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Risk factors of anastomotic leak in elderly patients undergoing colorectal cancer surgery

Ruth Blanco Colino

Universitat Autònoma de Barcelona

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Doctoral thesis presented by ***Ruth Blanco Colino*** *to obtain the* ***PhD degree***

Directors:

- Eloy Espín Basany
- Francesc Vallribera Valls

Tutor: Eloy Espín Basany

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Department of Surgery

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"All we have to decide is what to do with the time that is given to us"

J.R.R. Tolkien

Abbreviatures list

ACS-NSQIP - American College of Surgeons National Surgical Quality Improvement Program

AL – Anastomotic leak

ASA - American Society of Anesthesiologists (Physical classification system)

BMI – Body Mass Index

CAPOX - Oxaliplatin and Capecitabine

CD – Clavien – Dindo

CEA - Carcinoembryonic Antigen

CFS - Clinical Frailty Scale

CGA - Comprehensive Geriatric Assessment

CI – Confidence Interval

CLASSIC - Classification of Intraoperative Complications

CR - POSSUM - ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity

CRC – Colorectal Cancer

CRP - C-Reactive Protein

CT - Computed Tomography

ERAS - Enhanced Recovery After Surgery

ESMO - European Society for Medical Oncology

FOLFOX - Folinic acid, Fluorouracil and Oxaliplatin

HR - Hazard Ratio

ICG - Indocyanine Green

IHD – Ischaemic Heart Disease

LCRT - Long-course ChemoRadiotherapy

LOS – Length of Stay

mFI - Modified Frailty Index

MIS – Minimally Invasive Surgery

MRI - Magnetic Resonance Imaging

OR - Odds Ratio

PCT – Procalcitonin

POD – Postoperative Day

RCT - Randomized Controlled Trials

SCRT - Short-Course Radiotherapy

TME - Total Mesorectal Excision

TNM – Tumour, Node, and Metastasis

TNT - Total Neoadjuvant Therapy

WHO – World Health Organisation

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Abstract

Abstract

Background: Anastomotic leak (AL) remains one of the most serious postoperative complications following colorectal cancer (CRC) surgery. The incidence of CRC is expected to rise due to the increased in ageing in the population, therefore it is important to identify risk factors related to AL in this cohort.

Methods: A systematic review was conducted to identify already published experience in the literature and a meta-analysis on morbidity and mortality. A retrospective cohort study was done including patients aged ≥75 years who underwent colorectal surgery and anastomosis for cancer between 2015-2019 at a colorectal surgery unit in a tertiary centre. Patient characteristics, surgical, oncological, perioperative variables were collected. Univariable and multivariable logistic regression analysis were used to identify predictors of AL, and survival outcomes were assessed with Kaplan Meier and Cox analysis. An international survey to assess management of older patients requiring anastomosis in different scenarios was distributed and descriptive data was analysed.

Results: For the systematic review 59 studies were identified and in total 15 studies provided data for the meta-analysis. In the retrospective study, 416 patients were included with an AL rate of 12.26%. Predictors of AL included higher ASA status, history of ischaemic heart disease, higher CR-POSSUM physiological, CFS ≥5 and ECOG ≥2. The preoperative hypoalbuminemia <3 g/dL (OR 7.70, p = 0.009) and elevated CRP on postoperative day 3 (OR 1.14 per unit increase, p<0.001) remained significative independent factors in the multivariable analysis. AL was significantly associated with major complications, longer hospital stay, discharge to a rehabilitation centre or hospital-at-home discharge (OR 4.57, p = 0.011) and an increased 30-day and 5-year mortality (p < 0.0001).

207 surgeons took part in the survey indicating they would prefer stoma and no anastomosis in the elderly in acute settings comparing to elective procedures.

Conclusion: Anastomotic leak in elderly patients undergoing CRC surgery can be influenced by several factors. Early identification of high-risk patients, frailty assessment and optimisation of modifiable perioperative parameters may reduce AL incidence and improve outcomes.

Resumen

Antecedentes: La fuga anastomótica (FA) sigue siendo una de las complicaciones postoperatorias más graves tras la cirugía por cáncer colorrectal (CCR). Se espera que la incidencia de CCR aumente debido al envejecimiento de la población, por lo que es importante identificar los factores de riesgo relacionados con la FA en esta cohorte.

Métodos: Se realizó una revisión sistemática para identificar la experiencia publicada en la literatura y un metaanálisis sobre morbilidad y mortalidad. Se llevó a cabo un estudio de cohorte retrospectivo incluyendo pacientes de ≥75 años que se sometieron a cirugía colorrectal con anastomosis por cáncer entre 2015 y 2019 en una unidad de cirugía colorrectal de un centro terciario. Se recopilaron características del paciente, variables quirúrgicas, oncológicas y perioperatorias. Se utilizaron análisis de regresión logística univariable y multivariable para identificar factores predictores de FA, y se realizaron análisis de supervivencia con Kaplan-Meier y análisis de Cox. Se remitió una encuesta internacional para evaluar el manejo de pacientes mayores que requieren anastomosis en diferentes escenarios, y se analizaron los datos de forma descriptiva.

Resultados: Para la revisión sistemática se identificaron 59 estudios y un total de 15 estudios proporcionaron datos para el metaanálisis. En el estudio retrospectivo se incluyeron 416 pacientes, con una tasa de FA del 12.26%. Los factores predictores de FA incluyeron un grado ASA elevado, antecedentes de cardiopatía isquémica, puntuación fisiológica elevada en el CR-POSSUM, CFS ≥5 y ECOG ≥2. La hipoalbuminemia preoperatoria <3 g/dL (OR 7.70, p = 0.009) y el aumento de la PCR en el 3º día postoperatorio (OR 1.14, p<0.001) se mantuvieron como factores independientes significativos en el análisis multivariable. La FA se asoció significativamente con complicaciones mayores, estancia hospitalaria prolongada, alta a un centro de rehabilitación o atención hospitalaria domiciliaria tras el alta (OR 4.57, p = 0.011) y un aumento en la mortalidad a 30 días y a 5 años (p < 0.0001).

Participaron un total de 207 cirujanos en la encuesta, indicando que preferirían estoma y no anastomosis en pacientes ancianos en cirugía de urgencias comparado con la electiva.

Conclusión: La fuga anastomótica en pacientes ancianos sometidos a cirugía por CCR está influenciada por múltiples factores. La identificación de pacientes de alto riesgo, la

evaluación de la fragilidad y la optimización de parámetros perioperatorios modificables pueden reducir potencialmente la incidencia de FA y mejorar los resultados.

Background

1. Background

Elderly population is progressively increasing in developed countries. This is mostly due to an improvement in healthcare systems with a better control and management of comorbidities in the Western world. Therefore, we are facing the aging of our surgical population being more common to attend elderly patients in colorectal surgery units. At European level, a rate of 21% of population was over 65 years in 2020 compared to 16% in 2001. The group of 80 years old, represented the 6% in 2020 while in 2001 they were the 3.4% of the population. (1)

In Spain, elderly population represents 19.3% of the total, 6.1% regarding octogenarian according to Spanish Statistics National Institute (INE) data in 2019. (2) Predictions from INE are expecting them to represent 29.4% of the population in 2068.

At the same time, colorectal cancer is one of the most frequent diseases that is treated in surgical practice, being more common in older patients. It corresponds to the third most common cancer and fourth cause of death globally. (3)

In colorectal cancer management, the impact of aging in the population could be even larger, especially considering that colorectal cancer risk and incidence is greater in older patients. The burden of colorectal cancer is expected to increase in high income countries in the next years and age is one of the influencing factors related to this rising problem. (4) Understanding the management and special requirements of our elderly population may help improve our surgical outcomes and to develop strategies to prepare our healthcare systems.

1.1. Elderly definition

The definition of “elderly” is controversial and nowadays defining this group just considering the age as a number is outdated.

Historically an older person was defined as someone with an age over 60-65 years old, usually related to the age of working life. However, due to an improvement in the life expectancy and quality of life, level of function has been proposed to be considered in the aged population. (5)

According to the United Nations, an older person is someone over 60 years old, though this number can be even lower down to 50 if the population in question has a low expectancy of life.(6) So the way we define “elderly” if only chronological age is considered, also can be different depending in the population / area we are analysing it.

For the World Health Organization (WHO), they introduce the concept of “healthy aging” as “the process of developing and maintaining the functional ability that enables well-being in older age.”(7) They move away from the chronological definition of age and introduce functionality as part of it, being this an intrinsic capacity of the individual but also their environment and the interactions developed.

WHO calculates that by 2050, a total of 2 billion people worldwide will be over 60 years representing 20% of the global population. Therefore, they developed an action plan on ageing and health in 2016. If a longer life is expected, we can rethink the way we live and face new opportunities not imagined before. However, this depends on keeping a “good health” which is not always the case at older age. An important key action point is working towards both, increasing life expectancy but keeping a healthy life for everyone. In their “objective 3.2.” WHO aims to develop and ensure affordable access to quality older person-centred and integrated clinical care. They advocate for assessing the patient needs and to provide a personalised care plan with the goal of maintaining functional ability, and this also includes cancer management. They recognise that new clinical guidelines are needed or an update it is necessary to recognise the impact on the capacity of individuals, and to ensure that all older people in need can access palliative care. The rapid deteriorations in health seen in older ages, are also highlighted as part of exacerbation or deterioration of an already existing condition. In the objective

5.3. point 105, WHO states that is urgent to develop high-quality research in the causes and management of health conditions in older patients, to assess age-related differences and the presence of other morbidity and to explore interventions that could modify changes related to age (physically and psychologically). (7,8)

Some large public healthcare providers, like National Health Service (NHS) in United Kingdom, have already started to work towards that WHO definition aiming to improve the care of older people but keeping the "wellbeing". (9)

"Older age" and "elderly" are not synonymous, and defining elderly purely on chronological age number, as already described, is limited. (10) There are many surgical implications this could bring. There is heterogeneity in the group proposed as "elderly" or "older age", no matter if the cut-off age is 65, 75 or 80 as we know that the ageing process is not uniform. There are many factors that can interfere with age, like genetics, lifestyle, increased morbidities and polymedication. All of them have an impact and biological age may be different so, someone age 75 can be healthier than other frail person whose age is 65. Differences in the definition of "elderly" in the published literature makes even more challenging the decision making during the surgical perioperative management. (5,11,12)

It has already been suggested that treating older "fit" populations similar as younger patients has similar outcomes, but it is not that clear with frail comorbid patients. A major challenge we face in trying to treat our patients following the latest evidence is that current trials or major studies tend to recruit younger patients and therefore, underrepresenting frail individuals in cancer treatment. (12)

The concept of "frailty" interacts with the "older age" and what we understand as "elderly". As per previous comments before and current literature, it is necessary to move from the chronological age to a more individual characterisation of the "older population".

1.2. Frailty

1.2.1. Definition

Frailty can be defined as “a medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death” according to the consensus from 6 major international societies published in 2013 by Morley et al.

Though multi-morbidity and disability can be related and present similarly to frailty, are different conditions and need to be distinguished. Frailty is related to the capability of someone to be able to recover from an incident or illness and it is a long-term condition. For that reason, prevention and early identification are key to be able to manage and support those individuals at higher risk. (13,14)

1.2.2. Assessment of frailty

There are multiple tools that can be used to measure frailty. The different scores/scales differ among them in the parameters they include. Some are more prompted to measure the individual phenotype or functional status, while others include comorbidities or symptoms.

One of the most used tools for frailty assessment is the Comprehensive Geriatric Assessment (CGA) in medicine. It includes different domains covering functionality, nutrition, cognition, psychological state, social support, comorbidities and medication. It has been related to increased risk for complications after colorectal surgery. (12,15)

However, it has limited feasibility in clinical setting, as it is complex and ideally should be performed preoperatively by a geriatrician. (16,17)

Clinical Frailty Scale (CFS) proposed by Rockwood et al. (18) has been also suggested to correlate with postoperative morbidity identifying frail patients and being easy to calculate. (19) All items can be found in Table 1 adapted from Rockwood et al. (18) .

Score	Definition	Description
1	Very Fit	Robust, active, energetic, motivated; exercises regularly; among the fittest for their age.
2	Well	No active disease symptoms but less fit than category 1; occasionally active (e.g. seasonally).
3	Managing Well	Medical problems well controlled but not regularly active beyond routine walking.
4	Vulnerable	Not dependent, but symptoms limit activities; often complain of being "slowed up" or tired during the day.
5	Mildly Frail	Evident slowing; need help in high-order IADLs (finances, transport, heavy housework, medications); shopping and outside walking increasingly impaired.
6	Moderately Frail	Need help with all outside activities and keeping house; problems with stairs; need help with bathing and possibly minimal dressing assistance.
7	Severely Frail	Completely dependent for personal care (physical or cognitive) but stable and not at high risk of dying within 6 months.
8	Very Severely Frail	Completely dependent; approaching end of life; unlikely to recover even from minor illness.
9	Terminally Ill	Life expectancy <6 months; not otherwise evidently frail.

Table 1. Items included in the Clinical Frailty Scale by Rockwood et al. *(18)*

The Modified Frailty Index (mFI) was proposed in 2013 and is the product of combining the CFS already mentioned to 11 variables collected by the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). This tool has also been related to correlate with postoperative complications in general and colorectal surgery. (19,20)

The list of items included for assessment can be found in Table 2 from Subramaniam et al. (21). A score of more than 0.18 is considered frail.

1. Functional health status before surgery (either partially or totally dependent)
2. Diabetes mellitus (noninsulin or insulin)
3. History of COPD or Current pneumonia
4. Congestive heart failure within 30 days before surgery
5. History of myocardial infarction within past 6 months before surgery
6. Previous percutaneous coronary intervention or previous cardiac surgery or history of angina 1 month prior to surgery
7. Hypertension requiring medication
8. Delirium - Impaired sensorium
9. History of transient ischemic attack or cerebrovascular accident with no residual deficits
10. Cerebrovascular accident or stroke with neurologic deficit
11. History of revascularization or amputation due to peripheral vascular disease or rest pain or gangrene

Table 2. Items from Modified Frailty Index by Subramaniam et al.*(21)*

Beyond frailty, other more specific scores related to the outcomes after colorectal surgery were developed long time ago and demonstrated to be stronger predictors of morbimortality. These are the POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) scores, including the POSSUM physiological score, POSSUM mortality and POSSUM operative severity scores. (22)

They are a surgical risk scoring system combining physiological and surgery related factors. Though it does not measure frailty, indirectly a higher score can indicate multimorbidity and has been proven to correlate with poor outcomes in colorectal surgery. (23–25)

Parameter	Score 1	Score 2	Score 4	Score 8
Age (years)	**<60**	**61–70**	**71–80**	**>80**
Cardiac signs	No failure	Diuretic/ digoxin therapy	Peripheral oedema, warfarin, CXR changes	Raised JVP or cardiomegaly
Respiratory signs	No dyspnoea	Dyspnoea on exertion	Limiting dyspnoea or steroids	Dyspnoea at rest, consolidation
Systolic BP (mmHg)	110–130	131–170 or 100–109	90–99	<90 or >171
Pulse rate (/min)	50–80	81–100	101–120	<50 or >120
Glasgow Coma Scale	15	12–14	9–11	<9
Haemoglobin (g/dL)	13–16	11.5–12.9 or 16.1–17	10–11.4 or >17	<10
White cell count (10^9/L)	4–10	10.1–20 or <4	>20	—
Urea (mmol/L)	<7.5	7.6–10	10.1–15	>15

Sodium (mmol/L)	136–145	131–135 or 146–150	126–130 or 151–155	<126 or >155
Potassium (mmol/L)	3.5–5	3.2–3.4 or 5.1–5.3	2.9–3.1 or 5.4–5.9	<2.9 or >6
ECG	Normal	AF (rate controlled) or minor abnormalities	>5 ectopics/min or significant abnormalities	MI within 6 months

Table 3. POSSUM Physiological Score

Parameter	Score 1	Score 2	Score 4	Score 8
Operative severity	Minor	Moderate	Major	Major+
Number of procedures	1	2	3	>3
Blood loss (mL)	<100	101–500	501–999	>1000
Peritoneal contamination	None	Serous fluid	Local pus	Free bowel content or faecal contamination
Malignancy	None	Primary only	Nodal metastases	Distant metastases
Timing of operation	Elective	Scheduled urgent (<24h)	Emergency (<2h)	Immediate life-saving

Table 4. POSSUM Operative Severity Score

1.3. Colorectal cancer

1.3.1. Epidemiology and demographics

Colorectal cancer in the developed countries is the 3rd most common cancer worldwide with 1.8 million cases in 2018. (26)

There are many risk factors associated to it which are also more common in high socioeconomic countries due to processed meat, alcohol, tobacco, obesity and age. (27) Colorectal cancer is strongly related to age, being infrequent in younger and having a peak at 70. 75% after 65 years old and 50% of the patients approximately, are older than 70 years old in Europe. (28) Regardless of the higher risk for morbimortality in the older age, as a factor, age alone should not restrict the therapy options and a careful patient assessment is needed to offer more individualised approach. (12,28)

1.3.2. Diagnostic

In terms of diagnosis, screening pathways are usually part of healthcare national systems usually after the age of 50, that is the case for Spain or for United Kingdom. (29,30) A faecal immunochemical test (FIT) is offered to detect asymptomatic rectal bleeding, and if positive is followed by a colonoscopy. Patients at higher risk of developing colorectal cancer due to family risk, genetic predisposition or chronic inflammatory bowel disease should also be part of the screening. (31)

Depending on the presentation, staging investigations order can differ. In an emergency presentation, CT abdomen is part of the diagnosis especially for bowel obstruction. If presentation is acute rectal bleeding, an urgent colonoscopy may be performed. For urgent suspected cancer pathway investigations, colonoscopy is usually the primary investigation followed by staging investigations including a thoraco-abdomino-pelvic CT to rule out the presence of metastases and tumour markers like CEA to monitor disease response / relapse later. (31) For staging in rectal cancer endorectal US and pelvic magnetic resonance imaging are usually performed. (26)

1.3.3. Pathological features

The predominant type is adenocarcinoma, classified as well, moderately or poorly differentiated.

Staging for colon cancer according to TNM system is presented in Table 5.

Category	Description
Tis	*Carcinoma in situ:* intraepithelial (within basement membrane) or invasion of lamina propria (intramucosal), no extension through muscularis mucosae into submucosa
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades beyond muscularis propria into subserosa or non-peritonealised pericolic/perirectal tissues
T4	Tumour directly invades other organs/structures and/or perforates visceral peritoneum
T4a	Perforates visceral peritoneum
T4b	Direct invasion into other organs or structures
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	One node positive
N1b	Two or three nodes positive
N1c	Tumour deposits in subserosa without regional node metastasis
N2	Metastasis in ≥4 regional lymph nodes
N2a	Four to six nodes positive
N2b	Seven or more nodes positive
M1	Distant metastasis
M1a	Metastasis to one organ

M1b	Metastasis to more than one organ or peritoneum
Resection Status	
R0	Tumour completely excised (no residual)
R1	Microscopic involvement of margin (<1 mm)
R2	Macroscopic residual tumour or gross margin involvement

Table 5. TNM Staging of Colorectal Cancer (7th Edition) – table adapted from the Textbook "Coloproctology" from ESCP *(31)*

Stage	Criteria
Stage I	pT1/T2 N0 M0
Stage II	pT3/T4 N0 M0
Stage III	Any pT, N1–2, M0
Stage IV	Any pT, any N, M1

Table 6. Stage Grouping for Colorectal Cancer from the Textbook "Coloproctology" from ESCP *(31)*

1.3.4. Management and surgical treatment

Treatment for colon cancer

For localised disease, non-invasive adenocarcinomas (pTis) are managed with endoscopic resection alone, while pT1 invasive cancers with high-risk histological features require surgical resection with lymphadenectomy. Infiltrative colon cancers are treated by wide segmental colectomy including en-bloc lymphadenectomy (≥12 nodes), being laparoscopic / minimal invasive colectomy preferred when expertise is available. Adjuvant therapy is decided based on the patients' risk. Stage II low-risk patients are observed; intermediate-risk patients receive fluoropyrimidine monotherapy; and high-

risk stage II or stage III patients benefit from combining chemotherapy with fluoropyrimidine and oxaliplatin, with CAPOX for 3 months or FOLFOX for 6 months depending on risk stratification and tolerance. (26,32)

Follow-up aims for early detection of recurrence, and usually include CEA monitoring and clinical review every 3–6 months for 3 years, then 6–12 monthly to the 5th year, with CT imaging in high-risk cases and colonoscopy at 1 year post-resection then in intervals of 3 to 5 years. Long-term care should address bowel dysfunction, stoma management, psychological wellbeing, and lifestyle modification to optimise survivorship outcomes. (32)

Treatment for rectal cancer

For early-stage cT1N0 lesions with favourable features, local excision may be sufficient, while total mesorectal excision (TME) remains the standard surgical approach for most cases, especially for mid and lower rectal tumours.

For stage II and III rectal cancers, neoadjuvant therapy is decided based on risk features. Short-course radiotherapy (SCRT) or long-course chemoradiotherapy (CRT) are used to downstage tumours, reduce local recurrence risk, and facilitate resection. Total neoadjuvant therapy (TNT), incorporating chemotherapy either before or after CRT/SCRT, is increasingly used in high-risk tumours to achieve better pathological response rates. Organ preservation strategies, including the “watch-and-wait” after clinical complete response to neoadjuvant therapy, are emerging for selected patients to avoid the morbidity of radical surgery while maintaining an oncological safety. (26,33)

Adjuvant chemotherapy may be offered based on pathological findings and prior treatment, although its benefit is less clear than in colon cancer. Long-term follow-up focuses on early detection of local regrowth and distant metastases, with structured surveillance involving clinical assessment, MRI, sigmoidoscopy, and CEA monitoring, during the first two years post-treatment. For survivors it is important to take into account other outcomes that can impact on the quality of life including bowel and urinary dysfunction, sexual health, psychosocial impacts, and lifestyle modification to optimise the recovery. (31,33)

1.4. Anastomotic leak definition

Anastomotic leakage (AL) is still one of the most feared complications in colorectal surgery. It is known to have an impact in the postoperative morbidity and mortality rates. (34,35)

AL can be defined according to Rahbari et al. proposal (36) “a defect of the intestinal wall at the anastomotic site leading to a communication between the intraluminal and extraluminal compartments”, also considering a pelvic abscess in the proximity of the anastomosis as AL. The International Study Group of Rectal cancer also presented a grading system to understand the impact of AL grades depending on the clinical management required.

- Grade A when no change in patients’ management was required
- Grade B if active therapeutic intervention was needed without surgical intervention
- Grade C when relaparotomy/laparoscopy was performed

This definition and severity grading has been validated by Kulu et al. (37) proving to be an easily applicable, simple and valid classification.

AL is present in different rates according to anatomic location of anastomosis ranging from 1% to 19%: ileocolic (1% to 8%); colocolic (2% to 3%); ileorectal (3% to 7%); colorectal or coloanal (5% to 19%). (3,4,5) In the Rectal Cancer Project of the Spanish Society of Surgeons, the rate of AL for rectal cancer surgery was 10%. (38,39)

Different factors have been reported in the literature associated to greater AL risk: male gender, preoperative comorbidities, high American Society of Anaesthesiologists grade (ASA), malnutrition, obesity, smoking, immunosuppression, neoadjuvant treatment, advanced tumour stage, low anastomoses, prolonged operative time, among other intraoperative conditions. (40–42)

In case of elderly population, there exist some controversial studies, most cohorts not finding significant association between age and AL. (43–46) For older patients above 75 years old some of the literature reports rates around 8-10% similarly. (47,48) However,

some have pointed a protective effect in age for AL presentation but being related to higher mortality for those older individuals affected. (46) Even, it has been suggested that frailty could be a predictor of severe postoperative complications, not being specifically assessed for anastomotic leak risk. (49)

A better understanding of the risk factors of anastomotic leak in older population undergoing colorectal cancer resections can help to develop preventive strategies and to improve the postoperative care. In terms of decision making in the colorectal cancer management, it is extremely relevant to adapt to expectations of surgical outcomes and to find out the true effect of morbidity in the long term.

1.5. Other surgical complications

1.5.1. CLASSIC classification for intraoperative complications

Intraoperative adverse events have been related to an increased risk of postoperative complication in surgery. (50) Using the Classification of Intraoperative Complications (CLASSIC) (51) can help to grade these events and report them in research studies.

Grade	Definition
Grade 0	No deviation from the ideal intraoperative course.
Grade I	Any deviation from the ideal intraoperative course without the need for any additional treatment or intervention.
Grade II	Any deviation from the ideal intraoperative course with the need for any additional treatment or intervention, but not life-threatening and not leading to permanent disability.
Grade III	Any deviation from the ideal intraoperative course with the need for any additional treatment or intervention, and life-threatening and/or leading to permanent disability.
Grade IV	Any deviation from the ideal intraoperative course resulting in death of the patient.

Table 7. CLASSIC – Classification of intraoperative complications by Rosenthal et al. *(51)*

1.5.2. Clavien Dindo Classification for postoperative complications

Clavien Dindo Classification was proposed initially in 2004 by Dindo et al. (52), and has become a widely used and validated system to audit postoperative complications in surgical research. (53) Grades from I to II, are usually considered minor complications, while grades from III to V are major complications involving intervention, ICU or the death of the patient.

Grade	Definition (examples listed in italics)
I	Any deviation from the normal postoperative course without the need for pharmacological (other than the "allowed therapeutic regimens"), surgical, endoscopic or radiological intervention. Allowed therapeutic regimens are: selected drugs (antiemetics, antipyretics, analgesics, diuretics and electrolyte replacement), physiotherapy and wound infections opened at the bedside but not treated with antibiotics.
II	Requiring pharmacological treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention *Examples: Therapeutic endoscopic therapy (do not include diagnostic procedures); interventional radiology procedure, return to theatre*
IV	Life-threatening complications requiring critical care management, neurological complications including brain haemorrhage and ischemic stroke (excluding TIA).
V	Death of a patient

Table 8. Clavien-Dindo classification for postoperative complications *(52)*

Justification

2. Justification

We are seeing a global change where population is ageing rapidly. It is known that colorectal cancer tends to affect in greater proportion to older patients, being the peak rate after 65-70 years old. Therefore, to face an increased population of elderly patients requiring surgical interventions for colorectal cancer we need to be prepared. Anastomotic leak (AL) is one of the most severe postoperative complications in colorectal surgery, associated with increased morbidity, prolonged hospitalisations, and higher mortality.

WHO has stated the urgency in carrying out high-quality research for better understanding of age related differences, the relation with other morbidities and the management of health conditions in older patients. At the same time developing strategies and interventions that could compensate the changes related to age can help us to improve our surgical outcomes.

Despite extensive research on AL risk factors in the general population, there is limited and conflicting evidence specifically focusing on the elderly. Current studies often do not stratify risks adequately for patients over 75, despite their different physiological status, comorbidities, and frailty profiles, all of which may influence surgical outcomes differently compared to younger patients. Furthermore, factors such as frailty remain underexplored or inconsistently evaluated in this subgroup, as historically elderly have been defined by chronological age.

Given the ageing demographic, it is crucial to identify specific predictors of AL in elderly patients to improve preoperative risk stratification, guide surgical decision-making and consent process while helping to tailor perioperative management strategies. This study will address this gap by systematically reviewing current evidence, analysing retrospective data from a dedicated large volume colorectal surgery unit, and surveying international surgical practices. Its findings will inform clinical pathways and potential strategies to reduce AL rates and postoperative complications in older adults undergoing colorectal cancer surgery, ultimately improving patient safety, outcomes, and healthcare resource utilisation.

Hypothesis

3. Hypothesis

We hypothesise that anastomotic leak rates in colorectal cancer surgery among patients older than 75 years are associated with specific factors, including patient comorbidities, physiological status, frailty, oncological stage, and surgical variables such as technique, urgency, and operative approach.

Furthermore, we hypothesise that anastomotic leaks in this population are associated with worse long-term outcomes, including higher postoperative morbidity and mortality.

Study aims

4. Study aims

Primary study aim:

To identify and assess specific factors associated with an increased risk of anastomotic leak in elderly patients (≥75 years) undergoing colorectal cancer surgery.

Secondary aims:

1. To evaluate the impact of anastomotic leak on early postoperative morbidity, as measured by Clavien-Dindo classification, and on 30-day mortality in this population.
2. To explore the long-term outcomes associated with anastomotic leak in elderly colorectal cancer patients.
3. To assess current surgical practices and approaches to colorectal anastomosis in elderly patients through an international survey of general and colorectal surgeons.

Material and methods

5. Material and methods

5.1. Study plan and research strategy

The study questions will be addressed by running different study approaches. These are summarised below in Figure 1. and further developed in this section regarding methodology.

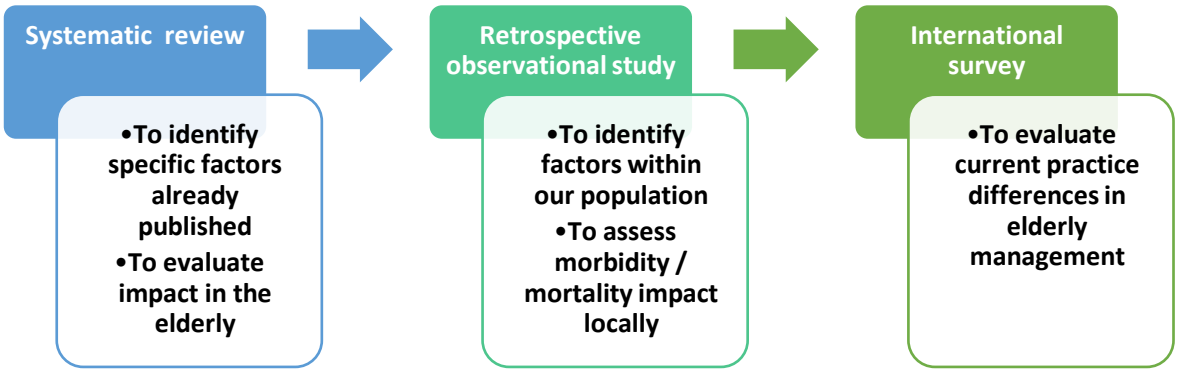


Figure 1. Research plan and study design process

With the systematic review, the aim was to identify factors already published and stated in the literature that can be later tested and screening in our population. We planned to perform after that a retrospective observational study using the prospective dataset of our colorectal surgery unit in a tertiary hospital. This should provide real data and the impact of AL in morbidity / mortality in our local setting. Finally, an international survey should help to evaluate different practices across the globe.

5.2. Systematic review and meta-analysis

A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (54) This systematic review was not registered in PROSPERO, as the registry primarily accepts reviews assessing the effects of interventions rather than those focusing on exposures or prognostic factors.

5.2.1. Search strategies

A systematic search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library up to July 2021.

The literature search was performed combining MeSH terms and keywords to identify studies on elderly patients undergoing colorectal surgery with anastomotic leaks in the context of colorectal cancer. The search strategy included terms for the elderly population ("elderly," "aged," "aged, 80 and over," "frail elderly," "frailty," "80 years," "90 years," "octogenarian," "nonagenarian"), anastomotic complications ("anastomotic leak," "anastomotic leakage," "anastomosis, surgical," "surgical anastomosis"), colorectal procedures ("colorectal surgery," "colon surgery," "rectal surgery," "colorectal resection"), and cancer ("oncological," "cancer").

5.2.2. Eligibility criteria

Studies evaluating the risk of AL according to age or in relation to specific risk factors in patients over 70 years were included. Only those including patients undergoing colorectal cancer surgery were considered. This can be under any approach and be elective or urgent setting. Studies including patients undergoing colorectal cancer without anastomosis (like pelvic exenteration) or benign procedures like stoma closure were excluded. Those without an accessible full-text were also excluded as those on a different language to English, Spanish or French.

The primary outcome was AL, with at least 30 days follow up. Secondary outcomes included postoperative morbidity defined by Clavien-Dindo classification and mortality.

Randomized Controlled Trials (RCTs), cohort studies, case-control studies and quasi-randomised studies were considered for inclusion.

5.2.3. Data extraction

Data regarding the characteristics of studies included, sample size, procedure performed, factors assessed, and population were extracted.

For the studies selected for inclusion, localisation of cancer (colon vs rectum), factor assessed, age cut-off an approach if assessed were included. From these, studies including comparable data, were selected for meta-analyses.

5.2.4. Statistical analysis

Analysis comparing AL risk on age groups when possible were performed. Complications according to Clavien-Dindo and mortality related to AL by age were also assessed separately.

Odds ratios (OR) with 95% confidence intervals (CI) were pooled when available from the original data. Mantel–Haenszel (M–H) method and random-effects models were employed for quantitative statistical analysis of dichotomous variables as intrinsic heterogeneity within the studies was explored by I^2 test and visual inspection of forest plots. Statistical analyses were performed using Review Manager (RevMan) software version 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020).

5.2.5. Risk of bias assessment

ROBINS-E was the tool used to evaluate the risk of bias for non-randomized studies assessing exposure effects. (55) Seven domains were covered including confounding, measurement of exposure, participant selection, post-exposure intervention, missing data, measurement of outcomes and selection of the reported result. After this an overall risk for each study included in the meta-analysis was given.

5.3. Retrospective analysis of tertiary hospital experience

This is a retrospective cohort study from a prospectively maintained database from the Colorectal Surgery unit of a single tertiary centre, Hospital Universitari Vall d'Hebron.
Elderly patients undergoing colorectal cancer surgery in our centre were consecutively included from January 2015 up to March 2019. Patients were followed up until 5 years from surgical procedure.
STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines were followed for the design and reporting of this study. (56)

5.3.1. Eligibility criteria

Patients younger than 75 years old at the time of the surgery were excluded. No maximum age limit was applied. Also, those patients undergoing colorectal cancer surgery but without an enteric anastomosis where not included. Procedures under any approach including open, laparoscopic and robotic surgery were included.

5.3.2. Dataset

Data regarding preoperative management, patient comorbidities, as well as intraoperative factors and approach were collected. Postoperative 30-day complications including anastomotic leak, mortality and length of stay were sought.
The variables included in this study for the preoperative period were demographic factors such as age and gender, but physical status assessments like ASA grade, the Clinical Frailty Scale (57), the Modified Frailty Index(21), and ECOG performance status (58) were also collected and/or calculated from medical records retrospectively.
POSSUM physiological score, POSSUM mortality and operative severity scores (22) were also captured. For comorbidities smoking status, BMI, history of previous abdominal surgery, presence of a pre-existing stoma, ischaemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, and immunosuppressive status were recorded. Preoperative albumin level when available, and oncological details as well as oncological stage, neoadjuvant and adjuvant therapy were collected. For intraoperative data urgency of the operation, surgical approach, primary operation performed, anastomosis creation and type (mechanical vs manual, intracorporeal vs extracorporeal,

end to side vs side to side vs end to end), stoma formation, documented air leak or ICG perfusion test, operative duration, intraoperative complications using CLASSIC score (50) and whether intraoperative drains were used were included in the dataset. Postoperative outcomes recorded contained length of hospital stay, 30-day readmission, Clavien-Dindo complication grading (59), anastomotic leak (AL) and its grading defined by Rahbari et al (36), other 30-day complications, and postoperative inflammatory markers such as CRP on the third and fourth postoperative days, and PCT when available. Postoperative serum albumin, and mortality was evaluated at 30 days, 90 days, 1 year, and 5 years.

A complete list of variables collected can be found in the *Study data collection form* included in Appendix A as well as the scores used in the data collection.

5.3.3. Study aims and outcome measures

The main aim was to assess different factors related to AL in colorectal cancer anastomosis in elderly patients over 75 years.

As primary outcome measure, AL diagnosed in the postoperative period whether this was managed conservatively or surgically. The definition and the grading by The International Study Group of the Rectal Cancer and Rahbari et al. was used. (36)

In the unit, there is an existing protocol for proactively diagnose early anastomotic leaks which includes obtaining CRP levels for all patients on the 3rd postoperative day. If CRP is over 140 mg/L, then 4th postoperative day CRP and PCT were evaluated. If at 4th day CRP was over 125 and PCT was over 0.4 ng/mL, then a CT scan with intravenous contrast was performed adding rectal contrast if a rectal or low sigmoid anastomosis present.

As secondary outcome measures, postoperative morbidity based in Clavien-Dindo classification at 30 days and mortality at 30 days, 90 days, 1 year and 5 years were taken into consideration.

5.3.4. Statistical analysis

All datasets, analytical code, and results were electronically stored and archived at the Applied Statistics Service of the University Autonomous of Barcelona. Descriptive

statistics were used to summarise the data. For quantitative variables were reported using the number of observations, rates, mean, standard deviation, median, interquartile range, minimum, maximum, and number of missing values; for qualitative variables were presented as absolute and relative frequencies. Bivariate analysis was conducted to explore associations with the outcome of anastomotic leak (AL) and mortality. For quantitative variables, the Shapiro-Wilk test was used to assess normality. Depending on the distribution, comparisons were made using either the parametric t-test or the non-parametric Wilcoxon test. Associations between variables and AL were assessed using logistic regression models, with AL as the dependent variable. For each model, p-values and odds ratios (OR) with 95% confidence intervals (CI) were reported for pair comparisons between categories. Statistical significance was set at a p-value < 0.05. Survival analysis was performed using Kaplan–Meier curves with log-rank tests to compare groups, and Cox proportional hazards models to identify independent predictors of survival. Results were reported as hazard ratios (HR) with 95% confidence intervals, using a significance level of p – value < 0.05.

Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Multivariable logistic regression and survival analyses were performed using IBM SPSS Statistics version 20 and graphical representation of OR forest plots were generated using RStudio (R version 4.5.1) with the ggplot2 package on the Windows x86_64 platform.

5.4. International survey on current practices

5.4.1. Survey Design and Content

An international, cross-sectional online survey was designed to assess current practices in the management of elderly patients undergoing colorectal cancer surgery, with a particular focus on anastomotic decisions. The survey included 27 questions, including 14 clinical scenarios that explored variations in surgical approach, anastomotic technique, and perioperative management for patients aged 75 years and older. The remaining questions addressed demographic information and institutional characteristics of the participants.

5.4.2. Survey Distribution

The survey was distributed internationally between September 2022 and June 2023 via multiple dissemination channels, including social media platforms like Twitter/ WhatsApp and mailing lists from international colorectal surgical networks were targeted, including the European Society of Coloproctology (ESCP) WhatsApp groups. Further participation was promoted by adding a QR to the link in other presentations from this research study during national and international coloproctology meetings (ESCP 2022 in Dublin and AECP 2023 in Madrid).
Participation was voluntary and responses were anonymous.

5.4.3. Survey Content

The full survey items and clinical scenarios are provided in Appendix B. For distribution the survey was provided in a Google Form © with a shareable link. A spreadsheet with the replies was obtained from the same platform.

5.4.4. Data Analysis

A descriptive analysis of the data was carried out. For the categoric variables, rates and percentages were included. Data was analysed with SPSS version 20.0. Results are presented as frequencies and percentages to summarise current practice patterns

across respondents. Response rate could not be estimated due to the nature of the survey distribution.

Report of results follows the CHERRIES checklist for internet E-Surveys. (60)

5.5. Ethical approval

Local Ethics Committee approval was obtained prior the start of the research study (**PR(AG)549/2020)**. For the retrospective review of data, the requirement of informed consent was waived. For the international survey, anonymity of participants was agreed, and consent was requested prior the start of the survey for responses to be analysed and included.

Complete approval document from Hospital Vall d'Hebron CEIC can be found in Appendix C.

This study was conducted in accordance with the Declaration of Helsinki.

Results

6. Results

6.1. Results from the systematic review and meta-analysis

A total of 59 studies were included in the review of factors related to AL in elderly. Literature search and selection process is presented in the PRISMA flowchart of study inclusion in Figure 2.

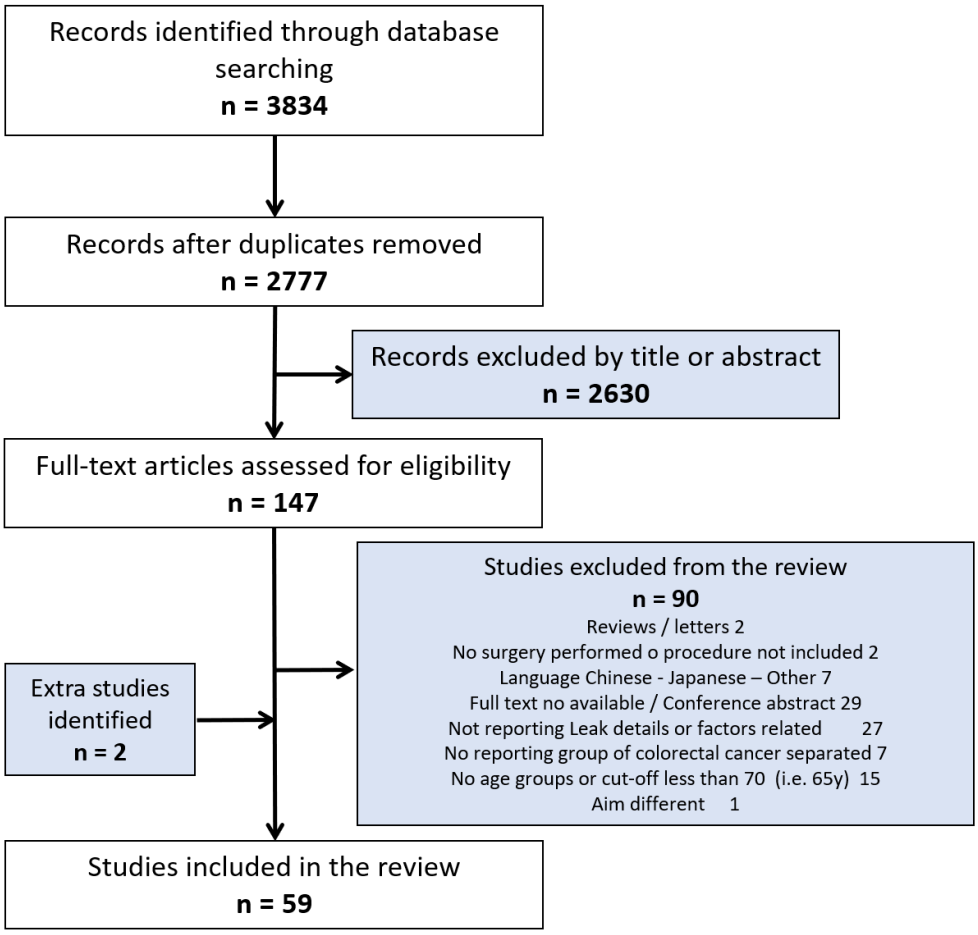


Figure 2. PRISMA flowchart of study inclusion

In table 9 the study characteristics for the 59 studies identified and if other factors apart from age are assessed are presented. Factors associated with AL in these studies included frailty, sarcopenia, emergency surgery, and low adherence to ERAS protocols.

Study (author)	Year	Country	N	Surgery Colon / Rectum	Age cut-off	Approach	Frailty	Sarcopenia	Emergency	ERAS	Mortality for AL	Other
Akiyoshi (61)	2009	Japan	44	R	75	Laparoscopic / Open						
Antonsen (62)	1987	Denmark	178	R	70	Open						
Aquina (63)	2017	USA	24426	C	75	Laparoscopic / Open						
Arenal (64)	1999	Spain	316	CR	70	Open						
Arimoto (65)	2017	Japan	289	CR	75	Laparoscopic						
Artiles-Armas (66)	2021	Spain	149	CR	70	Laparoscopic / Open	X					
Baré (67)	2020	Spain	1976	C	70/80/85	Laparoscopic / Open						
Barina (68)	2020	Italy	47704	CR	65 / 74 / 85	Laparoscopic						Comparison of colon vs rectum
Barlehner (69)	2003	Germany	179	R	70	Laparoscopic						
Bouassida (70)	2015	Tunisia	124	CR	70 /85	NC			X			
Chern (71)	2018	China	1133	CR	75	Laparoscopic / Open			X			
Chung (72)	2021	Taiwan	40451	CR	80	Laparoscopic / Open						Comparison of colon vs rectum
De Simone (73)	2017	Italy	19	CR	90	NC			X			
Denet (74)	2017	France	507	C	65/75/>85	Laparoscopic						
Depalma (75)	2020	Italy	162	CR	80	Laparoscopic				X		
Duraes (76)	2016	USA	2485	CR	65/80	Laparoscopic / Open						
Feng (77)	2006	China	172	CR	70	Laparoscopic / Open						
Fiscon (78)	2010	Italy	100	CR	75	Laparoscopic						
Gonzalez-Ayora (79)	2016	Spain	188	CR	70	Laparoscopic				X		
Govaert (80)	2016	Netherlands	9913	CR	85	Laparoscopic / Open						
Inoue (81)	2019	Japan	493	CR	80	Laparoscopic / Open						
Issa (82)	2011	Israel	93	CR	80	Laparoscopic / Open						
Jeong (83)	2013	Korea	824	CR	75	Laparoscopic / Open						
Kitahara (84)	2019	Japan	20	CR	85	Laparoscopic						Comparison of colon vs rectum
Koh (85)	2015	Singapore	36	CR	80	Laparoscopic / Open						
Landi (86)	2016	Spain	408	R	80	Laparoscopic / Open						
Lehmann (47)	2021	Germany	18 959	CR	80	Laparoscopic / Open						
Li (87)	2021	China	326	R	70 (75)	Laparoscopic / Open						TNM, Type anastomosis, QT/RT
Manceau (88)	2017	France	446	R	75	Laparoscopic						
Margadant (89)	2016	Netherlands	373	CR	70	Laparoscopic / Open		X				
Miyasaka (90)	2014	Japan	196	CR	70	Laparoscopic / Open						
Moon (91)	2016	Korea	280	CR	80	Laparoscopic / Open						
Mukai (92)	2014	Japan	44	CR	85	Laparoscopic / Open						
Nakamura (93)	2014	Japan	80	CR	85	Laparoscopic / Open						

Nishikawa (94)	2016	Japan	150	CR	80	Laparoscopic / Open						
Okabe (49)	2018	Japan	269	CR	65	Laparoscopic / Open	X	X				
Okamura (95)	2016	Japan	1554	CR	80	Laparoscopic / Open						
Okkabaz (96)	2019	Turkey	156	CR	70	Laparoscopic / Open / CONVERSION						
Pirrera (97)	2016	Italy	1397	CR	80	NC					X	
Roque-Castellano(98)	2020	Spain	40	CR	90	NC						
Rossi (99)	2020	UK	293	CR	80	Laparoscopic / Open						
Sakamoto (100)	2020	Japan	148	CR	75	Laparoscopic / Open						
Scharfenberg (101)	2007	Germany	74	CR	70	Laparoscopic / Open						
Schiffmann (102)	2008	Germany	517	CR	75	Laparoscopic / Open						
Shiga (103)	2017	Japan	506	CR	80	Laparoscopic / Open						
Shigeta (104)	2016	Japan	107	CR	80	Laparoscopic / Open						
Sotirova (105)	2020	Greece	78	CR	75	Laparoscopic / Open						
Souwer (106)	2020	Netherlands	174	CR	70	Laparoscopic / Open		X				
Tabbakh (107)	2016	uk	67	CR	80	Laparoscopic / Open						
Tarazona-Santabalbina (108)	2019	Spain	310	CR	70	Laparoscopic / Open						Estancia en UCI
Tejedor (109)	2018	Spain	312	CR	70	Laparoscopic / Open				X		
Tokuhara (110)	2016	Japan	208	CR	75	Laparoscopic / Open						
Van Schaik (111)	2010	Netherlands	207	CR	75	Laparoscopic / Open						
Webster (112)	2020	UK	341	CR	75	Laparoscopic / Open			X			
Wydra (113)	2013	Polonia	440	CR	75	Laparoscopic / Open						
Yamamoto (114)	2017	Japan	601	CR	80	Laparoscopic / Open						
Zaimi (46)	2018	Netherlands	45488	CR	70	Laparoscopic / Open / CONVERSION					X	Stoma, reintervention
Zeng (115)	2015	China	294	CR	70	Laparoscopic / Open						
Zhou (116)	2019	China	288	R	80	Laparoscopic / Open						Operative time, Firings stapler, transfusion, ileostomy

Table 9. Study characteristics from the systematic review

For a total of 15 studies with similar elderly definition and outcome it was possible to perform a meta-analysis to determine the primary and secondary outcome measures.

Study	Year	Country	N	Groups compared	AL in Elderly		AL in no elderly	
					N	%	N	%
Denet (74)	2017	France	507	Complications, oncological outcomes	13	7.78	19	5.6
Fiscon (78)	2010	Italy	100	Complications	1	0.01	1	0.01
Jeong (83)	2017	South Korea	824	Complications, mortality	2	2.2	20	2.4
Lehmann (117)	2017	Germany	18959	Complications, mortality	3169	8.6	15790	9.7
Li (87)	2021	China	326	Anastomotic leak	24	18.18	39	20
Manceau (118)	2017	France	446	Postoperative morbidity	8	13	54	14.75
Pirrera (97)	2016	Italy	80	Complications, mortality	18	7.5	49	5.1
Sakamoto (100)	2020	Japan	148	Postoperative morbidity	9	5.5	20	5.5
Schiffmann (102)	2008	Germany	517	Complications, mortality, oncological outcome	6	5	31	9.56
Shiga (103)	2017	Japan	506	Complications	1	1.5	11	10
Tokuhara (110)	2016	Japan	208	Complications, oncological outcome	0	0	2	3.77
Van Schaik (111)	2010	Netherlands	207	Complications	4	5	7	5
Webster (112)	2020	UK	341	Complications, mortality	6	7	4	4
Wydra (113)	2013	Poland	440	Complications, mortality	2	1.8	8	2.4
Zaimi (46)	2018	Netherlands	45488	Anastomotic leak	319	4.8	2181	5.6

Table 10. Study characteristics and AL rates in between the presented groups for meta-analysis

For patients aged over or equal to 75 years, age was associated with an increased AL risk (OR 1.19; 95% CI 1.12–1.27). Forest plot is presented in Figure 3.

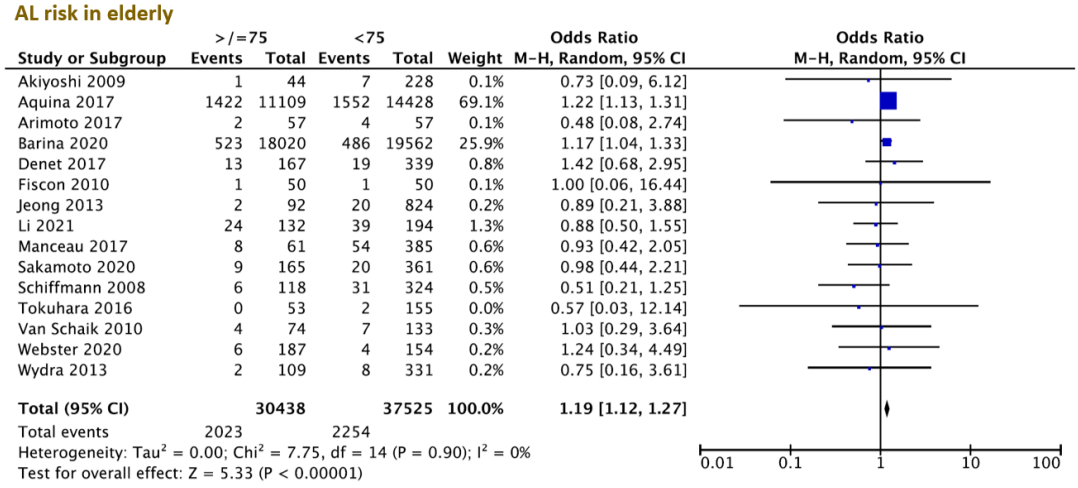


Figure 3. AL risk for patients below or over 75 years old, forest plot

Surgical approach (laparoscopic vs open) did not influence AL risk (OR 1.32; 95% CI 0.82–2.14). An increased risk of major Clavien-Dindo complications was observed (OR 1.12; 95% CI 1.01–1.25), as well as dehiscence-related mortality (OR 3.53; 95% CI 2.85–4.36) in the elderly group compared to younger aged, presented in forest plots in figure 4 and 5 respectively.

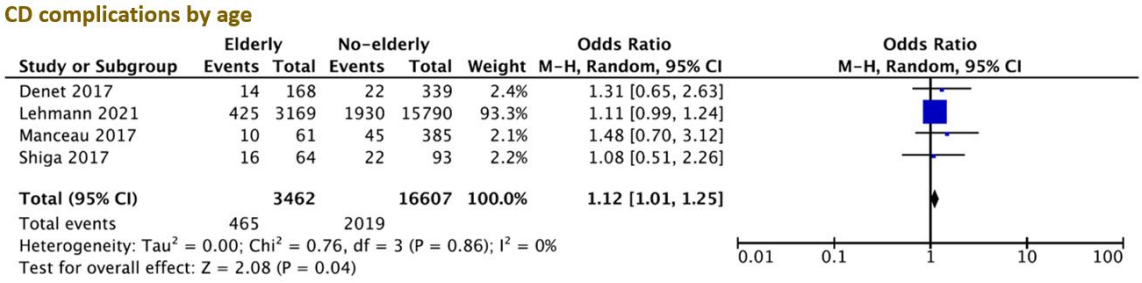


Figure 4. CD major complications in elderly vs no-elderly, forest plot

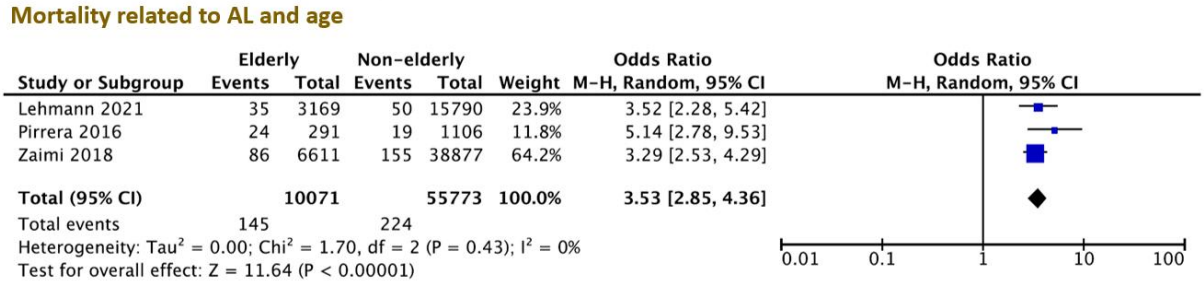


Figure 5. Mortality in elderly vs no-elderly, forest plot

Bias and quality assessment with ROBINS tool

ROBINS-E tool (55) was used to assess the risk of bias for the studies included in the meta-analysis. Across the 15 studies, confounding was a common limitation, with moderate risk in studies adjusting for age and comorbidity but not other factors like frailty, and serious risk in studies lacking any multivariable adjustment or clear definitions of AL. Measurement of exposure, selection of participants, post-exposure interventions, missing data and measurement of outcomes generally had low risk. Selection of reported results showed moderate risk in several studies due to incomplete reporting of secondary outcomes or due to unclear pre-specification. A complete table for each study can be found in Table 11.

Study	Confounding	Measurement of exposure	Selection of participants	Post-exposure interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall risk of bias
Denet et al. 2017	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Fiscon et al. 2010	Serious	Low	Moderate	Low	Low	Low	Moderate	Serious
Jeong et al. 2017	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Lehmann et al. 2021	Serious	Low	Moderate	Low	Low	Low	Moderate	Serious
Li et al. 2021	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Manceau et al. 2017	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Pirrera et al. 2016	Serious	Low	Moderate	Low	Low	Low	Moderate	Serious
Sakamoto et al. 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Schiffmann et al. 2008	Serious	Low	Moderate	Low	Low	Low	Moderate	Serious
Shiga et al. 2017	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Tokuhara et al. 2016	Serious	Low	Moderate	Low	Low	Low	Moderate	Serious
Van Schaik et. Al 2010	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Webster et al. 2020	Serious	Low	Moderate	Low	Low	Low	Moderate	Serious
Wydra et al. 2013	Serious	Low	Moderate	Low	Low	Low	Moderate	Serious
Zaimi et al. 2018	Moderate	Low	Low	Low	Low	Low	Low	Moderate

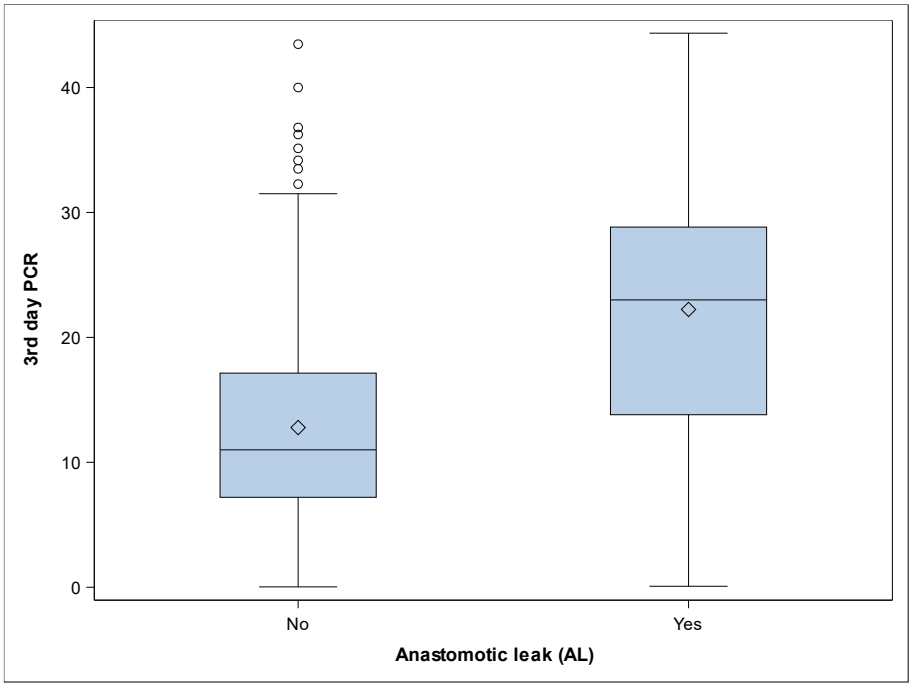
Table 11. Risk assessment with ROBINS-E

6.2. Results from the retrospective analysis of tertiary hospital experience

A total of 416 elderly patients undergoing colorectal cancer surgery were included in the study. The mean age was 81.3 ± 4.7 years, and 234 (56%) were male. Most patients (94.53%) had ASA II-III grade. The prevalence of comorbidities included history of ischemic heart disease (10.82%) and congestive heart failure (10.58%). Mean preoperative albumin was 3.67 ± 0.606 g/dL and mean haemoglobin of 11.764 ± 1.958 g/dL. Regarding functional status and frailty, the mean mFI was 0.17 ± 0.137, and 10.1% had a Clinical Frailty Scale ≥5. Regarding oncologic staging and therapeutic strategies, most patients presented with stage II or III colorectal cancer. A total of 59 (14%) had a tumour located in the rectum. 40 patients (9.62%) received neoadjuvant therapy, which in 72% corresponded to combined chemotherapy and radiotherapy. 105 patients received also adjuvant chemotherapy. Most of the procedures were elective 398 (95.6%) and performed via minimally invasive approaches as laparoscopic 293 (70.43%) or robotic 49 (11.78%). Anastomotic leak occurred in 51 patients (12.26%), which following the Rahbari et al. classification (36) distributed as Grade A: 9 patients (2.16%), Grade B: 14 patients (3.37%), and Grade C: 28 patients (6.73%).

Risk Factors for Anastomotic Leak

Anastomotic leak was evaluated for risk factors associated with it. In the univariable analysis, higher ASA grade (p = 0.0255), history of ischemic heart disease (p = 0.010), higher CR-POSSUM physiological score (p = 0.0133) were identified as significantly associated with leak. A complete list of the preoperative variables assessed can be found in Table 12. Frailty was a significant risk factor, with Clinical Frailty Scale ≥5 (p = 0.008) and ECOG ≥2 (p = 0.007) demonstrating higher leak rates. No differences were found when comparing oncological characteristics, Table 13 or intraoperative characteristics, Table 14 at univariable level. In the multivariable logistic regression, Table 16 and Figure 7, preoperative albumin <3 g/dL (OR 7.70, 95% CI 1.66–35.73, p = 0.009) and high CRP on postoperative day 3 (OR 1.14, 95% CI 1.078-1.201, p < 0.001) were identified as anastomotic leak significant associated factors. Intraoperative drain placement was significant in the multivariable analysis as protective factor (OR 0.34, p = 0.040).



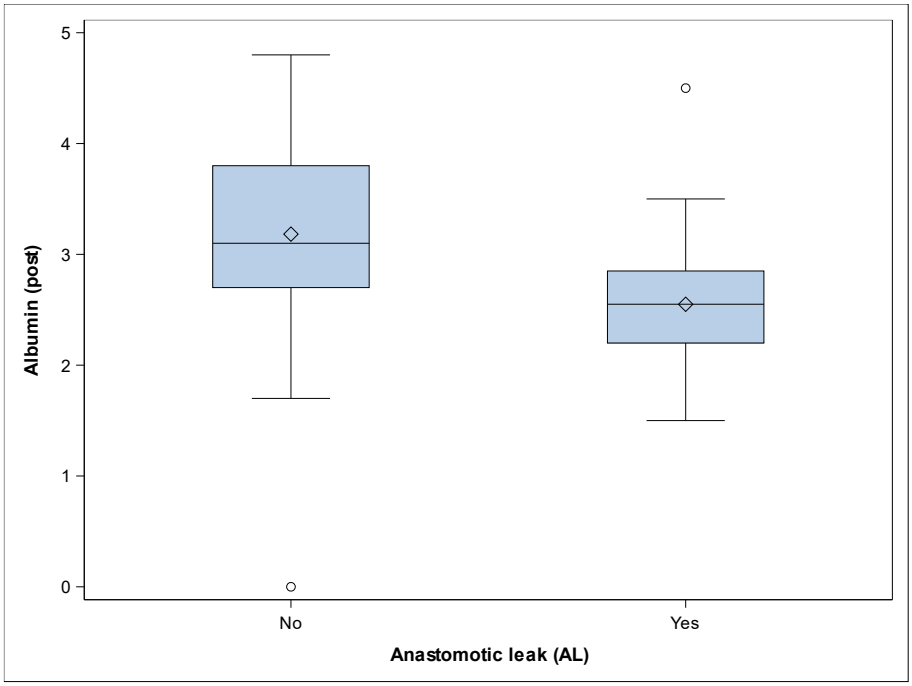


Figure 6. Box plot for analytic values statistically significant in the univariable analysis

Variable	Levels	Leak *(n, %) or (mean, SD)*	No Leak *(n, %) or (mean, SD)*	Missing values	p-value
Age (years)		82.16 (± 4.56)	81.23 (± 4.73)	0	p = 0.124
Gender	Male	33 (14.10%)	201 (85.90%)	0	p = 0.196
	Female	18 (9.89%)	164 (90.11%)	0	
ASA	I	0 (0%)	6 (100%)	0	**p = 0.0255**
	II	22 (11.64%)	167 (88.36%)	0	
	III	23 (11.27%)	181 (88.73%)	0	
	IV	6 (35.29%)	11 (64.71%)	0	
Smoker	Yes	5 (15.15%)	28 (84.85%)	0	p = 0.1313
	Ex-smoker	20 (16.95%)	98 (83.05%)	0	
	No	26 (9.81%)	239 (90.19%)	0	
BMI		27.24 (±4.32)	26.92 (±3.95)	68	p = 0.940
Previous Abdo. Surgery	Yes	20 (11.83%)	149 (88.17%)	0	p = 0. 827
	No	31 (12.55%)	216 (87.45%)	0	
History of IHD	Yes	11 (24.44%)	34 (75.56%)	0	**p = 0.010**
	No	40 (10.78%)	331 (89.22%)	0	
History of CHD	Yes	9 (20.45%)	35 (79.55%)	0	p = 0.0848
	No	42 (11.29%)	330 (88.71%)	0	
Diabetes Mellitus	Yes	13 (10.57%)	110 (89.43%)	0	p = 0.496
	No	38 (12.97%)	225 (87.03%)	0	
Immuno. treatment	Yes	1 (14.29%)	6 (85.71%)	0	p = 0.869
	No	50 (12.22%)	359 (87.78%)	0	
Preop. Albumin (g/dL)		3.60 (± 0.58)	3.68 (±0.61)	42	p= 0.202
Preop. haemoglobin		11.55 (±2.26)	11.79 (±1.91)	1	p= 0.40
CR-POSSUM Physiological Score		12.39 (± 2.19)	11.50 (± 2.21)	1	**p = 0.0133**
CR-POSSUM Mortality		10.53 (±15.32)	8.85 (± 22.13)	1	**p = 0.0339**
CR-POSSUM		7.35 (± 0.96)	7.48 (± 1.40)	1	p = 0.832
Operative Severity Score					
Clinical Frailty Scale	1-3	31 (9.84%)	284 (90.16%)	0	**p = 0.008**
	4	9 (15.25%)	50 (84.75%)	0	
	≥5	11 (26.19%)	31 (73.81%)	0	
Modified Frailty Index	Yes	0.21 (± 0.18)	0.16 (± 0.13)	0	p = 0.152
Urgency	Elective	47 (11.81%)	351 (88.19 %)	0	p = 0.1973
	Urgent	4 (22.22%)	14 (77.78%)	0	

Table 12. Preoperative characteristics, comorbidities, functional status and oncological stage of patients with anastomotic leak

Variable	Levels	Leak *(n, %) or (mean, SD)*	No Leak *(n, %) or (mean, SD)*	Missing values	p-value
Oncological T- staging	TiS	3 (9.67%)	28 (90.32%)	0	P = 0.7044
	T1	1 (3.57%)	27 (96.43%)	0	
	T2	12 (15.58%)	65 (84.42%)	0	
	T3	25 (12.38%)	177 (87.62%)	0	
	T4	10 (12.82%)	68 (87.18%)	0	
Oncological N- staging	N0	32 (12.40%)	226 (87.60%)	0	P = 0.6915
	N1	12 (10.62%)	101 (89.38%)	0	
	N2	7 (15.56%)	38 (84.44%)	0	
Oncological M- staging	M0	48 (12.21%)	345 (87.79%)	0	P = 0.9061
	M1	3 (13.04%)	20 (13.04%)	0	
Neoadjuvant treatment	Yes	4 (10%)	36 (90%)	0	P = 0.647
	No	47 (12.50%)	329 (87.50%)	0	
Adjuvant treatment	Yes	9 (8.41%)	98 (91.59%)	0	P = 0.1631
	No	42 (13.59%)	267 (86.41%)	0	
ECOG ≥2	0-1	41 (10.8%)	339 (89.2%)	0	**P= 0.007**
	≥2	10 (27.8%)	26 (72.2%)	0	
Cancer diagnosis location	Colon	45 (26%)	312 (87.4%)	0	P = 0.597
	Rectum	6 (10.2%)	53 (89.8%)	0	

Table 13. Oncological characteristics

Variable	Levels	Leak *(n, %) or (mean, SD)*	No Leak *(n, %) or (mean, SD)*	Missing values	p-value
Minimally Invasive Approach	Laparoscopic	32 (10.92%)	261 (89.08%)	0	p = 0.3359
	Laparoscopic converted to open	2 (10.53%)	17 (89.47%)	0	
	Open	10 (18.87%)	43 (81.13%)	0	
	Robotic	6 (12.24%)	43 (87.76%)	0	
	Robotic converted to open	1 (50%)	1 (50%)	0	
Anastomosis technique	Manual	17 (10.56%)	144 (89.44%)	0	p = 0.4018
	Mechanical	34 (13.33%)	221 (86.67%)	0	
Site of anastomosis formation	Extracorporeal	25 (11.85%)	186 (88.15%)	0	p = 0.7953
	Intracorporeal	26 (12.68%)	25 (11.85%)	0	
Anastomosis configuration	End to End	21 (13.91%)	130 (86.09%)	0	p = 0.6355
	End to Side	3 (13.04%)	20 (86.96%)	0	
	Side to End	3 (20%)	12 (80%)	0	
	Side to Side	23 (10.65%)	193 (89.35%)	0	
Stoma Formation	No	47 (12.5%)	329 (87.5%)	0	p = 0.4354
	Yes	4 (10%)	36 (90%)		
Intraoperative complications	No	31 (10.30%)	270 (89.70%)	0	p = 0.0510
	Yes	20 (17.39%)	95 (82.61%)		
Duration of procedure (min)		225.69 (± 70.66)	215.22 (±62.65)	1	p = 0.3026
Intraoperative Drain	No	26 (10.08%)	232 (89.92%)	0	p = 0.1564
	Yes	23 (14.74%)	133 (85.26%)		

Table 14. Intraoperative characteristics

Variable	Levels	Leak *(n, %) or (mean, SD)*	No Leak *(n, %) or (mean, SD)*	Missing values	p-value
30-day major complications – CD ≥ 3	No	16 (4.46%)	343 (95.54%)	0	p < 0.0001
	Yes	35 (61.40%)	22 (38.60%)	0	
3rd POD CRP		22.24 (± 10.69)	12.78 (±8.13)	118	p < 0.0001
Postoperative Albumin (g/dL)		2.55 (± 0.55)	3.18 (± 0.72)	44	p < 0.0001
Readmission	No	47 (12.40%)	332 (87.60%)	0	p = 0.7785
	Yes	4 (10.81%)	33 (89.19%)		
LOS (days)		26.80 (± 16.56)	9.15 (±11.91)	0	p < 0.0001
30-day Mortality	No	42 (10.50%)	358 (89.50%)	0	p < 0.0001
	Yes	9 (56.25%)	7 (43.75%)	0	
Discharge to Rehab centre or Home hospitalisation	No	32 (8.8%)	332 (91.2%)	0	p < 0.0001
	Yes	19 (36.5%)	33 (63.5%)		
5- year Mortality	No	18 (6.95%)	241 (93.05%)	9	p < 0.0001
	Yes	32 (21.62%)	116 (78.38%)		
5-year cancer related mortality	No	40 (9.6%)	312 (75%)	4	p = 0.237
	Yes	11 (2.6%)	49 (11.8%)		

Table 15. Postoperative outcomes

Clinical Impact of Anastomotic Leak

Anastomotic leak was associated with significantly higher rates of major complications Clavien-Dindo ≥3 (p <0.0001), and an increased 30-day and 5 years mortality (p <0.0001). In the postoperative period hypoalbuminemia seems to be significantly associated with leak 2.55 ± 0.55 vs 3.18 ± 0.72, see Table 15 and figure 6. Some of the important factors identified to correlate with anastomotic leak in the univariable and multivariable analysis were length of hospital stay (OR 1.06 per day, p < 0.001), and discharge to a rehabilitation / recovery centre or "hospital-at-home" discharge (OR 4.57, p = 0.011).

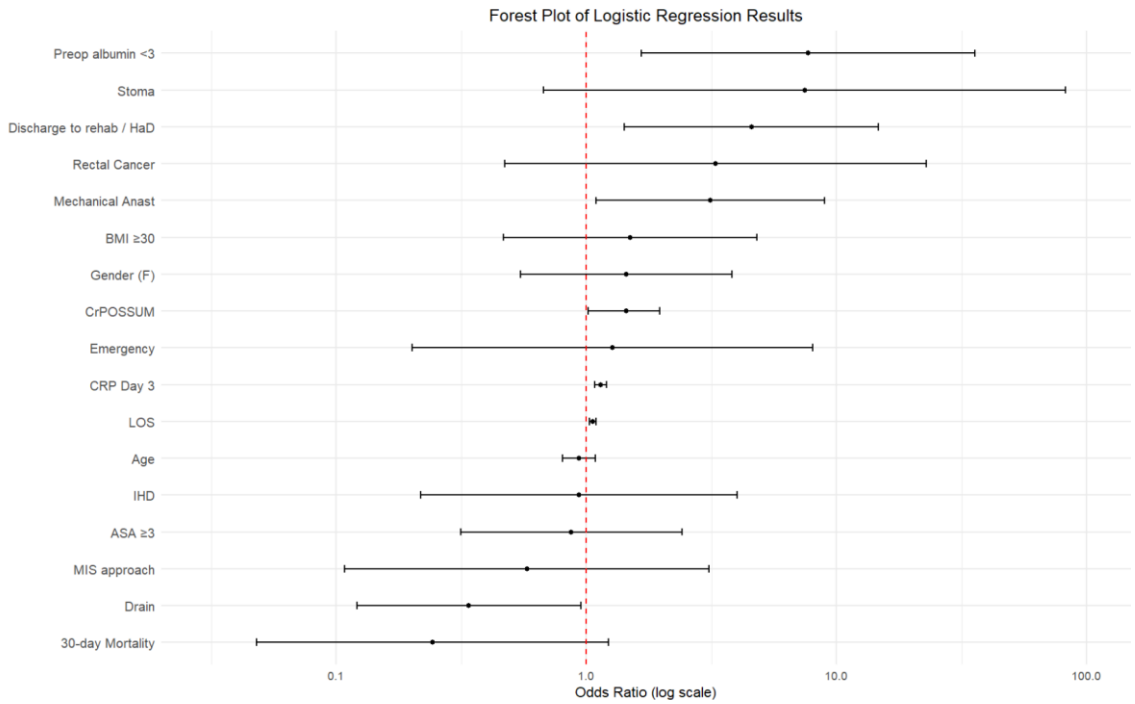


Figure 7. Forest plot of multivariable logistic regression on factors for anastomotic leak

Although CFS was significant in univariable analysis, it did not retain independent significance in the multivariable models. This may be due to collinearity with other patient risk factors like age and physiological status. Additionally, exclusion of CFS

improved model sensitivity, maximising detection of anastomotic leaks. Therefore, CFS was excluded from the final model.

In this study, mechanical anastomosis was not significant in univariable analysis but became significant in one of the multivariable models (OR 3.13, 95% CI 1.09–8.95, p = 0.033). This suggests that adjustment for confounding variables revealed an independent association. However, its lack of significance in alternative multivariable models indicates that the finding is sensitive to model specification and may be influenced by collinearity or sample variability. Therefore, results for this variable should be interpreted with caution.

Variable	OR	IC 95% Lower	IC 95% Upper	p - value
CrPOSSUM	1.441	1.015	1.961	p = 0.40
Age	0.936	0.805	1.089	p = 0.392
Gender (Female)	1.443	0.545	3.823	p = 0.460
ASA ≥3	0.871	0.314	2.413	p = 0.790
IHD	0.934	0.218	3.999	p = 0.927
BMI ≥30	1.495	0.465	4.801	p = 0.500
Preop albumin <3	7.701	1.660	35.728	**p = 0.009**
Rectal Cancer	3.287	0.473	22.844	p = 0.229
Emergency	1.270	0.201	8.010	p = 0.799
MIS approach	0.579	0.108	3.089	p = 0.522
Mechanical Anast	3.129	1.094	8.947	**p = 0.033**
Stoma	7.445	0.673	82.352	p = 0.102
Drain	0.339	0.121	0.953	**p = 0.040**
CRP Day 3	1.138	1.078	1.201	**p < 0.0001**
LOS	1.061	1.031	1.091	**p < 0.0001**
Discharge to rehab / HaD	4.565	1.421	14.667	**p = 0.011**
30-day Mortality	0.243	0.048	1.225	p = 0.087

Table 16. Multivariable logistic regression analysis for factors related to anastomotic leak

Long-Term Mortality Analysis

The Kaplan-Meier curve, Figure 8 shows a statistically significant difference in survival between patients who experienced an anastomotic leak (AL) and those who did not (Log-Rank test: $\chi^2 = 14.493$, df = 1, $p < 0.001$) in a follow-up of 5 years.

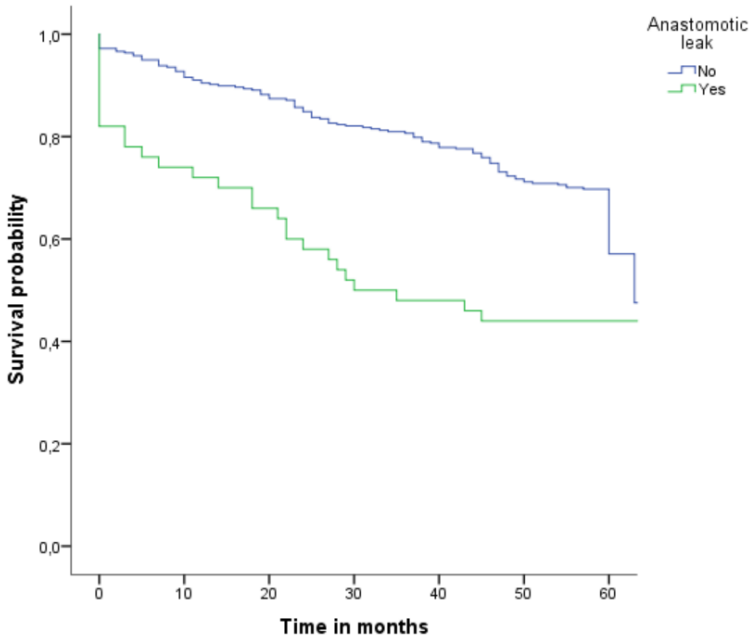


Figure 8. Kaplan Meier overall survival leak vs no leak (p < 0.0001)

No significant association was found between mortality related to disseminated / recurrent oncological disease and anastomotic leak (p = 0.237) in the univariable analysis or multivariable.

Survival analysis using Cox regression demonstrated that emergency surgery (HR 0.268, p < 0.001), worse ECOG performance status (HR 1.665, p = 0.001), and higher Clinical Frailty Scale scores (HR 1.215, p = 0.01) were independently associated with increased mortality. Oncological stage was also significant overall (p = 0.02). Anastomotic leak showed a trend towards increased mortality (HR 1.543, p = 0.05).

Variable	HR (Exp(B))	p-value
Age	1.032	0.18
IHD	0.876	0.60
Physiology Score	1.000	0.99
Oncological Stage (overall)	-	**0.02**
Diagnosis	1.438	0.21
Urgency	0.268	**< 0.001**
Albumin cat (1)	1.193	0.31
Albumin cat (2)	0.913	0.51
ECOG	1.665	**< 0.001**
AL	1.543	**0.05**
Clinical Frailty Scale	1.215	**0.02**
Modified Frailty Index	1.016	0.21

Table 17. Multivariable Cox Regression Results

6.3. Results from the international survey on current practices

Participation

A total of 208 responses were obtained from surgeons from 25 different countries. 1 response was deleted as missing consent for sharing the data. The origin of most of responders were Spain 32% (67), Italy 11.59% (24) and United Kingdom 7.7% (16). Full participation according to country can be seen in Figure 9.

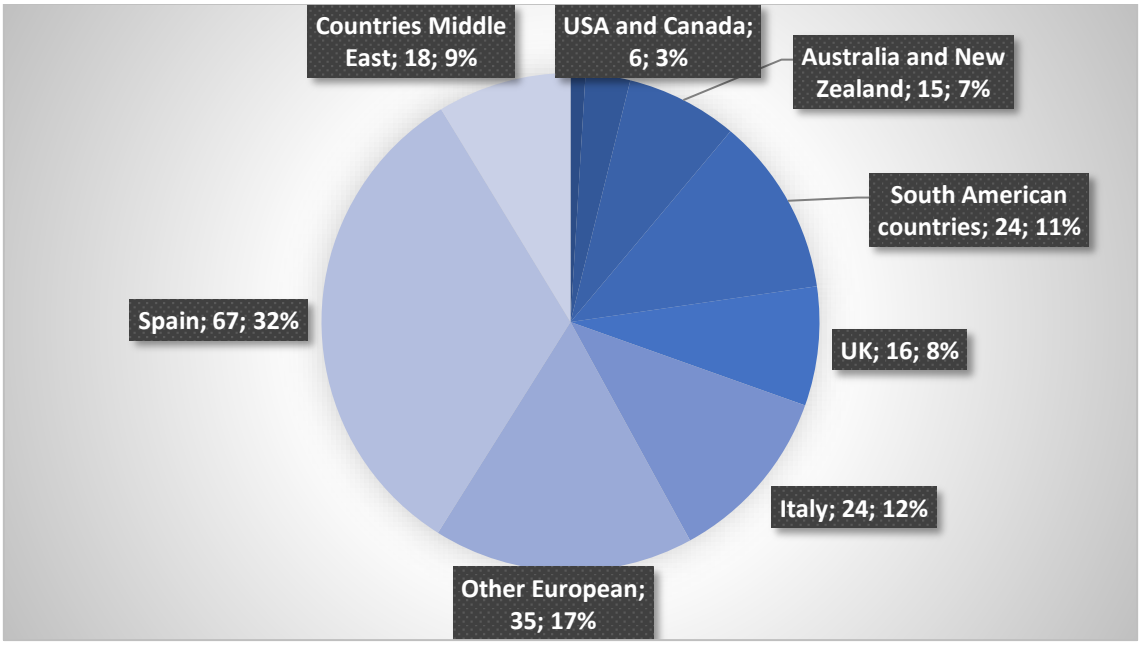


Figure 9. Countries participant representation (survey)

From them the 94.2% of the participants corresponded to surgeons usually performing elective and/or urgent colorectal procedures and specifically 59% of them identified themselves as colorectal surgeons.

In the table 18, baseline characteristics of the responders is included.

		N	%
Gender (male)		133	64.25
Age	Less than 40 years	114	55,07
	40-50 years	66	31,88
	over 50 years	28	13,53
Attending elective colorectal surgery		195	94,20
Attending emergency colorectal surgery		195	94,20
Specialised colorectal surgeon	Chief of Colorectal Surgery Unit	19	9,18
	Chief of General Surgery Department	8	3,86
	Colorectal Surgery Consultant	92	44,44
	Colorectal Surgery Registrar	11	5,31
	General Surgery Consultant	47	22,71
	General Surgery Resident	23	11,11
	Other (fellow, phD student, oncological surgery…)	7	3,38

Table 18. Survey participants characteristics

Regarding the type of hospital, 50.7% (n= 105) worked in a hospital with more than 500 beds and 21.7% (n= 45) worked in a hospital with 300-500 beds. The 39.6% responded that emergency procedures that imply colorectal surgery are performed by a colorectal surgeon in their centres. Regarding decisions of colorectal cancer management in their centres, 92.3% have a multidisciplinary committee dedicated to that.

Differences for each setting

In elective colon surgery in older patients, the preferred approach was laparoscopic in 82% of cases. In urgent colon surgery, laparotomy would be performed in 73.4% of cases.

If anastomosis was performed in colon surgery, 98% would perform it in elective surgery vs. 57.5% in emergencies.

In rectal surgery anastomosis would be performed in 92.8% of elective surgeries vs 19.3% in emergency setting.

In urgent left colectomies, 20% would perform anastomosis, 38% of the patients would have a stoma (protective or terminal) and 42% would choose according to the patient's status.

Full results regarding approach or technique in elective or urgent setting for patients older than 75 years according to responders can be found in Table 19.

Frailty assessment

72.9% in scheduled surgery vs 53.1% in emergencies would assess frailty. For the ones replying affirmative, 66 responders (31.9%), would not use any scale/score just general assessment/judgement. If a scale was used, the “Clinical Frailty Scale” is the most used of them with 45 responders (21.7%).

In 63.5% of the centres for the participants in the survey followed ERAS protocols.

		Elective		*Urgent*	
Procedure	**Technique / approach**	**N**	**%**	**N**	**%**
Colon cancer resection	*Laparoscopic*	170	82,1	51	24,6
	Open	24	11,6	152	73,4
	Robotic	13	6,3	3	1,4
Rectal cancer resection	*Laparoscopic*	144	69,6	41	19,8
	Open	24	11,6	154	74,4
	Robotic	37	17,9	4	1,9
Perform an anastomosis in colon resection	*No*	3	1,4	88	42,5
	Yes	203	98,1	119	57,5
Perform an anastomosis in rectal resection	*No*	15	7,2	166	80,2
	Yes	192	92,8	40	19,3
Right hemicolectomy	*Handsewn anastomosis*	52	25,1	44	21,3
	It depends on the bowel and patient status	15	7,2	75	36,2
	Mechanical anastomosis	140	67,6	80	38,6
	No anastomosis + terminal stoma	0	0,0	8	3,9
Left colectomy	*It depends on the intestine and patient status*	19	9,2	87	42,0
	Handsewn anastomosis	18	8,7	6	2,9
	Handsewn anastomosis + protective ileostomy	2	1,0	6	2,9
	Mechanical anastomosis	151	72,9	36	17,4
	Mechanical anastomosis + protective ileostomy	17	8,2	30	14,5
	No anastomosis + terminal stoma	0	0,0	42	20,3
Rectal resection	*Anastomosis*	30	14,5	0	0
	Anastomosis + protective ileostomy	123	59,4	27	13,0
	It depends on the intestine and patient status	52	25,1	87	42,0
	No anastomosis + terminal stoma	2	1,0	93	44,9

Table 19. Survey responses results

Discussion

7. Discussion

This study evaluated risk factors, clinical impact, and long-term outcomes of anastomotic leak (AL) following colorectal cancer surgery in older patients.

The design of the research study allowed to first identify factors and later validate findings over a local cohort of patients. Though many studies have been published around elderly and colorectal surgery, studies assessing AL in elderly are controversial and not always showing an association in between. The main problem identified is the definition of "elderly", with different cut-offs for chronological age to compare some starting at 65 years and few studies identifying "frailty" as a factor to take into account or compare. The question, when "old age" begins, remains unsolved though we know that functionality / frailty have an impact on it. As WHO already warned in their global strategy plan for ageing on the world population, healthy ageing needs to come with a "functional" component. (8) Therefore, frailty and its assessment play an important role in the "elderly" definition, identifying the impact in the functionality of the individual no matter the numeric age.

In the meta-analysis of the studies identified showing a similar definition of elderly with a cut-off on 75 years old, elderly had a significant 19% higher odds of AL compared to younger patients. In our cohort of patients ≥ 75, age was not a significant factor for AL, however we didn't compare with a younger population as the main aim was to identify factors unique for this specific population.

The overall leak rate in elderly over 75 years in our cohort was 12.26%, with most leaks classified as Grade C and therefore undergoing surgical management. The rates are in accordance with the ones reported in the literature report rates between 1% and 19% depending on anastomosis location (colon vs rectum), patient comorbidities and surgical complexity. (38) For older patients above 75 years old some of the literature reports rates around 8-10% similarly. (47,48)

In the systematic review we identified studies assessing frailty, sarcopenia, urgency and adherence to ERAS as factors that can be related to AL.

Among the factors we found significantly related to anastomotic leak in our cohort there were patient-related comorbidities including ASA grade, previous history of ischaemic heart disease, or postoperative hypoalbuminemia. High CR-POSSUM Physiological Score was also found related to higher risk for leak. Some of them have already been pointed out by some authors to be important in older age groups, highlighting nutritional status, ASA grade or adherence to ERAS protocols in perioperative management. (119–121)

Nutritional status, reflected by hypoalbuminemia, was an independent predictor of leak, aligning with evidence that malnutrition impairs healing. This supports prehabilitation strategies focusing on nutritional optimisation before surgery to reduce risk. We did not measure sarcopenia in this study, but this is a common factor that can be accentuated in both older age and cancer. It has already been described as an independent factor for complications and leak. (122,123) A decreased level of serum albumin in the preoperative or postoperative early days can be an indirect reflection of sarcopenia. (124)

In our cohort we did not found differences in the intraoperative factors related to surgical approach open vs laparoscopic vs robotic though in the literature MIS has already been proven to be safe and with better short-term outcomes when compared to younger groups. (86,125,126) Mechanical anastomosis was found to have a higher risk for leak in the multivariable analysis but this needs to be taken with caution as did not keep significance in alternative multivariable models and therefore its result may be influenced by collinearity or sample variability.

However, surprisingly, when surgeons requested to choose a surgical option in different scenarios for patients over or 75 year old, the most common approach is open in urgent surgery and terminal stoma without anastomosis or a protective stoma when compared to elective setting. Same happens with mechanical anastomosis which would be more commonly planned for elective rather than urgent surgeries. This demonstrates that though there is no published evidence or found in our cohort with regards of intraoperative / surgical technique factors, most surgeons base their choices differently depending on the setting of urgency for elderly. This is relevant, as some patients will

be planned for stoma even if this does not prevent from leak and makes an important part of the counselling during the informed consent.

Some strategies that are part since many years ago of the Colorectal Unit protocol at Vall d'Hebron Hospital are the blood test on the 3rd postoperative day including the CRP and further strategies in the algorithm explained above in the methods section. A high CRP is an independent factor for leak in our study in the univariable and multivariable analysis. This is a cheap resource that can help on the early track and detection of leak after surgery. In a similar way, intraoperative drain was found to be a protective factor for leak. However, previous larger cohort studies in colorectal surgery have reported drains not to prevent postoperative collections (127) and are not part of the ERAS recommendations from which octogenarian patients could benefit. (79,109)

Regarding oncological characteristics, tumour stage or neoadjuvant or adjuvant treatment were similar between AL and no AL groups. The only factor interestingly related to be higher in the leak group and later with a higher risk for mortality was an ECOG higher than 2, which represents a worse functional status.

To date, few studies exist in current literature studying frailty impact in older population undergoing colorectal cancer and their outcomes. Frailty was a significant determinant, with a Clinical Frailty Scale score ≥5 indicating clinical frailty and associated with higher AL risk and mortality. No significant differences were seen with the Modified Frailty Index. These results align with the frailty scoring meta-analysis recently published by Ding L et al. (19) Previous literature highlights the elderly's vulnerability due to poor physiological reserve, other comorbidities, and functional status, as a combined risk for poor outcomes in cases where an anastomotic leak happens. (128,129) These findings support the need for preoperative frailty assessment as part of surgical decision-making and as part of the information given to the patient and relatives at time of consent or when dealing with expectations after a complication.

Interestingly, from the survey we found that most surgeons consider "frailty" prior surgery, 73% in elective and 53% in urgent procedures, but they do a general judgement rather than using a structured score / scale. The scale more utilised among the

responders was the Clinical Frailty Scale in 29% of the cases. This is one of the easiest scoring systems, does not need a geriatrician for testing and can be done in the outpatient clinic before surgery.

Another interesting finding associated with leak is an increased risk to require further hospitalization in a rehabilitation centre or at home due to IV antibiotic requirement. The length of stay was also longer in the patients with leak. This result may be of use when preparing strategies for efficiency in the department and a better planification given the risk.

Finally, both the meta-analysis and the retrospective study have shown higher risk of AL related mortality being this significant. Though no difference in the survival multivariable Cox regression for age was found for the population over 75, functionality and frailty matters seeing ECOG over 2 and higher CFS as independent predictive factors of mortality in this cohort.

Limitations

For the systematic review, some of the limitations underly in the definitions used for elderly or for leak, not well structured always. When risk of bias assessment was performed, the overall for most of them was from moderate to serious.

For the retrospective study some of the limitations are inherent to its retrospective design and single-centre setting. However, its strengths include a large, well-characterised elderly cohort with comprehensive long-term follow-up in a high volume certified colorectal surgery unit.

Regarding the survey, it was planned to be a scenario testing for surgeons so does not translate real clinical data.

Conclusions

8. Conclusions

Primary study aim:

To identify and assess specific factors associated with an increased risk of anastomotic leak in elderly patients (≥75 years) undergoing colorectal cancer surgery.

1. Age over 75 years seems to be associated with an increase in AL risk comparing to younger patients. However, age is not a factor independently related to leak in this population with a range of age over 75. Some of the factors identified to increase the risk for AL are related to preoperative nutrition status and functional status / frailty / sarcopenia. Scores identified to be usable in this range of patients include ASA, ECOG, CFS and CR-POSSUM.
2. Early identification of high-risk patients, frailty assessment and optimisation of modifiable perioperative parameters may reduce AL incidence and improve outcomes.

Secondary aims:

To evaluate the impact of anastomotic leak on early postoperative morbidity, as measured by Clavien-Dindo classification, and on 30-day mortality in this population.

3. There is a higher risk for major complications defined by Clavien-Dindo, but more importantly, it has an impact in 30-day mortality and discharge to a rehabilitation centre.

To explore the long-term outcomes associated with anastomotic leak in elderly colorectal cancer patients.

4. The survival at 5 year is shorter for individuals with anastomotic leak. No significant association was found between mortality related to disseminated / recurrent oncological disease and anastomotic leak.
5. Given the significantly increased mortality associated with AL in elderly patients, complete preoperative assessment and individualised decision-making are essential.

To assess current surgical practices and approaches to colorectal anastomosis in elderly patients through an international survey of general and colorectal surgeons.

6. There seems to be significant variations in the management of elderly patients undergoing colorectal cancer surgery depending on the clinical scenario. Open approach and stoma are of choice in emergency procedures in this population.

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Appendix

10. Appendix

10.1. Appendix A: Study data collection form

Preoperative data		
1	Age	*(years)*
2	Gender	Male/Female
3	ASA	I, II, III, IV, V
4	Smoker	Yes/No
5	Body Mass Index *(if available)*	Underweight (<18.5), Normal range (18.5-24.9), Overweight (25-30), Obese (>30)
6	Previous abdominal surgery history	Sí / No
7	Pre-existing abdominal stoma	Yes – colostomy / Yes – jejunostomy or ileostomy / No stoma
8	History of ischaemic heart disease	Yes (Myocardial infarction or Angina) / No
9	History of congestive heart failure	Yes / No
10	History of cerebrovascular disease	Yes (transient ischemic attack or stroke) / No
11	History of diabetes mellitus	Yes, insulin controlled / Yes, tablet controlled / Yes, diet controlled / No

12	Immunosupressive status	Yes (considering high dose of corticosteroids or other treatments; VIH) / No
13	POSSUM operative severity score	
14	POSSUM physiologic score	
15	Clinical Frailty Scale	
16	Modified Frailty Index	
17	Total protein (albumin if available)	
18	Oncological preoperative staging	• T1/T2/T3/T4/Unknown • N0/N1/N2/Unknown • M0/M1/Unknown
19	Neoadjuvant treatment	• NO / Yes -chemotherapy / Yes – Radiotherapy / Yes - Both
20	Adjuvant treatment	• NO / Yes -chemotherapy
Intraoperative data		
21	Diagnosis at time of surgery	• Colon cancer • Rectal cancer
22	Operative urgency	• Immediate • Urgent • Expedited

		• Elective
23	Surgical approach	• Open • Laparoscopic • Laparoscopic-assisted • Laparoscopic converted to open • Robotic • Robotic converted to open
24	Primary operation performed	
25	Anastomosis creation	Yes/No
26	If yes – Anastomosis type	• Intraperitoneal /Extraperitoneal • T-T / L-L / T-L • Mechanical (linear/circular) / Handsewn • In rectum: high/mid/low
27	Stoma formation	• Yes – colostomy • Yes – ileostomy • No stoma
28	Documented air leak	• Recorded (positive) • Recorded (Negative) • Not recorded
29	Documented ICG test	• Recorded (Right perfussion)

		• Recorded (Bad perfussion – change in surgical plan) • Not recorded / No performed
30	Duration procedure	Minutes
31	Intraoperative complications	None / Vascular injury / Bowel injury / Injury to other organs or structures
32	Intraoperative drain	Yes / No
Postoperative data		
Outcomes		
33	Lenght of stay	*Days*
34	30-day readmission	Yes/No
35	Clavien-Dindo Grades	I , II, IIIA, IIIB, IVA, IVB, V
36	Other 30-day complications	Ileus / Acute kidney injury / Sepsis / ICU admission / Myocardial infarction/ SSI
37	3rd day PCR	
38	4th day PCR / PCT *if available/performed*	
39	Mortality 30-day	Yes/No

40	Mortality 90-day	Yes/No
41	Final cancer staging	• T1/T2/T3/T4/Unknown • N0/N1/N2/Unknown • M0/M1/Unknown • Margins R0/R1/R2/Unknown

10.2. Appendix B: International Survey on anastomosis management in elderly patients undergoing surgery for colorectal cancer

This survey should be replied preferably by a consultant or a senior trainee. Replies are anonym. A minimum of 1 reply per person is allowed, and therefore replies will be accepted from individual email accounts.

	Items	**Data points**
1	Age from the responder	Years
2	Gender from the responder	Male / Female
3	Country from the responder	
4	Details from the responder - grade	● Chief of Surgical Department ● General surgery consultant ● Colorectal surgeon specialist ● Senior general Surgery Resident ● Other:
5	Do you have specialised units in your hospital (i.e. colorectal unit, etc.)	Yes / No
6	Hospital grade	● University or centre of first reference hospital ● Secondary hospital ● Tertiary hospital
7	Number of beds in the hospital	< 300 300-500 >500

8	Do you attend elective colorectal surgery?	Yes / No
9	Do you attend emergency colorectal surgery?	Yes / No
10	Are emergency colorectal procedures atended by a specialised colorectal surgeon?	Yes / No
11	Are colorectal cancer management decisions, taken by a multidisciplinary board in your centre?	Yes/No
12	For patients ≥ 75 years, which approach do you usually use in elective colorectal cancer resections? *Please answer this question by most of patients (>50%) treated at your hospital*	• Open • Laparoscopic • Robotic • Other
13	For patients ≥ 75 years, which approach do you usually use in emergency colorectal cancer resections? *Please answer this question by most of patients (>50%) treated at your hospital*	• Open • Laparoscopic • Robotic • Other
14	For patients ≥ 75 years, do you usually perform colorectal anastomosis in elective surgery? *Please answer this question by most of patients (>50%) treated at your hospital*	Yes / No
15	For patients ≥ 75 years, do you usually perform colorectal anastomosis in emergency surgery? *Please answer this question by most of patients (>50%) treated at your hospital*	Yes / No
16	For patients ≥ 75 years, in elective right hemicolectomy, which kind of anastomosis do you usually perform? *Please answer this question by most of patients (>50%) treated at your hospital*	• Manual • Handsewn

17	For patients ≥ 75 years, in elective left colectomy, which kind of anastomosis do you usually perform? *Please answer this question by most of patients (>50%) treated at your hospital*	• Manual • Handsewn *+ protective ileostomy* *+ No anastomosis / Terminal stoma*
18	For patients ≥ 75 years, in rectal resection, do you perform? *Please answer this question by most of patients (>50%) treated at your hospital*	• Anastomosis • Anastomosis + protective ileostomy • No-anastomosis + terminal stoma
19	Do you usually assess frailty prior surgery? *Please answer this question by most of patients (>50%) treated at your hospital*	• Yes • No • No, but this is usually assessed by anesthesia team
19.1.	If you replied "Yes", how is frailty assessed?	• Clinical Frailty Scale • Modified Frailty Score • General funtional assessment / no score • Barthel • Other scores:
20	Are ERAS protocols followed at your department/unit? *Please answer this question by most of patients (>50%) treated at your hospital*	Yes / No

10.3. Appendix C: Ethical approval of the study by Hospital Vall d'Hebron CEIC

INFORME DEL COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS Y COMISIÓN DE PROYECTOS DE INVESTIGACIÓN DEL HOSPITAL UNIVERSITARI VALL D'HEBRON

Sra. Mireia Navarro Sebastián, Secretaria del COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitari Vall d'Hebron,

CERTIFICA

Que el Comité de Ética de Investigación con Medicamentos del Hospital Universitario Vall d'Hebron, en el cual la Comisión de proyectos de investigación está integrada, se reunió en sesión ordinaria nº 466 el pasado 27/11/2020 y evaluó el proyecto de investigación **PR(AG)549/2020**, titulado *"Risk factors of anastomotic leak in elderly patients undergoing colorectal cancer surgery"* que tiene como investigador principal al Dr. Eloy Espín Basany del Servicio de Cirugía General de nuestro Centro.

Versión de documentos

Memoria de Proyecto	versión 1.1 del 09/11/2020
Solicitud dispensa CI	versión 1 del 01/10/2020
Solicitud de evaluación CEIm	versión 1 del 30/09/2020
Annexes	versión 1.2 del 18/11/2020

El resultado de la evaluación fue el siguiente:

Aprobado

El Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, y su composición actual es la siguiente:

Presidente:
- SOLEDAD GALLEGO MELCÓN - Médico

Vicepresidente:
- JOAN SEGARRA SARRIES - Abogado

Secretario:
- MIREIA NAVARRO SEBASTIAN - Química

Vocales:
- LLUIS ARMADANS GIL - Médico
- FERNANDO AZPIROZ VIDAUR - Médico

- VALENTINA BALASSO - Médico
- INES M DE TORRES RAMÍREZ - Médico
- ELADIO FERNÁNDEZ LIZ - Farmacéutico Atención Primaria
- INMACULADA FUENTES CAMPS - Médico Farmacólogo
- JAUME GUARDIA MASSÓ - Médico
- JUAN CARLOS HORTAL IBARRA - Profesor de Universidad
- MARIA LUJAN IAVECCHIA - Médico Farmacólogo
- ALEXIS RODRIGUEZ GALLEGO - Médico Farmacólogo
- JUDITH SANCHEZ RAYA - Médico
- MARTA SOLÉ ORSOLA - Personal de Enfermería
- PILAR SUÑÉ MARTÍN - Farmacéutica Hospital
- VÍCTOR VARGAS BLASCO - Médico
- ESTHER CUCURULL FOLGUERA - Médico Farmacólogo
- GLORIA GÁLVEZ HERNANDO - Personal de Enfermería
- ORIOL ROCA GAS - Médico
- ESPERANZA ZURIGUEL PEREZ - Personal de Enfermería
- ANA BELÉN ESTÉVEZ RODRÍGUEZ - Abogada experta en protección de datos

En dicha reunión del Comité de Ética de Investigación con Medicamentos se cumplió el quórum preceptivo legalmente.

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

MIREIA NAVARRO SEBASTIAN

Firmado digitalmente por MIREIA NAVARRO SEBASTIAN
Fecha: 2020.11.27 14:56:23 +01'00'

Sra. Mireia Navarro

Secretaria técnica CEIM HUVH