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ERAS program adherence-institutionalization, major morbidity and anastomotic leakage after elective colorectal surgery: the iCral2 multicenter prospective study

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Abstract

Background Enhanced recovery after surgery (ERAS) programs influence morbidity rates and length of stay after colorectal surgery (CRS), and may also impact major complications and anastomotic leakage rates. A prospective multicenter observational study to investigate the interactions between ERAS program adherence and early outcomes after elective CRS was carried out.

Methods Prospective enrolment of patients submitted to elective CRS with anastomosis in 18 months. Adherence to 21 items of ERAS program was measured upon explicit criteria in every case. After univariate analysis, independent predictors of primary endpoints [major morbidity (MM) and anastomotic leakage (AL) rates] were identified through logistic regression analyses including all significant variables, presenting odds ratios (OR).

Results Institutional ERAS protocol was declared by 27 out of 38 (71.0%) participating centers. Median overall adherence to ERAS program items was 71.4%. Among 3830 patients included in the study, MM and AL rates were 4.7% and 4.2%, respectively. MM rates were independently influenced by intra- and/or postoperative blood transfusions (OR 7.79, 95% CI 5.46–11.10; $p < 0.0001$) and standard anesthesia protocol (OR 0.68, 95% CI 0.48–0.96; $p = 0.028$). AL rates were independently influenced by male gender (OR 1.48, 95% CI 1.06–2.07; $p = 0.021$), intra- and/or postoperative blood transfusions (OR 4.29, 95% CI 2.93–6.50; $p < 0.0001$) and non-standard resections (OR 1.49, 95% CI 1.01–2.22; $p = 0.049$).

Conclusions This study disclosed wide room for improvement in compliance to several ERAS program items. It failed to detect any significant association between institutionalization and/or adherence rates to ERAS program with primary endpoints. These outcomes were independently influenced by gender, intra- and postoperative blood transfusions, non-standard resections, and standard anesthesia protocol.

Keywords Colorectal surgery · ERAS · Major morbidity · Anastomotic leakage

Introduction

Several meta-analyses of randomized controlled trials [1–3] on Enhanced Recovery After Surgery (ERAS) have shown a marked reduction in overall morbidity rates and length of stay (LOS) in patients undergoing colorectal surgery (CRS). However, implementation of ERAS programs outside of clinical trials is still extremely variable [4–6]. Different aspects of the program are vulnerable to non-compliance and this may explain wide differences in reported adherence rates to program items [7–9]. Furthermore, the relative benefit of any specific item of the program and the role of overall, preoperative, intraoperative and postoperative adherence to the program itself are still debated [10–15].

During the early phase of program implementation, the adherence rate to program items rarely exceeds 50% [16], needing to reach at least 70% [17] to significantly improve outcomes. A recent Spanish multicenter cohort study [18] reported a mean adherence rate to ERAS items at 64%, reaching 73% in centers declaring an institutional ERAS

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program. Another European multicenter study also showed a mean overall adherence rate at 75% [13]. Even after a full ERAS program implementation, however, an adherence rate above 70% is generally achieved in less than a quarter of cases [19].

Earlier studies of ERAS programs in CRS have focused primarily on the benefits of reducing overall morbidity rates and LOS [3, 13, 20], with little or no impact on major complications and anastomotic leakage (AL). More recent series have shown that high adherence rate to ERAS program items can have a significant impact also on major complications; in particular, the adherence rate to post-operative ERAS items, usually representing the Achilles' heel of any ERAS program even after a well-structured implementation, was particularly significant [15, 18, 21, 22]. The Italian ColoRectal Anastomotic Leakage (iCral) study group, after completing a first multicenter prospective observational study [23–26], started a second prospective observational study (iCral2) to investigate the interaction between adherence to the items of the ERAS program and early postoperative outcomes.

Materials and methods

Prospective enrollment was carried out from January 2019 to June 2020 in 38 surgical centers, participating to iCral2 on a voluntary basis. All patients submitted to elective CRS with anastomosis were assessed for inclusion in the study according to explicit inclusion/exclusion criteria (Table 1).

According to the median number of cases assessed per month of recruitment, each single center was defined as high volume (≥ 10 cases/month) or low volume (< 10 cases/month). The existence of an institutional ERAS protocol (having local implemented ERAS team and protocol, supported by a specific resolution of the hospital/company strategic management) was declared by 27 (71.0%) participating centers.

All data of the included patients were prospectively uploaded into a web-based database via an electronic case report form, specifically designed for iCral2, protected by access credentials for each center/investigator. Continuous and discrete variables related to biometric data, patient-related risk factors, indication and type of surgical procedure, adherence to the ERAS program items, and outcomes were recorded. Quality control of data for consistency, plausibility and completeness was performed on each single record by local investigators and subsequently validated by the study coordinator, resolving any discrepancy through strict cooperation. The 21 items of the ERAS program and the specific adherence criteria (Table 2) were adapted from the 2013 ERAS Society™ guidelines [27].

During the perioperative period patients were examined daily by local investigators, who were free to decide for complementary imaging and any further action according to their local criteria.

Outcomes

During the follow-up, any complication (intended as any adverse event) was recorded and graded according to Clavien-Dindo [28, 29], as well as any unplanned readmission, any reoperation, any death and overall length of stay (LOS), inclusive of any readmission. AL was defined and graded according to international consensus [30, 31]. Patients were followed up on an outpatient basis for up to 6 weeks after hospital discharge.

Primary endpoints were AL and major morbidity (MM, any adverse event grade > II according to Clavien-Dindo) rates; secondary endpoints were overall morbidity (OM, any adverse event) and failure to achieve optimal recovery (FAOR), a composite endpoint based on cases without MM, AL, readmission, reoperation and/or death, with overall LOS ≤ the median value [15].

Statistical analysis

All quantitative values were expressed as mean ± standard deviation (SD) and 95% confidence intervals (95% CI), categorical data with percentage frequencies and discrete variables with median and interquartile range (IQR).

A descriptive analysis of the whole cohort according to the presence/absence of an institutional ERAS

Table 1 Inclusion–exclusion criteria

Inclusion criteria	Patients undergoing colo-rectal resection with anastomosis (laparoscopic, robotic, open or converted approach), including Hartmann's reversals
	American Society of Anesthesiologists (ASA) class I, II or III
	Elective or delayed urgency (> 48 h from admission) surgery
	Patient's written informed consent for inclusion in the study and processing of sensitive data
Exclusion criteria	Patients with a protective derivative stoma (proximal to the anastomosis)
	Transanal resection
	Pregnancy
	Hyperthermic chemotherapy (HIPEC) for carcinomatosis

Table 2 Definition and criteria of adherence to ERAS program items

Item		Adherence criteria
Preoperative	Prehabilitation	All patients showing MNA-SF < 12 (malnourished or suspect for malnutrition) and BMI > 30 (obesity) receive specific nutritional consultation. Patients receive a standard protocol of physical activity to be accomplished in the preoperative period;
	Counseling	Patients receive full information and suggestions regarding perioperative program from surgeon, anesthesiologist and case-manager
	Preoperative Immunonutrition	Patient is administered Impact Oral ™ (Nestlè Health Science, Italy) 330 ml per os, three briks per day during 5 days preceding surgery or two bricks per day during 7 days preceding surgery
	Antithrombotic prophylaxis	Patient receives graduate compression stockings and/or pneumatic compression device, together with prophylaxis with low molecular weight heparin during the perioperative period, to be extended up to 28 days after surgery in case of malignancy
	Antibiotic prophylaxis	Patient is administered i.v. antibiotic 30 to 60 min before incision, according to local protocols
	No bowel preparation	No routine bowel preparation is used, except in case of anticipated need for covering stoma
	Oral carbohydrates load & preoperative fasting	Carbohydrates rich beverage (12.5% maltrodextrins, PreOp™, Nutricia Italy) is given preoperatively (800 ml on the evening before surgery and 400 ml 2 to 3 h before surgery). Preoperative fasting is limited to two hours for clear liquids (water, coffee, tea) and to 6 h for milk and solid food
	No premedication	No long- or medium-action sedatives. Short and ultra-short acting sedatives (e.g. Lorazepam, Midazolam, Methohexital, Dexmedetomidine, Ketamine) are allowed before performing spinal, epidural or loco-regional anesthesia
Intraoperative	PONV prophylaxis	Postoperative nausea/vomiting prophylaxis is administered according to individual risk assessment (Apfel score) through a multimodal approach
	Normothermia	Body temperature is monitored during surgery, utilizing fluid warmers and/or thermic blankets as necessary
	Standard anesthesia protocol	General anesthesia through short-acting anesthetics, cerebral activity monitoring to enhance recovery and to reduce postoperative delirium, anesthesia level monitoring and complete reversal of neuromuscular blockade
	Intraoperative fluid management	Restrictive fluid therapy (defined as maintenance fluids at < 2 ml/kg/h) or goal-oriented fluid therapy (stroke volume)
	Multimodal analgesia	Use of more than two drugs or analgesia strategies (TAP-block or spinal anesthesia for minimally invasive surgery; thoracic epidural anesthesia for open surgery) in order to reduce the use of opiates
	Minimally invasive surgery	Patient submitted to laparoscopic, robotic or video-assisted surgery (conversions to open surgery included on a intention-to-treat basis)
	No nasogastric tube	Nasogastric tube, if used, is removed at the end of surgery
	No drain	No drain is placed in the abdominal cavity (pelvic drain allowed for pelvic surgery with low colorectal anastomosis)
Postoperative	Bladdder catheter	Urinary catheter removed on POD 1 (up to POD 2 in case of pelvic surgery)
	Early mobilization	Patient receives passive mobilization on POD 0, active mobilization on POD 1
	Gut motility stimulation	Patient receives chewing-gum twice daily starting on POD 1
	Early oral feeding	Patient receives liquid oral diet starting 6 h after surgery and semisolid diet starting on POD 1
	Pre-discharge check	Patient is checked just before discharge at home concerning adequate oral intake, bowel function, adequate pain control, active mobilization, no clinical/serological evidence of any postoperative complication, full agreement to go home

MNA-SF mini nutritional assessment short form, *PONV* postoperative nausea/vomiting;

program and univariable analyses for the endpoints were performed using cross-tabulations with Chi-square and/or Fisher tests for categorical data, Mann–Whitney *U* test or Kruskal–Wallis test for continuous and discrete variables. In order to measure variable multicollinearity [32], the variance inflation factor (VIF) was calculated using multiple linear regression for all the endpoints.

Any significant variable at univariate analysis (excluding any variable showing VIF > 4) was then included in a multivariate analysis model using logistic regression, presenting odds ratio (OR) and 95% CI. Quantitative variables such as age (years), operation length (minutes) and adherence rates (%) to ERAS program items were categorized below or above their median values. Other variables were categorized

according to predefined ranges: mini nutritional assessment—short form (MNA-SF, [33]) < 12, indicating potential malnutrition; BMI (body mass index, Kg/m^2) ≤ 25.0, 25.1 to 30.0 and > 30.0. Surgical procedures were categorized as standard (anterior resection, right colectomy, left colectomy) versus non-standard (splenic flexure resection, transverse colectomy, Hartmann's reversal, subtotal and total colectomy, other) resections.

For all statistical tests the significant level was set at $p < 0.05$. All analyses were conducted using StatsDirect™ statistical software (StatsDirect Ltd., UK).

Sample size

The sample size has been estimated based on data reported in literature [17]; specifically, it has been reported that adherence to ≥ 70% of the items of an ERAS program determines a significant reduction in surgical complications after colorectal surgery (from approximately 25% to approximately 18%). We performed the sample size estimation using a two-sided two-sample comparison of proportions ($p\ 1 = 0.25$; $p\ 2 = 0.18$). We set the significance level at 5% and the power at 95%, with a total of 1748 cases required (approximately 874 cases per arm predicted in low (< 70%) versus high (≥ 70%) adherence to the ERAS program items).

Ethics

The study was conducted on the basis of the Declaration of Helsinki and the principles of the guidelines for good clinical practice E6 (R2). The study protocol was approved by the ethics committee of the coordinating center (Marche Regional Ethics Committee—CERM—2018/334 released on 11/28/2018) and then registered at *ClinicalTrials.gov* (*Anastomotic Leakage and Enhanced Recovery Pathways After Colorectal Surgery [iCral2]; NCT03771456*). Subsequently, all other centers were authorized to participate from their local ethics committee. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies [34]. Individual participant-level anonymized datasets will be available upon reasonable request by contacting the study coordinator.

Results

Outcome data

After a mean ± SD (standard deviation) recruitment period of 14.9 ± 3.6 months (range 6.7–18.0; median 16.5; interquartile range [IQR] 11–18), 6627 potentially eligible cases were assessed, of which 3830 (57.8%) included in the study (Fig. 1).

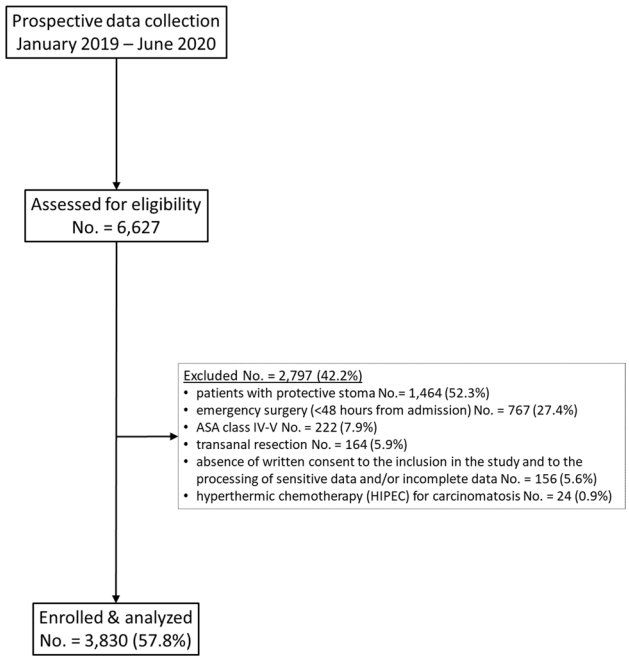

Fig. 1 Study flowchart according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines

Median (IQR) number of assessed patients per single center was 136 (105–198), while the median (IQR) number of included patients per single center was 82 (51–116). After a median follow-up of 57 days (IQR 47–88), 1,475 adverse events (Table 3) were recorded in 1107 patients (OM rate 28.9%), of which 344 (23.3%) were Clavien-Dindo grade > II in 181 patients (MM rate 4.7%).

There were 161 ALs (rate 4.2%), diagnosed after a median (IQR) of 5 (3–9) days. AL diagnosis was established by intravenous contrast CT scan in 58 (36.0%), clinical criteria in 57 (35.4%), endoluminal contrast CT scan in 36 (22.4%), endoluminal contrast enema in 6 (3.7%) and gross findings at reoperation in the remaining 4 cases (2.5%). Regarding AL grading, a grade A leak was recorded in 2 cases (1.2%), grade B in 36 (22.4%) and grade C in the remaining 123 cases (76.4%). There were 1487 cases (38.8%) with FAOR and 26 deaths (mortality 0.7%). Median overall LOS (IQR) was 6 (4–8) days, with 114 re-admissions (3.0%) and 196 re-operations (5.1%).

ERAS adherence, institutionalization and outcome data

Median (IQR) overall ERAS items adherence rate (Fig. 2; Table 4) was 71.4% (52.4–80.9). Patients treated within an institutional ERAS program had a significantly higher

Table 3 Adverse events and grading

Clavien Dindo Grade	I	II	IIIa	IIIb	IVa	IVb	Total
Anastomotic leakage	2	28	8	108	11	4	161
Intra-abdominal bleeding	1	12	3	14	2	2	34
Intra-abdominal abscess	1	26	22	5	0	1	55
Acute mesenteric ischemia	0	0	0	3	0	0	3
Acute peptic ulcer/erosive gastritis	0	3	3	0	0	0	6
Anastomotic bleeding	25	32	25	2	1	0	85
Anemia	17	174	0	2	0	1	194
DVT/pulmonary embolism	0	6	0	0	0	3	9
Fever	34	79	0	1	0	0	114
Bowel obstruction	0	19	2	21	0	0	42
Neurologic	3	4	1	0	0	0	8
Other	80	85	11	11	4	6	197
Paralytic ileus	69	92	1	0	0	0	162
Pneumonia/respiratory failure	5	51	3	1	12	5	77
Small bowel perforation	0	0	1	7	0	0	8
Surgical site infections	63	91	10	7	0	0	171
Trocar/wound bleeding	14	4	1	2	0	0	21
Urinary retention	31	25	1	0	0	0	57
Acute renal failure	9	9	0	0	1	2	21
Cardiac dysfunction/failure	6	31	3	0	7	3	50
Total	360	771	95	184	38	27	1475

DVT deep venous thrombosis

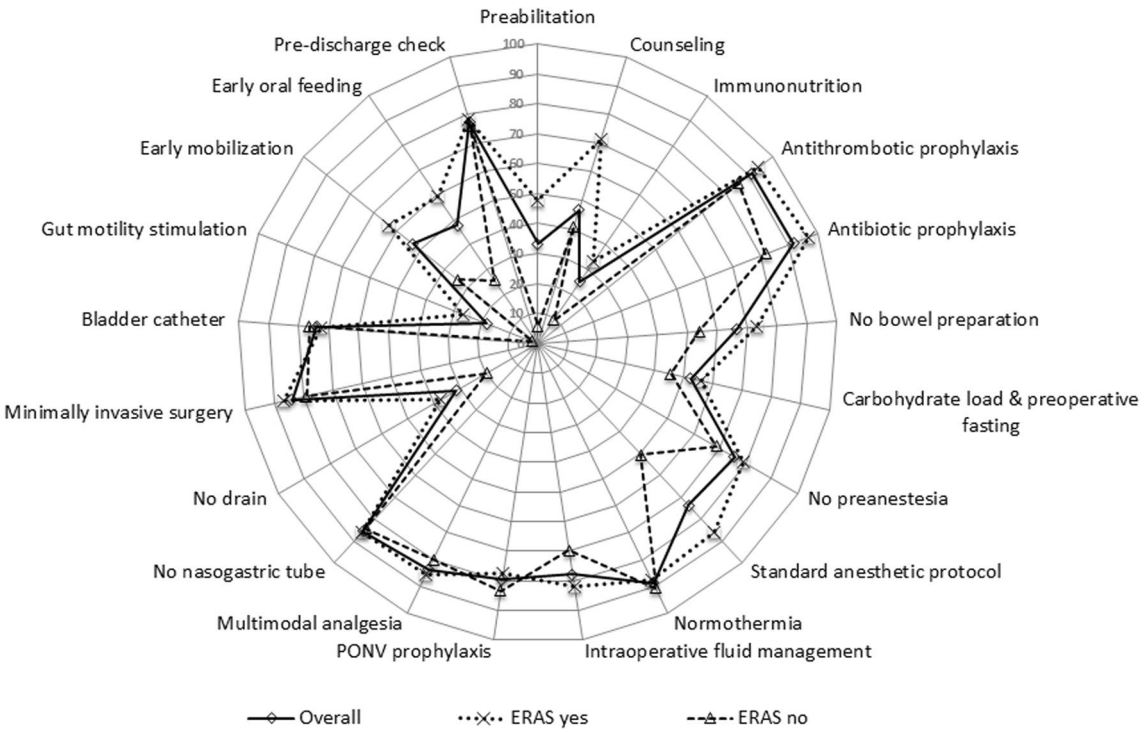

Fig. 2 Adherence rates (%) to ERAS program items in the whole population (Overall) and according to the presence (ERAS yes) or absence (ERAS no) of an institutional ERAS protocol

Table 4 Study variables (patients, procedures and ERAS program items) and outcomes in the whole population and according to the presence/absence of an institutional ERAS program

	Overall (No. = 3830)	Institutional ERAS (No. = 2501)	No Institutional ERAS (No. = 1329)	
Patients' variables	No. (%)	No. (%)	No. (%)	*p* value
Age, median (IQR), years	69.4 (58.1–78.0)	69.2 (57.0–79.4)	69.7 (60.4–77.4)	0.055
Male gender	1909 (49.8)	1201 (48.0)	708 (53.3)	0.002
Body Mass Index, median (IQR), Kg/m^2	25.00 (22.49–27.76)	24.74 (22.22–27.68)	25.63 (23.05–28.04)	< 0.0001
ASA class I-II	2429 (63.4)	1660 (66.4)	769 (57.9)	< 0.0001
Diabetes	565 (14.7)	327(13.1)	238 (17.9)	< 0.0001
Chronic renal failure	177 (4.6)	106 (4.2)	71 (5.3)	0.121
Dialysis	11 (0.3)	5 (0.2)	6 (0.5)	0.206
Perioperative steroids	58 (1.5)	33 (1.3)	25 (1.9)	0.175
Neo-adjuvant therapy	108 (2.8)	45 (1.8)	63 (4.7)	< 0.0001
Preoperative blood transfusion(s)	191 (5.0)	127 (5.1)	64 (4.8)	0.722
Intra- and/or postoperative blood transfusion(s)	256 (6.7)	151 (6.0)	105 (7.9)	0.028
Chronic liver disease	33 (0.9)	23 (0.9)	10 (0.8)	0.594
MNA-SF, median (IQR)	13 (12–13)	13 (12–13)	12 (11–13)	< 0.0001
Surgical procedure				
Anterior resection	569 (14.9)	407 (16.3)	162 (12.2)	< 0.0001
Right colectomy	1532 (40.0)	997 (39.9)	535 (40.3)	
Left colectomy	1167 (30.5)	761 (30.4)	406 (30.5)	
Splenic flexure resection	118 (3.1)	72 (2.9)	46 (3.5)	
Hartmann's reversal	121 (3.2)	82 (3.3)	39 (2.9)	
Transverse colectomy	81 (2.1)	56 (2.2)	25 (1.9)	
(sub)total colectomy	74 (1.9)	32 (1.3)	42 (3.2)	
Other resection	168 (4.4)	94 (3.8)	74 (5.6)	
Surgery for malignancy	2766 (72.2)	1729 (69.1)	1037 (78.0)	< 0.0001
Stapled anastomosis	3428 (89.5)	2236 (89.4)	1192 (89.7)	0.782
Intracorporeal anastomosis	2506 (65.4)	1713 (68.5)	793 (59.7)	< 0.0001
Operation length, median (IQR), minutes	170 (125–210)	172 (125–220)	168 (120–205)	0.002
High volume (≥ 10.0 cases/month)	2604 (68.0)	1633 (65.3)	971 (73.1)	< 0.0001
Surgical approach				
Converted	169 (4.4)	113 (4.5)	56 (4.2)	< 0.0001
Laparoscopic	2827 (73.8)	1995 (79.8)	832 (62.6)	
Open	608 (15.9)	330 (13.2)	278 (20.9)	
Robotic	226 (5.9)	63 (2.5)	163 (12.3)	
ERAS program items				
Overall items adherence, median (IQR), %	71.4 (52.4–80.9)	76.2 (61.9–85.7)	57.1 (42.9–71.4)	< 0.0001
Prehabilitation	1269 (33.1)	1193 (47.7)	76 (5.7)	< 0.0001
Counseling	2327 (60.7)	1785 (71.4)	542 (40.8)	< 0.0001
Preoperative immunonutrition	952 (24.8)	827 (33.1)	125 (9.4)	< 0.0001
Antithrombotic prophylaxis	3489 (91.1)	2352 (94.0)	1137 (85.6)	< 0.0001
Antibiotic prophylaxis	3511 (91.7)	2426 (97.0)	1025 (77.1)	< 0.0001
No bowel preparation	2549 (66.5)	1831 (73.2)	718 (54.0)	< 0.0001
Oral carbohydrates load & preoperative fasting	1996 (52.1)	1393 (55.7)	603 (45.4)	< 0.0001

Table 4 (continued)

	Overall (No. = 3830)	Institutional ERAS (No. = 2501)	No Institutional ERAS (No. = 1329)	
No premedication	2894 (75.6)	1981 (79.2)	913 (68.7)	< 0.0001
Preoperative items adherence, median (IQR), %	57.1 (42.9–85.7)	71.43 (42.9–85.7)	42.9 (28.6–57.1)	< 0.0001
PONV prophylaxis	3049 (79.6)	1940 (77.6)	1109 (83.4)	< 0.0001
Normothermia	3392 (88.6)	2188 (87.5)	1204 (90.6)	0.004
Standard anesthesia protocol	2826 (73.8)	2154 (86.1)	672 (50.6)	< 0.0001
Intraoperative fluid management	2981 (77.8)	2055 (82.2)	926 (69.7)	< 0.0001
Multimodal analgesia	3205 (83.7)	2140 (85.6)	1065 (80.1)	< 0.0001
Minimally invasive surgery	3222 (84.1)	2171 (86.8)	1051 (79.1)	< 0.0001
No nasogastric tube	3273 (85.4)	2153 (86.1)	1120 (84.3)	0.142
No drain	1206 (31.5)	943 (37.7)	263 (19.8)	< 0.0001
Intraoperative items adherence, median (IQR), %	88.9 (66.7–88.9)	88.9 (77.8–88.9)	77.8 (55.7–88.9)	< 0.0001
Early removal of bladder catheter	2834 (74.0)	1819 (72.7)	1015 (76.4)	0.014
Gut motility stimulation	697 (18.2)	673 (26.9)	24 (1.8)	< 0.0001
Early mobilization	2038 (53.2)	1583 (63.3)	455 (34.2)	< 0.0001
Early oral feeding	1825 (47.6)	1488 (59.5)	337 (25.4)	< 0.0001
Pre-discharge check	2959 (77.2)	1950 (78.0)	1009 (75.9)	0.162
Postoperative items adherence, median (IQR), %	60.0 (20.0–80.0)	80.0 (40.0–80.0)	40.0 (20.0–60.0)	< 0.0001
Outcomes				
Overall morbidity	1107 (28.9)	716 (28.0)	391 (29.4)	0.607
Major morbidity	181 (4.7)	107 (4.3)	74 (5.5)	0.073
Anastomotic leakage	161 (4.2)	110 (4.4)	51 (3.8)	0.410
Mortality	26 (0.7)	11 (0.4)	15 (1.1)	0.013
Optimal recovery	2343 (61.2)	1541 (61.6)	802 (60.3)	0.443
Readmission	114 (3.0)	81 (3.2)	33 (2.5)	0.226
Reoperation	196 (5.1)	135 (5.4)	61 (4.6)	0.315
LOS, median (IQR), days	6 (4–8)	6 (4–8)	6 (4–8)	0.09

ASA American Society of Anesthesiologists, *MNA-SF* mini nutritional assessment short form, *PONV* postoperative nausea/vomiting, *LOS* length of stay

overall adherence rate to ERAS program items as well as significantly higher adherence rates to most of the single program items, the only exceptions being normothermia, no nasogastric tube, PONV (postoperative nausea/vomiting) prophylaxis, early removal of bladder catheter and pre-discharge check. Concerning patient-related variables, patients treated within an institutional ERAS program had significantly lower rates of male gender, ASA class III cases, diabetes, neo-adjuvant treatments and perioperative blood transfusions, significantly lower BMI and significantly higher MNA-SF values. Concerning treatment-related variables, they showed a significantly lower rate of cases treated in a high-volume center, surgery for malignancy, open and robotic approach, a significantly higher rate of intra-corporeal anastomosis and significantly longer operative time.

No significant differences regarding outcomes were recorded, the only exception being a significantly lower mortality rate (0.4% vs 1.1%, $p = 0.013$) in patients treated within an institutional ERAS program.

Primary endpoints analyses

MM rates (Table 5) were independently influenced by (Fig. 3) intra- and/or postoperative blood transfusions (OR 7.79, 95% CI 5.46–11.10; $p < 0.0001$) and standard anesthesia protocol (OR 0.68, 95% CI 0.48–0.96; $p = 0.028$).

AL rates (Table 6) were independently influenced by (Fig. 4) male gender (OR 1.48, 95% CI 1.06–2.07; $p = 0.021$), intra- and/or postoperative blood transfusions (OR 4.29, 95% CI 2.93–6.50; $p < 0.0001$) and non-standard resections (OR 1.49, 95% CI 1.01–2.22; $p = 0.049$).

Table 5 Univariate and multivariate analyses for major morbidity

Variable	Pattern	Total		Univariate			Multivariate[a]				
		No	%	No	%	*p*	β	β SE	OR	95% CI	*p*
Age (years)	≤68.9	1916	50.0	75	3.9	< 0.0001					
	> 68.9	1914	50.0	106	5.5		0.1107	0.6309	1.12	0.79–1.57	0.528
Body Mass Index (Kg/m^2)	≤25.0	1926	50.3	109	5.7	0.010					
	25. 1–30.0	1385	36.2	47	3.4		−0.0016	−0.0298	0.99	0.89–1.11	0.976
	> 30.0	519	13.6	26	5.0						
ASA class	I-II	2429	63.4	92	3.8	0.001					
	III	1401	36.6	89	6.4		0.1198	1.3147	1.13	0.94–1.35	0.188
Surgical approach	Converted	169	4.4	12	7.1	< 0.0001					
	Laparoscopic	2827	73.8	112	4.0		−0.1094	−1.2710	0.89	0.75–1.06	0.204
	Open	608	15.9	49	8.1						
	Robotic	226	5.9	8	3.5						
Intra- and postoperative blood transfusions	No	3574	93.3	119	3.3	< 0.0001					
	Yes	256	6.7	62	24.2		2.0527	11.3523	7.79	5.46–11.10	< 0.0001
Anastomosis 2	Extracorp	1324	34.6	82	6.2	0.002					
	Intracorp	2506	65.4	99	4.0		−0.0967	−0.8710	0.91	0.73–1.13	0.384
Standard anesthesia protocol	No	1004	26.2	65	6.5	0.003					
	Yes	2826	73.8	116	4.1		−0.3853	−2.1964	0.68	0.48–0.96	0.028
Minimally invasive surgery	No	608	15.9	49	8.1	< 0.0001					
	Yes	3222	84.1	132	4.1		−0.5706	−1.7578	0.56	0.29–1.07	0.079
Bladder catheter removed POD 1-2	No	996	26.0	70	7.0	< 0.0001					
	Yes	2834	74.0	111	3.9		−0.2154	−1.2399	0.81	0.57–1.13	0.215
Overall ERAS items adherence rate (%)	≤71.4	2216	57.9	119	5.4	0.027					
	> 71.4	1614	42.1	62	3.8		VIF 4.3				
Postoperative ERAS items adherence rate (%)	≤60.0	2183	57.0	116	5.3	0.048	VIF 5.8				
	> 60.0	1647	43.0	65	3.9						

ASA American Society of Anesthesiologists, *VIF* variance inflation factor

[a]Deviance (likelihood ratio) chi-square = 152.503463 df = 9 $P < 0{,}0001$

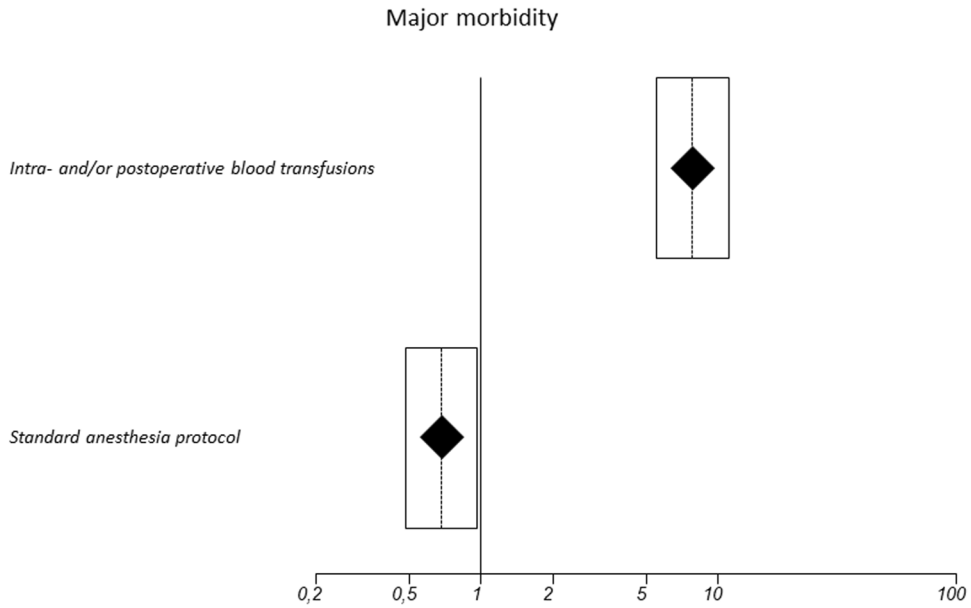

Fig. 3 Forest plot (log scale) of independent variables for major morbidity; diamonds show ORs, boxes show 95% CIs

Table 6 Univariate and multivariate analyses for anastomotic leakage

		Total		Univariate			Multivariate[a]				
Variable	Pattern	No	%	No	%	*p*	β	β SE	OR	95% CI	*p*
Gender	Female	1921	50.2	64	3.3	0.007					
	Male	1909	49.8	97	5.1		0.3951	2.3341	1.48	1.06–2.07	0.019
ASA class	I–II	2429	63.4	90	3.7	0.043					
	III	1401	36.6	71	5.1		0.0087	0.0481	1.01	0.71–1.44	0.961
Diabetes	No	3265	85.2	127	3.9	0.027					
	Yes	565	14.8	34	6.0		0.3200	1.4945	1.38	0.90–2.09	0.135
Intra- and postoperative blood transfusions	No	3574	93.3	122	3.4	< 0.0001					
	Yes	256	6.7	39	15.2		1.4742	7.2587	4.36	2.93–6.50	< 0.0001
Standard resection	No	562	14.7	34	6.0	0.018	0.3992	1.9638	1.49	1.01–2.22	0.049
	Yes	3268	85.3	127	3.9						
Operation length (minutes)	≤ 170	1965	51.3	69	3.5	0.028					
	> 170	1865	48.7	92	4.9		0.2522	1.4940	1.29	0.92–1.79	0.135
Restrictive or goal-directed fluid therapy	No	849	22.2	47	5.5	0.036					
	Yes	2981	77.8	114	3.8		− 0.2159	− 1.0770	0.80	0.54–1.19	0.281
Bladder catheter removed POD 1–2	No	996	26.0	57	5.7	0.005					
	Yes	2834	74.0	104	3.7		− 0.1754	− 1.3641	0.79	0.42–1.15	0.173
Postoperative ERAS items adherence rate (%)	≤ 60.0	2183	57.0	105	4.8	0.031	VIF 5.8				
	> 60.0	1647	43.0	56	3.4						

[a]Deviance (likelihood ratio) chi-square = 81,629,129; df = 8 $P < 0.0001$

ASA American Society of Anesthesiologists, *Standard resections are* anterior resection, right colectomy, left colectomy; non-standard resections are: splenic flexure resection, Hartmann's reversal, transverse colectomy, (sub)total colectomy, other resection; *VIF* variance inflation factor

Secondary endpoints analyses

OM rates (Table 7) were independently influenced (Fig. 5) by the following variables: age > 68.9 years (OR 1.35, 95% CI 1.13–1.62; $p = 0.001$), MNA-SF > 12 (OR 0.79, 95% CI 0.65–0.96; $p = 0.015$), intra- and/or postoperative blood transfusions (OR 72.46, 95% CI 37.00–141.90; $p < 0.0001$), non-standard resections (OR 1.66; 95% CI 1.33–2.06; $p < 0.0001$), operation length > 170 min (OR 1.47, 95% CI 1.24–1.74; $p < 0.0001$), no preoperative immunonutrition (OR 1.45, 95% CI 1.19–1.76; $p < 0.001$); no bowel preparation (OR 1.38, 95% CI 1.14–1.67; $p < 0.001$); minimally

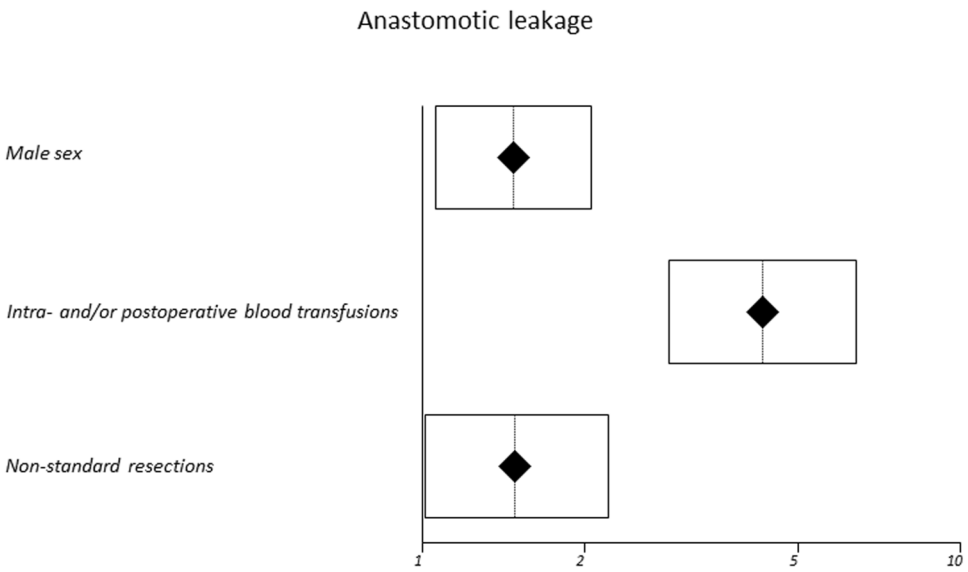

Fig. 4 Forest plot (log scale) of independent variables for anastomotic leakage; diamonds show ORs, boxes show 95% CIs

invasive surgery (OR 0.58, 95% CI 0.41–0.82; $p=0.002$) and early removal of bladder catheter (OR 0.69, 95% CI 0.56–0.86 $p<0.001$).

FAOR rates (Table 8) were independently influenced by the following variables (Fig. 6): age > 68.9 years (OR 1.39, 95% CI 1.15–1.67; $p<0.001$), MNA-SF > 12 (OR 0.73, 95% CI 0.59–0.90; $p=0.002$), stapled anastomosis (OR 0.56, $p<0.001$), intracorporeal anastomosis (OR 0.78, 95% CI 0.56–0.94; $p=0.038$), operation length > 170 min (OR 1.31, 95% CI 1.09–1.57; $p=0.002$), no bowel preparation (OR 0.49, 95% CI 0.41–0.61; $p<0.0001$), oral carbohydrates load and 2–6 h preoperative fasting (OR 0.60, 95% CI 0.47–0.76; $p=0.002$), non-standard anesthesia protocol (OR 1.59, 95% CI 1.19–2.13; $p=0.003$), minimally invasive surgery (OR 0.50, 95% CI 0.35–0.71; $p=0.0002$), no drain (OR 0.67, 95% CI 0.53–0.85; $p=0.0009$), early bladder catheter removal (OR 0.63, 95% CI 0.50–0.79; $p=0.0001$), pre-discharge check (OR 0.52, 95% CI 0.41–0.67; $p<0.0001$) and overall morbidity (OR 16.50, 95% CI 13.26–20.54; $p<0.0001$).

A complete description of all variables included in univariate analyses for primary and secondary endpoints is available as supplemental material.

Discussion

This prospective multicenter observational study investigated the effects of a declared institutional ERAS program and adherence to 21 ERAS program items on early outcomes after elective colorectal surgery in more than 3800 patients enrolled over a 18 months period in 38 Italian surgical centers, without any limitation concerning the presence of an institutional enhanced recovery pathway or center caseload.

The outcomes recorded in this study (OM rate 28.7%, MM rate 4.7%, AL rate 4.2% and mortality rate 0.7%) are similar to those recorded in the previous iCral prospective observational study [23, 25] and well within the ranges reported in most recent literature dealing with colorectal ERAS program adherence [14, 18, 21, 22].

Median value of overall adherence rate to ERAS program was 71.4% (Table 4), significantly higher ($p<0.0001$) in centers declaring an institutional ERAS program (76.2%) than in others (57.1%), as previously recorded [18]. Nearly all ERAS program items reached a significantly higher adherence in institutional ERAS centers (Fig. 2), but PONV prophylaxis, normothermia, removal of nasogastric tube (if used) at the end of surgical procedure, early removal of bladder catheter and pre-discharge check were used in non-institutional ERAS centers as well, demonstrating that these items can be considered now standard care after colorectal resection even outside of established ERAS pathways. The presence of an institutional ERAS program, however, had no significant effect on all the endpoints of this study. The significant reduction of mortality rates in patients treated within an institutional ERAS program (0.4% vs 1.1%, Table 4) was probably the result of a selection bias of best performers in this specific subgroup, even though the limited number of deaths in the present study did not allow any multivariate analysis for this outcome. This underlines that having or declaring "an ERAS protocol is not enough" [7], structured implementation and auditing processes possibly being more important to improve program adherence and outcomes [22].

Previous similar studies on large prospective series [18, 21] detected an independent effect of ERAS program adherence on major morbidity rates, but little or no effect on AL rates; the present study failed to detect any significant effect on both primary endpoints. There are several possible

Table 7 Univariate and multivariate analyses for overall morbidity

Variable	Pattern	Total		Univariate			Multivariate[a]				
		No	%	No	%	*p*	β	β SE	OR	95% CI	*p*
Age (years)	≤68.9	1916	50.0	467	24.4	<0.0001					
	>68.9	1914	50.0	640	33.4		0.3002	3.2978	1.35	1.13–1.62	0.001
Gender	Female	1921	50.2	519	27.0	0.009					
	Male	1909	49.8	588	30.8		0.1446	1.7262	1.15	0.98–1.36	0.843
[a]ASA class	I–II	2429	63.4	617	25.4	<0.0001					
	III	1401	36.6	490	35.0		0.0757	0.7767	1.08	0.89–1.30	0.437
[b]MNA-SF	≤12	911	23.8	321	35.2	<0.0001					
	>12	2919	76.2	786	26.9		−0.2307	−2.3134	0.79	0.65–0.96	0.015
Diabetes	No	3265	85.2	915	28.0	0.004					
	Yes	565	14.8	192	34.0		0.0446	0.3748	1.04	0.83–1.32	0.708
Chronic renal failure	No	3653	95.4	1027	28.1	<0.0001					
	Yes	177	4.6	80	45.2		0.0332	0.1628	1.03	0.69–1.54	0.871
Dyalisis	No	3819	99.7	1099	28.8	0.003					
	Yes	11	0.3	8	72.7		1.3346	1.7021	3.79	0.81–17.66	0.087
Chronic liver disease	No	3797	99.1	1090	28.7	0.007					
	Yes	33	0.9	17	51.5		0.6971	1.6141	2.01	0.86–4.68	0.106
Center volume	Low	1226	32.0	381	31.1	0.042					
	High	2604	68.0	726	27.9		−0.1088	−1.1153	0.89	0.74–1.08	0.265
Surgical approach	Converted	169	4.4	90	53.3	<0.0001					
	Laparoscopic	2827	73.8	715	25.3		−0.1673	−1.9323	0.84	0.71–1.01	0.056
	Open	608	15.9	238	39.1						
	Robotic	226	5.9	64	28.3						
Preoperative blood transfusions	No	3639	95.0	1022	28.1	<0.0001					
	Yes	191	5.0	85	44.5		0.0323	0.1637	1.03	0.70–1.52	0.869
Intra- and postoperative blood transfusions	No	3574	93.3	854	23.9	<0.0001					
	Yes	256	6.7	253	98.8		4.2751	12.3812	72.46	37.00–141.90	<0.0001
[c]Standard resection	No	562	14.7	212	37.7	<0.0001	0.5059	4.5152	1.66	1.33–2.06	<0.0001
	Yes	3268	85.3	895	27.4						
Anastomosis 1	handsewn	402	10.5	137	34.1	0.018					
	stapled	3428	89.5	970	28.3		−0.1576	−1.0633	0.85	0.64–1.14	0.287
Anastomosis 2	extracorp	1324	34.6	460	34.7	<0.0001	0.0597	0.4694	1.06	0.83–1.36	0.639
	intracorp	2506	65.4	647	25.8						
Operation length (minutes)	≤170	1965	51.3	512	26.1	<0.0001					
	>170	1865	48.7	595	31.9		0.3877	4.5160	1.47	1.24–1.74	<0.0001
Counseling	No	1503	39.2	463	30.8	0.037					
	Yes	2327	60.8	644	27.7		−0.1942	−1.6583	0.82	0.65–1.03	0.097

Table 7 (continued)

Variable	Pattern	Total		Univariate			Multivariate[a]				
		No	%	No	%	*p*	β	β SE	OR	95% CI	*p*
Preoperative immunonutrition	No	2878	75.1	874	30.4	0.002	0.3703	3.7607	1.45	1.19–1.76	< 0.001
	Yes	952	24.9	233	24.5						
No bowel preparation	No	1281	33.4	336	26.2	0.010					
	Yes	2549	66.6	771	30.2		0.3249	3.3286	1.38	1.14–1.67	< 0.001
Restrictive or goal-directed fluid therapy	No	849	22.2	281	33.1	0.003					
	Yes	2981	77.8	826	27.7		− 0.0300	− 0.2246	0.97	0.74–1.26	0.822
Multimodal analgesia	No	625	16.3	202	32.3	0.044					
	Yes	3205	83.7	905	28.2		− 0.0894	− 0.6458	0.91	0.69–1.20	0.518
Minimally invasive surgery	No	608	15.9	238	39.1	< 0.0001					
	Yes	3222	84.1	869	27.0		− 0.5417	− 3.0667	0.58	0.41–0.82	0.002
No nasogastric tube	No	557	14.5	189	33.9	0.005	0.1603	1.1467	1.17	0.89–1.54	0.251
	Yes	3273	85.5	918	28.0						
No drain	No	2624	68.5	794	30.3	0.007					
	Yes	1206	31.5	313	26.0		− 0.0719	− 0.6781	0.93	0.75–1.14	0.498
Bladder catheter removed POD 1–2	No	996	26.0	379	38.1	< 0.0001					
	Yes	2834	74.0	728	25.7		− 0.3695	− 3.3812	0.69	0.56–0.86	< 0.001
Overall ERAS items adherence rate (%)	≤ 71.4	2216	57.9	675	30.5	0.013					
	> 71.4	1614	42.1	432	26.8		VIF 4.3				
Intraoperative ERAS items adherence rate (%)	≤ 77.8	1909	49.9	613	32.1	< 0.0001					
	> 77.8	1921	50.1	494	25.7		0.0064	0.0489	1.00	0.78–1.30	0.961
Postoperative ERAS items adherence rate (%)	≤ 60.0	2183	57.0	668	30.6	0.008	IF 5.8				
	> 60.0	1647	43.0	439	26.6						

ASA American Society of Anesthesiologists, *MNA-SF* mini nutritional assessment short form, *Standard resections are* anterior resection, right colectomy, left colectomy; non-standard resections are: splenic flexure resection, Hartmann's reversal, transverse colectomy, (sub)total colectomy, other resection; *VIF* variance inflation factor

[a]Deviance (likelihood ratio) chi-square = 752,499,009 df = 26 $P < 0.0001$

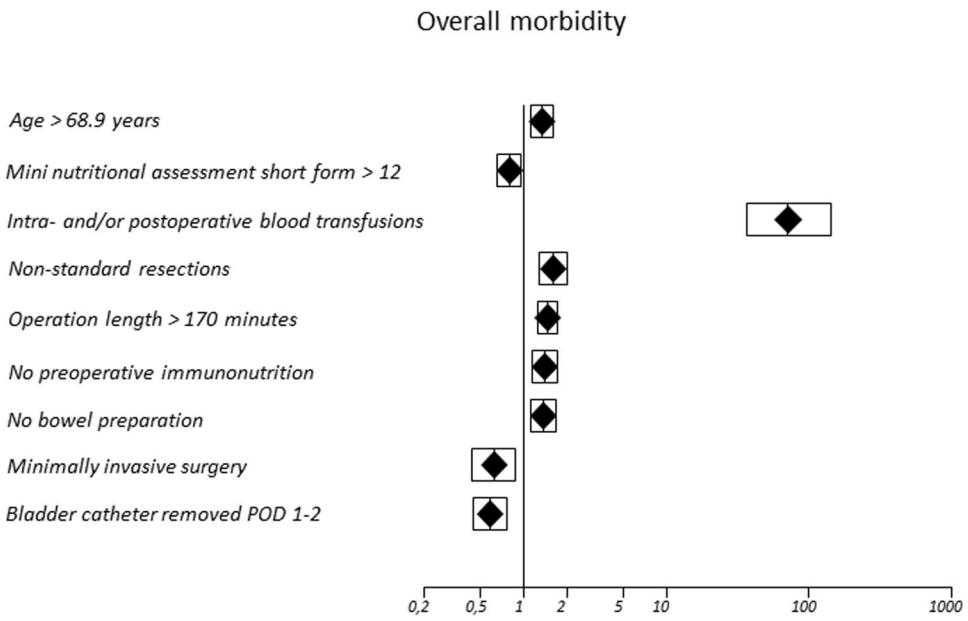

Fig. 5 Forest plot (log scale) of independent variables for overall morbidity; diamonds show ORs, boxes show 95% CIs

reasons behind this finding: first of all, the existence of variables multicollinearity [32], that was not addressed in previous studies, led to the exclusion of preoperative, postoperative and overall ERAS program items adherence rates from logistic regression models; second, it is possible that median adherence rates to pre- (57.1%) and postoperative (60.0%) ERAS program items recorded in the present study were too low to gather any effect; finally, is it possible that patients experiencing major morbidity and/or AL were more exposed to noncompliance with ERAS program items.

As a matter of fact, primary endpoints in this study (Tables 5, 6; Figs. 3, 4) were independently influenced by patient-related (male gender) and procedure-related (intra- and/or postoperative blood transfusions, non-standard resections) factors, standard anesthesia protocol being the only ERAS program item independently influencing major morbidity rates. Male gender is a well-known risk factor for leakage in pelvic colorectal anastomoses [35], and non-standard resections for transverse or splenic flexure lesions entail a higher AL risk [36, 37]. The independent role of intra- and/or postoperative blood transfusions confirmed the findings of the previous iCral prospective study [25]. We are probably facing an egg-hen issue in which it is still unclear if blood transfusions are a definite risk factor for poorer outcomes rather than a marker of bad performers (i.e. major comorbidities, larger and longer procedures, more advanced cancer stages); the well-known wide variability of perioperative transfusion practices in surgical units [38] and the recent introduction of "anemia management" item into ERAS programs [39, 40] deserve further prospective investigation, measuring intraoperative blood losses, hemoglobin levels and timing of blood transfusions vs timing of adverse events. The last 30 years witnessed a dramatic reduction of anesthesia related mortality rates [41]; the results of the present study highlight that these advances in anesthesiology have a significant impact on major complications as well [42].

Many variables independently influenced secondary endpoints (Tables 7, 8; Figs. 5, 6). Apart from patient-, procedure- and center-related factors, several ERAS program items independently influenced these outcomes. Preoperative immunonutrition showed a low compliance rate (24.8%), probably because it was not recommended [27] when this study protocol was developed. Anyway, it independently reduced overall morbidity rates and will probably receive higher compliance considering that a strong recommendation for preoperative nutritional support was given in most recent guidelines [39, 40]. No bowel preparation was performed in about two-thirds of cases, demonstrating controversial effects on the two secondary endpoints: it had a negative independent effect (OR 1.36) on overall morbidity (Table 7; Fig. 5), fueling the ongoing controversy with North-American ERAS guidelines [43] that recommend mechanical bowel preparation combined to the administration of oral antibiotics; on the other hand, it showed a protective independent effect (OR 0.49) on failure to achieve optimal recovery (Table 8; Fig. 6) rates, confirming its relevance as a core-item of ERAS program [14]. Minimally invasive surgery showed high (84%) adherence rate, independently reducing both overall morbidity (Table 7; Fig. 5) and failure to achieve optimal recovery (Table 8; Fig. 6) rates, and confirming the evidence of previous randomized studies [1–3, 20]. More than 100 years after the statements of Robert Lawson Tait *"When in doubt, drain"* and of William Stewart Halsted *"No drainage at all is better than the ignorant employment of it"* [44], drainage of the abdominal

Table 8 Univariate and multivariate analyses for failure to achieve optimal recovery

Variable	Pattern	Total		Univariate			Multivariate				
		No	%	No	%	*p*	β	β SE	OR	95% CI	*p*
Age (years)	≤ 68.9	1916	50.0	645	33.7	< 0.0001					
	> 68.9	1914	50.0	842	44.0		0.3267	3.4240	1.39	1.15–1.67	< 0.001
Body Mass Index (Kg/m^2)	≤ 25.0	1926	50.3	789	41.0	0.023					
	25.1–30.0	1385	36.2	510	36.8		− 0.0944	1.4883	0.91	0.80–1.03	0.137
	> 30.0	519	13.6	188	36.2						
ASA class	I-II	2429	63.4	869	35.8	< 0.0001	− 0.1001	− 0.9534	0.90	0.74–1.11	0.340
	III	1401	36.6	618	44.1						
MNA-SF	≤ 12	911	23.8	433	47.5	< 0.0001					
	> 12	2919	76.2	1054	36.1		− 0.3072	− 2.9257	0.73	0.59–0.90	0.003
Diabetes	No	3265	85.2	1236	37.9	0.003					
	Yes	565	14.8	251	44.4		0.0253	0.1988	1.02	0.80–1.31	0.824
Chronic renal failure	No	3653	95.4	1389	38.0	< 0.0001					
	Yes	177	4.6	98	55.4		0.2235	1.0676	1.25	0.83–1.88	0.286
Center volume	Low	1226	32.0	540	44.0	< 0.0001	0.0184	0.1685	1.01	0.82–1.26	0.886
	High	2604	68.0	947	36.4						
Surgical approach	Converted	169	4.4	101	59.8	< 0.0001					
	Laparoscopic	2827	73.8	947	33.5						
	Open	608	15.9	382	62.8						
	Robotic	226	5.9	57	25.2		− 0.2811	− 3.0573	0.75	0.63–0.90	0.002
Preoperative blood transfusions	No	3639	95.0	1383	38.0	< 0.0001					
	Yes	191	5.0	104	54.5		0.1508	0.7630	1.16	0.79–1.71	0.445
Intra- and postoperative blood transfusions	No	3574	93.3	1292	36.1	< 0.0001	− 0.3599	9.3853	0.69	0.48–1.01	0.059
	Yes	256	6.7	195	76.2						
[c]Standard resection	No	562	14.7	280	49.8	< 0.0001	0.1436	1.1611	1.15	0.90–1.47	0.245
	Yes	3268	85.3	1207	36.9						
Anastomosis 1	handsewn	402	10.5	236	58.7	< 0.0001					
	stapled	3428	89.5	1251	36.5		− 0.5445	− 3.5093	0.58	0.43–0.79	< 0.001
Anastomosis 2	extracorp	1324	34.6	721	54.5	< 0.0001					
	intracorp	2506	65.4	766	30.6		− 0.3165	− 2.4384	0.78	0.56–0.94	0.015
Operation length (minutes)	≤ 170	1965	51.3	691	35.2	< 0.0001					
	> 170	1865	48.7	796	42.7		0.2741	2.9780	1.31	1.09–1.57	0.003
Prehabilitation	No	2561	66.9	1069	41.7	< 0.0001	0.1068	0.6586	1.11	0.81–1.53	0.510
	Yes	1269	33.1	418	32.9						
Counseling	No	1503	39.2	691	46.0	< 0.0001	0.1055	0.7167	1.11	0.83–1.48	0.474
	Yes	2327	60.8	796	34.2						

Table 8 (continued)

Variable	Pattern	Total		Univariate			Multivariate				
		No	%	No	%	*p*	β	β SE	OR	95% CI	*p*
Preoperative immunonutrition	No	2878	75.1	1177	40.9	< 0.0001					
	Yes	952	24.9	310	32.6		− 0.0738	− 0.4427	0.93	0.67–1.29	0.658
Antithrombotic prophylaxis	No	341	8.9	171	50.1	< 0.0001	0.0484	0.2579	1.05	0.73–1.52	0.796
	Yes	3489	91.1	1316	37.7						
No bowel preparation	No	1281	33.4	633	49.4	< 0.0001					
	Yes	2549	66.6	854	33.5		− 0.6916	− 6.7475	0.50	0.41–0.61	< 0.0001
Carbohydrates load and 2–6 h fasting	No	1834	47.9	872	47.5	< 0.0001					
	Yes	1996	52.1	615	30.8		− 0.5104	− 4.1867	0.60	0.47–0.76	< 0.0001
No preanesthesia	No	936	24.4	450	48.1	< 0.0001					
	Yes	2894	75.6	1037	35.8		− 0.1880	− 1.3528	0.83	0.63–1.09	0.176
Normothermia	No	438	11.4	222	50.7	< 0.0001	0.3056	1.7251	1.36	0.96–1.92	0.084
	Yes	3392	88.6	1265	37.3						
Standard anesthesia protocol	No	1004	26.2	431	42.9	0.002	0.4679	3.1678	1.59	1.19–2.13	0.002
	Yes	2826	73.8	1056	37.4						
Restrictive or goal-directed fluid therapy	No	849	22.2	419	49.4	< 0.0001	0.1036	0.6909	1.11	0.83–1.49	0.489
	Yes	2981	77.8	1068	35.8						
Multimodal analgesia	No	625	16.3	349	55.8	< 0.0001					
	Yes	3205	83.7	1138	35.5		− 0.0438	− 0.2819	0.96	0.70–1.29	0.778
PONV prophylaxis	No	781	20.4	399	51.1	< 0.0001					
	Yes	3049	79.6	1088	35.7		− 0.1147	− 0.8078	0.89	0.67–1.18	0.419
Minimally invasive surgery	No	608	15.9	382	62.8	< 0.0001					
	Yes	3222	84.1	1105	34.3		− 0.6971	− 3.7687	0.50	0.35–0.71	0.0002
No nasogastric tube	No	557	14.5	311	55.8	< 0.0001	0.2110	1.3989	1.23	0.92–1.66	0.162
	Yes	3273	85.5	1176	35.9						
No drain	No	2624	68.5	1199	45.7	< 0.0001					
	Yes	1206	31.5	288	23.9		− 0.3934	− 3.3101	0.67	0.53–0.85	0.0009
Bladder catheter removed POD 1–2	No	996	26.0	584	58.6	< 0.0001					
	Yes	2834	74.0	903	31.9		− 0.4657	− 3.8851	0.63	0.50–0.79	0.0001
Gut motility stimulation	No	3133	81.8	1228	39.2	0.318					
	Yes	697	18.2	259	37.2						
Early mobilization	No	1792	46.8	850	47.4	< 0.0001	− 0.1623	− 1.4127	0.85	0.67–1.06	0.158
	Yes	2038	53.2	637	31.3						
Early oral feeding	No	2005	52.3	961	47.9	< 0.0001					
	Yes	1825	47.7	526	28.8		VIF 4.4				

Table 8 (continued)

Variable	Pattern	Total		Univariate			Multivariate				
		No	%	No	%	*p*	β	β SE	OR	95% CI	*p*
Pre-discharge check	No	871	22.7	486	55.8	< 0.0001					
	Yes	2959	77.3	1001	33.8		− 0.6479	− 5.0259	0.52	0.41–0.67	< 0.0001
Overall morbidity	No	2723	71,.1	626	23.0	< 0.0001					
	Yes	1107	28.9	861	77.8		2.8033	25.1049	16.50	13.26–20.54	< 0.0001
Overall ERAS items adherence rate (%)	≤ 71.4	2216	57.9	1066	48.1	< 0.0001	VIF 4.3				
	> 71.4	1614	42.1	421	26.1						
Preoperative ERAS items adherence rate (%)	≤ 57.1	2142	55.9	984	45.9	< 0.0001	VIF 4.5				
	> 57.1	1688	44.1	503	29.8						
Intraoperative ERAS items adherence rate (%)	≤ 77.8	1909	49.9	943	49.4	< 0.0001					
	> 77.8	1921	50.1	544	28.3		− 0.2043	− 1.4695	0.81	0.62–1.07	0.142
Postoperative ERAS items adherence rate (%)	≤ 60.0	2183	57.0	1036	47.4	< 0.0001					
	> 60.0	1647	43.0	451	27.4		VIF 5.8				

ASA American Society of Anesthesiologists, *MNA-SF* mini nutritional assessment short form, *Standard resections are* anterior resection, right colectomy, left colectomy; non-standard resections are: splenic flexure resection, Hartmann's reversal, transverse colectomy, (sub)total colectomy, other resection; *PONV* postoperative nausea and vomiting, *VIF* variance inflation factor

*Deviance (likelihood ratio) chi-square = 1562.977107 df = 34; $P < 0.0001$

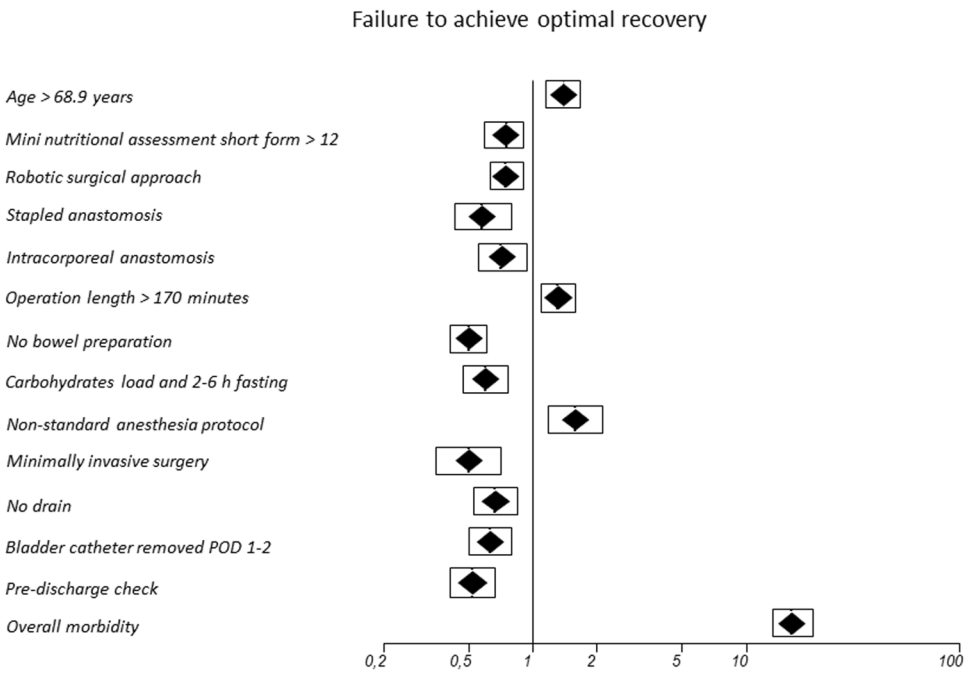

Fig. 6 Forest plot (log scale) of independent variables for failure to achieve optimal recovery; diamonds show ORs, boxes show 95% CIs

cavity was used in more than two thirds of cases enrolled in the present study (Table 4), confirming that its theoretical advantages (early diagnosis of hemorrhage and/or anastomotic leakage) are clearly still attractive for Italian surgeons, notwithstanding the existing evidence [45] and current guidelines [39, 40, 43] against its routine use. This finding should be balanced against the potential disadvantages of routine drainage (increased rates of infection, abdominal pain, decreased pulmonary function, prolonged hospital stay), that significantly reduced optimal recovery rates in the present study (Table 8; Fig. 6). Finally, early removal of bladder catheter had an independent protective effect on overall morbidity and on optimal recovery (Tables 7, 8; Figs. 5, 6) rates, being rather straightforward that its late removal may be a significant factor for minor morbidity (i.e. urinary tract infection) and delayed discharge.

This study has several strengths: the large number of enrolled patients in a well-defined time-lapse; in order to avoid any bias due to changes in ERAS program adherence over years [13, 46], the accrual period was initially designed over a one-year period (2019), but just ten out of the 38 participating centers were able to start in time, the others having up to four months delay; the severe slowdown of elective colorectal resections recorded during the first hit of COVID19 pandemic in Italy [47, 48] forced us to extend the accrual period up to June 2020. Second, the participating centers represent a wide sample of surgical units performing colorectal resections in Italy, with 21 general surgery units in general or regional hospitals (55.2%), 5 specialized colorectal surgery units in teaching or academic hospitals (13.2%), 5 oncologic surgery units in general or academic hospitals (13.2%) and 7 general surgery units in academic hospitals (18.4%). Third, prospective design of the study allowed to measure outcomes through the adherence to ERAS program items in all the enrolled cases, responding to clear and sheer compliance criteria (Table 2), comparing it with well-defined risk factors and to the existence or absence of an institutional ERAS pathway. It offered the chance to perform a prospective audit of clinical data regarding perioperative management of colorectal surgery patients among different centers outside pre-defined labels such as pre-post ERAS implementation [16, 17], large clinical databases including only patients treated in fully implemented ERAS centers [14, 49] or large clinical databases with predefined cutoff for compliance [15]. On the other hand, the study has several limitations, The first one is intrinsic to any observational study, with the potential for residual, measured and unmeasured confounding. Second, although a strict quality control of data was performed at various levels, we cannot exclude measurement errors from the investigators regarding items such as standard anesthesia protocol and/or perioperative fluid balance, that are definitely more prone to misinterpretation and misclassification than other straightforward items such as the presence or absence of a drain, a nasogastric tube or a urinary catheter. Third, as reported above, we are unable to assess the reasons behind non-adherence, with sicker patients potentially being taken off the enhanced recovery pathway by their physicians versus non-compliance induced by lack of human and/or organizational resources or by lack of implementation of a specific item. Finally, the exclusion of a large number of potentially eligible patients (roughly 42%), mainly because of protective

stoma proximal to the anastomosis and emergency cases, representing about 80% of patients excluded from analysis (Fig. 1). A proximal stoma created at the index operation in order to protect the anastomosis adds significant bias to the definition, diagnosis and clinical relevance of AL, requiring routine testing of anastomotic integrity through imaging and/or endoscopy; the iCral2 study protocol derived from the previous observational study from the same study group, designed to test the diagnostic value of clinical and serum markers for AL [24], and early during the investigators' meetings we decided to maintain the same exclusion criteria [50]. Nevertheless, the iCral study group recently started enrolling patients in its third prospective observational study [*ERAS Program Items Adherence, PROMs and RIOT After Colorectal Surgery (iCral3); ClinicalTrials.gov Identifier NCT04397627*]. Eigthy-eight surgical centers in Italy are now recruiting, including patients with proximal stoma and emergency cases.

This prospective multicenter study disclosed wide room of improvement for compliance to ERAS programs in colorectal surgery. Neither the existence of an institutional ERAS program or adherence rates to ERAS program items had significant effects on major morbidity and AL rates, both independently influenced by patient-related (male gender) and procedure-related (intra- and/or postoperative blood transfusions, non-standard resections) factors. A standard anesthesia protocol was the only ERAS program item independently influencing major morbidity rates.

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Declarations

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