Original Article

Age-related rates of colorectal cancer and the factors associated with overall survival

Emmanuel Gabriel[1], Kristopher Attwood[2], Eisar Al-Sukhni[3], Deborah Erwin[4], Patrick Boland[5], Steven Nurkin[3]

[1]Department of Surgery, Section of Surgical Oncology, Mayo Clinic, Jacksonville, FL, USA; [2]Department of Biostatistics, [3]Department of Surgical Oncology, [4]Department of Epidemiology, [5]Department of Medical Oncology, Roswell Park Cancer Institute, Buffalo, NY, USA

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Correspondence to: Steven Nurkin, MD, MS. Department of Surgical Oncology, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA. Email: steven.nurkin@roswellpark.org.

Background: The purpose of this study was to identify differences in both demographic and pathologic factors associated with the age-related rates of colorectal cancer (CRC) and overall survival (OS).

Methods: The National Cancer Data Base (NCDB), 2004–2013, was queried for patients with CRC. Patients were stratified by age (≤50 *vs.* ≥60 years). Multivariable analysis was performed to identify factors associated with OS.

Results: A total of 670,030 patients were included; 488,121 with colon, and 181,909 with rectal or rectosigmoid cancer. For colon cancer, patients ≤50 years had higher proportions of pathologic stage III and IV disease than patients ≥60 (III: 33.7% *vs.* 28.6%, IV: 25.5% *vs.* 14.3%, respectively; P≤0.001). Similar differences were found for patients with rectal cancer (III: 35.8% *vs.* 28.6%, IV: 16.5% *vs.* 11.6%, respectively for age ≤50 and ≥60 years; P≤0.001). More aggressive pathologic factors were identified in the ≤50 cohort and were associated with worse OS, including higher tumor grade, lymphovascular invasion (LVI), perineural invasion (PNI), and elevated serum carcinoembryonic antigen (CEA). Disparities associated with OS were also identified for both colon and rectal cancer. For patients ≤50 with CRC, African-American and Hispanic race, lower income and lower education were associated with increased risk of mortality compared to the ≥60 cohort.

Conclusions: There are clear differences in biological factors and in racial and socioeconomic disparities of patients with early onset CRC. Earlier screening should be seriously considered in patients under 50 years who are African-American and Hispanic, as these populations present with more aggressive and advanced disease.

Keywords: Colorectal cancer (CRC); early onset; National Cancer Data Base (NCDB)

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Introduction

In the US, the incidence of early onset colorectal cancer (CRC) for people under the age of 50 years has been increasing (1). This trend is alarming, with a statement highlighting its importance added to the most recent version of the National Comprehensive Cancer Network (NCCN) guidelines for colon and rectal cancer (2,3). Several causes for this increase have been described. From a biological perspective, more aggressive pathologic, molecular or genetic features have been identified which may be contributing to the increased incidence (4-7).

Changes in risk factors among younger adults over time, including diets higher in fat and increasing obesity, are also in part, contributing to this rising trend (8,9).

In addition to these biologic etiologies, disparities in access to care for diagnosis and treatment of CRC among young adults has also been described. Several studies have characterized differences in the treatment of CRC, including access to surgery and chemotherapy based on age, race, geographic location and other socioeconomic factors like insurance status and income (10-15). Importantly, differences in access to these treatments have been associated with worse survival outcomes for patients with early-onset CRC of minority racial populations (16,17). The purposes of this study were to identify differences in both demographic and pathologic factors associated with the age-related rates of CRC and to assess the interaction these variables on overall survival (OS) in early onset CRC.

Methods

Patients

Jointly sponsored by the American Cancer Society and the American College of Surgeons, the National Cancer Data Base (NCDB) captures approximately 70% of the country's cancer cases through its participating hospitals. A query of the NCDB 2006–2012 participant user files (PUFs) was performed to identify all patients with adenocarcinoma of the colon, rectosigmoid or rectum. At the time this study was performed, the NCDB provided data until 2013. Patients within the rectosigmoid and rectum PUFs were combined into a single group designated as rectum.

Patients with histology other than adenocarcinoma were excluded. For adenocarcinoma, the following International Statistical Classification of Diseases (ICD-O-3) codes were used: 8140–8148, 8200, 8260–8263, and 8480–8496. Patients were stratified by age (≤50 *vs.* ≥60 years), with ages 51–59 intentionally omitted from the analysis to minimize overlapping trends between these two age groups.

Patient factors reported in the NCDB include gender, race, ethnicity, income, education, insurance status, treatment facility type, geographic setting and Charlson-Deyo comorbidity score as a measure of comorbid conditions. Income is reported by the NCDB as the median household income based on zip code derived from the 2000 US Census. Similarly, level of education is captured in the NCDB as the proportion of residents in a patient's zip code who did not graduate high school, which is divided this into four categories based on the proportion who did not graduate high school: lowest (≥29%), low (20–28.9%), high (14.1–19.9%), and highest (≤14%). The Charlson-Deyo comorbidity score is based on a number of reported ICD-9-CM secondary diagnosis codes and is reported as a single cumulative summary score as 0, 1, or ≥2.

Pathologic variables included site of tumor as it pertains to colon cancer (right, transverse, left, overlapping or not specified), grade, clinical and pathological TNM stage, serum carcinoembryonic antigen (CEA) level, lymphovascular invasion (LVI), and perineural invasion (PNI). Site of tumor was not applicable for patients with rectal cancer. For the purposes of this study, CEA level was analyzed by normal or elevated. LVI and PNI were also analyzed as dichotomous variables. The inclusion LVI status as a variable in the NCDB began 2010, and therefore the analysis was limited to these years (2010–2013) for LVI.

As this study used a national de-identified database, this was deemed exempt from our institutional review board.

Statistical analysis

Patient characteristics were reported by age group (≤50 *vs.* ≥60 years) using means, medians and standard deviations for continuous variables; and frequencies and relative frequencies for categorical data. Comparisons were made using the Wilcoxon rank sum and Pearson Chi-Square tests for continuous and categorical variables, respectively. The Holm-Bonferroni method was used to control the family-wise error rate within each analysis cohort.

OS was summarized by age group (≤50 *vs.* ≥60 years) using standard Kaplan-Meier methods and adjusted for Charlson-Deyo comorbidity status, where estimates of median and 3-/5-year OS were obtained with 95% confidence intervals (CI). Within each age group, the association between patient characteristics and OS were examined using Cox regression models. The models were fit using Firth's method and hazard ratios (HRs) were obtained from model estimates. In order to identify any age effect on these associations, OS was then modeled as a function of each patient characteristic, age, and their interaction using a multivariable stratified Cox regression model after adjusting for the Charlson-Deyo comorbidity score. The test about the interaction term evaluated whether the HRs associated with the given patient characteristics differ between the two age groups. Separate models were fit for each patient characteristic. For each model a test about the interaction terms was conducted, which evaluated whether the HRs

associated with the given patient characteristic differed between the two age groups. All models were adjusted by the Charlson-Deyo comorbidity status (stratification factor). The HRs with corresponding 95% CI were obtained from model estimates using standard methods. All model assumptions and fit were assessed graphically using Schoenfeld and Cox-Snell residual plots.

All analyses were conducted in SAS v9.4 (Cary, NC, USA) at a nominal significance level of 0.05.

Results

A total of 670,030 patients met the inclusion criteria as described above. Of these, there were 488,121 patients with colon cancer and 181,909 patients with rectal/rectosigmoid cancer. *Table 1* shows the patient demographic and tumor characteristics for the colon cohort, and *Table 2* shows data for the rectum cohort stratified by age group (≤50 and ≥60 years). Because of the large sample size, nearly all of these variables reached statistical significance (unless otherwise specified). As to be expected for both colon and rectum, patients ≥60 years had higher Charlson-Deyo comorbidity scores and were more likely to have Medicare for insurance. Non-White races comprised a higher proportion of patients in the ≤50 years group. Patients ≤50 years had lower levels of education in the colon group. Regarding pathologic variables, patients ≤50 years had higher overall rates of stage III/IV disease, more LVI, and more PNI compared to patients ≥60 years.

The Kaplan-Meier curves for OS are shown in *Figure 1*. The median follow-up was similar for patients with colon cancer and rectal cancer (62.4 and 62.1 months respectively). Overall, patients ≤50 years had superior outcomes to patients ≥60 years. For colon, the median OS for patients ≤50 years was not reached (NR) (95% CI: 127.5 months–NR) as compared to 57.5 months (95% CI: 57.1–57.9) for patients ≥60 years; and for rectum, the median OS was also not reached for ≤50 group compared to 59.1 months (95% CI: 58.5–59.7) for ≥60 group.

The multivariable analysis of patient demographic and tumor-related variables on OS for colon cancer when stratified by age is shown in *Table 3*. Analyses were adjusted for the Charlson-Deyo comorbidity scores. The ≤50 and ≥60 groups HRs correspond to the variable for the respective age groups. The ≤50 and ≥60 P values correspond to the overall effect of the variable on OS for the respective age groups. The interaction column contains two P values: (I) the first P value (corresponding to the row where the HRs are 1.00) is an overall test of whether the effect of the patient characteristic on OS differs between age groups; (II) the remaining P values compare the specific HRs between age groups.

Most of the patient characteristics were significantly associated with OS, which in part may be due to the large sample size. Most strikingly, the association between many of these characteristics and OS differs between the age groups (i.e., have significant P values under the interaction column). The largest of these differences was observed for pathologic stage whereby stage IV disease had a significantly greater association on OS for patients ≤50 as compared to ≥60 (HR: 15.60 *vs.* 6.67, respectively). Other notable differences were found with respect to patients of Black/African American race and Hispanic ethnicity who demonstrated increasing tumor grade, elevated CEA, LVI and PNI. These interactions demonstrate that while having these factors is associated overall with poorer OS, the extent of the association was worse for patients ≤50.

The multivariable analysis of patient demographic and tumor-related variables on OS for rectal cancer when stratified by age is shown in *Table 4*. The largest of the differences was again observed for pathologic stage whereby stage IV disease had a significantly greater association on OS for patients ≤50 as compared to ≥60 (HR: 20.72 *vs.* 6.13, respectively). Other differences were found with respect to Black/African American race, Hispanic ethnicity, lower income level, increasing tumor grade, elevated CEA, LVI and PNI.

Tables S2-S5 show the distribution of pathologic factors by race or ethnicity stratified by age group for colon and rectum, respectively. The pathologic factors differed to a greater extent in the rectum group than in the colon group. For the colon group, the site of disease was also statistically significant with African Americans having a nearly 10% higher number of right sided colon cancer compared to Caucasians in the ≤50 group (*Tables S2*,*S3*). In contrast, the proportion of African Americans and Caucasians with right sided colon cancer in the ≥60 group was similar.

Discussion

This study is the first that uses a large nationwide database to investigate both demographic and pathologic factors as they pertain to early onset CRC and OS. The incidence of early onset CRC in the US has been increasing as noted through other databases such as the Surveillance, Epidemiology, and End Results Program (SEER) database or the North American Association of Central Cancer

Table 1 Baseline characteristics of patients with colon cancer from the NCDB, years 2004–2013, based on available data (with missing data shown in *Table S1*)

Patient characteristic	Group, n (%)		Overall, n (%)
	≤50 years	≥60 years	
Overall	59,567 (12.2)	428,554 (87.8)	488,121 (100.0)
Gender			
Male	30,107 (50.5)	202,019 (47.1)	232,126 (47.6)
Female	29,460 (49.5)	226,535 (52.9)	255,995 (52.4)
Race			
White	45,271 (76.0)	367,197 (85.7)	412,468 (84.5)
Black	10,543 (17.7)	45,369 (10.6)	55,912 (11.5)
Other	3,753 (6.3)	15,988 (3.7)	19,741 (4.0)
Ethnicity			
Not Hispanic	50,361 (91.0)	379,371 (95.8)	429,732 (95.2)
Hispanic	4,982 (9.0)	16,689 (4.2)	21,671 (4.8)
Insurance			
None	5,205 (9.0)	6,204 (1.5)	11,409 (2.4)
Private	42,739 (73.6)	81,866 (19.4)	124,605 (26.0)
Medicaid	6,564 (11.3)	9,365 (2.2)	15,929 (3.3)
Medicare	2,856 (4.9)	322,048 (76.3)	324,904 (67.7)
Other government	734 (1.3)	2,426 (0.6)	3,160 (0.7)
Income			
≤$30,000	8,121 (14.2)	56,407 (13.7)	64,528 (13.7)
$30,000–$34,999	9,699 (17.0)	75,171 (18.2)	84,870 (18.1)
$35,000–$45,999	15,380 (26.9)	118,145 (28.6)	133,525 (28.4)
≥$46,000	23,951 (41.9)	163,293 (39.5)	187,244 (39.8)
Education			
≥29%	10,990 (19.2)	68,234 (16.5)	79,224 (16.9)
20–28.9%	13,291 (23.3)	96,372 (23.3)	109,663 (23.3)
14–19.9%	12,658 (22.2)	100,636 (24.4)	113,294 (24.1)
≤14%	20,203 (35.4)	147,751 (35.8)	167,954 (35.7)
Facility type			
CCP	5,856 (9.8)	66,752 (15.6)	72,608 (14.9)
Comprehensive CCP	21,564 (36.2)	225,318 (52.6)	246,882 (50.6)
Academic/research	15,871 (26.6)	105,240 (24.6)	121,111 (24.8)
Integrated	3,485 (5.9)	30,730 (7.2)	34,215 (7.0)

Table 1 (*continued*)

Table 1 (*continued*)

Patient characteristic	Group, n (%)		Overall, n (%)
	≤50 years	≥60 years	
Urban/rural			
Metro	49,015 (85.4)	344,204 (83.3)	393,219 (83.6)
Urban	7,454 (13.0)	59,920 (14.5)	67,374 (14.3)
Rural	929 (1.6)	9,035 (2.2)	9,964 (2.1)
Charlson-Deyo comorbidity score			
0	52,106 (87.5)	278,953 (65.1)	331,059 (67.8)
1	6,172 (10.4)	106,079 (24.8)	112,251 (23.0)
2	1,289 (2.2)	43,522 (10.2)	44,811 (9.2)
Tumor location			
Right	22,320 (37.5)	225,942 (52.7)	248,262 (50.9)
Transverse	4,797 (8.1)	42,584 (9.9)	47,381 (9.7)
Left/sigmoid	28,972 (48.7)	140,023 (32.7)	168,995 (34.6)
Overlapping	790 (1.3)	5,214 (1.2)	6,004 (1.2)
Not specified	2,651 (4.5)	14,637 (3.4)	17,288 (3.5)
Grade			
Well differentiated	5,565 (10.4)	43,453 (11.2)	49,018 (11.1)
Moderately differentiated	35,865 (67.2)	264,185 (67.8)	300,050 (67.7)
Poorly differentiated	10,805 (20.2)	74,419 (19.1)	85,224 (19.2)
Undifferentiated	1,124 (2.1)	7,550 (1.9)	8,674 (2.0)
Clinical stage			
0	794 (2.9)	5,980 (3.4)	6,774 (3.3)
I	5,864 (21.3)	54,080 (30.5)	59,944 (29.2)
II	4,938 (17.9)	41,662 (23.5)	46,600 (22.7)
III	4,711 (17.1)	26,295 (14.8)	31,006 (15.1)
IV	11,241 (40.8)	49,456 (27.9)	60,697 (29.6)
Pathologic stage			
0	594 (1.2)	4,149 (1.2)	4,743 (1.2)
I	7,984 (15.8)	84,677 (23.8)	92,661 (22.8)
II	12,063 (23.9)	114,343 (32.2)	126,406 (31.1)
III	17,015 (33.7)	101,494 (28.6)	118,509 (29.2)
IV	12,864 (25.5)	50,817 (14.3)	63,681 (15.7)
CEA			
Normal	17,797 (51.5)	119,327 (52.6)	137,124 (52.4)
Elevated	16,788 (48.5)	107,596 (47.4)	124,384 (47.6)

Table 1 (*continued*)

Table 1 (*continued*)

Patient characteristic	Group, n (%)		Overall, n (%)
	≤50 years	≥60 years	
LVI			
No	10,514 (64.9)	78,870 (71.9)	89,384 (71.0)
Yes	5,683 (35.1)	30,826 (28.1)	36,509 (29.0)
PNI			
No	13,208 (83.8)	97,707 (89.4)	110,915 (88.7)
Yes	2,548 (16.2)	11,621 (10.6)	14,169 (11.3)

All P values ≤0.001. NCDB, National Cancer Data Base; CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion; CCP, community cancer program.

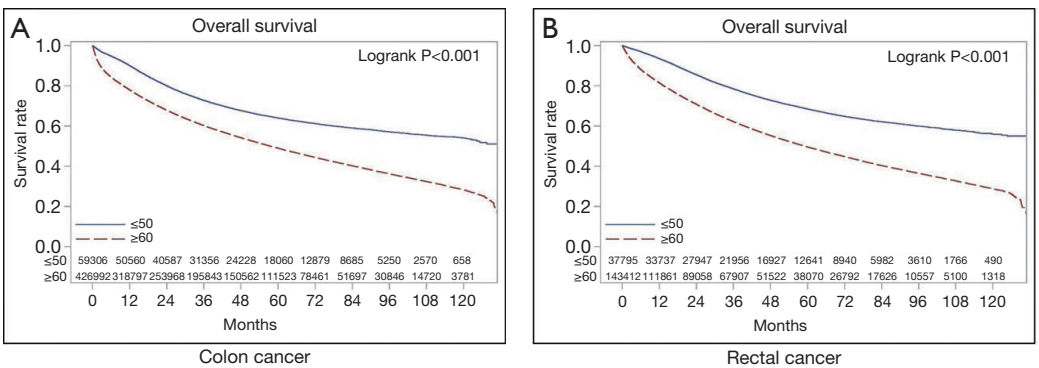

Figure 1 Overall survival of patients with colon cancer (A) and rectal cancer (B) by age ≤50 and ≥60, adjusted by Charlson-Deyo comorbidity status.

Registries (NAACCR) dataset (1-3,6,16,18,19). While these studies have focused on either the disparate demographic aspects or the pathologic features associated with early onset CRC, our study sought to look at both sets of characteristics and determine the association of these variables with OS of patients ≤50 and ≥60 years.

The current screening guidelines in the US recommend the age of 50 years to start screening the average risk individual and may therefore miss early onset CRC (20,21). In addition to issues related to the timing of CRC screening, behavioral factors are thought to contribute to the increased incidence of early onset CRC. Obesity and diet are associated with increased risk for CRC, and the rate of obesity among Americans has been reported to be as high as 34% (22). Physical inactivity, lack of exercise, tobacco use and consumption of alcohol are also related to increased CRC risk (23,24). These behavioral risk factors are more pervasive in populations with lower socioeconomic status in the US, thereby reflecting a relationship of demographic disparities and behavioral patterns that is associated with CRC (25,26).

Pathologic factors associated with increased early onset CRC have also been studied, and these factors may explain why CRC presents at advanced stages for younger patients as we and other have shown (27). These include tumor differentiation, LVI and PNI, which have been reported in other studies and were also included in our analysis (4,28). Signet-ring differentiation has been associated with poorer prognosis in patients with CRC (29,30). LVI and PNI have each been demonstrated to have prognostic significance in CRC (31-34). Our study provides the largest published cohort characterizing the association of both LVI and PNI on OS and supports its consideration in the prognostication of patients. Moreover, what is particularly novel with our

Table 2 Baseline characteristics of patients with rectal cancer from the NCDB, years 2004–2013, based on available data (with missing data shown in *Table S1*)

Patient characteristic	Group, n (%)		Overall, n (%)
	≤50 years	≥60 years	
Overall	37,979 (20.9)	143,930 (79.1)	181,909 (100.0)
Gender*			
Male	21,750 (57.3)	82,771 (57.5)	104,521 (57.5)
Female	16,229 (42.7)	61,159 (42.5)	77,388 (42.5)
Race			
White	31,322 (82.5)	125,270 (87.0)	156,592 (86.1)
Black	4,131 (10.9)	11,606 (8.1)	15,737 (8.7)
Other	2,526 (6.7)	7,054 (4.9)	9,580 (5.3)
Ethnicity			
Not Hispanic	32,270 (91.3)	126,390 (94.9)	158,660 (94.2)
Hispanic	3,062 (8.7)	6,725 (5.1)	9,787 (5.8)
Insurance			
None	2,938 (8.0)	2,807 (2.0)	5,745 (3.2)
Private	27,774 (75.3)	33,296 (23.6)	61,070 (34.3)
Medicaid	4,112 (11.1)	4,068 (2.9)	8,180 (4.6)
Medicare	1,572 (4.3)	99,713 (70.6)	101,285 (56.8)
Other government	512 (1.4)	1,437 (1.0)	1,949 (1.1)
Income			
≤$30,000	4,836 (13.3)	19,806 (14.3)	24,642 (14.1)
$30,000–$34,999	6,249 (17.1)	26,789 (19.3)	33,038 (18.9)
$35,000–$45,999	9,918 (27.2)	39,459 (28.5)	49,377 (28.2)
≥$46,000	15,443 (42.4)	52,583 (37.9)	68,026 (38.9)
Education			
≥29%	6,572 (18.0)	24,652 (17.8)	31,224 (17.8)
20–28.9%	8,440 (23.2)	33,743 (24.3)	42,183 (24.1)
14–19.9%	8,362 (22.9)	34,242 (24.7)	42,604 (24.3)
≤14%	13,070 (35.9)	45,987 (33.2)	59,057 (33.7)
Facility type			
CCP	3,182 (8.9)	19,994 (13.9)	23,176 (12.9)
Comprehensive CCP	13,411 (37.4)	72,443 (50.3)	85,854 (47.8)
Academic/research	11,313 (31.6)	41,677 (29.0)	52,990 (29.5)
Integrated	2,186 (6.1)	9,676 (6.7)	11,862 (6.6)

Table 2 (*continued*)

Table 2 (*continued*)

Patient characteristic	Group, n (%)		Overall, n (%)
	≤50 years	≥60 years	
Urban/rural			
Metro	30,372 (82.9)	111,631 (80.4)	142,003 (80.9)
Urban	5,539 (15.1)	23,643 (17.0)	29,182 (16.6)
Rural	713 (1.9)	3,568 (2.6)	4,281 (2.4)
Charlson-Deyo comorbidity score			
0	34,173 (90.0)	102,946 (71.5)	137,119 (75.4)
1	3,226 (8.5)	30,506 (21.2)	33,732 (18.5)
2	580 (1.5)	10,478 (7.3)	11,058 (6.1)
Grade			
Well differentiated	2,962 (9.0)	12,889 (10.4)	15,851 (10.1)
Moderately differentiated	24,027 (73.4)	92,458 (74.8)	116,485 (74.5)
Poorly differentiated	5,315 (16.2)	16,839 (13.6)	22,154 (14.2)
Undifferentiated	434 (1.3)	1,339 (1.1)	1,773 (1.1)
Clinical stage			
0	407 (1.6)	2,032 (2.4)	2,439 (2.2)
I	4,790 (19.3)	23,540 (28.1)	28,330 (26.1)
II	5,676 (22.9)	23,048 (27.5)	28,724 (26.4)
III	7,950 (32.0)	18,138 (21.6)	26,088 (24.0)
IV	5,987 (24.1)	17,108 (20.4)	23,095 (21.3)
Pathologic stage			
0	503 (1.9)	1,858 (2.0)	2,361 (2.0)
I	6,810 (25.7)	30,426 (32.6)	37,236 (31.1)
II	5,306 (20.1)	23,556 (25.2)	28,862 (24.1)
III	9,466 (35.8)	26,692 (28.6)	36,158 (30.2)
IV	4,365 (16.5)	10,784 (11.6)	15,149 (12.6)
CEA[†]			
Normal	11,138 (51.8)	38,366 (51.2)	49,504 (51.4)
Elevated	10,353 (48.2)	36,527 (48.8)	46,880 (48.6)
LVI			
No	6,618 (74.8)	23,588 (78.7)	30,206 (77.8)
Yes	2,233 (25.2)	6,395 (21.3)	8,628 (22.2)
PNI			
No	8,217 (85.7)	28,916 (89.4)	37,133 (88.5)
Yes	1,373 (14.3)	3,432 (10.6)	4,805 (11.5)

*, P=0.40; [†], P=0.24. Other P values ≤0.001. NCDB, National Cancer Data Base; CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion; CCP, community cancer program.

Table 3 Analysis of factors associated with overall survival by age group (≤ 50 and ≥ 60 years) for patients with colon cancer

Patient characteristic	≤50 years		≥60 years		Interaction P value
	HR	P value	HR	P value	
Gender		≤0.001		≤0.001	
Male	1.00		1.00		≤0.001
Female	0.91 (0.89, 0.94)		0.96 (0.95, 0.97)		≤0.001
Race		≤0.001		≤0.001	
White	1.00		1.00		≤0.001
Black	1.30 (1.26, 1.35)		1.11 (1.10, 1.13)		≤0.001
Other	0.89 (0.83, 0.95)		0.82 (0.80, 0.84)		0.028
Ethnicity		≤0.001		≤0.001	
Not Hispanic	1.00		1.00		0.033
Hispanic	0.91 (0.86, 0.96)		0.85 (0.83, 0.87)		0.033
Insurance		≤0.001		≤0.001	
None	1.00		1.00		≤0.001
Private	0.61 (0.58, 0.64)		0.72 (0.69, 0.75)		≤0.001
Medicaid	1.13 (1.07, 1.20)		1.07 (1.02, 1.12)		0.13
Medicare	1.02 (0.95, 1.10)		1.07 (1.03, 1.11)		0.29
Other government	0.71 (0.62, 0.82)		0.92 (0.86, 0.99)		0.001
Income		≤0.001		≤0.001	
≤$30,000	1.00		1.00		≤0.001
$30,000–$34,999	0.94 (0.90, 0.99)		0.94 (0.93, 0.95)		0.85
$35,000–$45,999	0.87 (0.83, 0.91)		0.90 (0.89, 0.92)		0.087
≥$46,000	0.70 (0.67, 0.74)		0.85 (0.84, 0.86)		≤0.001
Education		≤0.001		≤0.001	
≥29%	1.00		1.00		≤0.001
20–28.9%	0.95 (0.91, 0.99)		0.98 (0.97, 0.99)		0.13
14–19.9%	0.86 (0.82, 0.90)		0.96 (0.94, 0.97)		≤0.001
≤14%	0.74 (0.71, 0.77)		0.90 (0.89, 0.91)		≤0.001
Facility type		≤0.001		≤0.001	
CCP	1.00		1.00		≤0.001
Comprehensive CCP	0.99 (0.94, 1.04)		0.94 (0.93, 0.96)		0.073
Academic/research	1.09 (1.04, 1.15)		0.90 (0.89, 0.92)		≤0.001
Integrated	0.96 (0.89, 1.04)		0.94 (0.92, 0.96)		0.53
Setting		≤0.001		≤0.001	
Metro	1.00		1.00		≤0.001
Urban	1.22 (1.17, 1.27)		1.03 (1.01, 1.04)		≤0.001
Rural	1.17 (1.05, 1.30)		1.03 (1.00, 1.06)		0.028

Table 3 (*continued*)

Table 3 (*continued*)

Patient characteristic	≤50 years		≥60 years		Interaction P value
	HR	P value	HR	P value	
Tumor location		≤0.001		≤0.001	
Right	1.00		1.00		≤0.001
Transverse	0.92 (0.87, 0.97)		1.01 (0.99, 1.02)		0.002
Left/sigmoid	0.83 (0.80, 0.85)		0.93 (0.92, 0.94)		≤0.001
Overlapping	1.26 (1.13, 1.41)		1.29 (1.24, 1.34)		0.742
Not specified	2.06 (1.94, 2.18)		2.09 (2.05, 2.13)		0.633
Grade		≤0.001		≤0.001	
Well differentiated	1.00		1.00		≤0.001
Moderately differentiated	1.59 (1.49, 1.70)		1.21 (1.19, 1.23)		≤0.001
Poorly differentiated	3.07 (2.87, 3.28)		1.85 (1.82, 1.88)		≤0.001
Undifferentiated	3.53 (3.18, 3.92)		1.93 (1.87, 2.00)		≤0.001
Clinical stage		≤0.001		≤0.001	
0	1.00		1.00		≤0.001
I	0.77 (0.62, 0.96)		0.97 (0.93, 1.02)		0.041
II	1.27 (1.03, 1.58)		1.26 (1.20, 1.32)		0.94
III	2.21 (1.79, 2.73)		1.67 (1.59, 1.75)		0.011
IV	11.28 (9.20, 13.83)		6.37 (6.09, 6.67)		≤0.001
Pathologic stage		≤0.001		≤0.001	
0	1.00		1.00		≤0.001
I	0.73 (0.54, 0.98)		0.98 (0.92, 1.03)		0.058
II	1.47 (1.10, 1.97)		1.41 (1.33, 1.49)		0.76
III	3.29 (2.47, 4.38)		1.98 (1.88, 2.10)		≤0.001
IV	15.60 (11.73, 20.75)		6.67 (6.31, 7.06)		≤0.001
CEA		≤0.001		≤0.001	
Normal	1.00		1.00		≤0.001
Elevated	3.61 (3.47, 3.75)		2.27 (2.24, 2.30)		≤0.001
LVI		≤0.001		≤0.001	
No	1.00		1.00		≤0.001
Yes	3.01 (2.79, 3.24)		2.12 (2.07, 2.16)		≤0.001
PNI		≤0.001		≤0.001	
No	1.00		1.00		≤0.001
Yes	2.71 (2.51, 2.93)		2.11 (2.05, 2.17)		≤0.001

The test about the interaction term evaluated whether the HRs associated with a given patient characteristic differ between the two age groups (interaction P value). CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion; CCP, community cancer program.

Table 4 Analysis of factors associated with overall survival by age group (≤50 and ≥60) for patients with rectal cancer

Patient characteristic	≤50 years		≥60 years		Interaction P value
	HR	P value	HR	P value	
Gender		≤0.001		0.53	
Male	1.00		1.00		≤0.001
Female	0.78 (0.75, 0.81)		1.00 (0.98, 1.01)		≤0.001
Race		≤0.001		≤0.001	
White	1.00		1.00		≤0.001
Black	1.50 (1.42, 1.58)		1.23 (1.20, 1.26)		≤0.001
Other	0.96 (0.89, 1.04)		0.83 (0.80, 0.86)		≤0.001
Ethnicity		≤0.001		≤0.001	
Not Hispanic	1.00		1.00		≤0.001
Hispanic	1.16 (1.09, 1.25)		0.86 (0.83, 0.89)		≤0.001
Insurance		≤0.001		≤0.001	
None	1.00		1.00		≤0.001
Private	0.49 (0.46, 0.53)		0.64 (0.61, 0.68)		≤0.001
Medicaid	1.06 (0.98, 1.14)		1.03 (0.95, 1.10)		0.58
Medicare	1.02 (0.93, 1.12)		1.04 (0.98, 1.10)		0.78
Other government	0.61 (0.51, 0.72)		0.94 (0.85, 1.03)		≤0.001
Income		≤0.001		≤0.001	
≤$30,000	1.00		1.00		≤0.001
$30,000–$34,999	0.86 (0.81, 0.92)		0.92 (0.90, 0.94)		0.058
$35,000–$45,999	0.78 (0.74, 0.83)		0.91 (0.89, 0.93)		≤0.001
≥$46,000	0.60 (0.56, 0.63)		0.82 (0.81, 0.84)		≤0.001
Education		≤0.001		≤0.001	
≥29%	1.00		1.00		≤0.001
20–28.9%	0.90 (0.85, 0.96)		0.96 (0.94, 0.99)		0.042
14–19.9%	0.79 (0.74, 0.83)		0.93 (0.91, 0.95)		≤0.001
≤14%	0.63 (0.60, 0.67)		0.88 (0.86, 0.90)		≤0.001
Facility type		≤0.001		≤0.001	
CCP	1.00		1.00		≤0.001
Comprehensive CCP	0.85 (0.80, 0.91)		0.89 (0.87, 0.90)		0.31
Academic/research	0.85 (0.80, 0.92)		0.80 (0.78, 0.81)		0.065
Integrated	0.85 (0.77, 0.94)		0.85 (0.83, 0.88)		0.98

Table 4 (*continued*)

Table 4 (*continued*)

Patient characteristic	≤50 years		≥60 years		Interaction P value
	HR	P value	HR	P value	
Setting		≤0.001		0.317	
Metro	1.00		1.00		≤0.001
Urban	1.15 (1.09, 1.21)		0.98 (0.97, 1.00)		≤0.001
Rural	1.18 (1.04, 1.35)		1.01 (0.96, 1.05)		0.026
Grade		≤0.001		≤0.001	
Well differentiated	1.00		1.00		≤0.001
Moderately differentiated	1.30 (1.19, 1.41)		1.14 (1.11, 1.17)		0.003
Poorly differentiated	2.57 (2.35, 2.82)		1.75 (1.70, 1.81)		≤0.001
Undifferentiated	3.13 (2.67, 3.67)		1.75 (1.62, 1.89)		≤0.001
Clinical stage		≤0.001		≤0.001	
0	1.00		1.00		≤0.001
I	0.92 (0.67, 1.27)		0.99 (0.92, 1.07)		0.65
II	1.84 (1.34, 2.52)		1.34 (1.24, 1.45)		0.055
III	2.14 (1.57, 2.92)		1.34 (1.24, 1.45)		0.004
IV	12.51 (9.18, 17.05)		5.86 (5.43, 6.34)		≤0.001
Pathologic stage		≤0.001		≤0.001	
0	1.00		1.00		≤0.001
I	1.29 (0.88, 1.91)		1.03 (0.94, 1.12)		0.26
II	3.05 (2.07, 4.49)		1.53 (1.40, 1.67)		≤0.001
III	4.80 (3.27, 7.04)		1.94 (1.78, 2.12)		≤0.001
IV	20.72 (14.14, 30.38)		6.13 (5.61, 6.70)		≤0.001
CEA		≤0.001		≤0.001	
Normal	1.00		1.00		≤0.001
Elevated	3.34 (3.17, 3.52)		2.27 (2.22, 2.31)		≤0.001
LVI		≤0.001		≤0.001	
No	1.00		1.00		≤0.001
Yes	2.64 (2.35, 2.96)		1.80 (1.72, 1.89)		≤0.001
PNI		≤0.001		≤0.001	
No	1.00		1.00		≤0.001
Yes	2.87 (2.56, 3.23)		1.81 (1.71, 1.92)		≤0.001

The test about the interaction term evaluated whether the HRs associated with a given patient characteristic differ between the two age groups (interaction P value). CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion; CCP, community cancer program.

study is the analysis of these factors as they relate to patients with early onset CRC.

Disparities in CRC care are becoming increasingly relevant in the US. For example, a recent study using the SEER database showed that OS for young patients with CRC was adversely associated with race whereby Black/African American and Hispanic patients had worse OS across all pathological stages as compared to White patients (16). Another study using the SEER database suggested that a reduction of racially-based treatment disparities may translate into improved survival for minorities (35). These findings are important as they may have implications on the guidelines published by the United States Preventive Services Task Force (USPSTF), which recommend CRC screening at age 50 (36). Other aspects of socioeconomic disparities, such as a lack of health insurance or being underinsured, have been shown to play a significant role in access to care including preventive services (37,38). These disparities may partly explain the increasing rates of early onset CRC, which often presents at an advanced stage as demonstrated by this and other studies (18,39,40). This study is the first to examine not only racial disparities but also other important socioeconomic disparities, including income and education level, that are related to early onset CRC and their association with OS.

We acknowledge that there are limitations to the study. Regarding pathologic variables, LVI was included in the NCDB starting in 2010, and therefore the analysis with respect to LVI is more limited. In contrast, PNI was recorded in 2004. However, missing data and differences among contributing institutions with respect to pathologic analysis and interpretation are other limitations to the analysis. *Table S1* lists the percentages of missing data within the colon and rectal PUF datasets. With respect to the disparities analysis, although the NCDB captures the majority of cancer cases in the US and allows for a robust statistical analysis, patients in minority populations or those with lower socioeconomic status may be less likely to be treated at the cancer centers participating in the NCDB. Therefore, the sample represented by the NCDB may be skewed toward White patients with higher socioeconomic status. While in general, the demographic variables included in the NCDB are quite comprehensive, the categories within each variable can be more limiting. For example, the NCDB uses the Charlson-Deyo comorbidity score as a measure of patient comorbidities, which is truncated to three values (zero indicates no comorbidities, one indicates a single selected comorbidity, and two indicate ≥1 of the selected comorbidities). Similarly, the NCDB has defined cutoff values for income and education derived from 2000 US Census data which are somewhat narrow and may be outdated in our study population.

Conclusions

In conclusion, this study reports new findings regarding both the pathologic and racial/socioeconomic disparities associated with age-related CRC and OS. Not only have younger patients presented at advanced stages (pathologic stage III/IV), they also had more aggressive biologic features including higher rates of CEA positivity, LVI and PNI. In addition, racial/socioeconomic disparities are also related to the increasing rate of early onset CRC and the poorer OS outcomes for minority patients. Interventions to address the disparities aspects of early onset CRC are highly needed. Earlier screening should be seriously considered in patients under 50 years who are African-American and Hispanic, as these populations present with more aggressive and advanced disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: As this study used a national de-identified database, this was deemed exempt from the institutional review board.

Disclaimer: The American College of Surgeons Commission on Cancer provided the Participant User File from the National Cancer Data Base, but has not reviewed or validated the results or conclusions of this study.

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Supplementary

Table S1 Percentage of missing data for selected variables (in *Tables 1-4*) for both the colon and rectum PUFs from the NCDB, 2004–2013

Variable	Missing (%)			
	Colon		Rectum	
	≤50 years	≥60 years	≤50 years	≥60 years
Gender	0.0	0.0	0.0	0.0
Race	0.0	0.0	0.0	0.0
Ethnicity	7.1	7.6	7.0	7.5
Income	4.1	3.6	4.0	3.7
Education	4.1	3.6	4.0	3.7
Facility type	0.0	0.0	0.0	0.0
Urban/rural	3.6	3.6	3.6	3.5
Charlson-Deyo	0.0	0.0	0.0	0.0
Grade	10.4	9.1	13.8	14.2
Clinical stage	53.8	58.6	34.7	41.7
Pathologic stage	15.2	17.1	30.4	35.2
CEA	41.9	47.0	43.4	48.0
LVI	72.8	74.4	76.7	79.2
PNI	73.5	74.5	74.7	77.5
Tumor location	0.1	0.0	NA	NA

All disease is confined to the rectum or rectosigmoid. NA, not applicable. PUFs, participant user files; NCDB, National Cancer Data Base; CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion.

Table S2 Pathologic factors analyzed by race stratified by age group (≤50 and ≥60 years) for patients with colon cancer, based on available data (with missing data shown in *Table S1*)

Group	Caucasian, n (%)	African- American, n (%)	Other, n (%)	Overall, n (%)	P value
Age ≤50 years					
Overall	45,271 (76.0)	10,543 (17.7)	3,753 (6.3)	59,567 (100.0)	–
Site					≤0.001
Right	16,505 (36.5)	4,645 (44.1)	1,170 (31.2)	22,320 (37.5)	
Transverse	3,605 (8.0)	897 (8.5)	295 (7.9)	4,797 (8.1)	
Left	22,627 (50.0)	4,300 (40.8)	2,045 (54.5)	28,972 (48.7)	
Overlapping	585 (1.3)	143 (1.4)	62 (1.7)	790 (1.3)	
Not specified	1,922 (4.2)	551 (5.2)	178 (4.7)	2,651 (4.5)	
Grade					≤0.001
I	4,275 (10.5)	964 (10.3)	326 (9.7)	5,565 (10.4)	
II	27,090 (66.7)	6,571 (70.1)	2,204 (65.9)	35,865 (67.2)	
III	8,361 (20.6)	1,697 (18.1)	747 (22.3)	10,805 (20.2)	
IV	908 (2.2)	146 (1.6)	70 (2.1)	1,124 (2.1)	
Pathologic stage					≤0.001
0	462 (1.2)	96 (1.1)	36 (1.1)	594 (1.2)	
I	6,270 (16.2)	1,258 (14.4)	456 (14.5)	7,984 (15.8)	
II	9,214 (23.9)	2,048 (23.4)	801 (25.5)	12,063 (23.9)	
III	12,862 (33.3)	3,028 (34.6)	1,125 (35.8)	17,015 (33.7)	
IV	9,804 (25.4)	2,332 (26.6)	728 (23.1)	12,864 (25.5)	
CEA					≤0.001
Normal	14,208 (54.0)	2,473 (40.3)	1,116 (52.3)	17,797 (51.5)	
Elevated	12,106 (46.0)	3,663 (59.7)	1,019 (47.7)	16,788 (48.5)	
LVI					0.56
No	7,941 (64.6)	1,855 (65.4)	718 (66.9)	10,514 (64.9)	
Yes	4,347 (35.4)	980 (34.6)	356 (33.1)	5,683 (35.1)	
PNI					0.56
No	9,993 (83.9)	2,326 (83.0)	889 (84.8)	13,208 (83.8)	
Yes	1,914 (16.1)	475 (17.0)	159 (15.2)	2,548 (16.2)	
Age ≥60 years					
Overall	367,197 (85.7)	45,369 (10.6)	15,988 (3.7)	428,554 (100.0)	–
Site					≤0.001
Right	196,179 (53.4)	22,748 (50.2)	7,015 (43.9)	225,942 (52.7)	
Transverse	36,855 (10.0)	4,342 (9.6)	1,387 (8.7)	42,584 (9.9)	
Left	117,819 (32.1)	15,444 (34.1)	6,760 (42.3)	140,023 (32.7)	
Overlapping	4,357 (1.2)	651 (1.4)	206 (1.3)	5,214 (1.2)	
Not specified	11,859 (3.2)	2,166 (4.8)	612 (3.8)	14,637 (3.4)	
Grade					≤0.001
I	37,378 (11.2)	4,586 (11.4)	1,489 (10.4)	43,453 (11.2)	
II	225,042 (67.1)	29,034 (72.5)	10,109 (70.5)	264,185 (67.8)	
III	65,928 (19.7)	5,968 (14.9)	2,523 (17.6)	74,419 (19.1)	
IV	6,854 (2.0)	474 (1.2)	222 (1.5)	7,550 (1.9)	
Pathologic stage					≤0.001
0	3,478 (1.1)	486 (1.4)	185 (1.4)	4,149 (1.2)	
I	74,010 (24.1)	7,910 (22.1)	2,757 (21.6)	84,677 (23.8)	
II	100,032 (32.6)	10,404 (29.0)	3,907 (30.6)	114,343 (32.2)	
III	86,792 (28.3)	10,635 (29.7)	4,067 (31.9)	101,494 (28.6)	
IV	42,539 (13.9)	6,428 (17.9)	1,850 (14.5)	50,817 (14.3)	
CEA					≤0.001
Normal	105,221 (54.1)	10,196 (41.8)	3,910 (48.0)	119,327 (52.6)	
Elevated	89,147 (45.9)	14,206 (58.2)	4,243 (52.0)	107,596 (47.4)	
LVI					0.26
No	67,218 (71.8)	8,566 (72.5)	3,086 (72.3)	78,870 (71.9)	
Yes	26,392 (28.2)	3,254 (27.5)	1,180 (27.7)	30,826 (28.1)	
PNI					≤0.001
No	83,594 (89.6)	10,307 (87.7)	3,806 (88.8)	97,707 (89.4)	
Yes	9,701 (10.4)	1,439 (12.3)	481 (11.2)	11,621 (10.6)	

CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion.

Table S3 Pathologic factors analyzed by ethnicity stratified by age group (≤50 and ≥60 years) for patients with colon cancer, based on available data (with missing data shown in *Table S1*)

Group	Non-Hispanic, n (%)	Hispanic, n (%)	Overall, n (%)	P value
Age ≤50 years				
Overall	50,361 (91.0)	4,982 (9.0)	55,343 (100.0)	–
Site				0.22
Right	18,971 (37.7)	1,779 (35.7)	22,320 (37.5)	
Transverse	4,069 (8.1)	385 (7.7)	4,797 (8.1)	
Left	24,430 (48.5)	2,516 (50.5)	28,972 (48.7)	
Overlapping	658 (1.3)	72 (1.4)	790 (1.3)	
Not specified	2,200 (4.4)	229 (4.6)	2,651 (4.5)	
Grade				0.84
I	4,658 (10.3)	487 (10.8)	5,565 (10.4)	
II	30,350 (67.3)	2,988 (66.5)	35,865 (67.2)	
III	9,079 (20.1)	938 (20.9)	10,805 (20.2)	
IV	979 (2.2)	83 (1.8)	1,124 (2.1)	
Pathologic stage				≤0.001
0	511 (1.2)	44 (1.1)	594 (1.2)	
I	6,894 (16.1)	512 (12.3)	7,984 (15.8)	
II	10,046 (23.5)	1,102 (26.5)	12,063 (23.9)	
III	14,309 (33.4)	1,499 (36.1)	17,015 (33.7)	
IV	11,042 (25.8)	1,001 (24.1)	12,864 (25.5)	
CEA				0.63
Normal	15,062 (51.4)	1,441 (49.9)	17,797 (51.5)	
Elevated	14,220 (48.6)	1,444 (50.1)	16,788 (48.5)	
LVI				0.21
No	9,091 (64.6)	973 (67.4)	10,514 (64.9)	
Yes	4,990 (35.4)	470 (32.6)	5,683 (35.1)	
PNI				0.84
No	11,472 (83.6)	1,181 (84.9)	13,208 (83.8)	
Yes	2,243 (16.4)	210 (15.1)	2,548 (16.2)	
Age ≥60 years				–
Overall	379,371 (95.8)	16,689 (4.2)	396,060 (100.0)	
Site				≤0.001
Right	200,476 (52.9)	8,254 (49.5)	225,942 (52.7)	
Transverse	38,085 (10.0)	1,414 (8.5)	42,584 (9.9)	
Left	123,278 (32.5)	6,241 (37.4)	140,023 (32.7)	
Overlapping	4,646 (1.2)	190 (1.1)	5,214 (1.2)	
Not specified	12,751 (3.4)	583 (3.5)	14,637 (3.4)	
Grade				≤0.001
I	38,311 (11.1)	1,683 (11.3)	43,453 (11.2)	
II	234,017 (67.8)	10,312 (69.2)	264,185 (67.8)	
III	65,939 (19.1)	2,687 (18.0)	74,419 (19.1)	
IV	6,881 (2.0)	221 (1.5)	7,550 (1.9)	
Pathologic stage				≤0.001
0	3,717 (1.2)	174 (1.3)	4,149 (1.2)	
I	75,198 (23.9)	2,941 (21.6)	84,677 (23.8)	
II	101,521 (32.2)	4,252 (31.2)	114,343 (32.2)	
III	89,798 (28.5)	4,238 (31.1)	101,494 (28.6)	
IV	44,875 (14.2)	2,013 (14.8)	50,817 (14.3)	
CEA				≤0.001
Normal	106,143 (52.8)	4,250 (49.1)	119,327 (52.6)	
Elevated	95,064 (47.2)	4,403 (50.9)	107,596 (47.4)	
LVI				0.63
No	71,622 (71.9)	3,318 (71.6)	78,870 (71.9)	
Yes	27,992 (28.1)	1,318 (28.4)	30,826 (28.1)	
PNI				0.44
No	88,825 (89.4)	4,252 (89.9)	97,707 (89.4)	
Yes	10,564 (10.6)	476 (10.1)	11,621 (10.6)	

CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion.

Table S4 Pathologic factors analyzed by race stratified by age group (≤50 and ≥60 years) for patients with rectal cancer, based on available data (with missing data shown in *Table S1*)

Group	Caucasian, n (%)	African-American, n (%)	Other, n (%)	Overall, n (%)	P value
Age ≤50 years					
Overall	31,322 (82.5)	4,131 (10.9)	2,526 (6.7)	37,979 (100.0)	–
Grade					0.016
I	2,491 (9.2)	307 (8.8)	164 (7.6)	2,962 (9.0)	
II	19,928 (73.5)	2,528 (72.7)	1,571 (72.8)	24,027 (73.4)	
III	4,320 (15.9)	607 (17.5)	388 (18.0)	5,315 (16.2)	
IV	365 (1.3)	34 (1.0)	35 (1.6)	434 (1.3)	
Pathologic stage					≤0.001
0	442 (2.0)	35 (1.3)	26 (1.5)	503 (1.9)	
I	5,834 (26.4)	587 (21.8)	389 (23.2)	6,810 (25.7)	
II	4,373 (19.8)	602 (22.4)	331 (19.7)	5,306 (20.1)	
III	7,833 (35.5)	962 (35.8)	671 (39.9)	9,466 (35.8)	
IV	3,599 (16.3)	503 (18.7)	263 (15.7)	4,365 (16.5)	
CEA					≤0.001
Normal	9,485 (53.6)	947 (39.8)	706 (50.4)	11,138 (51.8)	
Elevated	8,227 (46.4)	1,431 (60.2)	695 (49.6)	10,353 (48.2)	
LVI					0.11
No	7,941 (64.6)	5,545 (75.2)	639 (73.6)	434 (70.8)	
Yes	4,347 (35.4)	1,825 (24.8)	229 (26.4)	179 (29.2)	
PNI					≤0.001
No	6,884 (86.4)	770 (81.2)	563 (83.5)	8,217 (85.7)	
Yes	1,084 (13.6)	178 (18.8)	111 (16.5)	1,373 (14.3)	
Age ≥60 years					–
Overall	125,270 (87.0)	11,606 (8.1)	7,054 (4.9)	143,930 (100.0)	
Grade					0.17
I	11,305 (10.5)	1,003 (10.4)	581 (9.6)	12,889 (10.4)	
II	80,702 (74.8)	7,174 (74.7)	4,582 (75.9)	92,458 (74.8)	
III	14,695 (13.6)	1,320 (13.7)	824 (13.7)	16,839 (13.6)	
IV	1,187 (1.1)	106 (1.1)	46 (0.8)	1,339 (1.1)	
Pathologic stage					≤0.001
0	1,628 (2.0)	138 (2.0)	92 (2.0)	1,858 (2.0)	
I	27,106 (33.1)	1,947 (28.6)	1,373 (30.6)	30,426 (32.6)	
II	20,648 (25.2)	1,739 (25.5)	1,169 (26.0)	23,556 (25.2)	
III	23,326 (28.4)	1,997 (29.3)	1,369 (30.5)	26,692 (28.6)	
IV	9,306 (11.3)	992 (14.6)	486 (10.8)	10,784 (11.6)	
CEA					≤0.001
Normal	34,294 (52.5)	2,407 (39.6)	1,665 (47.5)	38,366 (51.2)	
Elevated	31,021 (47.5)	3,665 (60.4)	1,841 (52.5)	36,527 (48.8)	
LVI					0.99
No	20,545 (78.7)	1,808 (78.6)	1,235 (78.7)	23,588 (78.7)	
Yes	5,567 (21.3)	493 (21.4)	335 (21.3)	6,395 (21.3)	
PNI					≤0.001
No	25,206 (89.6)	2,154 (86.2)	1,556 (90.0)	28,916 (89.4)	
Yes	2,915 (10.4)	345 (13.8)	172 (10.0)	3,432 (10.6)	

CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion.

Table S5 Pathologic factors analyzed by ethnicity stratified by age group (≤50 and ≥60 years) for patients with rectal cancer, based on available data (with missing data shown in *Table S1*)

Group	Non-Hispanic, n (%)	Hispanic, n (%)	Overall, n (%)	P value
Age ≤50 years				
Overall	32,270 (91.3)	3,062 (8.7)	35,332 (100.0)	–
Grade				0.006
I	2,510 (9.0)	242 (9.3)	2,962 (9.0)	
II	20,563 (73.7)	1,831 (70.5)	24,027 (73.4)	
III	4,455 (16.0)	479 (18.4)	5,315 (16.2)	
IV	361 (1.3)	45 (1.7)	434 (1.3)	
Pathologic stage				≤0.001
0	435 (1.9)	37 (1.8)	503 (1.9)	
I	5,887 (26.0)	414 (20.6)	6,810 (25.7)	
II	4,554 (20.1)	416 (20.7)	5,306 (20.1)	
III	8,058 (35.6)	778 (38.8)	9,466 (35.8)	
IV	3,704 (16.4)	360 (18.0)	4,365 (16.5)	
CEA				≤0.001
Normal	9,527 (52.2)	803 (45.9)	11,138 (51.8)	
Elevated	8,710 (47.8)	948 (54.1)	10,353 (48.2)	
LVI				1.00
No	5,806 (74.8)	529 (75.0)	6,618 (74.8)	
Yes	1,956 (25.2)	176 (25.0)	2,233 (25.2)	
PNI				1.00
No	7,189 (85.6)	671 (86.0)	8,217 (85.7)	
Yes	1,205 (14.4)	109 (14.0)	1,373 (14.3)	
Age ≥60 years				
Overall	126,390 (94.9)	6,725 (5.1)	133,115 (100.0)	–
Grade				0.90
I	81,220 (74.9)	4,314 (75.3)	92,458 (74.8)	
II	14,831 (13.7)	794 (13.9)	16,839 (13.6)	
III	1,216 (1.1)	52 (0.9)	1,339 (1.1)	
IV	1,803 (2.4)	91 (2.2)	2,032 (2.4)	
Pathologic stage				≤0.001
0	26,910 (32.7)	1,222 (28.7)	30,426 (32.6)	
I	20,694 (25.2)	1,137 (26.7)	23,556 (25.2)	
II	23,473 (28.5)	1,295 (30.4)	26,692 (28.6)	
III	9,492 (11.5)	528 (12.4)	10,784 (11.6)	
IV	21,320 (78.6)	1,148 (77.6)	23,588 (78.7)	
CEA				≤0.001
Normal	32,016 (48.6)	1,777 (52.2)	36,527 (48.8)	
Elevated	26,151 (89.4)	1,478 (89.5)	28,916 (89.4)	
LVI				0.97
No	5,804 (21.4)	332 (22.4)	6,395 (21.3)	
Yes	33,831 (51.4)	1,625 (47.8)	38,366 (51.2)	
PNI				0.97
No	3,117 (10.6)	173 (10.5)	3,432 (10.6)	
Yes	126,390 (94.9)	6,725 (95.5)	143,930 (100.0)	

CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion.