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Association Between Colorectal Cancer Screening and Survival in Patients Older Than 70 Years: Results of A National Multicenter Retrospective Study

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ABSTRACT

Background: Colorectal cancer screening mainly targets a population between 50 and 70 years of age; however, it is inconsistently implemented in people over 70. The aim of this study was to analyze the association between colorectal cancer (CRC) screening, postoperative mortality, and perioperative and oncologic outcomes in a large population of patients over 70 years of age who underwent surgery for CRC.

Methods: Data regarding people over 70 who underwent CRC surgery were retrieved from a nationally validated retrospective database, including four consecutive years (2018–2021) and 81 centers. The patients were divided into two groups according to their participation in the CRC screening program: Screening versus No Screening. The outcomes of the study were 30-day mortality; urgent, palliative and minimally invasive surgery rates; Clavien-Dindo ≥ III; advanced oncologic stage; R0 resection and length of hospital stay (LOS). Logistic regression analysis was carried out and adjusted for multiple confounders.

Results: Of the 10,346 patients over 70,676 were in the screening group, and 9670 were in the no screening group. At logistic regression, CRC screening was significantly associated with a reduction in 30-day mortality (OR 0.41, 95% CI 0.18–0.92, $p = 0.032$), urgent surgery (OR 0.06, 95% CI 0.02–0.14, $p < 0.001$), palliative surgery (OR 0.32, 95% CI 0.19–0.54, $p < 0.001$), Clavien-Dindo ≥ III complications (OR 0.69, 95% CI 0.51–0.93, $p = 0.016$) and advanced oncologic stage (OR 0.53, 95% CI 0.45–0.62, $p < 0.001$), and a significant increase in R0 resections (OR 3.15, 95% CI 1.67–5.94, $p < 0.001$) and laparoscopic surgery (OR 1.93, 95% CI 1.57–2.38, $p < 0.001$). The crude and adjusted Odds Ratio similarity confirmed this correlation, regardless of the comorbidities and confounders.

Conclusions: Adherence to CRC screening should be further encouraged and standardized for people over 70.

Matteo Rottoli and Giacomo Calini shared first authorship.

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1 | Introduction

Globally, approximately 1.9 million people are diagnosed with colorectal cancer (CRC) every year, with 900,000 dying as a result of the disease. The majority of these patients are over 70 years of age [1]. This elevated rate of mortality is also due to a lack of CRC screening which mainly targets a population between 50 and 70 years of age [2].

The most recent guidelines recommend extending the CRC screening to the age of 75, while it should be considered individually in people over 75 [3, 4]. However, healthcare regulators implement this age limit inconsistently, often including only people between 50 and 69 in mass CRC screening programs [5–7]. Extending CRC screening requires large cohort studies which demonstrate a significant reduction in CRC-related morbidity and mortality in order to justify the harm caused by false-positive results, their impact on the healthcare system, and their socio-economic effect. Much doubt exists regarding the lack of benefits of the screening program in terms of reduction in mortality in elderly patients, regardless of the early diagnosis of the disease. Perioperative complications and poor survival account for the major part of the CRC-related morbidity and mortality, especially in patients over 70 years of age. The correlation between the application of the screening program in these patients and their perioperative outcomes might contribute to clarifying the potential benefits of the screening and strengthening its broader indications.

The aim of this study was to analyze the association between CRC screening, postoperative mortality, and perioperative and oncologic outcomes in a large population of patients over 70 years of age who underwent colorectal surgery for cancer.

2 | Methods

2.1 | Study Design and Settings

The COVID-CRC collaborative study dataset retrospectively included 18,284 consecutive patients who underwent surgery for colorectal cancer in 81 Italian hospitals between January 1st, 2018, and December 31st, 2021 [8–11]. The study did not impose limits in terms of minimum number of cases, hospital volume and type of center. The data were put into a REDCap (Research Electronic Data Capture; Vanderbilt University) database by a defined team of clinicians in each participating center [12]. A data validator (not involved in the data collection) checked 20% of the cases at the end of the data inclusion period. The Ethics Committees of the coordinating center (08/09/2020; no. 854/2020/Oss/AOUBo) and all of the participating centers approved the COVID-CRC collaborative study, including subsequent analyses of the dataset. The study was carried out according to the STROBE (Strengthening the reporting of observational studies in epidemiology) guidelines [13].

2.2 | Participants

Patients ≥ 70 years of age who underwent surgery in elective, urgent, or emergent settings with curative or palliative intent were included in the study. The exclusion criteria were age under 70 years, benign lesions, final histology profile of other malignant entities, recurrent cancer, and perioperative SARS-CoV-2 infection (Flowchart in Figure 1). Potential biases arising from the COVID-19 pandemic, from different screening pathways of patients with recurrent cancer, from different malignant entities (e.g., neuroendocrine tumors, gastrointestinal stromal tumors, melanomas, lymphomas), and benign tumors were addressed by excluding patients from the analysis. Geographical distribution of the patients according to the region of the hospitals was similar between the two groups. After applying the exclusion criteria (Figure 1), 10,346 patients over 70 years of age were included in the final analysis; they were divided into two groups according to participation in the CRC screening program. The **Screening group** included patients who were asymptomatic and diagnosed with CRC by means of voluntary screening. Colorectal screening consists of a fecal occult blood test (FOBT) and a subsequent colonoscopy in the case of a positive test. The **No Screening group** included patients who did not do the CRC screening, were symptomatic (e.g., occlusion, gastrointestinal bleeding, perforation, weight loss), or had done the FOBT as a means of identifying the origin of anemia. During the study period, the national mass CRC screening was implemented for individuals between

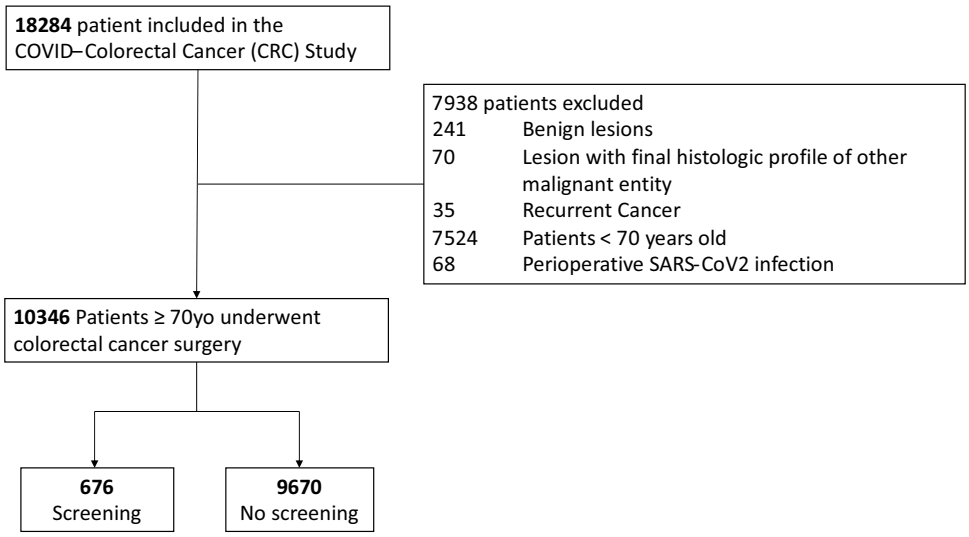

FIGURE 1 | Flowchart of patient selection of the 18,284 patients included in the dataset.

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50 and 69, allowing voluntary CRC screening in patient over 70 years old [5–7].

2.3 | Variables

The variables collected included the details of the CRC screening, CRC clinical presentation, patient demographics, comorbidities, American Society of Anesthesiologists (ASA) score, use of preoperative chemoradiotherapy, details of the surgery (type, approach, setting, and intraoperative complications), postoperative Intensive Care Unit (ICU) stay, histopathological details, oncologic outcomes, length of hospital stay (LOS), mortality, and complications at 30 days after surgery (according to the Clavien-Dindo classification) [14].

2.4 | Study Aims

The primary outcome of the study was to determine whether or not there was a reduction in 30-day postoperative mortality associated with the screening program. The secondary outcomes were the rates of urgent, palliative, and minimally invasive surgery (laparoscopic or robotic), severe complications (defined as Clavien-Dindo grade ≥ III), advanced oncologic stage, R0 resection, and LOS. The advanced oncologic stage was defined as a stage greater than IIb (T4 + , N + , M +), according to the American Joint Committee on Cancer (AJCC) [15]. Urgent surgery was defined as a surgical procedure performed during the index unplanned admission, while palliative surgery was defined as surgery with no curative intent.

2.5 | Data Analysis

The association between screening status and each selected outcome was initially evaluated using standard univariate analyses (chi-squared test for the categorical variables; t-test for the continuous variables). Multivariable analyses were then used to assess whether screening status was an independent predictor of each outcome after adjusting for age, sex, body mass index (BMI), current smoking habit, ASA score, cancer location, comorbidities, and use of multiple drugs. Binomial logistic regression was used for the dichotomous variables, and multiple linear regression was carried out to assess the only continuous variable: LOS. All of the above covariates were included in each model a priori. However, since the variable "current smoking habit" was missing for 2082 patients, and its inclusion or exclusion from the models did not substantially influence screening status estimates, it was excluded from the final models to avoid the loss of power and increase the precision of the estimates.

Each covariate was tested in its original form or transformed if needed (e.g., the presence of comorbidities was dichotomized as "< 2", or "2 or more"). In addition, each variable included was tested for multicollinearity, potential interaction, and/or quadratic/cubic terms [16].

In the logistic regression analyses, standard diagnostic procedures were adopted to check the validity of the final model: influential observation analysis (Dbeta, change in Pearson chi-square, and similar), the Hosmer-Lemeshow test for the goodness of fit, and the C statistic (area under the Receiving Operator Curve). The validity of the final linear regression model was assessed as follows: the assumption of constant error variance was checked graphically, plotting Pearson residuals versus fitted values, and formally, using the Cook-Weisberg test for heteroskedasticity.

The results of the logistic analyses are presented as odds ratios (OR) and 95% confidence intervals (95% CI), while the results of the linear regression analyses are presented as beta-coefficients (β) and 95% CIs. Statistical significance was defined as a two-sided p-value < 0.05 for all the analyses carried out using STATA 13.1 (Stata Corp., College Station, TX, U.S.A., 2007).

3 | Results

The study included 10,346 patients over 70 years of age of which 676 were diagnosed by means of CRC screening, while the other 9670 patients were not.

The characteristics and outcomes of the overall sample and the two groups are shown in Table 1. Patients in the screening group were younger (mean age 76 vs. 79, $p < 0.001$), and had a greater number of males (58% vs. 54%, $p = 0.072$), smokers (12% vs. 9%, $p = 0.043$), and patients with obesity (18% vs. 11%, $p < 0.001$), while they had a lower number of patients having an ASA score > 2 (43% vs. 60%, $p < 0.001$), multiple comorbidities (22% vs. 26%, $p = 0.038$), polypharmacy (8% vs. 10%, $p = 0.077$) and rectal cancer (18% vs. 23%, $p = 0.008$).

Postoperative 30-day mortality (primary outcome) was lower in the screening group (0.9% vs. 3.2%, $p = 0.001$). Of the secondary outcomes, the rates of urgent surgery (0.7% vs. 13%, $p < 0.001$), palliative surgery (2% vs. 8%, $p < 0.001$), severe postoperative complications (7% vs. 11%, $p = 0.001$), postoperative need for ICU (14% vs. 20%, $p < 0.001$), advanced oncologic stage (IIb +) (33% vs. 48%, $p < 0.001$), AJCC stage IV (7% vs. 13%, $p < 0.001$) and LOS (8 days vs. 11 days, $p < 0.001$) were significantly lower in the screening group, while the proportion of R0 resections (99% vs. 95%, $p < 0.001$) and minimally invasive surgery (83% vs. 69%, $p < 0.001$) were significantly higher in the screening group.

At logistic regression, CRC screening was significantly associated with a reduction in 30-day postoperative mortality (OR 0.41, 95% CI 0.18–0.92, $p = 0.032$), urgent surgery (OR 0.06, 95% CI 0.02–0.14, $p < 0.001$), palliative surgery (OR 0.32, 95% CI 0.19–0.54, $p < 0.001$), Clavien-Dindo ≥ III postoperative complications (OR 0.69, 95% CI 0.51–0.93, $p = 0.016$) and advanced oncologic stage (OR 0.53, 95% CI 0.45–0.62, $p < 0.001$), and a significant increase of R0 resections (OR 3.15, 95% CI 1.67–5.94, $p < 0.001$) and laparoscopic surgery (OR 1.93, 95% CI 1.57–2.38, $p < 0.001$) (Table 2).

Outcomes and multivariate analysis of patients over 75 years of age were reported in the supporting material (Tables S1 and S2) as this threshold is adopted in other countries.

The causes of 30-day mortality were analyzed. In the screening group ($n = 6$) they were a composite of sepsis and multi-organ failure following anastomotic leak (3/6, 50%), pneumonia (2/6, 33%), and bleeding (1/6, 17%). In the no screening group, the 30-day mortality ($n = 306$) was affected more by medical (211/306, 69%) than surgical (95/306, 31%) complications. Among them, the most common medical complications were respiratory

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TABLE 1 | Characteristics and outcomes of patients ≥ 70 years of age overall and by CRC screening.

Variables	Overall sample ($n = 10,346$)	Screening ($n = 676$)	No screening ($n = 9670$)	p value[A]
Mean age in years (SD)	78.9 (5.7)	76.3 (5.2)	79.1 (5.6)	< 0.001
Male sex, % (n)	54.7 (5655)	58.0 (392)	54.4 (5263)	0.072
Current smoking habit, % (n)[B]	9.3 (766)	11.7 (63)	9.1 (703)	0.043
Body weight				
Mean BMI (SD)	25.4 (3.8)	26.3 (4.1)	25.3 (3.8)	< 0.001
Obesity (BMI ≥ 30), % (n)	11.6 (1195)	17.5 (118)	11.1 (1077)	< 0.001
ASA > 2, % (n)	58.4 (6041)	43.1 (291)	59.5 (5750)	< 0.001
Rectal cancer, % (n)	23.0 (2375)	18.8 (127)	23.3 (2248)	0.008
≥ 2 comorbidities, % (n)	25.2 (2611)	21.9 (148)	25.5 (2463)	0.038
≥ 3 drugs, % (n)	10.3 (1064)	8.3 (56)	10.4 (1008)	0.077
30-day mortality, % (n)	3.0 (312)	0.9 (6)	3.2 (306)	0.001
Urgent surgery, % (n)	12.5 (1293)	0.7 (5)	13.3 (1288)	< 0.001
Palliative surgery, % (n)	7.5 (775)	2.2 (15)	7.9 (760)	< 0.001
Laparoscopic surgery, % (n)	69.4 (7182)	83.3 (563)	68.5 (6619)	< 0.001
Stoma formation, % (n)[C]	12.4 (1114)	9.8 (60)	12.6 (1054)	0.042
Postoperative complications, % (n)				
- Overall	32.7 (3380)	27.1 (183)	33.1 (3197)	0.001
- Medical	19.8 (2051)	14.0 (95)	20.2 (1956)	< 0.001
- Surgical	18.1 (1876)	16.3 (110)	18.3 (1766)	0.19
Clavien-Dindo grade ≥ III,% (n)	10.8 (1118)	6.9 (47)	11.1 (1071)	0.001
Postoperative ICU	19.6 (2025)	13.5 (91)	20.0 (1934)	< 0.001
Advanced stage (IIb +), % (n)	47.3 (4889)	32.5 (220)	48.3 (4669)	< 0.001
AJCC stage 4, % (n)[D]	12.5 (1274)	6.6 (44)	12.9 (1230)	< 0.001
≥ 12 lymph nodes, % (n)[E]	85.2 (8292)	84.4 (537)	85.3 (7755)	0.55
R0 resection, % (n)[F]	94.8 (9707)	98.5 (653)	94.6 (9054)	< 0.001
Mean length of stay in days (SD)	10.4 (9.4)	8.4 (7.2)	10.5 (9.5)	< 0.001

Abbreviations: Advanced stage IIb + : T4 +, N +, M +; AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists score; BMI, Body mass index; CRC, colorectal cancer; ICU, Intensive care unit; SD, standard deviation.
[A]T-test for continuous variables; chi-squared test for categorical variables.
[B]Due to missing data, the sample consisted of 8264, 538, and 7726 patients, respectively.
[C]Due to missing data, the sample consisted of 9012, 615, and 8397patients, respectively.
[D]Due to missing data, the sample consisted of 10,202, 671, and 9531 patients, respectively.
[E]Due to missing data, the sample consisted of 9728, 636, and 9092 patients, respectively.
[F]Due to missing data, the sample consisted of 10,235, 663, and 9572 patients, respectively.

failure (93/306, 30%), sepsis (64/306, 21%), anemia (56/306, 18%), acute kidney injury (48/306, 16%), pneumonia (47/306, 15%), myocardial infarction (26/306, 9%), deep venous thrombosis and pulmonary embolism (15/306, 5%), and stroke (6/306, 2%). The most common surgical complications leading to 30-day mortality were anastomotic leak (59/306, 19%), abscesses/peritonitis (19/306, 6%), postoperative ileus (4/306, 1%), and intestinal occlusion (3/306, 1%).

4 | Discussion

The present study showed that the CRC screening program was associated with reduced mortality, morbidity, urgent and palliative surgery, advanced oncologic stage, and increased R0 resections and laparoscopic surgery, specifically in patients over 70 years of age. The crude and adjusted Odds Ratio similarity confirmed this correlation, regardless of the comorbidities and potential confounders. These findings support the implementation of CRC screening programs in the elderly population. Regardless of the long-term survival rate after surgery, which was not assessed in the present study and could be affected by several confounders, such a significant improvement in all postoperative outcomes should be considered to be solid proof for the strong association between screening and the overall survival of patients of 70 years of age and over affected by colorectal cancer.

Previous studies and recent guidelines have recommended CRC screening through age 75, and in people over 75 without significant comorbidities [3, 4, 17–19]. However, national and regional healthcare systems implement this age limit differently. In fact, this study was carried out on a national healthcare system in which mass CRC screening is offered to people between 50 and 69 [5–7].

In this large cohort study, over-70-year-old CRC screening with FOBT showed improved postoperative survival and oncologic

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TABLE 2 | Multivariable analyses predict the outcomes of patients ≥ 70 years of age who underwent CRC screening versus no screening.

Outcomes	Crude OR (95% CI)	Adj. OR (95% CI)	Adj. p[A]
30-day mortality	0.27 (0.12–0.62)	0.41 (0.18–0.92)	0.032
30-day mortality (also adjusted for advanced stage)	0.30 (0.13–0.69)	0.45 (0.20–1.02)	0.056
Urgent surgery	0.05 (0.02–0.12)	0.06 (0.02–0.14)	< 0.001
Palliative surgery	0.27 (0.16–0.45)	0.32 (0.19–0.54)	< 0.001
Laparoscopic surgery	2.30 (1.87–2.82)	1.93 (1.57–2.38)	< 0.001
Postoperative complications			
- Overall	0.75 (0.63–0.90)	0.86 (0.72–1.03)	0.11
- Medical	0.64 (0.52–0.81)	0.78 (0.62–0.98)	0.033
- Surgical	0.87 (0.70–1.07)	0.91 (0.73–1.13)	0.4
Clavien-Dindo grade ≥III	0.60 (0.44–0.81)	0.69 (0.51–0.93)	0.016
Postoperative ICU	0.62 (0.50–0.78)	0.77 (0.61–0.98)	0.033
Advanced stage (IIb +)	0.52 (0.44–0.61)	0.53 (0.45–0.62)	< 0.001
AJCC stage 4, % (n)[C]	0.47 (0.35–0.65)	0.48 (0.35–0.65)	< 0.001
R0 resection[E]	3.74 (1.99–7.02)	3.15 (1.67–5.94)	< 0.001
	Crude Reg. Coeff. (95% CI)	**Adj. Reg. Coeff. (95% CI)**	**Adj. p[A]**
Length of stay in days	2.1 (−2.8; −1.3)	1.6 (−2.3; −0.9)	< 0.001

Abbreviations: Adj, Adjusted; Advanced stage (IIb +): T4 +, N +, M +; AJCC, American Joint Committee on Cancer; CI, Confidence Interval; Coeff., Coefficient; CRC, colorectal cancer; ICU, Intensive care unit; OR, Odds ratio; Reg., Regression.
[A]Logistic model for categorical variables; multiple regression models for continuous variables. All the models have been adjusted for age, gender, BMI, ASA group, cancer location (rectum or not), multiple comorbidities, and drugs.
[C]Due to missing data, the model included only 10,202 observations.
[E]Due to missing data, the model included only 10,235 observations.

outcomes. Extending CRC screening requires studies that balance all the potential effects (reduction of CRC incidence and mortality, the harm of false-positive results, adverse events in screening, healthcare readiness, and socio-economic evaluation). According to the data presented, one should expect a correlation between the decreased risks of complications, urgent surgery, postoperative ICU admission, and LOS with decreased stress on the healthcare system and reduced costs [18, 19]. Since the rate of patients over 70 years of age was approximately 60% of all the 18,284 patients included in the COVID-CRC dataset (Figure 1), the implementation of CRC screening is even more relevant in order to extend its benefits to the population affected by the highest incidence of CRC [1].

The present study has some limitations. First, the retrospective and observational nature, and the voluntary participation of the centers may have introduced selection bias, potentially making the study population unrepresentative of the general population of patients undergoing surgery for CRC. However, this effect was mitigated by the large sample size which included centers having varying volumes, and the accurate patient inclusion carried out to reduce the effect of confounders, such as perioperative SARS-CoV-2 infection and different screening pathways.

Second, patients who underwent non-operative management and/or endoscopic treatment, and patients having unresectable metastatic cancer were not included in the dataset. This could attenuate the negative effect of non-performing CRC screening on mortality and on palliative surgery.

Third, this collaborative study dataset analyzed the 30-day postoperative outcomes, preventing the exploration of long-term outcomes. However, reduced 30-day mortality, AJCC stage, and R0 resection rates in patients over 70 years of age undergoing CRC screening represented valid surrogates impacting the tendency of the long-term outcomes.

Fourth, results were not adjusted for socioeconomic status. However, its effect should be little considering the cost of a voluntary CRC screening in a universal healthcare system that provides non-essential medical services (like FOBT after 70 years old) through income-based healthcare co-payments and free care in case of oncologic diagnosis. Also, cost-effectiveness was not reported in the present study, which will be a topic for further general population studies.

In conclusion, considering the findings of the present study, adherence to CRC screening programs should be further encouraged and standardized in people over 70 years of age.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data will be made available upon reasonable request to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Table S1: Subgroup analysis of the outcomes of patients ≥ 75 years of age, overall and by screening participation. **Table S2:** Subgroup multivariable analyses predicting the outcomes of patients ≥75 years who underwent CRC screening versus no screening (sample restricted to the 7607 subjects aged ≥75 years).

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