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High adherence to enhanced recovery pathway independently reduces major morbidity and mortality rates after colorectal surgery: a reappraisal of the iCral2 and iCral3 multicenter prospective studies

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Background: Enhanced recovery after surgery (ERAS) offers lower overall morbidity rates and shorter hospital stay after colorectal surgery (CRS); high adherence rates to ERAS may significantly reduce major morbidity (MM), anastomotic leakage (AL), and mortality (M) rates as well.

Methods: Prospective enrollment of patients submitted to elective CRS with anastomosis in two separate 18- and 12-month periods among 78 surgical centers in Italy from 2019 to 2021. Adherence to ERAS pathway items was measured upon explicit criteria in every case. After univariate analysis, independent predictors of primary endpoints (MM, AL, and M rates) were identified through logistic regression analyses, presenting odds ratios (OR) and 95% confidence intervals.

Results: An institutional ERAS status was declared by 48 out of 78 (61.5%) participating centers. The median overall adherence to ERAS was 75%. Among 8,359 patients included in both studies, MM, AL, and M rates were 6.3%, 4.4%, and 1.0%, respectively. Several patient-related and treatment-related variables showed independently higher rates for primary endpoints: male gender, American Society of Anesthesiologists class III, neoadjuvant treatment, perioperative steroids, intra- and/or postoperative blood transfusions, length of the operation >180', surgery for malignancy. On the other hand, ERAS adherence >85% independently reduced MM (OR, 0.91) and M (OR, 0.25) rates, whereas no mechanical bowel preparation independently reduced AL (OR, 0.68) rates.

Conclusions: Among other patient- or treatment-related variables, ERAS adherence >85% independently reduced MM and M rates, whereas no mechanical bowel preparation independently reduced AL rates after CRS.

Keywords: Anastomotic Leakage; Colorectal surgery; ERAS; Major morbidity

Introduction

Several meta-analyses of randomized controlled trials[1–3] on enhanced recovery after surgery (ERAS) in colorectal surgery (CRS) showed a marked reduction in overall morbidity rates and length of stay. Different aspects of the ERAS program are vulnerable to noncompliance and this may explain wide differences in reported adherence rates to program items.[4–6] During the early phase of program implementation, the adherence rate

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to program items rarely exceeds 50%,[7] needing to reach at least 70%[8] to significantly improve outcomes. In this context, the relative benefit of any specific item of the program and the role of overall, preoperative, intraoperative, and postoperative adherence to the program itself is still debated.[9–11]

More recent observational studies showed that a high adherence rate to ERAS items may have a significant impact also on major complications, anastomotic leakage (AL), and mortality.[12–15] However, the previous multicenter prospective study by the Italian ColoRectal Anastomotic Leakage (iCral2) study group[16] failed to detect any significant association between institutionalization and/or adherence rates to ERAS and these endpoints. Having recently completed a third multicenter prospective study (iCral3) designed to test the impact of adherence to ERAS on patient-reported outcomes and return to intended oncologic therapy,[17] using a protocol similar to the previous study, the iCral study group decided to reappraise this issue by merging the results of the two studies.

Methods

Both studies were based on prospective voluntary enrollment in Italy, carried out from January 2019 to June 2020 in 38 surgical centers (iCral2), and from October 2020 to September 2021 in 76 surgical centers (iCral3). Seventy-eight centers were involved in 1 (42 centers) or both (36 centers) studies. A subgroup analysis of the 36 centers involved in both studies (data not shown) disclosed no time-related change in ERAS adherence rates and outcomes.

All patients submitted to elective CRS with anastomosis were assessed for inclusion according to explicit inclusion/exclusion criteria shared by the two studies (**Table 1**). The iCral2 study excluded patients with a protective stoma proximal to the anastomosis; conversely, these cases were included in the iCral3 study; delayed urgency resections were enrolled in both studies, being defined >48 hours from admission in iCral2 and >24 hours from admission in iCral3 studies.

All data were accounted for on an individual patient basis. The only center-related variables were: (1) enrollment volume, based on the median number of enrolled cases per month of accrual, defined as high volume (≥4 cases/month) or low volume (<4 cases/month) and (2) the self-declared institutional ERAS center status, defined as the existence of a locally implemented ERAS team and protocol, supported by a specific resolution of the hospital/company strategic management, present in 48 (61.5%) 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 both studies, 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 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 ERAS protocol included 21 items in iCral2, adapted from the 2013 ERAS Society guidelines.[18] They were 26 in iCral3, adapted from the 2019 ERAS society[19] and national[20] guidelines. For the present analysis, we selected 20 items shared by the two studies, with their specific adherence criteria (**Table 2**): adherence to the ERAS protocol was calculated both based on all the 20 items and on 16 pre- and intraoperative items (excluding postoperative items such as early mobilization, early oral feeding, early removal of foley catheter and predischarge check).[7] During the perioperative period patients were examined daily by local investigators, who were free to decide on complementary imaging and any further action according to their local criteria.

Outcomes

During the follow-up, planned on an outpatient basis for 8 weeks after hospital discharge, any adverse event was recorded and graded according to Clavien-Dindo[21,22] and the Japanese Clinical Oncology Group (JCOG) extended criteria,[23] as well as unplanned readmission, reoperation, death, and overall length of stay (LOS, days), inclusive of any readmission. AL was defined and graded according to the international[24] consensus. All the outcomes were calculated at 60 days after surgery.

Primary endpoints were AL, major morbidity (MM, defined as any adverse event grade >II), and mortality (M, any death) rates; secondary endpoints were overall morbidity (defined as any adverse event), surgical site infections (SSIs, according to the definitions of the Centers for Disease Control and Prevention[25]), infectious morbidity, readmission, reoperation rates, and overall LOS.

Statistical analysis

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

Descriptive and univariable analyses of the whole cohort according to the self-declared institutional ERAS center status 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 for all the endpoints.

Quantitative variables such as age (years) and operation length (minutes) were categorized below or above their median values. Other variables were categorized according to predefined ranges: nutritional status measured through the mini nutritional assessment—short form (MNA-SF,[26]) ≤11, indicating a potential or clear malnutrition status; body mass index (BMI, kg/m^2) ≤25.0, 25.1–30.0 and > 30.0. Surgical procedures were categorized as standard (anterior resection, right colectomy, and left colectomy) versus nonstandard (splenic flexure resection, transverse colectomy, Hartmann's reversal, subtotal and total colectomy, and other) resections. ERAS adherence rates, calculated

Table 1

Inclusion and exclusion criteria shared by the two studies

Inclusion criteria	• Patients undergoing colorectal resection with anastomosis (laparoscopic, robotic, open, or converted approach), including Hartmann's reversals
Exclusion criteria	• American Society of Anesthesiologists (ASA) class I, II, or III • Elective or delayed urgency (>24–48 hours from admission) surgery • Patient's written informed consent for inclusion in the study and processing of sensitive data • Pregnancy • Hyperthermic chemotherapy (HIPEC) for carcinomatosis • Incomplete data

Table 2

Definition of adherence to ERAS items shared by the two studies

Item	Adherence criteria
Prehabilitation	All patients showing MNA-SF <12 (malnourished or suspected for malnutrition) and BMI >30 (obesity) receive specific nutritional consultation. Patient receives a standard protocol of physical activity to be accomplished in the preoperative period. Patient and his familiars/caregivers are screened for anxiety/depression concerning diagnosis and related procedure; if present, psychologic consultation is warranted
Counseling	Patient and his familiars/caregivers receive full information and suggestions regarding perioperative program from the 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 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 30–60 minutes before incision, according to local protocols
No mechanical bowel preparation	No routine mechanical bowel preparation is used, except in case of the 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– 3 hours before surgery). Preoperative fasting is limited to 2 hours for clear liquids (water, coffee, or tea) and to 6 hours 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
PONV prophylaxis	Postoperative nausea/vomiting (PONV) 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
Fluid management	Intraoperative 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) to reduce the use of opiates
Minimally invasive surgery	Patient submitted to laparoscopic, robotic, or video-assisted surgery (conversions to open surgery included on an 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)
Bladder 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
Early oral feeding	Patient receives liquid oral diet starting 6 hours after surgery and semisolid diet starting on POD 1
Predischarge 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

on 20-items and 16-items, were categorized in quartiles, below or equal versus above the median values, and considering the 4th versus 1st–3rd quartiles.

All variables showing significance at univariate analysis were tested for variable multicollinearity[27] through a multiple linear regression model measuring the variance inflation factor (VIF) and then included (excluding those with VIF >4) in a logistic regression multivariate analysis model for primary endpoints, weighted for the variable with the highest VIF below the threshold, presenting odds ratio (OR) and 95% CI.

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

Ethics

Both studies were conducted according to the Declaration of Helsinki and the principles of the guidelines for good clinical practice E6 (R2). The study protocols were approved by the ethics committee of the coordinating center (Marche Regional Ethics Committee—CERM—2018/334 released on November 28, 2018, for iCral2; CERM—2020/192 released on July 30, 2020, for iCral3) and then registered at ClinicalTrials.gov (NCT03771456 for iCral2 and NCT04397627 for iCral3). Subsequently, all other centers were authorized to participate from their local ethics committee. Both studies followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.[28] Individual participant-level anonymized datasets are available for both studies upon reasonable request by contacting the study coordinator.

Results

Outcome data

A total of 12,801 potentially eligible cases were assessed, of which 8,359 (65.3%) were included in the present analysis (**Figure 1**). Median (IQR; range) number of enrolled patients per single center was 62 (42–140; 12–674). After a median (IQR; range) follow-up of 65 days (55–100; 0–378), 3,171 adverse events (**Table 3**) were recorded in 2,321 patients (overall morbidity rate 27.8%), of which 774 (24.2%) were Clavien-Dindo grade >II in 523 patients (MM rate 6.3%). There were 366 ALs (rate 4.4%), diagnosed after a median (IQR; range) of 5 (3–10; 1–99) days. AL diagnosis was established by intravenous contrast computed tomography scan in 149 (40.8%), clinical criteria in 129 (35.3%), endoluminal contrast computed tomography scan in 68 (18.7%), endoluminal contrast enema in 11 (2.7%), and gross findings at reoperation in the remaining 9 cases (2.5%). Regarding AL grading, a grade A leak was recorded in 44 cases (12.0%), grade B in 62 (17.0%), and grade C in the remaining 260 cases (71.0%). There were 88 deaths (mortality rate 1.0%). SSIs and infectious morbidity rates were 4.6% and 6.3%, respectively. Median overall LOS (IQR; range) was 6 (4–8; 0–108) days, with 288 re-admissions (3.4%) and 429 re-operations (5.1%).

ERAS institutionalization, adherence, and outcome data

The median (IQR) overall ERAS adherence rate (**Figure. 2 and Table 4**) was 75% (55–85) considering 20 items, and 75% (56.2–87.5) considering 16 items. Patients treated within a self-declared institutional ERAS center had a significantly higher overall and single-item ERAS adherence rate,

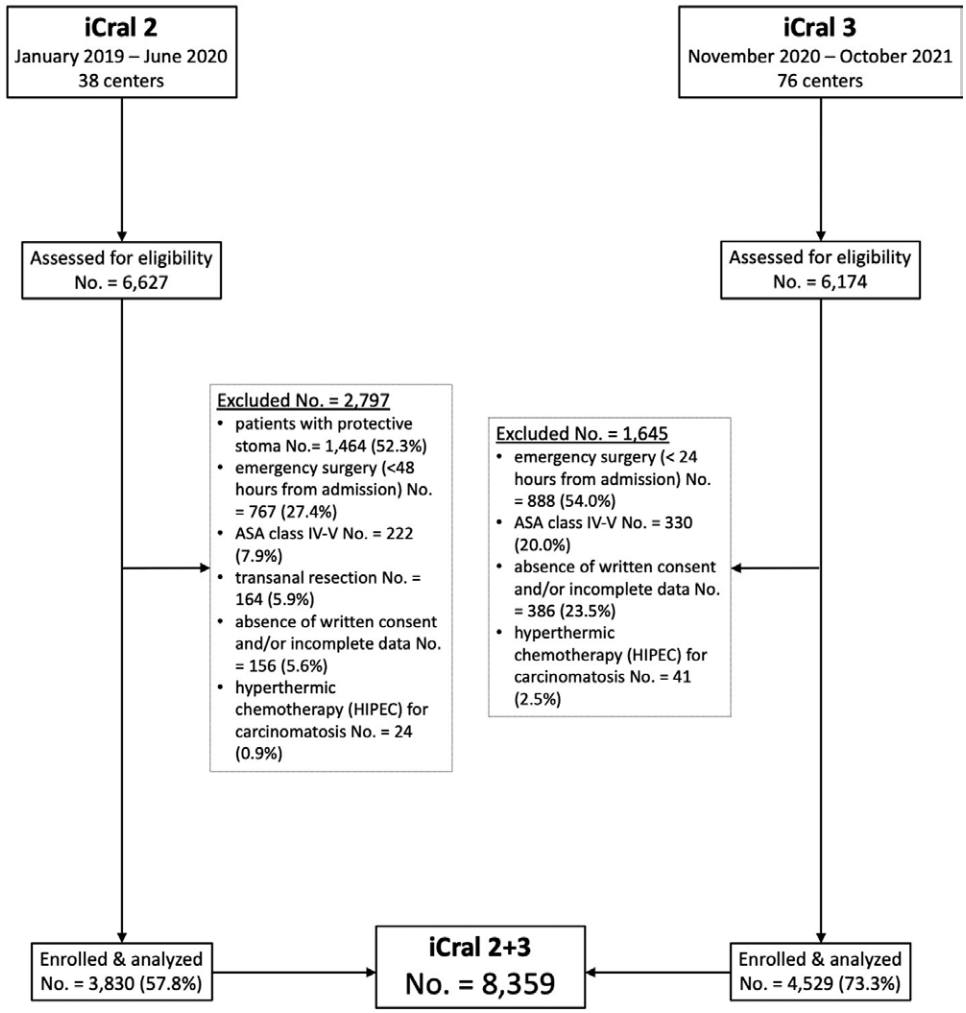

Figure 1. Flowchart of iCral2 and iCral3 studies according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines.

Table 3

Adverse events and grading

Clavien-Dindo & JCOG grade	I	II	IIIa	IIIb	IVa	IVb	Total
Anastomotic leakage	16	56	34	218	30	12	366
Surgical site infections	124	131	13	13	0	0	281
Abdominal collection/abscess	4	30	53	15	0	2	104
Small bowel obstruction	9	35	4	62	2	0	112
Anastomotic bleeding	58	52	40	3	1	0	154
Abdominal bleeding	5	35	7	36	4	2	89
Small bowel perforation	0	0	1	19	2	0	22
Deep wound dehiscence	5	8	3	4	0	0	20
Trocar/wound site bleeding	20	7	2	3	0	0	32
Anemia	40	366	1	2	0	1	410
Paralytic ileus	173	169	1	3	0	0	346
Fever	97	171	3	3	0	0	274
DVT/pulmonary embolism	1	17	1	0	3	5	27
Neurologic	25	17	1	1	0	1	45
Pneumonia & pulmonary failure	14	89	8	2	21	9	143
Urinary retention	62	47	2	0	0	0	111
Urinary tract infection	6	22	1	0	0	0	29
Acute renal failure	25	28	3	0	6	2	64
Acute mesenteric ischemia	0	0	0	4	0	1	5
Acute peptic ulcer/erosive gastritis	0	4	4	1	0	0	9
Other	195	152	27	21	9	12	416
Total	895	1,502	213	412	91	58	3,171

DVT indicates deep venous thrombosis; JCOG, Japanese Clinical Oncology Group.

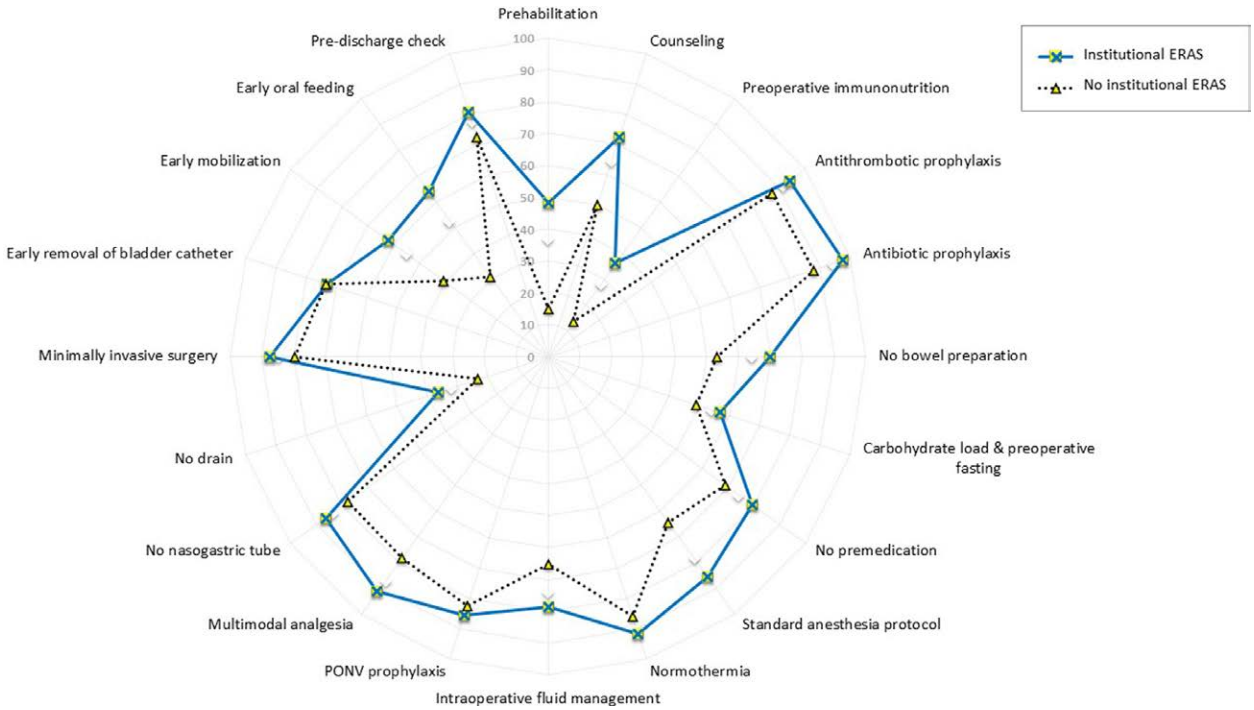

Figure 2. Adherence rates (%) to ERAS items in the whole population (Overall) and according to the presence or absence of an institutional ERAS pathway.

the only exception being the early removal of bladder catheter. Concerning patient-related variables, patients treated in a self-declared institutional ERAS center had significantly lower median age and median BMI, lower rates of male gender, American Society of Anesthesiologists (ASA) class III cases, and diabetes. Concerning treatment-related variables, they showed a significantly lower rate of nonstandard resections, surgery for malignancy, and open or robotic surgery; on the other hand, they had significantly more cases treated in a high-volume center and significantly longer operative time. No significant differences regarding outcomes were recorded, the only exception being a significantly higher overall morbidity rate and shorter LOS in patients treated in a self-declared institutional ERAS center. When measured on a 20-item base, ERAS adherence quartiles were significantly linked to all the endpoints, except AL, readmission, and reoperation rates (**Figure 3**); when measured on a 16-items base, they were significantly linked to mortality, SSIs, and infectious morbidity rates (**Table 5**).

Primary endpoints analyses

MM rates (**Table 6**) were independently higher by (**Figure 4**) male sex (OR, 1.41; 95% CI, 1.14–1.74; $P = 0.002$), ASA class III (OR, 1.36; 95% CI, 1.07–1.71; $P = 0.011$), neoadjuvant therapy (OR, 1.65; 95% CI, 1.19–2.28), intra- and/or postoperative blood transfusions (OR, 5.54; 95% CI, 4.25–7.24; $P < 0.0001$), and operation length >180 minutes (OR, 1.54; 95% CI, 1.25–1.90; $P < 0.0001$). They were independently lower by ERAS 20-items adherence >85% (OR, 0.84; 95% CI, 0.72–0.98; $P = 0.028$).

AL rates (**Table 7**) were independently higher by (**Figure 5**) male sex (OR, 1.32; 95% CI, 1.09–1.58; $P = 0.004$), ASA class III (OR, 1.30; 95% CI, 1.07–1.58; $P = 0.008$), neoadjuvant treatment (OR, 1.59; 95% CI, 1.19–2.13; $P = 0.002$), intra- and/or postoperative blood transfusions (OR, 5.36; 95% CI, 4.26–6.73; $P < 0.0001$), and length of the operation >180' (OR, 1.41; 95% CI, 1.18–1.70; $P < 0.001$). They were independently lower in patients with no mechanical bowel preparation (OR, 0.68; 95% CI, 0.54–0.86; $P = 0.001$).

Mortality rates (**Table 8**) were independently higher (**Figure 6**) in ASA class III patients (OR, 1.96; 95% CI, 1.06–3.62; $P = 0.031$) and patients receiving perioperative steroids (OR, 4.33; 95% CI, 1.55–12.06; $P = 0.005$); they were independently lower in patients with normal nutritional status (MNA-SF >11; OR, 0.40; 95% CI, 0.24–0.68; $P = 0.0006$), and ERAS 20-items adherence rate >85% (OR, 0.25; 95% CI, 0.07–0.82; $P = 0.022$).

A complete description of all variables included in univariate analyses for primary endpoints is available as ematerial; http://links.lww.com/IA9/A4.

Discussion

The reappraisal and merging of the two multicenter observational prospective iCral studies[16,17] allowed to achieve a noteworthy cohort of more than 8,000 patients treated in 78 Italian surgical units over 30 months, representing, by far, one of the largest prospective multicenter cohorts used to investigate the effects of a self-declared ERAS status and ERAS adherence rates on early outcomes after CRS in a nationwide sample.

The first finding of this merged analysis clearly demonstrates that more than 20 years after its inception, there still is clear room for improvement of adherence rates to the ERAS pathway after CRS. In particular (**Figure 2**), even the most basic elements of perioperative care, such as antibiotic and antithrombotic prophylaxis, showed an elevated (>90%) but far from perfect compliance; several other items showed an overall suboptimal (<70%) adherence rate: prehabilitation, counseling, immunonutrition, no bowel preparation, carbohydrates load and 2–6 hours fasting, no drain, early mobilization, and early oral feeding.

This finding could be expected for some of these. Given the heterogeneity of studies to date, the role of prehabilitation for specific patients and surgical procedures needs to be confirmed by high-quality randomized studies.[29] More recent evidence[30,31] clearly indicates preoperative immunonutrition for selected (malnourished and/or oncologic) patients and not for all comers. Preoperative carbohydrate load results in reduced postoperative insulin resistance, anxiety, discomfort, nausea, and hospital

Table 4

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

	Overall (No. = 8,359)	Institutional ERAS (No. = 5,502)	No Institutional ERAS (No. = 2,857)	
Patients' variables	**No. (%)**	**No. (%)**	**No. (%)**	***P***
Age, median (IQR), years	69 (58–78)	69 (57–78)	69 (60–77)	0.032
Male gender	4298 (51.4)	2747 (49.9)	1551 (54.3)	0.0002
Body mass index, median (IQR), Kg/m^2	25.13 (22.66–27.78)	24.82 (22.32–27.68)	25.71 (23.18–28.30)	<0.0001
ASA class I–II	5421 (64.8)	3687 (67.0)	1734 (60.7)	<0.0001
Diabetes	1195 (14.3)	714(13.0)	481 (16.8)	<0.0001
Chronic renal failure	366 (4.4)	238 (4.3)	128 (4.5)	0.743
Dialysis	17 (0.2)	12 (0.2)	5 (0.2)	0.873
Perioperative steroids	147 (1.8)	99 (1.8)	48 (1.7)	0.694
Neoadjuvant therapy	618 (7.4)	398 (7.2)	220 (7.7)	0.439
Preoperative blood transfusion(s)	464 (5.6)	301 (5.5)	163 (5.7)	0.657
Intra- and/or postoperative blood transfusion(s)	559 (6.7)	354 (6.4)	205 (7.2)	0.198
Chronic liver disease	85 (1.0)	55 (1.0)	30 (1.0)	0.827
MNA-SF, median (IQR) (mean)	12 (11–13) (12.00)	12 (11–13) (12.01)	12 (11–13) (11.98)	0.055
Surgical procedure				
Anterior resection	1621 (19.4)	1147 (20.8)	474 (16.6)	<0.0001
Right colectomy	3196 (38.2)	2102 (38.2)	1094 (38.3)	
Left colectomy	2319 (27.7)	1497 (30.4)	822 (28.8)	
Splenic flexure resection	251 (3.0)	159 (2.9)	92 (3.2)	
Hartmann's reversal	232 (2.8)	147 (2.7)	85 (3.0)	
Transverse colectomy	172 (2.1)	116 (2.1)	56 (2.0)	
(Sub)total colectomy	161 (1.9)	89 (1.6)	72 (2.5)	
Other resection	407 (4.9)	245 (4.4)	162 (5.6)	
Surgery for malignancy	6043 (72.3)	3823 (69.5)	2220 (77.7)	<0.0001
Operation length, median (IQR), minutes	180 (130–225)	180 (135–230)	170 (125–215)	<0.0001
High volume (≥4 enrolled cases/month)	6414 (76.7)	4414 (80.2)	2000 (70.0)	<0.0001
Surgical approach				
Converted	422 (5.0)	284 (5.2)	138 (4.8)	<0.0001
Laparoscopic	5965 (71.4)	4249 (77.2)	1716 60.1)	
Open	1238 (14.8)	679 (12.3)	559 (19.6)	
Robotic	734 (8.8)	290 (5.3)	444 (15.5)	
ERAS items				
Overall adherence (20 items), median (IQR), %	75 (55–85)	80 (65–90)	65 (45–75)	<0.0001
Overall adherence (16 items), median (IQR), %	75 (56.2–87.5)	81.2 (62.5–87.5)	68.7 (50–75)	<0.0001
Prehabilitation	3082 (36.9)	2655 (48.2)	427 (14.9)	<0.0001
Counseling	5406 (64.7)	3975 (72.2)	1431 (50.1)	<0.0001
Preoperative immunonutrition	2370 (28.4)	1988 (36.1)	382 (13.4)	<0.0001
Antithrombotic prophylaxis	7649 (91.5)	5160 (93.8)	2489 (87.1)	<0.0001
Antibiotic prophylaxis	7866 (94.1)	5358 (97.4)	2508 (87.8)	<0.0001
No bowel preparation	5356 (64.1)	3840 (69.8)	1516 (53.1)	<0.0001
Oral carbohydrates load & preoperative fasting	4523 (54.1)	3125 (56.8)	1398 (48.9)	<0.0001
No premedication	6190 (74.0)	1981 (79.2)	913 (68.7)	<0.0001
PONV prophylaxis	7065 (84.5)	4712 (85.6)	2353 (82.3)	<0.0001
Normothermia	7490 (89.6)	5040 (91.6)	2450 (85.7)	<0.0001
Standard anesthesia protocol	6541 (78.2)	4705 (85.5)	1836 (64.3)	<0.0001
Intraoperative fluid management	6188 (74.0)	4322 (78.5)	1866 (65.3)	<0.0001
Multimodal analgesia	7259 (86.8)	5022 (91.3)	2237 (78.3)	<0.0001
Minimally invasive surgery	7084 (84.7)	4812 (87.4)	2272 (79.5)	<0.0001
No nasogastric tube	6981 (83.5)	4757 (86.4)	2224 (77.8)	<0.0001
No drain	2667 (31.9)	2004 (36.4)	663 (23.2)	<0.0001
Early removal of bladder catheter	6121 (73.2)	4023 (73.1)	2098 (73.4)	0.758
Early mobilization	4580 (54.8)	3424 (62.2)	1156 (40.5)	<0.0001
Early oral feeding	4404 (52.7)	3518 (63.9)	886 (31.0)	<0.0001
Predischarge check	6499 (77.7)	4437 (80.6)	2062 (72.2)	<0.0001
Outcomes				
Overall morbidity	2321 (27.8)	1579 (28.7)	742 (26.0)	0.009
Major morbidity	523 (6.3)	347 (6.3)	176 (6.2)	0.793
Anastomotic leakage	366 (4.4)	248 (4.5)	118 (4.1)	0.424
Mortality	88 (1.0)	53 (1.0)	35 (1.2)	0.266
Surgical site infections	388 (4.6)	233 (4.2)	155 (5.4)	0.014
Infectious morbidity	524 (6.3)	325 (5.9)	199 (7.0)	0.058
Readmission	288 (3.4)	197 (3.6)	91 (3.2)	0.347
Reoperation	429 (5.1)	301 (5.5)	128 (4.5)	0.058
LOS, median (IQR) [mean], days	6 (4–8) (7.3)	6 (4–8) (7.2)	6 (4–8) (7.5)	0.003

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

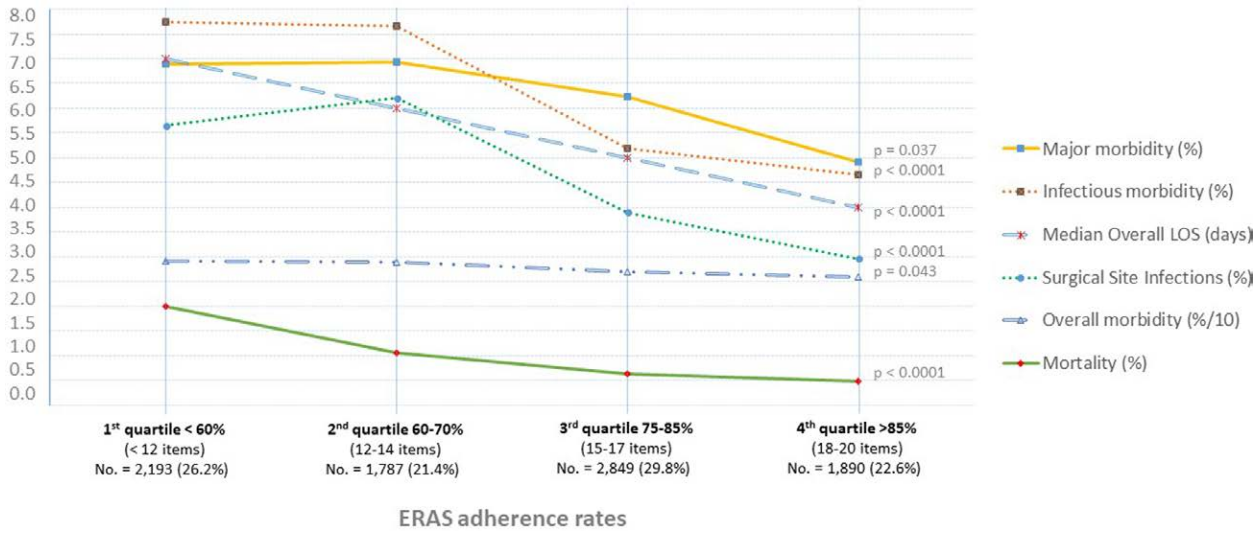

Figure 3. Curves of univariate analyses for the endpoints according to the quartiles of ERAS adherence rate (based on 20 items); to overlap the graphs on the same scale, overall morbidity rates were reduced by a magnitude of tenfold.

Table 5

Univariate analyses according to ERAS adherence quartiles

ERAS 20 items	Overall		1st quartile adherence <60% (< 12 items)		2nd quartile adherence 60–70% (12–14 items)		3rd quartile adherence 75–85% (15–17 items)		4th quartile adherence >85% (18–20 items)		*P*
	No.	%	No.	%	No.	%	No.	%	No.	%	
Overall	8,359	100.0	2,193	26.2	1,787	21.4	2,489	29.8	1,890	22.6	–
Overall morbidity	2321	27.8	638	29.1	524	29.3	668	26.8	491	26.0	0.043
Major morbidity	523	6.3	151	6.9	124	6.9	155	6.2	93	4.9	0.037
Anastomotic leakage	366	4.4	107	4.9	85	4.8	107	4.3	67	3.5	0.165
Mortality	88	1.0	44	2.0	19	1.1	16	0.6	9	0.5	<0.0001
SSIs	388	4.6	124	5.7	111	6.2	97	3.9	56	3.0	<0.0001
Infectious morbidity	524	6.3	170	7.8	137	7.7	129	5.2	88	4.7	<0.0001
Readmission	288	3.4	67	3.1	63	3.5	92	3.7	66	3.5	0.677
Reoperation	429	5.1	113	5.2	92	5.1	136	5.5	88	4.7	0.695
	Mean; median; IQR		Mean; median; IQR		Mean; median; IQR		Mean; median; IQR		Mean; median; IQR		*P*
Overall LOS, days	7.3; 6; 4–8		8.8; 7; 6–9		8.0; 6; 5–8		6.9; 5; 4–7		5.5; 4; 3–6		<0.0001

ERAS 16 items	Overall		1st quartile adherence ≤ 56.2% (≤ 9 items)		2nd quartile adherence 62.5–75% (10–12 items)		3rd quartile adherence 81.2–87.5% (13–14 items)		4th quartile Adherence > 87.5% (15–16 items)		*P*
	No.	%	No.	%	No.	%	No.	%	No.	%	
Overall	8,359	100.0	2,162	25.9	2,671	31.9	2,160	25.8	1,366	16.4	–
Overall morbidity	2321	27.8	603	27.9	772	28.9	575	26.6	371	27.1	0.333
Major morbidity	523	6.3	134	6.2	179	6.7	132	6.1	78	5.7	0.639
Anastomotic leakage	366	4.4	100	4.6	120	4.5	93	4.3	53	3.9	0.744
Mortality	88	1.0	36	1.7	26	1.0	21	1.0	5	0.4	0.003
SSIs	388	4.6	115	5.3	155	5.8	76	3.5	42	3.1	<0.0001
Infectious morbidity	524	6.3	157	7.3	195	7.3	106	4.9	66	4.8	0.0002
Readmission	288	3.4	65	3.0	110	4.1	65	3.0	48	3.5	0.105
Reoperation	429	5.1	102	4.7	141	5.3	114	5.3	72	5.3	0.794
	Mean; median; IQR		Mean; median; IQR		Mean; median; IQR		Mean; median; IQR		Mean; median; IQR		*P*
Overall LOS, days	7.3; 6; 4–8		8.5; 7; 5–9		7.9; 6; 5–8		6.4; 5; 4–7		5.8; 4; 3–6		<0.0001

LOS, length of stay; SSIs, surgical site infections.

stay, but failure to show reduced complication rates[32] has caused this item to remain controversial. In a recent European study,[15] avoidance of an abdominal drain was the only independent item of the ERAS pathway associated with a significant reduction of moderate-to-severe complications, confirming the existing evidence[33] and current guidelines[19,20] against its routine use because of increased rates of infection, abdominal pain, decreased pulmonary function and prolonged hospital stay; current analysis showed that an abdominal drain is still used in three-quarters of cases and in more than half of cases in a recent EuroSurg Collaborative international study in 22 countries.[34] It could be inferred that asking a surgeon not to leave a drain in place after a colorectal resection is a task harder than trying to remove a pacifier from a toddler's mouth. This clear decoupling between evidence-based recommendations and every day clinical practice deserves further investigation. Early postoperative feeding and mobilization are generally considered human resource-consuming items[35,36] and may therefore not receive the proper priority within the ERAS pathway implementation.[10] At the same time, the omission of mechanical bowel preparation is still a matter of

Table 6

Logistic regression analysis for major morbidity, weighted for minimally invasive surgery

Variable	Pattern	No.	%	Events	%	*P*	VIF	Beta	Beta SE	OR	95%CI	*P*
Age (years)	≤69	4,233	50.6	234	5.5	0.005	1.245	−0.078	0.670	0.92	0.74–1.16	0.503
	>69	4,126	49.4	289	7.0							
Sex	Female	4,061	48.6	213	5.2							
	Male	4,298	51.4	310	7.2	<0.001	1.032	0.342	3.190	1.41	1.14–1.74	0.002
ASA class	I–II	5,421	64.9	288	5.3							
	III	2,938	35.1	235	8.0	<0.0001	1.266	0.305	2.551	1.36	1.07–1.71	0.011
MNA-SF	≤11	2,430	29.1	180	7.4							
	>11	5,929	70.9	343	5.8	0.006	1.068	−0.048	−0.418	0.95	0.76–1.19	0.676
Neoadjuvant therapy	No	7,741	92.6	463	6.0							
	Yes	618	7.4	60	9.7	<0.001	1.016	0.501	3.032	1.65	1.19–2.28	0.002
Surgical approach	Converted	422	5.0	40	9.5							
	Laparoscopic	5,965	71.4	320	5.4	<0.0001	1.288	0.010	0.129	1.01	0.87–1.17	0.897
	Open	1,238	14.8	112	9.0							
	Robotic	734	8.8	51	6.9							
Intra- and postoperative blood transfusions	No	7,800	93.3	392	5.0							
	Yes	559	6.7	131	23.4	<0.0001	1.035	1.713	1.607	5.54	4.25–7.24	<0.0001
Surgery for malignancy	No	2,316	27.7	120	5.2							
	Yes	6,043	72.3	403	6.7	0.012	1.132	0.016	0.124	1.02	0.79–1.31	0.901
Operation length (minutes)	≤180	4,736	56.7	253	5.3							
	>180	3,623	43.3	270	7.5	<0.0001	1.069	0.434	4.074	1.54	1.25–1.90	<0.0001
Minimally invasive surgery	No	1,238	14.8	112	9.0	<0.0001	1.381	WEIGHT				
	Yes	7,121	85.2	411	5.8							
ERAS 20 items adherence rate (%)	≤85	6,469	77.4	430	6.6							
	>85	1,890	22.6	93	4.9	0.007	1.144	−0.171	−2.195	0.84	0.72–0.98	0.028

Deviance (likelihood ratio) chi-square = 195.335; df = 10; $P < 0.0001$.

95% CI indicates 95% confidence intervals; ASA, American Society of Anesthesiologists; ERAS, enhanced recovery after surgery; MNA-SF, mini nutritional assessment short form; OR, odds ratios; SE, standard error; VIF, variance inflation factor.

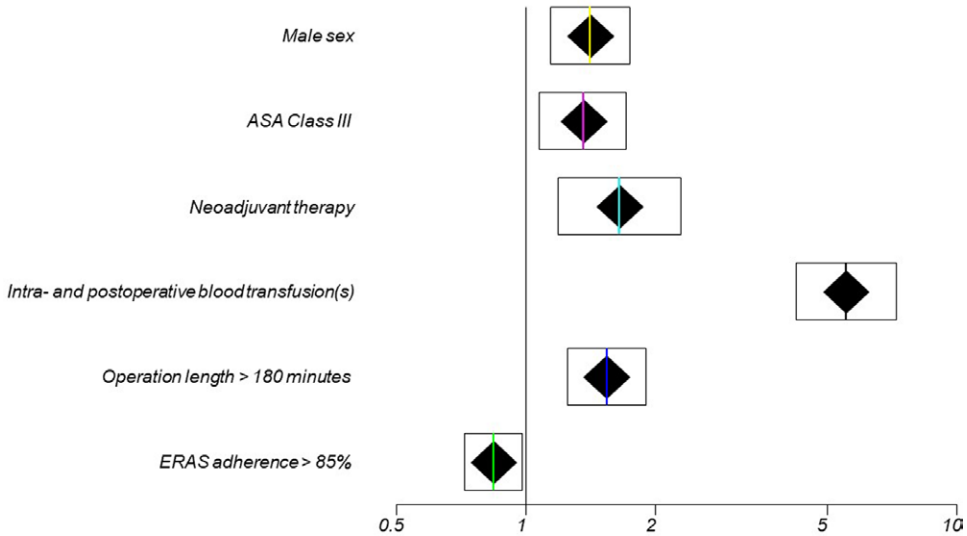

Figure 4. Forest plot (log scale) of independent variables for major morbidity; diamonds show ORs, boxes show 95%CIs.

ongoing controversy with North American ERAS guidelines,[37] that support it coupled with oral antibiotic prophylaxis.

On the other hand, it remains hard to explain why preoperative counseling remains underutilized since it is self-evident that the greater involvement of patients in their healthcare is an essential factor affecting adherence to any medical treatment.[38]

After multivariate analyses, male sex, ASA class III, neoadjuvant therapy, intra- and/or postoperative blood transfusions, and length of the operation >180' resulted as independent risk factors for higher MM and AL rates (**Tables 6, 7, and Figures 4, 5**); ASA class III and perioperative steroids were independent determinants of higher M rates (**Table 8 and Figure 6**). This finding was somehow expected, as these patient-related or treatment-related variables are well-established risk factors for adverse outcomes after CRS.[39–43] In this context, while it appears difficult, if not possible at all, to change the sex, age, ASA class, or neoadjuvant management of the patient, there is plenty of room to reduce the number of perioperative blood transfusions[44–46]: in recent years, various strategies have been studied to reduce the use of blood transfusions to prevent transfusion-related adverse events,[47] increase patient safety, and reduce costs. Consequently, a new concept was born: patient blood management (PBM). According to the World Health Organization, PBM is defined as "the timely application of evidence-based medical and surgical concepts designed to maintain a patient's hemoglobin concentration, optimize hemostasis and minimize blood loss in an

Table 7

Logistic regression analysis for anastomotic leakage, weighted for early oral feeding

Variable	Pattern	No.	%	Events	%	*P*	VIF	Beta	Beta SE	OR	95% CI	*P*
Sex	Female	4,061	48.6	140	3.4							
	Male	4,298	51.4	226	5.3	<0.0001	1.022	0.355	3.170	1.43	1.14–1.78	0.001
ASA class	I–II	5,421	64.9	207	3.8							
	III	2,938	35.1	159	5.4	<0.001	1.129	0.159	1.362	1.17	0.93–1.47	0.173
Diabetes	No	7,164	85.7	299	4.2							
	Yes	1,195	14.3	67	5.6	0.025	1.083	0.133	0.909	1.14	0.86–1.52	0.363
Neoadjuvant therapy	No	7,741	92.6	319	4.1							
	Yes	618	7.4	47	7.6	<0.0001	1.015	0.530	3.183	1.70	1.23–2.35	0.002
Intra- and postoperative blood transfusions	No	7,800	93.3	289	3.7							
	Yes	559	6.7	77	13.8	<0.0001	1.025	1.366	9.667	3.92	2.97–5.17	<0.0001
Surgery for malignancy	No	2,316	27.7	71	3.1							
	Yes	6,043	72.3	295	4.9	<0.001	1.084	0.289	2.064	1.34	1.02–.76	0.039
Operation length (minutes)	≤180	4,736	56.7	168	3.5							
	>180	3,623	43.3	298	8.2	<0.0001	1.019	0.419	3.822	1.52	1.23–1.88	<0.0001
No bowel preparation	No	3,003	35.9	161	5.4							
	Yes	5,356	64.1	205	3.8	0.001	1.152	–0.379	–3.235	0.68	0.54–0.86	0.001
Early oral feeding	No	3,955	47.3	197	5.0							
	Yes	4,404	52.7	169	3.8	0.012	1.433	Weight				
ERAS 20 items adherence rate (%)	≤85	6,469	77.4	299	4.6	0.044	1.295	0.079	0.474	1.08	0.78–1.50	0.635
	>85	1,890	22.6	67	3.5							

Deviance (likelihood ratio) chi-square = 43.155; df = 9; $P < 0.0001$.

95% CI indicates 95% confidence intervals; ASA, American Society of Anesthesiologists; ERAS, enhanced recovery after surgery; OR, odds ratios; SE, standard error; VIF, variance inflation factor.

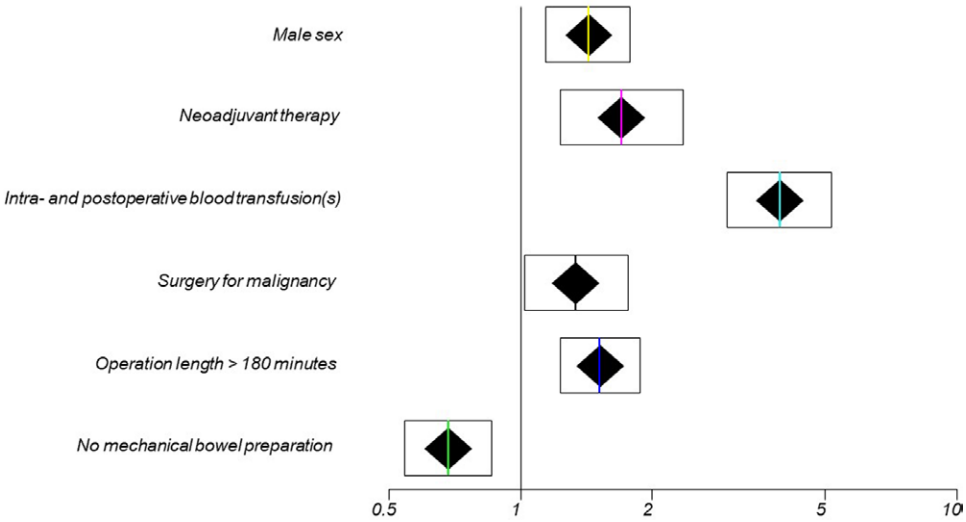

Figure 5. Forest plot (log scale) of independent variables for anastomotic leakage; diamonds show ORs, boxes show 95%CIs.

effort to improve the outcomes."[48] The iCral study group is currently enrolling patients in its 4th observational study designed to test the effect of adherence to a combined ERAS-PBM pathway on blood transfusions rate and outcomes.[49]

Notwithstanding significantly higher overall ERAS adherence rates, patients treated in a self-declared ERAS center experienced higher overall morbidity rates and shorter LOS at univariate analysis (**Table 4**). This controversial finding is probably due to significant residual confounders in the individual patient group assignment and in the distribution of the other variables. However, the self-declared ERAS center status did not appear to influence any primary endpoint at multivariate analyses, similar to what was recently observed in a large European prospective cohort,[15] confirming that "having or declaring ERAS" is not enough to impact on early outcomes.[50]

On the other hand, there was a solid and independent impact of the highest quartile (>85%) of ERAS 20-items adherence on MM (OR, 0.84; 95% CI, 0.72–0.98; $P = 0.028$) and M (OR, 0.25; 95% CI, 0.07–0.82; $P = 0.022$) rates. Although significant at univariate analysis, it was not an independent predictor of AL rates (OR, 0.92; 95% CI, 0.66–1.28; $P = 0.635$). The question triggered by this finding is "Should we struggle to reach high adherence in most cases to achieve better outcomes?." Considering that the protective role of high adherence to the pathway recorded in the present analysis was clearly independent from other confounding variables related to the patient, the disease, or the operation performed, the most intuitive answer is yes. Moreover, several studies[5–8] have already demonstrated that the ERAS dose-effect on outcomes acts as a whole, with pre- and intraoperative items designed to allow patients' early mobilization, early oral feeding, early removal of urinary catheter, and early discharge. In this regard, several authors consider these postoperative items as outcomes rather than variables of the program[7]: to be able to eat, drink or mobilize at all can only be achieved with proper care delivered during the pre- and intraoperative phase to allow for it. For

Table 8

Logistic regression analysis for mortality, weighted for age

Variable	Pattern	No.	%	Events	%	*P*	VIF	Beta	Beta SE	OR	95%CI	*P*
Age (years)	≤69	4233	50.6	15	0.4							
	>69	4126	49.4	73	1.8	<0.0001	3.835	Weight				
Sex	Female	4061	48.6	32	0.8							
	Male	4298	51.4	56	1.3	0.021	1.039	0.487	1.834	1.63	0.97–2.74	0.066
ASA class	I–II	5421	64.9	26	0.5							
	III	2938	35.1	62	2.1	<0.0001	1.259	0.674	2.162	1.96	1.06–3.62	0.031
MNA-SF	≤11	2430	29.1	50	2.1							
	>11	5929	70.9	38	0.6	<0.0001	1.069	–0.904	–3.416	0.40	0.24–0.68	0.0006
Chronic renal failure	No	7993	95.6	79	1.0							
	Yes	366	4.4	9	2.5	0.014	1.015	0.574	1.508	1.78	0.84–3.75	0.131
Perioperative steroids	No	8212	98.2	83	1.0							
	Yes	147	1.8	5	3.4	0.019	1.009	1.465	2.802	4.33	1.55–12.06	0.005
Surgical approach	Converted	422	5.0	10	2.4							
	Laparoscopic	5965	71.4	34	0.6	<0.0001	4.077	Excluded				
	Open	1238	14.8	31	2.5							
	Robotic	734	8.8	13	1.8							
Preoperative blood transfusions	No	7895	94.4	75	0.9							
	Yes	464	5.6	13	2.8	0.001	1.068	0.176	0.496	1.19	0.59–2.39	0.619
Intra- and postoperative blood transfusions	No	7800	93.3	70	0.9							
	Yes	559	6.7	18	3.2	<0.0001	1.051	0.548	1.756	1.73	0.94–3.19	0.079
Surgery for malignancy	No	2316	27.7	13	0.6	0.009	1.203	–0.167	–0.459	0.84	0.41–1.73	0.646
	Yes	6043	72.3	75	1.2							
Standard procedure	No	1223	14.6	20	1.6							
	Yes	7136	85.4	68	1.0	0.04	1.079	–0.213	–0.642	0.80	0.42–1.55	0.521
Prehabilitation	No	5277	63.1	68	1.3							
	Yes	3082	36.9	20	0.6	0.008	1.942	–0.359	–1.040	0.70	0.35–1.37	0.298
Antibiotic prophylaxis	No	493	5.9	11	2.2							
	Yes	7366	88.1	77	1.0	0.015	1.202	–0.498	–1.216	0.61	0.27–1.35	0.224
Standard anesthesia protocol	No	1818	21.7	29	1.6							
	Yes	6541	78.3	59	0.9	0.015	1.871	–0.259	–0.776	0.77	0.40–1.48	0.437
Restrictive or goal-directed fluid therapy	No	2171	26.0	35	1.6							
	Yes	6188	74.0	53	0.9	0.004	1.851	–0.259	–0.807	0.77	0.41–1.45	0.419
Multimodal analgesia	No	1100	13.2	21	1.9							
	Yes	7259	86.8	67	0.9	0.004	1.452	–0.387	–1.108	0.68	0.34–1.35	0.267
Minimally invasive surgery	No	1238	14.8	31	2.5							
	Yes	7121	85.2	57	0.8	<0.0001	1.495	–0.340	–1.196	0.71	0.41–1.24	0.232
No nasogastric tube	No	1378	16.5	24	1.7	0.009	1.498	0.534	1.553	1.70	0.87–3.34	0.120
	Yes	6981	83.5	64	0.9							
No drain	No	5692	68.1	72	1.3							
	Yes	2667	31.9	16	0.6	0.008	1.402	–0.722	–1.880	0.48	0.23–1.03	0.06
Bladder catheter removed POD 1–2	No	2238	26.8	45	2.0							
	Yes	6121	73.2	43	0.7	<0.0001	1.599	–0.341	–1.097	0.71	0.39–1.31	0.272
Early mobilization	No	3779	45.2	61	1.6							
	Yes	4580	54.8	27	0.6	<0.0001	2.430	–0.591	–1.500	0.55	0.25–1.20	0.133
Early oral feeding	No	3955	47.3	66	1.7							
	Yes	4404	52.7	22	0.5	<0.0001	2.529	–0.194	–0.470	0.82	0.37–1.85	0.638
ERAS 20 items adherence rate (%)	<60	2193	26.2	44	2.0							
	60–70	1787	21.4	19	1.1	<0.0001	10.581	Excluded				
	75–85	2489	29.8	16	0.6							
	>85	1890	22.6	9	0.5							
ERAS 16 items adherence rate (%)	≤56.2	2162	25.9	36	1.7	0.003	10.933	Excluded				
	62.5–75	2671	31.9	26	1.0							
	81.2–87.5	2160	25.8	21	1.0							
	>87.5	1366	16.4	5	0.4							
ERAS 20 items adherence rate (%)	≤75	4771	57.1	67	1.4	0.0004	5.259	Excluded				
	>75	3588	42.9	21	0.6							
ERAS 16 items adherence rate (%)	≤75	4833	57.8	62	1.3							
	>75	3523	42.2	26	0.7	0.015	5.748	Excluded				
ERAS 20 items adherence rate (%)	≤85	6469	77.4	79	1.2	0.008	2.781	1.375	2.286	3.95	1.22–12.86	0.022
	>85	1890	22.6	9	0.5							
ERAS 16 items adherence rate (%)	≤87.5	6993	83.6	83	1.2							
	>87.5	1366	16.4	5	0.4	0.003	2.875	–0.786	–1.181	0.46	0.12–1.68	0.237

Deviance (likelihood ratio) chi-square = 77.093; df = 22; $P < 0.0001$.

95% CI indicates 95% confidence intervals; ASA, American Society of Anesthesiologists; ERAS, enhanced recovery after surgery; MNA-SF, mini nutritional assessment short form; OR, odds ratios; POD: postoperative day; SE, standard error; VIF, variance inflation factor.

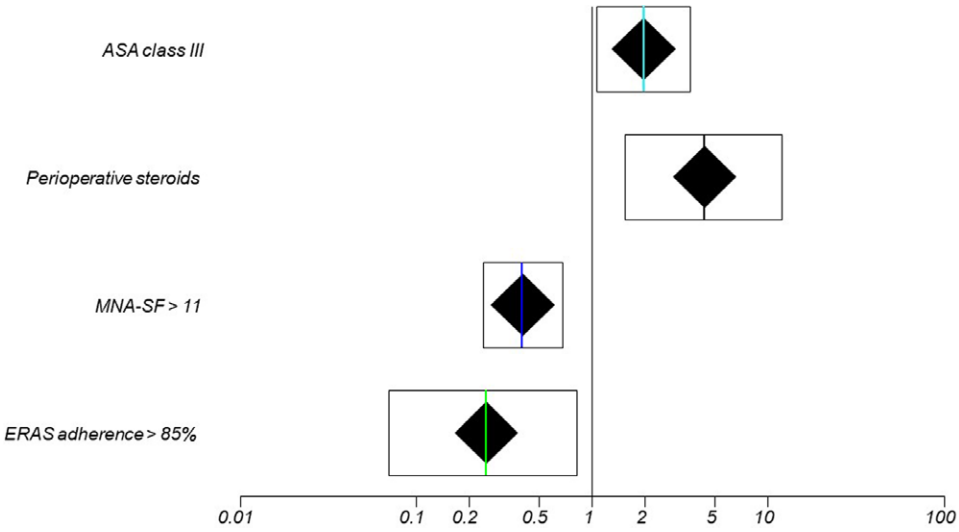

Figure 6. Forest plot (log scale) of independent variables for mortality; diamonds show ORs, boxes show 95%CIs.

this reason, we calculated overall ERAS adherence on both 20- and 16-items base (i.e. excluding postoperative items), recording the same median adherence value (75%) and a significant reduction of the number of patients included in the 4th quartile of adherence (from 1890 or 22.6% to 1366 or 16.4%). At the same, the significant correlation between ERAS 20-items adherence quartiles and overall and major morbidity rates recorded at univariate analysis (**Figure 3**) disappeared when considering ERAS 16-items adherence quartiles (**Table 5**). This finding seems to confirm that noncompliance with postoperative ERAS items may be significantly linked to the occurrence of postoperative adverse events making the patient unable to resume early mobilization, early oral feeding, and early discharge, thus making the 4th quartile of ERAS adherence a simple reservoir of the best performers. Conversely, other studies underlined that primary noncompliance with postoperative items induced by a lack of human and/or organizational resources or by lack of implementation is a key cause of program failure.[5,6,8,11] Unfortunately, both iCral studies were not designed to solve this issue, and, as a randomized controlled trial appears unpractical, the problem should be probably analyzed with a propensity score-matched analysis considering multiple treatments, using adherence to pre-, intra-, and postoperative ERAS items as treatment variables.[51]

Avoiding mechanical bowel preparation (MBP) resulted in an independent protective factor for AL (OR, 0.68; 95% CI, 0.54–0.86; P = 0.001), confirming the recommendation of European and national guidelines.[19,20] Unfortunately, we could not ascertain to what extent oral antibiotics (OAB), alone or in combination with MBP, were used in our cohorts, as it was not requested per protocol. The recent resurgence of interest in OAB,[52] combined or not with MBP, is fueling the controversy with North American guidelines,[37] upon which OAB is routinely used by 83.2% and MBP by 98.6% of respondents to a recent survey among members of the American Society of Colon and Rectal Surgeons.[53] Results from ongoing, well-designed, and appropriately powered multicenter studies that randomize participants to three groups to receive no preparation, OAB alone, or a combination of MBP and OAB, are eagerly awaited.

This analysis carries on the strengths and limitations of the merged studies. Strengths are the large number of enrolled patients in a well-defined time-lapse in a large number of centers, representing a broad sample of surgical units performing colorectal resections in Italy, coupled with the prospective design of the study allowing to measure outcomes through the adherence to any single ERAS item in all the enrolled cases, responding to clear and sheer compliance criteria (**Table 2**). The main limitation relies on merging the two studies: while it had no influence on the self-declared institutional ERAS center status, it undoubtfully determined a change in the adherence rate denominator or the total number of items considered in the pathway. Adherence was based on 21 items in the iCral 2 study, with a 71.4% overall median adherence rate,[16] and on 26 items in iCral3, with a slightly lower (69.2%) overall median adherence rate[17]; the 4th quartile threshold remained similar in both studies (80.8% and 80.9%, respectively). Using a denominator based on 20 items shared by the two studies raised the median overall adherence rate to 75% and 4th quartile threshold to >85%, which may well be considered a "Will Rogers effect."[54] It should be noticed, however, that the items not recorded in this merged analysis were gut motility stimulation, separate consideration of nutritional, physical, and psychological prehabilitation, separate consideration of carbohydrates load and 2–6 hours fasting, preoperative anemia screening and correction, and no postoperative major opiates, and that the rate of patients included in the 4th quartile group remains very similar across the two studies and in the present analysis. Other limitations are intrinsic to any observational study, with the potential for residual, measured, and unmeasured confounding. Moreover, although quality control of data was performed and repeated at various levels, we could not exclude any measurement error from the investigators.

This merged analysis of two prospective multicenter studies confirmed the need for improving overall compliance to ERAS after CRS in Italy since high adherence resulted in an independent protective factor for major morbidity and mortality rates. At the same time, it confirmed the independent negative influence of perioperative blood transfusions on anastomotic leakage and major morbidity rates, calling urgent attention to implementing patient blood management programs.

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