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Competitive Risk Analysis of Prognosis in Patients With Cecum Cancer: A Population-Based Study

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Abstract

Background: The presence of competing risks means that the results obtained using the classic Cox proportional-hazards model for the factors affecting the prognosis of patients diagnosed with cecum cancer (CC) may be biased.

Objective: The purpose of this study was to establish a competitive risk model for patients diagnosed with CC to evaluate the relevant factors affecting the prognosis of patients, and to compare the results with the classical COX proportional risk model.

Methods: We extracted data on patients diagnosed with CC registered between 2004 and 2016 in the Surveillance, Epidemiology, and End Results (SEER) database. The univariate analysis utilized the cumulative incidence function and Gray's test, while a multivariate analysis was performed using the Fine-Gray, cause-specific (CS), and Cox proportional-hazards models.

Results: The 54463 eligible patients diagnosed with CC included 24387 who died: 12087 from CC and 12300 from other causes. The multivariate Fine-Gray analysis indicated that significant factors affecting the prognosis of patients diagnosed with CC include: age, race, AJCC stage, differentiation grade, tumor size, surgery, radiotherapy, chemotherapy and regional lymph nodes metastasis. Due to the presence of competitive risk events, COX model results could not provide accurate estimates of effects and false-negative results occurred. In addition, COX model misestimated the direction of association between regional lymph node metastasis and cumulative risk of death in patients diagnosed with CC. Competitive risk models tend to be more advantageous when analyzing clinical survival data with multiple endpoints.

Conclusions: The present study can help clinicians to make better clinical decisions and provide patients diagnosed with CC with better support.

Keywords

cecum cancer, competing-risks model, SEER, fine-gray model, cause-specific model, colorectal cancer, laterality differences

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Introduction

Colorectal cancer (CRC) is the third-most-common malignant tumor and the fourth leading cause of cancer-related deaths worldwide,[1] and hence is a cancer of worldwide concern. It has been reported that 1.65 million new cases of CRC and nearly associated 835,000 deaths occurred in 2015. The incidence and mortality are both higher in males than in females.[2] Although the incidence and mortality of CRC are slowly declining in the US, CRC remains the third-most-common cancer and the second leading cause of cancer-related deaths among males and females in the US.[3]

Cecum cancer (CC) is reported to account for about 20% of colorectal cancers.[4] It's worth noting that because the symptoms of early CC are often nonspecific, many patients diagnosed with CC are already in the middle and advanced stages of cancer at the time of diagnosis.[5] Compared with other colorectal cancers, patients diagnosed with CC often have a poor prognosis. In addition, epidemiological studies have shown that the incidence of left-side colorectal cancers (LCCs) is steadily declining, while the incidence of right-side colorectal cancers (RCCs) has increased.[6,7] The incidence of primary CC has increased the most. Compared with patients with LCCs, patients with RCCs showed significant exogenous pathological behavior and lower overall survival.[8-10] CC and ascending colon cancer (ACC) are the 2 main types of cancer in RCCs. Although both the CC and ACC are thought to originate in the midgut, there may be differences between adenocarcinomas of the 2 types of cancers due to their different locations of origin and developmental processes. The prognosis for patients diagnosed with CC is still worse than for those with ACC, which means that patients diagnosed with CC need to bear more disease burden, according to a recent study.[11] Therefore, explorations of the risk factors that affect the prognosis of patients diagnosed with CC will help clinicians to develop personalized diagnosis and treatment programs that will be beneficial to these patients.

Kaplan-Meier marginal regression and the Cox proportional-hazards model are widely used to identify prognostic risk factors in patients diagnosed with CC.[12-14] In the current era of greater emphasis on personalized cancer treatments, it is important to determine the impact that both cancer and noncancer factors have on patient mortality. In fact, cancer is only one of the causes of death in cancer patients. Suicides, traffic accidents, and deaths from other diseases are also often reported as causes of cancer patients' deaths.[15,16] Noncancer factors on patient mortality is often considered a competitive risk event when studying factors that influence the prognosis of cancer patients. However, when competing risk events are present, multiple endpoints often coexist and compete with each other to produce competing-risks data.[17-19] The presence of multiple endpoint events will produce biased results in a single-endpoint analysis of the estimated probabilities of endpoint events due to competing risks.[20-22] For this reason, the use of competitive risk model to analyze the risk factors affecting the prognosis of patients diagnosed with CC and to compare the results with the traditional survival analysis method is more helpful to discover the true effect of variables and to determine the relevant risk factors more accurately.

The study used data from the Surveillance, Epidemiology, and End Results (SEER) database to conduct a competing-risks analysis of patients diagnosed with CC with the aim of comparing the results of the competitive risk model with those of the COX proportional hazard model to determine more accurate factors influencing the prognosis of patients diagnosed with CC.

Materials and Methods

Data Collection and Patient Selection

Data on patients diagnosed with CC were extracted from the SEER database using the SEER*Stat software (version 8.3.6).[23] The SEER program has collected demographic, clinical, and outcome information on all cancer diagnoses in a representative geographic area and subpopulation of the US that covers 30% of the US population from 18 registries across the country. We searched the SEER registry for all cases of CC using ICD-O-3 tumor-site diagnostic code C18.0. We then used the SEER*Stat software to obtain records on patients who were registered from 2004 to 2016, including demographic data, primary tumor location, Tumor Size (TS), AJCC stage at diagnosis, surgery status, radiotherapy status, chemotherapy status, regional lymph node metastasis, and life status. The TS was divided into 4 groups: TS I (Largest dimension, or the diameter less than or equal to 1 cm), TS II (Largest dimension, or the diameter greater than 1 cm and less than or equal to 3 cm), TS III (Largest dimension, or the diameter greater than 3 cm and less than or equal to 5 cm) and TS IV (Largest dimension, or the diameter more than 5 cm).The exclusion criteria were (1) no surgery, diagnosis, or microscopy confirmation, (2) age $\leq$18 years, (3) only autopsy findings, or (4) incomplete variables. All patients were followed up for cecum-cancer-specific death, competing events, and deletions based on the SEER etiological specific death classification and life-status record entries in the SEER database. The application of these criteria resulted in 54463 patients being included in this study.

Statistical Analyses

The baseline data were described using number and percentage values. We analyzed competing risks by treating death from other tumors and death from nontumor causes as competing events. The cumulative-risk rate was estimated in the single-factor analysis using the cumulative incidence function (CIF) as $\mathrm{CIF}k(t) = \Pr(T \leq t, D = k)$, where function $\mathrm{CIF}k(t)$ represents the probability of the k-th event occurring before time t and other class events, and D represents the type of events that occur. Gray's test was used to perform between-group comparisons.[24] The multifactor analysis used the following 2 different competing-risks models to explore mortality in the CC: (1) the Fine-Gray model (also known as

the subdistribution hazard function) and (2) the cause-specific (CS) model.[17,22,25] We compared the results obtained in the multifactor analysis with those from the traditional Cox proportional-hazards model, since Cox regression might not accurately estimate the risk of a particular event when competing risks exist. When no competing risk event is present, the formula for the Cox proportional-hazards model is $\log[\lambda(t)]=\log[\lambda 0(t)]+ X\beta^2$, where $\lambda(t)$ is the net risk and $\lambda 0(t)$ is the baseline risk function; that is, the risk function when the covariate vector is 0, which can be written as $\lambda(t)=\lambda 0(t)\exp(X\beta)$. When there are competing risk events and the deletion-independence condition is not satisfied, we provide the results of both the Fine-Gray and CS competing-risks models.

The formula used for the Fine-Gray model was $\lambda_K^{SD}(t) = \lim_{\Delta t\to 0}\frac{P[t\le T<t+\Delta t, D=k|T>t\cup(T<t\cap K\neq k)]}{\Delta t}$, where *SD* represents the instantaneous probability of the occurrence of the *k*-th event being observed in the individual at time *t*. The formula used for the CS model was $\lambda_K^{CS}(t) = \lim_{\Delta t\to 0}\frac{P(t\le T<t+\Delta t, D=k|T\ge t)}{\Delta t}$, where *CS* represents the instantaneous probability of a class-*k* event being observed in the individual who did not experience any event at time *t*. The Fine-Gray model is suitable for establishing a clinical prediction model and predicting the risk only of a single endpoint of interest. In contrast, the CS model is suitable for answering etiological questions, and the regression coefficient reflects the relative effect of covariates on the increased incidence of the main endpoint in the target event-free risk set.[26]

All statistical analyses were performed using SAS software (version 9.4, SAS Institute) and Stata statistical software (version 15.0). All statistical tests were 2-sided, with a probability value of $P < 0.05$ considered to indicate statistical significance. The SEER database can be accessed free of charge, and this study was exempted from the need to obtain informed consent from the included patients by the institutional research committee of the First Affiliated Hospital of Xi'an Jiaotong University.

Results

Patient Characteristics

The 54463 eligible patients diagnosed with CC included 24387(44.78%) who died (12087 from CC and 12300 from other causes), with 30076(55.22%) patients being alive (Table 1).

Most of the patients who death from CC were older than 65 years ($n = 8187$, 66.73%), male ($n = 6342$, 52.47%), white ($n = 9691$, 80.18%), had received surgery ($n = 11702$, 96.81%), had not received radiation therapy ($n = 8744$, 72.34%), had not received chemotherapy ($n = 9819$, 81.24%), were differentiation grade II ($n = 7018$, 58.06%), were AJCC stage IV ($n = 5352$, 44.28%), had a TS of greater than 5cm(TS IV) ($n = 6031$, 49.90%), and had regional lymph node metastasis ($n = 9041$, 74.80%).

Results of the Univariate Analysis

The univariate analysis included applying Gray's test and the CIF. When competing risks were present, the results of Gray's test showed that age, sex, race, AJCC stage, differentiation grade, tumor size, surgery status, radiation status, chemotherapy status and regional lymph nodes metastasis significantly affected the prognosis of CC ($P < 0.05$). The CIF for almost all variables increased over 1, 3, and 5 years, and were higher for the elderly and in patients diagnosed with CC who were black, male, AJCC stage IV, and differentiation grade IV, had not received surgery, and had a larger tumor, had received chemotherapy, had received radiotherapy, and had regional lymph nodes metastasis. The data are presented in detail in Table 2.

Results of the Multivariate Analysis

The factors that were statistically significant in the univariate analysis ($P < 0.05$) were added to the Cox regression model and the competing-risks model for the multivariate analyses.

The results obtained from the Cox proportional-hazards model showed that the independent risk factors affecting the prognosis of CC included age, race, AJCC stage, differentiation grade, tumor size, surgery status, radiation status, chemotherapy status and regional lymph nodes metastasis. The prognosis is worse for patients diagnosed with CC with the characteristic of age at diagnosis >65 years [vs age at diagnosis ≤65 years: hazard ratio (HR) = 1.98, 95% confidence interval (CI) = 1.92-2.04, $P < 0.001$]. Compared with whites, blacks had a worse prognosis (vs white: HR = 1.09, 95% CI = 1.05–1.13, $P < 0.001$), but other races had a better prognosis (vs white: HR = 0.83, 95% CI = 0.78-0.88, $P < 0.001$). The risk of poor prognosis was positively correlated with the AJCC stage, the patients diagnosed with CC at the AJCC stage IV had the worst prognosis(vs AJCC stage I: HR = 6.10, 95% CI = 5.65-6.60, $P < 0.001$), followed by AJCC stage III(vs AJCC stage I: HR = 1.57, 95% CI = 1.44-1.70, $P < 0.001$) and AJCC stage II(vs AJCC stage I: HR = 1.30, 95% CI = 1.25–1.36, $P < 0.001$). Similarly, patients with higher differentiation grade had worse prognosis, such as differentiation grade III (vs differentiation grade I: HR = 1.37, 95% CI = 1.30-1.45, $P < 0.001$) and differentiation grade IV (vs differentiation grade I: HR = 1.53, 95% CI = 1.41-1.65, $P < 0.001$), but the differentiation grade II had no significant statistical significance. For CC patients, surgery, radiotherapy and chemotherapy are 3 common treatment methods. The results showed that surgery (vs no surgery: HR = 0.32, 95% CI = 0.30-0.35, $P < 0.001$), radiotherapy (vs no radiotherapy: HR = 0.53, 95% CI = 0.51-0.55, $P < 0.001$) and chemotherapy (vs no chemotherapy: HR = 0.56, 95% CI = 0.54-0.58, $P < 0.001$) had different degrees of positive impact on the prognosis of patients. In addition, COX model results suggested that patients with larger tumors might have a worse prognosis, especially patients in TS IV group (vs TS I: HR = 1.36, 95% CI = 1.24-1.49, $P < 0.001$), but patients with regional lymph

Table 1. Baseline Characteristics of Patients.

Variable	All patients (%)	Concerned (%)	Competition (%)	Censored (%)
N	54463	12087	12300	30076
Age				
≤65	16292(29.91)	3900(32.27)	1363(11.08)	11029(36.67)
>65	38171(70.09)	8187(67.73)	10937(88.92)	19047(63.33)
Sex				
male	28442(52.22)	6342(52.47)	6154(50.03)	15946(53.02)
female	26021(47.78)	5745(47.53)	6146(49.97)	14130(46.98)
Race				
white	44885(82.41)	9691(80.18)	10633(86.45)	24561(81.66)
black	6645(12.20)	1735(14.35)	1236(10.05)	3674(12.22)
other	2933(5.39)	661(5.47)	431(3.50)	1841(6.12)
AJCC Stage				
I	11478(21.07)	549(4.54)	2698(21.93)	8231(27.37)
II	16691(30.65)	1854(15.34)	4162(33.84)	10675(35.49)
III	17364(31.88)	4332(35.84)	3728(30.31)	9304(30.93)
IV	8930(16.40)	5352(44.28)	1712(13.92)	1866(6.21)
Surgery				
yes	53739(98.67)	11702(96.81)	12100(98.37)	29937(99.54)
no	724(1.33)	385(3.19)	200(1.63)	139(0.46)
Chemotherapy				
yes	6199(11.38)	2268(18.76)	1061(8.63)	2870(9.54)
no	48264(88.62)	9819(81.24)	11239(91.37)	27206(90.46)
Radiotherapy				
yes	11591(21.28)	3343(27.66)	1312(10.67)	6936(23.06)
no	42872(78.72)	8744(72.34)	10988(89.33)	23140(76.94)
Differentiation Grade				
I	4342(7.97)	572(4.73)	1009(8.20)	2761(9.18)
II	36023(66.15)	7018(58.06)	7949(64.63)	21056(70.01)
III	12141(22.29)	3893(32.21)	2924(23.77)	5324(17.70)
IV	1957(3.59)	604(5.00)	418(3.40)	935(3.11)
Tumor size				
I	1969(3.62)	119(0.98)	383(3.12)	1467(4.88)
II	10704(19.65)	1570(12.99)	2552(20.75)	6582(21.88)
III	19761(36.28)	4367(36.13)	4645(37.76)	10749(35.74)
IV	22029(40.45)	6031(49.90)	4720(38.37)	11278(37.50)
Regional lymph nodes metastases				
yes	25016(45.93)	9041(74.80)	5144(41.82)	10831(36.01)
no	29447(54.07)	3046(25.20)	7156(58.18)	19245(63.99)

Note: Concerned: Patients who died of cecum cancer; Competition: Patients who died of competitive risk events; Censored: Patients who are alive; Tumor size I: Largest dimension, or the diameter less than or equal to 1cm; Tumor size II: Largest dimension, or the diameter greater than 1cm and less than or equal to 3cm; Tumor size III: Largest dimension, or the diameter greater than 3cm and less than or equal to 5cm; Tumor size IV: Largest dimension, or the diameter more than 5 cm.

node metastasis might have a better prognosis (vs no regional lymph node metastasis: HR = 0.92, 95% CI = 0.89-0.96, $P < 0.001$). Table 3 showed more detailed information.

The results from the Fine-Gray model showed that the independent risk factors for survival in patients diagnosed with CC included age, race, AJCC stage, differentiation grade, tumor size, surgery status, radiation status, chemotherapy status and regional lymph nodes metastasis. In the results of the competitive risk model, age was still an independent risk factor for the prognosis of patients diagnosed with CC, and patients with age diagnosed >65 years were more likely to have a poor prognosis (vs age at diagnosis ≤65 years HR = 1.07, 95% CI = 1.03–1.11, $P = 0.0011$). Blacks (vs white HR = 1.16, 95% CI = 1.10-1.23, $P < 0.001$) still had the highest risk among people of different races, but no statistically significant difference was found for other races. Lower AJCC stage were associated with better prognosis, obviously, patients in AJCC stage II(vs AJCC stage I: HR = 2.08, 95% CI = 1.89-2.30, $P < 0.001$), AJCC stage III(vs AJCC stage I: HR = 3.76, 95% CI = 3.31-4.28, $P < 0.001$) and AJCC stage IV(vs AJCC stage I: HR = 13.33, 95% CI = 11.78-15.08, $P < 0.001$) had a higher cumulative risk of death than patients in AJCC stage I. A higher level of differentiation grade is not conducive to the prognosis of patients diagnosed with CC, for example, patients in differentiation grade II(vs differentiation grade I: HR = 1.14, 95% CI = 1.05-1.24, $P < 0.001$), differentiation grade III(vs differentiation grade I: HR = 1.45, 95% CI = 1.33-1.59, $P < 0.001$) and differentiation grade IV (vs differentiation grade I: HR = 1.46, 95% CI

Table 2. Univariate Analysis of Prognostic Factors in Patients With Cecum Cancer.

Variable	**Gray's test**	p-value	CIF		
			12-months	36-months	60-months
Age	42.61	<0.001			
≤65			0.087	0.231	0.286
>65			0.117	0.204	0.24
Sex	4.27	0.0389			
male			0.111	0.214	0.256
female			0.105	0.209	0.25
Race	83.05	<0.001			
white			0.107	0.206	0.245
black			0.119	0.249	0.303
other			0.108	0.222	0.266
AJCC Stage	13027.37	<0.001			
I			0.022	0.037	0.049
II			0.045	0.093	0.122
III			0.101	0.229	0.291
IV			0.351	0.624	0.689
Surgery	816.15	<0.001			
yes			0.104	0.207	0.249
no			0.426	0.607	0.624
Chemotherapy	501.49	<0.001			
yes			0.115	0.311	0.388
no			0.107	0.198	0.234
Radiotherapy	541.14	<0.001			
yes			0.103	0.297	0.373
no			0.11	0.19	0.224
Differentiation Grade	1246.78	<0.001			
I			0.057	0.117	0.146
II			0.081	0.18	0.226
III			0.189	0.317	0.353
IV			0.218	0.336	0.375
Regional lymph nodes metastases	5575.46	<0.001			
yes			0.181	0.356	0.419
no			0.047	0.089	0.114
Tumor size	1076.22	<0.001			
I			0.027	0.054	0.068
II			0.058	0.131	0.167
III			0.099	0.207	0.251
IV			0.148	0.268	0.314

Abbreviations: CIF, Cumulative incidence function; AJCC, American Joint Committee on Cancer.
Note: Tumor size I: Largest dimension, or the diameter less than or equal to 1cm; Tumor size II: Largest dimension, or the diameter greater than 1cm and less than or equal to 3cm; Tumor size III: Largest dimension, or the diameter greater than 3cm and less than or equal to 5cm; Tumor size IV: Largest dimension, or the diameter more than 5 cm.

=1.30-1.65, $P < 0.001$) might bear a higher cumulative risk of death. Surgery(vs no surgery: HR = 0.50, 95% CI = 0.44-0.57, $P < 0.001$), radiotherapy(vs no radiotherapy: HR = 0.74, 95% CI = 0.70-0.77, $P < 0.001$) and chemotherapy(vs no chemotherapy: HR = 0.88, 95% CI = 0.84-0.92, $P < 0.001$) can help improve the prognosis of patients diagnosed with CC, but larger tumors may lead to poor prognosis TS II (vs TS I: HR = 1.35, 95% CI = 1.12-1.63, $P < 0.001$), TS III(vs TS I: HR = 1.60, 95% CI = 1.33-1.93, $P < 0.001$), TS IV(vs TS I: HR = 1.80, 95% CI = 1.49-2.16, $P < 0.001$)). Interestingly, in the COX model, regional lymph node metastasis was a protective factor for poor prognosis in CC patients, but the Fine-Gray model showed that patients with regional lymph node metastasis (vs no regional lymph node metastasis: HR = 1.08, 95% CI = 1.03-1.15, $P = 0.0258$) had a higher cumulative risk of death. The results of the CS model are similar to those of the Fine-Gray model, and the outcomes and risk factors have the same correlation direction with the Fine-Gray model, only different at the level of point estimation. More details can be obtained from Table 3.

Discussion

CRC is one of the most-common cancers worldwide, and therefore also of worldwide concern. According to some estimates, the annual incidence of CRC is 1.2 million, and more than 600,000 patients die from this cancer every year.[27,28] Recent studies

Table 3. Multivariate Analysis of 3 Models of Prognostic Factors in Patients With Cecum Cancer.

	Cox model			Fine-gray model			CS model		
Prognostic factors	P-value	HR	95%CI	P-Value	HR	95%CI	P-Value	HR	95%CI
Age									
≤65		reference			reference			reference	
>65	<0.001	1.98	1.92-2.04	0.0011	1.07	1.03-1.11	<0.001	1.30	1.25-1.35
Race									
white		reference			reference			reference	
black	<0.001	1.09	1.05-1.13	<0.001	1.16	1.10-1.23	<0.001	1.17	1.12-1.24
other	<0.001	0.83	0.78-0.88	0.1362	1.06	0.98-1.15	0.9613	1.00	0.93-1.08
AJCC Stage									
I		reference			reference			reference	
II	<0.001	1.30	1.25-1.36	<0.001	2.08	1.89-2.30	<0.001	2.15	1.95-2.37
III	<0.001	1.57	1.44-1.70	<0.001	3.76	3.31-4.28	<0.001	4.03	3.56-4.56
IV	<0.001	6.10	5.65-6.60	<0.001	13.33	11.78-15.08	<0.001	19.66	17.45-22.16
Surgery									
No		reference			reference			reference	
Yes	<0.001	0.32	0.30-0.35	<0.001	0.50	0.44-0.57	<0.001	0.34	0.30-0.37
Radiotherapy									
No		reference			reference			reference	
Yes	<0.001	0.53	0.51-0.55	<0.001	0.74	0.70-0.77	<0.001	0.57	0.55-0.60
Differentiation Grade									
I		reference			reference			reference	
II	0.0582	1.06	1.00-1.11	0.003	1.14	1.05-1.24	<0.001	1.17	1.07-1.27
III	<0.001	1.37	1.30-1.45	<0.001	1.45	1.33-1.59	<0.001	1.62	1.49-1.77
IV	<0.001	1.53	1.41-1.65	<0.001	1.46	1.30-1.65	<0.001	1.77	1.58-1.99
Regional lymph nodes metastasis									
No		reference			reference			reference	
Yes	<0.001	0.92	0.89-0.96	0.0258	1.08	1.03-1.15	0.0335	1.06	1.01-1.12
Chemotherapy									
no		reference			reference			reference	
yes	<0.001	0.56	0.54-0.58	<0.001	0.88	0.84-0.92	<0.001	0.66	0.63-0.70
Tumor Size									
I		reference			reference			reference	
II	0.0034	1.15	1.05-1.26	0.0018	1.35	1.12-1.63	0.0032	1.33	1.10-1.60
III	<0.001	1.27	1.16-1.39	<0.001	1.60	1.33-1.93	<0.001	1.60	1.33-1.93
IV	<0.001	1.36	1.24-1.49	<0.001	1.80	1.49-2.16	<0.001	1.83	1.53-2.21
Sex									
male		reference			reference			reference	
female	0.6613	0.99	0.97-1.02	0.1361	0.97	0.94-1.01	0.0707	0.97	0.93-1.00

Abbreviations: HR, Hazard radio; CI, Confidence interval; CS, Cause-specific hazard.
Note: Tumor size I: Largest dimension, or the diameter less than or equal to 1cm; Tumor size II: Largest dimension, or the diameter greater than 1cm and less than or equal to 3cm; Tumor size III: Largest dimension, or the diameter greater than 3cm and less than or equal to 5cm; Tumor size IV: Largest dimension, or the diameter more than 5 cm.

have shown increases in right-side colorectal cancer both in the US and globally, with this increase being greatest for primary CC. Most of the relevant studies have found that the survival rate is lower for colorectal cancer on the right side than for that on the left, and patients diagnosed with CC had the worst prognosis.[8,11,29] Because of this difference, it is very important to more accurately analyze the risk factors that affect the survival and prognosis of patients diagnosed with CC in the current era of greater emphasis on personalized cancer treatments.[30]

Classic survival analyses (e.g., Kaplan-Meier marginal regression and the Cox proportional-hazards model) generally consider only a single endpoint, such as the impact on patient survival time. However, when competing risk events are present, the use of single-endpoint analysis methods will result in bias in the estimated probabilities of the endpoint events. The present study used a competing-risks model to identify the risk factors affecting the prognosis of patients diagnosed with CC, because such a model takes into account not only deaths caused by CC, but also deaths caused by other types of cancer and other events, as well as their effects. We have presented the results obtained by analyzing 2 competing-risks models: (1) the CS model, which is suitable for etiological studies,[17] and (2) the Fine-Gray model, which is suitable for estimating disease risk and prognostic factors.[31] Because the Fine-Gray model considers other competing endpoint events while

calculating the target endpoint events, its results will be more realistic. In comparison with competitive risk model, we found that in addition to the difference in point estimation, COX model may also misestimate the direction of independent risk factors and outcome correlation. The competitive risk model is more helpful to accurately determine the factors affecting the prognosis of CC patients.

Differences in age distributions exert important effects on survival rates.[30,32] Patients who are older at the time of a diagnosis have a higher risk of death.[30,32] In the Fine-Gray model, compared with those aged ≤65 years, the HR for overall mortality among patients aged >65 years was 1.07 (95% CI = 1.03-1.11). In comparison, both the Cox and CS models overestimated the effect of age on the prognosis of patients diagnosed with CC, which represents evidence of the need to consider the impact of competing risk events in survival analyses in order to avoid bias in the results.

All 3 models suggest that blacks have a worse prognosis than whites, which is consistent with previous findings.[3,33,34] In the United States, racial disparities in access to health insurance and health care are often an important factor in racial disparities in survival.[35,36] Whites tend to have higher rates of health insurance and access to treatment, and more frequent early screening helps improve patient outcomes.[35,37,38] Although COX model results suggest that patients diagnosed with CC of other race may have a better prognosis than whites, neither of the 2 competitive risk models found this effect, and we infer that this result is due to bias due to competitive risk events.

The Fine-Gray model showed that AJCC stage II (HR = 2.08, 95% CI = 1.89-2.30, $P < 0.001$), AJCC stage III (HR = 3.76, 95% CI = 3.31-4.28, $P < 0.001$), and AJCC stage IV (HR = 13.33, 95% CI = 11.78-15.08, $P < 0.001$) were risk factors for death in patients diagnosed with CC compared with AJCC stage I, and this conclusion is consistent with previous research.[39] It is clear that the COX model results underestimate the risks at all AJCC stages. Although this is only a difference in point estimates, the results of competitive risk models are still more accurate.

Similarly, both the Fine-Gray and CS models indicated that the cumulative risk of death increased with the tumor size, whereas Cox regression still underestimated the risk. A previous study of tumor size in patients diagnosed with CRC based on the SEER database also found a negative correlation between tumor size and survival.[40] A recent study of patients with right-side CRC using propensity-score matching showed that the prognosis might be worse in patients with a tumor diameter of <4 cm than in those with a tumor diameter of >4 cm.[41] Those researchers proposed that this could be due to general-colonoscopy screening being more difficult for right-side CRC, and tumors smaller than 4 cm often exhibiting earlier malignant behaviors. Some researchers believe that tumor size has no effect on the prognosis, while others believe that tumor size can affect the prognosis, but other factors exert greater effects.[42-44] Based on these different conclusions, we propose using tumor size as a supplementary indicator that is combined with the results of a pathological examination to determine the prognosis and develop more-effective treatment plans.

We also investigated the effects of different treatment methods on the prognosis of patients diagnosed with CRC. Surgery is currently the most-common clinical treatment,[45] including for CC, but some studies have found that combined treatments such as radiotherapy plus chemotherapy can reduce the risk of death in patients. The 3 models analyzed in the present study showed that surgery, radiotherapy and chemotherapy were independent risk factors for the prognosis and could reduce the risk of death, confirming the findings of previous studies. Among the 3 treatment methods, surgery can reduce the risk of poor prognosis to a greater extent and remains the preferred treatment at present.

Regional lymph node metastasis is believed to be an essential step in tumor cell dissemination in CRC.[46] Although the underlying mechanism is not clear, it is suggested that tumor cells spread from the primary tumor site to the lymph nodes via lymphatic vessels and, consequently, to the next distant organ, therefore, regional lymph node metastasis is often reported as a risk factor for poor prognosis.[47] In present study, the COX model and the competitive risk model presented different results. In the COX model, regional lymph node metastasis was considered to reduce the risk of poor prognosis, while in the competitive risk model, regional lymph node metastasis was considered to be a risk factor for poor prognosis. Obviously, due to the existence of competitive risk events, COX model produces wrong estimates of risk factors, and the use of competitive risk model effectively avoids the occurrence of such errors.

Despite the differentiation grade of cancer having been reported for a long time, it is rarely used as an independent prognostic factor, which is largely due to its inherent variability resulting from the use of different grading systems and the subjective nature of such assessments.[48] The results obtained using all 3 models in the present study showed that higher levels of differentiation may lead to a worse prognosis. The same conclusion was found in another study based on data derived from the SEER database.[49] Only in the results of COX model, differentiation grade II was not found to be statistically significant, and we concluded that this was due to false negatives due to competitive risk events. Since the differentiation grade may be closely related to the degree of tumor invasion and metastasis, we believe that when the same classification criteria are applied, the differentiation level can still be regarded as an independent risk factor for CC.

Finally, many studies have found that the prognosis of CRC patients is closely related to the tumor location, with this possibly being worse for a tumor on the right side.[50] Different sites of colon cancer are attracting more and more attention from researchers. The only report we found on prognostic risk factors in patients with left-side CRC after surgery showed that the prognosis was only related to staging.[8-10,51] CC is one of the most rapidly increasing types of right colon cancer with a poor

prognosis, and our study will contribute to the development of this field.

In previous studies, age, AJCC stage, differentiation grade, surgery status and regional lymph node metastasis have been widely reported as independent risk factors for the prognosis of CC patients, and our study further confirms these conclusions.[14,49,52] In addition, through the competitive risk model, our study also has some new findings compared with previous studies. In a previous study based on the SEER database, the authors used COX regression to identify race as an independent risk factor for prognosis in CC patients and found that other races had a lower risk of poor prognosis compared to whites.[11] This was consistent with the COX model results in our study, but the results of the competitive risk model did not support this conclusion, and we speculated that this may be due to the bias caused by competitive risk events. Similarly, competitive risk models suggest that patients with larger tumors may have a poorer prognosis, but a multicenter CC study from Iran found no association between tumor size and prognosis in CC patients.[52] The deviation of COX model from the estimate of variable effects is one possible reason, on the other hand, the previous study was also limited by the sample size. The effect of adjuvant therapy on the prognosis of CC patients has not been widely reported, and only a few small sample studies suggest that radiotherapy and chemotherapy may contribute to the survival of patients.[53] In present study, based on a larger number of data and competitive risk models, we found that radiotherapy and chemotherapy were related to long-term survival of CC patients and were independent risk factors affecting survival of CC patients.

By comparing the results of the traditional survival analysis method and the competitive risk model, we found that COX model could not provide accurate estimates of the effect value because it only considered the outcome of a single endpoint, and could overestimate or underestimate the effects brought by independent risk factors, and these effects are most commonly seen in right-censored data, which is widely used in survival analysis. In this study, COX models failed to provide accurate estimates of effects, produced false negatives, and misestimated the direction of association between risk factors and outcomes, all of which were effectively avoided by the use of competitive risk models. That is because a competing-risks model establishes the dependency relationship between the incidence and the covariates, which enables a better and more-intuitive explanation of the covariate effect, and standardizes the distribution functions of different types of competing risks. The above observations indicate that the competing-risks model had significant advantages in the multivariate analysis when there were multiple outcome endpoints. It is worth noting that the results of the Fine-Gray model and the CS model in this study have close point estimates, and the correlation direction is the same. However, previous reports also mentioned inconsistent results between the Fine-Gray model and the CS model.[18] Providing the results of 2 competitive risk models at the same time helps to further distinguish the role of risk factors. Generally, CS model is used to study etiological problems, and Fine-Gray model mainly focuses on absolute incidence and is used to construct clinical prediction model and risk score. Therefore, in this study, we mainly adopt the conclusion of Fine-Gray model. In addition, the results of present study suggested that the bias from death of patients, represented by competitive risk events, should be reconsidered when exploring prognostic risk factors in cancer patients.

Our study was based on the large and high-quality SEER database, which increased the accuracy of identifying independent risk factors that affect the prognosis of CC patients. However, it was undeniable that this study had some limitations. First, we used data from the SEER database from 2004 to 2016, and shorter follow-up events may have influenced our estimate of cumulative morbidity. Second, the retrospective design of this study meant that selection bias was difficult to avoid. Third, the prognosis of patients diagnosed with CC might also be related to various other factors such as lifestyle and genes, but there was no way to obtain such information from the SEER database. Therefore, further research was needed to explore other factors.

Conclusion

In summary, this study is the first to establish a competing-risks model based on the SEER database for assessing the prognostic risk factors among patients diagnosed with CC. Compared with COX model, the competitive risk model is more accurate in estimating the effect value. The obtained results will help clinicians to better understand CC and make better clinical decisions that benefit patients in an era of personalized cancer treatment.

Authors' Note

The present study was performed in compliance with the Declaration of Helsinki. Permission was obtained to access the SEER program research data.

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