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ORIGINAL INVESTIGATION

# Association between enhanced recovery after surgery protocol compliance and clinical complications: a cohort study

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**KEYWORDS**
Anesthesiology;
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## Abstract

*Background:* Enhanced Recovery After Surgery (ERAS) protocol is composed by evidence-based interventions that aim to improve recovery through a reduction in surgical stress response. Although ERAS protocols have been introduced across the globe, exhaustive implementation is not as common. We aimed to study the ERAS protocol compliance in colorectal surgery, assessing the relationship between compliance and postoperative complications.
*Methods:* A single-center cohort study was conducted. All consecutive patients admitted to elective colorectal surgery were included. We assessed study endpoints according to ERAS protocol perioperative compliance score above 75%. Our primary endpoint was a composite of postoperative events, which includes in-hospital postoperative complications and need for reoperation after 30 days and need for readmission after discharge. Secondary endpoints were surgery-to-discharge time, postoperative use of only non-opioid adjuvants and the individual components of the primary endpoint.
*Results:* A total of 224 colorectal patients were included. The primary endpoint occurred in 59.2% (n = 58) of non-compliant patients comparing to 34.1% (n = 43) in compliant patients. In univariate analysis, compliance to ERAS protocol had an inferior risk for the primary endpoint ($p$ < 0.001). In a logistic regression model, compliance was independently associated with a reduced risk for the primary endpoint with a odds-ratio of 0.42 (95% CI 0.23–0.75, $p$ = 0.004).

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*Conclusion:* Compliance with the ERAS protocol is associated with less complications, a reduced surgery-to-discharge time and use of only non-opioid adjuvants in the postoperative period. More studies are needed to target the most appropriate compliance goal.
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## Introduction

Enhanced Recovery After Surgery (ERAS) guidelines for colorectal surgery were published for the first time in 2005.[1] Since then, they have been in continuous development and the most recent guidelines were published in 2018.[2] ERAS protocol is composed by evidence-based interventions that aim to improve recovery through a reduction in surgical stress response.[3] Ultimately, they may reduce complications, length of stay and time to return to work, thus improving patient satisfaction.[4] ERAS protocols have been implemented in Europe,[5,6] America,[3] Asia,[7] and Oceania,[8] and in several surgical areas (colorectal, vascular, thoracic, urologic, spine, neurosurgery, orthopedic, liver, pancreatic, and cardiac surgery).[9] In Brazil, first data has been published in 2019, and it included colorectal surgery[10] and liver surgery,[11] both with feasible and beneficial results. Although ERAS protocols have been implemented across the globe, exhaustive implementation is not as common.[3,12,13] The main limiting factor for wider acceptance is that it requires a challenge on adopted local protocols and a multidisciplinary collaboration including the Colorectal Surgical and Anesthesiology teams, the Physical Medicine and Rehabilitation Unit, ward nurses, and a nutrition network support.[14] Anesthesiologists play a pivotal role in the implementation of such protocols, since preoperative assessment and preparation, perioperative fluid management, and perioperative pain relief constitute part of the core of the ERAS program.[9]

The main focus of research has been on the implementation and the limiting factors of the adoption of the program.[5,14] The impact of each intervention on patient outcomes remains uncertain,[12] and there is still a lack of standardization methods to ascertain outcomes. This uncertainty contributes to partial protocol implementation in some centers.[8] In fact, there have been studies evaluating the inclusion in ERAS protocols while others assessed the actual compliance with ERAS items. This distinction is important, as mean compliance rate among patients included in ERAS protocols varies between 60% and 80% in some published cohorts.[13]

In our view, actual compliance rather than mere inclusion in ERAS protocols should be assessed and correlated with outcomes in order to successfully implement these protocols in clinical practice. We aimed to study the impact of high compliance perioperative ERAS protocol in in-hospital complications reinterventions, rehospitalizations and time to discharge.

## Methods

### Setting

Our hospital has an overall 700 bed capacity, and manages 200 colorectal surgical patients per year.

Our center was certified as an ERAS Center for colorectal surgery by ERAS society in October 2018. The ERAS group is in charge of program implementation and auditing. Our institution ERAS protocol is summarized in Table 1.

### Study hypothesis

The compliance with ERAS protocols is variable among patients submitted to elective colorectal surgery. We aimed to assess the hypothesis that high compliance with ERAS protocols is associated with decreased incidence of in-hospital complications, reinterventions, rehospitalizations, and time to discharge.

### Study design, institutional review board approval

We performed a single-center cohort study of all consecutive patients admitted to elective colorectal surgery in the defined study periods.

The study includes data on two separate time periods (Fig. 1). Between March and September 2017, which was previous to ERAS training, data was registered retrospectively; Between June 2018 and December 2019, data was registered prospectively. In between these periods, patients admitted during a transition phase between pre- and post-ERAS protocols, while training was performed, were not included in the study.

Patients admitted pre-ERAS were managed according to local approved protocols at the time of surgery. Patients admitted post-ERAS were managed according to ERAS protocol policies and compliance with every single item was actively encouraged. Between these two periods, ERAS training and accreditation was taking place and patients operated in the meantime were not included in the analysis.

This study was done in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[15] as well as the Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) checklist.[4] Revised Standards for the Quality Improvement Reporting Excellence (SQUIRE 2.0)[16]

**Table 1** Overview of local ERAS protocol.

| Our institution ERAS protocol (according to the Guidelines for Perioperative Care in Elective Colonic and Rectal Surgery: ERAS Society Recommendations)(2) |
|---|
| **1. Preadmission education (4-5 weeks before surgery, at least one week before surgery)** |
| • Meeting with Anesthesiologist, ERAS nurse specialist, Nutritionist, Stoma counseling, and Physiatrist; |
| • Booklet describing the protocol. |
| **2. Preoperative screening** |
| • Nutritional deficiency: Malnutrition Universal Screening Tool – MUST and the Scored Patient-Generated Subjective Global Assessment (PG-SGA); |
| • Prescription of a diet; |
| • Tobacco and ethanol: referred preoperatively for counseling. |
| **3. Prehabilitation** |
| • Physical exercises according to Physiatrist. |
| **4. Fasting and carbohydrate loading guidelines** |
| • Normal diet until midnight and hydration encouraged; |
| • One carbohydrate drink (200 mL) until 21 h and half until 23 h the day before surgery; |
| • Half carbohydrate drink (100 mL) until 2 h before surgery; |
| • Fasting is according to international guidelines. |
| **5. Bowel preparation** |
| • Colonic surgery: administration of laxative therapy only; |
| • Rectal surgery: bowel preparation with a 2-L electrolytic solution the day before surgery. |
| **6. Thromboembolic prophylaxis** |
| • Prophylactic-dose enoxaparin subcutaneously 12 h before surgery and regular administration at the same schedule (starting 6 h after surgery); |
| • Use of compression socks since the day of surgery until discharge day. |
| **7. Antibiotic prophylaxis** |
| • Cefoxitin 2 g and metronidazole 1 g, 60–30 min before surgical incision; |
| • Intraoperatively, cefoxitin 1 g is administered every 2 h and metronidazole 500 mg every 6 h. |
| **8. Preemptive analgesia** |
| • We usually do not administer preemptive analgesia. |
| **9. Anti-emetic prophylaxis** |
| • According to Apfel score; |
| • All patients are administered at least on anti-emetic; common agents are dexamethasone and ondansetron. |
| **10. Standard Anesthetic protocol – general principles** |
| • Avoiding pre-medication and long-acting opioids; |
| • Monitoring neuromuscular block; |
| • Use of cerebral monitoring for depth of anesthesia. |
| **11. Intraoperative fluid management strategy** |
| • Restrictive fluid approach with ''zero balance''; |
| • Hypotension is preferably approached according to etiology. If patient is not hypovolemic, vasopressors are preferred; |
| • If high risk patient, or expected relevant blood loss, goal-directed therapy is encouraged. |
| **12. Patient warming strategy** |
| • The warming measures start at the induction room; |
| • Forced air heating and intravenous fluids warming; |
| • Esophageal temperature monitorization to $T \geq 36.1\ ^{\circ}C$. |
| **13. Surgical access** |
| • Preferably minimal invasive approaches. |
| **14. Plan for intraoperative opioid minimization** |
| • Open surgery: thoracic epidural (colonic surgery – T7/T9 level; rectum surgery – T10/T11 level); |
| • Laparoscopic surgery: Other locoregional techniques can be useful (in our institution, a transverse abdominis plane (TAP) block is the most frequent option). |
| **15. Drain and line management** |
| • No routine wound drains; |
| • Nasogastric tube is removed in the operating room; |
| • Foley catheter: If colonic surgery, removal at day 1 postoperative; if rectal surgery, its removal is decided individually. |
| **16. Postoperative fluids** |
| • Balanced solutions until 24 h post-surgery at 1 $mL.kg^{-1}.h^{-1}$. |
| **17. Postoperative analgesia** |
| • Visual Analogue Scale (VAS) punctuation < 4; |

Table 1 (*Continued*)

| Our institution ERAS protocol (according to the Guidelines for Perioperative Care in Elective Colonic and Rectal Surgery: ERAS Society Recommendations)(2) |
|---|
| • Open surgery: epidural analgesia. The catheter is removed by postoperative day 2, if colonic surgery, and by postoperative day 4, if rectal surgery; |
| • Open surgery and laparoscopic surgery: non-opioid adjuvants (paracetamol and metamizol) during first 48 h at 6 h-intervals; after which NSAIDs or COX-2 inhibitors can be added. Tramadol can also be administered, if needed; |
| • In the first 24 h, analgesics are administered intravenously. |
| **18. Early mobilization strategy** |
| • Ambulation to chair at day 0 postoperative, for 2 h; |
| • At day 1 postoperative, the patient starts to walk in hallways (3 times during the day, minimum 2 h). |
| **19. Postoperative diet and bowel regimen management** |
| • Gut motility stimulation with Bisacodyl 5 mg. |
| • On the day of surgery: liquid diet, 2–4 h after surgery. Goal: 600 mL and 300 Kcal; End of first day: low-residue diet. |
| **20. Criteria for discharge** |
| • Postoperative autonomy guaranteed; |
| • Pain well controlled on oral medication (VAS < 4); |
| • Gastrointestinal transit recovered. |
| **21. Tracking of post-discharge outcomes** |
| • Follow-up at 48 h and at 30-days; |
| • Phone call by the ERAS team nurse. |

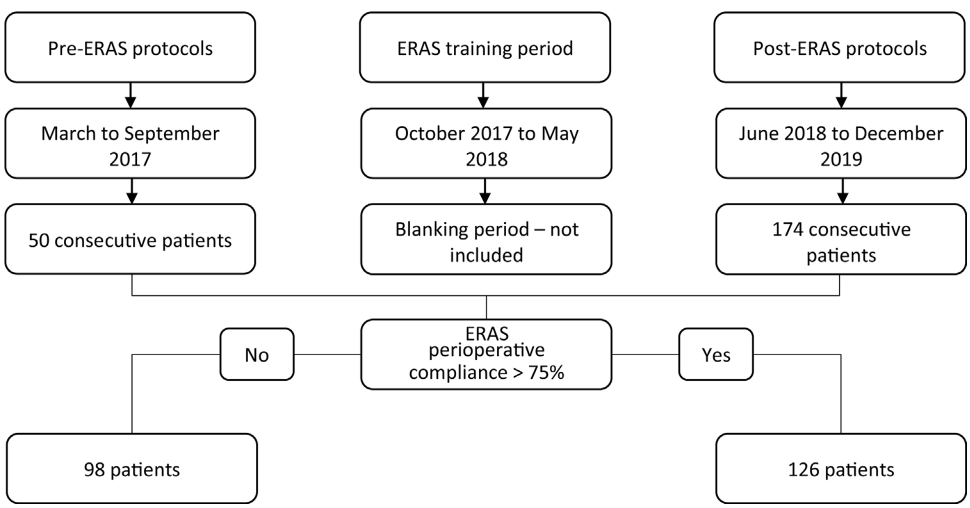


**Figure 1** Time frame and patients included flowchart.

checklist was also considered and relevant topics were included. The ethics and investigation committee gave its approval on the 14th April 2020 (protocol number 33/2020). Informed consent for the study was dismissed regarding the rigorous confidentiality provided by the ERAS database. Patients did not receive any financial compensation.

## Enhanced recovery auditing

Data was registered by the same ERAS team nurse in the auditing official ERAS tool – ERAS Interactive Audit Tool System® (EIAS). Individual compliance elements and outcomes were reviewed by the ERAS surgical and anesthesiology team.

## Perioperative compliance score

We assessed study endpoints according to ERAS protocol perioperative compliance. Therefore, we divided our population in two groups according to a score threshold of 75% (Fig. 1).[17,18]

Perioperative compliance score was calculated based in the EIAS compliance score in the pre-admission, preoperative and intraoperative period. The postoperative period was excluded from perioperative compliance score, since compliance with these recommendations is dependent on postoperative complications, which are a part of our defined primary endpoint. Therefore, from the 32 compliance variables only 19 entered the perioperative compliance score.

## Endpoints

The primary endpoint was a composite of postoperative events, which includes in-hospital postoperative complications at 30 days (medical and surgical complications described in Supplement 1 and part of ERAS outcomes assessment form), need for reoperation at 30 days and need for readmission after discharge. The secondary endpoints were surgery-to-discharge time, postoperative use of only non-opioid adjuvants and the individual components of the primary endpoint.

The ERAS team nurse was responsible for assessing the primary outcomes. The ERAS team nurse was not blinded for study period, i.e., pre- or post-ERAS implementation, but was unaware of the perioperative compliance score which was the main focus of our analysis. The ERAS team received specific training regarding outcomes assessment for accurate auditing of the program.

## Statistical analysis

Categorical variables are presented as absolute numbers and frequencies and are compared using the Pearson $X^2$ or Fisher exact test. Continuous variables are presented as mean +/- standard deviation (SD) or median with 25th and 75th percentiles for normal and non-normal distribution, respectively. Normality was tested using the Kolmogorov-Smirnov test.

The $H_0$ for our study is that occurrence of the primary and secondary endpoints would be similar between high and low compliance with ERAS protocols. The alternative hypothesis, as stated above, would be for decreased incidence of the primary and secondary outcomes in patients with high compliance to ERAS protocols, irrespective of the study period. A two-sided $\alpha$ level of 0.05 was assumed to be statistically significant. The observational and exploratory nature of the study, as well as the variability of previously reported data on the effects of ERAS compliance, did not allow for sample size calculations.

For normal distributed variables, the Student's *t*-test was used for comparison between groups. For non-normal distributed variables, the non-parametric Mann-Whitney or Kruskal-Wallis tests were chosen.

Regression models for multivariate analysis of the primary endpoint and individual components of the secondary endpoints included variables that were clinically relevant for the study endpoints and had a statistically significant association with the primary endpoint in univariate analysis. Therefore, compliance $\geq$ 75%, age, gender, ASA physical status, laparoscopic surgery, hemicolectomy (left or right), anterior rectum resection, and preoperative chemotherapy or any radiotherapy to operating field were included in the multivariate models.

Logistic regression was used for binary endpoints, using the enter method with fixed effects, whereas surgery-to-discharge time was analyzed through Cox-regression and Kaplan-Meyer of time vs. the proportion of discharged patients. Statistical analysis was performed using SPSS software® (SPSS 23, IBM).

## Results

A total of 224 patients were included in the study: 50 consecutive patients operated previously to ERAS protocol implementation and 174 consecutive patients operated after ERAS protocol implementation. All colorectal elective patients were eligible to be introduced in EIAS and, therefore, analyzed. All included patients were divided according to ERAS protocol perioperative compliance score threshold of 75% in two groups: perioperative compliance score < 75% (98 patients) and perioperative compliance score $\geq$ 75% (126 patients), as clarified in Figure 1.

## Baseline characteristics

The clinical and demographic characteristics of patients with high and low perioperative compliance are shown in Table 2. Previous abdominal surgery was more frequent in non-compliant patients − 49% (n = 48) vs. 32.5% (n = 41), $p = 0.013$ − while hemicolectomy was more common in compliant patients − 33.7% (n = 33) vs. 48.4% (n = 61), $p = 0.027$. Analyzing compliance to individual measures, it is interesting to note that compliance with smoking, iron replacement treatment, preoperative oral bowel preparation, PONV prophylaxis compliance, resection-site drainage compliance, and nerve blocks or local anesthetic compliance were not significantly different between non-compliant and compliant patients. On the contrary, pre-admission education, nutritional support, and epidural compliance, among others, were significantly different between groups (Table 2).

## The effect of compliance on the primary endpoint of postoperative events

Our primary endpoint was a composite of postoperative events including in-hospital postoperative complications, need for reoperation at 30-days and need for readmission after discharge.

The primary endpoint occurred in 59.2% (n = 58) of non-compliant patients comparing to 34.1% (n = 43) in compliant patients (Table 3). In univariate analysis, compliance to ERAS protocol had an inferior risk for the primary endpoint ($p < 0.001$). The same finding is observed when comparing high vs. low compliance only in patients treated after ERAS implementation ($p < 0.001$).

In univariate analysis of co-variates (Table 4), male sex ($p = 0.005$), ASA III or IV classification ($p = 0.034$), preoperative chemotherapy, or any radiotherapy to operating field ($p = 0.015$) and anterior rectum resection ($p = 0.05$) were associated with increased risk for the primary endpoint. In contrast, hemicolectomy ($p = 0.023$) and laparoscopic surgery ($p < 0.001$) were associated with decreased risk for the primary endpoint. Other relevant clinical variables, such as previous abdominal surgery, were not associated with different rates of the primary outcome and therefore were not included in the multivariate models described below. These results are summarized in Table 4, which describes the variables that were associated with the occurrence of the primary endpoint in univariate analysis, as well as the results of multivariate analysis using logistic regression.

**Table 2** Baseline patient characteristics according to perioperative compliance ≥ 75%.

| Characteristic | Non-compliant (n = 98) | Compliance ≥ 75% (n = 126) | *p*-value |
|---|---|---|---|
| **Patient characteristics** | | | |
| **Age, median (IQR), years** | 68 (58–78.25) | 70 (61–76.25) | 0.533 |
| **Male sex (%)** | 57 (58.2) | 71 (56.3) | 0.785 |
| **BMI, mean (SD)** | 25.6 (4.7) | 26.5 (4.5) | 0.167 |
| **ASA classification (%)** | – | – | – |
| I or II | 66 (67.3) | 94 (74.6) | 0.233 |
| III or IV | 32 (32.7) | 32 (25.4) | |
| **Diabetes mellitus (%)** | 24 (24.5) | 27 (21.4) | 0.588 |
| **Severe heart disease (%)** | 15 (15.3) | 13 (10.3) | 0.263 |
| **Severe pulmonary disease (%)** | 5 (5.1) | 15 (11.9) | 0.077 |
| **WHO performance score pre-operative (%)** | – | – | – |
| 0 | 62 (63.3) | 80 (63.5) | 0.072 |
| 1 | 35 (35.7) | 36 (28.5) | |
| 2 | 1 (1) | 9 (7.1) | |
| 4 | 0 | 1 (0.8) | |
| **Recent immunosuppressive treatment (%)** | 6 (6.1) | 2 (1.6) | 0.142 |
| **Preoperative chemotherapy or any radiotherapy to operating field (%)** | 20 (20.4) | 20 (15.9) | 0.379 |
| **Previous surgery to same abdominal region (%)** | 48 (49) | 41 (32.5) | **0.013** |
| **Surgical procedure (%)** | – | – | – |
| Anterior rectum resection | 39 (39.8) | 43 (34.1) | 0.382 |
| Hemicolectomy (left or right) | 33 (33.7) | 61 (48.4) | **0.027** |
| **Surgical major procedure (%)** | 91 (92.9) | 115 (91.3) | 0.665 |
| **Laparoscopic surgery (%)** | 36 (36.7) | 76 (60.3) | **< 0.001** |
| **Adherence to ERAS protocol recommendations** | | | |
| **Pre-admission education compliance (%)** | 39/98 (39.8) | 102/126 (81) | **< 0.001** |
| **Preoperative nutritional status assessment compliance (%)** | 55/87 (63.2) | 123/126 (97.6) | **< 0.001** |
| **Preoperative nutritional treatment compliance (%)** | 52/86 (60.5) | 123/126 (97.6) | **< 0.001** |
| **Alcohol usage compliance (%)** | 91/98 (92.9) | 125/126 (99.2) | **0.023** |
| **Smoking compliance (%)** | 89/98 (90.8) | 122/126 (96.8) | 0.056 |
| **Patient screened for anemia preop compliance (%)** | 21/21 (100) | 106/106 (100) | – |
| **Iron replacement treatment given compliance (%)** | 21/21 (100) | 104/106 (98.1) | 1.00 |
| **Carbohydrates preload compliance (%)** | 45/98 (45.9) | 126/126 (100) | **< 0.001** |
| **Preoperative oral bowel preparation (%)** | 71/92 (77.2) | 107/126 (84.9) | 0.144 |
| **Sedative compliance (%)** | 82/93 (88.2) | 126/126 (100) | **< 0.001** |
| **Antibiotic prophylaxis compliance (%)** | 89/98 (90.8) | 126/126 (100) | **< 0.001** |
| **Antithrombotic prophylaxis compliance (%)** | 58/95 (61.1) | 124/126 (98.4) | **< 0.001** |
| **PONV prophylaxis compliance (%)** | 96/96 (100) | 125/126 (99.2) | 1.00 |
| **Resection-site drainage compliance (%)** | 48/98 (49) | 76/126 (60.3) | 0.090 |
| **Systemic opioids given compliance (%)** | 57/98 (58.2) | 124/126 (98.4) | **< 0.001** |
| **Epidural/spinal compliance (%)** | 58/98 (59.2) | 108/126 (85.7) | **< 0.001** |
| **Nerve blocks or LA compliance (%)** | 7/90 (7.8) | 20/126 (15.9) | 0.076 |
| **Forced air heating compliance (%)** | 56/98 (57.1) | 124/126 (98.4) | **< 0.001** |
| **Nasogastric tube used postoperatively compliance (%)** | 53/98 (54.1) | 120/126 (95.2) | **< 0.001** |

Bold values indicates that p value is assumed to be statistically significant.

In order to assess the independent effect of compliance status on the primary endpoint, we performed a logistic regression model including the variables associated with the primary endpoint in univariate analysis (Table 4). In this model, compliance was independently associated with a reduced odds of the primary endpoint with an odds-ratio of 0.42 (95% CI 0.23–0.75, $p$ = 0.004). Moreover, laparoscopic surgery was also independently associated with a reduced odd, having an odds-ratio of 0.46 (95% CI 0.25–0.84, $p$ = 0.012) whereas male sex was associated with increased odds with an odds-ratio of 1.85 (95% CI 1.02–3.37, $p$ = 0.044).

## The analysis of secondary endpoints

The individual components of the primary endpoint were assessed as a secondary endpoint. Regarding postoperative complications, high compliance was independently associated with reduced risk of in-hospital complications with a odds-ratio of 0.45 (95% CI 0.25–0.81, $p$ = 0.008) – 52.6% (n = 51) in non-compliant vs. 30.2% (n = 38) in compliant patients. Infectious complications and postoperative paralytic ileus were the most frequent complications (Supplement 1).

Table 3 Assessment of postoperative outcomes according to perioperative compliance.

| | | | Univariate Analysis | Multivariate Analysis[a] | |
|---|---|---|---|---|---|
| Outcome | Non-compliant (n = 98) | Compliance ≥ 75% (n = 126) | *p*-value | OR 95% CI | *p*-value |
| **Composite postoperative event (complications + reoperations + readmissions) (%)** | 58/98 (59.2) | 43/126 (34.1) | **< 0.001** | 0.42 (0.23−0.75) | **0.004** |
| **In-hospital postoperative complications (%)** | 51/97 (52.6) | 38/126 (30.2) | **0.001** | 0.45 (0.25−0.81) | **0.008** |
| **Reoperations at 30 days (%)** | 11/98 (11.2) | 10/126 (7.9) | 0.402 | 0.66 (0.26−1.71) | 0.394 |
| **Readmissions (%)** | 9/98 (9.2) | 6/126 (4.8) | 0.189 | 0.51 (0.16−1.58) | 0.241 |
| **Analgesic adjuvants only (paracetamol, NSAIDs) (%)** | 69/98 (70.4) | 111/126 (88.1) | **0.001** | 3.36 (1.62−6.95) | **0.001** |
| **30-day survival (%)** | 93/96 (96.9) | 123/123 (100) | − | − | − |
| **Surgery-to-discharge time, mean (SEM)** | 13.4 (1.8) | 7.71 (0.7) | **0.002** | **< 0.001** | |

Bold values indicates that p value is assumed to be statistically significant.

[a] Adjusted for: Laparoscopic surgery, Preoperative chemotherapy or any radiotherapy to operating field, Hemicolectomy (left or right), Anterior rectum resection, age, gender, ASA physical status, compliance ≥ 75%.

The rate of reoperation was not different between non-compliant and compliant patients although the number of events was low in both groups. Similarly, the rate of readmissions was not different between groups (Table 3).

The rate of use of only non-opioid adjuvants was also a secondary endpoint in our study. In fact, compliance was independently associated with reduced opioid prescription having a odds-ratio of OR 3.36, 95% CI 1.62−6.95 (Table 3).

Surgery-to-discharge time was included as a secondary endpoint and analyzed using a multivariate model. We performed a Cox regression adjusting for sex, ASA physical status, preoperative chemotherapy or any radiotherapy to operating field, anterior rectum resection, hemicolectomy (left or right), and laparoscopic surgery. In our model, perioperative compliance was independently associated with inferior surgery-to-discharge time. In fact, mean surgery-to-discharge time was 13.4 ± 1.8 in non-compliant patients and 7.71 ± 0.7 in compliant patients ($p < 0.001$) (Fig. 2).

## Discussion

Our study analyzed the effects of high perioperative compliance with ERAS protocols on short-term surgical outcomes. We have found that a compliance score ≥ 75% was independently associated with decreased risk of the composite endpoint of in-hospital complications, reoperations and readmissions. Furthermore, surgery-to-discharge time was also reduced with protocol compliance independently of other covariates.

The study data was collected in order to audit the implementation of the ERAS program at our center. There were 224 consecutive patients included that were admitted to elective colorectal surgery in two different time periods − one before implementation of the ERAS program and other after ERAS protocols had been fully implemented. In our analysis, we compared patients with high compliance to the perioperative ERAS protocols, defined as compliance ≥ 75%,[19] with patients with low compliance. Our study hypothesis was that higher compliance to protocols would be associated with improved results in what should be regarded as a hypothesis generator study. Below, we discuss the potential advantages and main limitations of our study in light of the published literature on this topic.

The ERAS guidelines were first published in 2005, but adoption of protocol principles has been slow in many countries and hospitals. There are huge barriers to protocol implementation like strong individualized surgeon and anesthesiologist-based preferences, complex systems of care, financial settlements and focus in traditional endpoints of mortality.[20] The published papers on ERAS protocols have focused most often on comparing patients included in the protocol vs. those managed with local guidelines. This comparison has been done independently of compliance. However, ERAS protocol is a perioperative assembly of elements, and benefits come from its whole application. The role of each separated element is hard to

**Table 4** Multivariate analysis of the primary endpoint – composite of postoperative events.

| Parameter | Total (n) | No composite postoperative event (n = 123) | Composite postoperative event (n = 101) | Univariate Analysis *p*-value | Multivariate analysis[a] OR 95% CI | Multivariate analysis[a] *p*-value |
|---|---|---|---|---|---|---|
| **Perioperative compliance ≥ 75% (%)** | 126 | 83 (65.9) | 43 (34.1) | **< 0.001** | 0.42 (0.23–0.75) | **0.004** |
| **Age, median (IQR), years** | 70 (61–76.25) | 69 (60–76) | 70 (60.5–78.5) | 0.401 | 1 (0.98–1.02) | 0.974 |
| **Male sex (%)** | 128 | 60 (46.9) | 68 (53.1) | **0.005** | 1.85 (1.02–3.37) | **0.044** |
| **ASA classification (%)** | – | – | – | – | – | – |
| I or II | 160 | 95 (59.4) | 65 (40.6) | **0.034** | 1.47 (0.74–2.9) | 0.273 |
| III or IV | 64 | 28 (43.8) | 36 (56.3) | | | |
| **Preoperative chemotherapy or any radiotherapy to operating field (%)** | 40 | 15 (37.5) | 25 (62.5) | **0.015** | 1.81 (0.8–4.2) | 0.156 |
| **Surgical procedure (%)** | – | – | – | – | – | – |
| Anterior rectum resection | 82 | 38 (46.3) | 44 (53.7) | **0.05** | 1.33 (0.59–2.97) | 0.494 |
| Hemicolectomy (left or right) | 94 | 60 (63.8) | 34 (36.2) | **0.023** | 0.97 (0.43–2.2) | 0.949 |
| **Laparoscopic surgery (%)** | 112 | 77 (68.8) | 35 (31.3) | **< 0.001** | 0.46 (0.25–0.84) | **0.012** |

Bold values indicates that p value is assumed to be statistically significant.
[a] Adjusted for: Laparoscopic surgery, Preoperative chemotherapy or any radiotherapy to operating field, Hemicolectomy (left or right), Anterior rectum resection, age, gender, ASA physical status, compliance ≥ 75%.

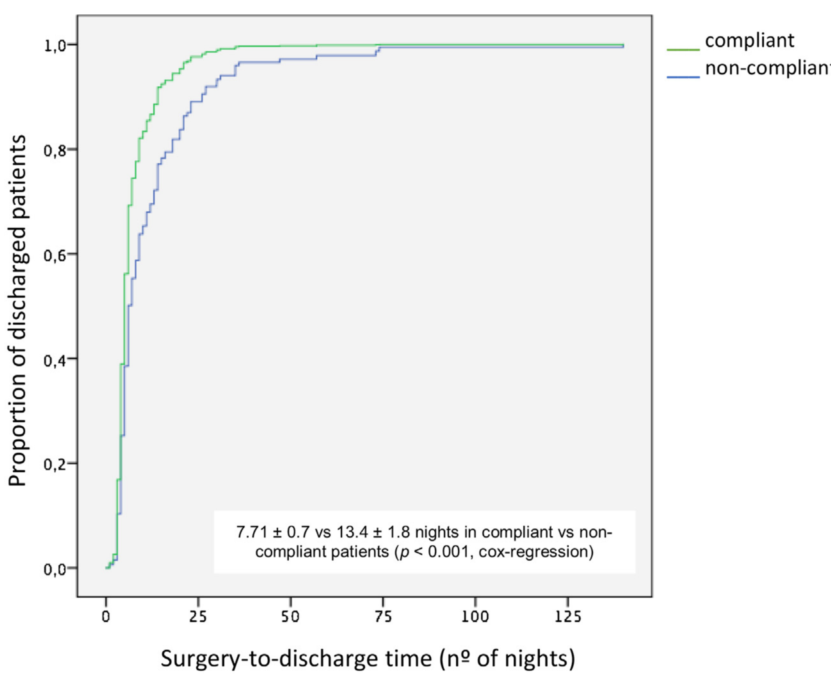


**Figure 2** Adjusted length of stay according to compliance ≥ 75%.

define and probably not enough on its own to change outcomes. In order to increase ERAS protocol adherence, it is very important to demonstrate a beneficial effect of ERAS compliance on surgical outcomes. Furthermore, since in-hospital mortality for elective surgery is currently a rare event we should focus on alternative endpoints related to improved patient care.

When analyzing the impact of ERAS programs implementation, a shift towards compliance evaluation would further allow the assessment of individual elements and guide future versions of the protocol. However, there are some barriers to assess compliance. Overall compliance, as it is calculated by the EIAS, looks at protocol adherence and includes postoperative aspects (e.g., mobilization or energy intake). Postoperative events can also be regarded as outcomes. Therefore, it would be of outmost interest if the EIAS would be modified in order to exclude every variable that can be simultaneously an outcome and a protocol adherence parameter to properly evaluate compliance role in the perioperative period.

In order to avoid this limitation, several observational studies have tried to calculate their own compliance scores based on the analysis of individual elements. Authors have selected the variables of interest for their particular study and compliance thresholds have also been selected in a case-by-case manner.[17,21,22] This scenario imposes several limitations to the comparison across surgical programs and makes it virtually impossible to conduct metanalysis of the effects of compliance on surgical outcomes.

In our work, the mean between pre-admission, preoperative and intraoperative compliance, as it is reported by the EIAS, was calculated in order to define the score of perioperative compliance. The 75% compliance threshold was defined in line with previously published data. Arrick et al. 2019[19] has also used the 75% threshold; however, in literature, other thresholds can be found.[21] A group of non-compliant patients, that comprise all the patients operated before ERAS implementation and the 27.6% (n = 48) of non-compliant patients operated after the implementation of the ERAS protocol was created.

The comparison between high vs. low compliance patients has several advantages. Firstly, the focus is on ERAS compliance rather a comparison between pre- or post-ERAS implementation outcomes where other treatment variables might also have changed. Secondly, given the observational nature of the study, the investigators were aware of the changes brought by ERAS implementation. However, since the research team were unaware of the compliance status when recording the outcomes, this helped to minimize bias in the evaluation of study results. Thirdly, by analyzing the effects of ERAS on surgical outcomes, we can estimate the event rates of each treatment group and contribute with our data for a sample size calculation used in a future trial.

A topic that deserves detailed discussion is the choice of outcomes for the assessment of ERAS protocols. Outcome measures should reflect the personal, social, and economic consequences of adverse events after major abdominal surgery. Our primary endpoint – composite postoperative event – includes the main incidents after major abdominal surgery. Compliant patients had an inferior risk of postoperative events independently of covariates. Furthermore, compliant patients had a shorter surgery-to-discharge time and less frequent postoperative systemic opioid analgesia also independently of other risk factors. Off note, laparoscopic surgery was also independently associated with decreased risk of the postoperative primary endpoint whereas male sex was associated with increased risk.

Our results are in line with studies in different surgical fields that have shown that higher compliance with the protocol can improve surgical outcomes by allowing decreased morbidity and shortening the length of stay.[13,17,21,23] Pisarka et al.,[13] in a prospective cohort study, showed that full implementation of the ERAS protocol significantly improves short term outcomes. Patients with higher compliance had less postoperative morbidity rate and a shorter median length of stay. Gianotti et al.,[17] in a report of observational data described association between an ERAS compliance > 70% and a reduced risk of complications. Zaouter et al., in a cardiac surgery population, suggested that the preoperative and intraoperative elements of the study's ERAS protocol offered appropriate conditions to start early mobilization, early feeding and early physiotherapy compared with the standard protocol.[18] Together with these results, our conclusions reinforce that adherence to perioperative protocol guidelines improves postoperative outcomes.

Regarding pain management, we were able to demonstrate that the use of opioids was less frequent in our compliant patients' cohort. Pain control is a fundamental component of patient care. It is directly related to patient quality of life inside hospital and after discharge. Multimodal analgesia to minimize opioid consumption is of utmost importance in colorectal surgery to reduce postoperative ileus.[2] Regional analgesia with epidural analgesia for colorectal surgery is recommended in ERAS Society guidelines.[2] Lumbar supplementary analgesia and spinal adjunct to general anesthesia (the latter mainly in case of laparoscopic surgery) has been more recently added to guidelines and protocols and its use is still on growing. Spinal analgesia is considered simpler to administer and manage compared to epidural analgesia.[24] In Kjolhede et al.,[24] a randomized trial, spinal analgesia was given to patients submitted to midline laparotomy for gynecological malignancy under ERAS protocol routines. They have reported shorter length of stay in the spinal analgesia group, similar quality of life parameters and similar overall assessment of pain between both groups. This opioid-sparing approach in combination with early hospital discharge contributes to improving patient care.

The pathophysiological mechanisms behind the impact of ERAS protocols on surgical endpoints are varied. The catabolic effect[9] associated with surgical procedures is believed to be detrimental to patients, and probably the main factor leading to postoperative morbidity. The ERAS protocols address these metabolic changes by minimizing stress response through controlling preoperative fasting and optimization of pre-operative status, by controlling intraoperative anesthetic and surgical factors associated with the stress response, by performing multimodality pain management and enhancing early postoperative rehabilitation.[25] This may justify the importance of a thorough implementation and compliance to the protocol.

## Limitations

We acknowledge the limitations of our work in several domains. We have performed an observational study and therefore confounding factors cannot be eliminated from our analysis. We adopted a composite endpoint and individual components may not have the same importance to patients and magnitude of effect across components.[26] The research team was not blinded to the ERAS program implementation, although it was unaware of the compliance status of each patient when assessing the study outcomes. Moreover, neither the compliance threshold that we used nor the perioperative score are completely established in the literature, although we expect to have contributed to improvements in this regard. Our sample size is relatively small, it is a single center study, and the included patients were treated during a 3-years period which introduces heterogeneity. However, by focusing our analysis on compliance irrespective of the time of surgery with minimized the potential bias of comparing cohorts treated in a different time period.

Despite the acknowledged limitations, we believe that our study has merits in auditing our program and in generating the hypothesis that ERAS compliance might be of benefit to our patients. We firmly believe that only a randomized clinical trial will fully assess the effects of ERAS implementation. We hope that the data from our study can be used to prepare a clinical trial on this matter.

## Conclusions

In our study, higher compliance to perioperative ERAS protocols is associated with less postoperative complications and a reduced surgery-to-discharge time. Given the observational nature of the data, the current study should be regarded as a hypothesis generator and the results confirmed in a randomized control trial. We recommend that a standardized definition of compliance thresholds and outcomes should be implemented in future ERAS programs to foster research on this important topic.

## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.08.018.

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