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

Matteo Rottoli<sup>1,2</sup>  | Giacomo Calini<sup>1,2</sup>   | Giovanni Castagna<sup>1,2</sup>  | Alice Gori<sup>1,2</sup>  | Stefano Cardelli<sup>1,2</sup>  | Antonino Spinelli<sup>3,4</sup>  | Gianluca Pellino<sup>5,6</sup>  | Alessandro Bianconi<sup>2</sup> | Matteo Fiore<sup>2</sup> | Riccardo Rosati<sup>7</sup> | Mario Morino<sup>8</sup> | Nicolò de Manzini<sup>9</sup> | Andrea Pietrabissa<sup>10</sup> | Luigi Boni<sup>11</sup> | Gilberto Poggioli<sup>1,2</sup> | COVID-CRC Study Group

<sup>1</sup>Surgery of the Alimentary Tract, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy | <sup>2</sup>Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy | <sup>3</sup>Department of Biomedical Sciences, Humanitas University, Milan, Italy | <sup>4</sup>IRCCS Humanitas Research Hospital, Milan, Italy | <sup>5</sup>Department of Advanced Medical and Surgical Sciences, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy | <sup>6</sup>Colorectal Surgery, University Hospital Vall d'Hebron, Barcelona, Spain | <sup>7</sup>Gastrointestinal Surgery Division, IRCCS San Raffaele Hospital, Milan, Italy | <sup>8</sup>AOU Città della Salute e della Scienza, Turin, Italy | <sup>9</sup>General Surgery Department, University Hospital of Trieste, Trieste, Italy | <sup>10</sup>Department of Surgery, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy | <sup>11</sup>Department of General and Minimally Invasive Surgery, Fondazione IRCCS - Ca' Granda - Ospedale Maggiore Policlinico di Milano, University of Milan, Milan, Italy

**Correspondence:** Matteo Rottoli ([matteo.rottoli2@unibo.it](mailto:matteo.rottoli2@unibo.it)) | Giacomo Calini ([giacomo.calini2@unibo.it](mailto:giacomo.calini2@unibo.it); [giacomo.calini@unibo.it](mailto:giacomo.calini@unibo.it))

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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  $\geq$  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  $\geq$  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

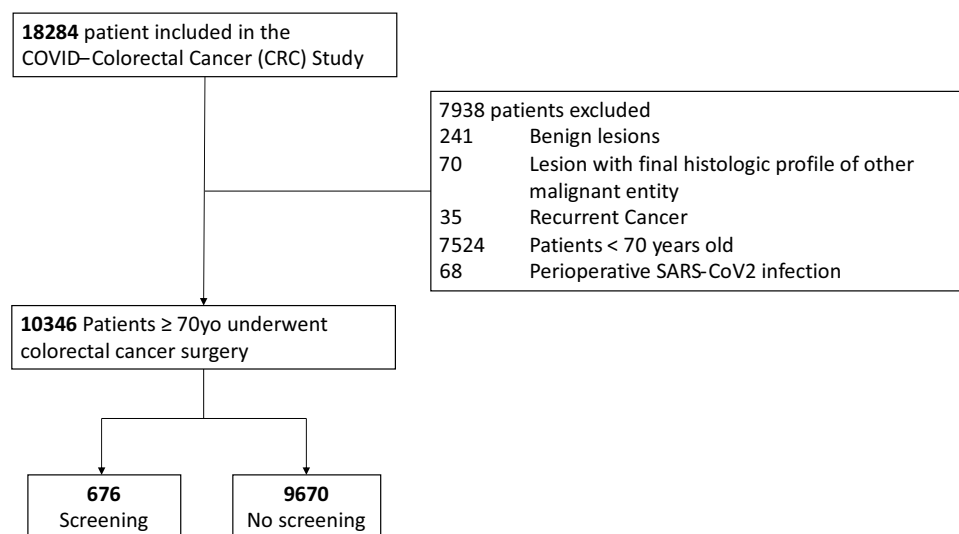
### 2.1 | Study Design and Settings

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  $\geq 70$  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.

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  $\geq$  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 ( $\beta$ ) 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  $\geq$  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

**TABLE 1** | Characteristics and outcomes of patients  $\geq 70$  years of age overall and by CRC screening.

Variables	Overall sample ( <i>n</i> = 10,346)	Screening ( <i>n</i> = 676)	No screening ( <i>n</i> = 9670)	<i>p</i> value <sup>A</sup>
Mean age in years (SD)	78.9 (5.7)	76.3 (5.2)	79.1 (5.6)	< 0.001
Male sex, % ( <i>n</i> )	54.7 (5655)	58.0 (392)	54.4 (5263)	0.072
Current smoking habit, % ( <i>n</i> ) <sup>B</sup>	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 $\geq 30$ ), % ( <i>n</i> )	11.6 (1195)	17.5 (118)	11.1 (1077)	< 0.001
ASA > 2, % ( <i>n</i> )	58.4 (6041)	43.1 (291)	59.5 (5750)	< 0.001
Rectal cancer, % ( <i>n</i> )	23.0 (2375)	18.8 (127)	23.3 (2248)	0.008
$\geq 2$ comorbidities, % ( <i>n</i> )	25.2 (2611)	21.9 (148)	25.5 (2463)	0.038
$\geq 3$ drugs, % ( <i>n</i> )	10.3 (1064)	8.3 (56)	10.4 (1008)	0.077
30-day mortality, % ( <i>n</i> )	3.0 (312)	0.9 (6)	3.2 (306)	0.001
Urgent surgery, % ( <i>n</i> )	12.5 (1293)	0.7 (5)	13.3 (1288)	< 0.001
Palliative surgery, % ( <i>n</i> )	7.5 (775)	2.2 (15)	7.9 (760)	< 0.001
Laparoscopic surgery, % ( <i>n</i> )	69.4 (7182)	83.3 (563)	68.5 (6619)	< 0.001
Stoma formation, % ( <i>n</i> ) <sup>C</sup>	12.4 (1114)	9.8 (60)	12.6 (1054)	0.042
Postoperative complications, % ( <i>n</i> )				
- 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 $\geq$ III, % ( <i>n</i> )	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 +), % ( <i>n</i> )	47.3 (4889)	32.5 (220)	48.3 (4669)	< 0.001
AJCC stage 4, % ( <i>n</i> ) <sup>D</sup>	12.5 (1274)	6.6 (44)	12.9 (1230)	< 0.001
$\geq 12$ lymph nodes, % ( <i>n</i> ) <sup>E</sup>	85.2 (8292)	84.4 (537)	85.3 (7755)	0.55
R0 resection, % ( <i>n</i> ) <sup>F</sup>	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.

<sup>A</sup>T-test for continuous variables; chi-squared test for categorical variables.

<sup>B</sup>Due to missing data, the sample consisted of 8264, 538, and 7726 patients, respectively.

<sup>C</sup>Due to missing data, the sample consisted of 9012, 615, and 8397 patients, respectively.

<sup>D</sup>Due to missing data, the sample consisted of 10,202, 671, and 9531 patients, respectively.

<sup>E</sup>Due to missing data, the sample consisted of 9728, 636, and 9092 patients, respectively.

<sup>F</sup>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

**TABLE 2** | Multivariable analyses predict the outcomes of patients  $\geq 70$  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 $\geq$ 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) <sup>C</sup>	0.47 (0.35–0.65)	0.48 (0.35–0.65)	< 0.001
R0 resection <sup>E</sup>	3.74 (1.99–7.02)	3.15 (1.67–5.94)	< 0.001
	<b>Crude Reg. Coeff. (95% CI)</b>	<b>Adj. Reg. Coeff. (95% CI)</b>	<b>Adj. <math>p^A</math></b>
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.

<sup>A</sup>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.

<sup>C</sup>Due to missing data, the model included only 10,202 observations.

<sup>E</sup>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.

### List of COVID-CRC Clinical Investigators

Angela Romano, Angela Belvedere, Antonio Lanci Lanci, Daniele Parlanti, Gabriele Vago, Anna Paola Pezzuto, Anna Canavese, Gerti Dajti, Stefano Cardelli, Caterina Catalioto, Iris S. Russo, Tommaso Violante, Daniele Morezzi, Ludovica Maurino, Eleonora Filippone, Dajana Cuicchi (*Surgery of the Alimentary Tract, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*); Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy); Elio Jovine, Raffaele Lombardi, Chiara Cipressi, Maria F. Offi, Cristina Larotonda, Silvana B. Puglisi (*Chirurgia A e d'Urgenza IRCCS AOU c/o OM, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*); Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy); Augusto Barbosa, Roberto Vaiana, Paolo M. Bianchi, Carlo Tonti, Claudio

Codignola (*Fondazione Poliambulanza Brescia*); Luigi Zorcolo, Angelo Restivo, Simona Deidda, Marcello E. Marchetti, Luca Ippolito (*Unità operativa di Chirurgia Coloproctologica - AOU Cagliari*); Gaya Spolverato, Salvatore Pucciarelli, Francesco Marchegiani, Giacomo Ghio, Gaia Zagolin, Dajana Glavas, Monica Tomassi (*Department of Surgical Oncological and Gastroenterological Sciences, University of Padova - General Surgery 3, Azienda Ospedale Università di Padova*); Ugo Elmore, Lorenzo Gozzini, Riccardo Calef, Francesco Puccetti, Andrea Cossu, Andrea Vignali (*Gastrointestinal Surgery Division, IRCCS San Raffaele Hospital, Milan*); Marco E. Allaix, Gaspare Cannata, Erica Lombardi, Carlo A. Ammirati, Chiara Piceni (*AOU Città della Salute e della Scienza, Turin, Italy*); Piero Bucciatti, Riccardo Balestri, Marco Puccini, Daniele Pezzati, Roberto d'Ischia, Vito F. Asta, Benedetta Sargenti, Giacomo Taddei, Federica Bonari, Giulia Boni (*Azienda Ospedaliero-Universitaria Pisana*); Alessandro Ferrero, Michela Mineccia, Federica Gonella, Marco Palisi, Francesco Danese, Valeria Cherubini, Serena Perotti (*Azienda Sanitaria Ospedaliera Ordine Mauriziano Umberto I°, Torino*); Michele Carvello, Fabio Carbone, Antonio Luberto, Eleonora Calafiore, Francesca De Lucia, Matteo Sacchi (*IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy*); Diego Sasia, Maria C. Giuffrida, Edoardo Ballauri, Mathieu Cardile, Serena Armentano, Elsa Beltrami, Gabriele Preve, Barbara Vercellone (*Santa Croce and Carle Hospital, Cuneo*); Marta Mozzon, Cristina Folliero, Chiara Lirusso, Massimo Vecchiato, Antonio Ziccarelli, Davide Gattesco, Luisa Moretti, Sara Crestale (*Chirurgia Generale, Azienda ospedaliero-universitaria S. Maria della Misericordia Udine-ASUFC*); Filippo Banchini, Patrizio Capelli, Andrea Romboli, Gerardo Palmieri, Luigi Conti, Nicholas Rizzi (*UO Chirurgia Generale Vascolare di Piacenza*); Deborah Bonfili (*Dipartimento di Chirurgia, Università degli Studi di Parma*); Paola Germani, Edoardo Osenda, Sara Cortinovis, Carlotta Giunta, Stefano Fracon, Hussein Abdallah, Selene Bogoni (*General surgery department, University Hospital of Trieste*); Nazario Portolani, Riccardo Nascimbeni, Sarah Molfino, Guido A. M. Tiberio, Ilenia Garosio, Giulia Lamperti, Diego Rigosa (*U.O. Chirurgia Generale 3 - ASST Spedali Civili Brescia, Università di Brescia*); Giorgio Ercolani, Leonardo Solaini, Davide Cavaliere, Andrea Avanzolini, Fabrizio D'Acapito, Leonardo L. Chiarella, Daniela Di Pietrantonio, Domenico Annunziata (*Chirurgia generale e TOA, Ospedale Morgagni-Pierantoni, Forlì*); Roberta Piccolo, Mario Sorrentino, Mauro Pansini, Alessandro Cojutti, Michele Graziano, Francesco Callegari (*U.O. Chirurgia Generale Ospedale di Latisana-Palmanova, Azienda Ospedaliera Universitaria Friuli Centrale*); Laura Balzarotti, Vitale R. Dameno, Antonio Cattaneo, Giuliano Santolamazza, Caterina Altieri, Riccardo Magarini (*Ospedale civile "G. Fornaroli", Magenta*); Tommaso Dominioni, Luigi Pugliese, Andrea Peri, Marta Botti, Benedetta Sargenti, Francesco Salvetti (*Department of Surgery, University of Pavia and Fondazione IRCCS Policlinico San Matteo*); Elisa Cassinotti, Ludovica Baldari, Valentina Messina, Vera D'Ambrosia (*SC Chirurgia Generale e Mini-invasiva, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - Milano*); Pasquale Cianci, Rocco Tumolo, Domenico Gattulli, Enrico Restini, Marina Minafra, Maria Grazia Sederino, Bernardino Bottalico (*UOC Chirurgia Generale, Ospedale Lorenzo Bonomo, Andria*); Pierluigi Pilati, Boris Franzato, Genny Mattara, Ottavia De Simoni, Andrea Barina, Marco

Tonello (*Unit of Surgical Oncology of Digestive Tract, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy*); Andrea Muratore, Marcello Calabrò, Nicoletta S. Federico Pipitone, Bruno Cuzzola, Elena Herranz Van Nood, Mariangela Azzellino (*Chirurgia Generale Ospedale E. Agnelli, Pinerolo*); Nicola Passuello, Alvise Frasson, Enzo Mammano, Luca Faccio, Fabrizio Vittadello, Alice Bressan, Giacomo Sarzo (*U.O.C. Chirurgia Generale OSA, io DIDAS Chirurgia, Azienda Ospedale-Università Padova*); Nicolò Tamini, Massimo Oldani, Luca Cigagna, Francesca Carissimi, Giulia De Carlo, Edoardo Baccalini, Luca Nespoli (*UO Chirurgia 1, Fondazione IRCCS San Gerardo dei Tintori, Università di Milano-Bicocca*); Alessio Giordano, Stefano Cantafio, Lucrezia Grifoni, Davide Matani, Serena Livi (*UO di Chirurgia Generale, Nuovo Ospedale "S. Stefano", Azienda ASL Toscana Centro*); Daniele Delogu, Fabrizio Scognamillo, Antonio Marrosu, Luca Guerrini (*Patologia Chirurgica AOU, Sassari*); Giampaolo Ugolini, Federico Ghignone, Giacomo Frascaroli, Nicola Albertini, Davide Zattoni, Giovanni Taffurelli, Isacco Montroni (*UO Chirurgia Generale di Ravenna-Faenza, AUSL Romagna*); Francesco Colombo, Piergiorgio Danelli, Andrea Bondurri, Anna Maffioli, Alessandro Bonomi, Isabella Pezzoli, Francesco Cammarata (*Division of General Surgery - L. Sacco University Hospital-Milano*); Orlando Goletti, Mattia Molteni, Alberto Assisi, Giorgio Quartierini (*Chirurgia Generale Humanitas Gavazzeni Bergamo, Italy*); Corrado Da Lio, Daunia Verdi, Isabella Mondì, Claudia Peluso, Lorenzo Macchi, (*Department of General Surgery, Mirano Hospital, Venice*); Marta Tanzanu, Federico Zanzi, Sara Pellegrini (*Chirurgia d'Urgenza, Santa Maria delle Croci - Ravenna*); Jacopo Andreuccetti, Rossella D'Alessio, Giusto Pignata, Michele De Capua, Iliaria Canfora, Luca Ottaviani (*General Surgery 2, ASST Spedali Civili of Brescia*); Pasquale Lepiane, Andrea Balla, Antonio De Carlo, Federica Saraceno, Rosa Scaramuzza, Anna Guida, Daniele Aguzzi (*Ospedale San Paolo, Civitavecchia, Roma*); Paolo Bellora, Sergio Gentilli, Manuela Monni, Herald Nikaj (*Clinica Chirurgica Ospedale Maggiore della Carità - Novara*); Nicola Cillara, Alessandro Cannavera, Antonello Deserra, Carla Margiani, Roberta Cabula (*UOC Chirurgia Generale PO Santissima Trinità ASL Cagliari*); Manuela Dettori (*Oncologia Medica, PO Businco, ARNAS Cagliari*); Giulia Gramignano (*SSD Oncologia, PO Nostra Signora di Bonaria San Gavino, ASL Medio Campidano*); Giovanni Lezoche, Monica Ortenzi, Elena S. Orlandoni, Federica Curzi, Francesca Vitali, Perla Capomagi, Miriam Palmieri (*Clinica di Chirurgia Generale e d'urgenza, Ancona Torrette*); Mario Giuffrida, Paolo Del Rio, Elena Bonati, Tommaso Loderer, Federico Cozzani, Matteo Rossini, Stefano Agnesi, (*Clinica Chirurgica Generale - AOU Parma*); Gabriella T. Capolupo, Marco Caricato, Filippo Carannante, Gianluca Mascianà, Martina Marrelli, Valentina Miacci, Sara Lauricella (*UOC Chirurgia coloretale, Fondazione Policlinico Campus Bio Medico, Roma*); Valeria Tonini, Maurizio Cervellera, Salvatore Pisconti, Concetta Lozito, Juliana Shahu, Claudia Mongelli, Giulia Morelli, Lodovico Sartarelli (*Ospedale Santissima Annunziata, Taranto*); Giuseppe S. Sica, Leandro Siragusa, Giulia Bagagnoli, Andrea M. Guida, Marzia Franceschilli, Vittoria Bellato, Cristina Fiorani (*Policlinico Tor Vergata, Roma*); Antonio Taddei, Matteo Risaliti, Ilenia Bartolini, Maria N. Ringressi, Luca Tirloni (*Azienda Ospedaliero Universitaria Careggi, Firenze*); Letizia Laface, Emmanuele Abate, Massimiliano Casati, Pietro Gobbi (*Ospedale*

**Vittorio Emanuele III Carate Brianza**); Enrico Opocher, Nicolò M. Mariani, Andrea Pisani Ceretti, Marco Giovenzana, Beatrice Giuliani, Martina Sironi (*ASST Santi Paolo e Carlo, Milano*); Ugo Grossi, Giacomo Zanusi, Giulio Aniello Santoro, Marco Brizzolari, Eugenio De Leo, Simone Novello, Krizia Aquilino, Francesco Milardi (*II Surgery Unit, Regional Hospital Treviso, DISCOG, University of Padua, Italy*); Stefano Olmi, Matteo Uccelli, Marta Bonaldi, Giovanni C. Cesana, Marco Bindi (*Policlinico San Marco GSD, Zingonia*); Raffaele Galleano, Antonio Langone, Massimiliano Botto, Angelo Franceschi, Elena Gambino (*Ospedale San Paolo Savona*); Maurizio Ronconi, Silvia Casiraghi, Giovanni Casole, Salvatore L. Ciulla (*Ospedale di Gardone V.T. - ASST Spedali Civili di Brescia*); Giovanni Terrosu, Sergio Calandra, Edoardo Scarpa, Vittorio Cherchi, Giacomo Calini, Lisa Martinuzzo, Lucrezia Clocchiatti, Davide Muschitiello (*Clinica Chirurgica, Azienda Sanitaria Universitaria Friuli Centrale ASUFC, Udine*); Andrea Romanzi, Barbara Vignati, Alberto Vannelli, Roberta Scolaro, Maria Milanese, Fabrizio Rossi (*Department of General Surgery, Valduce Hospital, Como, Italy*); Giuseppe Canonico, Alessandro Anastasi, Tommaso Nelli, Marco Barletta, Riccardo Fratarcangeli, Carmela Di Martino, Andrea Damigella, Elvira Adinolfi (*Ospedale San Giovanni di Dio, Firenze*); Arianna Birindelli, Lucio Taglietti, Sara E. Dester (*UOC Chirurgia - Ospedale di Esine (BS) - ASST Valcamonica - Italy*); Francesco Fleres, Eugenio Cucinotta, Francesca Viscosi, Santino A. Biondo, Giorgio Badessi, Nivia Catarsini, Carmelo Mazzeo (*AOU G Martino Policlinico di Messina, Department of General and Emergency Surgery - Italy*); Daniela Rega, Paolo Delrio, Carmela Cervone, Alessia Aversano, Silvia De Franciscis, Massimiliano Di Marzo, Bruno Marra, Ugo Pace (*Colorectal Surgical Oncology, Department of Abdominal Oncology, Istituto Nazionale Tumori-IRCCS "Fondazione G. Pascale", Naples, Italy*); Antonio Amato, Paola Batistotti, Elisa Mina, Alberto Serventi (*SC Chirurgia Generale Imperia*); Pierfrancesco Lapolla, Andrea Mingoli, Paolo Sapienza, Gioia Brachini, Bruno Cirillo, Enrico Fiori, Daniele Crocetti, Ilaria Clementi (*Policlinico Umberto I Sapienza Università di Roma*); Gennaro Martines, Arcangelo Picciariello, Giovanni Tomasicchio, Rigers Dibra, Giuseppe Trigianta, Marcella Rinaldi, Giuliano Lantone (*Chirurgia Generale "M. Rubino" Azienda Ospedaliero Universitaria Policlinico Bari Italy*); Alberto Porcu, Teresa Perra, Antonio M. Scanu, Claudio F. Feo, Alessandro Fancellu, Maria L. Cossu, Giorgio C. Ginesu, (*Azienda Ospedaliero Universitaria di Sassari, Italia*); Alberto Patriti, Diego Coletta, Filippo Petrelli, Paola A. Greco, Claudia Spadoni, Giovanna Cassiani, Federica Bianchini (*AO Ospedali Riuniti Marche Nord*); Marco Arganini, Matteo Bianchini, Bruno Perotti, Matteo Palmeri, (*Ospedale Unico della Versilia - Azienda Usl Toscana Nord-ovest*); Stefano Scabini, Selene Deiana, Giacomo Carganico, Davide Pertile, Domenico Soriero, Emanuela Fioravanti, Beatrice Sperotto (*Unità Operativa Chirurgia Generale ad Indirizzo Oncologico - IRCCS Ospedale Policlinico San Martino, Genova*); Bruno Nardo, Daniele Paglione, Veronica Crocco, Marco Doni, Mariasara Osso, Roberto Perri (*U.O.C. di Chirurgia Generale "Falcone" - Azienda Ospedaliera di Cosenza - Università della Calabria*); Gianluca M. Sampietro, Carlo Corbellini, Leonardo Lorusso, Carlo A. Manzo, Maria Cigognini, Caterina Baldi (*Division of Surgery, Rho Memorial Hospital - ASST*

*Rhodense - Rho, Milan*); Giuseppe Palomba, Giovanni Aprea, Marianna Capuano, Raffaele Basile (*AOU Federico II di Napoli - UOC chirurgia endoscopica*); Roberta Tutino, Marco Massani, Laura Marinelli, Nicola Canitano (*Chirurgia 1 - Azienda ULSS2 Marca Trevigiana - Ospedale Regionale di Treviso*); Tiziana Pilia, Mauro Podda, Adolfo Pisanu, Valentina Murzi, Silvia Incani, Federica Frongia, Giuseppe Esposito (*Policlinico di Monserrato, Chirurgia d'urgenza, Cagliari*); Gaetano Luglio, Francesca P. Tropeano, Gianluca Pagano, Eduardo Spina, Giuseppe De Simone, Michele Cricri (*Azienda Ospedaliera Universitaria Federico II*); Fausto Catena, Carlo Vallicelli, Nicola Zanini, Diana Ronconi, Francesco Favi, Carlo Mazzucchelli, Girolamo Convertini (*Chirurgia Generale e d'Urgenza, Ospedale Bufalini di Cesena, AUSL della Romagna*); Leonardo Vincenti, Valeria Andriola, Cinzia Bizzoca (*Chirurgia Generale Ospedaliera, Policlinico di Bari*); Carlo V. Feo, Nicolò Fabbri, Marta Fazzin, Antonio Pesce, Silvia Gennari, Marco Torchiario, Silvia Severi (*Azienda Unità Sanitaria Locale di Ferrara, Università di Ferrara*); Alice Frontali, Greta Bracchetti, Stefano Granieri, Christian Cotsoglou (*General Surgery Unit, ASST Vimercate, Vimercate, Italy*); Massimo Carlini, Giorgio Lisi, Domenico Spoletini, Maria R. Mastrangeli, Michela Campanelli (*UOC Chirurgia Generale, Ospedale Sant'Eugenio, Roma, Italia*); Michele Manigrasso, Marco Milone, Giovanni D. De Palma, Sara Vertaldi, Alessia Chini, Francesco Maione, Alessandra Marelo (*Department of Clinical Medicine and Surgery, "Federico II" University of Naples, Naples, Italy*); Francesco Selvaggi, Guido Sciaudone, Lucio Selvaggi, Francesco Menegon Tasselli, Giacomo Fuschillo, Lidia Oddis (*Università della Campania Luigi Vanvitelli, Napoli*); Simona Grande, Michele Grande (*UOSD Chirurgia d'urgenza Tor Vergata*); Simona Ascanelli, Laura Chimisso, Filippo Aisoni, Eleonora Rossin, Francesco Pepe, Francesco Marchetti (*UO Chirurgia 2 Azienda Ospedaliero-Universitaria Ferrara*); Biagio Picardi, Stefano Rossi, Simone Rossi Del Monte, Matteo Picarelli, Irnerio A. Muttullo (*Chirurgia Generale e d'Urgenza Ospedale San Filippo Neri ASL Roma 1*); Carlo Ratto, Angelo A. Marra, Angelo Parello, Francesco Litta, Paola Campenni, Veronica De Simone (*Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Roma*); Francesco Pata (*Department of Surgery, Nicola Giannettasio Hospital, Corigliano-Rossano, Italy*) (*La Sapienza University, Rome, Italy*); Cristiana Riboni (*EOC Ospedale Regionale di Lugano, Lugano, Switzerland*); Emanuele Rausa (*Unit of Hereditary Digestive Tumors, Fondazione IRCCS-National Cancer Institute, Milan, Italy*) Valerio Celentano (*Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom*) (*Department of Surgery and Cancer, Imperial College, London, United Kingdom*).

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## Conflicts of Interest

The authors declare no conflicts of interest.

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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  $\geq 75$  years of age, overall and by screening participation. **Table S2:** Subgroup multivariable analyses predicting the outcomes of patients  $\geq 75$  years who underwent CRC screening versus no screening (sample restricted to the 7607 subjects aged  $\geq 75$  years).