

***Project:***

**The management of complicated colorectal cancer in older patients in a global perspective: the CO-OLDER study.**

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## **Background**

### **Last data about Colorectal Cancer epidemiology.**

Colorectal cancer (CRC) is the second leading cause of cancer death. In 2020, more than 1.9 million new cases of colorectal cancer and more than 930 000 colorectal cancer-related deaths occurred globally with wide geographical variations in incidence and mortality. The incidence rates were highest in Europe, Australia and New Zealand, while mortality rates were highest in Eastern Europe. By 2040 the burden of colorectal cancer will increase to 3.2 million new cases per year (an increase of 63%) and 1.6 million deaths per year (an increase of 73%). Incidence rates of colorectal cancer have been decreasing in high-income countries, largely as a result of effective screening programs. However, colorectal cancer remains common. [1Morgan ].

The incidence of CRC is strongly related to age, with the highest incidence rates being in older people. Nearly 60 % of cases develop over the age of 65; 30% are 75 years or older [2 CDC].

During 2016-2018 in the UK, more than 4 in 10 new cases of CRC (43%) were in people aged 75 and over. Age-specific incidence rates rise steeply from around age 50-54. The highest rates are in the 85 to 89 age group for both females and males.[3<https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-One>]

In the US, those above 65 years old are about three times more likely to be diagnosed with CRC than those 50–64 years old, and about 30 times more likely to be diagnosed than those 25–49 years old. While the incidence rate for the disease has decreased over the past decades among those over 50 years old, the incidence rate for those under 50 years old has increased [4 SEER\*]

### **Focusing on older patients.**

CRC is becoming a disease of the elderly. The median age for CRC diagnosis is 67 years, with 56% of newly diagnosed cases occurring in patients having an age  $\geq 65$  years, 31% in the age of  $\geq 75$  years. The median age at death is 72 years. 45% of the deaths occur in patients of 75 years old or more, and 21% in patients of 85 years or more [5 Howlader]

Ageing is the most significant risk factor for CRC.

Every country in the world is experiencing growth in both the size and the proportion of older persons in the population. By 2030, 1/6 of the global population will be aged 60 years or over. At this time, the population aged 60 years and over will increase from 1 billion in 2020 to 1.4 billion. By 2050, the world's population of people aged 60 years and older will double (2.1 billion). The number of persons aged 80 years or older is expected to triple between 2020 and 2050 to reach 426 million [6 <https://www.who.int/news-room/fact-sheets/detail/ageing-and-health>].

With increased life expectancy, the incidence of CRC in the oldest-old patients will increase.

The significant age shift in the incidence of CRC is having an important impact on health care including cancer care, because cancer in patients aged over 80 years, represents an ethical dilemma for families, general practitioners, surgeons and oncologists.

The screening for CRC is recommended for subjects of 50-year-old or more and is carried out mainly in patients between 60 and 70 years of age [7 Wolf].

Both the U.S. Preventive Services Task Force and the American Cancer Society recommend CRC screening until the age of 75 years (when life expectancy is greater than 10 years) and individualization in patients between 76 to 85 years old because the benefits of screening decrease while the risk of suffering associated complications increases in this age group [8 Force]. The U.S.

Multi-Society Task Force of Colorectal Cancer suggests continuing screening for up to 85 years only if no previous screening has been done and stopping it at 75 years if prior screening tests have been negative [9Rex]. The management of the oldest patients is usually suboptimal, because of the lack of high-quality data to guide our care for eldest patients.

**Patients over 75 years old are usually not screened for CRC. Moreover, patients over 80 years old are managed only when they are symptomatic, often in the emergency setting** and often treated less aggressively because of their age and comorbidity with a certain reluctance to submit these patients to a surgical procedure, and some people even considered that no treatment was the best treatment option in this population [10 Kitagawa].

In addition to this, **delay in diagnosis has increased after the Covid-19 pandemic.**

Due to the re-allocation of resources and disruption of screening programs since March 2020 and a slow resumption of surgical elective activities following the control of the Covid-19 Pandemic, it has been estimated that between 2020 and 2023, approximately 1,179,642 to 2,014,164 cases of colorectal cancer screening, 8346 to 12,894 cases of colorectal cancer diagnosis, and 6113 to 9301 cases of early-stage diagnoses for this cancer will be missed [11 Issaka RB].

A cohort multicenter Italian study investigating whether the SARS-CoV-2 pandemic was associated with more advanced oncologic stage and change in clinical presentation for patients with colorectal cancer, among 17 938 patients (10 007 men [55.8%]; mean [SD] age, 70.6 [12.2] years) enrolled in the study, reported that 7796 (43.5%) during the pandemic period and 10 142 (56.5%) during the pre-pandemic period were respectively submitted to surgery for CRC. With logistic regression analysis, the pandemic period was significantly associated with an increased rate of advanced-stage colorectal cancer (odds ratio [OR], 1.07; 95% CI, 1.01-1.13; P = .03), aggressive biology (OR, 1.32; 95% CI, 1.15-1.53; P < .001), and stenotic lesions (OR, 1.15; 95% CI, 1.01-1.31; P = .03) [12 Rottoli M].

During the ongoing pandemic, the use of emergency colonoscopy due to the patient's emergency (bowel perforation or obstruction) increased [13 Shinkwin;14 Wassie].

Surveillance colonoscopy that is performed periodically for people at high risk for colorectal cancer due to age or previous screening results also showed a significant reduction compared to the pre-period of COVID-19 [14 Wassie, 15 Tinmouth J,16 Rutter MD]. Furthermore, cancellation of appointments or non-response to calls increased [17 D'Ovidio].

Furthermore, most elderly comorbid people experienced isolation to avoid Covid infection in healthcare facilities and the difficulty to access care due to long waiting lists.

COVID-19 Pandemic had a psychological impact on the population. It is anticipated that this may have affected the elderly more as they were afraid to be infected. This would have affected their physical activity and frailty, especially in the eldest [18 Sheek-Hussein M, Abu-Zidan FM, Stip E. Disaster management of the psychological impact of the COVID-19 pandemic. Int J Emerg Med. 2021 Mar 24;14(1):19. doi: 10.1186/s12245-021-00342-z.]. Accordingly, the number of older, aged over 75 years old people presenting with acute abdomen admitted to the emergency department is increasing. Most of them need to be managed surgically on the first presentation of advanced colorectal cancer which can be complicated by obstruction, bleeding and perforation.

To the best of our knowledge, there are no available studies investigating how this delay is impacting elderly people at high risk of presenting CRC only for ageing.

Elderly patients with CRC who had planned colic resection showed good outcomes in terms of morbidity and mortality mainly due to improvements in perioperative care and the laparoscopic approach in a study including nonagenarian patients [19 Hashimoto-20 Zeng-21Roque-Castellano C-22Franco I-23 S, Kurian].

Emergency surgery is associated with increased morbidity and mortality. For older patients undergoing emergency abdominal surgery, mortality increases with age and invasiveness of the procedure by up to 50% [24 Svenningsen P-25 Racz J]. Factors increasing morbidity and mortality

in older patients can be divided into patient factors, such as decreased physiological reserve, comorbidity, poly-pharmacy and frailty, and into environmental factors such as the quality of primary evaluation on arrival to the emergency department, the presence of staff trained to assess and deal with frailty, and using a standardized protocol of shared decision-making which is an essential component of patient-centred care to decrease futility in managing advanced surgical diseases in frail and older patients. Frailty, which is a syndrome characterized by a physiological multi-system decline resulting in greater vulnerability to stressors such as surgery, has been reported to be associated with worse outcomes, long hospital stays, higher readmission rates, and mortality after elective and emergency surgery [26 Fehlmann CA-27 Leiner T-28 Ward MAR].

The preoperative evaluation of frailty, including cognition and functional status, is a crucial tool in assessing surgical risk and predicting postoperative complications for elderly surgical patients. The Comprehensive Geriatric Assessment (CGA) and optimisation is a multi-dimensional, multi-disciplinary process of care including the assessment of medical, mental, social and functional needs of the elderly people, and the formulation of an integrated and coordinated care plan that provides treatment and long-term follow-up with specific intervention tools in form of exercise regimes or tailored plan of re-adaptation and rehabilitation. The original tailored plan is reassessed at appropriate intervals with the interventions reconsidered accordingly [29 CampbellAJ].

CGA is considered the gold standard for screening, diagnosing and managing frailty and provides the coordinated work of a multidisciplinary team which includes geriatricians, geriatric nurses, anesthesiologists, surgeons, physiotherapists, occupational therapists and dietitians [30 S G Parker,].

How to best address and monitor frailty preoperatively in the emergency setting is not standardised.

In the acute care setting, delay in management increases the risk of negative outcomes and mortality. In this scenario, the main limits to CGA methodology implementation are the admission of a critically ill patient presenting with advanced surgical disease and signs of hemodynamic

instability; the unavailability of a multidisciplinary team including a geriatrician at night; the lack of trained professionals in geriatric medicine and physiology in the emergency department, and the necessity of making a prompt diagnosis and treatment to avoid poor outcomes and in-hospital death.

The management of elderly patients with acute abdomen is often challenging due to patients' confusion, dementia, anxiety, delirium, and atypical clinical features compared with younger patients that may delay diagnosis and access to the operating room [31 BDS DHS].

In the emergency setting, it is challenging to recognize whether the presenting surgical condition represents an end-of-life situation. Considerations of medical ethics, prior quality of life, and patient and family preferences of goals of care must be utilized to help avoid non-beneficial surgery and futility [32].

Deciding not to operate can be difficult for an emergency surgeon faced with the time pressure, and the patient, family, and other health care professionals' desires, even when there are low chances of surgical procedure success [32 Grant SB]. According to the principles of realistic medicine, the management of a patient in a critical setting should be evidence-based but also be personalized, and aims to reduce harm and waste [33 Stephen J.]. Few studies focused on emergency abdominal surgery in over 75 years old patients; and even fewer studies on the oldest, aged over 85 years old, patients admitted to ED with complicated CRC. Outcomes are controversial; the main limits of these studies are the short-term follow-up and small cohort size [34 Spangler, R. 35 De Simone B, 36 Pacilli, A].

In a multicenter retrospective study [35], 19 patients over 90 years old who had undergone emergency surgery for complicated CRC were included in the study. The mean age was 92.52 years (range: 90-97 years; SD 1.49). Preoperative assessment of surgical risk was made using the American Society of Anesthesiologists (ASA) score. The in-hospital mortality rate was 21 % (n=4). No statistically significant difference was reported in terms of in-hospital mortality between



patients with an ASA score  $\leq 3$  and patients with an ASA score  $>3$ . Primary anastomosis was performed in 6 of 19 patients (31.57%), all of whom had right-side colon cancer. Diverting stoma was created for 12 of 19 patients (63.15%). There was a statistically significant difference in the incidence of postoperative complications between patients with right-side colon cancer and patients with left-side colon cancer ( $p=0.0498$ ). The mean length of hospital stay was 12.78 days (range: 2-31 days; SD 6.31). The in-hospital mortality rate was 21% ( $n=4$ ). At follow-up, overall survival was 47.36% ( $n=9$ ).

A retrospective single-centre study [36], including 32 patients with a mean age of 86 years, managed in the emergency setting, showed no statistically significant differences among patients presenting bowel obstruction, bowel perforation and bleeding in terms of postoperative hospital stay, postoperative complications, reoperation rate and 30-day mortality. In this study, the CR-POSSUM score was used to assess the surgical risk.

A systematic review assessing the evidence for managing complicated CRC in patients over 90 years reported that [37 De Simone B]:

- Chronological age itself is not an independent negative prognostic factor for complicated CRC surgery;
- Careful selection and preoperative evaluation of the patient maximize surgical outcomes;
- ASA classification, evaluating the global health status of the patient is the best tool quickly available for the emergency surgeon to assess individualized risk with high predictive value for postoperative morbidity and mortality
- The level of albuminemia (nutritional status) and the degree of independence of the patient in the daily activities before hospitalization (quality of life) have to be considered in the preoperative evaluation of geriatric patients.

-ASA I-III nonagenarian patients not having hypoalbuminemia, with high independence in daily activities, have the same surgical risk as younger patients and can have surgery with good outcomes.

-In the emergency settings, one-stage surgery is the best choice, when it is possible, in selected patients; two-stage surgery is indicated in case of peritonitis, in patients hemodynamically unstable and in case of patients with hypoalbuminemia, due to the high risk of anastomotic leakage; decompressive colostomy or ileostomy is indicated as a bridge to elective surgery in patients fit for surgery, or as a palliative procedure, in advanced neoplastic disease and peritoneal carcinomatosis;

-The use of colorectal stents should be considered, whenever appropriate and when available, both as a bridge to surgery and as a palliative procedure. However, to the best of our knowledge, there are no clinical studies focused on nonagenarian patients confirming these statements. Emergency surgeons have a crucial role in managing this group of vulnerable patients in critical scenarios, balancing the risks and benefits of a surgical or non-surgical procedure, and assessing frailty before involving the geriatricians in the lack of a CGA model for a multidisciplinary approach.

#### **Critical issues:**

- **CRC is increasing among older patients (=>75 yo);**
- **Older patients are not included in focused screening program for CRC;**
- **In the early COVID-19 pandemic, screening programs for cancer were paused and elective surgical procedures, including oncological surgical procedures, were postponed;**
- **An increasing number of older and frail patients will be managed in the emergency setting for a complicated CRC with high mortality.**

**Our hypothesis is that after the Covid-19, older patients presenting with obstructed CRC in the emergency setting and submitted to surgery is increased with higher mortality rate.**

**Our study aims to assess modifiable risk factors for negative outcomes and mortality correlated to emergency surgical management of 75 years old and over patients admitted with a complicated CRC and to assess the management of this frail group of patients and improve cancer care in geriatric patients before and after Covid-19 outbreak.**

**The rationale for the trial:**

- 1) to investigate the management of older patients aged 75 years old and over presenting with a complicated CRC in the emergency setting;
- 2) to report the outcomes of surgical management in terms of morbidity and mortality from a global perspective;
- 3) to analyze the demographics, clinical and surgical data that could predict a poor outcome in this group of patients;
- 4) to propose individualized risk assessment and personalized surgical treatment for this group of patients.

**Objectives**

to evaluate the cohort of older patients presenting with complicated CRC in the emergency setting;  
to investigate the risk factors for negative outcomes after emergency surgery in geriatric patients;  
To report the morbidity and mortality rates before and after the COVID pandemic outbreak.

**Primary Endpoint:**

Morbidity and mortality of emergency surgical procedures in patients aged 75 years old and over presenting with colorectal cancer complicated by obstruction and perforation.

**Secondary Endpoint:**

Define the risk factors associated with a negative surgical outcome.

**Study Design:**

The CO-OLDER study is an international study, designed as a multicenter observational cohort study, analysing data collected in 2 periods:

before the 11th March, 2020 that is before the COVID-19 Pandemic outbreak (retrospective);

After the 11th March 2020, during the COVID-19 Pandemic till 30th September 2023 (retrospective and prospective);

The protocol of the study will be submitted for evaluation to a selected international steering committee and a panel of experts in emergency colorectal surgery and geriatric patient management. Revisions to the protocol will be made according to experts' suggestions and comments and the final protocol will be approved and registered in the [ClinicalTrials.gov](https://clinicaltrials.gov).

**Study population:**

All patients aged 75 years old and over who were admitted to the surgical department with acute abdomen caused by colorectal cancer and managed surgically.

**Inclusion criteria**

Patients aged 75 years old and over who were admitted to the emergency department presenting with obstruction due to advanced colorectal cancer and submitted to surgery.

**Exclusion criteria**

Patients having an age of less than 75 years and those over 75 non presenting with complicated colorectal cancer in the emergency department.

**Study period**

The project will be conducted over a 12-months period

Data from 1st January 2018 to 30th August 2023 will be collected.

Data analysis will start the 1st October 2023.

Data will be presented in January 2024.

**Data collection**

All demographic, clinical and surgical data will be collected on an online case report form, designed on the Google form platform. Every clinical center collaborating with the CO-OLDER study will be identified by an ID number assigned by the principal investigator and the coordinator of the study before starting data collection. Each local CO-OLDER collaborator will coordinate a local team which will be responsible to include the patients, collect the data and enter the online case report form into a protected and anonymised database. The link for accessing the online CRF will be sent to the local investigator by the PI. All epidemiological, clinical, surgical and follow-up data will be collected over 6 months. Only the principal investigator of the study will be able to access the database which is anonymised and secured by a username and password.

**Statistical analysis**

The patients will be divided into two groups: pre-Covid and post-Covid groups.

Qualitative data will be presented as number (%). Quantitative and ordinal data will be presented as median (25-75 interquartile range (IQR)). The qualitative data of the two groups will be done using Pearson Chi-Square. Fisher's exact will be used if the expected value of a cell was  $< 0.5$ .

Continuous and ordinal data will be analyzed using Mann Whitney U Test. All tests will be two-sided, and a p-value of 0.05 will be accepted as statistically significant.

To investigate the factors associated with death, a univariate comparison will be done between those who died and those who survived. A logistic regression model will be done including variables which had a loose  $p < 0.1$  in the univariate analysis.

### **Sample size**

This is an explorative study and data will be used to investigate the management of CRC in older patients in terms of mortality and morbidity rates, in the emergency setting in 2 periods: before the Covid-19 pandemic and after Covid-19 pandemic broke out. GLOBOCAN reported that mortality correlated to CRC was estimated at 9.4% in all age groups. Mortality after emergency colectomy in elderly ranges 15%. Sample size is calculated to 1810 patients to be enrolled in this study.

### **Ethical Aspects**

The present study is an observational study which will not change or modify the clinical practice of all participating investigators. All surgeons involved in the patient's recruitment will be responsible for the local ethical committee approval if it will be required according to the regulations of each country. Data collection will be anonymous. No personal identifiers will be collected like hospital

number, name, or national identifier. The study will meet and conform to the standards outlined in the Declaration of Helsinki and Good Epidemiological Practices.

### **Informed consent**

The present observational study will not attempt to change or modify the clinical practices of the participating physicians, consequently, informed consent will be required according to each country's legislation. Each eligible patient for this study will be informed about the study and will be asked to authorise the anonymous use of his/her personal data, according to standard local clinical practice.

### **Dissemination of Results and Publication Policy**

The results of the study will be presented at clinical congresses. The CO-OLDER study embraces corporate authorship and all collaborators that will contribute to this study will form the CO-OLDER collaborative group. This group will be listed and acknowledged as collaborators in all publications in which CO-OLDER study data will be used.

### **Budget and Financing**

The study was conceived, and designed and will be carried out without any financial support.

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