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ORIGINAL ARTICLE

Risk factors of short-term survival in the aged in elective colon cancer surgery: a population-based study

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Abstract

Purpose Patients aged ≥ 80 years represent an increasing proportion of colon cancer diagnoses. Selecting patients for elective surgery is challenging because of possibly compromised health status and functional decline. The aim of this retrospective, population-based study was to identify risk factors and health measures that predict short-term mortality after elective colon cancer surgery in the aged.

Methods All patients ≥ 80 years operated electively for stages I–III colon cancer from 2005 to 2016 in four Finnish hospitals were included. The prospectively collected data included comorbidities, functional status, postoperative surgical and medical outcomes as well as mortality data.

Results A total of 386 patients (mean 84.0 years, range 80–96, 56% female) were included. Male gender (46% vs 35%, $p = 0.03$), higher BMI (51% vs 37%, $p = 0.02$), diabetes mellitus (51% vs 37%, $p = 0.02$), coronary artery disease (52% vs 36%, $p = 0.003$) and rheumatic diseases (67% vs 39%, $p = 0.03$) were related to higher risk of complications. The severe complications were more common in patients with increased preoperative hospitalizations (31% vs 15%, $p = 0.05$) and who lived in nursing homes (30% vs 17%, $p = 0.05$). The 30-day and 1-year mortality rates were 6.0% and 15% for all the patients compared with 30% and 45% in patients with severe postoperative complications ($p < 0.001$). Severe postoperative complications were the only significant patient-related variable affecting 1-year mortality (OR 9.60, 95% CI 2.33–39.55, $p = 0.002$).

Conclusions The ability to identify preoperatively patients at high risk of decreased survival and thus prevent severe postoperative complications could improve overall outcome of aged colon cancer patients.

Keywords Colon cancer · Surgery · Aged patients · Risk factors · Short-term mortality

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Introduction

The incidence of colorectal cancer has tripled during the past five decades, and the risk of having colorectal cancer increases with age [1]. According to the Finnish Cancer Registry data from 2016, 27% of all colorectal patients were aged 80 years or more [1]. The number of aged people diagnosed with colorectal cancer will increase as the population ages [2].

If possible, colon cancer is managed by radical surgical resection [3, 4]. Previous studies show comparable disease-specific survival rates for all age groups, which advocates tumour resection with curative purpose [5, 6]. In the EUROCARE-5 study, 5-year overall survival rate was 49% for colon cancer patients of 75 years or older while overall survival rate for all ages was 57% in Europe [7]. Corresponding numbers from 2016 in Finland were 60% for

patients of 75 years and 66% for all ages [1]. In the oldest patients, however, the survival benefit of operative treatment (compared with other treatments) is only apparent after the first two postoperative years due to the risks of surgery [8–10].

Increased age, physical and cognitive disabilities, and previous hospitalizations may predispose to postoperative morbidity and mortality [11]. Colorectal cancer surgery is considered high risk, with reported postoperative major complication and 30-day mortality rates of 16–24% and 1–6%, respectively [12, 13]. Operative treatment of colorectal cancer in the aged is associated with higher morbidity (35–45%) and mortality rates both in the immediate postoperative period and during the first year after surgery (6–16% in 30 days, 14–37% at 1 year) [12–17]. Compared with younger people, the 30-day mortality in the group of aged patients underestimates 1-year mortality due to prolonged impact of the perioperative period [8, 18]. However, a recent Dutch study shows better postoperative outcome with almost equal 1-year survival rates for older and younger colorectal patients, supporting tailor-made decisions on surgical treatments for older patients [19].

It is important to have relevant and reliable data concerning older aged colorectal cancer patient's surgery and postoperative morbidity and survival numbers. Surgeons and oncologists treating patients with colon cancer should become aware of that 43% of their patients are > 75 years and that many of these older patients are frail with comorbidities which demand careful patient assessment [20]. Proper patient selection and careful consideration of appropriate surgical candidates including preoperative optimization of medical comorbidities, nutritional status and physical performance enables colorectal cancer surgery to be performed with reduced morbidity and mortality rates with improved survival [21, 22].

The aim of this study was to identify preoperative risk factors and measures of overall health status affecting postoperative morbidity and mortality and their impact on 30-day and 1-year survival in colon cancer patients aged 80 years and older. In addition, the aim was to investigate time-trends in postoperative short-term mortality and possible factors affecting the outcome.

Material and methods

All patients aged 80 years and over who underwent an elective resection for colon cancer during the period of 2005 and 2016 in four Finnish hospitals were retrospectively analyzed. The catchment area of these hospitals ranged from 100,000 to 250,000 inhabitants (in total, approximately 750,000 inhabitants). Exclusion criteria were metastatic or recurrent disease and palliative or emergency surgery. Treatment of malignant diseases is almost exclusively performed by public health care system in Finland. We consider this study population-based because patients are referred to certain hospital based on their place of residence.

All the patients had histologically confirmed primary adenocarcinoma of the colon, and preoperatively had colonoscopy and computed tomography. They underwent radical surgery for the primary tumour. Patients were evaluated for their fitness for elective surgery with general anaesthesia but were not preselected any other way. Decision to proceed with surgery was based on patient's general condition and comorbidities. Prior geriatric evaluation was not routinely used.

For this study, cancer- and surgery-related data was collected from prospectively maintained, institutionally approved and password-protected electronic colorectal databases in the study hospitals and was supplemented by review of medical records. Patients with colorectal cancer were identified using ICD codes C18-C19 [23]. The collected clinical data included patients´ characteristics, living status, hospitalizations in the 6 months before surgery, comorbidities, modified age-adjusted Charlson Comorbidity Index [24] score (4–15; solid tumour excluded with two points, all patients ≥ 80 years which contributes four points for all patients), other malignancies, symptoms, operative procedures and postoperative recovery. Postoperative complications were defined and determined using the Clavien-Dindo classification [25], and severe complications were graded into classes III–V. Tumours were staged according to the Union for International Cancer Control (UICC) TNM classification [26] and graded according to the World Health Organization histological classification system [27]. The number of lymph nodes was recorded in every case. Patients with macroscopic or residual tumour were excluded.

Postoperative surveillance was performed in out-patient clinics according to the follow-up programs of the four hospitals. Local recurrences and distant metastasis were identified radiologically (ultrasound, computed tomography) or histologically. The information was collected from the hospital medical records and Statistics Finland for all patients with or without arranged follow-up program.

The primary outcome measures were postoperative morbidity (surgical and non-surgical complications) and mortality 30 days and 1 year after primary treatment. Mortality data including causes of death were obtained from the population-based statistics of Statistics Finland. Mortality was assessed at 30 days and 1 year following surgery. The follow-up duration data was calculated from the date of surgery to the date of death or date of active follow-up in the clinics (1 year after surgery).

The associations between categorical variables were tested with the chi-square test or the Fisher exact test, when appropriate, and continuous variables with the Student's *t* test. Survival rates were calculated from the time of primary surgery using the Kaplan-Meier method and were compared by the log-rank test. A uni- and multivariable analysis of the

factors which influenced 30-day and 1-year mortality was carried out using binary logistic regression. All variables (Table 4) that were statistically significant in the univariate model were included in the multivariable model. Statistical analyses were performed using SPSS version 23.

The study was approved by the ethics committee of Pirkanmaa Hospital District, Tampere, Finland (R18188).

Results

A total of 386 patients were identified from the prospective records of the four hospitals. The mean age of the study population was 84.1 years (range 80–96 years). Most of the patients were female (56%), had an ASA III classification (69%) and CCI score 4–5 (62%). Most of the patients lived at home (90%), were not dependent on others for daily help (56%) and had no hospital admission in the previous 6 months (73%). Of the patients, 106 (28%) were operated in 2005–2008, 143 (37%) in 2009–2012 and 137 (35%) in 2013–2016. Table 1 shows the patients` baseline characteristics.

Most of the operative procedures were performed for right-sided colon cancer (68%). An intended laparoscopic resection was performed in 252 patients (65%) and in 35 cases (14%), the operation was converted to an open surgery due to anatomical or technical reasons. One hundred eighty-seven patients (50%) were discharged to other hospitals or wards of healthcare centres. Readmission within 30 days of discharge occurred for 6.5% of the patients. Postoperative adjuvant chemotherapy was given to 46% (67/146) of stage III patients. Table 2 shows surgical characteristics and outcomes.

Table 1 Patients' baseline characteristics ($n = 386$)

	n / med	% / (range)
Gender		
Female	217	56.2
Male	169	43.8
Age, years	83.0	(80–96)
BMI, kg/m^2	24.9	(15.4–40.6)
< 25	163	50.9
25–29.9	111	34.7
30-	46	14.4
Not available	66	
Type of living		
Home	336	90.1
Nursing home	37	9.9
Not known	13	
Aid at home		
No	152	55.9
Relatives	62	22.8
Other	58	21.3
Not known	114	
Hospital admissions < 6 months		
No	279	73.4
One	88	23.3
Two or more	13	3.3
ASA score		
2	36	9.5
3	263	69.0
4	82	21.5
Not known	5	
CCI score (4–15)		
4	109	28.2
5	131	33.9
6	82	21.3
7–15	64	16.6
Operation year		
2005–2008	106	27.5
2009–2012	143	37.0
2013–2016	137	35.5

Morbidity

Overall postoperative morbidity was 40% (154/386), with 24% (92/386) of patients having surgical complications. The most common surgical complications were ileus (7.0%), intra-abdominal or anastomotic bleeding (6.2%) and anastomotic leakage (5.7%). The most common non-surgical complications were cardiovascular (6.0%) and pulmonary (4.7%). Both surgical and non-surgical complications were recorded only for 1.8% (7/386) of the patients. According to the Clavien-Dindo classification, 18% (69/386) of patients had severe complications (grades III–V), accounting for 45% (69/154) of all complications. (Table 3).

Male gender (46% vs 35%, $p = 0.03$), diabetes mellitus (51% vs 37%, $p = 0.02$), coronary artery disease (52% vs 36%, $p = 0.003$) and rheumatic diseases (67% vs 39%, $p = 0.03$) were related to higher number of complications. Patients with complications had higher BMI (26 vs 25, $p = 0.04$). Operative approach (open or laparoscopic) and operating time were not associated with increased rate of complications.

More severe postoperative complications (Clavien-Dindo III–V) were experienced by patients living in a nursing home compared with those living in their own home (30% vs 17%, $p = 0.05$), and by those who had hospital admissions during the 6 months prior surgery compared with those who had none (31% vs 15%, $p = 0.05$). Patients with severe complications also had more intraoperative blood loss (median 50 ml vs 100 ml, $p = 0.006$).

Table 2 Surgical characteristics and outcomes

	n / med	% / (range)
Procedure		
Right hemicolectomy	261	67.6
Transversum resection	6	1.6
Left hemicolectomy	22	5.7
Sigmoid resection	83	21.5
Other colonic resection	14	3.6
Type of surgery		
Open	134	34.7
Laparoscopy	252	65.3
Conversion	35	13.9
Operation time (min)	130	33–445
Bleeding (ml)	50	5–1000
Postoperative length of hospital stay (days)	7	1–58
Discharge destination		
Home	172	45.6
Other hospital or health centre	187	49.6
Death during hospital stay	18	4.8
Reoperation	39	10.1
Readmission	25	6.5
TNM stage		
1	41	12.7
2	191	49.5
3	146	37.8
Number of lymph nodes	14.8	3–71

Mortality

The overall 30-day mortality was 6.0% (23/386). Six patients died due to anastomotic leakage and three due to other surgical complications (ileus, intraoperative haemorrhage and small intestine perforation). Seven patients died due to cardiac complications, three due to pulmonary problems and three due to cerebral haemorrhage. One patient died of a ruptured abdominal aneurysm 6 days after surgery.

The overall 1-year mortality was 15% (59/386). The most important causes of death were cardiopulmonary (43%) and surgery-related postoperative complications (17%). Cancer-related mortality was 4.4%, accounting for 29% (17/59) of deaths within 1 year. Over half (55%, 17/31) of the patients who had severe, surgery-related complications (anastomotic leakage, intra-abdominal haemorrhage, ileus) died within 1 year after surgery whereas 1-year mortality was 8.6% (20/232) for the patients without postoperative complications. In patients with mild complications (Clavien-Dindo I–II), mortality was 9.4%. Patients with severe postoperative complications (Clavien-Dindo III–V) had mortality 45% (31/69). (Fig. 1).

Patients with stage III disease ($n = 146$) and treated with postoperative chemotherapy had lower 1-year mortality rate compared with patients not receiving adjuvant treatment (10.4% vs 27.8%, $p = 0.007$).

Table 3 Postoperative complications and mortality

	N	%
Surgical complications		
No	294	76.2
Yes	92	23.8
Ileus	27	7.0
Bleeding	24	6.2
Anastomotic leakage	22	5.7
Wound dehiscence	7	1.8
Wound infection	2	0.5
Others	10	2.6
Non-surgical complications		
No	317	82.1
Yes	69	17.9
Cardiovascular	23	6.0
Respiratory	18	4.7
Urinary	11	2.8
Delirium	5	1.3
Other	12	3.1
30-day mortality	23	6.0
90-day mortality	29	7.5
1-year mortality	59	15.3

Univariate logistic regression analysis showed that living in a nursing home, hospital admissions 6 months before surgery, CCI score ≥ 6, longer operation time, greater intraoperative blood loss and severe postoperative complications were significant patient-related variables affecting 30-day mortality. Higher age, hospital admissions 6 months before surgery, open compared with laparoscopic operation, longer operative time, greater intraoperative blood loss and severe postoperative complications were associated with greater 1-year mortality after surgery (Table 4). In multivariate logistic regression analysis, hospital admissions 6 months before surgery and

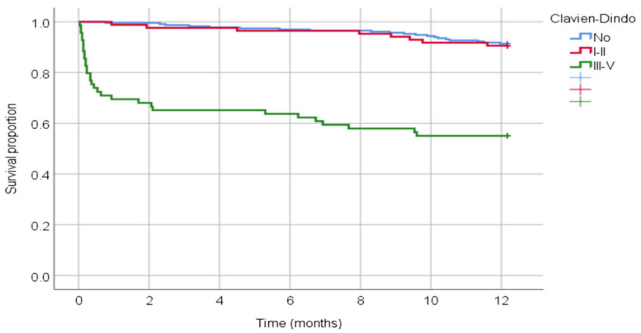

Fig. 1 Kaplan-Meier analysis of 1-year overall survival in electively operated colon cancer patients ≥ 80 years of age with and without complications according to Clavien-Dindo classification ($p < 0.001$, log-rank)

Table 4 Predictors of 30-day and 1-year mortality in elective colon cancer surgery in the aged (univariate analysis)

	30-day mortality			1-year mortality		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.11	0.99–1.24	0.079	1.12	1.04–1.21	*0.004*
Gender						
Female	1			1		
Male	2.09	0.88–4.95	0.095	1.10	0.63–1.92	0.739
BMI (kg/m^2)	0.94			0.96		
< 25	1			1		
25–29.9	1.19	0.45–3.11	0.725	0.95	0.49–1.85	0.887
>=30	0.34	0.04–2.73	0.310	0.64	0.23–1.78	0.395
Type of living						
Home	1			1		
Nursing home	3.63	1.34–9.88	*0.012*	1.93	0.86–4.34	0.112
Hospital admissions ≤ 6 months						
No	1			1		
One or more	3.97	1.68–9.38	*0.002*	1.88	1.04–3.38	*0.035*
ASA						
2	1			1		
3	0.88	0.19–4.09	0.875	1.86	0.54–6.36	0.324
4	1.86	0.38–9.23	0.447	3.14	0.86–11.5	0.083
CCI score (4–15)						
4	1			1		
5	2.57	0.51–13.0	0.254	1.15	0.55–2.42	0.710
6	5.0	1.01–24.7	*0.049*	1.05	0,45–2.45	0.910
7–15	7.64	1.57–37.2	*0.012*	2.08	0.93–4.65	0.075
Stage						
1–2	1			1		
3	0.87	0.36–2.11	0.757	1.74	0.99–3.03	0.053
Type of surgery						
Laparoscopy/conversion	1			1		
Open	1.79	0.67–4.17	0.178	1.88	1.08–3.30	*0.027*
Operation time (min)	1.01	1.00–1.01	*0.038*	1.01	1.00–1.01	*0.010*
Blood loss (10 ml) $n = 197$	1.03	1.01–1.05	*0.005*	1.03	1.01–1.05	*0.001*
Clavien-Dindo classification						
No	1			1		
I–II	2.75	0.17–44.46	0.480	1.10	0.47–2.60	0.830
III–V	101.06	13.3–769.5	*< 0.001*	8.65	4.47–16.73	*< 0.001*
Complications						
No	1			1		
Surgical	25.05	3.13–200.7	*0.002*	2.76	1.40–5.46	*0.004*
Non-surgical	61.29	7.83–479.5	*< 0.001*	5.05	2.50–10.20	*< 0.001*
Operation year						
2005–2008	1			1		
2009–2012	0.73	0.26–2.00	0.536	0.62	0.32–1.21	0.161
2013–2016	0.66	0.23–1.88	0.436	0.54	0.27–1.08	0.082

Italic entries were statistically significant

severe postoperative complications were the only significant patient-related variables affecting 30-day mortality (OR 3.05, 95% CI 1.25–7.43, $p = 0.014$ and OR 85.61, 95% CI 10.68–686.1, $p < 0.001$). Severe postoperative complications were

the only significant patient-related variable affecting 1-year mortality (OR 9.60, 95% CI 2.33–39.55, $p = 0.002$).

Mortality rates in 30 days seemed to decrease between operation years 2005–2008 (7.5%), 2009–2012 (5.6%) and 2013–2016 (5.1%). The corresponding numbers in 1 year were 21% (2005–2008), 14% (2009–2012) and 12% (2013–2016). For severe complications (CD III–V), the 30-day mortality rates were 2005–2008 (30.8%), 2009–2012 (35%) and 2013–2016 (26.1%). The corresponding numbers in 1 year were 50% (2005–2008), 45% (2009–2012) and 39% (2013–2016). There was no statistically significant difference between time-trends and mortality.

Table 4 shows predictors for 30-day and 1-year mortality in univariate analysis (binary logistic regression).

Discussion

For this retrospective population-based, cohort study, short-term morbidity and mortality differences were analyzed in the electively operative non-metastatic colon cancer patients aged 80 years and over in a large, regionally representable materials. To our knowledge, our material consisting of 386 patients is the largest dataset regarding elective colon cancer surgery with curative intent and focusing on both postoperative complications and short-term mortality in this age group. Most of the similar studies featured surgical patients with colorectal cancers [6, 8, 14, 28]. Patients undergoing resection for rectal cancer have more personalized, multimodal treatment options and a greater number of severe complications such as anastomotic leakage compared with colon cancer surgery [29]. Thus, the patient data in our study was more homogenous focusing only on colon surgery. Furthermore, in Finland, treatment of colorectal cancer is based on national EBM guidelines [30]. The study hospitals also had standardized protocols for colon cancer treatments, and the patients' baselines as well as operative outcomes and tumour characteristics were similar.

For non-metastatic colorectal cancer patients, surgical resection is the best option for curative treatment [3, 4]. A recent multinational study showed that patients over 80 years have 30-day and 1-year mortality rates of 5.5–11.4% and 17.1–23.6%, respectively [16]. In the present study, 1-year survival rate was 91.4% for the patients without postoperative complications, and the overall 1-year mortality was 15.3%. Most of the older patients do as well as younger patients after elective surgery and have acceptable survival numbers. For example, recent data from Netherlands showed similar 1-year overall survival rates for patients under and over 75 years [18]. However, 30-day mortality rate remains high among the oldest, and it continues to increase well beyond the initial postoperative month causing excess 1-year mortality. Previous studies show that major postoperative complications are related to higher mortality rates and are among the strongest risk factors for reduced survival in the aged [28, 31]. Our data showed similar postoperative morbidity and survival numbers reflecting the results of previous studies considering excess mortality beyond initial postoperative month [8, 13]. In our study, 1-year mortality rate of patients with major postoperative complications was 44.9%, this being the most important factor for diminished short-term survival after colon surgery.

Our study indicated high morbidity rates in early postoperative period. Almost 40% (153/386) of the patients developed postoperative complications, and 45% (69/153) of these were major complications. These figures are comparable with other studies of colorectal cancer surgery reporting total complication rates 35–45% and major complications 20–25%, respectively [14–17, 31]. Our data included all patients who were willing and fit enough for surgery according to ASA classification and other comorbidities. Risk factors for complications were male gender, diabetes, coronary artery and rheumatic diseases. Severe complications were more common in patients who had increased preoperative hospitalizations and who lived in nursing homes. These findings support recent studies from Norway and Japan [32, 33] emphasizing the importance of preoperative evaluation of patient's physical and cognitive performance, to prevent complications in colon cancer surgery. In Finland, aged people move to nursing homes when they cannot survive with maximal help at home and most of them have some degree of cognitive impairment. Therefore, residing in a nursing home is a kind of proxy for cognitive impairment and disability in activities of daily living. Unfortunately, the diagnoses for hospitalizations before surgery were not documented accurately in our study data, and the reasons for hospitalizations were heterogenous.

Postoperative complications are associated with a disproportionately high risk of 30-day and 1-year mortality in elderly patients [28, 31]. In our study, the overall 30-day mortality rate was 6.0% but increased to 30.4% in patients with severe postoperative complications. Other factors associated with increased 30-day mortality included living in a nursing home, hospital admissions 6 months before surgery, CCI score $\geq$ six, longer operation time, greater intraoperative blood loss and severe postoperative complications. Patients with diminished physical and mental resources had more severe postoperative complications leading to higher mortality rates indicating that limited performance state of patients plays an important role in postoperative outcome [33]. Cardiopulmonary problems and surgery-related issues were the most important factors contributing to 1-year mortality whereas cancer-related mortality was significantly low. This finding emphasizes the importance of preoperative evaluation on patient's physical and cognitive performance with specific focus on preoperative cardiopulmonary status and medical optimization. Non-surgical, symptomatic treatments are worth considering when individualized treatment decisions are made for patients with limited performance status. On the contrary, patients with stage III disease

treated with postoperative chemotherapy had significantly lower 1-year mortality rate compared with those who were not giving postoperative adjuvant treatment. That underlines the importance of identify patients who can benefit from the radical cancer treatments.

30-day and 1-year mortality rates decreased progressively between operation years 2005–2008, 2009–2012 and 2013–2016, but this was not statistically significant. During the study period, there were no preoperative arrangements for nutrition and physical performance status assessment, or geriatric assessment. Conversely, all the participating hospitals in our study had high proportion (56%) of operations done by laparoscopy, and enhanced recovery after surgery (ERAS) program was gradually adopted to clinical work during the study period. A recent meta-analysis demonstrated that laparoscopic colorectal surgery has positive impact in terms of significant decrease in postoperative morbidity and mortality among the aged compared with open colorectal surgery [34]. ERAS is a multimodal approach that aims to optimize perioperative management [35]. Old patients adhered to and benefited from an ERAS program have similar postoperative outcome advantages to their younger counterparts [36]. These facts can partly explain the similar time-trends in morbidity and mortality between the study years, together with developments in perioperative anaesthesia care, surgical performance (laparoscopy, technical standardization) and oncological treatments.

Some limitations exist in our study. First, although we were able to categorize specific comorbidities, we found little relationship between multiple morbidities and overall survival. This may reflect the fact that there was no information available regarding the severity of the comorbidities. Additionally, we were unable to fully assess disability and functional as well as cognitive performance state of patients because of imprecise patient files. Information about daily physical and cognitive functional activity and general performance was not routinely recorded. It is likely that the conditions that lead to a patient being considered frail are only documented in those patients whose condition had significant negative impact on their overall well-being. The same applies to comorbidities. However, undervaluation of such conditions would lead to underrate of the risks and false negative results, and hence, the reported risks are rather underestimates than overestimates. In addition, and result of the previous reasons, healthier patients were likely selected for surgical treatment. However, our findings suggest that surgical treatment in aged patients diagnosed with colon cancer can lead to acceptable and similar results compared with younger patients.

Our data indicate that postoperative morbidity following elective colon cancer surgery is common in aged patients and results in a significant increase in mortality, which lasts beyond the first postoperative month. Age, comorbidities, disability and the occurrence of severe postoperative complications were factors most strongly associated with reduced 30-day and 1-year survival after surgery. Although we have demonstrated an increase in survival rates, the impact of surgical treatment on postoperative functional outcome is not clear. Regardless of the new achievements, there seems to be a tendency to offer fewer surgical resections to older compared with younger patients [37, 38]. Therefore, the information on present-day postoperative morbidity and mortality rates of older patients is important for shared decision-making regarding surgical treatment. If aged colon cancer patients survive the first year after surgery, they have a reasonably good long-term survival. Older patients often give higher priority to functional outcomes than to survival [39]. Further research should therefore focus not only on further increasing postoperative survival rates in older patients but also on quality of life and improvement of postoperative physical functioning. Prehabilitation programs could play a role in achieving this goal [40, 41].

In conclusion, mortality in the present study is related to postoperative complications. Identifying effective strategies for both prevention and tailor-made treatments of postoperative complications in colon cancer surgery in the aged could potentially improve patient overall outcomes.

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Conflict of interest The authors declare that they have no conflicts of interest.

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