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Incorporation of functional status, frailty, comorbidities and comedication in prediction models for colorectal cancer survival

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Abstract

Limitations in functional status, frailty, multiple comorbidities and comedications are common among older colorectal cancer (CRC) patients. We investigated whether adding these factors could improve the predictive value of a reference model containing age, sex, tumor stage and location for prediction of 5-year overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), recurrence-free survival (RFS) and nondisease-specific survival (nDSS) for all CRC patients as well as for younger (<65 years) and older patients (≥65 years). Overall, 3410 CRC patients from the *DACHS* study were analyzed and area under receiver operating characteristic curves (AUC) and net reclassification improvements (NRI) were assessed. In prediction of OS, the reference model plus functional status was identified as the best model among all CRC patients (AUC: 0.762) and younger CRC patients (AUC: 0.820). In older CRC patients, comorbidity should additionally be added (AUC: 0.747). For nDSS, the reference model plus comorbidity and frailty had the best predictive performance in all CRC patients (AUC: 0.776). For the outcomes DFS (AUC: 0.727), DSS (AUC: 0.838) and RFS (AUC: 0.784), the reference model was already the best model in all CRC patients because no significant NRIs were observed. The pattern "The less CRC-specific the survival outcome and the older the CRC patients, the more relevant the inclusion of functional status, comorbidity, and frailty in CRC prognostic scores is" was observed. Thus, different nomograms for younger and older CRC patients for 1-, 3- and 5-year OS prognosis estimation are being suggested.

KEYWORDS
colorectal cancer prognosis, comedication, comorbidity, frailty, functional status

Abbreviations: AIC, Akaike's information criterion; ASA, American Society of Anesthesiologists; ATC classification, Anatomical Therapeutic Chemical classification; AUC, area under the curve; CCI, Charlson comorbidity index; CGA, comprehensive geriatric assessment; CI, confidence interval; CRC, colorectal cancer; DACHS, Darmkrebs: Chancen der Verhütung durch Screening; DFS, disease-free survival; DSS, disease-specific survival; ECOG, Eastern Cooperative Oncology Group; FI, frailty index; FORTA, Fit fOR The Aged; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Revision; IDI, integrated discrimination improvement; KPS, Karnofsky performance status; nDSS, nondisease-specific survival; NRI, net reclassification improvement; NSAIDs, nonsteroidal antiinflammatory drugs; OS, overall survival; PIM, potentially inappropriate medication; RCT, randomized controlled trial; RFS, recurrence-free survival; ROC, receiver operating characteristic; TNM, tumor-node-metastasis.

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What's new?

Colorectal cancer (CRC) patients over age 70 often are affected by comorbidities, frailty, and other physical limitations. Whether this information can be leveraged to improve prediction of CRC prognosis remains uncertain. Here, to assess the relevance of various factors in CRC survival prediction, a reference model for prognosis, with data on age, sex, and tumor stage and location, was compared to models incorporating information on geriatric factors and functional status combined with reference data. The reference model plus functional status was superior in predicting overall survival in all CRC patients. The incorporation of comorbidities improved prediction performance among older patients.

1 | INTRODUCTION

Colorectal cancer (CRC) is one of the most frequently diagnosed cancers worldwide.[1] It is a disease of great public health relevance accounting for more than 1.9 million incident cases and more than 900 000 deaths in 2020.[1,2] Although prognosis of CRC patients has improved substantially in many countries as a result of increased uptake of CRC screening and adoption of best practices in CRC treatment,[3,4] approximately 40% of CRC patients still die within 5 years of CRC diagnosis.[4,5] Therefore, tools that predict CRC prognosis are crucial to facilitate clinical decision making.

Efforts to build prediction models have been made to pursue more accurate prediction of CRC prognosis during the past decade.[6-17] Besides TNM (tumor-node-metastasis) staging system,[18] which is critical to prognostication of CRC, previously proposed prediction models included additional relevant tumor characteristics such as tumor size, location, histology, differentiation, infiltration depth and surgery extent and exhibited greater predictive power than tumor stage alone.[10,12,14-17]

In the era of personalized oncology, patient-relevant factors such as functional status, comorbidity, frailty and polypharmacy could also play important roles in CRC prognosis.[19,20] Some previous prediction models encompassed functional status,[6,7,11,13] comorbidity,[6,8,9] and frailty[21-24] in CRC prognostication. Polypharmacy, in contrast, received less attention in prediction models for CRC prognosis but it was usually assessed as a part of a comprehensive geriatric assessment (CGA) serving as one of the components to define frailty.[24] Polypharmacy as well as comedication quality could have individual prognostic value for CRC survival because studies from our group previously showed that they are strongly associated with survival.[25,26]

Given that more than half of CRC patients are diagnosed after the age of 70,[5] limitations in functional status, multiple comorbidities, frailty and comedications are anticipated to be common in CRC patients. We hypothesized that incorporating these important geriatric factors into prediction models can improve personalized prediction of CRC prognosis—especially in older patients. Therefore, we aimed to investigate in a large, population-based cohort of CRC patients, whether adding functional status, comorbidity, frailty index (FI), polypharmacy or a comedication quality score could improve the predictive value of the reference model containing age, sex, tumor stage and tumor location for CRC survival and to identify the model with the best predictive performance for various survival outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The research question in our study was examined using data of CRC patients (cases) who were diagnosed in 2003-2016 and recruited into the ***Da**rmkrebs: **Ch**ancen der Verhütung durch **S**creening* (DACHS) study. The DACHS study is an ongoing population-based case-control study with recruitment of CRC cases in 22 hospitals and randomly selects control participants with no history of colorectal cancer in the Rhine-Neckar-Heilbronn area, Germany. Details of the DACHS study design have been described elsewhere.[27-29] Briefly, patients with a histologically confirmed first diagnosis of CRC (International Classification of Diseases, 10th Revision [ICD-10], codes C18–C20),[30] aged at least 30 years (no upper age limit) and being able to speak German are eligible to participate.

At baseline, shortly after CRC surgery (if patients had any), trained study nurses carry out personal interviews with the study participants in the collaborating hospitals. Information on sociodemographic and lifestyle factors, medical history and drug use is collected using a standardized questionnaire. Moreover, tumor and patient characteristics, including comorbidities, functional status and last medication are being extracted from patients' hospital records. Comorbidities are coded with the ICD-10 coding algorithm validated by Quan et al[31] and drugs are coded according to a German adaption of the WHO's Anatomical Therapeutic Chemical (ATC) code (2019 version).[32]

Vital status and the cause of death of deceased patients are ascertained from population registries and public health authorities. Detailed information on newly diagnosed cancers and recurrence history is further gathered from questionnaires sent to gastroenterologists in the outpatient setting about 3, 5 and 10 years after diagnosis. If patients have died during follow-up or were lost to follow-up, information on recurrence is being collected from the last attending physician.

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2.2 | In- and exclusion criteria

The current analysis was restricted to CRC patients diagnosed between 2003 and 2016 within the DACHS study in order to have follow-up for at least 3 years (n = 5485, including n = 108 who did not undergo any surgery). Patients with no complete information on age, sex, tumor stage, tumor location, functional status, comorbidity, medication and variables needed for the FI were excluded. Furthermore, a few patients without any mortality follow-up information were excluded as well, which left n = 3410 study participants for the analysis (Appendix Figure A1). Patients with incomplete data did not differ in baseline characteristics from study participants with complete data (data not shown).

2.3 | Ascertainment of comorbidity

We extracted ICD-10 codes for comorbidities diagnosed either prior to or upon CRC diagnosis from medical records. In addition, self-reported comorbidities collected from the standardized questionnaire were also considered. To ensure comparability with previous studies, we computed an overall comorbidity score using the Charlson comorbidity index (CCI)[33] with the adaption by Deyo et al.[34] In brief, the CCI consists of 19 weighted comorbidities, with weights ranging from 1 to 6 based on the magnitude of the adjusted 1-year mortality risk.[33] The ICD-10 codes used in our study to score the CCI have been outlined previously.[6] Besides, we assumed that in our study population of hospitalized CRC patients, cancers other than CRC were localized (nonmetastatic) cancers.

2.4 | Assessment of functional status

As perioperative functional status was recorded by different instruments in medical records from the various hospitals (American Society of Anesthesiologists (ASA) Physical Status Classification System,[35] the Eastern Cooperative of Oncology Group (ECOG)[36] and the Karnofsky performance status),[37] we used a harmonized indicator variable for functional status, which was created as previously prescribed.[6] In brief, patients were classified into three functional status groups based on each instrument's respective grade or score: excellent (ASA = I-II, ECOG = 0 or KPS = 100), fair (ASA = III, ECOG = 1 or KPS = 70-90) and poor functional status (ASA = IV, ECOG = 2-4 or KPS = 10-60).

2.5 | Definition of frailty

A continuous FI was created for all CRC patients in the DACHS study by adopting the method proposed by Mitnitski and Rockwood,[38,39] which defines frailty as an accumulation of deficits. These deficits could be signs, symptoms, diseases, medications, disabilities and disease markers. We included in the FI 30 deficits (Appendix Table A1), which fulfilled the following three criteria:

1. Deficits should be associated with the general health status (judged by subject matter knowledge) and accumulate with age (Statistically significant Spearman correlation coefficient >0.08).
2. The chosen deficits should not be too common at younger age (ie, prevalence <50% in age group 40-59 years) and should not be too rare at older age (ie, prevalence >1% in age group 70-79 years).
3. Deficits that constitute the FI should cover a sufficient range of systems (ie, no items should have an overall kappa coefficient with any other item >0.5).

The FI is the ratio of the number of existing deficits divided by the total number of deficits included. Binary variables were given values of 0 (indicates the absence of a deficit) and 1 (indicates the presence of a deficit), and nonbinary variables were assigned values within the range of 0 to 1, depending on how many categories are in the nonbinary variables. To verify the construct validity of the FI, it is linear increase with the patient's age was checked (Appendix Figure A2).

2.6 | Medication assessment and definition of polypharmacy and comedication quality

We reviewed the drugs recorded in the discharge letters and additionally took the patients' self-reported medications at baseline into consideration to achieve as complete drug information as possible. Polypharmacy was defined by the use of five or more medications in our study. We applied a modified definition and counted only potentially clinically relevant drugs as previously described.[25,40] In brief, we counted combination drugs based on the number of active substances rather than from the perspective of pill number. Furthermore, we did not count drugs which are known to be safe, that is, food supplements, homeopathic or anthroposophical drugs, some herbal drugs and nonsystematically acting drugs. Besides, three further drug classes (antithrombotic agents, nonsteroidal antiinflammatory drugs [NSAIDs] and drugs against peptic ulcer disease) listed only in the discharge letters were excluded because they are often prescribed to CRC patients during or shortly after CRC surgery for short-term use only.

Comedication quality was assessed by the Fit fOR The Aged (FORTA) list because it assesses not only potentially inappropriate medication (PIM) but also medication over- and underuse and combines these three aspects into one score of total comedication quality.[41] Furthermore, FORTA is being updated regularly and its clinical usefulness has been validated in a previous randomized controlled clinical trial (RCT).[42] We calculated scores for underuse, overuse and PIM use for every patient in our study as previously described and summed the three scores up to obtain the total FORTA score.[26,42] Higher FORTA scores indicate poorer comedication quality.

2.7 | Survival outcomes

The primary outcome in our study was 5-year overall survival (OS; time from hospital release to death from any cause). Our secondary outcomes

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TABLE 1 Baseline characteristics of study population (in N = 3410)

Characteristics	n	%	Median (range)
Sex			
Female	1345	39.4	–
Male	2065	60.6	–
Age at CRC diagnosis (years)	–	–	70 (30-96)
30-49	177	5.2	–
50-59	490	14.4	–
60-69	928	27.2	–
70-79	1187	34.8	–
≥80	628	18.4	–
Tumor location			
Colon	2145	62.9	–
Rectum	1265	37.1	–
Tumor stage			
I	735	21.5	–
II	1069	31.4	–
III	1071	31.4	–
IV	535	15.7	–
Functional status			
Excellent	1767	51.8	–
Fair	1435	42.1	–
Poor	208	6.1	–
Charlson comorbidity index	–	–	0 (0-7)
CCI0	1813	53.2	–
CCI1-2	1182	34.7	–
CCI3	230	6.7	–
CCI4+	185	5.4	–
Number of comedications	–	–	4 (0-20)
0-4	1855	54.4	–
5-7	889	26.1	–
≥8	666	19.5	–
Comedication quality score (FORTA score)	–	–	2 (0-28)
0-1	991	29.1	–
2-3	1228	36.0	–
4-6	765	22.4	–
≥7	426	12.5	–
Frailty index	–	–	0.23 (0-0.70)
T1	994	29.1	–
T2	1202	35.2	–
T3	1214	35.6	–

Abbreviations: CCI, Charlson comorbidity index; CRC, colorectal cancer; FORTA, Fit fOR The Aged; T, tertile.

were 5-year disease-free survival (DFS; time from hospital release to death from any cause or recurrence of CRC, whichever occurs first), disease-specific survival (DSS, time from hospital release to death from CRC), recurrence-free survival (RFS, time from hospital release to death from CRC or recurrence of CRC, whichever occurs first), and nondisease-specific survival (nDSS, time from hospital release to death from causes other than CRC). Patients who were still alive and/or not encountering any recurrence at the end of follow-up were censored.

2.8 | Statistical analyses

We assessed the associations of the five variables of interest (Functional status, CCI, polypharmacy, total FORTA score and FI) with the five survival outcomes of interest (OS, DFS, nDSS, DSS and RFS) with separate Cox proportional hazards regression models adjusted for age, sex, tumor stage and tumor location. The proportional hazard assumption was carefully assessed using a macro program of a score

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TABLE 2 Comparison of associations of variables of interest with overall, disease-free and nondisease-specific survival in models containing five variables (the four variables of the reference model plus one variable of interest)[a] (in N = 3410)

	Overall survival			Disease-free survival			Nondisease-specific survival		
Variables of interest	N_{total}	N_{cases}[b] (%)	HR [95% CI]	N_{total}	N_{cases}[c] (%)	HR [95% CI]	N_{total}	N_{cases}[d] (%)	HR [95% CI]
Functional status									
Excellent (Ref)	1767	368 (20.8)	Ref	1736	481 (27.7)	Ref	1767	103 (5.8)	Ref
Fair	1435	537 (37.4)	**1.54 [1.34-1.77]**	1411	606 (43.0)	**1.42 [1.25-1.61]**	1435	200 (13.9)	**1.56 [1.22-2.01]**
Poor	208	121 (58.2)	**2.63 [2.11-3.26]**	204	124 (60.8)	**2.08 [1.68-2.55]**	208	59 (28.4)	**3.32 [2.35-4.65]**
Charlson comorbidity index									
Per 1 SD increase[e]	–	–	**1.28 [1.20-1.35]**	–	–	**1.27 [1.20-1.34]**	–	–	**1.52 [1.41-1.65]**
CCI0 (Ref)	1813	476 (26.3)	Ref	1780	579 (32.5)	Ref	1813	105 (5.8)	Ref
CCI1-2	1182	359 (30.4)	1.11 [0.97-1.28]	1165	426 (36.6)	1.14 [0.99-1.29]	1182	145 (12.3)	**1.56 [1.21-2.02]**
CCI3	230	83 (36.1)	**1.43 [1.12-1.81]**	226	90 (39.8)	**1.34 [1.06-1.67]**	230	38 (16.5)	**2.11 [1.43-3.04]**
CCI4+	185	108 (58.4)	**2.69 [2.15-3.34]**	180	116 (64.4)	**2.71 [2.19-3.33]**	185	74 (40.0)	**5.00 [3.66-6.79]**
Polypharmacy									
Per 1 SD increase[f]	–	–	**1.15 [1.08-1.22]**	–	–	**1.12 [1.06-1.19]**	–	–	**1.34 [1.21-1.47]**
0-4 (Ref)	1855	492 (26.5)	Ref	1819	616 (33.9)	Ref	1855	124 (6.7)	Ref
5-7	889	274 (30.8)	**1.18 [1.01-1.37]**	878	307 (35.0)	1.05 [0.91-1.20]	889	113 (12.7)	**1.53 [1.18-1.98]**
≥8	666	260 (39.0)	**1.40 [1.19-1.63]**	654	288 (44.0)	**1.32 [1.14-1.53]**	666	125 (18.8)	**1.93 [1.50-2.50]**
Comedication quality score (FORTA score)									
Per 1 SD increase[g]	–	–	**1.27 [1.20-1.34]**	–	–	**1.20 [1.13-1.26]**	–	–	**1.35 [1.24-1.45]**
0-1 (Ref)	991	219 (22.1)	Ref	970	272 (28.0)	Ref	991	51 (5.2)	Ref
2-3	1228	328 (26.7)	1.12 [0.95-1.34]	1210	417 (34.5)	**1.19 [1.02-1.39]**	1228	91 (7.4)	1.25 [0.89-1.78]
4-6	765	297 (38.8)	**1.63 [1.36-1.96]**	750	326 (43.5)	**1.54 [1.31-1.82]**	765	121 (15.8)	**2.20 [1.58-3.09]**
≥7	426	182 (42.7)	**2.14 [1.74-2.63]**	421	196 (46.6)	**1.88 [1.54-2.28]**	426	99 (23.2)	**3.13 [2.21-4.47]**
Frailty Index									
Per 1 SD increase[h]	–	–	**1.25 [1.16-1.34]**	–	–	**1.22 [1.14-1.31]**	–	–	**1.59 [1.42-1.78]**
T1 (Ref)	994	271 (27.3)	Ref	969	334 (34.5)	Ref	994	36 (3.6)	Ref
T2	1202	325 (27.0)	0.97 [0.82-1.15]	1186	391 (33.0)	1.00 [0.86-1.17]	1202	100 (8.3)	**1.62 [1.11-2.42]**
T3	1214	430 (35.4)	**1.35 [1.13-1.61]**	1196	486 (40.6)	**1.37 [1.16-1.61]**	1214	226 (18.6)	**2.66 [1.84-3.96]**

Note: Values in bold are statistically significant ($P < .05$).

Abbreviations: ASA, American Society of Anesthesiologists; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology (ECOG) score; FORTA, Fit fOR The Aged; HR, hazard ratio; KPS, Karnofsky performance score; Ref, reference.

[a]The results in this table for every survival outcome will be obtained from five different models. In this table, we will only show the main result of the association of one variable of interest with every survival outcome adjusted for the variables of the reference model (age, sex, cancer stage and cancer location).

[b]Number of deaths from any cause.

[c]Number of deaths from any cause or recurrence of colorectal cancer.

[d]Number of deaths from causes other than colorectal cancer.

[e]SD for CCI was 1.282.

[f]SD for number of comedications was 3.3.

[g]SD for FORTA score was 3.01.

[h]SD for frailty index was 0.131.

test based on scaled Schoenfeld residuals using SAS PROC IML. We used restricted cubic spline functions for CCI, polypharmacy, FORTA score and FI to examine potential nonlinear associations with OS and to determine clinically relevant cut-offs for categorical variables.[43] No strong deviations from linear dose-response relationships were detected (Appendix Figure A3).

To examine the predictive value of different models, we assessed the overall model fit (by Akaike's information criterion [AIC]) and the area under the receiver operating characteristic (ROC) curve (AUC). The AUCs (95% CIs) were computed with SAS macro "%survcstd." Furthermore, we quantified the incremental benefit of adding single variables to a model by the continuous net reclassification

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TABLE 3 Comparison of associations of variables of interest with disease-specific and recurrence-free survival in models containing five variables (the four variables of the reference model plus one variable of interest)[a] (in N = 3410)

	Disease-specific survival			Recurrence-free survival		
Variables of interest	N_{total}	N_{cases}[b] (%)	HR [95% CI]	N_{total}	N_{cases}[c] (%)	HR [95% CI]
Functional status						
Excellent (Ref)	1767	265 (15.0)	Ref	1737	396 (22.8)	Ref
Fair	1435	337 (23.5)	**1.53 [1.29-1.82]**	1411	419 (29.7)	**1.33 [1.15-1.53]**
Poor	208	62 (29.8)	**2.12 [1.58-2.82]**	204	73 (35.8)	**1.66 [1.28-2.14]**
Charlson comorbidity index						
Per 1 SD increase[d]	–	–	**1.09 [1.01-1.19]**	–	–	**1.11 [1.05-1.18]**
CCI0 (Ref)	1813	371 (20.5)	Ref	1780	493 (27.7)	Ref
CCI1-2	1182	214 (18.1)	0.97 [0.82-1.15]	1165	290 (24.9)	1.07 [0.95-1.21]
CCI3	230	45 (19.6)	1.25 [0.90-1.70]	226	54 (23.9)	1.13 [0.89-1.43]
CCI4+	185	34 (18.4)	1.46 [0.99-2.07]	180	51 (28.2)	**1.53 [1.18-1.96]**
Polypharmacy						
Per 1 SD increase[e]	–	–	1.05 [0.96-1.14]	–	–	1.03 [0.97-1.09]
0-4 (Ref)	1855	368 (19.8)	Ref	1819	511 (28.1)	Ref
5-7	889	161 (18.1)	1.02 [0.84-1.23]	878	202 (23.0)	0.92 [0.81-1.06]
≥8	666	135 (20.3)	1.15 [0.94-1.42]	654	175 (26.7)	1.13 [0.97-1.31]
Comedication quality score (FORTA score)						
Per 1 SD increase[f]	–	–	**1.18 [1.08-1.28]**	–	–	**1.07 [1.00-1.13]**
0-1 (Ref)	991	168 (16.9)	Ref	970	232 (23.9)	Ref
2-3	1228	237 (19.3)	1.10 [0.91-1.35]	1210	335 (27.7)	1.14 [0.99-1.32]
4-6	765	176 (23.0)	**1.43 [1.15-1.79]**	751	213 (28.4)	**1.20 [1.02-1.41]**
≥7	426	83 (19.5)	**1.62 [1.22-2.14]**	421	108 (25.7)	**1.30 [1.06-1.58]**
Frailty index						
Per 1 SD increase[g]	–	–	1.07 [0.97-1.18]	–	–	1.05 [0.99-1.13]
T1 (Ref)	994	235 (23.6)	Ref	969	309 (31.9)	Ref
T2	1202	225 (18.7)	0.92 [0.76-1.11]	1186	303 (25.6)	0.97 [0.84-1.11]
T3	1214	204 (16.8)	1.06 [0.85-1.32]	1197	276 (23.1)	1.10 [0.95-1.27]

Note: Values in bold are statistically significant ($P < .05$).

Abbreviations: ASA, American Society of Anesthesiologists; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology (ECOG) score; FORTA, Fit fOR The Aged; HR, hazard ratio; KPS, Karnofsky performance score; Ref, reference.

[a]The results in this table for every survival outcome will be obtained from five different models. In this table, we will only show the main result of the association of one variable of interest with every survival outcome adjusted for the variables of the reference model (age, sex, cancer stage and cancer location).

[b]Number of deaths from colorectal cancer.

[c]Number of deaths from colorectal cancer or recurrence of colorectal cancer.

[d]SD for CCI was 1.282.

[e]SD for number of comedications was 3.3.

[f]SD for FORTA score was 3.01.

[g]SD for frailty index was 0.131.

improvement (NRI) and integrated discrimination improvement (IDI).[44,45] Since NRI statistics are dependent on the number of cut-offs and the choice of risk categories,[44] we a priori decided on three cut-offs for all analyses. The cut-offs differed for each survival outcome because we aimed to obtain an even distribution of study participants among the four risk categories by having no group with less than n = 650 study participants.

The search for the best prediction model for each of the five survival outcomes was also done with Cox proportional hazards regression and started with a reference model, which included age, sex, tumor stage (Union for International Cancer Control, stage I-IV),[18] and tumor location. First, the reference model was extended by functional status, CCI, polypharmacy, total FORTA score and FI, which were put into the model one by one and not combined. Functional status was

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TABLE 4 Evaluation of various prediction models for survival outcomes in the total study population (N = 3410)

Model performance measures	Overall survival						
	Ref model[a]	Ref[a] + Functional status	Ref[a] + CCI	Ref[a] + Polypharmacy	Ref[a] + FORTA score	Ref[a] + Frailty	Ref[a] + Functional status + CCI[b]
Overall model fit							
AIC	14 819.8	14 745.5	14 757.8	14 803.1	14 762.4	14 785.1	14 705.1
Discrimination							
AUC (95% CI)	0.753 (0.738-0.769)	0.762 (0.747-0.777)	0.763 (0.748-0.778)	0.756 (0.741-0.771)	0.760 (0.745-0.775)	0.759 (0.744-0.774)	0.768 (0.754-0.783)
Reclassification							
Events n_{up}/n_{down}	Ref	88/52	81/71	44/49	60/53	68/56	52/60
Nonevents n_{up}/n_{down}	Ref	179/201	154/181	109/98	145/179	159/159	116/148
NRI % (*P*)[c]	Ref	**4.4% (.002)**	2.1% (.139)	−0.9% (.396)	2.1% (.100)	1.2% (.375)	0.6% (.649)
IDI % (*P*)	Ref	**0.5% (<.001)**	**0.4% (<.001)**	**0.1% (.008)**	**0.4% (<.001)**	**0.3% (<.001)**	**0.3% (<.001)**

Model performance measures	Disease-free survival					
	Ref Model[a]	Ref[a] + Functional status	Ref[a] + CCI	Ref[a] + Polypharmacy	Ref[a] + FORTA score	Ref[a] + Frailty
Overall model fit						
AIC	17 443.8	17 394.1	17 376.9	17 430.6	17 407.5	17 411.3
Discrimination						
AUC (95% CI)	0.727 (0.711-0.742)	0.733 (0.718-0748)	0.736 (0.721-0.751)	0.729 (0.714-0.744)	0.731 (0.715-0.746)	0.732 (0.716-0.747)
Reclassification						
Events n_{up}/n_{down}	Ref	109/60	113/87	63/47	67/69	98/59
Nonevents n_{up}/n_{down}	Ref	214/142	170/181	111/98	140/164	186/149
NRI % (*P*)[d]	Ref	0.7% (.623)	2.7% (.068)	0.7% (.516)	0.9% (.448)	1.5% (.267)
IDI % (*P*)	Ref	**0.5% (<.001)**	**0.5% (<.001)**	**0.1% (.007)**	**0.3% (<.001)**	**0.3% (<.001)**

Model performance measures	Nondisease specific survival						
	Ref model[a]	Ref[a] + Functional status	Ref[a] + CCI	Ref[a] + Polypharmacy	Ref[a] + FORTA score	Ref[a] + Frailty	Ref[a] + CCI + FI[e]
Overall model fit							
AIC	5416.8	5377.7	5323.0	5386.8	5371.9	5355.1	5316.4
Discrimination							
AUC (95% CI)	0.735 (0.710-0.760)	0.750 (0.726-0.774)	0.773 (0.750-0.796)	0.748 (0.724-0.772)	0.755 (0.731-0.779)	0.763 (0.739-0.787)	0.776 (0.753-0.799)

(Continues)

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TABLE 4 (Continued)

Model performance measures	Nondisease specific survival						
	Ref model[a]	Ref[a] + Functional status	Ref[a] + CCI	Ref[a] + Polypharmacy	Ref[a] + FORTA score	Ref[a] + Frailty	Ref[a] + CCI + FI[e]
Reclassification							
Events n_{up}/n_{down}	Ref	46/54	58/56	39/31	35/31	52/50	17/12
Nonevents n_{up}/n_{down}	Ref	341/577	282/758	258/457	199/441	326/681	163/226
NRI % (*P*)[f]	Ref	**5.5% (.059)**	**16.2% (<.001)**	**8.7% (<.001)**	**9.0% (<.001)**	**12.2% (<.001)**	**3.4% (.034)**
IDI % (*P*)	Ref	**0.03% (<.001)**	**0.5% (<.001)**	**0.1% (<.001)**	**0.1% (<.001)**	**0.3% (<.001)**	**0.02% (.034)**

Note: Bold print: Statistically significant difference ($P < .05$).

Abbreviations: AIC, Akaike's information criterion; AUC, area under the receiver characteristic curve; CCI, Charlson comorbidity index; CI, confidence interval; FORTA, Fit fOR The Aged; IDI, integrated discrimination improvement; LR, likelihood ratio; nexp, nobs, number of expected and observed events; NRI, net reclassification improvement; Ref, reference.

[a]Reference model contains age, sex, tumor stage and tumor location.

[b]Reclassification measures (NRI and IDI) in the final model were calculated compared to Ref model + functional status.

[c]The cut-offs for 5-year overall survival were set at probabilities for the adverse endpoint of 10%, 25% and 50%.

[d]The cut-offs for 5-year disease-free survival were set at probabilities for the adverse endpoint of 15%, 30% and 55%.

[e]Reclassification measures (NRI and IDI) in the final model were calculated compared to Ref model + CCI.

[f]The cut-offs for 5-year nondisease specific survival were set at probabilities for the adverse endpoint of 5%, 10% and 17.5%.

modeled as a categorical variable (excellent/fair/poor), whereas CCI, polypharmacy, FORTA score and FI were modeled continuously. We also tested logarithm-transformation for the continuous variables, but this transformation did not improve the AUC of any model. If a statistically significant NRI was detected by adding the five variables of interest one by one, the variables with the highest and second highest NRI were chosen and the model including two variables of interest was tested against the model with one variable of interest. This iterative process of adding single variables of interest to the reference model was stopped as soon as no statistically significant NRI was detected. This search for the best predictive models for the five survival outcomes was first done in the total population and then in strata by age (<65/≥65 years). In the final models, we carried out multicollinearity tests. We used the regression coefficients of the variables included in the final model to calculate nomogram points (from 0 to 100, with higher points indicating worse prognosis). The nomograms were tested for their robustness by plotting the nomogram-predicted survival probabilities against the observed survival probabilities estimated by the Kaplan-Meier method (ie, nomogram calibration) on the entire population using 200 bootstrapped resamples.

Construction of nomograms was developed with the R program (version 4.1.2.) using the rms package. All other analyses were conducted with the SAS software, version 9.4 (SAS Institute, Cary, NC). Statistical tests were two-tailed, with significance level (α) equal to .05.

3 | RESULTS

3.1 | Baseline characteristics

We included 3410 participants and their baseline characteristics are shown in Table 1. Their median age was 70 years and 39.4% were females. Approx. two thirds (62.9%) had the tumor located in colon. The distribution of cancer stage I to IV was 21.5%, 31.4%, 31.4% and 15.7%, respectively. Approx. half (51.8%) of the study population had an excellent functional status and 6.1% had a poor functional status. The medians of the CCI, the number of comedications, the FORTA score and the FI were 0, 4, 2 and 0.23, respectively.

3.2 | Associations of variables of interest with survival outcomes

Poorer functional status, higher CCI, polypharmacy (higher number of comedications), higher FORTA score and higher FI were consistently associated with significantly worse OS, DFS and nDSS (Table 2). Hazard ratios (HRs) [95% confidence intervals (CIs)] for OS per 1 SD (SD) increase in CCI (1.28 [1.20-1.35]), FORTA score (1.27 [1.20-1.34]) and FI (1.25 [1.16-1.34]) were comparable whereas the HR was a little weaker for polypharmacy (1.15 [1.08-1.22]). Fair (1.54 [1.34-1.77]) and poor (2.63 [2.11-3.26]) functional status were strongly associated with OS when compared to subjects with excellent functional status. The strengths of the associations of the variables of interest with

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TABLE 5 Evaluation of various prediction models for survival outcomes in the total study population (N = 3410)

Model performance measures	Disease-specific survival					
	Ref model[a]	Ref[a] + Functional status	Ref[a] + CCI	Ref[a] + Polypharmacy	Ref[a] + FORTA score	Ref[a] + Frailty
Overall model fit						
AIC	9171.6	9139.5	9169.4	9172.6	9159.3	9171.5
Discrimination						
AUC (95% CI)	0.838 (0.823-0.853)	0.843 (0.828-0.857)	0.839 (0.824-0.854)	0.839 (0.824-0.854)	0.840 (0.825-0.854)	0.838 (0.823-0.853)
Reclassification						
Events n_{up}/n_{down}	Ref	40/14	13/9	7/5	18/17	11/7
Nonevents n_{up}/n_{down}	Ref	153/75	65/48	32/31	129/91	63/36
NRI % (*P*)[b]	Ref	1.1% (.384)	−0.02% (.983)	0.3% (.657)	−1.2% (.237)	−0.4% (.604)
IDI % (*P*)	Ref	**0.09% (.020)**	−0.03% (.887)	−0.01% (.799)	**−0.01% (.029)**	−0.02% (.841)
Model performance measures	**Recurrence-free survival**					
	Ref model[a]	Ref[a] + Functional status	Ref[a] + CCI	Ref[a] + Polypharmacy	Ref[a] + FORTA score	Ref[a] + Frailty
Overall model fit						
AIC	12 555.9	12 539.1	12 549.1	12 557.1	12 551.0	12 555.1
Discrimination						
AUC (95% CI)	0.784 (0.769-0.800)	0.788 (0.773-0.804)	0.785 (0.770-0.801)	0.785 (0.770-0.801)	0.785 (0.769-0.801	0.785 (0.770-0.801)
Reclassification						
Events n_{up}/n_{down}	Ref	65/29	43/27	13/7	26/35	24/18
Nonevents n_{up}/n_{down}	Ref	267/111	177/94	49/43	156/93	128/80
NRI % (*P*)[c]	Ref	−2.3% (.091)	−1.6% (.175)	0.4% (.497)	**−3.6% (.001)**	−1.3% (.174)
IDI % (*P*)	Ref	**0.08% (.009)**	−0.04% (.184)	−0.01% (.842)	0.01% (.077)	−0.02% (.355)

Note: Bold print: Statistically significant difference ($P < .05$).

Abbreviations: AIC, Akaike's information criterion; AUC, area under the receiver characteristic curve; CCI, Charlson comorbidity index; CI, confidence interval; FORTA, Fit fOR The Aged; IDI, integrated discrimination improvement; nexp, nobs, number of expected and observed events; NRI, net reclassification improvement; Ref, reference.

[a]Reference model contains age, sex, tumor stage and tumor location.

[b]The cut-offs for 5-year disease-specific survival were set at probabilities for the adverse endpoint of 2.5%, 7.5% and 30%.

[c]The cut-offs for 5-year recurrence-free survival were set at probabilities for the adverse endpoint of 5%, 15% and 40%.

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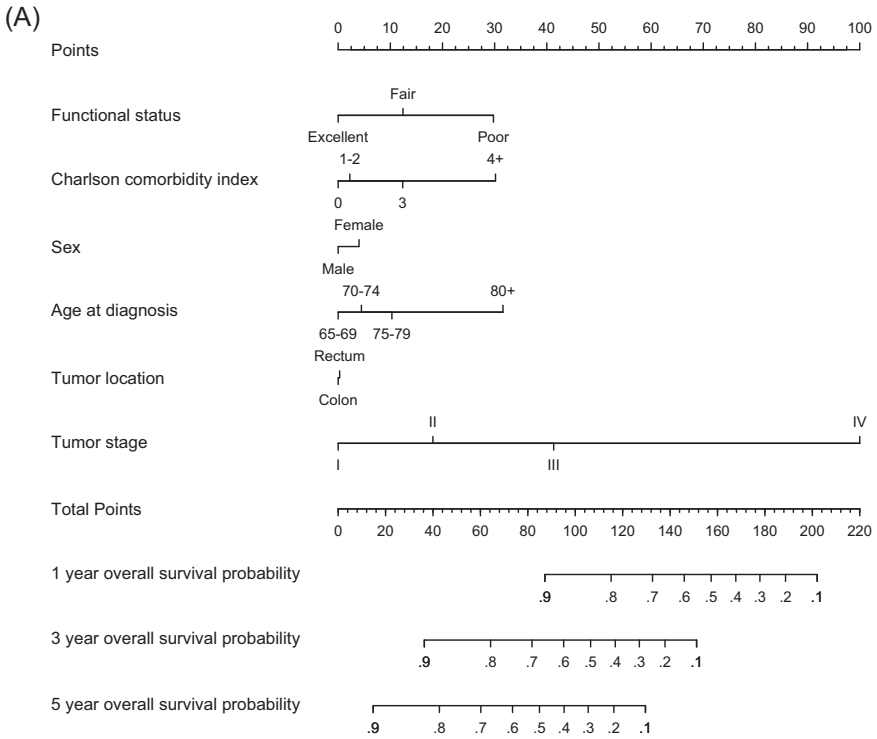

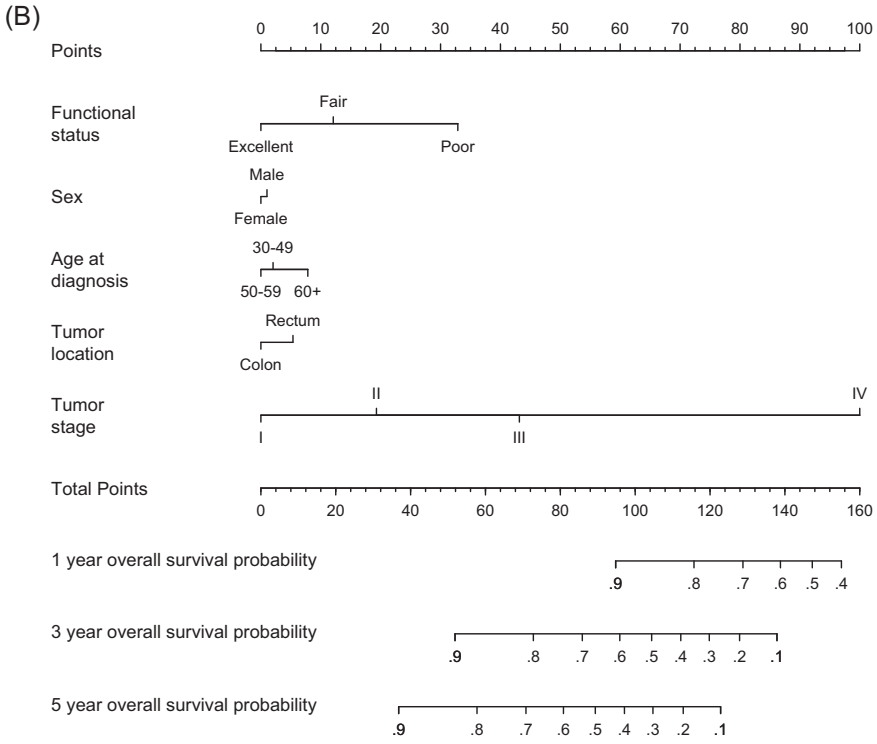

FIGURE 1 Nomograms for predicting 1-, 3- and 5-year overall survival in participants (A) aged 65 years or above and in participants (B) aged less than 65 years. Total points were obtained by summing up individual points from the respective predictive factors. Higher points indicate poorer survival

DFS were comparable to those observed for OS while those with nDSS were more pronounced. Especially for CCI and FI, the excess risks were approximately twice as high for nDSS as for OS.

Overall, the strengths of the associations of all variables of interest were weaker with DSS and RFS than with OS, DFS and nDSS. Functional status, CCI and comedication quality were statistically significantly associated with both DSS and RFS, whereas polypharmacy and the FI were not (Table 3).

3.3 | Evaluation of prediction models for survival outcomes

Table 4 shows the evaluation of prediction models for OS, DFS and nDSS. For OS, adding any of the five variables of interest to the reference model marginally improved overall model fit and AUC, and significant IDIs were observed but only functional status also provided a statistically significant NRI (4.4%, $P = .002$). The reference model plus

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functional status was not substantially further improved by adding the second-best variable of interest, CCI (NRI, 0,6%, $P = .649$). Thus, the reference model plus functional status was judged to be the best model for OS prediction in CRC patients with an AUC of 0.762.

For DFS, though adding any of five variables of interest to the reference model marginally improved overall model fit, no statistically significant NRIs were observed. Thus, the reference model was judged to be the best model for DFS prediction in CRC patients with an AUC of 0.727.

For nDSS, substantial improvements of all model performance measures were observed and the highest NRI was detected for CCI (16.2%, $P < .001$). To evaluate whether the reference model plus CCI can be further improved, we added the second-best variable of interest, which was the FI with an NRI of 12.2%. The reference model plus CCI and FI outperformed the reference model plus CCI with a statistically significant NRI of 3.4% ($P = .034$). We further added the comedication quality, the variable with the third highest NRI, but this did not lead to better model performance. Thus, the model containing the variables of the reference model, CCI and FI was judged to have the best predictive performance for nDSS with an AUC of 0.776.

For DSS and RFS, the evaluation of the best predictive models is presented in Table 5. Adding any of five variables of interest to the reference model did not or only modestly improve overall model fit and AUC compared to the reference model for both DSS and RFS. As none of the NRI values were statistically significant, the reference model was judged to be the best predictive model for both DSS and RFS with AUCs of 0.838 and 0.784, respectively.

In summary, only for the outcomes OS and nDSS variables were added to the reference model and we tested these extended models for collinearity. Collinearity was neither detected in the final model for OS predication (The reference model plus functional status had condition indices between 1.00 and 21.20) nor in the final model for nDSS (The reference model plus CCI and FI had condition indices between 1.00 and 22.36).

The search for the best predictive models for the five survival outcomes was also conducted stratified for younger (<65 years) and older CRC patients (≥65 years) and the results are shown in Appendix Tables A2-A5. For OS, adding functional status to the reference model had the best predictive value for younger adults and adding functional status + CCI for older adults. For DFS, the reference model was already the best model for younger adults whereas functional status and the CCI improved the reference model for older adults. For nDSS, again the reference model was sufficient for younger adults whereas CCI and the FI significantly improved prediction for older adults. In agreement with the results for the total population, the reference model was the best predictive model for the outcomes DSS and RFS in both younger and older CRC patients.

3.4 | Prognostic nomograms for overall survival

Figure 1 shows the nomograms for best prediction models for 1-, 3- and 5-year OS in participants aged ≥65 and <65 years. As reflected by the nomogram points, tumor stage was the most prominent factor in both nomograms. In CRC patients aged ≥65 years, comorbidity and functional status contributed to a similar extent to OS prediction and were both the second important factors. In participants aged <65 years, functional status was also the second important factor. As depicted in the calibration plots (Appendix Figure A4), the predicted 3-year and 5-year OS probabilities from the nomograms were very close to the observed survival probabilities, indicating robustness of the nomograms in both older and younger CRC patients.

4 | DISCUSSION

This large cohort of CRC patients showed that the best model for survival prediction varies by outcome and age of the patients. For the primary outcome, OS, which is also the most patient-relevant survival outcome, the results indicate clearly that a model containing the factors age, sex, tumor stage, tumor location and functional status predicts OS well in the total CRC population, and among both younger (<65 years) and older (≥65 years) CRC patients. However, in older CRC patients, CCI could be a valuable addition. For the prediction of the CRC-specific survival outcomes, DSS and RFS, the basic model of only age, sex, tumor stage and location was sufficient in both younger and older subjects. In contrast, for nDSS prediction, the basic model profits from an extension by the CCI and FI in older but not younger CRC patients. Observed patterns were that the less CRC specific the survival outcome and the older the CRC patients, the higher the predictive value of functional status, comorbidity and frailty is. These geriatric syndromes dominated polypharmacy and comedication quality in the models and the latter were not selected for any of the final survival models.

The TNM (tumor-node-metastasis) staging system is by far the most crucial factor in prognostication and treatment decision in CRC care.[18] However, extensive research has been conducted about the research question, which factors, apart from stage, are essential in CRC survival prediction. Several previous studies, including our own, observed that age, sex, tumor stage, tumor location, functional status, comorbidity, polypharmacy, the FORTA comedication quality score and frailty are independently associated with worse survival in CRC patients.[6,19-26,46] However, we are not aware of a previous study that simultaneously tested the predictive performance of all the named factors. Thus, there is no other study we can directly compare our results with and an external validation analysis is warranted. This future cohort study analysis should not only test the predictive value with the AUC, but also assess the reclassification measures NRI and IDI to quantify how many patients with and without the event of interest get correctly reclassified in higher or lower risk categories when an additional factor is added to a reference model.[44,45]

For prediction of OS in our total study population and younger CRC patients, the best model performance was found for a model comprising age, sex, tumor stage, tumor location and functional status. Although this final model is simple, its AUC (all ages: 0.76; <65 years: 0.82) is comparable to previous studies, which incorporated more variables into their models (AUC range: 0.75-0.79).[6,9,14,15,17] In our study

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population aged ≥65 years, further adding CCI substantially improved the predictive performance of the model and this finding resonates with the nomogram built by Boakye et al,[6] which incorporated CCI and functional status. Boakye et al[6] also analyzed the DACHS study but used an earlier dataset (CRC patients who were diagnosed in 2015-2016 were not available at that time), did not stratify by age and did not test frailty and comedication for incorporation in prediction models for CRC survival.

This high value of CCI in older CRC patients also highlights the importance of properly managing comorbidities in these patients because they can interact with CRC leading to an accelerated disease progression,[19] and can increase the risk of noncancer death.[47] Speaking of nDSS, it was an interesting result in our study that this was the only survival outcome among CRC patients, for which frailty was included in the final model in addition to CCI (especially for older patients). This finding reveals that frailty plays a crucial role in predicting nDSS in older CRC patients independently from comorbidity. Chronic inflammation, which leads to reduced functional reserve for stress adaption and lower tolerability for side effects brought by cancer treatment in frail patients, might explain this finding.[19,48,49] Other studies used specific frailty assessments when assessing its predictive value in CRC patients,[21-24] and are therefore not directly comparable with our findings for the FI. The FI we created has the great advantage for clinicians that it can be easily calculated from accessible information from hospital charts without the need to examine or test the patient. Thus, this frailty assessment of all CRC patients in a hospital can be done automatically from digital hospital charts and made available to physicians without medical examination costs. This might enhance the translation of frailty assessments into regular care.

For the prediction of the survival outcomes, which are most CRC-specific, that is, DFS and RFS, frailty and comorbidity played no role and the reference model containing age, sex, tumor stage and tumor location was already the best model for their predictions. Despite fewer variables, the AUCs in our study (DFS: 0.73; RFS: 0.78) were comparable to those obtained by a previous study using more variables (DFS: 0.74-0.75; RFS: 0.77-0.79).[6] Our findings have its merit to augment clinical practice by providing proof that age, sex, tumor stage and tumor location are sufficient for prognosis for survival outcomes which are very CRC-specific.

We acknowledge that there are some limitations in our study despite its unique strengths. Because the availability of functional status information varied among collaborative hospitals, we had to exclude nearly one third of participants with incomplete information on functional status from our study. Besides, the original CCI version used was developed over three decades ago and might not be able to accurately reflect the comorbidity status of today due to improved treatments for some diseases. Nevertheless, a recent study observed that the original CCI version did not predict OS worse than newer comorbidity indices in CRC patients.[50] Thus, applying the original CCI version remains appropriate and has the advantage to allow comparisons with previous studies. Furthermore, we did not consider multiple testing and did not validate our findings internally or in external populations. Thus, an external validation of our findings is needed, and we would like to encourage other scientists with access to CRC cohort study data to undertake this important task. In addition, our results may only apply to the German health care setting and should only be generalized with utmost care to other countries. Lastly, patients with the same nomogram points could have different survival rates because of intrinsic uncertainties in prediction models. For example, CCI and functional status could change over follow-up time, but we operationalized them as fixed variables in our prediction models, which might have negative influence on the accuracy of our models to some extent. Therefore, physicians should be aware of these limitations when applying the nomogram in clinical practice.

5 | CONCLUSIONS

This large study of CRC patients observed that the best model for survival prediction varied by outcome and age of the CRC patients. For OS, the most patient-relevant outcome, a model containing age, sex, tumor stage, tumor location and functional status has good prediction performance in the total CRC population and among younger (<65 years) patients, whereas a CCI assessment is additionally useful for older (≥65 years) CRC patients. For the prediction of the CRC-specific survival outcomes, DSS and RFS, the basic model consisting of only age, sex, tumor stage and location is already sufficient in both younger and older subjects. In contrast, for nDSS prediction, the basic model profits from an extension by CCI and FI in older but not younger patients. In summary, the less CRC-specific the survival outcome to be predicted and the older the CRC patients, the more relevant is the inclusion of functional status, comorbidity and frailty in the prognostic models. Therefore, in clinical practice, an assessment of functional status, comorbidity and frailty is particularly important for survival prognosis in older adults (≥65 years) with a high probability to be cured for CRC.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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AUTHOR CONTRIBUTIONS

Li-Ju Chen and Ben Schöttker contributed to the concept and design of this research. Li-Ju Chen and Thi Ngoc Mai Nguyen extracted medication information from the discharge letters. Hermann Brenner, Jenny Chang-Claude and Michael Hoffmeister designed and led the DACHS study and coordinated data acquisition. Li-Ju Chen performed the statistical analyses. Li-Ju Chen drafted the manuscript and Ben Schöttker revised and edited it. Thi Ngoc Mai Nguyen, Jenny Chang-Claude, Michael Hoffmeister and Hermann Brenner commented critically on an advanced manuscript version regarding the interpretation of the results and the discussion. All authors read and approved the final version of the manuscript. Li-Ju Chen and Ben Schöttker take responsibility for the integrity and accuracy of the data and the statistical analysis. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

DATA AVAILABILITY STATEMENT

Research data from DACHS are available upon request.

ETHICS STATEMENT

The DACHS study was approved by the ethics committees of the University of Heidelberg and the state medical boards of Baden-Württemberg and Rhineland-Palatinate. All participants sign a written informed consent.

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