Sex-Based Differences in Clinicopathologic Features and Survival Outcomes in Colon Cancer

Bilal Turan[1], *Ahmet Necati Sanli*[2], *Sibel Yaman*[3]

1 Department of General Surgery, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey
2 Department of General Surgery, Abdulkadir Yuksel State Hospital, Gaziantep, Turkey
3 Department of General Surgery, Gaziantep City Hospital, Gaziantep, Turkey

Abstract

Aim: Sex-related differences in the epidemiology and clinical behavior of colon cancer have gained increasing attention, yet existing findings remain inconsistent. This study aimed to compare demographic, clinicopathologic characteristics and survival outcomes between female and male patients with colon cancer using a large population-based cohort from the SEER database.

Methods: This retrospective cohort study included adults diagnosed with colon cancer between 2010-2021 in the Surveillance, Epidemiology, and End Results (SEER) program. Cases with appendiceal or rectal tumors, diagnosis by autopsy or death certificate, missing sex information, or incomplete survival data were excluded. Demographic and tumor-related variables were compared using the chi-square test. Overall survival (OS) and cancer-specific survival(CSS) were estimated with Kaplan-Meier analysis and compared using the log-rank test. Cox proportional hazards models were applied to evaluate the independent effect of sex on survival.

Results: A total of 314,706 patients were included (154,387 women;160,319 men). Women were older at diagnosis and more frequently had right-sided tumors, mucinous histology, and high-grade disease. Men more often presented with stage IV disease and had higher rates of cardiovascular and other-cause mortality. OS favored women across all time points (10-year OS:37.6%vs.35.7%), while long-term CSS was similar (10-year CSS:62.8%vs.62.6%). In multivariable analyses, male sex remained an independent adverse prognostic factor for OS (HR 1.21) and CSS (HR 1.10).

Conclusion: This large-scale population-based analysis demonstrates clear sex-related differences in the presentation and prognosis of colon cancer. Male sex is an independent predictor of poorer survival, underscoring the need for sex-sensitive and individualized management strategies.

Keywords: *Colon cancer; sex differences; survival; prognosis*

1. Introduction

Colon cancer is one of the most significant malignancies worldwide in terms of both incidence and mortality, and according to 2020 global estimates, it ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths [1,2]. Over the past two decades, it has consistently remained among the five most prevalent cancer types in both men and women, with steadily increasing incidence rates [3].

The biological behavior of the disease, timing of diagnosis, therapeutic decision-making, and survival outcomes are influenced by numerous clinical and demographic factors, including age, sex, tumor location, histologic subtype, and genetic characteristics. Among these factors, sex has emerged as a prominent and increasingly recognized variable with substantial impact on the epidemiology and biology of colorectal cancer [4-6].

In colorectal cancer, sex-based differences in biological behavior, clinical presentation, and treatment-related outcomes have been increasingly emphasized in recent years. Notably, the literature has demonstrated that sex and gender differences exert significant effects on tumor biology, immune response, drug pharmacokinetics, and treatment toxicities [7].

The existing literature demonstrates significant differences between female and male patients with respect to the incidence of colon cancer, age distribution, tumor location, and survival outcomes. More frequent right-sided colon tumors in women, their tendency to be diagnosed at an older age, and variations in the prevalence of certain biological subtypes represent key examples of these differences. In contrast, men are reported to present at younger ages, to be diagnosed with more advanced-stage disease, and to have poorer overall survival [5,6,8].

Although sex-related clinical and survival differences in colon

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cancer have been investigated in numerous studies, the consistency of findings remains limited. Variations in sample structures, age distributions, tumor locations, molecular profiles, and treatment approaches across studies have resulted in outcomes that do not always align. This situation indicates that the impact of sex on the biology and prognosis of colon cancer has not yet been fully clarified. Therefore, large population-based analyses that encompass different stages, tumor subtypes, and a broad diversity of patients allow for a more comprehensive interpretation of existing data and enable sex-based differences to be delineated more clearly.

The aim of this study is to examine the distribution of demographic and clinicopathological characteristics between female and male patients with colon cancer using the SEER database, and to compare their survival outcomes. Clearly delineating sex-based differences will provide an important contribution to the existing literature by highlighting the need for individualized approaches in the management of colon cancer.

2. Materials and Methods

This retrospective cohort study utilized data from the Surveillance, Epidemiology, and End Results (SEER) database and included adult patients (≥18 years) diagnosed with colon cancer between 2010 and 2021. Cases with appendiceal or rectal malignancies, diagnosis by autopsy or death certificate, missing sex information, or incomplete survival data were excluded. In total, 314,706 eligible patients were identified (154,387 women and 160,319 men).

Extracted variables included age, race, marital status, tumor location (right vs. left colon), histologic subtype, tumor grade, T and N stage, AJCC stage, Summary Stage (2004+), carcinoembryonic antigen (CEA) level, and receipt of chemotherapy. Survival outcomes were defined as overall survival (OS) and cancer-specific survival (CSS), measured from diagnosis to death from any cause or colon cancer, respectively. Patients alive at last follow-up were censored. As SEER data are de-identified and publicly available, institutional review board approval was not required.

2.1. Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Categorical variables were compared between female and male patients using the chi-square test. Survival curves for OS and CSS were generated using the Kaplan–Meier method, and differences were assessed with the log-rank test. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariable models adjusted for age, race, marital status, tumor location, CEA level, tumor grade, histologic subtype, AJCC stage, and chemotherapy status. A two-sided p-value <0.05 was considered statistically significant. Analyses were performed using standard statistical software.

This study utilized de-identified data from the SEER database, which is publicly available and maintains patient anonymity, ethical approval and informed consent were not required.

3. Results

A total of 314,706 patients diagnosed with colon cancer between 2010 and 2021 were included in the analysis, comprising 154,387 women (49.1%) and 160,319 men (50.9%). The distribution of baseline demographic and clinicopathological variables is summarized in Table 1. Women were older at diagnosis compared with men, with a higher proportion aged 65 years or older, whereas men more frequently belonged to the 50–64 age group. Marital status differed significantly between groups, with men showing a markedly higher proportion of married individuals. Racial distribution also showed small but significant differences, with women having a slightly higher proportion of Black patients.

Tumor characteristics varied meaningfully by sex. Right-sided colon cancers were substantially more common among women, while left-sided tumors predominated among men. Women demonstrated a higher frequency of mucinous adenocarcinoma and a greater proportion of high-grade (grade 3) tumors, whereas adenocarcinoma not otherwise specified was slightly more common in men. The distribution of T stage showed that women had a higher prevalence of T4 tumors, while men had marginally more T1 tumors. Nodal involvement did not differ significantly between groups. AJCC stage distributions indicated that men more frequently presented with stage IV disease, whereas earlier stages were slightly more common among women. CEA positivity was marginally higher in women, and chemotherapy utilization was significantly higher among men.

Figure 1

Overall survival by sex (log-rank p < 0.0001). Number at risk is shown below

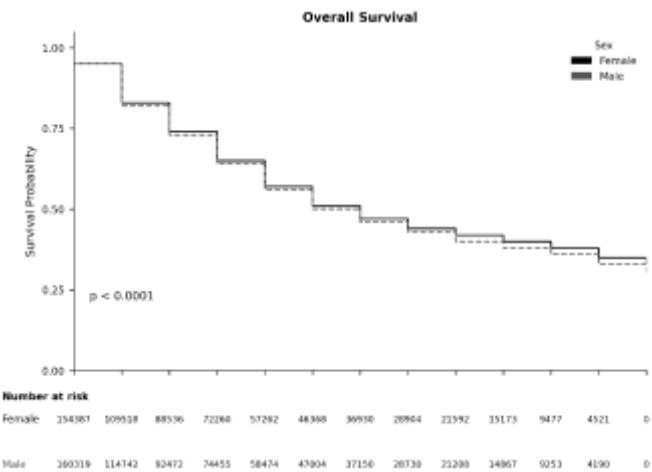

Figure 2

Cancer-specific survival by sex (log-rank p < 0.0001). Number at risk is shown below

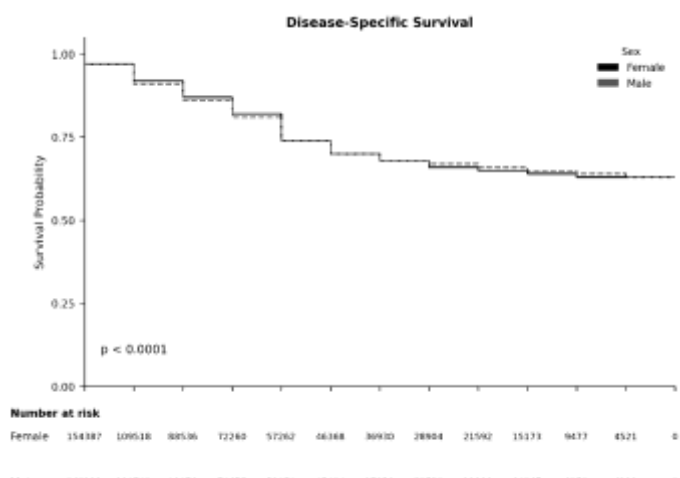

Table 1

Baseline demographic and clinicopathological characteristics stratified by sex

Characteristic	Female	Male	p-
Age group			<0.001
<50 years	9.5% (14,700)	10.0% (15,955)	
50–64 years	26.4% (40,819)	32.9% (52,682)	
≥65 years	64.0% (98,868)	57.2% (91,682)	
Marital status			<0.001
Married	40.3% (62,159)	58.5% (93,739)	
Unmarried	53.4% (82,495)	35.1% (56,286)	
Unknown	6.3% (9,733)	6.4% (10,294)	
Race			<0.001
White	77.1%	77.8%	
Black	12.4% (19,141)	11.7% (18,765)	
Other	9.7% (14,917)	9.5% (15,276)	
Unknown	0.8% (1,242)	1.0% (1,538)	
Tumor location			<0.001
Right colon	58.6%	49.8%	
Left colon	41.4%	50.2%	
Histologic subtype			<0.001
Adenocarcinoma	71.2%	72.1%	
Mucinous	6.7%	6.1%	
Signet-ring cell	1.0%	1.0%	
Other	21.1%	20.8%	
Tumor grade			<0.001
Grade 1	9.8%	10.6%	
Grade 2	69.0%	71.8%	
Grade 3	21.2%	17.6%	
T stage			<0.001
T0	3.4%	3.9%	
T1	17.4%	18.7%	
T2	12.8%	12.4%	
T3	46.8%	46.8%	
T4	19.6%	18.2%	
N stage			0.418
N0	61.5%	61.8%	
N1	24.5%	24.4%	
N2	14.0%	13.8%	
AJCC stage			<0.001
Stage 0	2.8%	3.3%	
Stage I	22.1%	22.3%	
Stage II	25.9%	24.6%	
Stage III	26.8%	25.7%	
Stage IV	22.4%	24.1%	
CEA level			<0.001
Negative	27.5%	29.3%	
Positive	28.4%	27.3%	
Unknown	44.1%	43.4%	
Chemotherapy			<0.001
Received	31.9%	35.0%	
Not received	68.1%	65.0%	

NOS: not otherwise specified; CEA: carcinoembryonic antigen; AJCC: American Joint Committee on Cancer.

Overall and Cancer-Specific Survival

Survival analyses demonstrated that women had better OS at all evaluated time points. Three-year OS was 62.6% in women compared with 62.0% in men, five-year OS was 51.7% versus 50.5%, and ten-year OS was 37.6% versus 35.7%, respectively. These differences were statistically significant. CSS was largely comparable between sexes. In the early period, CSS was marginally higher in men (3-year: 74.8% vs 74.0%; 5-year: 67.6% vs 67.2%), whereas long-term CSS was nearly identical, with ten-year CSS rates of 62.6% in men and 62.8% in women.

Cause-Specific Mortality and Regression Analysis

Mortality patterns differed between groups. Women had a slightly higher proportion of colon cancer–related deaths, whereas men experienced greater cardiovascular and other-cause mortality. Despite this, the proportion of surviving patients was modestly higher among women.

In univariate Cox regression analysis, male sex was associated with worse overall survival. This association became more pronounced after adjustment for age, race, marital status, tumor location, CEA level, tumor grade, histologic subtype, AJCC stage, and chemotherapy status. In the fully adjusted model, male sex remained an independent adverse prognostic factor for both OS (HR 1.21, 95% CI 1.19–1.23) and CSS (HR 1.10, 95% CI 1.08–1.12).

Table 2

Survival outcomes and cause-specific mortality by sex

Outcome	Female	Male	p-
Overall survival			<0.001
3-year OS	62.6%	62.0%	
5-year OS	51.7%	50.5%	
10-year OS	37.6%	35.7%	
Cancer-specific			<0.001
3-year CSS	74.0%	74.8%	
5-year CSS	67.2%	67.6%	
10-year CSS	62.8%	62.6%	
Cause of death			<0.001
Alive	52.9%	51.9%	
Colon cancer death	27.2%	26.5%	
Cardiovascular death	3.9%	4.4%	
Other causes	16.0%	17.2%	
Cox regression			
Overall survival HR	Reference	1.026	<0.001
Cox regression			
Adjusted OS HR (95%	Reference	1.210	<0.001
Adjusted CSS HR (95%	Reference	1.100	<0.001

OS: overall survival; CSS: cancer-specific survival; HR: hazard ratio; CI: confidence interval.

4. Discussion

In this large-scale SEER analysis, sex-related clinical, pathological, and survival differences among patients with colon cancer were comprehensively evaluated. The findings largely corroborate previously reported patterns in the literature and demonstrate a clear clinical divergence between female and male patients. The fact that women are older at the time of diagnosis, exhibit a higher proportion of right-sided colon tumors, and display sex-related variations in certain histopathological features (such as the prevalence of high-grade tumors) supports the notion that colon cancer is a heterogeneous disease influenced by sex from both biological and epidemiological perspectives.

In male patients, presentation with more advanced-stage disease, differences in screening behaviors, higher mortality from non-cancer causes, and lifestyle-related factors are important contributors that may influence survival disparities [9,10]. However, multivariable analyses demonstrated that even after controlling for all these clinical and pathological factors, male sex remained an independent adverse prognostic factor. This suggests that sex in colon cancer is not merely a demographic or sociocultural variable, but also a biological determinant.

Recent clinical trial data support the population-level findings observed in our study. In the CALGB/SWOG 80702 trial, which included 2,201 patients with stage III colon cancer receiving adjuvant FOLFOX therapy, women experienced significantly higher rates of severe chemotherapy-related toxicities and achieved lower relative dose intensity compared with men; nevertheless, women showed significantly better outcomes in terms of disease-free survival, recurrence-free survival, and overall survival [11].

The literature indicates that estrogens and androgens influence colorectal cancer development bidirectionally, both directly and through the intestinal microbiota [12]. Estrogen has been reported to inhibit tumor formation by enhancing DNA repair, suppressing inflammation, and promoting the growth of beneficial short-chain-fatty-acid-producing bacteria, whereas androgens may facilitate colorectal cancer progression through mechanisms involving gut microbiota-mediated dysbiosis, chronic inflammation, and impaired immune responses. Moreover, the interaction between sex hormones and the microbiota has been suggested to contribute to sex-specific differences in treatment outcomes, including responses to immune checkpoint inhibitors [12-14].

These findings suggest that, despite increased toxicity and dose reductions, female sex confers an independent survival advantage in the treatment of colon cancer. This observation is consistent with contemporary literature demonstrating pronounced sex differences in treatment response and toxicity [15].

Our analysis extends this observation beyond randomized clinical trials by demonstrating that women exhibit a comparable overall survival advantage across all stages and under real-world conditions. The concordance between clinical trial data and population-level findings underscores that sex is a biologically meaningful variable influencing treatment response, toxicity profiles, and long-term prognosis in colon cancer. It further highlights the need for sex-sensitive approaches in chemotherapy dosing, toxicity management, and survivorship care [11].

The mechanisms underlying the female survival advantage are multifactorial. Hormonal differences, immune responses, tumor biology (including MSI status and the distribution of BRAF mutations), comorbidity profiles, and lifestyle factors may partially account for this disparity. These biological and clinical mechanisms have been comprehensively described in recent studies that examine the impact of sex differences on cancer incidence, the tumor microenvironment, treatment response, and prognosis in detail [7,15,16]. Moreover, the higher cardiovascular mortality observed in men and their greater likelihood of presenting with advanced-stage disease further contribute to their survival disadvantage [17]. Therefore, our findings reflect a complex sex effect that encompasses both biological and behavioral components.

The strengths of our study include the very large patient population, the availability of long-term follow-up data, and the comprehensive assessment of clinical variables. However, several limitations should be considered, including its retrospective design and the constraints of the SEER database, which does not provide detailed information on chemotherapy regimens, comorbidity burden, molecular profiles (such as MMR status and KRAS/BRAF mutations), or lifestyle factors. Additionally, because the database reflects the U.S. population, the generalizability of the findings to different geographic or ethnic groups may be limited. Overall, our results demonstrate that sex has a strong and independent impact on the clinical course and survival of colon cancer, underscoring the importance of incorporating sex-sensitive approaches throughout diagnosis, treatment, and survivorship care. These results may support increased awareness of sex-based differences during postoperative surveillance and survivorship planning.

5. Conclusion

In this large-scale SEER analysis, clear clinical and pathological differences were identified between female and male patients with colon cancer. Although women were diagnosed at an older age, they exhibited better overall survival, whereas men presented more frequently with advanced-stage disease and had higher rates of mortality from non-cancer causes. Multivariable analyses confirmed that male sex is an independent adverse prognostic factor for both overall and cancer-specific survival. These findings highlight the importance of sex-sensitive approaches and individualized management strategies in colon cancer.

Statement of ethics

This study utilized de-identified data from the SEER database, which is publicly available and maintains patient anonymity, ethical approval and informed consent were not required.

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by all authors.

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Conflict of interest statement

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

B.T.: Conceptualization, Methodology, Supervision, Formal analysis, Writing – review & original draft.

A.N.S.: Data curation, Software, Formal analysis, Visualization, Writing – review & editing.

S.Y.: Supervision, Validation, Visualization, Writing – review & editing.

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