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Article

A Retrospective Clinical Study on Cardiovascular Complications from Colorectal Cancer

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Abstract

Objective: To investigate the incidence and risk factors of cardiovascular complications amongst patients with colorectal cancer (CRC). **Methods**: A retrospective cohort study was conducted on 2085 patients diagnosed with CRC in two tertiary hospitals in China between 2015 and 2020. The patients' medical records were reviewed to identify cardiovascular complications, including myocardial infarction, heart failure, stroke, hypertension, coronary heart disease, heart failure, and arrhythmia. The incidence rate of cardiovascular complications was calculated, and Cox proportional hazards regression analysis was used to identify risk factors. **Results**: Of the 2085 CRC patients, 329 (15.8%) experienced cardiovascular complications during the follow-up period, with an incidence rate of 17.4 cases per 1000 person-years. The risk was significantly higher in patients who were older than 60 years (adjusted hazard ratio [HR] 2.04, 95% confidence interval [CI] 1.22–3.41), had a higher level of low-density lipoprotein cholesterol (LDL-C) (adjusted HR 2.32, 95% CI 1.31–4.10), had higher levels of serum C-reactive protein (CRP) (adjusted HR 1.57, 95% CI 1.21–2.04), or who underwent chemotherapy or radiotherapy. CRC patients with cardiovascular complications had significantly higher levels of oxidative stress markers, including malondialdehyde (MDA) (5.8 ± 1.2 µmol/L *vs.* 3.4 ± 0.9 µmol/L, $p < 0.001$), lower levels of superoxide dismutase (SOD) (85.2 ± 15.6 U/mg protein *vs.* 112.5 ± 21.3 U/mg protein, $p < 0.001$), and lower levels of glutathione peroxidase (GPx) (15.6 ± 3.2 U/mg protein *vs.* 20.4 ± 4.1 U/mg protein, $p < 0.001$) compared to those without complications. A progressive increase was observed in the proportion of CRC patients with cardiovascular complications over time, rising from 10% in the first year to 38% by the tenth year of follow-up. **Conclusion**: Cardiovascular complications pose a high risk in CRC patients, particularly amongst older patients and those with higher levels of LDL-C or CRP. Regular monitoring of cardiovascular function should be considered in the management of patients with CRC.

Keywords

colorectal cancer; cardiovascular complications; retrospective study; risk factors; incidence rate

Introduction

Recent epidemiological data shows that CRC has become a significant burden in terms of incidence and mortality rates [1–4]. Despite advances in diagnostic and treatment approaches, the overall survival rate of CRC patients remains relatively low, indicating the need for further improvement in management strategies. Notably, cardiovascular events have emerged as important factors that contribute to increased overall mortality in CRC patients [5]. This is evidenced by previous studies showing the impact of cardiovascular events on progression-free survival (PFS) and overall survival (OS) outcomes. Therefore, understanding the incidence and risk factors of cardiovascular complications in CRC patients is crucial for optimizing patient outcomes [6].

Previous studies found that treatment for CRC, including chemotherapy, radiation therapy, and more recently, immune checkpoint inhibitors, can increase the risk of cardiovascular events [7–9]. Phase III clinical trials have reported adverse vascular events in patients with CRC, including myocardial infarction, stroke, and heart failure. These findings highlight the importance of considering cardiovascular events in the management of CRC patients, and highlight the need for further investigation and attention to this issue [10,11].

Furthermore, recent research suggests a potential link between oxidative stress, inflammation, and the development of both cardiovascular disease and CRC. Oxidative stress and inflammation play crucial roles in the pathogenesis of these two conditions, and their interplay may contribute to the increased risk of cardiovascular events in CRC patients [12,13]. Understanding the underlying mechanisms behind this association is vital for developing comprehensive management strategies that address both the cancer and cardiovascular aspects of patient care.

Therefore, investigating the incidence rate and risk factors of cardiovascular complications in patients with CRC is of utmost importance. By identifying and addressing these risk factors, healthcare providers can improve patient outcomes and optimize the overall management of CRC. The aim of this study was therefore to investigate the incidence rate and risk factors of cardiovascular complications in CRC patients.

Methods

Study Design and Participants

This retrospective cohort study was conducted at two tertiary hospitals in China. The study protocol was approved by the institutional review board, and the requirement for informed consent was waived due to the retrospective nature of the study. The study population consisted of 2085 patients diagnosed with CRC between 2015 and 2020.

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) diagnosis of CRC confirmed by histopathology to ensure diagnostic accuracy and consistency among study subjects; (2) patient age of 18 years and older; (3) complete medical records to ensure the study had access to all relevant data and information.

The exclusion criteria were: (1) patients with a previous history of cardiovascular disease or a pre-existing cardiovascular disease prior to CRC diagnosis were excluded, thereby ruling out possible interference and influence of prior cardiovascular disease on the results; (2) incomplete medical records, as this would prevent full assessment and data analysis; (3) patients that had other types of cancer and metastatic carcinoma, as this could interfere with data interpretation. The patient selection procedure is shown in Fig. 1.

Patient Grouping

Patients were categorized into two groups according to the occurrence of cardiovascular complications during the follow-up period. The "no complications group" comprised patients who did not experience any cardiovascular complications during the follow-up period. The "complication group" comprised patients who experienced any of the following cardiovascular complications during follow-up: myocardial infarction, heart failure, stroke, hypertension, coronary heart disease, heart failure, or arrhythmia. Subgroup analysis was performed based on age (<60 years, or 60 years and older), low-density lipoprotein cholesterol (LDL-C) level (<130 mg/dL or >130 mg/dL), C-reactive protein (CRP) level (<10 mg/L or >10 mg/L). The cut-off values for LDL-C and CRP levels were based on established clinical guidelines and prior research [14–16] that identified these thresholds as indicative of increased cardiovascular risk. The treatment groups comprised surgery alone, surgery combined with chemotherapy, and surgery combined with radiation therapy. The main chemotherapy drugs used in this study were fluorouracil, oxaliplatin and capecitabine, while the main chemotherapy regimens used were FOLFOX6 [17] or CapeOX (XELOX) [18].

Patients were divided into subgroups according to baseline characteristics and treatment. Subgroup analysis was performed based on the different treatment modalities received by the patient, thereby allowing investigation of the impact of different treatments on cardiovascular complications. Furthermore, a paired study design was used to match patients who received the same treatment, thus reducing interference due to treatment heterogeneity.

Data Collection

Patient Medical Records

Patient medical records were reviewed to obtain the following information: demographic characteristics (age, sex), clinical features (tumor stage, tumor location), treatment method (surgery, chemotherapy, radiation therapy), comorbidities (diabetes), patient medical history (hypertension, diabetes, kidney disease, other diseases), medication use (prescription medications, over-the-counter medications, supplements). All data were usually obtained through doctor history inquiries and patient self-reports. The follow-up period was from the date of diagnosis to the date of the first cardiovascular complication, death, or the end of the study (December 31, 2020), whichever occurred first.

Laboratory Test Results

Laboratory test results (lipid profile, blood glucose, LDL-C levels, serum CRP levels) were measured in blood samples and performed using a blood biochemical analyzer (LDL-C level). Highly sensitive C-reactive protein (hs-CRP) was evaluated by chemiluminescence [19].

Markers of oxidative stress (malondialdehyde [MDA], superoxide dismutase [SOD], glutathione peroxidase [GPx]) were measured as previously described [20,21]. Oxidative stress levels were assessed by measuring MDA levels (0–2.5 nmol/mL) in blood samples using the thiobarbituric acid reactant method. The MDA concentration is determined by measuring the absorbance of the products. SOD (800–1200 U/mL) levels in blood were measured using an antioxidant activity assay kit (Shanghai Zhenke Biotechnology, Shanghai, China). This is based on evaluating the antioxidant activity of SOD against the reducing agent. GPx (10–100 U/g Hb) levels in blood were measured using a GPx assay kit (Shanghai Renjie Biotechnology, Shanghai, China). This is based on evaluating the antioxidant activity of GPx against the

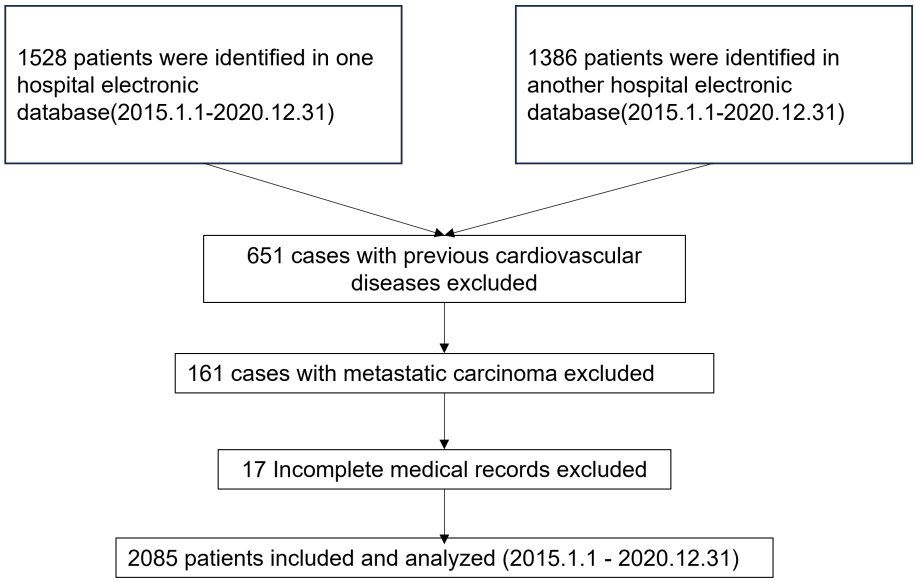

Fig. 1. Patient selection procedure.

reducing agent. The activity of GPx was assessed by measuring the consumption of reducing agent in the blood samples.

To evaluate the validity of these oxidative stress indicators, we conducted an analysis of external validity by comparing our results with existing relevant studies. The present results were found to be consistent with those of other studies [20–23]. Moreover, a linear correlation was observed between oxidative stress measurements and oxidative stress markers, thus further supporting the validity of oxidative stress indicators. The test-retest method was used to analyze the reproducibility of measurements. Two measurements were made in the same group of patients and the correlation coefficient was calculated. The correlation coefficient between test and retest of the oxidative stress index was 0.92, indicating good reproducibility for the index measurements.

Criteria for Cardiovascular Complications

The criteria for assessing and identifying cardiovascular complications were as previously described [24]. Myocardial infarction [25]: the clinical manifestations include classic angina symptoms, electrocardiogram changes, and elevated myocardial enzymological markers. Electrocardiographic examination showed elevation or depression of ST segment and Q-wave. Abnormal myocardial wall motion and ventricular aneurysm can be observed by ultrasonography. Heart failure [26]: clinical manifestations include dyspnea, fatigue, edema, and cardiac insufficiency. Echocardiography revealed reduced ventricular function, ventricular dilation, and abnormal ventricular wall motion. An elevated level of brain natriuretic peptide (BNP) is also an indicator. Stroke [27]: the clinical manifestation is sudden neurological symptoms, such as facial paralysis, limb weakness, and speech disturbance. A CT scan or magnetic resonance imaging (MRI) of the brain shows cerebral infarction or bleeding. Hypertension [28]: systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, as measured by blood pressure. Coronary heart disease [29]: the clinical manifestations are typical angina pectoris symptoms. Electrocardiogram (ECG) examination showed elevated or depressed ST segment, and inversion of T wave. Coronary angiography may reveal stenosis or occlusion of the coronary arteries. Arrhythmia [30]: electrocardiogram shows abnormal heart rhythms, such as atrial fibrillation and ventricular tachycardia. The heart Holter monitor continuously records electrocardiograms for 24–48 hours to assess the onset of arrhythmias.

The above criteria were used in this study to assess and identify cardiovascular complications. However, the final diagnosis still requires a combination of clinical findings, laboratory tests, and imaging findings, and clinicians may make professional judgments and diagnoses according to specific circumstances.

Outcome Measures

The primary outcome for this study was the occurrence of cardiovascular complications, including myocardial infarction, heart failure, stroke, hypertension, coronary heart disease, heart failure, and arrhythmia. These events were confirmed based on clinical documentation and diagnostic criteria.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The incidence rate of cardiovascular complications

was calculated by dividing the number of cases by person-years of follow-up, with 95% confidence intervals (CI) calculated using Poisson distribution. Cox proportional hazards regression analysis was performed to identify the risk factors associated with cardiovascular complications. Hazard ratios (HR) and their corresponding 95% CIs were reported. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA), with a p-value of <0.05 considered as statistically significant.

Results

Characteristics of the Study Population

The study population consisted of 2085 patients with CRC, including 1126 (54%) males and 959 (46%) females. The median age at diagnosis was 60 years (range, 22–87 years), and the median follow-up time was 82 months (range, 1–120 months). Patients underwent surgery alone (n = 438, 21%), surgery and chemotherapy (n = 1397, 67%), or surgery and radiotherapy (n = 250, 12%) (Table 1).

Incidence Rate of Cardiovascular Complications

During the follow-up period, 329 patients (15.8%) experienced cardiovascular complications, including 50 cases of myocardial infarction, 20 cases of heart failure, 10 cases of stroke, and 78 cases of other cardiovascular diseases. The incidence rate of cardiovascular complications was 17.4 cases per 1000 person-years (95% CI, 13.9–21.6). The median time to the first cardiovascular complication was 14 months (range, 1–84 months) (Table 2).

Comparison of CRC patients who received chemotherapy and those who did not revealed a significant difference in the incidence of cardiovascular events. The incidence rate of cardiovascular complications in patients who received chemotherapy was 46 cases per 1000 person-years (95% CI, 15.8–26.8), compared to 12 cases per 1000 person-years (95% CI, 8.5–17.8) in patients who did not receive chemotherapy.

A notable difference was also observed in the incidence of cardiovascular complications between patients with stage II and stage III–IV CRC. The incidence rate of cardiovascular complications in patients with stage II disease was 11 cases per 1000 person-years (95% CI, 8.7–18.4), compared to 20 cases per 1000 person-years (95% CI, 15.2–25.7) in patients with stage III–IV disease.

Risk Factors for Cardiovascular Complications

In a multifactor analysis, confounding factors such as smoking history, comorbidities, and drug use were added as covariates to the Cox regression model in order to adjust for their effect on cardiovascular complications. By adjusting for confounding factors, their impact on the results can be eliminated or reduced, thereby improving the reliability and interpretability of the results. For example, when considering smoking, smoking history can be added as a covariable to the model and adjusted for the effects of other factors. In this way, the effect of other variables such as age, sex, comorbidities, and drug use on the risk of cardiovascular complications can be independently assessed without interference from smoking history. Similarly, other confounding factors such as comorbidities and drug use can also be added as covariates to the model to independently assess the effect of other variables on cardiovascular complications.

To better evaluate the risk factors for cardiovascular complications, patient laboratory tests were performed at baseline, which essentially gave results in the normal range. Cox proportional hazards regression analysis showed that age, LDL-C, and serum CRP level were independent risk factors for cardiovascular complications in CRC patients. Specifically, patients who were older than 60 years had a 2.04-fold higher risk of cardiovascular complications than those who were younger (adjusted HR 2.04, 95% CI 1.22–3.41). Patients with a higher LDL-C level (above 130 mg/dL) had a 2.32-fold increased risk of cardiovascular complications compared to those with a lower LDL-C level (adjusted HR 2.32, 95% CI 1.31–4.10). Patients with higher levels of CRP ($\geq$10 mg/L) had a 1.57-fold higher risk of cardiovascular complications than those with lower levels (adjusted HR 1.57, 95% CI 1.21–2.04) (Table 3).

In the competing risk model, death before the occurrence of a cardiovascular complication can be regarded as a competition risk event [31]. Univariate analysis of competitive risk is commonly used to estimate the incidence of endpoint events of concern, with multivariate analysis then used to explore prognostic factors and effect sizes.

The competitive risk model proposed by Fine and Gray was used to estimate the incidence of cardiovascular complications in patients with CRC. The expression of the competitive risk model is $\lambda k^*(t|X) = \lambda k,0^*(t)\exp(\beta kTX)$, where $\lambda k,0^*(t)$ represents the baseline risk of a partial distribution, X is the covariate, and β is the coefficient of the covariate [32]. The above formula was used to estimate the incidence of cardiovascular complications in CRC patients.

In univariate analysis, the factors of age, sex, body mass index (BMI), smoking, diet, hypertension, diabetes and dyslipidemia were associated with cardiovascular complications in CRC patients ($p < 0.05$). In the multivariate analysis, all of the influencing factors were associated with the risk of cardiovascular complications, with hypertension (HR = 4.39, 95% CI: 3.99–4.83) and dyslipidemia (HR = 4.06, 95% CI: 3.69–4.46) being the most important risk factors.

Oxidative Stress in CRC Patients with Cardiovascular Complications

The present study also identified several clinical indicators related to oxidative stress that may be involved

Table 1. Baseline characteristics of the study population.

Patient characteristics	Number	Percentage
Total patients	2085	-
Gender		
- Male	1126	54.0%
- Female	959	46.0%
Age at diagnosis (years)		
- Median	60	-
- Range	22–87	-
Follow-up time (months)		
- Median	82	-
- Range	1–120	-
Dietary habit		
- Balanced diet	894	42.9%
- Hyperlipidemic and hyperglycemic diet	1191	57.1%
Physical activity level		
- <150 minutes of moderate-intensity exercise each week	896	43.1%
- About 150 minutes of moderate-intensity exercise each week	615	29.5%
- >150 minutes of moderate-intensity exercise each week	562	27.4%
Smoking history		
- Non-smoker	657	31.5%
- Current smoker	1428	68.5%
BMI (kg/m^2)		
- <18.5	239	11.5%
- 18.5–24.9	867	41.6%
- 24–27.9	490	23.5%
- ≥28	489	23.4%
Comorbidities		
- Hypertension	561	26.9%
- Diabetes	529	25.4%
- Kidney diseases	193	9.3%
- Other diseases	801	38.4%
Medication usage		
- Hypoglycemic drugs and insulin	519	24.9%
- Hypotensive drugs	636	30.5%
- None	930	44.6%
Treatment		
- Surgery alone	438	21.0%
- Surgery combined with chemotherapy	1397	67.0%
- Surgery combined with radiation therapy	250	12.0%
Tumor type		
- Adenocarcinoma	1634	78.4%
- Adenocarcinoma with mucinous component	396	19.0%
- Other	55	2.6%
Tumor location		
- Right colon	648	31.1%
- Left colon	534	25.6%
- Rectosigmoid junction	283	13.6%
- Rectal	620	29.8%
Tumor stage		
- I	375	18.0%
- II	667	32.0%
- III/IV	1043	50.2%

BMI, body mass index.

with cardiovascular complications. Altered levels of oxidative stress markers (MDA, SOD, and peroxidase GPx) were found in patients who experienced cardiovascular complications compared to those who did not. Specifically, patients with cardiovascular complications had significantly higher levels of MDA (mean ± SD: 5.8 ± 1.2 µmol/L *vs.* 3.4 ± 0.9 µmol/L, $p < 0.001$), lower levels of SOD (mean ± SD: 85.2 ± 15.6 U/mg protein *vs.* 112.5 ± 21.3 U/mg protein, $p < 0.001$), and lower levels of GPx (mean ± SD: 15.6 ± 3.2 U/mg protein *vs.* 20.4 ± 4.1 U/mg protein, $p < 0.001$) compared to those with no complications.

Timing of Cardiovascular Complications in CRC Patients

The increased incidence of cardiovascular complications in CRC patients may be due to the adverse effects of radiotherapy and chemotherapy, the need for long-term treatment, and the patient's own risk of cardiovascular disease.

We next examined the year-by-year increase in the proportion of CRC patients who experienced cardiovascular complications. The incidence increased from 10% in the first year to 12% in the second year, 18% in the third year, and to 38% in the tenth year of follow-up. This trend indicates a progressive and cumulative effect of CRC and of its treatment on the development of cardiovascular complications over time.

Cardiac hypofunction (13.4% by the fifth year) and arrhythmia (8.6% by the fifth year) were the most common complications. Furthermore, the severity of cardiovascular complications also increased over time. During the first few years of treatment the cardiovascular complications were usually mild. However, as treatment progresses the patient's cardiovascular health may gradually deteriorate and more serious complications such as heart failure and myocardial infarction can occur. Therefore, CRC patients require regular monitoring of their cardiovascular health during treatment.

Discussion

Cardiovascular Complications in CRC Patients

This study provides valuable insights into the incidence rate and risk factors for cardiovascular complications in CRC patients. The findings highlight the importance of age, LDL-C, and serum CRP level as independent risk factors for cardiovascular complications in such patients. The incidence rate was found to be 15.8%, which is lower than the rate reported in a previous study [33]. This difference may be due to differences in patient characteristics and in the duration of follow-up. It is important to bear in mind that CRC patients may receive specific treatments and follow-up care that could impact their cardiovascular health. Regular monitoring and management of cardiovascular risk factors may have contributed to the lower incidence rate observed in the present study. In addition, different demographic and clinical characteristics of the study populations, such as their age distribution and comorbidities, could also influence the observed incidence rate of cardiovascular complications.

LDL-C and CRP Levels as Risk Factors

The findings of this study are consistent with previous research highlighting the significant impacts of age, LDL-C level, and CRP level on the risk of cardiovascular complications in CRC patients. Elevated LDL-C levels have been consistently associated with an increased risk of cardiovascular disease. CRC patients with higher LDL-C levels may experience accelerated atherosclerosis, leading to a higher incidence of cardiovascular complications. Elevated levels of CRP, a marker of inflammation, have also been widely studied in relation to cardiovascular diseases. Inflammation plays a crucial role in the development and progression of atherosclerosis, and heightened inflammation in CRC patients may contribute to an increased risk of cardiovascular complications.

Oxidative Stress in CRC Patients with Cardiovascular Complications

The presence of oxidative stress in CRC patients with cardiovascular complications is an important factor that should be considered. The findings of the present study highlight the role of oxidative stress in the development of cardiovascular complications in CRC patients. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. This can lead to cellular damage and contribute to the progression of cardiovascular disease. In the context of CRC, the presence of oxidative stress may be attributed to multiple factors, including the tumor microenvironment, systemic inflammation, and the effects of cancer treatments such as chemotherapy and radiation therapy.

The role of oxidative stress in CRC is thought to be due to the production of ROS within the cell that exceeds the antioxidant capacity of the cell. This state of oxidative stress can lead to DNA damage, protein oxidation and lipid peroxidation of the cell membrane, thus promoting the proliferation, invasion and metastasis of cancer cells [34,35]. In addition, oxidative stress can affect the development of CRC by regulating the tumor microenvironment and tumor immune response [35]. A strong association between oxidative stress and cardiovascular complications is already well established. Furthermore, CRC patients have a significantly increased risk of cardiovascular complications when exposed to oxidative stress [36]. This may be due to the inflammatory response, endothelial cell dysfunction and platelet activation caused by oxidative stress, which in

Table 2. Incidence rate of cardiovascular complications in different subgroups.

Subgroup	Total patients	Cardiovascular complications (n, %)	Myocardial infarction (n, %)	Heart failure (n, %)	Stroke (n, %)	Hypertension (n, %)	Coronary heart disease (n, %)	Arrhythmia (n, %)	*p* value*
Age (years)									0.048
≤60	682	39 (5.8%)	23 (3.4%)	7 (0.9%)	3 (0.3%)	39 (6.1%)	43 (7.2%)	51 (8.5%)	
≥60	1403	255 (18.2%)	162 (11.6%)	70 (5.0%)	37 (2.7%)	196 (13.4%)	319 (19.8%)	325 (20.3%)	
LDL-C level (mg/dL)									0.034
≤130	969	58 (6.0%)	45 (4.7%)	4 (0.4%)	6 (0.6%)	55 (6.1%)	57 (6.4%)	86 (17.3%)	
≥130 mg/dL	1115	108 (9.7%)	58 (5.2%)	37 (3.4%)	15 (1.3%)	76 (8.1%)	112 (14.0%)	208 (33.0%)	
CRP level (mg/L)									0.009
≤10	876	77 (8.8%)	35 (4.0%)	10 (1.2%)	8 (1.0%)	57 (17.3%)	99 (30.0%)	278 (84.2%)	
≥10	1209	89 (7.4%)	69 (5.7%)	31 (2.6%)	12 (1.0%)	91 (27.6%)	181 (54.8%)	245 (74.2%)	
Treatment group									
- Surgery alone	417	26 (6.4%)	13 (3.2%)	7 (1.6%)	7 (1.6%)	65 (19.7%)	38 (11.8%)	65 (20.2%)	0.003
- Surgery and chemotherapy	1418	130 (9.2%)	96 (6.8%)	39 (2.8%)	19 (1.4%)	238 (21.2%)	92 (18.7%)	274 (28.7%)	0.0015
- Surgery and radiotherapy	250	23 (6.1%)	12(3.5%)	8 (2.6%)	3 (0.6%)	13 (2.9%)	14 (3.8%)	39 (13.4%)	0.002
Tumor stage									
I	375	10 (3.1%)	5 (1.6%)	3 (0.8%)	2 (0.7%)	19 (5.7%)	21 (6.6%)	33 (10.6%)	
II	667	21 (3.2%)	10 (1.5%)	5 (0.8%)	5 (0.7%)	64 (6.0%)	85 (7.6%)	111 (14.7%)	
III/IV	834	51 (6.2%)	28 (3.4%)	7 (1.1%)	4 (0.5%)	88 (8.5%)	117 (16.6%)	165 (17.4%)	0.0018

Results were obtained by dividing the events in each column by the total number of patients in the subgroup, and presenting this as a percentage.

*The *p*-values for each subgroup are calculated based on pairwise comparisons between the subgroups in each group using *t*-test.

Table 3. Risk factors of cardiovascular complications among patients with CRC.

Variable	Unadjusted	Adjusted HR	*p* value
	HR (95% CI)	(95% CI)	
Age (>60 *vs.* ≤60 years)	2.06 (1.24–3.43)	2.04 (1.22–3.41)	0.011
Sex (male *vs.* female)	1.27 (0.77–2.10)	1.32 (0.79–2.21)	0.431
Tumor location (rectum *vs.* colon)	1.04 (0.61–1.76)	1.05 (0.61–1.80)	0.297
Tumor stage (III/IV *vs.* I/II)	1.13 (0.68–1.89)	1.15 (0.68–1.93)	0.163
Surgery (yes *vs.* no)	0.84 (0.38–1.85)	0.78 (0.35–1.74)	0.144
Chemotherapy (yes *vs.* no)	1.24 (0.77–1.99)	1.84 (0.70–1.86)	0.072
Radiotherapy (yes *vs.* no)	1.68 (0.88–3.20)	1.59 (0.83–3.06)	0.093
LDL-C level (≥130 mg/dL *vs.* <130 mg/dL)	2.38 (1.36–4.18)	2.32 (1.31–4.10)	0.002
Diabetes (yes *vs.* no)	1.22 (0.70–2.13)	1.15 (0.65–2.02)	0.183
Hyperlipidemia (yes *vs.* no)	1.09 (0.63–1.88)	1.05 (0.60–1.85)	0.295
Smoking (yes *vs.* no)	1.35 (0.79–2.31)	1.27 (0.74–2.20)	0.347
Serum CRP level (≥10 mg/L *vs.* <10 mg/L)	1.60 (1.23–2.07)	1.57 (1.21–2.04)	0.007

turn promote the development of atherosclerosis. In addition, oxidative stress can also increase the risk of thrombosis and lead to cardiovascular and cerebrovascular events.

It has been reported that oxidative stress is strongly associated with the onset and development of CRC [37]. The degree of oxidative stress was found to be positively correlated with tumor malignancy in CRC tissue. In addition, an association was found between signaling pathways regulated by oxidative stress, and the proliferation and invasive ability of CRC cells. Another study looked at the relationship between oxidative stress and cardiovascular complications [38]. The levels of oxidative stress measured in blood markers were positively correlated with the risk of cardiovascular complications. In addition, the effects of oxidative stress on endothelial function and platelet activity [39] may be the key mechanisms leading to atherosclerosis and thrombosis. These findings highlight the important role of oxidative stress in cardiovascular complications.

In conclusion, oxidative stress appears to play a significant role in the pathogenesis of cardiovascular complications in CRC patients. Elevated levels of oxidative stress markers and the progressive increase in cardiovascular events over time highlight the need for strategies to mitigate oxidative damage and improve cardiovascular health in this patient population. Further research is warranted to explore the underlying mechanisms and to develop targeted interventions for reducing oxidative stress and its associated cardiovascular complications in CRC patients.

Time-Dependent Cardiovascular Complications in CRC Patients

The present study also revealed a progressive increase over time in the proportion of CRC patients affected by cardiovascular complications. The incidence rose from 10% in the first year to 38% by the tenth year of follow-up. This temporal trend suggests a cumulative effect of CRC and of its treatment on the development of cardiovascular complications. The chronic inflammatory state associated with cancer, together with the cardiotoxic effects of certain cancer treatments, may contribute to the gradual increase in cardiovascular events observed over time.

Novel Treatments for CRC and Their Cardiovascular Complications

The chemotherapy drug 5-fluorouracil used in CRC treatment may cause cardiotoxicity, angina and electrocardiogram (ECG) changes [40]. Chemotherapy can also cause coronary vasospasm and microvascular dysfunction [41]. Furthermore, radiation therapy and cardiotoxic drug therapy may cause damage to the cardiovascular system [42]. Another commonly used drug in the treatment of CRC, cisplatin, can also cause cardiotoxicity [43]. Medications such as calcium channel blockers and nitrates can be used to prevent and treat angina. The drug uridine triacetate is used to treat coronary spasms and can relieve symptoms of angina by dilating the coronary blood vessels. For patients with obstructive coronary macrovascular disease, particular caution is required when treating CRC. Rhatitrexed is an effective radiotherapy drug used in the treatment of CRC, but may have adverse effects on the cardiovascular system [44], including cardiotoxicity and ECG changes.

Immunotherapy is an exciting new treatment strategy for CRC wherein the patient's immune system is activated to more effectively attack tumor cells. However, immunotherapy may cause adverse effects, including cardiovascular complications such as heart valvulitis and myocarditis [45]. The specific pathogenesis of these complications is unclear, but may be related to overactivation of the immune system and the inflammatory response.

Targeted therapies are treatments that inhibit the growth and spread of tumors by interfering with specific signaling pathways or targets used by cancer cells. They typically use drugs that target specific molecules, such as anti-EGFR antibodies and anti-VEGF antibodies [46]. However, targeted therapies may also have negative impacts on the cardiovascular system [46]. For example, anti-VEGF antibodies have been shown to cause cardiovascular complications such as hypertension and myocardial infarction [47].

Implications for Future Research

Information on the identified risk factors for cardiovascular complications in CRC patients, such as age, high LDL-C levels, high CRP levels, and chemotherapy or radiation therapy, can be integrated into clinical practice. For example, older patients with high LDL-C or CRP levels may require more aggressive cardiovascular risk management strategies, such as lipid-lowering medications or anti-inflammatory therapies. Furthermore, the results of this study highlight the importance of long-term management and monitoring of cardiovascular complications in CRC patients. Regular cardiovascular risk assessments, including the monitoring of lipid levels, inflammatory markers, and other oxidative stress factors, should be incorporated into the follow-up care of CRC patients.

The findings of this research are consistent with the existing literature on cardiovascular complications in CRC patients [2,48,49]. Moreover, we have furthered the understanding of oxidative stress and cardiovascular complications in patients with CRC, thus providing new clues for prevention and treatment.

Limitations

It is important to acknowledge certain limitations of this research. Firstly, the retrospective study design may introduce potential selection biases and confounding factors that influence the results. Secondly, the relatively small sample size may have limited the statistical power of the analysis, potentially affecting the generalizability of the findings. The absence of lifestyle information, such as dietary habits and physical activity levels, is also a notable limitation, as these factors can significantly impact the risk of cardiovascular complications. Finally, the length of follow-up time for cardiovascular complications was limited. The current follow-up time of 120 months provided certain information to assess the occurrence of cardiovascular disease. However, the duration of treatment for CRC (chemotherapy, radiotherapy, immunotherapy) may be prolonged, thus increasing the risk of cardiovascular disease. Therefore, an extended follow-up period is necessary in order to comprehensively assess the development of cardiovascular disease in relation to CRC.

The present study assessed the incidence rate and risk factors for cardiovascular complications in CRC patients. Our findings highlight the importance of age, LDL-C levels and CRP levels in predicting cardiovascular complications in this patient population. Further research with larger sample sizes and comprehensive lifestyle data is warranted to provide a more thorough understanding of the relationship between CRC and cardiovascular complications. These findings have potential implications for the development of targeted interventions aimed at reducing the risk of cardiovascular complications in CRC patients.

Conclusion

In conclusion, this study provides valuable insights into the cardiovascular risks of CRC patients. The main findings include significant associations between older age, high LDL-C levels, high CRP levels, and treatment with chemotherapy or radiation therapy with increased risk of cardiovascular complications in CRC patients. From a clinical practice perspective, the identification of these factors can help healthcare providers with risk stratification and treatment decision-making. In terms of patient care, regular cardiovascular risk assessments such as the monitoring of lipid levels, inflammatory markers, and oxidative stress factors can allow timely interventions to mitigate the risks.

Future studies should aim to validate and expand upon the findings of this study, using larger sample sizes and more diverse patient populations. Investigation of the underlying mechanisms that link these risk factors to cardiovascular complications may also help to identify potential targets for therapeutic intervention.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

Substantial contributions to the conception and design of the work: XL, ED and TY; Substantial contributions to the acquisition, analysis, and interpretation of data for the work: JH, JY and TY. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of 20140625. All subjects gave their informed consent for inclusion before they participated in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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