Magnitude of the Age-Advancement Effect of Comorbidities in Colorectal Cancer Prognosis

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ABSTRACT

Background: Comorbidities and old age independently compromise prognosis of patients with colorectal cancer (CRC). The impact of comorbidities could thus be considered as conveying worse prognosis already at younger ages, but evidence is lacking on how much worsening of prognosis with age is advanced to younger ages in comorbid versus noncomorbid patients. We aimed to quantify, for the first time, the impact of comorbidities on CRC prognosis in “age advancement” of worse prognosis. **Methods:** A total of 4,602 patients aged ≥ 30 years who were diagnosed with CRC in 2003 through 2014 were recruited into a population-based study in the Rhine-Neckar region of Germany and observed over a median period of 5.1 years. Overall comorbidity was quantified using the Charlson comorbidity index (CCI). Hazard ratios and age advancement periods (AAPs) for comorbidities were calculated from multivariable Cox proportional hazards models for relevant survival outcomes. **Results:** Hazard ratios for CCI scores 1, 2, and ≥ 3 compared with CCI 0 were 1.25, 1.53, and 2.30 ($P < .001$) for overall survival and 1.20, 1.48, and 2.03 ($P < .001$) for disease-free survival, respectively. Corresponding AAP estimates for CCI scores 1, 2, and ≥ 3 were 5.0 (95% CI, 1.9–8.1), 9.7 (95% CI, 6.1–13.3), and 18.9 years (95% CI, 14.4–23.3) for overall survival and 5.5 (95% CI, 1.5–9.5), 11.7 (95% CI, 7.0–16.4), and 21.0 years (95% CI, 15.1–26.9) for disease-free survival. Particularly pronounced effects of comorbidity on CRC prognosis were observed in patients with stage I–III CRC. **Conclusions:** Comorbidities advance the commonly observed deterioration of prognosis with age by many years, meaning that at substantially younger ages, comorbid patients with CRC experience survival rates comparable to those of older patients without comorbidity. This first derivation of AAPs may enhance the empirical basis for treatment decisions in patients with comorbidities and highlight the need to incorporate comorbidities into prognostic nomograms for CRC.

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Background

With an approximately 4.4% lifetime risk, colorectal cancer (CRC) remains the third most commonly diagnosed cancer in the world.¹ Although prognosis has improved recently, $>40\%$ of patients with CRC still die within 5 years of diagnosis.² Because of the aging population, the burden of CRC has been predicted to increase in the next decade.³

CRC is largely diagnosed at older age, when comorbidities are common.⁴ Some studies have examined the prognostic role of comorbidity in patients with CRC,^{5–16} wherein decreased survival was observed in patients with comorbidities. However, many previous studies could not adjust for important factors such as tumor stage.^{7,9,11} Furthermore, evidence on the role of comorbidities in recurrence-related outcomes is limited. It is also unclear whether the impact of comorbidities varies by tumor stage or site. In some previous studies, the effect of comorbidity on overall survival (OS) appeared to be more pronounced in patients with early-stage CRC,^{5,14,15} but further evidence on other outcomes and from population-based studies is needed for a more comprehensive conclusion regarding the effect of comorbidities on specific patient groups.

Comorbidities and old age independently affect CRC prognosis. Therefore, it is possible that the presence of comorbidities could be associated with worse prognosis at younger ages, but evidence on the “age equivalent” of worsening of prognosis in comorbid compared with noncomorbid patients is lacking. Estimating this could provide valuable information for personalized care and enhanced prediction of prognosis for patients with CRC. The goal of this study was to thoroughly assess the impact of comorbidities on OS and disease-free survival (DFS) in a cohort of patients with CRC and to quantify, for the first time, the “age-equivalent effects” of comorbidities with respect to CRC prognosis.

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Methods

Study Design and Population

Our study is based on data from 4,602 patients with CRC who were diagnosed in 2003 through 2014 and recruited into the DACHS study, which is an ongoing population-based case-control study in the Rhine-Neckar region of Germany that was initiated primarily to evaluate the effects of endoscopic screening on CRC risk. Cases are also being followed up to evaluate prognostic factors. Patients with first time diagnosis of CRC (ICD-10 codes C18–C20) and aged ≥ 30 years were eligible. Patients were recruited from all 22 hospitals providing first-line treatment of CRC in the study region of approximately 2 million inhabitants. According to estimates from cancer registries, approximately half of the eligible patients were recruited. Further details of the DACHS study have been described elsewhere.^{17,18} The DACHS study was approved by the ethics committees of the Medical Faculty of Heidelberg University and the state medical boards of Baden-Wuerttemberg and Rhineland-Palatinate. All participants provided written informed consent.

At baseline, trained interviewers conducted interviews with participants to collect information on lifestyle factors and medical history. Detailed information on treatment and comorbidities were also recorded in medical records. Follow-up started from CRC diagnosis; vital status and cause of death were ascertained from population registries and public health authorities approximately 3, 5, and 10 years after diagnosis. Information on CRC treatment, newly diagnosed cancers, and recurrence was obtained from physicians approximately 3 years after diagnosis using a standardized questionnaire (physicians abstracted the information from their patient databases). Recurrence history for patients who died during or were lost to follow-up was ascertained from the last attending physician.

Inclusion Criteria

Because of limited evidence on the impact of comorbidities within tumor stages, our analyses included patients with stage I–IV CRC (UICC stages).¹⁹ Patients who did not undergo surgery for CRC and those who died within 1 month of surgery were excluded (Figure 1).

Ascertainment of Comorbidities

ICD-10 codes for comorbidities diagnosed either before or at the time of CRC diagnosis were abstracted from discharge reports. To ensure comparability with previous studies, we used the Charlson comorbidity index (CCI),²⁰ adapted by Deyo et al,²¹ to quantify overall comorbidity.

Figure 1. Selection of analytic sample.
Abbreviation: CRC, colorectal cancer.

Briefly, the CCI comprises 19 weighted comorbidities, with weights ranging from 1 to 6 based on the magnitude of the adjusted 1-year mortality risk.²⁰ Similar to previous studies,^{13,16} we grouped patients into 4 groups, namely CCI score 0 (no comorbidity), 1, 2, or ≥ 3 (severe comorbidity).

Statistical Analysis

We assessed the distribution of the 4 comorbidity groups according to patient and tumor characteristics. Associations of CCI scores with OS (mortality from any cause), CRC-specific survival (CSS; mortality from CRC), non-CRC-specific survival (nCSS; mortality from causes other than CRC), DFS (recurrence of CRC, or mortality from any cause), and recurrence-free survival (RFS; recurrence of or mortality from CRC) were examined using Cox proportional hazards regression. Time was estimated from CRC diagnosis to the respective endpoints or end of follow-up, whichever occurred first.

Because participants entered the study at different times, we accounted for specific left-truncation, by

incorporating “delayed entry time” into the Cox models. Two adjustment levels defined a priori were applied: (1) adjustment for sex, age, tumor stage, tumor site, period of diagnosis, years of school education, smoking status, body mass index (BMI), lifetime physical activity, lifetime alcohol consumption, and use of nonsteroidal anti-inflammatory drugs and statins (ie,

model 1), and (2) additional adjustment for initiation of chemo(radio)therapy (ie, model 2). The covariates were incorporated into the models as categorical variables, as listed in supplemental eTable 1, available with this article at JNCCN.org. We assessed the proportional hazards assumption for all covariates by adding time-dependent interaction terms to the covariates and

Table 1. Association of Overall Comorbidity With Survival Outcomes

	At Risk n	Events n	HR ^a (95% CI) ^b	HR ^c (95% CI) ^b	Events n	HR ^a (95% CI) ^b	HR ^c (95% CI) ^b
CRC (N=4,602)				Overall Survival			
				CSS			
CCI 0	2,607	866	Ref	Ref	595	Ref	Ref
CCI 1	869	365	1.25 (1.10–1.42)	1.23 (1.08–1.39)	192	1.05 (0.89–1.24)	1.04 (0.88–1.23)
CCI 2	620	285	1.53 (1.34–1.76)	1.51 (1.32–1.74)	142	1.30 (1.08–1.57)	1.29 (1.07–1.55)
CCI ≥3	506	291	2.30 (1.99–2.66)	2.25 (1.95–2.60)	115	1.56 (1.26–1.93)	1.54 (1.24–1.91)

checking whether their effects were statistically significant. Time-dependent interaction terms (with age, tumor stage, year of diagnosis, BMI, and chemo[radio]therapy) were added to the model in case of violation of the proportional assumption. Subgroup analyses according to tumor site and stage were also performed, and stage-specific results for OS were furthermore illustrated with adjusted survival curves. We moreover investigated the associations of individual comorbidities with CRC prognosis. Results from model 1 are reported as main results and those from model 2 were used to assess potential mediating effects of chemo(radio)therapy initiation. In sensitivity analyses, we used the Fine-Gray model²² to account for non-CRC mortality (a competing event for CSS and RFS) and CRC mortality (a competing event for nCSS).

In addition to hazard ratios (HRs), we calculated age advancement periods (AAPs) to quantify “age-equivalent effects” of comorbidities following an approach that was previously introduced as “risk or rate advancement periods,”²³ which is increasingly used in epidemiology to quantify the age advancement of the risk of diseases

for which risk increases with age.^{24–28} A detailed description of the calculation of AAPs is provided in supplemental eAppendix 1. In brief, AAPs are derived as ratios of the regression coefficient for the risk factor under investigation (here, CCI scores 1, 2, or ≥ 3 vs CCI 0) to the regression coefficient for age (where age is included in the model as a linear term, in years). Regression coefficients from model 1 were used to derive AAPs to quantify the extent (age difference) to which worse survival rates occur earlier (at younger ages) in comorbid versus noncomorbid patients. All analyses were conducted using SAS 9.4 (SAS Institute Inc). Statistical tests were 2-sided, with $\alpha=0.05$.

Results

Characteristics of Study Participants

Of 4,916 patients with CRC diagnosed in 2003–2014, 4,829 underwent CRC surgery and 4,811 survived for ≥ 1 month. Of these, those with missing data on any of the covariates of interest were excluded (n=209),

Table 2. AAPs for Overall Comorbidity and Survival Outcomes

Outcome	All Stages		Stages I–III	
	HR ^a (95% CI) ^b	AAP ^a (95% CI) ^{b,c}	HR ^a (95% CI) ^b	AAP ^a (95% CI) ^{b,c}
Overall survival				
CCI 0	Ref	Ref	Ref	Ref
CCI 1	1.25 (1.10; 1.42)	5.02 (1.90; 8.14)	1.43 (1.23; 1.66)	6.01 (3.13; 8.89)
CCI 2	1.53 (1.34; 1.76)	9.70 (6.12; 13.28)	1.67 (1.43; 1.96)	8.67 (5.51; 11.83)
CCI ≥ 3	2.30 (1.99; 2.66)	18.86 (14.42; 23.30)	2.76 (2.35; 3.26)	17.48 (13.54; 21.42)
CRC-specific survival				
CCI 0	Ref	Ref	Ref	Ref
CCI 1	1.05 (0.89; 1.24)	2.11 (–5.21; 9.43)	1.25 (1.00; 1.57)	7.99 (–0.86; 16.84)
CCI 2	1.30 (1.08; 1.57)	11.53 (2.57; 20.49)	1.42 (1.11; 1.80)	12.11 (2.14; 22.08)
CCI ≥ 3	1.56 (1.26; 1.93)	19.07 (7.80; 30.34)	1.94 (1.47; 2.55)	24.26 (10.35; 38.17)
Non-CRC-specific survival				
CCI 0	Ref	Ref	Ref	Ref
CCI 1	1.70 (1.40; 2.07)	5.87 (3.32; 8.42)	1.63 (1.33; 2.00)	5.12 (2.65; 7.59)
CCI 2	1.98 (1.60; 2.44)	7.58 (4.81; 10.35)	1.93 (1.56; 2.38)	6.89 (4.22; 9.56)
CCI ≥ 3	3.62 (2.94; 4.45)	14.50 (11.29; 17.71)	3.54 (2.87; 4.37)	13.51 (10.44; 16.58)
Disease-free survival				
CCI 0	Ref	Ref	Ref	Ref
CCI 1	1.20 (1.06; 1.36)	5.46 (1.45; 9.47)	1.33 (1.15; 1.54)	6.49 (2.74; 10.24)
CCI 2	1.48 (1.30; 1.70)	11.68 (6.97; 16.39)	1.58 (1.35; 1.84)	10.31 (6.11; 14.51)
CCI ≥ 3	2.03 (1.77; 2.35)	21.01 (15.14; 26.88)	2.44 (2.08; 2.87)	20.48 (15.08; 25.88)

Abbreviations: AAP, age advancement period (in years); BMI, body mass index; CCI, Charlson comorbidity index score; CRC, colorectal cancer; HR, hazard ratio.

^aAdjusted for age, age $\times$ log (follow-up time), sex, tumor stage, tumor stage $\times$ log (follow-up time), years of school education, tumor site, period of diagnosis, period of diagnosis $\times$ log (follow-up time), smoking status, BMI, BMI $\times$ log (follow-up time), lifetime physical activity, lifetime alcohol consumption, and use of nonsteroidal anti-inflammatory drugs and statins.

^bBold indicates statistically significant results.

^cAge was included in the model as a linear term and “age $\times$ log (follow-up time)” was removed from the model.

resulting in a total of 4,602 patients included in the main analysis (Figure 1). We excluded 104 patients from the analyses of recurrence-related outcomes because they had recurrence before the interview date. A total of 1,807 (39%) deaths occurred during a median follow-up period of 5.1 years, of which 1,044 (58%) were caused by CRC.

Descriptive statistics of the 4,602 patients are summarized in supplemental eTables 2 and 3. More than 43% of the patients had CCI ≥ 1 (eTable 2). The 2 most common comorbidities were various cardiovascular diseases (CVDs; 18% overall) and diabetes (16%). Median age of the participants was 69 years. Comorbidity was particularly common in men, older and underweight/obese patients, former smokers, those recently diagnosed, those with right-sided colon cancer and stage I–II disease, and nonrecipients of chemo(radio)therapy (supplemental eTable 3).

Comorbidity and CRC Prognosis

Tables 1 and 2 show adjusted HRs for the associations of overall comorbidity and CRC prognosis. HRs for CCI scores 1, 2, and ≥ 3 , compared with CCI 0, were 1.25, 1.53, and 2.30 ($P < .001$) for OS, 1.05, 1.30, and 1.56 ($P < .001$) for CSS, 1.20, 1.48, and 2.03 ($P < .001$) for DFS, and 1.70, 1.98, and 3.62 ($P < .001$) for nCSS. The corresponding AAP estimates were 5.0, 9.7, and 18.9 years for all-cause mortality, 2.1, 11.5, and 19.1 years for CRC-specific mortality, 5.5, 11.7, and 21.0 years for worse DFS, and 5.9, 7.6, and 14.5 years for non-CRC mortality (Table 2). Noncomorbid patients aged 70 years, for example, had similar OS rates as 65-, 60-, and 51-year-old patients with CCI scores 1, 2, and ≥ 3 , respectively (Figure 2). Compared with patients with CCI 0, those with CCI scores 2 and ≥ 3 had 28% and 37% significantly poorer RFS, respectively. In sensitivity analyses that accounted for competing events in the associations of comorbidity

with CSS, RFS, and non-CRC mortality, HRs were attenuated (supplemental eTable 4). Supplemental eTable 1 shows adjusted HRs for the associations of the covariates adjusted for in the multivariable models with OS and CSS.

Subgroup Analyses by Tumor Site and Stage

Comorbidity was associated with poorer OS and CSS in all tumor sites, with comparable HRs (Table 1). The

Table 3. Association of Comorbidity With Recurrence-Free Survival

	All Stages		
	At Risk n	Events n	HR ^a (95% CI) ^b
Right-sided colon cancer (n=1,509) ^c			
CCI 0	771	183	Ref
CCI 1	307	73	1.07 (0.80–1.42)
CCI 2	220	57	1.43 (1.05–1.96)
CCI ≥ 3	211	53	1.25 (0.90–1.73)
			$P = .124$
Left-sided colon cancer (n=1,181) ^d			
CCI 0	701	187	Ref
CCI 1	211	52	1.06 (0.77–1.47)
CCI 2	147	39	1.32 (0.92–1.89)
CCI ≥ 3	122	34	1.53 (1.02–2.30)
			$P = .128$
Rectal and rectosigmoidal cancer (n=1,808) ^e			
CCI 0	1,073	317	Ref
CCI 1	333	92	1.02 (0.80–1.29)
CCI 2	239	73	1.23 (0.95–1.61)
CCI ≥ 3	163	46	1.55 (1.11–2.16)
			$P = .394$
Rectal cancer only (n=1,569)			
CCI 0	932	260	Ref
CCI 1	299	81	1.02 (0.78–1.32)
CCI 2	201	65	1.32 (1.00–1.75)
CCI ≥ 3	137	43	1.75 (1.23–2.48)
			$P = .006$

$P_{\text{interaction}} = .841$ for tumor site.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity score; HR, hazard ratio.

^aAdjusted for age, age, sex, years of school education, tumor stage, tumor stage $\times$ log (follow-up time), period of diagnosis, period of diagnosis $\times$ log (follow-up time), smoking status, BMI, BMI $\times$ log (follow-up time), lifetime physical activity, lifetime alcohol consumption, and use of nonsteroidal anti-inflammatory drugs and statins.

^bBold indicates statistically significant results.

^cFrom cecum to the transverse colon; 23 patients were excluded due to lack of information on recurrence or had recurrence before the interview date.

^dFrom the splenic colonic flexure to the sigmoid colon; 32 patients were excluded due to lack of information on recurrence or had recurrence before the interview date.

^e49 patients were excluded due to lack of information on recurrence or had recurrence before the interview date.

Figure 2. Age-equivalent effect of comorbidities on all-cause mortality.

Abbreviations: CCI, Charlson comorbidity index score; HR, hazard ratio.

association of comorbidity with RFS, however, seemed pronounced in patients with rectal cancer (Table 3). In stage-specific analyses (Table 4 and Figure 3), comorbidity was associated with decreased OS and CSS in patients with stage I–III disease only. HRs for both OS and CSS decreased steadily with increasing stage, whereas comorbidity was associated with increased non-CRC mortality in all stages, and HRs increased with increasing stage (Table 4). Significant interaction between comorbidity and stage was observed for OS ($P_{\text{interaction}} < .001$). When we restricted our analyses to stage I–III, the associations of comorbidity with the investigated outcomes were stronger than those reported for all stages, but the AAP estimates were mostly comparable (Table 2).

Subgroup Analyses by Individual Comorbidities

Table 5 summarizes the associations of individual comorbidities with survival outcomes, overall and restricted to patients with stage I–III. Heart failure, renal disease, diabetes, and other cancers were consistently associated with decreased OS. Comorbidities that had the most significant impact on OS were renal disease and heart failure; each had an AAP estimate of approximately

20 years. Renal disease, heart failure, myocardial infarction (stage I–III only), and other cancers were associated with poorer CSS. Heart failure, peripheral vascular disease, stroke, renal disease, diabetes, and other cancers were associated with increased non-CRC mortality.

Discussion

We aimed to thoroughly evaluate the impact of comorbidities on CRC prognosis. Comorbidity was associated with substantially poorer prognosis, especially in patients with stage I–III disease. Besides the conventional quantification of comorbidity effects by HRs, we also calculated AAPs to estimate the “age-equivalent effects” of comorbidity in CRC prognosis. Patients with CCI scores of 1, 2, and ≥ 3 experienced the same levels of all-cause mortality as noncomorbid patients aged 5, 10, and 19 years older, respectively.

The prevalence of comorbidities in our study (43%) is higher than reported in a study from Japan (25%)¹⁴ but lower than an estimate from the United States (58%) in patients with comparable age.²⁹ In particular, CVDs, diabetes, chronic obstructive pulmonary disease, and renal disease are higher in our study than in Japan but

Table 4. Associations of Overall Comorbidity With Survival Outcomes, Stratified by Tumor Stage

Stage I (n=1,086)			Stage II (n=1,407)		Stage III (n=1,510)		Stage IV (n=599)	
Event/At Risk n		HR ^a (95% CI) ^b	Event/At Risk n		Event/At Risk n		Event/At Risk n	
			HR ^a (95% CI) ^b		HR ^a (95% CI) ^b		HR ^a (95% CI) ^b	
Overall survival (<i>P</i> _{interaction} <.001)								
CCI 0	92/618	Ref	168/726	Ref	289/881	Ref	317/382	Ref
CCI 1	54/185	1.95 (1.37–2.77)	95/285	1.40 (1.08–1.82)	129/292	1.32 (1.06–1.64)	87/107	0.94 (0.73–1.21)
CCI 2	48/153	1.92 (1.33–2.77)	88/204	1.78 (1.36–2.32)	94/202	1.52 (1.20–1.93)	55/61	1.25 (0.93–1.68)
CCI ≥3	64/130	3.30 (2.33–4.68)	89/192	2.87 (2.17–3.82)	92/135	2.54 (1.96–3.29)	46/49	1.25 (0.90–1.75)
		<i>P</i> <.001	<i>P</i> <.001		<i>P</i> <.001		<i>P</i> =.245	
CRC-specific survival (<i>P</i> _{interaction} =.189)								
CCI 0	17/618	Ref	66/726	Ref	206/881	Ref	306/382	Ref
CCI 1	11/185	2.25 (1.00–5.07)	31/285	1.29 (0.83–2.01)	74/292	1.11 (0.84–1.47)	76/107	0.88 (0.68–1.15)
CCI 2	11/153	2.80 (1.25–6.25)	24/204	1.36 (0.84–2.19)	57/202	1.33 (0.99–1.80)	50/61	1.17 (0.86–1.59)
CCI ≥3	7/130	2.14 (0.84–5.46)	25/192	2.49 (1.52–4.10)	43/135	1.80 (1.26–2.56)	40/49	1.13 (0.79–1.61)
		<i>P</i> =.059	<i>P</i> =.005		<i>P</i> =.008		<i>P</i> =.443	
Non-CRC-specific survival (<i>P</i> _{interaction} =.826)								
CCI 0	75/618	Ref	102/726	Ref	83/881	Ref	11/382	Ref
CCI 1	43/185	1.82 (1.23–2.70)	64/285	1.58 (1.14–2.18)	55/292	1.86 (1.30–2.66)	11/107	3.12 (1.28–7.61)
CCI 2	37/153	1.75 (1.16–2.64)	64/204	2.23 (1.61–3.09)	37/202	2.09 (1.41–3.12)	5/61	3.32 (1.09–10.10)
CCI ≥3	57/130	3.45 (2.37–5.03)	64/192	3.37 (2.38–4.77)	49/135	4.37 (2.93–6.54)	6/49	5.10 (1.64–15.81)
		<i>P</i> <.001	<i>P</i> <.001		<i>P</i> <.001		<i>P</i> =.011	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index score; CRC, colorectal cancer; HR, hazard ratio.

^aAdjusted for age, age $\times$ log (follow-up time), sex, years of school education, tumor site, year of diagnosis, period of diagnosis $\times$ log (follow-up time), smoking status, BMI, BMI $\times$ log (follow-up time), lifetime physical activity, lifetime alcohol consumption, and use of nonsteroidal anti-inflammatory drugs and statins.

^bBold indicates statistically significant results.

Figure 3. Adjusted survival curves for comorbidity and colorectal cancer prognosis by tumor stage: (A) I, (B) II, (C) III, and (D) IV. Abbreviations: CCI, Charlson comorbidity index score; OS, overall survival.

lower than in the United States. These variations might reflect differences in assessment of comorbidities across countries. Several previous studies have investigated the effect of overall comorbidity on OS or CSS.^{5–16,30,31} Most found poorer prognosis in comorbid patients with CRC. However, many were small in size^{6,8,10,30} and could not adjust for stage.^{7,9,11} Our study, which addressed these limitations, showed even shorter OS and CSS in comorbid patients. In contrast to some studies that showed no significant association for CSS in comorbid patients,^{12,14,16,30} we found a significant decrease in CSS also, even after accounting for competing events. Binary grouping of CCI score (≥ 1 vs 0)¹⁴ or small sample size³⁰ might explain why some of the previous studies found no significant association for CSS. Our estimates are comparable to those from a meta-analysis of 5 cohort studies, which observed a 41% and 103% increased all-cause mortality in patients with CRC and CCI scores of 1 to 2 and ≥ 3 compared with patients with a CCI score of 0, respectively.³² Evidence regarding to what extent comorbidity impacts non-CRC mortality is limited.³³ In our study, comorbidity was associated with increased non-CRC mortality, and furthermore, HRs were higher than those of OS and CSS, suggesting that comorbidity affects prognosis in patients with CRC

mainly through non-CRC deaths (presumably directly comorbidity-related).

Previous evidence on whether the effect of comorbidity on CRC prognosis varies by tumor stage has been inconclusive. Results from some studies suggested that the prognostic impact of comorbidity decreases with increasing stage.^{5,14,15,29} Our study confirmed this trend and found no association in patients with stage IV CRC. Patients with stage IV disease have very poor survival, with death almost exclusively being due to the metastasized tumor itself. It is, therefore, plausible that the additional impact of comorbidity on prognosis in these patients may be very small. Conversely, for non-CRC mortality, the effect of comorbidity increased with increasing tumor stage. Although this has not been investigated previously, patients with advanced-stage disease might receive more aggressive treatments and thus have increased risk of adverse effects and complications, which could increase noncancer mortality.

Evidence on the impact of comorbidity on recurrence-related outcomes is sparse. The few available studies assessed DFS only and found significantly shorter DFS in comorbid patients with CRC.^{14,31} We evaluated to what extent comorbidity impacts RFS, overall and in subgroups according to tumor site. We observed significantly poorer RFS in moderately and severely comorbid patients and stronger associations in patients with rectal cancer. Reasons for this differential impact of comorbidity are unclear and call for further investigation into whether comorbidities affect therapeutic response at specific tumor sites or affect tumor biology, as results from a study suggested that comorbidities could accelerate CRC progression.³⁴ Evidence showing that right-sided CRC has poorer tumor features could also play a role,³⁵ as our data showed pronounced impact of comorbidity in tumor stages and sites with good prognosis.

Previous studies have shown that clusters of individual comorbidities impact CRC prognosis differently.^{30,33,36} We found renal disease to be the comorbidity with the strongest impact on CRC prognosis, followed by heart failure, and each advanced all-cause mortality by approximately 20 years. Renal disease includes end-stage renal disease, which is a contraindication of administration of chemo(radio)therapy according to the S3 guideline in Germany.³⁷ Renal disease also mostly results from complications of debilitating chronic diseases, including heart failure and diabetes,³⁸ and could thus represent accumulation of effects of several severe comorbidities. These factors might explain why it had a stronger prognostic impact than CVDs and other comorbidities.

Our study is the first to quantify the “age-equivalent effects” of comorbidities in CRC prognosis. Our estimates of AAPs, which range from approximately 2 to 6 years

Table 5. Associations of Individual Comorbidities With Survival Outcomes

	At Risk n	Overall Survival		CSS		Non-CSS	
		Events n	HR ^a (95% CI) ^b	Events n	HR ^a (95% CI) ^b	Events n	HR ^a (95% CI) ^b
Stage I–IV							
No comorbidity	2,607	866	Ref	595	Ref	271	Ref
MI only	97	41	1.27 (0.91–1.77)	25	1.19 (0.78–1.81)	16	1.43 (0.86–2.38)
Heart failure only	46	32	1.80 (1.24–2.63)	15	1.73 (1.00–3.00)	17	1.94 (1.15–3.26)
PVD only	108	35	1.08 (0.76–1.52)	18	0.76 (0.47–1.22)	17	1.85 (1.12–3.05)
Stroke only	87	39	1.57 (1.12–2.18)	16	1.24 (0.75–2.07)	23	1.78 (1.14–2.77)
COPD only	151	51	1.09 (0.82–1.46)	29	0.98 (0.67–1.43)	22	1.31 (0.84–2.04)
Renal disease only	71	37	2.14 (1.53–3.00)	20	1.91 (1.21–3.00)	17	2.31 (1.39–3.85)
Mild liver disease only	118	34	1.02 (0.72–1.44)	19	0.88 (0.55–1.40)	15	1.19 (0.70–2.00)
Diabetes only	364	160	1.35 (1.13–1.61)	86	1.11 (0.88–1.40)	74	1.77 (1.35–2.31)
Non-CRCs only	218	90	1.46 (1.17–1.82)	51	1.39 (1.04–1.86)	39	1.56 (1.11–2.20)
Stage I–III							
No comorbidity	2,225	549	Ref	289	Ref	260	Ref
MI only	83	32	1.67 (1.13–2.45)	16	1.79 (1.03–3.10)	16	1.55 (0.93–2.58)
Heart failure only	43	29	1.91 (1.28–2.85)	12	2.03 (1.09–3.75)	17	1.95 (1.16–3.29)
PVD only	96	27	1.26 (0.85–1.87)	13	1.09 (0.62–1.91)	14	1.61 (0.93–2.79)
Stroke only	78	31	1.36 (0.93–1.98)	10	1.01 (0.53–1.93)	21	1.60 (1.01–2.53)
COPD only	134	39	1.29 (0.93–1.80)	17	1.23 (0.75–2.02)	22	1.36 (0.88–2.12)
Renal disease only	62	28	2.00 (1.35–2.95)	12	1.80 (1.00–3.25)	16	2.21 (1.30–3.73)
Mild liver disease only	111	30	1.14 (0.79–1.66)	15	1.04 (0.61–1.75)	15	1.21 (0.72–2.05)
Diabetes only	313	113	1.42 (1.15–1.76)	45	1.18 (0.85–1.63)	68	1.69 (1.28–2.23)
Non-CRCs only	197	70	1.54 (1.19–1.98)	33	1.53 (1.06–2.21)	37	1.53 (1.07–2.17)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CSS, CRC-specific survival; HR, hazard ratio; MI, myocardial infarction; PVD, peripheral vascular disease.

^aAdjusted for age, age × log (follow-up time), sex, tumor stage, tumor stage × log (follow-up time), years of school education, tumor site, period of diagnosis, period of diagnosis × log (follow-up time), smoking status, BMI, BMI × log (follow-up time), lifetime physical activity, lifetime alcohol consumption, and use of nonsteroidal anti-inflammatory drugs and statins.

^bBold indicates statistically significant results.

for patients with CCI score of 1 to approximately 14 to 21 years for patients with CCI score ≥ 3 , show how comorbidities strongly impact CRC prognosis. For example, patients aged 70 years without comorbidities had a similar OS rate as 51-year-old patients with CCI ≥ 3 . This underlines the important role of comorbidities in the prediction of prognosis and in therapeutic decisions, in addition to age and tumor characteristics. Despite the strong effect of comorbidities on CRC prognosis, prognostic tools still focus on tumor characteristics only.^{39,40} Further studies using this concept could provide useful evidence for enhanced treatment of comorbid patients and on the need to incorporate comorbidities into nomograms for enhanced prediction of CRC prognosis. Future studies should also evaluate “age-equivalent effects” of other relevant clinicopathologic factors in CRC prognosis.

Several possible mechanisms exist through which comorbidities might affect CRC prognosis. Severe comorbidities could obscure CRC signs, leading to late diagnosis and worse outcomes.^{41,42} Also, despite the established benefits of neoadjuvant and adjuvant treatments, comorbid patients receive such treatments less often because of potentially increased risk of chemotoxicities.^{12,29,30} The associations in our study, however, persisted after adjusting for initiation of chemo(radio)therapy, suggesting that this mechanism might play a minor role. Lastly, diagnosis of CRC, like other cancer diagnoses, could lead to reduced adherence to treatment regimen for long-term conditions.⁴³ Medical care for patients with cancer might therefore benefit from more comprehensive, personalized consideration of both cancer and patient characteristics, including comorbidities.

Our study has limitations despite its unique strengths. Although we made extensive efforts to comprehensively include all patients across the study region, approximately 50% of the eligible patients were recruited. There was also an age gradient, with higher recruitment rates at younger ages. However, we did not set an upper age limit, which has merits when aiming to assess the impact of comorbidities. Nevertheless, the most comorbid patients who would not be able to actively participate in a study requiring an interview of approximately 1 hour are most likely underrepresented, which limited our ability to assess the effects of most severe comorbidities. Our results might therefore be less generalizable to populations with severe comorbidities. Although we adjusted for a large number of confounding factors, potential residual confounding cannot be excluded, which might affect the accuracy of our AAP estimates. We used comorbidities documented in medical records only for our analyses, because data on self-reported comorbidities were not complete. Comorbidity status could also change with cancer progression or aging, but, like previous studies, its impact could only be evaluated with baseline data in our study. The resulting inaccuracy of comorbidity classification most likely has led to underestimation of comorbidity effects.

Conclusions

In the era of personalized oncology, patient characteristics often receive less attention as prognostic factors but could be equally as important as tumor characteristics in the enhanced personalized care of patients with CRC. Our findings corroborate and expand prior evidence showing that comorbidities are important prognostic characteristics that require careful consideration in CRC care. Comorbid patients at substantially younger ages experience comparable survival rates to older patients without comorbidity. This first derivation of age-advancement periods may enhance the empirical

basis for treatment decisions in comorbid patients and highlight the need to incorporate comorbidities into prognostic nomograms for CRC.

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References

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- Hollecsek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 – results from the EUROCARE-5 study. *Eur J Cancer* 2015;51:2158–2168.
- Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683–691.
- Yancik R, Ershler W, Satariano W, et al. Report of the national institute on aging task force on comorbidity. *J Gerontol A Biol Sci Med Sci* 2007;62:275–280.
- Read WL, Tierney RM, Page NC, et al. Differential prognostic impact of comorbidity. *J Clin Oncol* 2004;22:3099–3103.
- Hines RB, Chatla C, Bumpers HL, et al. Predictive capacity of three comorbidity indices in estimating mortality after surgery for colon cancer. *J Clin Oncol* 2009;27:4339–4345.
- Iversen LH, Nørgaard M, Jacobsen J, et al. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006—a population-based cohort study. *Dis Colon Rectum* 2009;52:71–78.
- Kristjansson SR, Jordhoy MS, Nesbakken A, et al. Which elements of a comprehensive geriatric assessment (CGA) predict post-operative complications and early mortality after colorectal cancer surgery? *J Geriatr Oncol* 2010;1:57–65.
- Ostenfeld EB, Nørgaard M, Thomsen RW, et al. Comorbidity and survival of Danish patients with colon and rectal cancer from 2000-2011: a population-based cohort study. *Clin Epidemiol* 2013;5(Suppl 1):65–74.
- Marventano S, Grosso G, Mistretta A, et al. Evaluation of four comorbidity indices and Charlson comorbidity index adjustment for colorectal cancer patients. *Int J Colorectal Dis* 2014;29:1159–1169.
- Wu CC, Hsu TW, Chang CM, et al. Age-adjusted Charlson comorbidity index scores as predictor of survival in colorectal cancer patients who

- underwent surgical resection and chemoradiation. *Medicine (Baltimore)* 2015;94:e431.
12. Booth CM, Nanji S, Wei X, et al. Use and effectiveness of adjuvant chemotherapy for stage III colon cancer: a population-based study. *J Natl Compr Canc Netw* 2016;14:47–56.
 13. Nayak P, Luo R, Elting L, et al. Impact of rheumatoid arthritis on the mortality of elderly patients who develop cancer: a population-based study. *Arthritis Care Res (Hoboken)* 2017;69:75–83.
 14. Yamano T, Yamauchi S, Kimura K, et al. Influence of age and comorbidity on prognosis and application of adjuvant chemotherapy in elderly Japanese patients with colorectal cancer: a retrospective multicentre study. *Eur J Cancer* 2017;81:90–101.
 15. Brungs D, Aghmesheh M, de Souza P, et al. Sidedness is prognostic in locoregional colon cancer: an analysis of 9509 Australian patients. *BMC Cancer* 2017;17:251.
 16. Parés-Badell O, Banqué M, Macià F, et al. Impact of comorbidity on survival by tumour location: breast, colorectal and lung cancer (2000–2014). *Cancer Epidemiol* 2017;49:66–74.
 17. Brenner H, Chang-Claude J, Jansen L, et al. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. *Gastroenterology* 2014;146:709–717.
 18. Hoffmeister M, Jansen L, Rudolph A, et al. Statin use and survival after colorectal cancer: the importance of comprehensive confounder adjustment. *J Natl Cancer Inst* 2015;107:djv045.
 19. Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*, 7th edition. New York, NY: Wiley-Blackwell; 2009: 100–105.
 20. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
 21. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45:613–619.
 22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
 23. Brenner H, Gefeller O, Greenland S. Risk and rate advancement periods as measures of exposure impact on the occurrence of chronic diseases. *Epidemiology* 1993;4:229–236.
 24. Ordóñez-Mena JM, Schöttker B, Mons U, et al. Quantification of the smoking-associated cancer risk with rate advancement periods: meta-analysis of individual participant data from cohorts of the CHANCES consortium. *BMC Med* 2016;14:62.
 25. Keil U, Liese AD, Hense HW, et al. Classical risk factors and their impact on incident non-fatal and fatal myocardial infarction and all-cause mortality in southern Germany. Results from the MONICA Augsburg cohort study 1984–1992. *Monitoring Trends and Determinants in Cardiovascular Diseases*. *Eur Heart J* 1998;19:1197–1207.
 26. Ford ES, Zhao G, Tsai J, et al. Low-risk lifestyle behaviors and all-cause mortality: findings from the National Health and Nutrition Examination Survey III Mortality Study. *Am J Public Health* 2011;101: 1922–1929.
 27. Leenders M, Sluijs I, Ros MM, et al. Fruit and vegetable consumption and mortality: European prospective investigation into cancer and nutrition. *Am J Epidemiol* 2013;178:590–602.
 28. Raina P, Gilsing A, Freisling H, et al. The combined effect of cancer and cardio-metabolic conditions on the mortality burden in older adults. *J Gerontol A Biol Sci Med Sci* 2019;4:366–372.
 29. Hahn EE, Gould MK, Munoz-Plaza CE, et al. Understanding comorbidity profiles and their effect on treatment and survival in patients with colorectal cancer. *J Natl Compr Canc Netw* 2018;16:23–34.
 30. Sarfati D, Hill S, Blakely T, et al. The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. *BMC Cancer* 2009;9:116.
 31. Elliot AH, Martling A, Glimelius B, et al. Impact of pre-treatment patient-related selection parameters on outcome in rectal cancer. *Eur J Surg Oncol* 2016;42:1667–1673.
 32. Boakye D, Rillmann B, Walter V, et al. Impact of comorbidity and frailty on prognosis in colorectal cancer patients: a systematic review and meta-analysis. *Cancer Treat Rev* 2018;64:30–39.
 33. Cuthbert CA, Hemmelgarn BR, Xu Y, et al. The effect of comorbidities on outcomes in colorectal cancer survivors: a population-based cohort study. *J Cancer Surviv* 2018;12:733–743.
 34. Erichsen R, Horváth-Puhó E, Iversen LH, et al. Does comorbidity interact with colorectal cancer to increase mortality? A nationwide population-based cohort study. *Br J Cancer* 2013;109:2005–2013.
 35. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol* 2017;3:211–219.
 36. Jørgensen TL, Hallas J, Friis S, et al. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. *Br J Cancer* 2012;106:1353–1360.
 37. Schmiegel W, Pox C, Reinacher-Schick A, et al. S3 guidelines for colorectal carcinoma: results of an evidence-based consensus conference on February 6/7, 2004 and June 8/9, 2007 (for the topics IV, VI and VII). *Z Gastroenterol* 2010;48:65–136.
 38. Kazancioğlu R. Risk factors for chronic kidney disease: an update. *Kidney Int Suppl* (2011) 2013;3:368–371.
 39. Kawai K, Sunami E, Yamaguchi H, et al. Nomograms for colorectal cancer: a systematic review. *World J Gastroenterol* 2015;21: 11877–11886.
 40. Zhang ZY, Luo QF, Yin XW, et al. Nomograms to predict survival after colorectal cancer resection without preoperative therapy. *BMC Cancer* 2016;16:658.
 41. Gurney J, Sarfati D, Stanley J. The impact of patient comorbidity on cancer stage at diagnosis. *Br J Cancer* 2015;113:1375–1380.
 42. Mounce LTA, Price S, Valderas JM, et al. Comorbid conditions delay diagnosis of colorectal cancer: a cohort study using electronic primary care records. *Br J Cancer* 2017;116:1536–1543.
 43. Stuart BC, Davidoff AJ, Erten MZ. Changes in medication management after a diagnosis of cancer among Medicare beneficiaries with diabetes. *J Oncol Pract* 2015;11:429–434.

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Magnitude of the Age Advancement Effect of Comorbidities in Colorectal Cancer Prognosis

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eTable 1: Association of Covariates With OS and CSS

eTable 2: Definition and Frequency of Comorbidities

eTable 3: Comorbidity Scores by Sociodemographic, Lifestyle, and Tumor Characteristics

eTable 4: Associations of Overall Comorbidity With Survival Outcomes

eAppendix 1: Age Advancement Periods for Comorbidity and Survival Outcomes

eTable 1. Association of Covariates With OS and CSS

Characteristic	At Risk, N	OS		CSS	
		Events, n	HR ^a (95% CI) ^b	Events, n	HR ^a (95% CI) ^b
Sex					
Female	1,814	684	Ref	427	Ref
Male	2,788	1,123	1.13 (1.00–1.28)	617	0.97 (0.83–1.14)
Age, y					
30–59	995	266	Ref	219	Ref
60–69	1,392	471	1.33 (1.14–1.56)	308	1.25 (1.04–1.50)
70–79	1,535	639	1.83 (1.57–2.15)	348	1.58 (1.31–1.91)
≥80	680	431	3.60 (3.02–4.30)	169	2.17 (1.71–2.75)
Years of school education					
<9	3,010	1,263	1.07 (0.93–1.24)	675	0.90 (0.75–1.09)
9–10	818	292	1.06 (0.89–1.26)	196	1.03 (0.83–1.26)
>10	774	252	Ref	173	Ref
BMI, kg/m ²					
<18.5	90	44	1.28 (0.94–1.75)	26	1.28 (0.85–1.91)
18.5–24.9	1,678	695	Ref	399	Ref
25–29.9	1,959	747	0.89 (0.80–0.99)	437	0.98 (0.85–1.13)
≥30	875	321	0.89 (0.77–1.02)	182	0.94 (0.78–1.12)
Lifetime physical activity, MET-h/wk					
Q1 (3.3–112.2)	917	338	Ref	202	Ref
Q2 (112.3–161.1)	915	336	1.03 (0.89–1.21)	189	0.98 (0.80–1.21)
Q3 (161.2–211.1)	922	368	1.17 (1.01–1.37)	210	1.16 (0.95–1.42)
Q4 (211.2–287.5)	929	348	1.01 (0.87–1.18)	199	1.06 (0.86–1.30)
Q5 (287.6–788.2)	919	417	1.16 (0.99–1.35)	244	1.23 (1.00–1.50)
Smoking status					
Never-smoker	1,854	760	Ref	462	Ref
Former smoker	2,008	767	0.89 (0.80–1.00)	407	0.84 (0.73–0.97)
Current smoker	740	280	0.99 (0.85–1.14)	175	0.89 (0.74–1.08)
Lifetime alcohol consumption, g/d					
None	751	337	Ref	205	Ref
T1 (0.1–6.8)	1,280	462	0.83 (0.72–0.96)	279	0.81 (0.67–0.97)
T2 (6.9–20.6)	1,290	494	0.75 (0.64–0.88)	285	0.71 (0.58–0.87)
T3 (20.7–381.9)	1,281	514	0.87 (0.74–1.03)	275	0.78 (0.63–0.96)
Period of diagnosis					
2003–2005	1,195	609	Ref	334	Ref
2006–2008	1,102	529	0.89 (0.79–1.01)	284	0.82 (0.70–0.96)
2009–2011	1,198	386	0.95 (0.82–1.09)	233	0.80 (0.67–0.95)
2012–2014	1,107	283	0.81 (0.69–0.95)	193	0.72 (0.59–0.87)
Tumor site					
Right colon ^c	1,532	609	Ref	317	Ref
Left colon ^d	1,213	466	1.03 (0.91–1.16)	266	1.03 (0.87–1.22)
Rectum ^e	1,857	732	1.17 (1.03–1.33)	461	1.24 (1.04–1.47)

(continued on next page)

eTable 1. Association of Covariates With OS and CSS (cont.)

Characteristic	At Risk, N	OS		CSS	
		Events, n	HR ^a (95% CI) ^b	Events, n	HR ^a (95% CI) ^b
Tumor stage, UICC					
I	1,086	258	Ref	46	Ref
II	1,407	440	1.41 (1.21–1.65)	146	2.66 (1.90–3.72)
III	1,510	604	2.56 (2.14–3.07)	380	8.33 (5.92–11.72)
IV	599	505	15.13 (12.42–18.42)	472	61.29 (43.25–86.84)
Treatment initiation					
None	2,427	815	Ref	283	Ref
Radiotherapy only	77	32	0.90 (0.62–1.30)	19	0.95 (0.58–1.55)
Chemotherapy only	1,311	661	0.72 (0.62–0.84)	532	0.77 (0.63–0.94)
Chemoradiotherapy	787	299	0.80 (0.67–0.96)	210	0.84 (0.66–1.07)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; CSS, CRC-specific survival; HR, hazard ratio; MET, metabolic equivalent task hour; OS, overall survival; Q, quintile; T, tertile.

^aAdjusted for all the variables listed in the table and comorbidity scores.

^bBold indicates statistically significant results.

^cFrom the cecum to the transverse colon.

^dFrom the splenic colonic flexure to the sigmoid colon.

^eIncluding rectosigmoidal tumor (n=245).

eTable 2. Definition and Frequency of Comorbidities

Comorbidity	ICD-10 Codes	n (%)	CCI Weight
Myocardial infarction	I21.1, I21.3, I21.4, I21.9, I22, I23, I25.1, I25.2, I25.6	331 (7.2)	1
Congestive heart failure	I11.0, I13.0, I13.2, I50, I50.0, I50.1, I50.3, I50.4, I50.9	164 (3.6)	1
Peripheral vascular disease	I70, I71, I72, I73, I77, K55	265 (5.8)	1
Stroke and hemi/paraplegia		209 (4.5)	
Stroke ^a	G45, G46, I60–I69, Z86.7	196	1
Hemi/Paraplegia ^a	G11.4, G80, G81, G82, G83, I69.05	13	2
COPD	J40–J47, J60–J70, J84.1, J92, J96.1, J98.2, J98.3, I27.8, I27.9	339 (7.4)	1
Chronic renal disease	N01–N05, N07, N11, N17–N19, N25, I12.0, I13.1, I13.2, Z49, Z94.0, Z99.2	247 (5.4)	2
Chronic liver disease		239 (5.2)	
Mild ^a	K70–K76, B18	238	1
Moderate-severe ^a	K70.4, K71.1, K72.1, K72.9, K76.7, B15, B16, B19, Z94.4	1	3
Diabetes mellitus		746 (16.2)	
Without complications ^a	E10.×–E14.× (where ×=0, 1, or 9)	704	1
With complications ^a	E10.×–E14.× (where ×=2, 3, 4, 5, 6, 7, or 8)	42	2
Gastric/Duodenal ulcer	K25–K28	27 (0.6)	1
Rheumatoid disease	M05, M06, M08, M30–M36	29 (0.6)	1
Dementia	F00, F01, F02, F03, F05.1, G30, G30.9, G31.1	21 (0.5)	1
Noncolorectal cancer (except basal skin carcinoma)	C00–C17, C21–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97, Z85.× (where ×=0, 2, 3, 4, 5, 6, or 8)	422 (9.2)	2
CCI score ^b			
Median (range)		0 (0–8)	
0		2,607 (56.6)	
1		869 (18.9)	
2		620 (13.5)	
≥3		506 (11.0)	

Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease.

^aAre mutually exclusive (when both were present, the one with higher CCI weight was considered).

^bHIV/AIDS did not contribute to the overall comorbidity scoring because none of the patients had this condition.

eTable 3. Comorbidity Scores by Sociodemographic, Lifestyle, and Tumor Characteristics

Characteristic	Total N (%)	CCI 0 n (%)	CCI 1 n (%)	CCI 2 n (%)	CCI ≥3 n (%)	P Value ^a
Patients, n	4,602	2,607	869	620	506	
Sex						<.001
Female	1,814 (39.4)	1,091 (60.1)	312 (17.2)	245 (13.5)	166 (9.2)	
Male	2,788 (60.6)	1,516 (54.4)	557 (20.0)	375 (13.4)	340 (12.2)	
Age at diagnosis, y						<.001
30–59	995 (21.6)	760 (76.4)	125 (12.6)	82 (8.2)	28 (2.8)	
60–69	1,392 (30.2)	848 (60.9)	258 (18.5)	170 (12.2)	116 (8.3)	
70–79	1,535 (33.4)	737 (48.0)	324 (21.1)	242 (15.8)	232 (15.1)	
≥80	680 (14.8)	262 (38.5)	162 (23.8)	126 (18.5)	130 (19.1)	
Years of school education						<.001
<9	3,010 (65.4)	1,575 (52.3)	613 (20.4)	438 (14.5)	384 (12.8)	
9–10	818 (17.8)	523 (63.9)	138 (16.9)	96 (11.7)	61 (7.5)	
>10	774 (16.8)	509 (65.8)	118 (15.2)	86 (11.1)	61 (7.9)	
BMI, kg/m ²						<.001
<18.5	90 (2.0)	47 (52.2)	19 (21.1)	21 (23.3)	3 (3.3)	
18.5–24.9	1,678 (36.4)	1,042 (62.1)	257 (15.3)	232 (13.8)	147 (8.8)	
25–29.9	1,959 (42.6)	1,098 (56.1)	372 (19.0)	265 (13.5)	224 (11.4)	
≥30	875 (19.0)	420 (48.0)	221 (25.2)	102 (11.7)	132 (15.1)	
Lifetime physical activity, MET–h/wk						.255
Q1 (3.3–112.2)	917 (19.9)	515 (56.2)	171 (18.6)	140 (15.3)	91 (9.9)	
Q2 (112.3–161.1)	915 (19.9)	538 (58.8)	164 (17.9)	110 (12.0)	103 (11.3)	
Q3 (161.2–211.1)	922 (20.0)	514 (55.8)	165 (17.9)	131 (14.2)	112 (12.1)	
Q4 (211.2–287.5)	929 (20.2)	543 (58.4)	180 (19.4)	106 (11.4)	100 (10.8)	
Q5 (287.6–788.2)	919 (20.0)	497 (54.1)	189 (20.5)	133 (14.5)	100 (10.9)	
Smoking status						.004
Never-smoker	1,854 (40.3)	1,092 (58.9)	337 (18.2)	249 (13.4)	176 (9.5)	
Former smoker	2,008 (43.6)	1,078 (53.7)	402 (20.0)	270 (13.4)	258 (12.9)	
Current smoker	740 (16.1)	437 (59.0)	130 (17.6)	101 (13.7)	72 (9.7)	
Lifetime alcohol consumption, g/d						.015
None	751 (16.3)	396 (52.7)	150 (20.0)	115 (15.3)	90 (12.0)	
T1 (0.1–6.8)	1,280 (27.8)	774 (60.5)	221 (17.3)	164 (12.8)	121 (9.4)	
T2 (6.9–20.6)	1,290 (28.0)	744 (57.7)	253 (19.6)	159 (12.3)	134 (10.4)	
T3 (20.7–381.9)	1,281 (27.8)	693 (54.1)	245 (19.1)	182 (14.2)	161 (12.6)	
Period of diagnosis						<.001
2003–2005	1,195 (26.0)	740 (61.9)	204 (17.1)	158 (13.2)	93 (7.8)	
2006–2008	1,102 (23.9)	612 (55.5)	223 (20.2)	155 (14.1)	112 (10.2)	
2009–2011	1,198 (26.0)	678 (56.6)	228 (19.0)	147 (12.3)	145 (12.1)	
2012–2014	1,107 (24.1)	577 (52.1)	214 (19.3)	160 (14.5)	156 (14.1)	
Tumor site						<.001
Right colon ^b	1,532 (33.3)	782 (51.0)	311 (20.3)	225 (14.7)	214 (14.0)	
Left colon ^c	1,213 (26.4)	722 (59.5)	214 (17.6)	152 (12.5)	125 (10.3)	
Rectum and rectosigmoid ^d	1,857 (40.3)	1,103 (59.4)	344 (18.5)	243 (13.1)	167 (9.0)	

(continued on next page)

eTable 3. Comorbidity Scores by Sociodemographic, Lifestyle, and Tumor Characteristics (cont.)

Characteristic	Total N (%)	CCI 0 n (%)	CCI 1 n (%)	CCI 2 n (%)	CCI ≥3 n (%)	P Value ^a
Tumor stage, UICC						<.001
I	1,086 (23.6)	618 (56.9)	185 (17.0)	153 (14.1)	130 (12.0)	
II	1,407 (30.6)	726 (51.6)	285 (20.3)	204 (14.5)	192 (13.6)	
III	1,510 (32.8)	881 (58.3)	292 (19.3)	202 (13.4)	135 (8.9)	
IV	599 (13.0)	382 (63.8)	107 (17.8)	61 (10.2)	49 (8.2)	
Treatment initiation						<.001
None	2,427 (52.7)	1,222 (50.4)	488 (20.1)	360 (14.8)	357 (14.7)	
Radiotherapy only	77 (1.7)	45 (58.4)	16 (20.8)	9 (11.7)	7 (9.1)	
Chemotherapy only	1,311 (28.5)	836 (63.8)	230 (17.5)	150 (11.4)	95 (7.3)	
Chemoradiotherapy	787 (17.1)	504 (64.0)	135 (17.2)	101 (12.8)	47 (6.0)	

Abbreviations: BMI, body mass index (at diagnosis); CCI, Charlson comorbidity index score; CRC, colorectal cancer; MET, metabolic equivalent task hour; Q, quintile; T, tertile.

^aP values were calculated using chi-square test.

^bFrom the cecum to the transverse colon.

^cFrom the splenic colonic flexure to the sigmoid colon.

^dRectosigmoidal tumor (n=245).

eTable 4. Associations of Overall Comorbidity With Survival Outcomes

	Cox Model ^a	Fine-Gray Model ^b
	HR ^c (95% CI) ^d	sHR ^c (95% CI) ^d
CRC-specific survival		
CCI 0	Ref	Ref
CCI 1	1.05 (0.89–1.24)	1.00 (0.84–1.19)
CCI 2	1.30 (1.08–1.57)	1.22 (1.02–1.47)
CCI ≥3	1.56 (1.26–1.93)	1.26 (1.01–1.56)
Recurrence-free survival		
CCI 0	Ref	Ref
CCI 1	1.02 (0.87–1.19)	0.97 (0.83–1.15)
CCI 2	1.28 (1.08–1.53)	1.22 (1.03–1.45)
CCI ≥3	1.37 (1.13–1.67)	1.18 (0.97–1.43)
Non-CRC-specific survival		
CCI 0	Ref	Ref
CCI 1	1.70 (1.40–2.07)	1.62 (1.34–1.97)
CCI 2	1.98 (1.60–2.44)	1.83 (1.48–2.26)
CCI ≥3	3.62 (2.94–4.45)	3.06 (2.48–3.78)

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index score; CRC, colorectal cancer; HR, hazard ratio; sHR, subdistributional hazard ratio.

^aCompeting events not accounted for.

^bAccounted for competing events.

^cAdjusted for age, age × log (follow-up time), sex, tumor stage, tumor stage × log (follow-up time), years of school education, tumor site, period of diagnosis, period of diagnosis × log (follow-up time), smoking status, BMI, BMI × log (follow-up time), lifetime physical activity, lifetime alcohol consumption, and use of nonsteroidal anti-inflammatory drugs and statins.

^dBold indicates statistically significant results.

eAppendix 1.

Age Advancement Periods for Comorbidity and Survival Outcomes

If the regression coefficients from multivariable Cox proportional hazards models for the association of comorbidity (Charlson comorbidity index [CCI] scores 1, 2, or ≥ 3 compared with CCI 0) with survival outcomes (eg, all-cause mortality) and age (linear term in years) with survival outcomes are β_c and β_a , respectively;

then,

Point estimates of age advancement periods (AAP) are given as

$$(1) \quad \frac{\beta_c}{\beta_a}, \text{ and}$$

SE of AAP are given as $SE = \sqrt{\text{var}(\text{AAP})}$, where

$$(2) \quad \text{var}(\text{AAP}) = \left(\frac{1}{\beta_a}\right)^2 \left\{ \text{var}(\beta_c) - 2 * \left(\frac{\beta_c}{\beta_a}\right) * \text{cov}(\beta_c, \beta_a) + \left(\frac{\beta_c}{\beta_a}\right)^2 * \text{var}(\beta_a) \right\}$$

$\text{var}(\beta_c)$ and $\text{var}(\beta_a)$ denote the variances of comorbidity score and age, respectively, and $\text{cov}(\beta_c, \beta_a)$ denotes the covariance difference of comorbidity score and age

95% CIs of AAP are given as point estimates of

$$(3) \quad \text{AAP} \pm 1.96 * SE$$

Reference

1. Brenner H, Gefeller O, Greenland S. Risk and rate advancement periods as measures of exposure impact on the occurrence of chronic diseases. *Epidemiology* 1993;4:229–236.