Age-specific impact of comorbidity on postoperative outcomes in older patients with colorectal cancer

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Research Paper

Age-specific impact of comorbidity on postoperative outcomes in older patients with colorectal cancer

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ABSTRACT

Introduction: Age and comorbidity are considered the strongest predictors for adverse events after colorectal cancer (CRC) surgery. We aimed to study the interaction of age and comorbidity and to gain better insight in options to improve care for the growing group of older patients.

Materials and Methods: We included all patients ≥70 years undergoing elective surgery for non-metastatic CRC between 2011 and 2019 in the Netherlands. Baseline characteristics, surgical and non-surgical complications, readmission, and short-term mortality were collected from the Dutch Colorectal Audit (DCRA). The cohort was stratified by 70–79, 80–89, and ≥ 90 years. Comorbidity prevalence and postoperative outcomes were determined per age group. We analyzed the interaction (age-group*comorbidity) with all outcomes using multivariate logistic regression analysis. Age-stratified analysis was indicated if the interaction was significant.

Results: We included 25,727 patients of 70–79 years, 12,198 patients of 80–89 years, and 713 of ≥90 years. Non-surgical complications and mortality increased with older age, while surgical complications significantly decreased. However, the association of a Charlson Comorbidity Index (CCI) score ≥ 3, cardiovascular, and cardiopulmonary disease with adverse postoperative outcome decreased with older age. For example, the odds ratio (OR) of a CCI score ≥ 3 for non-surgical complications was 1.79 (confidence interval [CI] 95% 1.66–1.94), 1.50 (CI 95% 1.36–1.65), and 1.21 (CI 95% 0.80–1.81) for, respectively, 70–79, 80–89, and ≥ 90 years.

Discussion: The rate of non-surgical complications after CRC surgery increased with older age, although older age itself became less associated with comorbidity. Perhaps risk assessment in the oldest patients should shift towards other predictors, such as frailty.

1. Introduction

Colorectal cancer (CRC) is a major health issue in the Netherlands. Surgical resection is the primary treatment option for patients with non-metastatic CRC. As the incidence of CRC increases with age and life expectancy is rising, the focus of treatment for patients with CRC is shifting towards the older population. At this moment, CRC is diagnosed at an average age of 71 years [1]. Older patients are at increased risk for adverse outcome after surgery, such as postoperative complications, readmissions, or mortality [2–6].

Several studies report comorbidity as the strongest predictor for postoperative morbidity and mortality [7,8]. Although overall comorbidity increases with increasing age [9,10], the prevalence of several comorbid conditions has different patterns across the older age spectrum. For example, the prevalence of dementia or cardiac disease increases progressively with age, the presence of 'other malignancies' increases more gradually, while diabetes peaks around the age of 80 years and declines in later life [10,11]. As comorbidity prevalence varies at different ages, the predictive value of comorbidity for postoperative outcome may be different per age group as well. The oldest age group's longevity may be associated with milder and less comorbid diseases. Other preoperative factors – such as disability, nutritional status, or institutionalization (which are all elements of the geriatric assessment) – may therefore prevail in predicting postoperative outcome. Thus,

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investigating the age-specific impact of comorbidity could initiate a more targeted counseling and treatment for the 'old, older, and oldest' patients with CRC. Therefore, we aimed to determine the prevalence of several comorbid diseases in older patients undergoing CRC surgery and to assess the effect of comorbid diseases on adverse postoperative outcomes in the old, older, and oldest age groups.

2. Methods

2.1. Study Population and Design

The included patients were selected from the Dutch Colorectal Audit (DCRA). The DCRA is a national obligatory audit (and therefore approved by the institutional review boards of the participating hospitals) that prospectively collects patients' demographics, tumor, and treatment characteristics in combination with postoperative outcomes of all patients who received CRC surgery in the Netherlands. More detailed information about the DCRA has been extensively described elsewhere [12]. For the current study we included all patients aged 70 years and older who underwent elective surgery for non-metastatic CRC between 2011 and 2019. Patients who required stenting or decompressing stoma prior to primary resection or patients who underwent local excision were excluded. The same cohort were participants in an earlier study [2].

2.2. Baseline Variables

Age, sex, American Society Anesthesiology (ASA) score, tumor stage (TNM classification), surgical approach, and neoadjuvant therapy were all obtained through the DCRA. The DCRA registers the preoperative presence of 14 comorbid diseases that are included in the Charlson comorbidity index (CCI) [13]; myocardial infarction, congestive heart failure (CHF), peripheral vascular disease, cerebrovascular accident (CVA) or transient ischemic attack (TIA), dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease (mild or moderate to severe), diabetes mellitus (DM) (uncomplicated or with end-organ damage), hemiplegia or paraplegia, moderate to severe chronic kidney disease (CKD), other (localized or metastatic) malignancy, including leukemia and lymphoma, and acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV). We calculated the CCI score without adjusting for age. We distinguished two extra comorbid conditions: cardiovascular disease and cardiopulmonary disease. In clinical practice, patients with these conditions are considered at high risk of adverse outcome during and after surgical treatment. Furthermore, cardiovascular and cardiopulmonary disease place an enormous burden on the health care system [14–16]. 'Cardiovascular disease' included myocardial infarction, CVA, TIA, or peripheral vascular disease and 'cardiopulmonary disease' included chronic pulmonary disease, myocardial infarction, or CHF.

2.3. Outcome Measurements

The primary outcome was the occurrence of at least one postoperative complication, stratified by surgical and non-surgical complications. Surgical complications consisted of anastomotic leakage, abscess, bleeding, ileus, fascia dehiscence, bowel perforation, leakage from bladder or ureter, or surgical wound infection. Non-surgical complications were defined as pulmonary, cardiac, thromboembolic, and neurologic events, infection (other than pulmonary or wound infection), or other. The secondary outcomes were readmission and mortality. The DCRA registers several postoperative outcomes including postoperative complications, length of stay, readmission, and mortality within 30-days (2011–2017) and 90-days (2018–2019) after surgery.

2.4. Statistical Analysis

The study cohort was divided in three age groups: 70–79 years, 80–89 years, and ≥ 90 years. Baseline characteristics (including patient, tumor, and treatment features) were compared between these three age groups. The prevalence of a CCI score ≥ 3, cardiovascular disease, cardiopulmonary disease, and the 14 separate comorbid conditions were described. To assess whether the prevalence of several comorbid conditions varies across the older population, we used a five-year interval (70–74, 75–79, 80–84, 85–89, and ≥ 90 years) to graphically illustrate any prevalence changes. To evaluate adverse postoperative outcomes, the rate of non-surgical complications, surgical complications, readmissions, and mortality were determined in the three (10-year interval) age groups. To assess any interaction between comorbidity and the (10-years interval) age groups for postoperative outcome, we performed logistic regression analyses. The comorbid condition and age group were included as independent variables and the postoperative outcome as dependent variable. If the comorbid condition was not associated in univariate analysis, no multivariate analysis – in which we adjusted for clinically relevant variables (age, sex, tumor stage, tumor localization, neoadjuvant radiotherapy, and surgical approach) – was performed. Then, the interaction term "comorbid disease*age group" was added as independent variable. If the interaction term was significant ($p < 0.05$) in the multivariate analysis, it signified that the effect of the comorbid condition on the postoperative outcome was different between the age groups. Subsequently, age-stratified logistic regression was indicated. The age-stratified logistic regression analysis was univariate and only performed for surgical and non-surgical complications, due to the low number of events in the age group ≥90 year and low numbers of readmission and mortality. Based on the age-stratified logistic regression models, we were able to calculate a patient's individual risk of having a postoperative complication. The risk is scored on a scale from 0 to 1 (0 indicates the impossibility and 1 indicates the certainty of having a complication) and was graphically visualized. We only visualized CCI ≥3, cardiovascular disease, and cardiopulmonary disease, as those were considered the most clinically relevant. Missing data was excluded from analysis when the missing percentage was extremely small (<0.1%). *P*-values below 0.05 will be considered as statistically significant and all statistical analysis will be performed with SPSS 25.0.

3. Results

3.1. Study Population

As described earlier [2], 39,788 patients ≥70 years had elective surgery between 2011 and 2019 in the Netherlands for non-metastatic CRC. We excluded 1150 patients, as 862 patients received a local excision, 278 patients had stenting or a temporary decompressing stoma prior to elective CRC resection, and for 10 patients the age was unknown. The current study eventually consisted of 38,638 patients; 25,727 patients were 70–79 years, 12,198 patients were 80–89 years and 713 patients were ≥ 90 years.

3.2. Baseline Characteristics

Fig. 1 shows the differences in patient demographics, tumor, and treatment characteristics between the three age groups. All differences were statistically significant. With increasing age, the proportion of female patients increased, as well as the proportion of patients with ASA score III+ and higher CCI score. Rectal carcinoma was less common with older age. The proportion of patients presenting with a higher tumor stage increased with age. Regarding treatment, the proportion of patients receiving open surgery increased in the older age groups. Neoadjuvant therapy was less frequently initiated in the older patients

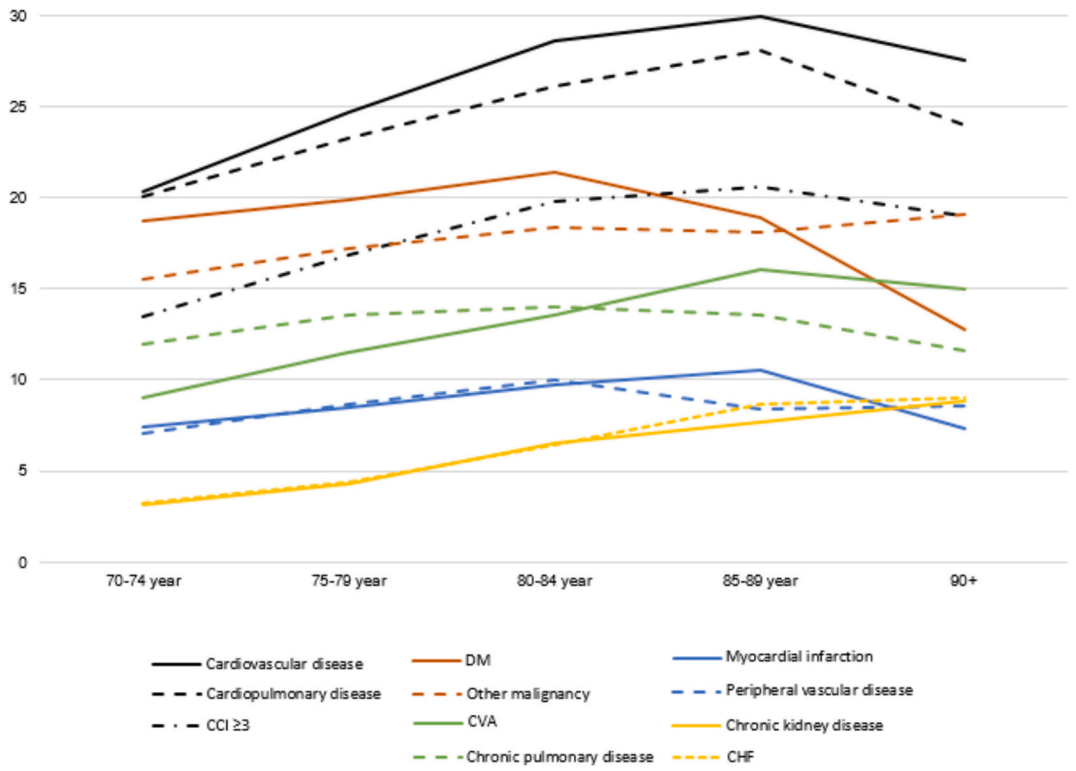

Fig. 1. Prevalence of several comorbid diseases within the older age spectrum.
Abbreviations: CCI; Charlson Comorbidity Index, DM; Diabetes Mellitus, CVA; cerebrovascular accident, CHF; congestive heart failure.

diagnosed with rectal cancer. Although a significant part of information about neoadjuvant chemotherapy was missing, chemotherapy was less common in the oldest patients.

3.3. Comorbidity Prevalence

The prevalences of several comorbid conditions are shown in Appendix Table 1; 6480 (16.8%) patients had a CCI score ≥ 3, 9512 (24.6%) had cardiovascular disease, and 9001 (23.3%) patients had cardiopulmonary disease. Myocardial infarction had occurred in 3311 patients (8.6%). The prevalences of other clinically relevant comorbidities were: 7569 (19.6%) patients had diabetes mellitus and 1854 (4.8%) patients had chronic kidney disease.

Fig. 1 shows the prevalence of frequently occurring comorbid diseases over the five-year interval age-spectrum. The prevalence of other malignancy, CHF, and chronic kidney disease continuously increased (respectively 15.5 to 19.1%, 3.2 to 9.0%, and 3.1 to 8.8% for patients aged 70–75 years compared to ≥90 years). Diabetes peaked in the age group 80–84 years (21.4%) and then sharply declined to 12.8% in patients ≥90 years. The prevalence of cardiovascular disease (30%), cardiopulmonary disease (28.1%), CCI ≥3 (20.6%), CVA/TIA (16.1%), and myocardial infarction (10.5%) reached its highest point in patients of 85–89 years.

3.4. Postoperative Adverse Outcome

In total, 8143 (21.1%) patients experienced non-surgical complications, 7166 (18.5%) surgical complications, 3099 (8.0%) required readmission, and 1132 patients (2.9%) died within 30 or 90 days after surgery. The rate of non-surgical complications significantly increased with older age: 4904 (19.1%) patients of 70–79 years experienced non-surgical complications, 3036 (24.9%) patients of 80–89 years, and 201 (28.2%) patients of ≥90 years. On the contrary, the rate of surgical complications significantly decreased: 4705 (18.3%) patients of 70–79 years experienced surgical complications, 2360 (19.3%) patients of 80–89 years, and 99 (13.9%) patients of ≥90 years. The rate of readmission decreased, while the mortality rate significantly increased (Table 2).

3.5. Interaction Between Comorbidity and Age

All comorbidities – except for peptic ulcer disease, connective tissue disease, and dementia – were significantly associated with surgical complications, non-surgical complications, readmissions, and short-term mortality in multivariate analysis (Appendix Tables 2 and 3).

We found a significant interaction between the age group and CCI score ≥ 3, cardiovascular disease, cardiopulmonary disease, CVA/TIA, and myocardial infarction for non-surgical and surgical complications. Peripheral vascular disease had a significant interaction with age for surgical complications as well. Only cardiovascular disease interacted with age for the risk of readmission. Cardiovascular disease, diabetes mellitus, CVA/TIA, myocardial infarction, peripheral vascular disease, and CHF had a significant interaction with age for the risk of mortality (Appendix Tables 2 and 3).

Based on the results of the age-stratified analysis (Appendix Table 4), the individual risk for postoperative complications with or without comorbidity per age group is visualized in Fig. 2 (non-surgical complications) and Fig. 3 (surgical complications).

Fig. 2 shows that in age group 70–79 years, non-surgical complications were more likely to occur in patients with a CCI score ≥ 3, cardiovascular disease, or cardiopulmonary disease compared to their counterparts without these comorbidities. With increasing age, the risk difference between patients with and without comorbidity gradually decreased. In the oldest age group, patients with comorbidity had similar risk of non-surgical complications compared to patients without comorbidity. For CCI score ≥ 3, this corresponds to an odds ratio (OR) of 1.79 (confidence interval [CI] 95% 1.66–1.94) for patients 70–79 years, 1.50 (CI 95% 1.36–1.65) for patients 80–89 years and 1.21 (CI 95%

Table 1
Baseline characteristics stratified by age group.

	Total $n = 38,638$	70–79 years $n = 25,727$	80–89 years $n = 12,198$	≥90 years $n = 713$
Median age (IQR)	76 (73–81)	74 (72–76)	83 (81–85)	91 (90–92)
Sex				
Male	20,895 (54.1)	14,680 (57.1)	5912 (48.5)	303 (42.5)
Female	17,740 (45.9)	11,045 (42.9)	6285 (51.5)	410 (57.5)
Median body mass index (IQR)	25.8 (23.4–28.7)	26.1 (23.7–29.1)	25.3 (23.0–28.0)	24.4 (22.2–26.7)
ASA score				
ASA I/II	25,852 (66.9)	18,691 (72.7)	6805 (55.8)	356 (50.0)
ASA III+	12,764 (33.1)	7022 (27.3)	5386 (44.2)	356 (50.0)
Charlson comorbidity index (CCI)				
0	15,184 (39.3)	10,913 (42.4)	4026 (33.0)	245 (34.4)
1	9801 (25.4)	6404 (24.9)	3191 (26.2)	206 (28.9)
2	7173 (18.6)	4512 (17.5)	2536 (20.8)	125 (17.5)
≥3	6480 (16.8)	3898 (15.2)	2445 (20.0)	137 (19.2)
Tumor localization				
Colon	28,577 (74.0)	18,521 (72.0)	9430 (77.3)	626 (87.8)
Rectum	10,053 (26.0)	7200 (28.0)	2766 (22.7)	87 (12.2)
TNM stage				
Stage I	11,412 (29.5)	8306 (32.3)	2977 (24.4)	129 (18.1)
Stage II	14,503 (37.5)	8881 (34.5)	5257 (43.1)	365 (51.2)
Stage III	12,077 (31.3)	8081 (31.4)	3790 (31.1)	206 (28.9)
Unknown	646 (1.7)	459 (1.8)	174 (1.4)	13 (1.8)
Surgical approach				
Open	9276 (24.0)	5625 (21.9)	3388 (27.8)	263 (36.9)
Laparoscopic	27,917 (72.3)	19,088 (74.2)	8396 (68.8)	433 (60.7)
Robot assisted	688 (1.8)	480 (1.9)	201 (1.6)	7 (1.0)
Other*	361 (0.9)	270 (1.0)	89 (0.7)	2 (0.3)
Unknown	396 (1.0)	264 (1.0)	124 (1.0)	8 (1.1)
Neoadjuvant radiotherapy[α]				
None	3902 (38.8)	2682 (37.3)	1163 (42.0)	57 (65.5)
Not specified	5023 (50.0)	3695 (51.3)	1306 (47.2)	22 (25.3)
5 × 5 Gy	564 (5.6)	368 (5.1)	188 (6.8)	8 (9.2)
Chemoradiation	555 (5.5)	448 (6.2)	107 (3.9)	0
Neoadjuvant chemotherapy[α]				
None	5859 (58.3)	4122 (57.3)	1690 (61.1)	47 (54.0)
Yes	1254 (12.5)	1073 (14.9)	181 (6.5)	0
Unknown	2940 (29.2)	2005 (27.8)	895 (32.4)	40 (46.0)

Table 2
Postoperative outcome per age group.

	Total n = 38,638 (%)	70–79 years $n =$ 25,727	80–89 years $n =$ 12,198	≥90 years $n = 713$
Non-surgical complications	8141 (21.1)	4904 (19.1)	3036 (24.9)	201 (28.2)*
Surgical complications	7164 (18.5)	4705 (18.3)	2360 (19.3)	99 (13.9)
Readmissions	3099 (8.0)	2099 (8.2)	964 (7.9)	36 (5.0)
Short-term mortality	1132 (2.9)	505 (2.0)	577 (4.7)	50 (7.0)

* All differences were significant.

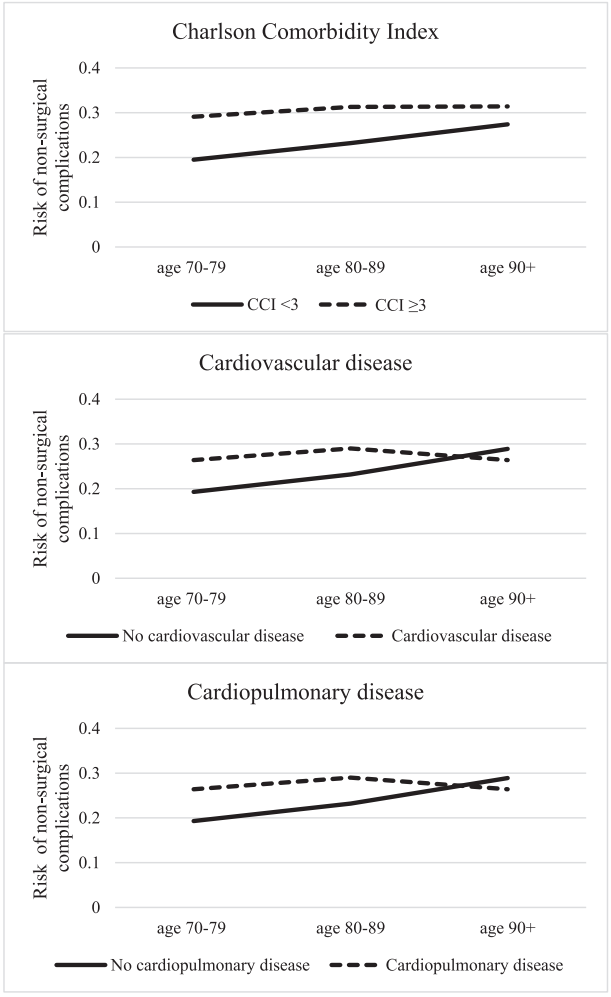

Fig. 2. Risk of non-surgical complication per age group.

0.81–1.81) for patients ≥90 years. For cardiovascular disease and cardiopulmonary disease, a decreasing OR with older age was found as well; respectively an OR of 1.57 (CI 95% 1.47–1.69) for patients 70–79 years, 1.36 (CI 95% 1.24–1.48) for patients 80–89 years, and 0.88 (CI 95% 0.61–1.28) for patients ≥90 years and an OR of 1.60 (CI 95% 1.49–1.72) for patients 70–79 years, 1.44 (CI 95% 1.32–1.58) for patients 80–89 years, and 0.92 (CI 95% 0.63–1.28) for patients ≥90 years.

Fig. 3 shows the individual risk of surgical complications. In the age group 70–79 years, surgical complications were more likely to occur in patients with CCI ≥3, cardiovascular disease, and cardiopulmonary disease. Again, with increasing age, the risk difference between patients with and without comorbidity disappears. For CCI score ≥ 3, this corresponds to OR of 1.50 (CI 95% 1.38–1.62) for patients 70–79 years, 1.22 (CI 95% 1.10–1.36) for patients 80–89 years, and 1.08 (CI 95% 0.63–1.82) for patients ≥90 years. The OR of surgical complications for cardiovascular disease and cardiopulmonary disease was, respectively, 1.42 (CI 95% 1.32–1.52) for patients 70–79 years, 1.08 (CI 95% 0.98–1.19) for patients 80–89 years, and 1.10 (CI 95% 0.69–1.76) for patients ≥90 years and an OR of 1.44 (CI 95% 1.38–1.55) for patients 70–79 years, 1.17 (CI 95% 1.06–1.29) for patients 80–89 years, and 1.08 (CI 95% 0.66–1.77) for patients ≥90 years.

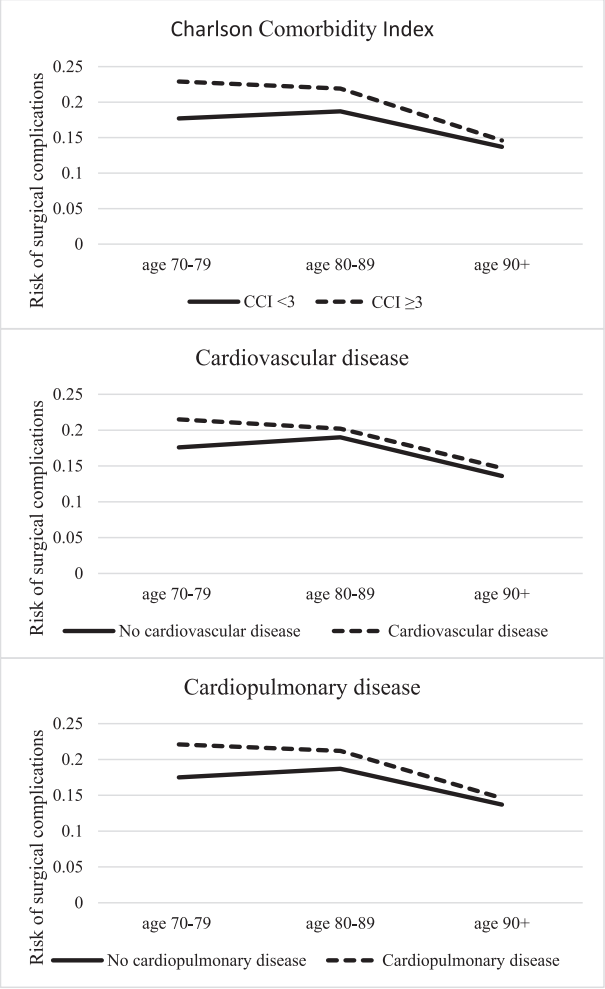

Fig. 3. Risk of surgical complication per age group.

4. Discussion

This nationwide population-based study showed that patient, tumor, and treatment characteristics are different between the old, older, and oldest patients who had elective surgery for non-metastatic CRC. Mortality and the total number of non-surgical complications increased with older age, while the rate of surgical complications and readmission decreased. The prevalence of several comorbid conditions varied within the older population. Although most common comorbid diseases were associated with adverse postoperative outcomes, the strength of the association of CCI score ≥ 3, cardiovascular disease, and cardiopulmonary disease with surgical and non-surgical complications reduced with increasing age.

The current study is the first to describe the prevalence trend of comorbid diseases in older adults with CRC who were selected for elective surgery. Studies performed in a somewhat different populations showed comparable results. Leersum et al. [11] included patients diagnosed with CRC at adult age with or without surgical treatment between 1995 and 2010 and showed a similar change in other malignancy, diabetes, peripheral vascular disease, CVA, and pulmonary disease across the older age spectrum. Piccirillo et al. [10] included patients diagnosed with cancer (10% CRC) between 1998 and 2003 at adult age and demonstrated the same pattern in other malignancy and diabetes.

Several studies found an association of comorbid diseases and adverse outcomes after CRC surgery [7]. However, none of these studies tested for an age-specific impact of comorbidity. Two studies – respectively in patients with SARS-CoV-2 [17] and patients selected for radical prostatectomy [18] – supported the age-specific impact of comorbidity by demonstrating a reduced association of comorbidity with adverse outcomes in the oldest patients.

The attenuated association of comorbidity with increasing age might be explained by a relatively fitter health status of the oldest patients. The longevity of these patients may be the result of milder comorbid conditions [10], they may have lived a healthier lifestyle, or have more favorable genetics that protects against health problems [19]. On the other hand, we need to be aware that selection bias occurred in this patient population. The study cohort consisted of patients who were elected for surgical treatment. As the proportion of patients receiving non-surgical treatment increases with age [20], a 'healthier' selection is more likely to occur in the oldest age category [20,21]. Furthermore, advanced age may serve as confounder for the increased proportion of female patients (Table 1) [22]. Female patients with CRC present less frequently with comorbidities and female patients with comorbidities are more likely to receive non-surgical treatment than male patients with the same comorbid diseases [23].

Despite the attenuated association of comorbidity with older age on postoperative outcome, the total number of non-surgical complications increased while the rate of surgical complications decreased (Table 2). Surgical complications, such as anastomotic leakage and surgical side infections, are associated with male sex, rectal carcinoma, obesity (high body mass index), and comorbid diseases [24–26]. These characteristics occurred less frequently in the older age categories (Table 1 and 2). On the contrary, the number of non-surgical complications and mortality increased. This indicates that – despite the reduced association of comorbidity - the oldest age group is still at higher risk of mortality and non-surgical complications than their younger counterparts. Another important factor associated with complications in older patients after CRC surgery that has not been addressed yet is frailty [8,27,28]. Frailty is a reduced physiological state based on several domains, e.g., the somatic, functional, cognitive, and psychosocial state [29] that increases with older age [30]. As frailty is thought to particularly affect non-surgical complications [31], it is possible that frailty is more strongly related to adverse postoperative outcome than comorbidity in the oldest age groups.

In clinical practice, identifying older patients at risk of complications is challenging due to the population's heterogeneity. Our findings support individualized preoperative care for older patients, aiming to improve postoperative outcomes. First, this study emphasized that several comorbid conditions are associated with adverse postoperative outcomes. Counseling patients about the risks and recovery process and consultation of organ specific medical specialists (e.g., cardiologist, pulmonologist) is therefore already part of standard care. Second, our findings show that some specific comorbid diseases (e.g., CCI ≥3, cardiopulmonary disease, and cardiovascular disease) have less predictive value in risk assessment for the oldest patients (≥90 years). This suggests that preoperative optimization in the oldest patients with CRC should not focus on comorbidity particularly. As stated before, maybe other predictors – such as frailty – are of more value in risk assessment in the oldest patients. To improve non-surgical complications, prehabilitation – enhancing preoperative functional capacity – could be advantageous, as prehabilitation may especially affect patients with frailty; several studies have described that prehabilitation particularly lowers non-surgical complications [31,32].

The main limitation of this study is the potential selection bias of patients fit for surgery. Furthermore, the three (10-year interval) age groups consisted of an unequal number of patients. However, the oldest patient group still included >700 patients. It would have been helpful to have information on frailty to define the age-specific impact of frailty. Including frailty characteristics in national audits could be considered. Furthermore, other long-term outcomes – such as remaining mobility and remaining cognitive function – could be more relevant than postoperative complications, readmission, and mortality. Nevertheless, the

current study is the first to describe an age-specific impact of comorbidity in patients ≥70 that undergo elective CRC resection. We used 'true' data; a large and complete nationwide population-based study cohort that described the results of eight years of elective surgery in the Netherlands. Additionally, the DCRA is a validated audit and over the 95% of the collected data is complete [12].

5. Conclusions

This nationwide population-based study showed that non-surgical complications and mortality increase with increasing age while surgical complications decrease. Baseline characteristics and comorbidity prevalence are different between the old, older, and oldest patients receiving elective surgery for non-metastatic CRC. In the oldest age group, the strength of the association of CCI ≥3, cardiopulmonary, and cardiovascular disease with surgical and non-surgical complications decreased. Our findings confirm that individualized preoperative care in the older population receiving elective CRC surgery is needed and preoperative risk assessment should shift towards frailty.

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None.

CRediT authorship contribution statement

Heleen C. van der Hulst: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Jessica M. van der Bol:** Writing – review & editing, Methodology, Conceptualization. **Esther Bastiaannet:** Writing – review & editing, Methodology, Formal analysis. **Johanna E.A. Portielje:** Writing – review & editing, Supervision, Methodology. **Jan Willem T. Dekker:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization.

Declaration of Competing Interest

None.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2024.101836.

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