Impact of Tumor Location on Survival in Patients With Colorectal Cancer: A Retrospective Cohort Study Based on Taiwan's Cancer Registry Database

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ABSTRACT

BACKGROUND: Colorectal cancer is one of the leading cancers worldwide. This study aimed to investigate the mortality differences between 2 primary tumor locations, the proximal/distal colon and rectosigmoid junction (RSJ)/rectum, after adjusting for comorbidities.

METHODS: The Taiwan Cancer Registry linked with Taiwan's National Health Insurance Research Database was used to estimate the 5-year mortality rate among patients with colorectal cancer. A total of 73 769 individuals were enrolled in the study, which included 44 234 patients with proximal and distal colon cancers and 29 535 patients with RSJ and rectal cancers. Potential mortality risk was calculated using Cox regression analysis.

RESULTS: The mortality rates due to the location of the cancer in the proximal/distal colon and RSJ/rectum were 45.27% and 42.20%, respectively. After adjustment for age, sex, comorbidities, and clinical stages, the proximal/distal colon had a 1.03-fold higher 5-year overall mortality rate than RSJ/rectal cancer (95% confidence interval = 1.00–1.05). Proximal and distal colon cancers had a worse prognosis and survival than RSJ and rectal colon cancers in women and older patients (⩾70 years). Comorbidities had different effects on mortality in the proximal/distal colon and RSJ/rectum.

CONCLUSIONS: Tumor location is associated with the prognosis of patients with colorectal cancer. It is important to treat patients beyond their cancer treatment, and to manage their comorbidities.

KEYWORDS: Colorectal cancer, survival, comorbidity, Taiwan Cancer Registry, tumor location

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Introduction

In the United States, more than 1.5 million men and women have a history of colorectal cancer, which is one of the most prevalent cancers in 2019.[1] Most of these patients are older than 65 years and have multiple comorbidities.[2] A previous study showed that comorbidities had the greatest prognostic effect on patients with the highest survival rate and the least prognostic effect on patients with the lowest survival rate.[3]

A study using the Adult Comorbidity Evaluation-27, National Institute on Aging and National Cancer Institute Comorbidity Index, and Charlson Comorbidity Index to evaluate the association between comorbidity and mortality found that comorbidities were associated with poor prognosis after surgery for colon cancer.[4] A registry database study identified patients with primary colorectal cancer between 2000 and 2011 and found that the Charlson Comorbidity Index scores were associated with prognosis.[5] In some studies, the impact of comorbidities on prognosis was strongly marked in patients with early cancer.[6,7]

In addition, studies have found many differences between proximal and distal colon cancers, including gene expression, clinical presentation, histological features, and molecular characteristics.[8-10] The proximal and distal colon are physiologically separate, originating from different embryonic cells with diverse biological developments, which express differing susceptibilities to tumor transformation.[9] The location of the tumor was found to be a prognostic factor in Australian patients with colon cancers[7] and Japanese patients.[11] Other studies also

indicated that tumor location may affect the overall survival of patients with metastatic colorectal cancer.[12]

Previous studies have indicated that rectal cancers are treated differently than other colon cancers, and the rectosigmoid junction (RSJ) may be treated similar to rectal cancer.[13-15] Therefore, we compared RSJ and rectal cancers with proximal and distal colon cancer. Our hypothesis was that the location of the RSJ with rectal tumor might be easy to monitor via colonoscopy or treat for a better survival rate. Published studies comparing proximal and distal colon cancers with RSJ and rectal cancers are lacking. As this could have an impact on prognosis, we aimed to estimate the mortality risk between patients with proximal/distal colon cancers and those with RSJ/rectal cancers. Furthermore, we evaluated this aspect to gain insight into the comorbidities of proximal, RSJ, and rectal cancers.

Materials and Methods

Data sources

The Taiwan Cancer Registry (TCR), a long-form database, was used in this study to identify patients with colon cancer. In 1979, TCR was established to monitor Taiwan's cancer incidence and mortality rates, and data collected were of high quality in terms of completeness and timeliness. To add more precise diagnosis and treatment items, the TCR established long-form data sets for oncology categories such as oral cavity and pharynx (except nasopharynx), colon and rectum, liver, lung, breast, and cervix in 2002, and prostate cancer in 2007.[16,17]

In addition, to screen the disease histories of colon cancer patients, administrative claims from Taiwan's National Health Insurance program, which covers all inpatient and outpatient health services, were also used in this study. For research purposes, Taiwan's Health and Welfare Data Science Center integrated the population database, which was linked to different health-related data sets, and managed the application to avoid violations against personal information protection.

Study population

Patients with colorectal cancer were selected from the TCR using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) with proximal and distal colon (ICD-O-3: C18), RSJ (ICD-O-3: C19), and rectum (ICD-O-3: C20) cancers from January 2007 to December 2015. The study cohort included proximal and distal colon cancers of the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, and sigmoid colon.[18] According to previous studies, the location of colorectal cancer could have a great influence on tumor staging and preoperative radiotherapy or chemotherapy.[19] Because RSJ may be treated with rectal cancer treatment protocols, RSJ and rectal cancer were set as the comparison cohorts in this study. Therefore, the estimated mortality risk ratio was calculated for patients with proximal and distal colon cancer compared with RSJ and rectal cancer patients.

Patients with other cancers before they were diagnosed with colon cancer were excluded. Patients with missing information on the location of the cancer and clinical stage were also excluded. Considering that technological advancements and medication may affect the treatment selection bias of illnesses, the study subjects only included patients with new-onset cancer between 2007 and 2015 to avoid potential selection bias in TCR. A flowchart illustrating the selection of study patients is presented in Figure 1.

Measurement

The demographics included age, sex, comorbidities, and clinical stage. Age was classified as <50, 50-59, 60-69, and ≥ 70 years. According to previous studies, the cancers of the proximal and distal colon have been suggested to be 2 cancer types with different molecular, pathological, and clinical features and prognoses.[20,21] Comorbidities were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) based on the Charlson comorbidity index score for the presence or absence of each comorbidity.[22,23] These comorbidities included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, paraplegia, hemiplegia, renal disease, and moderate or severe liver disease. The ICD-9-CM and ICD-10-CM codes for the listed comorbidities are presented in Supplementary Table 1.

The outcome of this study was 5-year mortality, which was defined as the pathological diagnosis of death for any reason. In addition, cancer-specific mortality was used to estimate the risk of mortality due to cancer. All study participants who withdrew or were lost to follow-up were right-censored on December 31, 2017. The maximum follow-up period of the study subjects was 5 years.

Statistical analysis

All categorical variables, including age, sex, comorbidities, cancer clinical stage, and number of deaths, are presented as counts with percentages, and Pearson's chi-square analysis was used to compare the differences between the study cohort (proximal and distal colon) and the comparison cohort (RSJ and rectum). The time to death was represented by the median with interquartile range, and Wilcoxon's rank-sum test was used to compare the differences.

The trend of mortality was calculated using the Kaplan–Meier method with the log-rank test to compare the differences between the 2 groups. The overall and cancer-specific

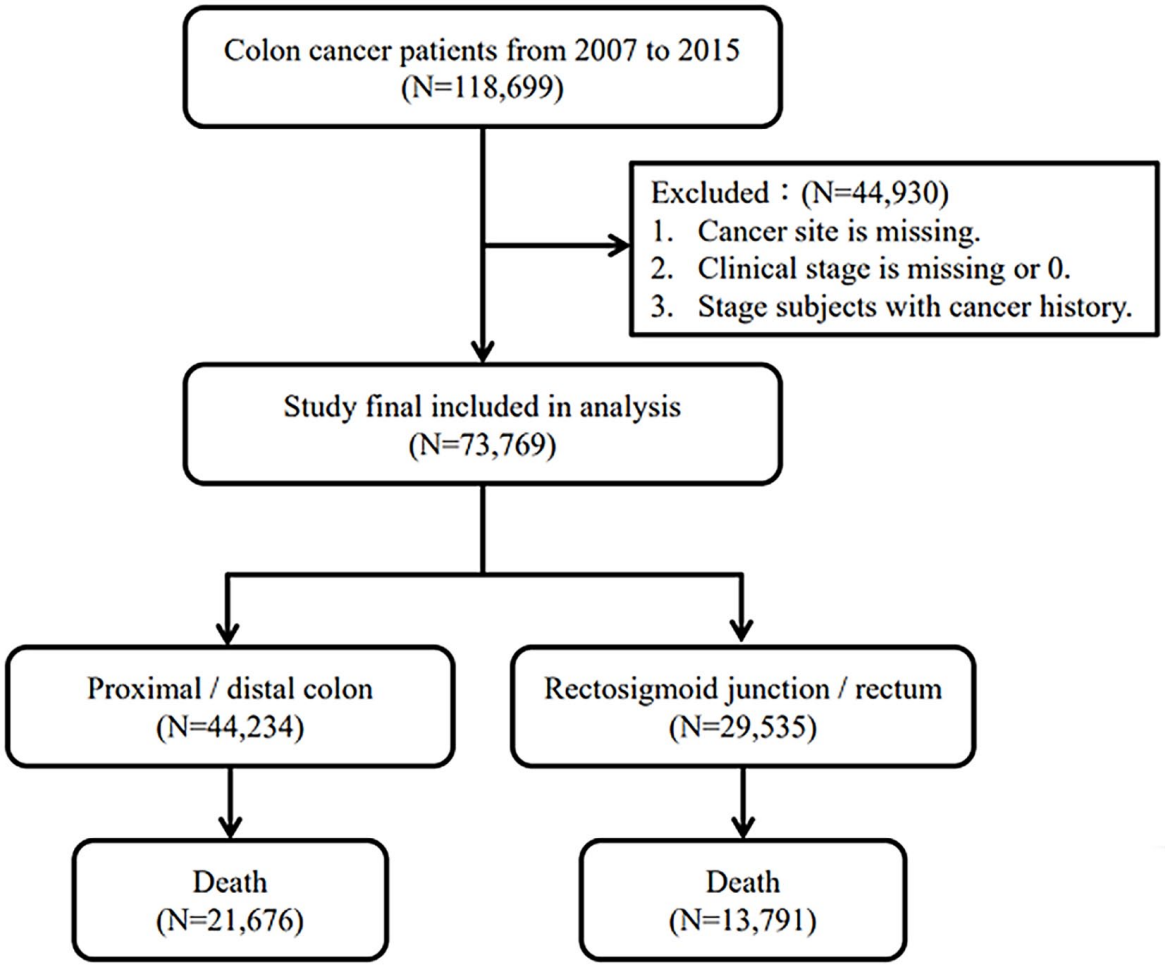

Figure 1. Flowchart of patient selection.

relative risks of mortality were estimated using a Cox proportional hazards model. This approach is usually used to estimate mortality risk in patients with colon cancer.[24] A stratified analysis of age and sex is also presented. A 2-tailed *P*-value of less than .05 was considered statistically significant. SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. Survival curves were plotted using STATA 12.0 (Stata Corp., College Station, TX, USA).

Results

A total of 73 769 individuals were enrolled in the study, which included 44 234 patients with proximal and distal colon cancers and 29 535 patients with RSJ and rectal cancers. Table 1 describes the demographics of the overall group and the 2 subgroups. More patients were aged ⩾ 70 years (total, 44.58%; proximal colon cancer, 47.27%; RSJ and rectal cancers, 40.56%), and there were significantly more men than women in each group (total, 57.14% vs 42.86%; proximal and distal colon cancer, 54.28% vs 45.72%; RSJ and rectal cancers, 61.43% vs 38.57%). Among the comorbidities, there were significant differences in diabetes without complications or renal disease. In addition, the median survival time of the RSJ and rectal cancer cohort were higher than those of the proximal and distal colon cancer cohort (3.41 vs 3.07, respectively). There were significant differences in clinical stage (Table 1). The trend of mortality between study cohort (proximal and distal colon) and the comparison cohort (RSJ and rectum) during the study periods presented in Figure 2. Kaplan-Meier analysis of the 2 groups also showed that the RSJ and rectum cancer cohort had a significantly higher survival probability than the proximal and distal colon cancer cohort over a 5-year period (Figure 2, log-rank test $P < .05$).

Table 2 presents the analysis of the 5 year overall and cancer-specific mortality rate ratios based on a Cox proportional hazard regression model after adjusting for colon cancer type, age, sex, comorbidities, and clinical stage. For the colon cancer type assessment, proximal and distal colon cancer was 1.03-fold higher than RSJ and rectal cancer in terms of 5 year overall mortality (95% confidence interval [CI] = 1.00-1.05); however, cancer-specific mortality was not statistically significant after adjustment. Age stratified by group showed that the ⩾ 70 years-old group had the highest mortality rate relative to the other younger groups. For the sex-stratified examination, the overall mortality rate ratio was 1.09-fold

Table 1. Patient demographics and clinical characteristics.

	TOTAL PATIENTS (N = 73 769)	PROXIMAL AND DISTAL COLON CANCERS (N = 44 234)	RSJ AND RECTUM CANCERS (N = 29 535)	*P*-VALUE
Age groups				
< 50 years	7974 (10.81)	4510 (10.2)	3464 (11.73)	<.0001
50-59 years	14 817 (20.09)	8237 (18.62)	6580 (22.28)	
60-69 years	18 089 (24.52)	10 577 (23.91)	7512 (25.43)	
⩾ 70 years	32 889 (44.58)	20 910 (47.27)	11 979 (40.56)	
Sex				
Male	42 154 (57.14)	24 011 (54.28)	18 143 (61.43)	<.0001
Female	31 615 (42.86)	20 223 (45.72)	11 392 (38.57)	
Clinical stage				
I	14 143 (19.17)	7619 (17.22)	6524 (22.09)	<.0001
II	14 536 (19.7)	8568 (19.37)	5968 (20.21)	
III	25 955 (35.18)	15 535 (35.12)	10 420 (35.28)	
IV	19 135 (25.94)	12 512 (28.29)	6623 (22.42)	
Comorbidities				
Myocardial infarction	297 (0.4)	175 (0.4)	122 (0.41)	.7139
Congestive heart failure	1079 (1.46)	666 (1.51)	413 (1.4)	.2343
Peripheral vascular disease	350 (0.47)	199 (0.45)	151 (0.51)	.2346
Cerebrovascular disease	1529 (2.07)	950 (2.15)	579 (1.96)	.0802
Dementia	673 (0.91)	401 (0.91)	272 (0.92)	.8403
Chronic pulmonary disease	1723 (2.34)	1020 (2.31)	703 (2.38)	.5126
Rheumatic disease	111 (0.15)	69 (0.16)	42 (0.14)	.6360
Peptic ulcer disease	2230 (3.02)	1362 (3.08)	868 (2.94)	.2759
Mild liver disease	1374 (1.86)	817 (1.85)	557 (1.89)	.7018
Diabetes without complications	2522 (3.42)	1420 (3.21)	1102 (3.73)	.0001
Diabetes with complications	806 (1.09)	456 (1.03)	350 (1.19)	.0484
Paraplegia and hemiplegia	201 (0.27)	124 (0.28)	77 (0.26)	.6165
Renal disease	1236 (1.68)	705 (1.59)	531 (1.8)	.0344
Moderate or severe liver disease	241 (0.33)	141 (0.32)	100 (0.34)	.6439
5-year target survival, median (Q1-Q3)	3.21 (1.43-5.00)	3.07 (1.22-5.00)	3.41 (1.74-5.00)	<.0001
Death	32 490 (44.04)	20 025 (45.27)	12 465 (42.20)	<.0001
Time to death, median (Q1-Q3)	1.19 (0.40-2.32)	1.05 (0.32-2.17)	1.43 (0.57-2.55)	<.0001
Death in colon	25 510 (34.58)	15 722 (35.54)	9788 (33.14)	<.0001
Time to death in colon, median (Q1-Q3)	1.14 (0.38-2.18)	0.98 (0.30-1.98)	1.41 (0.58-2.47)	<.0001

Abbreviation: RSJ, rectosigmoid junction.

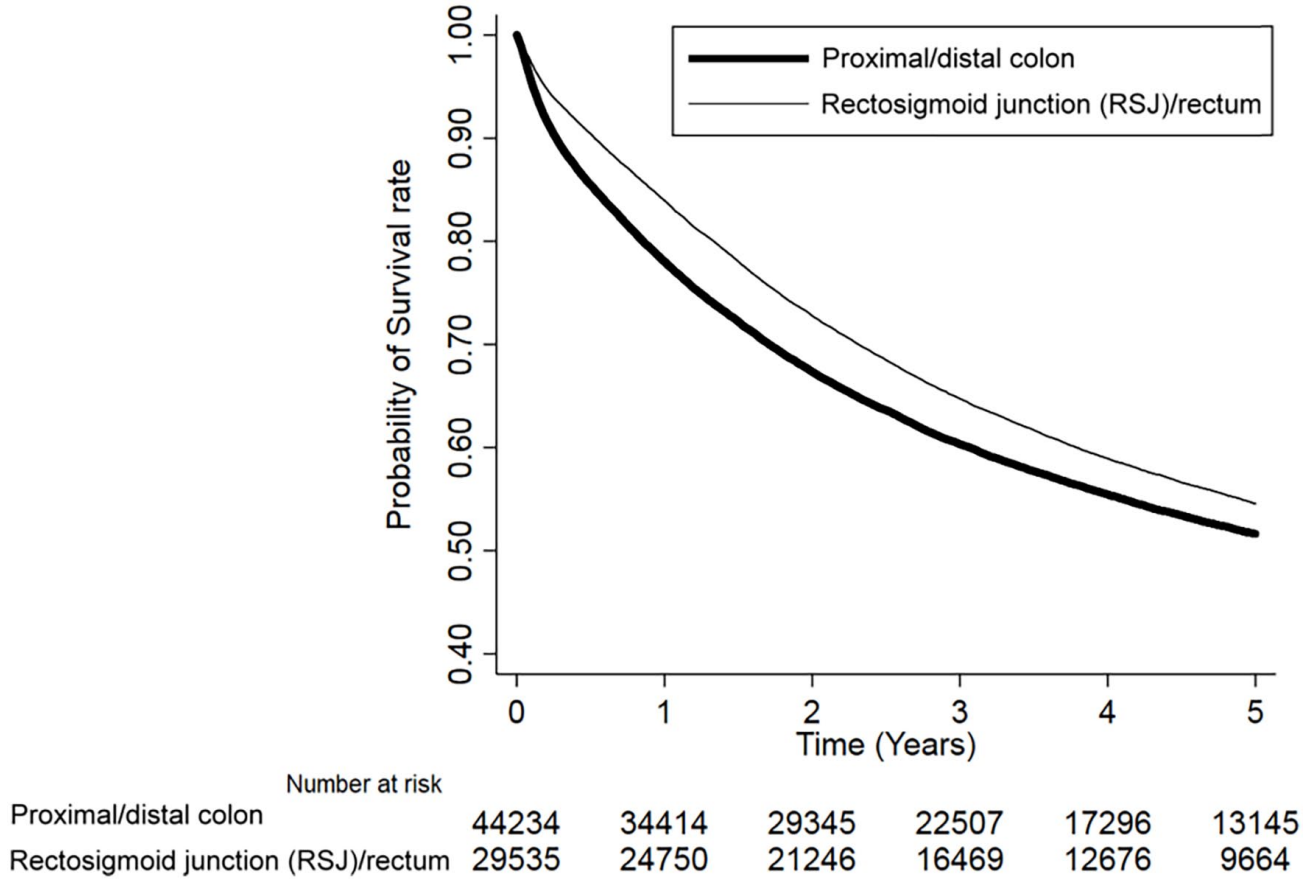

Figure 2. Survival probability trend in patients with colon cancer between different tumor locations.

higher in men (95% CI = 1.07-1.12, $P < .0001$) than in women, and borderline statistical significance of cancer-specific mortality was observed in men than in women. Patients with other comorbidities had the highest overall and cancer-specific mortality rates, followed by those with clinical stage IV. The top ten causes of mortality among patients with colon cancer are presented in Supplementary Table 2. More than 85% of patients died due to cancer.

Table 3 presents the stratified analysis of different sex and age groups for 5-year overall and cancer-specific mortality between colon cancer, RSJ, and rectal cancers. Females with proximal and distal colon cancer had a higher overall mortality risk (adjusted hazard ratio [AHR]: 1.04; 95% CI: 1.01-1.08) than females in the RSJ and rectum cancer cohort. The cancer-specific mortality in women with proximal colon cancer showed borderline significance compared with RSJ and rectal cancer. For the ⩾70-years-old group, patients with proximal colon cancer had a 1.04-fold higher overall mortality rate than the RSJ and rectum cancer cohort.

This study examined the overall and cancer-specific mortality risk using cancer sidedness analysis (Table 4). Whether the cancer side was in the proximal and distal colon or the RSJ and rectum, males presented a higher mortality rate than females. In addition, older age, comorbidities, and severe clinical stage also played significant roles in influencing higher mortality risk.

Discussion

Published data on proximal and distal colon cancers compared with RSJ and rectal cancers are lacking. Colon cancer sidedness has been compared previously. In our study, we identified differences within age, sex, comorbidities, and clinical stage in proximal and distal colon cancer compared with RSJ and rectal cancer. Proximal and distal cancers have higher 5-year mortality rates than RSJ and rectal cancer. Both older and male patients had poor prognoses in the above 2 cohorts. Multiple comorbidities predicted 5-year mortality in proximal and distal colon cancers, but some comorbidities did not increase the 5-year mortality risk in RSJ and rectal cancers, such as peripheral vascular disease, rheumatic disease, liver disease, diabetes with complications, paraplegia, and hemiplegia.

Comorbidity prevalence among colon cancer patient cohorts

A survey on the prevalence of comorbidities among cancer patients in England found that hypertension, chronic obstructive pulmonary disease, and diabetes were the most common comorbidities among colon cancer patient cohorts.[25] Our study also

Table 2. Overall risk factor analysis of 5-year overall and cancer-specific mortality based on the Cox proportional hazard regression model.

	OVERALL MORTALITY		CANCER-SPECIFIC MORTALITY	
	CRUDE HR (95% CI)	AHR (95% CI)	CRUDE HR (95% CI)	AHR (95% CI)
Colon cancer sidedness				
proximal and distal colon	1.15 (1.12-1.17)**	1.03 (1.00-1.05) *	1.15 (1.12-1.18) **	1.01 (0.99-1.04)
Rectosigmoid junction and rectum	Ref.	Ref.	Ref.	Ref.
Age groups				
<50 years	0.55 (0.53-0.57)**	0.48 (0.46-0.50) **	0.70 (0.67-0.73) **	0.57 (0.55-0.60) **
50-59 years	0.48 (0.47-0.50)**	0.46 (0.45-0.47) **	0.58 (0.56-0.60) **	0.54 (0.52-0.56) **
60-69 years	0.51 (0.49-0.52)**	0.52 (0.50-0.53) **	0.57 (0.56-0.59) **	0.58 (0.56-0.60) **
⩾70 years	Ref.	Ref.	Ref.	Ref.
Sex, male(vs females)	1.10 (1.07-1.12)**	1.09 (1.07-1.12) **	1.03 (1.00-1.05) *	1.03 (1.00-1.05)
Comorbidities				
Myocardial infarction, yes(vs no)	1.77 (1.54-2.03)**	1.18 (1.02-1.36) *	1.17 (0.97-1.42)	0.99 (0.81-1.20)
Congestive heart failure, yes(vs no)	1.95 (1.82-2.09)**	1.16 (1.07-1.26) **	1.41 (1.29-1.55) **	1.04 (0.94-1.15)
Peripheral vascular disease, yes(vs no)	1.62 (1.42-1.85)**	1.00 (0.87-1.14)	1.29 (1.09-1.52) *	1.01 (0.85-1.19)
Cerebrovascular disease, yes(vs no)	1.88 (1.77-2.00)**	1.17 (1.09-1.25) **	1.46 (1.35-1.58) **	1.09 (1.00-1.19)
Dementia, yes(vs no)	2.04 (1.87-2.23)**	1.21 (1.10-1.33) **	1.54 (1.38-1.73) **	1.17 (1.04-1.33) *
Chronic pulmonary disease, yes(vs no)	1.87 (1.77-1.98)**	1.17 (1.10-1.25) **	1.37 (1.28-1.48) **	1.01 (0.93-1.10)
Rheumatic disease, yes(vs no)	1.65 (1.31-2.08)**	0.94 (0.75-1.19)	1.49 (1.13-1.96) *	0.95 (0.72-1.26)
Peptic ulcer disease, yes(vs no)	1.83 (1.74-1.92)**	1.22 (1.15-1.30) **	1.56 (1.47-1.66)**	1.24 (1.16-1.33)**
Mild liver disease, yes(vs no)	1.68 (1.57-1.79)**	1.08 (1.00-1.16)	1.35 (1.25-1.47)**	0.94 (0.86-1.03)
Diabetes without complications, yes(vs no)	1.65 (1.57-1.73)**	1.10 (1.03-1.17) *	1.36 (1.28-1.45)**	1.09 (1.01-1.17)*
Diabetes with complications, yes(vs no)	1.55 (1.42-1.69)**	0.98 (0.89-1.09)	1.15 (1.02-1.29)*	0.88 (0.77-1.00)
Paraplegia and hemiplegia, yes(vs no)	1.66 (1.40-1.96)**	1.05 (0.88-1.25)	1.44 (1.18-1.77)**	1.08 (0.87-1.33)
Renal disease, yes(vs no)	1.79 (1.67-1.92)**	1.18 (1.09-1.27) **	1.33 (1.21-1.45)**	1.06 (0.96-1.17)
Moderate or severe liver disease, yes(vs no)	2.25 (1.95-2.59)**	1.43 (1.23-1.67) **	1.78 (1.48-2.12)**	1.21 (1.00-1.46)*
Clinical stage				
I	Ref.	Ref.	Ref.	Ref.
II	1.70 (1.62-1.78)**	1.59 (1.52-1.67)**	2.24 (2.10-2.39)**	2.12 (1.99-2.26)**
III	1.79 (1.71-1.86)**	1.76 (1.69-1.84)**	2.71 (2.56-2.87)**	2.68 (2.52-2.83)**
IV	9.07 (8.71-9.44)**	9.21 (8.84-9.59)**	16.51 (15.62-17.45)**	16.69 (15.79-17.64)**

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.
*$P < .05$; ** $P < .001$.

showed similar results, wherein the common comorbidities included diabetes, chronic pulmonary disease, and cerebrovascular disease. Our study was slightly different from the study of Fowler et al,[25] who found that peptic ulcer disease was a common comorbidity in colon, rectosigmoid, and rectal cancers. Peptic ulcer disease was not frequently mentioned when surveying cancer comorbidities. Søgaard et al[26] surveyed whether peptic ulcers could predict other gastrointestinal cancers and found that the highest absolute risk was for colon cancer. The possible mechanism was potentially related to *Helicobacter pylori* infection or patients who shared lifestyle factors. Peptic ulcer disease is not only a common comorbidity in colon cancer but

Table 3. The 5-year overall and cancer-specific mortality risk ratio of patients with proximal and distal colon cancer compared with RSJ and rectum cancers patients stratified by different sex and age groups.

PATIENTS WITH PROXIMAL AND DISTAL COLON VS PATIENTS WITH RSJ AND RECTUM CANCERS (REFERENCE GROUP)	OVERALL MORTALITY; AHR[A] (95% CI)	*P*-VALUE	CANCER-SPECIFIC MORTALITY; AHR[A] (95% CI)	*P*-VALUE
Sex				
Male	1.01 (0.99-1.04)	.3284	1.00 (0.96-1.03)	.7791
Female	1.04 (1.01-1.08)*	.0219	1.04 (1.00-1.08)	.0667
Age group				
<50 years	1.07 (0.99-1.15)	.0770	1.08 (1.00-1.16)	.0623
50-59 years	1.01 (0.96-1.07)	.6188	1.01 (0.95-1.08)	.6883
60-69 years	0.97 (0.92-1.02)	.2767	0.98 (0.92-1.03)	.3823
⩾70 years	1.04 (1.01-1.08)*	.0061	1.02 (0.98-1.05)	.3492

Abbreviations: CI, confidence interval; RSJ, rectosigmoid junction.
[a]AHR, adjusted hazard ratio by age, sex, commodities, and cancer clinical stages, excluding the selected stratified groups.
*$P < .05$; **$P < .001$.

also predicts the risk of colon cancer. Another study also found that *H pylori* infection can potentially increase the risk of peptic ulcer disease and colon cancer.[27] In addition, individuals with a lifestyle of dietary fiber intake also play an important role in peptic ulcer diseases[28] and colon cancer, which is inversely related to the risk of proximal and distal colon cancers.[29]

Impact of age and comorbidities on prognosis

Age was a significant predictor of mortality in patients with colorectal cancer.[2] In our study, we found no significant difference in mortality between proximal/distal colon cancer and RSJ/rectal cancers in patients aged ⩽ 69 years. In patients aged > 69 years, proximal and distal colon cancer increased mortality with an AHR of 1.04 (95% CI: 1.01-1.08) compared with RSJ and rectal cancers. Comorbidities are predictors of survival in colon, RSJ, and rectal cancers.

Different comorbidity scores based on the diagnostic codes in administrative data have been used in previous studies to evaluate the prognosis of colon cancer, including the Adult Comorbidity Index,[3] age-adjusted Charlson comorbidity index scores,[30] Charlson comorbidity score,[5,31,32] American Society of Anesthesiologists Physical Status classification score, and sum of diseased organ systems.[33]

We assessed the prevalence of comorbidities and calculated the relative risk for each comorbidity using a Cox proportional hazard regression model by age group. The impact of mortality, assessed as comorbid conditions, increased across the 4 age strata in both the study and comparison cohorts. We found that the influence of comorbidities on overall survival among older colon cancer patients was more important than that among younger patients. In patients aged less than 50 years, only 2 comorbidities (peptic ulcer disease and mild liver disease) had an impact on mortality. In patients aged > 60 years, 8 comorbidities contributed to the risk of mortality in patients with proximal/distal colon and RSJ/rectal cancer. The impact of comorbidity could increase with age in elderly patients because they have less physiological reserves and are less able to maintain physiological and emotional stress.[34] The psychological functions of elderly patients with existing comorbidities often interfere with disease prognosis and outcomes.[35] Therefore, the association between the stress of diseases and age may result in poorer overall survival.

Impact of sex and comorbidities on prognosis

Yamano et al[6] showed the influence of comorbidities on the prognosis of colorectal cancer in elderly patients and found that the risk factors for mortality included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, mild liver disease, diabetes without end-organ damage, hemiplegia, and moderate or severe renal disease. Our study showed similar results, but there were some differences. We further assessed the influence of sex and comorbidities on the prognosis of colon cancer and found that congestive heart failure had a significant impact on mortality in female patients but not in male patients. Mild liver disease and diabetes without complications had a significant impact on mortality in male patients but not in female patients. Comorbidities were associated with sex-related differences in colon cancer mortality. Although generalizations can be made about sex differences in comorbidities and mortality rates, most differences cannot be delineated using a simple method that describes the differences

Table 4. Overall risk factor analysis of 5-year overall and cancer-specific mortality based on the Cox proportional hazard regression model stratified by cancer sidedness.

	OVERALL MORTALITY		CANCER-SPECIFIC MORTALITY	
	PROXIMAL AND DISTAL COLON	RECTOSIGMOID JUNCTION AND RECTUM	PROXIMAL AND DISTAL COLON	RECTOSIGMOID JUNCTION AND RECTUM
	AHR (95% CI)	AHR (95% CI)	AHR (95% CI)	AHR (95% CI)
Age group				
<50 years	0.49 (0.46-0.51)**	0.47 (0.44-0.50)**	0.58 (0.55-0.61)**	0.56 (0.52-0.60)**
50-59 years	0.46 (0.44-0.48)**	0.46 (0.44-0.49)**	0.54 (0.51-0.56)**	0.54 (0.05-0.57)**
60-69 years	0.51 (0.49-0.53)**	0.53 (0.50-0.55)**	058 (0.55-0.60)**	0.58 (0.55-0.61)**
⩾70 years	Ref.		Ref.	Ref.
Sex, male (vs females)	1.08 (1.05-1.11)**	1.12 (1.08-1.17)**	1.01 (0.97-1.04)	1.06 (1.02-1.10)*
Comorbidities				
Myocardial infarction, yes (vs no)	1.22 (1.01-1.48)*	1.10 (0.89-1.38)	1.05 (0.80-1.36)	0.90 (0.67-1.22)
Congestive heart failure, yes (vs no)	1.12 (1.02-1.25)*	1.23 (1.09-1.40)*	1.03 (0.90-1.18)	1.07 (0.81-1.26)
Peripheral vascular disease, yes (vs no)	1.09 (0.92-1.30)	0.86 (0.70-1.06)	1.21 (0.97-1.50)	0.78 (0.59-1.03)
Cerebrovascular disease, yes (vs no)	1.18 (1.08-1.30)**	1.14 (1.01-1.28)*	1.08 (0.96-1.21)	1.09 (0.94-1.26)
Dementia, yes (vs no)	1.17 (1.03-1.33)*	1.28 (1.10-1.49)*	1.17 (0.99-1.37)	1.22 (1.01-1.47)*
Chronic pulmonary disease, yes (vs no)	1.15 (1.05-1.25)*	1.22 (1.10-1.35)**	0.96 (0.86-1.07)	1.09 (0.96-1.24)
Rheumatic disease, yes (vs no)	0.85 (0.63-1.14)	1.18 (0.80-1.73)	0.83 (0.58-1.18)	1.29 (0.83-2.02)
Peptic ulcer disease, yes (vs no)	1.21 (1.12-1.31)**	1.24 (1.13-1.36)**	1.22 (1.11-1.34)**	1.28 (1.15-1.43)**
Mild liver disease, yes (vs no)	1.06 (0.96-1.17)	1.09 (0.97-1.22)	0.91 (0.81-1.02)	0.98 (0.86-1.13)
Diabetes without complications, yes (vs no)	1.10 (1.01-1.19)*	1.11 (1.01-1.22)*	1.10 (1.00-1.22)	1.09 (0.97-1.22)
Diabetes with complications, yes (vs no)	0.92 (0.81-1.06)	1.05 (0.89-1.22)	0.77 (0.64-0.92)*	1.01 (0.83-1.22)
Paraplegia and hemiplegia, yes (vs no)	1.01 (0.80-1.26)	1.15 (0.87-1.52)	1.07 (0.81-1.40)	1.12 (0.80-1.56)
Renal disease, yes (vs no)	1.13 (1.03-1.25)*	1.26 (1.12-1.42)**	0.98 (0.86-1.12)	1.19 (1.02-1.37)*
Moderate or severe liver disease, yes (vs no)	1.50 (1.23-1.82)**	1.37 (1.11-1.72)*	1.05 (0.80-1.38)	1.40 (1.08-1.82)*
Clinical stage				
I	Ref.	Ref.	Ref.	Ref.
II	1.62 (1.52-1.73)**	1.56 (1.46-1.67)**	2.37 (2.16-2.59)**	1.92 (1.76-2.10)**
III	1.73 (1.63-1.83)**	1.83 (1.72-1.95)**	2.85 (2.62-3.10)**	2.60 (2.40-2.82)**
IV	9.66 (9.14-10.20)**	8.58 (8.08-9.11)**	19.45 (17.96-21.07)**	14.00 (12.95-15.13)**

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval.
*$P < .05$; **$P < .001$.

in all historical periods and countries. Sex differences in the prevalence of diseases, biological conditions, and physical status lead to different prognoses.[36] The prevalence of comorbidities in colorectal cancer could be related to the fact that some comorbidities may be related to diet or lifestyle, which have an impact on colon cancer.[37-39] In particular, infrequent fruit or vegetable intake and excessive meat consumption may increase the risk of colon cancer.[37,38] In addition, smoking is a common risk factor for peptic ulcer disease and increases the risk of colon cancer and their prognosis.[40] Alcohol consumption is associated with liver disease, peptic ulcer disease, and increased risk of colon and rectal cancers compared with no alcohol consumption.[41] Therefore, dietary pattern and lifestyle could lead to diabetes, hypertension, dyslipidemia, heart disease, gallbladder disease, etc., and the risk of comorbidities may cause joint effects in patients with colorectal cancer.[42]

Location of cancer on prognosis

Proximal and distal colon cancer had slightly higher mortality with an AHR of 1.03 (95% CI:1.00-1.05) than RSJ and rectal cancers. Both groups shared the most comorbidities that increased mortality, except that myocardial infarction increased mortality in proximal and distal colon cancer but not in RSJ and rectal cancers. Although analysis has shown that the prognosis of left-sided colon cancer is better than that of right-sided colon cancer,[43-45] some possible reasons are that right-sided colon cancer has a more advanced stage, mucinous tumors, and are more evident in older patients. In our study, proximal and distal cancers had poor prognoses. The reason for this could be that proximal and distal colon cancer is often associated with obscure bleeding, few changes in bowel habits, and bowel obstruction observed in the late stages.[46,47] Patients with proximal and distal colon cancer seek medical assistance later than those with RSJ and rectal cancers. Another factor is that sigmoidoscopy is less invasive than colonoscopy, with bowel preparation being less complicated and less painful for patients. Patients may more frequently and easily undergo sigmoidoscopy leading to earlier detection of the disease.

Cuthbert et al[48] surveyed colorectal cancer patients with stages I-III and divided the patients into 5 mutually exclusive comorbid groups. They found that patients with cardiovascular disease and diabetes had the worst prognoses. Another study enrolled 392 patients with colon cancer and 143 patients with rectal cancer, and showed that age and comorbidity were predictors of survival in colon cancer but not predictors for survival in rectal cancer.[2] The Colorectal Cancer South Africa study showed that comorbidities are uncommon and have no significant impact on survival. A study used hospital discharge registry data to identify patients with colorectal cancer and found that Charlson comorbidity scores were associated with mortality.[49] These studies, which focused on colon and rectal cancers, had controversial results regarding comorbidities and mortality, study population with heterogeneous enrollment criteria, and definitions of comorbidities. We divided our population into proximal/distal colon cancer and RSJ/rectal cancer according to tumor location. We found that comorbidity had a substantial impact on survival in patients with cancer at different locations.

Limitations

This study had some limitations. First, we had limited information regarding chemotherapy and patient clinical responses, which might have influenced prognosis. In addition to social and nutritional status, molecular information for this group of patients is also lacking. Moreover, another major limitation was that patients with colon cancer may die for any reason. Although cancer-specific mortality was also estimated in this study, the causes of death from comorbidities remain an interesting issue. To understand whether the patients died of comorbidities or cancer itself, Supplementary Table 3 presents the causes of death from cancers and comorbidities among all study subjects to reduce the potential bias in estimating outcome. Finally, the location of upper and lower rectal cancers could not be identified using ICD-O-3. The potential mortality difference in the tumor sites of colon and rectum cancer should be subdivided slightly to explore using other ways in future research.

Conclusions

In conclusion, the location of colorectal cancer was significantly associated with mortality. Because RSJ may be treated as rectal cancer, we found that proximal/distal cancers had a worse prognosis than RSJ/rectum cancers using the population database. In addition, age and comorbidities are significant predictors of prognosis in patients with proximal/distal cancer and RSJ/rectal cancers. In colorectal cancer patients with comorbidities, the negative impact on survival increased over time. Comorbidities had different impacts on mortality according to age, sex, and colon cancer at different locations. It is important to remind the physician to care for the intensity of surveillance colonoscopy on the above risk factors and to acknowledge the comorbidities of their patients in their cancer treatment plans.

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Author Contributions

S.-C.Y. and Y.-L.S. contributed to conceptualization; S.-C.Y., K.-M.L., C.-H.H., and Y.-L.S. contributed to methodology; C.-H.H. contributed to formal analysis; C.-L.C. and C.-H.H. contributed to visualization; S.-C.Y., K.-M.L., C.-L.C., and Y.-L.S. contributed to writing—original draft preparation; Y.-F.T., C.-H.H., and Y.-L.S. contributed to writing—review and editing; and C.-L.C., Y.-F.T., and C.-H.H. contributed to funding acquisition. All authors have read and agreed to the published version of the .

Data Availability Statement

The data sources are the Taiwan Nation Health Insurance Database and Taiwan Cancer Registry. The data are available with the permission from Taiwan Health and Welfare Data Science Center (https://dep.mohw.gov.tw/DOS/np-2497-113.html, accessed on 20 Dec 2021). Restrictions apply to the availability of these data, which were used under license for this study.

Institutional Review Board Statement

This study was conducted in compliance with the Declaration of Helsinki and has been approved by the Research Ethics Committee of Chi Mei Hospital (IRB no. 10912-E04). In addition, patient informed consent was waived by Research Ethics Committee of Chi Mei Hospital.

Informed Consent Statement

Patient consent was waived because the NHIRD contains anonymized information only.

Supplemental Material

Supplemental material for this article is available online.

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