReC *vs*. RCC (P = 0.344).

The same results were observed with patients at TNM stage III-IV *vs*. I-II, who presented statistically significant increased risk of mortality across all subsite location. For instance, patients at stage III-IV with RCC had 5.197 (95%CI (3.753–7.196), P < 0.0001) higher risk of mortality as compared at stage I-II patients with the same subsite cancer. Furthermore, there were statistically significant differences in prognoses for stage I-II patients with LCC *vs*. RCC (HR = 0.664,95%CI (0.464–0.951), P = 0.025) and ReC *vs*. RCC (HR = 0.578, 95%CI (0.432–0.774), P < 0.0001). At stage III-IV, patients with LCC or ReC showed decreased risk of mortality (HR = 0.687, 95%CI (0.513–0.920), P = 0.012) or (HR = 0.754, 95%CI (0.590–0.962), P = 0.023) as compared with RCC patients. Differences in prognoses have been also observed for the type of adjuvant therapy prescribed. There were statistically significant differences for patients with ReC under FOLFOX compared with FOLFIRI (HR = 0.713,95%CI (0.526–0.967), P = 0.030). Similarly, significant differences in prognoses were observed also between LCC *vs*. RCC (HR = 0.427, 95%CI (0.249–0.733), P = 0.002) and ReC *vs*. RCC (HR = 0.506, 95%CI (0.321–0.798), P = 0.003), for patients under FOLFIRI as shown in Table 3.

After using multivariate Cox regression, upon combining all subsites location, the following variables- age group (> 60 *vs*. ≤ 60 years), residence (urban *vs*. rural), T-stage (T3-4 *vs*. T1-2) and treatment regimen (FOLFIRI *vs*. FOLFOX) remained statistically significant (all P < 0.05). There were also statistically significant differences for the pairwise interaction between drinking and either smoking, N-stage, M-stage or TNM-stage as shown in Table S1. However, marked differences were observed when stratified by subsite location. There were three main independent prognostic variables including age group (> 60 *vs*. ≤ 60 years, HR = 1.529, 95%CI (1.072–2.183), P = 0.019), N-stage (N1 *vs*. N0, HR = 4.056, 95%CI (1.364–12.060), P = 0.012) and M-stage (M1 *vs*. M0, HR = 3.442, 95%CI (1.901–6.232), P < 0.0001) for RCC. There were also significant pairwise interactions between gender and either drinking (HR = 2.058, 95%CI (1.053–4.024), P = 0.035), M-stage (HR = 0.182, 95%CI (0.069-0.481), P = 0.001) or TNM-stage (HR = 2.663, 95%CI (1.227–5.778), P = 0.013) for patients with RCC.

LCC patients, however, showed only one main independent prognostic variable − tobacco smoking (smoker *vs*. nonsmoker, HR = 2.343, 95%CI (1.168–4.700), P = 0.017) and there were statistical significant differences for some pairwise interactions including age group and M-stage (HR = 2.881, 95%CI (1.172–7.083), P = 0.021), gender and drinking (HR = 8.882, 95%CI (2.471–31.923), P = 0.001), as well as smoking with either gender (HR = 0.064, 95%CI (0.017-0.235), P < 0.0001), residence (HR = 0.306, 95%CI (0.147-0.637), P = 0.002) or M-stage (HR = 6.480, 95%CI (2.259–18.588), P = 0.001). Similarly, there were five main independent prognostic variables including age group (> 60 *vs*. ≤ 60 years, HR = 2.199, 95%CI (1.674–2.889), P < 0.0001); drinking (drinker *vs*. nondrinker, HR = 0.510, 95%CI (0.274-0.949), P = 0.034); tumor grade (Poor *vs*. well/moderate, HR = 2.759, 95%CI (1.100–6.921), P = 0.031); T-stage (T3-4 *vs*. T1-2, HR = 1.742, 95%CI (1.332–2.277), P < 0.0001) and treatment regimen (FOLFIRI *vs*. FOLFOX, HR = 0.694, 95%CI (0.507-0.951), P = 0.023) for ReC patients. In addition, there were statistical significant pairwise interactions including age group (> 60 *vs*. ≤ 60

years) with either smoking (HR = 0.488, 95%CI (0.299-0.798), P = 0.004) or tumor grade (HR = 0.295, 95%CI (0.095-0.910), P = 0.034); and drinking (drinker *vs*. nondrinker) with either smoking (HR = 3.328, 95%CI (1.574–7.035), P = 0.002) or M-stage (HR = 2.846, 95%CI (1.150–7.043), P = 0.024), as shown in Table 2.

Moreover, there were statistically significant differences for LCC *vs*. RCC (OS: HR = 0.783, 95%CI (0.620–0.988), P = 0.039), but no significant differences in OS between ReC *vs*. RCC (P = 0.149) and LCC *vs*. ReC (P = 0.355). Nevertheless, significant differences in prognoses between ReC *vs*. RCC were observed in various subgroups including gender (male, HR = 0.591, 95%CI (0.398–0.878), P = 0.009), drinking status (drinker, HR = 0.396, 95%CI (0.207–0.761), P = 0.005), residence (rural, HR = 0.437, 95%CI (0.216–0.886), P = 0.022) tumor grade (well/moderate, HR = 0.475, 95%CI (0.272–0.830),P = 0.009), T-stage (T1-2, HR = 0.362, 95%CI (0.199–0.658), P = 0.001), N-stage (N0, HR = 0.604, 95%CI (0.410–0.890), P = 0.011), M-stage (M0, HR = 0.401, 95%CI (0.210–0.766), P = 0.006), TNM-stage (I-II, HR = 0.567, 95%CI (0.383–0.840), P = 0.005) and treatment regimen (FOLFIRI, HR = 0.563, 95%CI (0.325–0.975), P = 0.040). And regarding LCC *vs*. ReC, significant differences in prognoses remained for smoking status (smoker, HR = 1.951, 95%CI (1.281–2.971), P = 0.002) and M-stage (M0, HR = 2.291, 95%CI (1.329–3.952), P = 0.003). Similarly, there were significant differences in prognoses for LCC *vs*. RCC in various subgroups including gender (female, HR = 0.495, 95%CI (0.313–0.782), P = 0.003), T-stage (T1-2, HR = 0.417, 95%CI (0.214–0.811), P = 0.010) and treatment regimen (FOLFIRI, HR = 0.411, 95%CI (0.221–0.767), P = 0.005), as shown in Table 3.

4. Discussion

In this prospective study, we explored relevant factors affecting the post-surgical survival prognoses of patients with CRC. Patients with LCC or ReC were most likely to have well/moderately differentiated grade, low depth of invasion, no regional lymph nodes, no distant metastasis and an earlier stage compared to those with RCC. Conversely, patients with RCC included a greater proportion of older patients and women, poorly differentiated carcinomas, higher T stage, higher distant metastasis and higher TNM stage compared to those with LCC. These findings are consistent with previous studies [15,16,18,21,32,33]. We also found that patients from rural areas were most likely to be smoker or drinker, consistent with findings in previous studies [34–36] in China. Interestingly, these results might serve as baseline to explain the worse prognoses in patients with RCC, as well as the survival disparity between urban and rural patients.

Analogous to previous studies [15–18,32,33], our univariate survival analysis revealed that patients with RCC had a significantly greater risk of mortality compared to LCC or ReC patients, although, there were no statistically significant differences in prognoses for patients with LCC and ReC. Moreover, similar results of worse prognosis for patients with RCC compared with LCC or ReC were observed for each epidemiological characteristic, clinico-pathological features and treatment regimens. These findings corroborate with those by Weiss et al. [37] and Fangqi et al. [17]. In the study by Fangqi et al. [17], the authors evaluated 4, 426 Chinese patients with stages I-III CRC and found that for all stages, patients with RCC had an increased risk of mortality compared to LCC (HR = 1.68, 95%CI (1.28–2.21), P = 0.0002), showing the same range as our findings for LCC *vs*. RCC (HR = 0.779, 95%CI (0.622-0.976), P = 0.030), which might be presented as RCC *vs*. LCC (HR = 1.283, 95%CI (1.025–1.608), P = 0.030). In addition, Fangqi et al. [17] found that at stage III, patients with RCC also had a higher risk of mortality (HR = 1.79, 95%CI (1.30–2.46), P < 0.0001) compared to LCC. These observations were in accordance with our results, showing an increased risk of mortality for RCC, (LCC *vs*. RCC (HR = 0.687, 95%CI (0.513-0.920), P = 0.012)), which might be presented as RCC *vs*. LCC (HR = 1.456, 95%CI (1.087–1.950), P = 0.012). Compared with this study, we found a slightly lower risk of mortality (1.46 for our study *vs*. 1.79 for Fangqi et al. [17]).This may be possibly due to factors such age (young subjects for our study *vs*. older subjects for Fangqi et al. [17]); lifestyle (smoking and drinking) which was not considered by Fangqi et al. [17]), as well as the sample size and distribution of subsite pathology among patients, which might be pointed as one of limitation for our study.

Our multivariate analysis revealed that age, N-stage and M-stage were found to be independent predictors of mortality for RCC, whereas tobacco smoking was found to be a predictor of mortality for LCC. Age, alcohol consumption, tumor grade, T-stage and treatment regimen were found to be predictors of mortality for ReC. These results are consistent with the findings of previous studies [22,33,38–42]. Jiang et al. [41] for example, used the surveillance, epidemiology and end results (SEER) database to determine the effect of age on survival outcome in operated and non-operated patients. Of the 123, 356 patients with colon cancer, they found age to be an independent prognostic factor in stage I-IV of the disease and estimated that, at TNM stage I, older patients (41–80 years) were twice at risk of death (HR = 2.319, 95%CI (1.394–3.858), P = 0.001) compared with young patients (≤40 years). They also reported that, at the TNM stage IV, older patients had a 1.288-fold increased risk of mortality than the youngest (HR = 1.288, 95%CI (1.200–1.382), P < 0.001). Broadly, these findings were similar to our results (HR = 1.529, 95%CI (1.072–2.183), P = 0.019) for RCC patients with age (> 60 *vs*. ≤ 60 years) at TNM stage I-IV. Also, Amri et al. [22] used 922 patients with colon cancer to evaluate the effect of high grade disease on outcomes of surgery, and found that the colon cancer-related mortality doubled for patients with higher rate of nodal and distant metastasis, which is in accordance with our findings ((N-stage (N1 *vs*. N0), HR = 4.056, P = 0.012) and M-stage (M1 *vs*. M0, HR = 3.442, P < 0.0001)) for RCC. Regarding unhealthy behavior, our findings were in consonance with previous studies [5,43–45] and reinforce the importance of eliminating or reducing exposure to potentially modifiable risk factors such as cigarette smoking and alcohol consumption. Islami et al. [5] for instance, reported that more than half of all cancer deaths in men and one-third of cancer deaths in women in China in 2013 were attributable to the potentially modifiable risk factors. Meanwhile, our study found that there were statistically significant differences in pairwise interactions between gender and either alcohol consumption, M-stage or TNM-stage for RCC. For LCC patients, significant differences in pairwise interactions were found between age and M-stage, gender and unhealthy behavior (smoke or drink), smoke and either residence or M-stage. Similar observations were found between age and either smoking habits, tumor grade or M-stage, and for alcohol consumption with either smoking habits or M-stage for ReC patients. These findings are in line with previous studies [12,13,35,46,47]. For instance, Zeng et al. [13] used a population-based data from 17 cancer registries in China and found a great 5-year survival gap of CRC between urban patients (59.3%) and rural patients (52.6%) in China.

Furthermore, our findings of worse prognosis for patients with RCC compared with LCC or ReC in the following subgroups – gender, drinking (drinker), residence (rural), tumor grade (well/moderate), T-stage (T1-2), N-stage (no lymph node), M-stage (no distant metastasis), TNM-stage I-II and chemotherapy under FOLFIRI were also consistent with previous studies [22,38,40,43,48] with the exceptions of those of Weiss et al. [37] and Fangqi et al. [17]. Finally, we found an increased risk of mortality for LCC compared with ReC for patients smoking habits (HR = 1.951, 95%CI (1.281–2.971), P = 0.002) and patients without distant metastasis (HR = 2.291, 95%CI (1.329–3.952), P = 0.003).

Our study had some limitations despite the fact that it is a prospective cohort study of 1078 patients. First, the power of our study was only 78% using the Lakatos method, which limited further stratified multivariate analyses. Also, we were not able to account the genetic factors linked with CRC, including testing for MMR, P53 status or other

driver-gene mutations (BRAF). This prevented us from evaluating these factors as potential confounders or effect modifiers in the observed relationships. Our investigation was conducted in a single institution, with limited sample size and lack of information on the cause of each death, restricted our analysis to only overall survival (OS). The socio-demographic characteristics data might be subject-to-recall biased, especially the classification of lifestyle factors (smoking and drinking), which were self-reported.

5. Conclusion

In summary, the post-surgical survival disparities among Chinese patients with CRC was not straightforward. There is a need for consideration of both clinico-epidemiological factors and treatment regimen when analyzing the prognostic survival of Chinese patients. Like other known prognostic factors, tumor subsite location played a role in predicting survival. Compared with LCC or ReC, patients with RCC had worse survival especially in subgroups including gender, drinking (drinker), residence (rural), tumor grade (well/moderate), T-stage (T1-2), N-stage (no lymph node), M-stage (no distant metastasis), TNM-stage I-II and chemotherapy under another adjuvant than FOLFOX.

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Declaration of Competing Interest

The authors declare no potential conflicts of interest.

CRediT authorship contribution statement

Said Abasse Kassim: Conceptualization, Methodology, Data curation, Supervision. **Weiyan Tang:** Conceptualization, Methodology, Data curation. **Muhammad Abbas:** Data curation, Writing - review & editing, Supervision. **Shenzhen Wu:** Formal analysis, Writing - original draft. **Qingdao Meng:** Conceptualization, Formal analysis. **Chengcheng Zhang:** Methodology, Formal analysis. **Xiaobo Li:** Methodology, Data curation, Writing - review & editing, Project administration. **Rui Chen:** Writing - original draft, Writing - review & editing, Supervision, Project administration.

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