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Anastomotic Leak in Colorectal Cancer Surgery: From Diagnosis to Management or Failure - A Retrospective Cohort Study

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Abbreviations:
AL - Anastomotic Leak.
CR – ColoRectal.
CRC - ColoRectal Cancer.
CT - Computed Tomography.
DULK - Dutch leakage score.
DIACOLE - Diagnostic Leakage score.
FTR - Failure-to-Rescue.
ICU - Intensive Care Unit.
ISGRC - International Study Group of Rectal Cancer.
LOHS - Length of Hospital Stay.

ABSTRACT

Background: Anastomotic leakage (AL) after colorectal resections is a common surgical experience and the most frequent major adverse outcome. Early recognition of AL is critical to reduce mortality. We aim to evaluate the incidence, diagnostic criteria, morbidity, and mortality related with AL.
Methods: This is a cohort, descriptive retrospective, single-centred study of consecutive patients who underwent surgery with a colorectal anastomosis for colorectal cancer, over a 4-year period (2013-2016).
Results: From 2013 to 2016, a total of 480 patients were included. A total of 37 (7.7%) had an anastomotic leakage. AL was diagnosed after 6.8 days in average, most frequently on day 5. 25 out of the 37 patients were diagnosed based on clinical criteria, and the remaining had a CT scan imaging. Clavien-Dindo grade III and IV complications was significantly higher in the AL group (70.2 vs. 7.7%, $p<0.0005$). Mortality was higher in the leakage group (21.6% vs. 4.7%, $p< 0.0005$).
Conclusions: In this study, most patients were diagnosed early based on clinical criteria, and imaging studies were associated with a significant delay in diagnosis. Leakage group had higher morbidity, mortality and rate of reoperations. Early reoperation may have a positive impact in Failure-to-Rescue rate reduction, but additional prospective studies are needed.
Key words: failure-to-rescue, colorectal, surgery, anastomotic leak, mortality

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INTRODUCTION

Colorectal cancer (CRC) remains a public health issue worldwide, ranking third in leading causes of death from cancer in high income countries (1,2).

Surgery is usually required for CRC management, despite significant morbidity and mortality (3,4). Anastomotic leak (AL), a major complication, is not only associated with frequent reoperation, increased length of hospital stay (LOHS) and health-care costs, but also with a higher mortality risk. For AL survivors, an adverse impact on their quality of life is observed (3,5). Incidence of AL may vary from 0.5% to 21% (5-9), depending on the location of the anastomosis, patient co-morbidity profile, pre-operative treatment, and institutional experience (10,11).

Nonspecific signs and symptoms often precede the acute and rapid clinical deterioration of a patient with AL. Once late diagnosis and management increase the likelihood of an undesirable outcome, timely diagnosis is crucial. In daily practice several biomarkers and scores are used for supporting an appropriate clinical decision, that can prevent severe sepsis and death (12-14).

Prevention and treatment of AL have received attention in the last decades. Silber et al. (1992) introduced the Failure-to-Rescue (FTR) concept which reflects the estimated mortality rate in the group of patients who developed a specific postoperative complication (15). FTR differs among distinct institutions and suggests that different therapeutic strategies can influence the patient's survival being useful for institutional benchmarking (16,17). Therefore, as performance indicators for colorectal (CR) surgery, we should not only consider absolute mortality or AL ratios, but also the proportion of patients who died due to a specific complication (15, 18). The main objective of this study is to evaluate the incidence and diagnostic criteria of AL in our cohort, and secondly to assess morbidity, mortality (FTR) and long-term survival impact.

METHODS

Study design and ethics

Retrospective descriptive cohort study, approved by the Local Institutional Ethical Committee, including consecutive patients, who underwent CR resection with anastomosis for CRC from January 2013 to December 2016. All patients were managed in a non-academic Colorectal Referral Centre, which serves an area of 500,000 inhabitants.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), the official system of clinical coding in Portugal, was used to classify all patients. The follow-up ended in December 2018 or with death of the patient.

Definitions

Anastomotic leak was confirmed by the presence of one of the following: postoperative peritonitis found at reoperation, faecaloid drainage and presence of air or fluid collection in the anastomotic region on Computed Tomography (CT).

We differentiated two scenarios considering the timing of AL diagnosis: 1) in the same hospital admission; 2) diagnosed after the discharge (deferred AL). Time to AL detection was measured as the number of days between the index operation and diagnosis, according to the criteria. Retrospectively, AL was graded applying the definition and severity grading system developed by the International Study Group of Rectal Cancer (ISGRC) (13).

According to the AL management options, we considered two groups: "Salvage group", composed by patients managed with preservation of bowel continuity with anastomosis repair/refashion and covering stoma; and the "Anastomotic takedown group", when the creation of an end colostomy or ileostomy was necessary.

Surgical approach of the index procedure was divided into three groups: laparoscopy, laparotomy, and conversions (from laparoscopy to open surgery), and LOHS included the second admission, if caused by AL-related complications. Exitus (death) was counted within 30 days of index surgery. Stoma was considered as permanent if it was present at the end of follow-up period.

Exclusion criteria

The following groups of patients were excluded from this study: a) under 18 years old; b) pregnant women; c) mentally disabled; d) under 3 months of follow-up; e) missing data; f) with no anastomosis; g) stoma reversal operation; h) ileo-pouch-anal anastomosis procedures and, i) reoperations.

Included variables

Patient-related demographics, preoperative, intra-operative, and pathologic data were collected from institutional database (SClínico Hospitalar®). Postoperative variables including complications, LOHS, reoperations, intensive care unit (ICU) admissions, death and 30-day readmissions or mortality were also registered.

Statistical analysis

For data analysis, we used descriptive statistics, mean or median, according to the characteristics of the

interest variables. To analyze survival time variables, we used the Kaplan-Meier estimator. Equality of means or proportions between groups were assessed. A t-test was applied to continuous variables. Survival experience was assessed by the Gehan-Breslow-Wilcoxon test (IBM SPSS Statistics version 27.0).

RESULTS

From January 2013 to December 2016, 480 out of 915 patients met the inclusion criteria (*figure 1*), all with CRC and operated in the Colorectal Unit at the Leiria Central Hospital. We excluded procedures for benign disease (n=243; 26.6%), without anastomosis (n=72; 7.9%) and for stoma closure (n=65; 7.1%). Pouch surgery, reintervention or small bowel resection were also not considered.

This cohort (N = 480) is composed mostly by men (n= 287; 59.8%), with colon cancer (n=353; 73,5%) and a mean age of 70.4 ± 12.57 years. Thirty-seven patients developed AL (7.7%) and the rate decreased gradually each year, from 9.1% in 2013 to 5% in 2016 (*figure 2*). Anastomotic leak was more frequent in men (n=26; 70.3%), left colectomy and proctectomy (n=25; 67.5%) and in the laparotomic approach (n=13; 35.1%) or conversion (n=5; 13.5%). Clinical characteristics and different surgical approaches are summarized in *tables 1* and *2*.

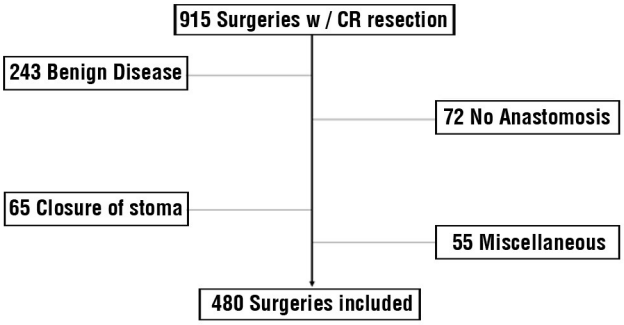

Figure 1 – Flow diagram of patients with inclusion and exclusion criteria

Table 1 – Cohort demographic and clinical characteristics (Leak vs. No leak groups)

	No Anastomotic Leakage (No AL) (N=443; 92.3%)	Anastomotic Leakage (AL) (N=37; 7.7%)	P value (95% CI)
Age (Mean ±SD)	70.25 ± 12.61	72.1 ± 12.05	0.390 (-2.4 to 6.1)
Sex (M/F)	261 (58.9%) /182 (41.1%)	26 (70.3%) / 11 (29.7%)	0.175 (-5.3 to 24.5)
ASA Score			
I – II	270 (60.9%)	24 (64.9%)	0.632 (-12.7 to 18.1)
III – IV	173 (39.1%)	13 (35.1%)	
Stage			
I	148 (33.4%)	9 (24.4%)	0.263 (-7.4 to 20.9)
II	127 (28.7%)	13 (35.1%)	0.411 (-7.6 to 22.9)
III	126 (28.4%)	12 (32.4%)	0.606 (-9.5 to 20.6)
IV	42 (9.5%)	3 (8.1%)	
Comorbidity			
<2	350 (79%)	32 (86.5%)	0,226 (-6.4 to 17.1)
2 or more	93 (21%)	5 (13.5%)	

Table 2 - Cohort demographic and clinical characteristics (Leak vs. No leak groups)

	No Anastomotic Leakage (No AL) (N=443; 92.3%)	Anastomotic Leakage (AL) (N=37; 7.7%)	P value (95% CI)
Timing			
Elective	363 (81.9%)	30 (81.1%)	0.909 (-9.4 to 16.4)
Urgent	80 (18.1%)	7 (18.9%)	
Approach			
Open	97 (21.9%)	13 (35.1%)	0.067 (-0.7 to 16.7)
Laparoscopic	333 (75.2%)	19 (51.4%)	0.002 (8.0 to 39.7)
Conversion	13 (2.9%)	5 (13.5%)	
Procedures			
Right	202 (45.6%)	10 (27.0%)	0.003 (2.0 to 15.9)
Left	128 (28.9%)	13 (35.1%)	0.427 (-7.1 to 22.8)
Rectum	84 (19.0%)	12(32.4%)	0.050 (0.0 to 29.9)
Others	28 (6,5%)	2 (5.5%)	
Covering Stoma			
Yes	53 (11.9%)	10 (27.1%)	0.008 (3.1 to 31.4)
No	390 (88.1%)	27 (72.9%)	

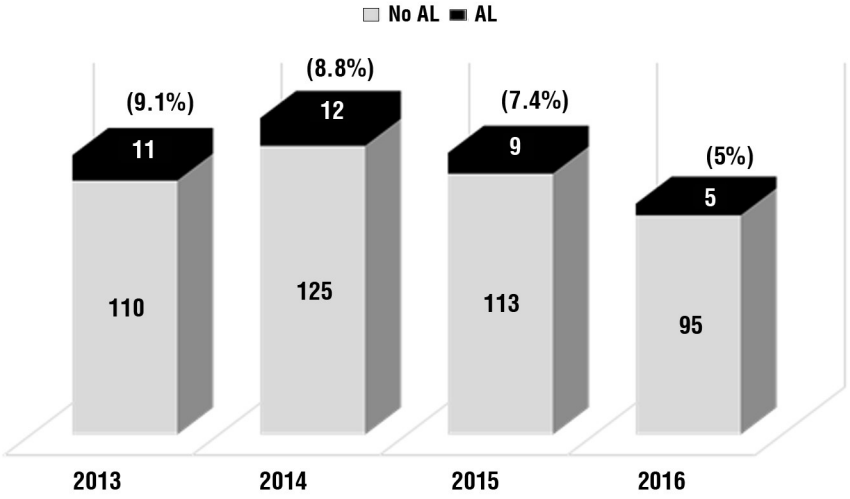

Figure 2 - Anastomotic leakage rate distribution, per year

Thirty-two patients (86.5%) had AL diagnosis at the first hospital admission and five had the diagnosis deferred. Mean time for AL detection was 6.8 days (day 2 to 17) and was most common on day 5. Twenty-five patients were diagnosed based on clinical criteria, including biomarkers (leukocyte and C-Reactive Protein), and in these sub-group, the diagnosis was made earlier (5.6 ± 2.1 days). These patients had a shorter LOHS (26.1 vs. 40.9 days), which is not statistically significant [(p=0.073; 95% CI (-1.0 to 34)]. The remaining twelve required additional exams, such as abdomen-pelvic CT scan and/or lower GI endoscopy. Three out of 12 AL patients scanned did not show unequivocal signs in CT scan. In this subgroup, diagnosis was reached later (8.5 ± 4.2 days), with statistical significance [(p=0.004; 95% CI (0.7 to 4.8)] – *tables 3* and *4*.

Six patients were managed non-operatively and four needed an image-guided drainage of intra-abdominal collections (one by transrectal access). Twenty-four out of 31 patients (64.8%) were submitted to anastomotic takedown and Hartmann's procedure, and six (16.2%) underwent refashion of the anastomosis with covering stoma. Twelve (32.4%) out of the 37 patients required ICU admission and fifteen (40.5%) received parenteral nutrition. Over 34.9 months of follow up, 20 out of 37 patients (54.1%) maintained bowel continuity, including preserved primary or refashioned anastomosis (n=10; 27%) and Hartmann reversal status (n=10; 27%). The main causes for not closing the stoma were patient refusal and morbidity (n=10) and cancer dissemination (n=4). The causes for secondary anastomotic failure were stenosis (n=2) and local recurrence (n=1) - *figure 3*.

Concerning morbidity, the rate of complications was significantly higher in the AL-patient group. Based on

Table 3 - Timing of AL diagnosis

AL DIAGNOSIS	
TIMING (Days):	
• Mean (SD)	6.8 (2.2)
• Median	6
• Mode	5
1ST EPISODE - N (%)	32 (86.5%)
DEFERRED (Readmission) - N (%)	5 / (13.5%)

Table 4 - Methods of AL diagnosis

	Clinic (biomarkers/reoperation) (N=25; 64.9%)	Others (CT scan ± endoscopy) (N=12; 35.1%)	P value (95% CI)
TIMING (days)			
Mean±SD	5.7 ± 2,1	8.5 ± 4.2	0.004
Median	5	8	(0.7 to 4.8)
Max	7	21	
Min	3	4	
LOHS – Days			
Mean±SD	26.1 ± 10.9	40.9 ± 41.5	0.073
Median	21	38	(-1.0 to 34)
Max	97	165	
Min	15	23	

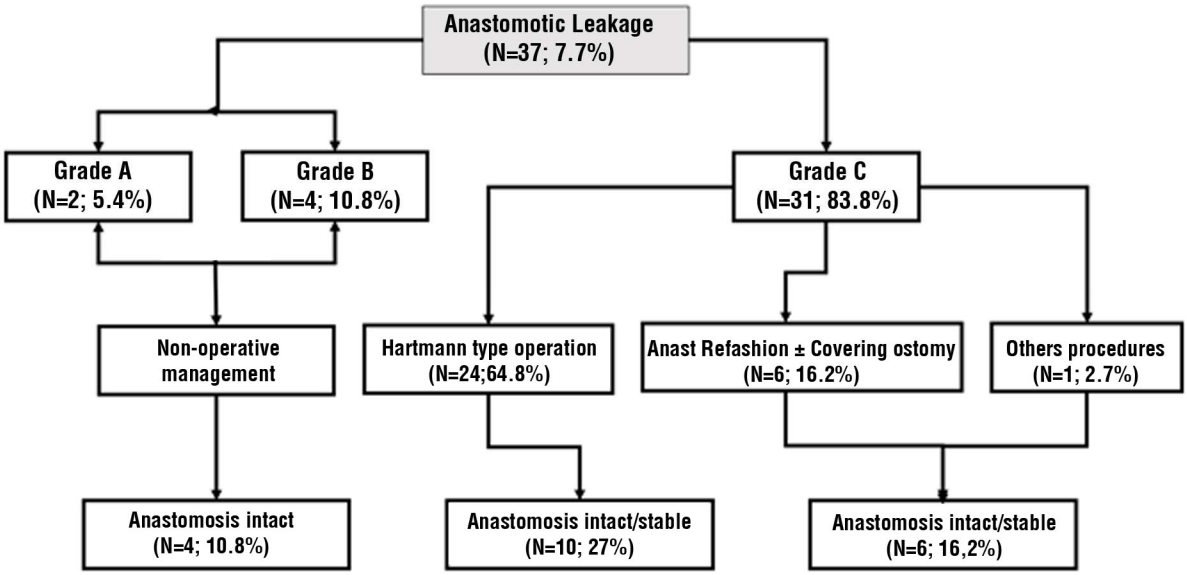

Figure 3 - Management and follow-up of AL patients (according to ISGRC severity grading system)

the Clavien-Dindo classification, 26 out of the 37 patients (70.2%) had grade III and IV complications, vs. 34 patients in the group who had no AL (7.7%) (*table 5*). Mean LOHS was significantly higher in the AL cohort [(10.5 vs. 31.3 days - < 0.0005 (14.9 to 21.9)].

In the first year, need for reoperation and 30-day mortality were more significant in AL-patient group, 83.8% vs. 6.1% (p< 0.0005; 95%CI 6 to 89.4) and 21.6% vs. 4.7% (p< 0.0005; 95%CI 8.1 to 32.9), respectively. Considering the elective cohort, 30-day mortality rate was higher in the AL group (13.5% vs. 1.8%). Furthermore, mortality was lower in the second biennium (2015-16) in both groups (with and without AL), 27.2% vs. 15.5% (p=0.417; 95%CI -17.6 to 34.9) and 6.1% vs. 2.3% (p=0.049; 95%CI – 0.1 to 7.8), respectively.

Concerning the impact of AL on the overall survival (OS), with an average follow-up of 47.4 ± 23.2 months, patients without AL had a 5-year OS (in all stages) of 63.3%, versus 52.9% in the AL-patients group. Comparing Kaplan-Meier's survival curves, the Gehan-Breslow-Wilcoxon test shown statistical significance in OS between the groups (50 ± 6.6 vs. 62.4 ± 1.5 months; p=0.009) – *figure 4*.

Regarding the survival analysis, the 5-year OS was 55.6, 50, 63.6 and 0% for the sub- group with AL complications, versus 76.3, 69.7, 59.7 and 10.5% in the sub-group without AL. Comparing Kaplan-Meier's survival curves, the Gehan-Breslow-Wilcoxon test shown significant differences in survival time between the two groups (p=0.005), at the different stages (*figure 5*).

Table 5 - Postoperative complications according to the Clavien-Dindo classification (Leak vs. no leak group)

	No Anastomotic Leakage (No AL) (N=443; 92.3%)	Anastomotic Leakage (AL) (N=37; 7.7%)	P value (95% CI)
LOHS – days			
Mean (range)	10.5 (3-138)	31.3 (15 -165)	< 0.0005 (14.9 to 21.9)
Median	7	27	
MORBIDITY – n (%)			
Clavien-Dindo I	39 (8.8 %)	2 (5.4%)	0.395 (-5.8 to 9)
Clavien-Dindo II	47 (10.6 %)	1 (2.7%)	0.059 (-0.3 to 11.3)
Clavien-Dindo III	16 (3.6%)	18 (48.6 %)	< 0.0005 (30.2 to 59.5)
Clavien-Dindo IV	18 (4.1 %)	8 (21.6%)	< 0.0005 (8.5 to 34.5)
REOPERATION – n (%)			
(W/in 12 months)	27 (6.1%)	31 (83.8%)	< 0.0005 (6 to 89.4)
30-DAY MORTALITY – n (%)			
Elective	8 (1.8 %)	5 (13.5 %)	< 0.0005 (5.1 to 26.9)
Overall	21 (4.7 %)	8 (21.6 %)	< 0.0005 (8.1 to 32.9)
FOLLOW-UP - months	35.7	34.9	0.818 (-4.7 to 3.9)

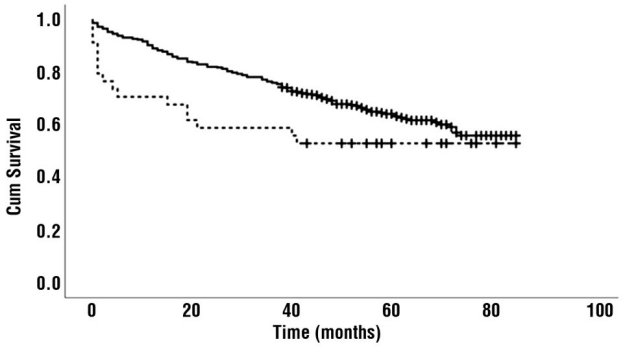

Figure 4 - Kaplan-Meier Overall Survival Curves. Leak group represented as the dashed line and No leak group represented as a straight line. The + symbol represents censored cases

Colon cancer patients who developed AL had a significant lower 5-year OS, 50%, versus 66.3% (p=0.002). This significant difference was not observed in the AL rectal cancer cohort, as the 5-year OS was 55.6% versus 65%, in the no-AL cohort (p>0.05) (*figure 6*).

DISCUSSION

In the literature, AL ranges from 0.5% to 21%, with colon and rectum-adjusted rates of 3–7% and 13–18%, respectively (5, 7-9, 19-22). This is the first retrospective study on this subject in the Portuguese population, and 37 out of 480 patients (7.7%) developed AL. It was higher in left-side anastomosis, in comparison with ileo-colic anastomosis (11.2 vs. 4.7%), decreasing gradually in the second biennium (9.8 to 6.7%). We may correlate this with the increase in surgeon volume, technical and technological progress, among others. Literature highlights this trend, in spite of scarce and controversial evidence (23).

Anastomotic leak may occur in patients without risk factors and non-specific signs often precede rapid and abrupt clinical deterioration. Consequently, early diagnosis is paramount for reducing morbidity and mortality: post-operative clinical assessment is useful but subjective, therefore tools such as the Dutch

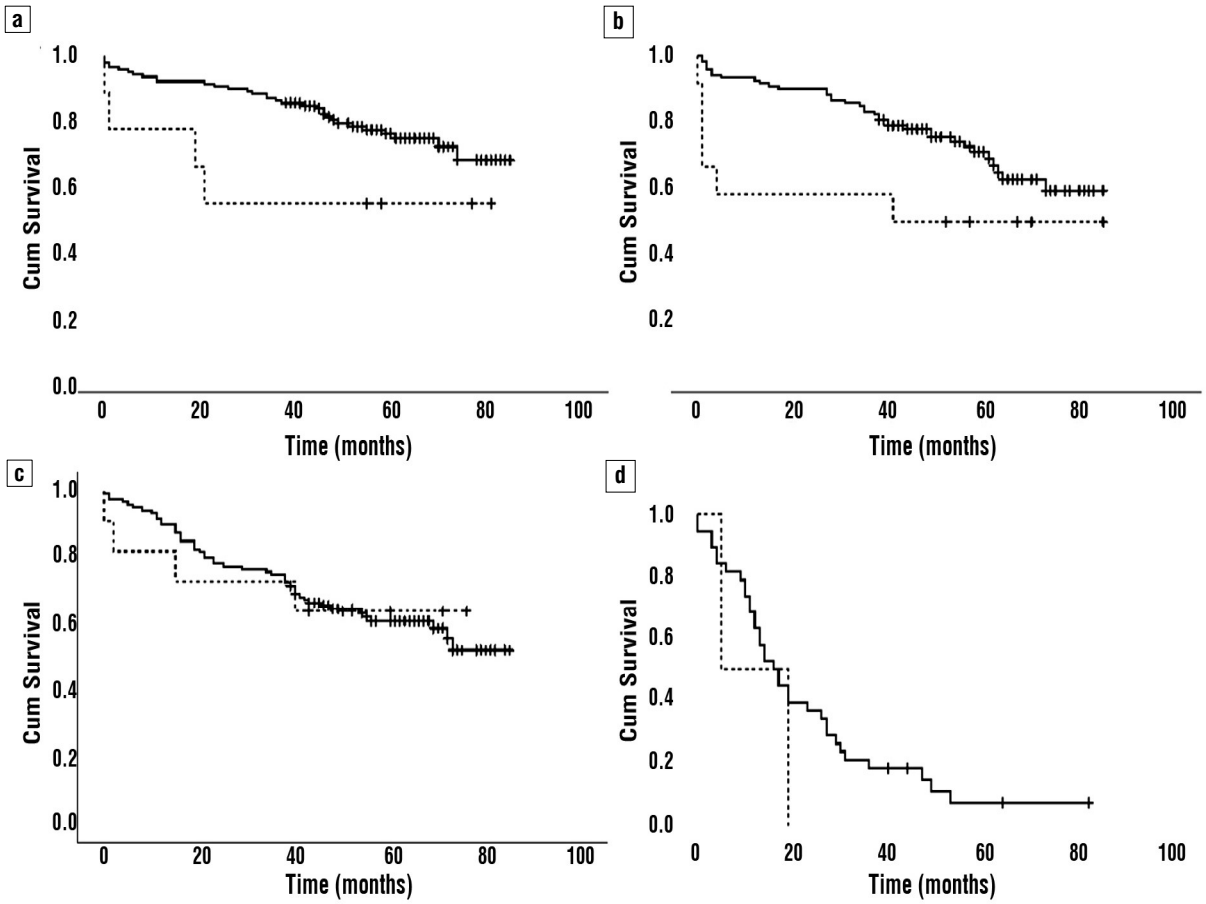

Figure 5- Kaplan-Meier Survival by UICC TNM stage. Panels a. to d. show data for patients in Stages I to IV, respectively. Leak group represented as the dashed line and No leak group represented as a straight line. The + symbol represents censored cases.

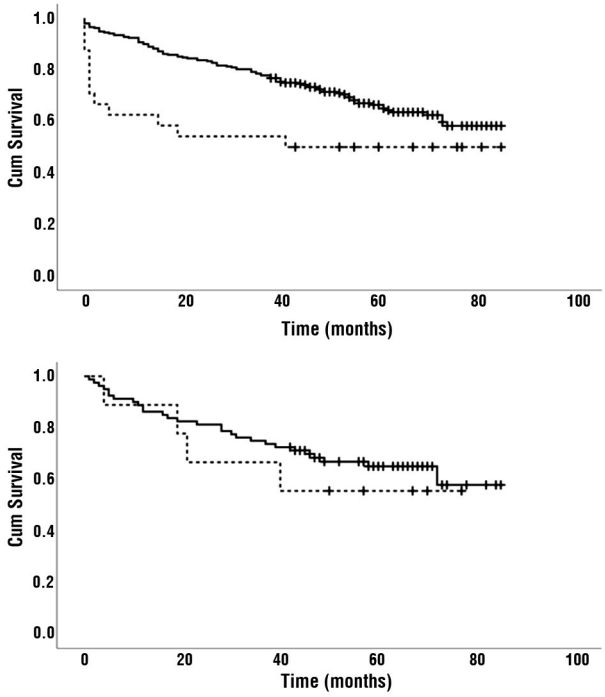

Figure 6 - Kaplan-Meier Survival, by location. Leak group represented as the dashed line and No leak group represented as a straight line. The + symbol represents censored cases

leakage (DULK) or the Diagnostic Leakage (DIACOLE) scores may help selecting patients for additional imaging tests or early reoperation (12,14). In our study, diagnosis was attained mostly at the first hospital admission, more commonly on the fifth postoperative day. Most patients (64.9%) were diagnosed earlier based on clinical criteria. In the remaining patients, diagnosis was complemented with CT scan, with 25% of false negatives but a non-significant delay in diagnosis. In the literature CT scan showed a low sensitivity and accuracy rates, around 60% (24,25). In a recently published study by the iCral group, the original DULK score was shown to be valuable for predicting AL on the second and third days after surgery (22,26,27). Currently we are introducing these predictive tools in daily clinical practice.

High mortality rate was published in large series ranging from 25 to 35%, despite the lower rates presented by Gessler et al. (from 5 to 8.3% at 30 and 90 days, respectively) (22, 25, 28-30). In AL cohort, eight patients (21.6%) died within 30 days, but mortality rate was lower both in elective surgery (13.5%) and in the second biennium (15.5%). This period roughly coincided with the implementation of the CR Unit in the institution. Consequently, FTR should be a useful outcome indicator for assessing the performance of CR surgical teams.

In line with the literature, this study suggests that AL had a negative impact on 5-year OS, excluding the rectal cancer cohort (31-36). However, Mrak et al. and Jörgren et al. did not find such negative correlation in the rectal cancer cohort (37,38), as observed in our series. Heterogeneous samples including different post-operative complications or tumour location may explain these controversial results. In a recent metanalysis with 18 cohort studies and 69,047 patients submitted to colectomy, AL didn't increase local or distant recurrence, but reduced OS (RR 0.85, 95% CI 0.77–0.94)(34).

The limitations of this study depend on its retrospective nature, in particular the quality of records. The size of the sample is another weakness that constrains the statistical strength of the analysis. The strengths are related to the quality of the sample, an unselected and consecutive cohort of patients, from a regional representative CR Unit. Finally, the current study provides information and knowledge that reinforce and improve the informed consent and supports providers in the perioperative decision-making process.

CONCLUSIONS

In this original study in the Portuguese population, two thirds of AL patients were diagnosed earlier based on clinical criteria and AL cohort had higher morbidity and mortality (78.3% and 21.6%, respectively), longer LOHS and rate of reoperations. Both systematic use of scores for AL diagnosis and early re-operation may have a positive impact on FTR rate reduction. This is a useful metric to evaluate different management options, to determine their impact on survival, and to perform institutional benchmarking. Further prospective studies will be useful to obtain added-value evidence in this topic.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

For performing this study ethical approval was obtained.

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