Association of co-medication quality with chemotherapy-related adverse drug reactions and survival in older colorectal cancer patients

Running head: Co-medication quality and survival

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Abstract

Background: Evidence about the clinical relevance of appropriate co-medication among older colorectal cancer (CRC) patients is sparse.

Methods: A cohort study was conducted with 3,239 CRC patients aged 65 years and older. To assess co-medication quality, we calculated the total Fit fOR The Aged (FORTA) score and its sub-scores for medication overuse, underuse, and potentially inappropriate medication use. Multivariable Cox proportional hazards or logistic regression models were performed to evaluate the association of co-medication quality with up to 5-year overall survival, CRC-specific survival, and chemotherapy-related adverse drug reactions (ADRs).

Results: Overall, 3,239 and 1,209 participants were included in analyses on survival and ADRs, respectively. The hazard ratios [95%-confidence intervals] for the total FORTA score ≥ 7 vs. 0-1 points were 1.83 [1.40-2.40] and 1.76 [1.22-2.52] for up to 5-year overall and CRC-specific survival, respectively. Worse up to 5-year OS and CSS was also evident for FORTA sub-scores for PIM use and overuse whereas no association was observed for underuse. Although results for the total FORTA and potentially inappropriate medication score were much stronger among patients receiving chemotherapy, no significant associations with chemotherapy-related ADRs were observed. Moreover, associations were particularly strong among men and rectal cancer patients as compared to women and colon cancer patients.

Conclusions: Poor total co-medication quality was significantly associated with worse up to 5-year overall and CRC-specific survival. Randomized controlled trials are needed to test whether improved cancer co-medication management in older CRC patients prolongs survival.

Keywords: Geriatric Oncology; Colorectal cancer; Potentially inappropriate medication; survival; Adverse Drug Reaction

Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed cancers worldwide. It is a disease of great public health relevance with an estimated 1,931,590 incident cases and 935,173 deaths in 2020.[1,2] More than half of CRC patients are diagnosed after the age of 70 and the 5-year relative survival rate for all stages of CRC combined has recently increased to surpass 60%.[1,3,4] Pharmacological treatment of older and often multi-morbid CRC patients is increasingly challenging, but also an area with great potential for improvement.

Co-medication quality is an important issue in older cancer patients. It is generally defined as mis-, over-, and underuse of drugs.[5] Misuse of drugs in older adults (≥65 years) is often referred to as potentially inappropriate medication (PIM) use.[6] In older cancer patients, PIM use and medication overuse (which is related to polypharmacy) occur at least as often as in the general older population.[7,8] Depending on cancer population and definition, the prevalence of polypharmacy and PIM use varied between 5.6% and 96%,[7,9] and 10.8% and 57.5%,[7,9] respectively in previous studies. Cancer patients are particularly prone to unintended consequences of polypharmacy and PIM use because they often receive chemotherapy and symptom relieving agents, which may entail additional risk of drug-drug interactions and unwanted adverse drug reactions (ADRs).[10]

To date, two previous cohort studies have investigated the association between PIM use and clinical outcomes in older CRC patients.[11-13] PIM use was found to be significantly associated with increased postoperative mortality (odds ratio, OR [95% confidence interval, CI]: 1.43 [1.11–1.85]) and prolonged hospital stay (OR [95% CI]: 1.14 [1.00–1.29]) in a Swedish study.[12] However, the results were not adjusted for comorbidities and may therefore be prone to indication bias.[14,15] Contrastingly, PIM use was not significantly associated with overall survival (OS) and hospitalization in older CRC patients in two analyses utilizing data from the Surveillance, Epidemiology and End Results (SEER)-Medicare database, which were adjusted for various comorbidities.[11,13] To our

knowledge, no studies have been published thus far about medication underuse among older cancer patients.

Given the sparseness and inconclusiveness of available evidence, we aimed to evaluate the association of PIM use with OS and CRC-specific survival (CSS) in a large cohort of older CRC patients, paying particular attention to widening the spectrum of co-medication quality assessment by additionally addressing medication overuse and underuse as well as using a total co-medication quality score for the first time. Furthermore, we report, for the first time, data on potential associations of co-medication quality with chemotherapy-related ADRs among older CRC patients.

Methods

Study design and population

This study has a cohort study design because only the CRC patients aged ≥65 years (cases) from the ongoing, population-based ***Da****rmkrebs:* ***Ch****ancen der Verhütung durch* ***S****creening* (DACHS) case-control study were included. The DACHS study recruits 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.[16,17] Briefly, patients with a histologically confirmed first diagnosis of CRC (International Classification of Diseases, 10th Revision (ICD-10), codes C18–C20),[18] aged ≥30 years, and being able to speak German are eligible to participate. The DACHS study was approved by the ethics committees of the Medical Faculty of Heidelberg University and the state medical boards of Baden-Württemberg and Rhineland-Palatinate. All participants sign a written informed consent.

At baseline, shortly after CRC surgery in the collaborating hospitals, trained study nurses carry out personal interviews with the study participants. Using a standardized questionnaire, socio-demographic information, lifestyle factors, medical history, and drug use are collected. Additionally,

comorbidities and last medication are extracted from the participants' hospital discharge letters. Comorbidities are coded with the ICD-10 coding algorithm validated by Quan et al.[19] and drugs are coded according to a German adaption of the WHO's Anatomical Therapeutic Chemical (ATC) code (2019 version).[20]

Detailed information on the participants' CRC treatment (chemotherapy and/or radiotherapy), chemotherapy-related ADRs, and potential CRC recurrence is further gathered from questionnaires sent to gastroenterologists in the outpatient setting 3 years after diagnosis. Vital status and the cause of death of deceased patients are ascertained from population registries.

Inclusion and exclusion criteria

We included CRC patients of the DACHS study recruited between 2003 and 2016 in order to have follow-up for at least three years. Patients aged less than 65 years, not having received any surgery (mostly stage IV patients with very poor survival prognosis who cannot be cured anymore by surgery), without documentation of discharge medication in the hospital release records or lost to follow-up with respect to mortality were excluded, leaving 3,239 patients for the survival analyses (Appendix Figure A1). For analyses on chemotherapy-related ADRs, patients without adjuvant/neoadjuvant chemotherapy or 3-year follow-up information from gastroenterologists were further excluded, leaving 1,209 patients for those analyses.

Ascertainment of co-medication quality

Nowadays, several different lists are available to identify PIM. We chose the Fit fOR The Aged (FORTA) list because it assesses not only PIM but also over- and underuse and combines these three aspects into one score of total co-medication quality.[21] Furthermore, FORTA is specifically designed for the German market and is being updated regularly. Its clinical usefulness has been validated in a previous randomized controlled clinical trial (RCT).[5]

The FORTA list designates the appropriateness of medications for 30 important indications by assigning negative and positive labels to drugs when used for long-term treatment in older patients.[21] Labels in the FORTA list include A (indispensable), B (beneficial), C (questionable), and D (avoid), depending on the state of evidence for safety, efficacy, and appropriateness in older patients.[22] In this study, we used the FORTA list to decide about the appropriateness of patients' medications for 30 indications. The following two exceptions were made:

1) Appropriateness of chemotherapy in CRC and other cancers was not evaluated because adjuvant chemotherapy had not started when drug use was assessed, i.e. during hospitalization for CRC surgery, and

2) Non-steroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors if given with NSAIDs, and anticoagulants were not considered as overuse because they can be indicated for short-term use during or shortly after CRC surgery.

We then calculated scores for underuse, overuse, and PIM use for every patient as described below and summed the three scores up to obtain the total FORTA score.[5]

a) Underuse (1 point): An indication is not treated.
b) Overuse (1 point): The medication is prescribed in the absence of an appropriate indication.
c) PIM use (2 points): The medication is indicated, but a drug classified as C (questionable) or D (avoid) is given despite available classes A (indispensable) or B (beneficial) alternatives.

Higher scores indicate poorer co-medication quality. We also provide a case example from our study population showing how underuse, overuse, PIM use, and the total FORTA score were calculated in Appendix Figure A2.

To achieve as complete drug and comorbidity information as possible, we combined information from the hospital discharge letters and the interview with the patients. In brief, to classify as underuse, the missing drugs needed to be absent in both hospital discharge letters and patient-reported

information. To classify as overuse, the missing indication needed to be present in both hospital discharge letters and patient-reported information.

Ascertainment of chemotherapy-related adverse drug reactions

Chemotherapy-related ADRs were collected from gastroenterologists in the outpatient setting via questionnaires sent at 3-year follow-up. We selected reported hematological, cardiac, neurological, and gastrointestinal ADRs as separate outcomes and defined them as dichotomized dependent variables (occurred yes/no) in logistic regression models. The Common Terminology Criteria for Adverse Events (CTCAE) grades of ADRs were not available.

Ascertainment of overall and CRC-specific survival

Information about the vital status, date, and cause of death of study participants was collected via inquiry at local population registries. The ICD-10 codes of the causes of death were verified by death certificates. Overall and CRC-specific survival were defined as time from CRC hospitalization to death from any cause or from CRC, respectively, or end of follow-up (February 2020).

Statistical analyses

The FORTA score was analyzed as a continuous variable (per 1-point increase) and as a categorical variable (0-1/2-3/4-6/≥7 points). The FORTA sub-scores for underuse (0/1/≥2 points), overuse (0/1/2/≥3 points) and PIM use (0/2/≥4 points) were modelled as categorical variables. A generalized linear model was used to assess the associations of the baseline patient characteristics with the total FORTA score. Multivariable logistic regression models were used to assess the associations with dichotomous variables for PIM use, underuse, and overuse (present: yes/no).

Associations of the total FORTA score, PIM use, underuse, and overuse with up to 5-year OS and CSS were assessed with Cox proportional hazards regression models. The follow-up time was limited to 5 years because drug exposure may change during longer follow-up and CRC patients can

be considered cured if there was no cancer recurrence within 5 years. Furthermore, more comparable mortality follow-up times between 3 and 5 years for all years of recruitment in the DACHS study were achieved by this restriction of the follow-up time. The proportional hazards assumption was assessed for the main determinants and all covariates by adding time-dependent interaction terms. Only the covariates smoking status, tumor stage, and whether neoadjuvant/adjuvant chemotherapy was received violated the assumption and their interaction terms with follow-up time were added to the models. Associations of the total FORTA score, PIM use, underuse, and overuse with chemotherapy-related ADRs were evaluated with multivariable logistic regression models.

Three sets of variables were used for multivariable logistic/Cox proportional hazards regression models. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, tumor stage, tumor location, year of CRC diagnosis, neoadjuvant/adjuvant chemotherapy (not included in models on chemotherapy-related ADRs), number of years of school education, smoking status, body mass index (BMI), lifetime physical activity, lifetime alcohol consumption, red meat consumption, and processed meat consumption. Model 3 additionally included the functional status (using a harmonized, categorical variable based on either the American Society of Anesthesiologists (ASA) Physical Status Classification System, Eastern Cooperative of Oncology Group (ECOG), and Karnofsky performance status as previously described),[23] and comorbidities (21 diseases of the FORTA list as single variables). The following diseases of the FORTA list were not considered because they were too rare (n<30 cases), overlapped largely with other FORTA diseases, or because almost all participants (>96%) with these indications had PIM use: Acute non-CRC solid cancers, acute hematological neoplasms, bipolar disorder, epilepsy, nausea/vomiting and depression/paranoia or hallucination/restlessness or agitation/sleep disorder as dementia-related symptoms.

Subgroup analyses were carried out for groups of patients defined by age (65-74/≥75 years), sex, tumor stage (I-II/III/IV), tumor location (colon/rectum), neoadjuvant/adjuvant chemotherapy (Yes/No), and functional status (excellent/fair/poor).

Multiple imputation was performed to impute missing covariate data using the Markov Chain Monte Carlo (MCMC)[24] technique with 200 burn-in iterations and 20 datasets were generated. All covariates of model 3 were used in the imputation model. All analyses were conducted with the SAS software, version 9.4 (SAS Institute, Cary, NC). Statistical tests were two-tailed, with a significance level (α) of 0.05. No adjustment for multiple testing was made.

Results

Cross-sectional analyses

We included 3,239 patients in the cross-sectional analyses and the analyses on survival endpoints (Appendix Figure A1). The distribution of the FORTA score was right-skewed (Appendix Figure A3). The mode was 2 score points, the median was 3 score points and 17.1% of the population had ≥7 score points. The baseline characteristics of the study population and their associations with the total FORTA score are shown in Table 1. The mean age of the included study participants was 75.0 years [standard deviation (SD), 6.5 years] at baseline and 1,334 (41.2%) were female. The age at CRC diagnosis, poor functional status, and 18 of the 21 included diseases were positively associated with the FORTA score, whereas ≥12 years of schooling, the calendar year of CRC diagnosis between 2013-2016, tumor stage II vs. I, BMI 25-29.9 vs. <25 kg/m^2, and lifetime physical activity middle vs. bottom tertile were inversely associated with the FORTA score. Sex, lifestyle factors except physical activity and BMI, tumor location, chemotherapy, and diagnoses of hypertension, gastrointestinal illness, and hypothyroidism were not associated with the FORTA score.

The cross-sectional analyses on associations of patient characteristics with the FORTA score's sub-scores for PIM use, medication underuse, and overuse are demonstrated in Table 2. An age at CRC diagnosis ≥75 years was significantly associated with increased odds for medication overuse (odds ratio (OR) [95% confidence interval (95%CI)]: 1.20 [1.01-1.41]). With increasing calendar

years of CRC diagnosis, the odds for PIM use and underuse decreased, while the odds for overuse increased. Subjects who received chemotherapy had significantly lower odds of overuse compared to those who did not received any (OR [95%CI]: 0.79 [0.63-0.98]**)**. Lifestyle factors were neither associated with PIM use, medication underuse nor overuse. The only exception was a significant association between the middle vs. bottom tertile of lifetime physical activity and medication overuse (OR [95%CI]: 0.75 [0.62-0.91]). Subjects with poor functional status had significantly higher odds for PIM use compared to those with excellent functional status (OR [95%CI]: 1.39 [1.06-1.83]**)**, while no associations of functional status were observed with medication underuse and overuse. With the exception of the association of history of myocardial infarction and medication underuse, the multiple statistically significant associations of comorbidities with PIM use and underuse showed a clear pattern of increased odds whereas the associations with overuse showed decreased odds.

Longitudinal analyses

During a minimum of 3 and a maximum of 5 years of follow-up for OS, 1,070 participants died, among whom 615 died of CRC as the primary cause of death (57.5%). In main model 3, the risk of all-cause and CRC-specific mortality was statistically significantly increased by 5% and 6%, respectively, if the FORTA score increased by 1 point (Table 3). The risk increased stepwise with increasing FORTA score points and was most pronounced for a comparison of subjects with ≥7 points and 0-1 points: 83% increased all-cause mortality and 76% increased CRC-specific mortality were observed. The increase in mortality by higher FORTA score points mainly resulted from increased risks by PIM use and overuse and the association of PIM use with up to 5-year OS and CSS as well as the association of medication overuse with up to 5-year OS were statistically significant. In contrast, no association of medication underuse with the two survival outcomes was observed. However, it should be acknowledged for medication underuse that many indications in the FORTA list do not directly lead to death. Medication underuse for many diseases, such as Parkinson's disease, is rather relevant for the quality of life than survival. Thus, we did a further analysis on medication

underuse with restriction to 10 FORTA indications, for which there is a relevant risk of death, if left untreated, and we observed a slightly stronger but also not statistically significant association between medication underuse and OS (HR [95%CI]: 1.13 [0.96-1.20]).

Stratified analyses revealed that the association between the total FORTA score, PIM use, and overuse with OS were restricted to males and not evident in females (Table 4). Furthermore, Appendix Table A1 shows that the association of PIM use and OS was particularly strong among CRC patients who received chemotherapy (odds ratio (OR), 95%CI: 2.98 [1.86-4.78] for the comparison of subjects with ≥4 and 0 PIM use score points). The detailed results for the other sub-group analyses by tumor location, tumor stage, functional status, and age are shown in Appendix Tables A2-A5, respectively. The extreme group comparisons are illustrated in Figure 1. Of note are particularly strong results for the associations of the FORTA score, underuse, and overuse with OS among rectum cancer patients. In analyses stratified by tumor stage, functional status, and age, the results seemed not to vary much in subgroups. We also tested potential interaction terms between all patient characteristics used for sub-group analyses and all co-medication quality scores. Only the interaction terms between tumor location and the FORTA score (p=0.004) and between tumor location and the underuse score (p=0.016) were statistically significant.

With respect to chemotherapy-related ADRs, neither the total FORTA score nor its three sub-scores were found to be associated with hematological, cardiac, neurological, or gastrointestinal ADRs in the fully adjusted model (Appendix Table A6).

Discussion

In this large-scale cohort study of CRC patients, poorer total co-medication quality upon hospital discharge after CRC surgery was significantly associated with worse 5-year OS and CSS. The two components of total co-medication quality, PIM use and overuse, exhibited similar associations to

survival, whereas no association of medication underuse and survival was observed. Particularly strong associations between co-medication quality and survival were evident among male patients, patients with rectum cancer, and patients who received chemotherapy. No associations of co-medication quality scores with chemotherapy-related ADRs were observed.

In this study, we identified earlier year of diagnosis, poor functional status, and 12 comorbidities as independent determinants of PIM use. As it can be expected that awareness of PIM use in older patients among physicians increased with time, it is a good sign that also the number of potential inappropriate prescriptions decreased in the studied years from 2003 to 2016. We also found that a high number of comorbidities were significantly associated with PIM use, which is in line with previous studies investigating the association of patient characteristics with PIM use.[11,25] Poor functional status has also already been recognized as one of the determinants of PIM use in older cancer patients before.[26] Functional status is linked to comorbidities, the number of prescribed drugs, and frailty, all of which describe the patients' health status and have all been found to be associated with PIM use by previous studies.[11,25,27,28]

The association of PIM use with all-cause mortality (risk ratio [95%CI]: 1.43 [1.08-1.88]) from a previous meta-analysis of cohort studies including older cancer patients[7] was similar to the HR [95%CI] from our study (1.42 [1.25-1.61]) with PIM use as a dichotomous variable (PIM use: yes/no). In our study, after additionally adjusting for the important confounders comorbidities and functional status, results were attenuated but still statistically significant (HR 95%CI, 1.23 [1.05-1.44]). Our results show for the first time that the number of drugs used as PIM is highly relevant in the overall survival of cancer patients. There was no substantially increased 5-year all-cause mortality under the use of 1 PIM (1.14 [0.97-1.35]) in the fully adjusted model; however, there was a 44% significantly higher mortality in CRC patients with 2 or more drugs used as PIM (1.44 [1.19-1.75]). Therefore, we recommend that future studies evaluating PIM use in cancer patients should be

adjusted for comorbidities and functional status to reduce confounding and to assess the extent of PIM use by the number of drugs and not only as a dichotomous variable.

Another important finding of our study was that PIM use and overuse showed similar associations as the total FORTA score and that there was no significant association of medication underuse with overall survival. This indicates that cancer co-medication quality should be assessed comprehensively, not only PIM use but also medication overuse should be considered.

An interesting result from the sub-group analyses was that 5-year all-cause mortality was significantly, almost 3-fold higher in patients who received neoadjuvant/adjuvant chemotherapy if they had a high FORTA score or used 2 or more PIM. The total drug burden for patients receiving chemotherapy can be considered higher than for those not receiving any chemotherapy. Drug-drug interactions and chemotherapy-related ADRs could therefore be a bigger concern.[10] However, as we did not find any significant associations of the FORTA score or PIM use with any types of chemotherapy-related ADRs, the reasons for the observed increased mortality among patients with neoadjuvant/adjuvant chemotherapy is likely to be found among the PIM used as co-medication. Despite a need for further research with a more comprehensive assessment of drug-drug interactions or ADRs to corroborate this, our study indicates that physicians should pay close attention to the co-medication of CRC patients undergoing chemotherapy.

Another striking observation from the sub-group analyses was that male CRC patients had substantially increased all-cause mortality if they had poorer co-medication quality, more PIM use, or more medication overuse, while female CRC patients did not. Sex differences in prescription patterns cannot explain this finding since our study showed that sex was neither associated with PIM use, underuse, nor overuse. Other studies presented inconsistent results with respect to sex differences in the risk of receiving PIM.[29-31] With respect to sex differences in CRC survival, a very large study based on cancer registry data from Germany observed poorer survival among men than women and only among CRC patients younger than 65 years,[32] which also cannot explain our findings from a

cohort of older CRC patients (≥65 years). It is thus of interest, whether the observed sex difference in the susceptibility towards worse outcomes under poor co-medication quality among older CRC patients can be replicated in future studies and if plausible explanations can be found.

In addition, poor co-medication quality in patients with rectal cancer was found to have a noticeably higher risk for 5-year all-cause mortality than in patients with colon cancer. This might be due to different patient characteristics. In accordance with previous studies,[33-36] rectal cancer patients were more frequently male and more frequently received (neo-)adjuvant chemotherapy in our study population. Both patient characteristics had stronger associations between co-medication quality and OS.

We acknowledge that there are some limitations in our study despite its unique strengths. Although we additionally took the patients' self-reported comorbidities and medications into account, potential under-reporting cannot be neglected. In addition, we had no information on prescription changes over time and medication adherence of study participants. The resulting inaccuracy of co-medication quality classification has most likely led to an underestimation of effect estimates. Another aspect that could have led to an underestimation is the healthy-user/sick-stopper bias[37] because a new-user design was not possible to apply in this study. A strength of our study is the comprehensive adjustment for potential confounders including functional status and 21 diseases. However, due to the observational study setting, residual confounding effects cannot be ruled out completely. Furthermore, our study lacked details about the severity of ADRs and future studies with CTCAE coding may find significant associations between co-medication quality and chemotherapy-related ADRs. Finally, our study was conducted in Germany and the generalizability of our results to other countries may be limited due to different prescription behaviors and populations. Studies from other countries are required to corroborate our results. Although developed in Germany, the FORTA list is available in English and should be applicable in other countries.

Conclusions

Poorer overall co-medication quality (as assessed by the FORTA score) was significantly associated with poorer 5-year OS and CSS. The association with OS was particularly strong among males, patients who underwent chemotherapy, and patients with rectal cancer. PIM use and overuse seemed to contribute to the similar extent to survival of CRC patients. The FORTA list could be a suitable tool to optimize the total co-medication quality for CRC patients in clinical settings. RCTs are warranted to examine whether the use of the FORTA list in this setting can improve CRC survival.

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Author Contributions

L.-J.C. and B.S. contributed to the concept and design of this study. L.-J.C. and N.T.N.M. extracted medication information from the discharge letters. J.C.-C., M.H., and H.B. made contribution to data acquisition and coordination of the DACHS study. L.-J.C. performed the statistical analyses. L.-J.C. drafted the manuscript and B.S. revised and edited it. N.T.N.M., D.C.L., J.C.-C., M.H., and H.B. 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. L.-J.C. and B.S. take responsibility for the integrity and accuracy of the data and the statistical analysis.

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Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Figure legend

Figure 1. Forest plots of stratified analyses assessing the associations of total co-medication quality (as assessed by the FORTA score), PIM use, medication underuse and overuse with up to 5-year overall survival in older CRC patients

Table 1. Associations of the baseline characteristics of a cohort of older colorectal cancer patients with total co-medication quality as assessed by the FORTA score (in N=3,239)

Characteristics	N (%)	Median FORTA score (IQR)	Multivariable generalized linear model	
			Estimate [a]	*P*-value
Sex				
Female	1334 (41.2)	3 (2; 6)	Ref	
Male	1905 (58.8)	3 (2; 5)	-0.09	0.368
Age at CRC diagnosis (years)				
65-74	1652 (51.0)	3 (2; 4)	Ref	
≥75	1587 (49.0)	4 (2; 6)	0.28	**<0.001**
Years of schooling				
≤9	2318 (71.6)	3 (2; 6)	Ref	
10-11	486 (15.0)	3 (2; 5)	-0.07	0.512
≥12	435 (13.4)	3 (1; 4)	-0.29	**0.016**
Year of CRC diagnosis				
2003-2007	1098 (33.9)	3 (2; 6)	Ref	
2008-2012	1223 (37.8)	3 (2; 5)	-0.14	0.128
2013-2016	918 (28.3)	3 (1; 5)	-0.30	**0.004**
Tumor location				
Colon	2088 (64.5)	3 (2; 5)	Ref	
Rectum	1151 (35.5)	3 (2; 5)	0.08	0.343
Tumor stage				
I	769 (23.7)	3 (2; 5)	Ref	
II	1082 (33.4)	3 (2; 5)	-0.23	**0.031**
III	985 (30.4)	3 (2; 5)	0.03	0.820
IV	403 (12.4)	3 (2; 5)	0.01	0.946
Adjuvant/neoadjuvant chemotherapy				
Yes	1211 (37.4)	3 (2; 5)	-0.12	0.270
No	2028 (62.6)	3 (2; 6)	Ref	
BMI (kg/m^2)				
< 25	1197 (37.0)	3 (2; 5)	Ref	
25-29.9	1417 (43.7)	3 (2; 5)	-0.19	**0.034**
≥30	625 (19.3)	4 (2; 6)	-0.04	0.750
Lifetime physical activity (MET-h/week)				
T1	1079 (33.3)	3 (2; 5)	Ref	
T2	1080 (33.3)	3 (2; 5)	-0.19	**0.046**
T3	1080 (33.3)	3 (2; 5)	-0.05	0.641
Smoking status				
Never smoker	1466 (45.3)	3 (2; 5)	Ref	
Former smoker	1473 (45.5)	3 (2; 5)	0.04	0.683
Current smoker	300 (9.3)	3 (1; 5)	0.13	0.349
Lifetime alcohol consumption				
None	603 (18.6)	4 (2; 6)	Ref	
T1	873 (27.0)	3 (2; 5)	-0.10	0.408
T2	883 (27.3)	3 (1; 5)	-0.10	0.420
T3	880 (27.2)	3 (2; 5)	-0.07	0.625
Red meat consumption				
<1 time/week	259 (8.0)	4 (2; 6)	Ref	
1 time/week	735 (22.7)	3 (2; 5)	0.17	0.290
Multiple times per week	2245 (69.3)	3 (2; 5)	0.13	0.410
Processed meat consumption				
<1 time/week	406 (12.5)	3 (2; 5)	Ref	
1 time/week	426 (13.2)	3 (2; 5)	-0.02	0.883
Multiple times per week	2407 (74.3)	3 (2; 5)	0.08	0.535
Functional status				
Excellent	629 (19.4)	2 (1; 4)	Ref	
Fair	1214 (37.5)	3 (2; 5)	0.15	0.161
Poor	1396 (43.1)	4 (2; 6)	0.30	**0.010**
Comorbidity				
Hypertension	2255 (69.6)	3 (2; 6)	0.16	0.070
Cardiac insufficiency	679 (21.0)	5 (3; 8)	0.93	**<0.001**
Acute coronary syndrome	394 (12.2)	5 (3; 8)	0.61	**<0.001**

Characteristics	N (%)	Median FORTA score (IQR)	Multivariable generalized linear model	
			Estimate [a]	*P*-value
History of myocardial infarction	599 (18.5)	4 (2; 7)	0.39	**<0.001**
History of stroke	390 (12.0)	5 (3; 8)	0.60	**<0.001**
Atrial fibrillation	423 (13.1)	7 (5; 10)	3.73	**<0.001**
COPD	306 (9.5)	6 (4; 8)	1.93	**<0.001**
Osteoporosis	60 (1.9)	4.5 (3; 7)	0.64	**0.026**
Type II diabetes mellitus	836 (25.8)	4 (3; 7)	0.97	**<0.001**
Dementia	31 (1.0)	10 (8; 13)	5.77	**<0.001**
Depression	254 (7.8)	6 (4; 9)	2.52	**<0.001**
Insomnia, sleep disorder	57 (1.8)	7 (4; 11)	3.20	**<0.001**
Chronic pain	1965 (60.7)	4 (2; 6)	1.29	**<0.001**
Parkinson's disease	31 (1.0))	5 (4; 8)	1.83	**<0.001**
Incontinence	30 (0.9)	5 (3; 8)	1.14	**0.004**
Gastrointestinal illness	708 (21.9)	3 (2; 6)	-0.14	0.146
Anemia	343 (10.6)	5 (3; 7)	0.81	**<0.001**
Obstipation	80 (2.5)	4 (2; 7)	0.87	**<0.001**
Hypothyroidism	167 (5.2)	3 (2; 6)	0.06	0.731
Bacterial infection	109 (3.4)	5 (3; 8)	1.33	**<0.001**
Indication for oncological supportive therapy	93 (2.9)	5 (4; 7)	0.73	**0.005**

Values in bold are statistically significant (p<0.05)

Abbreviations: BMI, body mass index; BPSD, Behavioral and psychological symptoms of dementia; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; FORTA, Fit fOR The Aged; h, hour; IQR, interquartile range; kg, kilogram; m, meter; MET, metabolic equivalent of task; Ref, reference.

[a] Effect estimates of a multivariable model comprising all variables shown in this table.

Table 2. Associations of patient characteristics with PIM use, medication underuse, and overuse (in N=3,239)

Variables	PIM use		Underuse		Overuse	
	N_{case} (%)	Multivariable OR [95% CI] [a]	N_{case} (%)	Multivariable OR [95% CI] [a]	N_{case} (%)	Multivariable OR [95% CI] [a]
Sex						
Female	737 (55.3)	Ref	691 (51.8)	Ref	911 (68.3)	Ref
Male	967 (50.8)	1.01 [0.78-1.29]	885 (46.4)	1.22 [0.98-1.52]	1250 (65.6)	0.91 [0.74-1.13]
Age at CRC diagnosis (years)						
65-74	755 (45.7)	Ref	772 (46.7)	Ref	1078 (65.3)	Ref
≥ 75	949 (59.8)	1.15 [0.95-1.40]	804 (50.7)	1.03 [0.86-1.23]	1083 (68.2)	**1.20 [1.01-1.41]**
Years of schooling						
≤9	1254 (54.1)	Ref	1134 (48.9)	Ref	1554 (67.0)	Ref
10-11	247 (50.8)	1.14 [0.88-1.48]	233 (47.9)	1.09 [0.86-1.38]	328 (67.5)	0.91 [0.73-1.14]
≥12	203 (46.7)	1.12 [0.84-1.50]	209 (48.1)	1.17 [0.91-1.50]	279 (64.1)	0.80 [0.63-1.01]
Year of CRC diagnosis						
2003-2007	605 (55.1)	Ref	609 (55.5)	Ref	680 (61.9)	Ref
2008-2012	660 (54.0)	0.96 [0.77-1.20]	581 (47.5)	**0.74 [0.60-0.90]**	832 (68.0)	**1.34 [1.11-1.61]**
2013-2016	439 (47.8)	**0.75 [0.59-0.97]**	386 (42.0)	**0.59 [0.48-0.74]**	649 (70.7)	**1.46 [1.19-1.80]**
Tumor location						
Colon	1136 (54.4)	Ref	1060 (50.8)	Ref	1386 (66.4)	Ref
Rectum	568 (49.4)	1.00 [0.82-1.22]	516 (44.8)	1.03 [0.86-1.22]	775 (67.3)	1.00 [0.85-1.18]
Tumor stage						
I	412 (53.6)	Ref	359 (46.7)	Ref	507 (65.9)	Ref
II	575 (53.1)	0.95 [0.74-1.21]	568 (52.5)	1.12 [0.90-1.40]	703 (65.0)	0.91 [0.74-1.13]
III	513 (52.1)	1.09 [0.80-1.50]	439 (44.6)	0.81 [0.61-1.06]	669 (67.9)	1.19 [0.91-1.54]
IV	204 (50.6)	1.16 [0.79-1.69]	210 (52.1)	1.13 [0.80-1.58]	282 (70.0)	1.35 [0.98-1.87]
Adjuvant/neoadjuvant chemotherapy						
Yes	568 (46.9)	0.99 [0.76-1.29]	554 (45.8)	1.08 [0.85-1.36]	802 (66.2)	**0.79 [0.63-0.98]**
No	1136 (56.0)	Ref	1022 (50.4)	Ref	1359 (67.0)	Ref
BMI (kg/m^2)						
< 25	592 (49.5)	Ref	583 (48.7)	Ref	826 (69.0)	Ref
25-29.9	741 (52.3)	0.93 [0.75-1.14]	658 (46.4)	0.93 [0.77-1.11]	923 (65.1)	0.90 [0.76-1.07]
≥30	371 (59.4)	0.90 [0.69-1.17]	335 (53.6)	1.15 [0.91-1.45]	412 (65.9)	1.02 [0.81-1.28]
Lifetime physical activity (MET-h/week)						
T1	541 (50.1)	Ref	531 (49.2)	Ref	761 (70.5)	Ref
T2	577 (53.4)	0.95 [0.75-1.19]	522 (48.3)	0.88 [0.72-1.07]	693 (64.2)	**0.75 [0.62-0.91]**
T3	586 (54.3)	1.15 [0.91-1.46]	523 (48.4)	0.85 [0.69-1.05]	707 (65.5)	0.85 [0.69-1.04]
Smoking status						
Never smoker	783 (53.4)	Ref	737 (50.3)	Ref	984 (67.1)	Ref
Former smoker	786 (53.4)	1.06 [0.85-1.32]	691 (46.9)	0.98 [0.81-1.19]	976 (66.3)	1.10 [0.92-1.31]
Current smoker	135 (45.0)	0.86 [0.61-1.20]	148 (49.3)	1.10 [0.82-1.49]	201 (67.0)	1.08 [0.81-1.44]

Variables	PIM use		Underuse		Overuse	
	N_{case} (%)	Multivariable OR [95% CI] [a]	N_{case} (%)	Multivariable OR [95% CI] [a]	N_{case} (%)	Multivariable OR [95% CI] [a]
Lifetime alcohol consumption						
None	350 (58.0)	Ref	325 (53.9)	Ref	413 (68.5)	Ref
T1	460 (52.7)	0.92 [0.69-1.22]	430 (49.3)	0.95 [0.74-1.22]	592 (67.8)	1.03 [0.81-1.30]
T2	424 (48.0)	0.85 [0.62-1.16]	403 (45.6)	0.92 [0.70-1.21]	589 (66.7)	0.97 [0.74-1.25]
T3	470 (53.4)	1.01 [0.72-1.41]	418 (47.5)	0.96 [0.71-1.28]	567 (64.4)	0.93 [0.70-1.22]
Red meat consumption						
<1 time/week	137 (52.9)	Ref	144 (55.6)	Ref	183 (70.7)	Ref
1 time/week	384 (52.2)	1.34 [0.90-2.00]	373 (50.8)	0.94 [0.66-1.32]	476 (64.8)	0.77 [0.56-1.08]
Multiple times per week	1183 (52.7)	1.28 [0.88-1.87]	1059 (47.2)	0.79 [0.57-1.09]	1502 (66.9)	0.90 [0.66-1.24]
Processed meat consumption						
<1 time/week	216 (53.2)	Ref	210 (51.7)	Ref	281 (69.2)	Ref
1 time/week	226 (53.1)	1.13 [0.78-1.62]	223 (52.4)	0.98 [0.71-1.36]	292 (68.5)	1.07 [0.78-1.46]
Multiple times per week	1262 (52.4)	1.00 [0.74-1.34]	1143 (47.5)	0.91 [0.70-1.19]	1588 (66.0)	0.92 [0.72-1.18]
Functional status						
Excellent	250 (39.8)	Ref	259 (41.2)	Ref	443 (70.4)	Ref
Fair	577 (47.5)	1.19 [0.92-1.54]	553 (45.6)	1.03 [0.82-1.30]	803 (66.1)	0.87 [0.70-1.08]
Poor	877 (62.8)	**1.39 [1.06-1.83]**	764 (54.7)	1.16 [0.91-1.47]	915 (65.5)	0.95 [0.75-1.20]
Comorbidity						
Hypertension	1355 (60.1)	**1.94 [1.57-2.39]**	1101 (48.8)	0.86 [0.71-1.03]	1462 (64.8)	**0.76 [0.63-0.91]**
Cardiac insufficiency	546 (80.4)	**2.32 [1.78-3.01]**	391 (57.6)	1.03 [0.83-1.29]	446 (65.7)	1.15 [0.94-1.42]
Acute coronary syndrome	300 (76.1)	**1.52 [1.09-2.14]**	195 (49.5)	0.89 [0.67-1.18]	231 (58.6)	0.88 [0.68-1.13]
History of myocardial infarction	445 (74.3)	**1.92 [1.44-2.55]**	275 (45.9)	**0.59 [0.46-0.76]**	344 (57.4)	**0.64 [0.51-0.80]**
History of stroke	291 (74.6)	**2.23 [1.63-3.04]**	216 (55.4)	**1.32 [1.03-1.69]**	254 (65.1)	0.92 [0.73-1.16]
Atrial fibrillation	404 (95.5)	**34.18 [20.54-56.89]**	255 (60.3)	**1.67 [1.30-2.15]**	282 (66.7)	1.03 [0.82-1.30]
COPD	245 (80.1)	**5.08 [3.54-7.30]**	223 (72.9)	**3.61 [2.68-4.85]**	200 (65.4)	1.02 [0.78-1.33]
Osteoporosis	41 (68.3)	1.78 [0.92-3.47]	41 (68.3)	**1.92 [1.01-3.62]**	41 (68.3)	1.19 [0.66-2.13]
Type II diabetes mellitus	596 (71.3)	**2.61 [2.09-3.25]**	477 (57.1)	**1.65 [1.36-2.00]**	563 (67.3)	1.14 [0.95-1.37]
Dementia	28 (90.3)	**16.07 [3.99-64.70]**	29 (93.6)	**16.76 [3.64-77.04]**	23 (74.2)	1.32 [0.57-3.09]
Depression	198 (78.0)	**4.86 [3.33-7.09]**	185 (72.8)	**3.16 [2.30-4.36]**	178 (70.1)	1.27 [0.94-1.70]
Insomnia, sleep disorder	40 (70.2)	1.48 [0.68-3.22]	55 (96.5)	Not included[b]	33 (57.9)	0.77 [0.44-1.35]
Chronic pain	1320 (67.2)	**6.68 [5.46-8.18]**	1127 (57.4)	**2.72 [2.29-3.24]**	1241 (63.2)	**0.68 [0.58-0.80]**
Parkinson's disease	25 (80.7)	**9.65 [3.19-29.21]**	19 (61.3)	1.65 [0.71-3.84]	24 (77.4)	1.49 [0.62-3.57]
Incontinence	22 (73.3)	1.73 [0.59-5.04]	29 (96.7)	Not included[b]	20 (66.7)	1.13 [0.51-2.52]
Gastrointestinal illness	405 (57.2)	1.04 [0.84-1.30]	442 (62.4)	**1.85 [1.52-2.25]**	373 (52.7)	**0.48 [0.40-0.58]**
Anemia	206 (60.1)	0.92 [0.65-1.32]	321 (93.6)	**22.43 [14.18-35.48]**	219 (63.9)	1.06 [0.80-1.41]
Obstipation	39 (48.8)	0.83 [0.46-1.51]	74 (92.5)	**19.36 [8.13-46.15]**	54 (67.5)	1.04 [0.64-1.71]
Hypothyroidism	97 (58.1)	1.09 [0.72-1.63]	91 (54.2)	1.19 [0.82-1.73]	98 (58.7)	**0.67 [0.48-0.93]**
Bacterial infection	65 (59.6)	1.08 [0.63-1.86]	106 (97.3)	Not included[b]	65 (59.6)	0.70 [0.46-1.06]
Indication for oncological supportive therapy	54 (58.1)	1.06 [0.57-1.97]	93 (100.0)	Not included[b]	53 (57.0)	**0.56 [0.34-0.93]**

Values in bold are statistically significant (p<0.05)

Abbreviations: BMI, body mass index; BPSD, Behavioral and psychological symptoms of dementia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; h, hour; kg, kilogram; m, meter; MET, metabolic equivalent of task; OR, odds ratio.

[a] Effect estimates of a multivariable model comprising all variables shown in this table.

[b] Almost all (>96%) or all patients had underuse. Variable was excluded for model stability.

Table 3. The associations of total co-medication quality (as assessed by the FORTA score), PIM use, medication underuse and overuse with up to 5-year overall and colorectal cancer-specific survival in older CRC patients (in N=3,239)

Variables	5-year Overall Survival					5-year Colorectal Cancer Specific Survival				
	N_{total}	N_{cases} (%)	Model 1 [a] HR [95% CI]	Model 2 [b] HR [95% CI]	Model 3 [c] HR [95% CI]	N_{total}	N_{cases} (%)	Model 1 [a] HR [95% CI]	Model 2 [b] HR [95% CI]	Model 3 [c] HR [95% CI]
FORTA score										
Per 1 point	-	-	**1.06 [1.04-1.07]**	**1.07 [1.06-1.09]**	**1.05 [1.03-1.08]**	-	-	1.02 [1.00-1.05]	**1.05 [1.02-1.07]**	**1.06 [1.02-1.11]**
0-1	688	156 (22.7)	Ref	Ref	Ref	671	109 (16.2)	Ref	Ref	Ref
2-3	1118	314 (28.1)	**1.26 [1.04-1.52]**	1.19 [0.98-1.44]	1.17 [0.96-1.43]	1090	204 (18.7)	1.16 [0.92-1.47]	1.03 [0.81-1.31]	1.01 [0.79-1.29]
4-6	880	352 (40.0)	**1.76 [1.45-2.12]**	**1.61 [1.32-1.95]**	**1.46 [1.18-1.82]**	861	194 (22.5)	**1.45 [1.14-1.84]**	1.25 [0.98-1.59]	1.27 [0.96-1.68]
≥7	553	248 (44.9)	**1.97 [1.60-2.41]**	**2.12 [1.72-2.61]**	**1.83 [1.40-2.40]**	523	108 (20.7)	**1.34 [1.02-1.76]**	**1.53 [1.16-2.02]**	**1.76 [1.22-2.52]**
PIM use										
0	1535	415 (27.0)	Ref	Ref	Ref	1495	283 (18.9)	Ref	Ref	Ref
2	844	283 (33.5)	**1.22 [1.05-1.43]**	**1.21 [1.04-1.41]**	1.14 [0.97-1.35]	826	162 (19.6)	1.05 [0.86-1.27]	1.04 [0.85-1.26]	1.04 [0.84-1.29]
≥4	860	372 (43.3)	**1.56 [1.35-1.80]**	**1.65 [1.43-1.91]**	**1.44 [1.19-1.75]**	824	170 (20.6)	1.12 [0.92-1.36]	**1.27 [1.04-1.55]**	**1.37 [1.06-1.77]**
Underuse										
0	1663	491 (29.5)	Ref	Ref	Ref	1620	302 (18.6)	Ref	Ref	Ref
1	1008	344 (34.1)	**1.16 [1.01-1.33]**	1.14 [0.99-1.31]	1.04 [0.90-1.20]	977	184 (18.8)	1.02 [0.85-1.23]	0.96 [0.80-1.15]	0.89 [0.74-1.09]
≥2	568	235 (41.4)	**1.41 [1.20-1.64]**	**1.37 [1.17-1.61]**	1.06 [0.87-1.29]	548	129 (23.5)	**1.30 [1.06-1.60]**	1.18 [0.96-1.47]	1.02 [0.78-1.32]
Overuse										
0	1078	333 (30.9)	Ref	Ref	Ref	1052	194 (18.4)	Ref	Ref	Ref
1	1262	406 (32.2)	1.03 [0.89-1.19]	0.98 [0.85-1.13]	1.01 [0.87-1.17]	1224	222 (18.1)	0.99 [0.82-1.20]	0.89 [0.73-1.08]	0.93 [0.77-1.14]
2	604	218 (36.1)	1.15 [0.97-1.36]	1.08 [0.91-1.28]	1.13 [0.95-1.35]	584	129 (22.1)	1.20 [0.96-1.50]	1.06 [0.84-1.33]	1.12 [0.89-1.41]
≥3	295	113 (38.3)	1.22 [0.99-1.51]	1.21 [0.98-1.51]	**1.28 [1.02-1.59]**	285	70 (24.6)	**1.37 [1.04-1.81]**	1.28 [0.97-1.68]	1.32 [0.99-1.75]

Values in bold are statistically significant (p<0.05)

Abbreviations: CI, confidence interval; HR, hazard ratio; PIM, potentially inappropriate medication.

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, tumor stage, tumor location, year of CRC diagnosis, neoadjuvant/adjuvant chemotherapy, year of schooling, smoking status, BMI, lifetime physical activity, lifetime alcohol consumption, red meat consumption, and processed meat consumption.

[c] Adjusted for age, sex, tumor stage, tumor location, year of CRC diagnosis, neoadjuvant/adjuvant chemotherapy, year of schooling, smoking status, BMI, lifetime physical activity, lifetime alcohol consumption, red meat consumption, processed meat consumption, functional status, and comorbidity.

Table 4. The associations of total co-medication quality (as assessed by the FORTA score), PIM use, medication underuse and overuse with up to 5-year overall survival (OS) in older CRC patients (Stratified by sex)

Variables	Female			Male		
	N_{total}	N_{cases} (%)	Model 3 [a] HR [95% CI]	N_{total}	N_{cases} (%)	Model 3 [a] HR [95% CI]
FORTA score						
Per 1 point	-	-	1.03 [0.99-1.08]	-	-	**1.07 [1.03-1.10]**
0-1	240	61 (25.4)	Ref	448	95 (21.2)	Ref
2-3	455	124 (27.3)	0.95 [0.69-1.32]	663	190 (28.7)	**1.35 [1.04-1.76]**
4-6	379	143 (37.7)	1.17 [0.83-1.66]	501	209 (41.7)	**1.71 [1.29-2.29]**
≥7	260	125 (48.1)	1.42 [0.92-2.19]	293	123 (42.0)	**2.14 [1.49-3.06]**
PIM use						
0	597	171 (28.6)	Ref	938	244 (26.0)	Ref
2	365	118 (32.3)	1.06 [0.82-1.37]	479	165 (34.5)	1.23 [0.98-1.55]
≥4	372	164 (44.1)	1.18 [0.87-1.60]	488	208 (42.6)	**1.67 [1.29-2.18]**
Underuse						
0	643	189 (29.4)	Ref	1020	302 (29.6)	Ref
1	437	159 (36.4)	1.08 [0.86-1.36]	571	185 (32.4)	1.00 [0.82-1.21]
≥2	254	105 (41.3)	1.11 [0.80-1.53]	314	130 (41.4)	1.09 [0.83-1.41]
Overuse						
0	423	130 (30.7)	Ref	655	203 (31.0)	Ref
1	493	165 (33.5)	0.98 [0.76-1.26]	769	241 (31.3)	1.03 [0.85-1.24]
2	284	114 (39.8)	1.14 [0.88-1.49]	320	105 (32.8)	1.07 [0.84-1.36]
≥3	134	45 (33.6)	1.05 [0.73-1.51]	161	68 (42.2)	**1.50 [1.13-1.99]**

Values in bold are statistically significant (p<0.05)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age, tumor stage, tumor location, year of CRC diagnosis, neoadjuvant/adjuvant chemotherapy, year of schooling, smoking status, BMI, lifetime physical activity, lifetime alcohol consumption, red meat consumption, processed meat consumption, functional status, and comorbidity.